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Natural History of Asymptomatic Patients With Normally Functioning or Minimally Dysfunctional Bicuspid Aortic Valve in the Community

Hector I. Michelena, MD; Valerie A. Desjardins, MD; Jean-François Avierinos, MD; Antonio Russo, MD; Vuyisile T. Nkomo, MD; Thoralf M. Sundt, MD; Patricia A. Pellikka, MD; A. Jamil Tajik, MD; Maurice Enriquez-Sarano, MD

Background—Bicuspid aortic valve is frequent and is reported to cause numerous complications, but the clinical outcome of patients diagnosed with normal or mildly dysfunctional valve is undefined.

Methods and Results—In 212 asymptomatic community residents from Olmsted County, Minn (age, 32 ± 20 years; 65% male), bicuspid aortic valve was diagnosed between 1980 and 1999 with ejection fraction $\geq 50\%$ and aortic regurgitation or stenosis, absent or mild. Aortic valve degeneration at diagnosis was scored echocardiographically for calcification, thickening, and mobility reduction (0 to 3 each), with scores ranging from 0 to 9. At diagnosis, ejection fraction was $63 \pm 5\%$ and left ventricular diameter was 48 ± 9 mm. Survival 20 years after diagnosis was $90 \pm 3\%$, identical to the general population ($P=0.72$). Twenty years after diagnosis, heart failure, new cardiac symptoms, and cardiovascular medical events occurred in $7 \pm 2\%$, $26 \pm 4\%$, and $33 \pm 5\%$, respectively. Twenty years after diagnosis, aortic valve surgery, ascending aortic surgery, or any cardiovascular surgery was required in $24 \pm 4\%$, $5 \pm 2\%$, and $27 \pm 4\%$ at a younger age than the general population ($P<0.0001$). No aortic dissection occurred. Thus, cardiovascular medical or surgical events occurred in $42 \pm 5\%$ 20 years after diagnosis. Independent predictors of cardiovascular events were age ≥ 50 years (risk ratio, 3.0; 95% confidence interval, 1.5 to 5.7; $P<0.01$) and valve degeneration at diagnosis (risk ratio, 2.4; 95% confidence interval, 1.2 to 4.5; $P=0.016$; $>70\%$ events at 20 years). Baseline ascending aorta ≥ 40 mm independently predicted surgery for aorta dilatation (risk ratio, 10.8; 95% confidence interval, 1.8 to 77.3; $P<0.01$).

Conclusions—In the community, asymptomatic patients with bicuspid aortic valve and no or minimal hemodynamic abnormality enjoy excellent long-term survival but incur frequent cardiovascular events, particularly with progressive valve dysfunction. Echocardiographic valve degeneration at diagnosis separates higher-risk patients who require regular assessment from lower-risk patients who require only episodic follow-up. (*Circulation*. 2008;117:2776-2784.)

Key Words: aorta ■ echocardiography ■ surgery ■ survival ■ valves

Bicuspid aortic valve (BAV) is a common congenital heart abnormality affecting 0.5% to 2% of the population.¹⁻³ It is often considered a serious condition with notable valvular risk, particularly of aortic valve endocarditis^{4,5}; frequent progression to aortic valve stenosis,^{6,7} especially in men⁷; and frequent aortic regurgitation requiring aortic valve replacement (AVR).^{8,9} Furthermore, BAV is not just a peculiar valve morphology; it is a disease of the ascending aorta characterized at an early stage by asymptomatic dilatation of the ascending aorta¹⁰ and later by frequent susceptibility to aneurysm formation of the aorta¹¹⁻¹³ and to the most dreaded complication, aortic dissection.^{2,9,14} However, these implied serious prognostic consequences of BAV were derived mostly from autopsy or studies at referral centers with a high

concentration of patients who already have these complications. Few longitudinal data are available on asymptomatic, initially uncomplicated patients detected in the community who are not referred and may never be accounted for until autopsy.¹ Thus, the real complication burden of BAV in the community has not been measured. Although it is well established that patients with clinically significant aortic valve stenosis or regurgitation incur serious outcome consequences whether they have bicuspid and tricuspid valves,^{15,16} limited data are available on patients with initially normally functioning or minimally dysfunctional BAV,^{17,18} in whom mortality and cardiac and vascular event rates are undefined. To resolve these uncertainties, assessment of all cases diagnosed in a geographically defined community with high use

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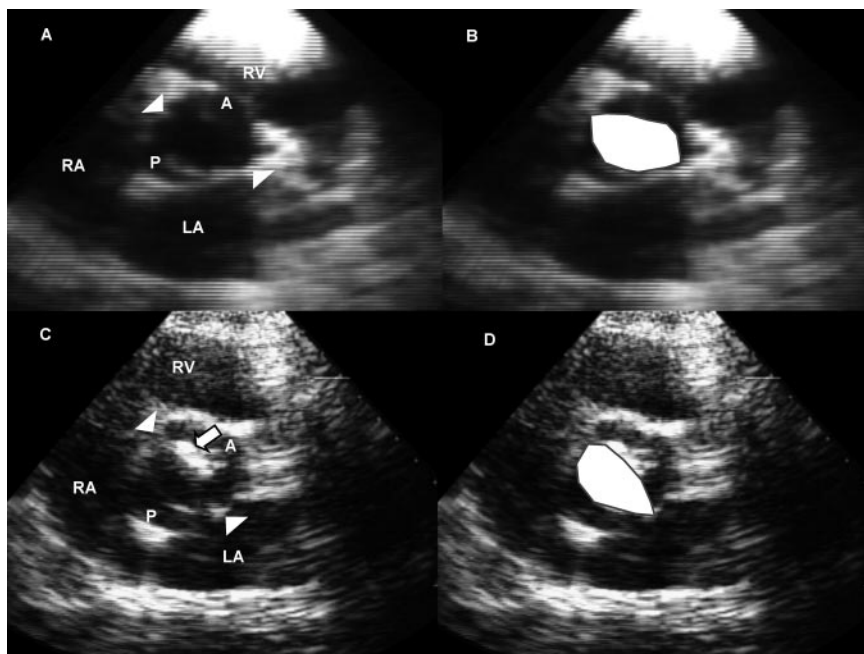


Figure 1. Echocardiographic short-axis views in systole at aortic cusp levels in 2 patients with BAVs. A, A patient with no valve degeneration; B, the same image superimposed with the drawing of the large valve orifice (white area). Arrowheads mark the commissures. C, A patient with valve degeneration (large arrow) involving mostly the anterior cusp; D, the patient's large orifice area (white area; labeling as in A). A indicates anterior cusp; P, posterior cusp; LA, left atrium; RA, right atrium; and RV, right ventricle.

of echocardiography and very long-term outcome assessment is essential for verifying the working hypothesis that BAV, even normally functioning or minimally dysfunctional, is associated with mortality in excess of that of the general population. We also wanted to define cardiovascular complications rates and determinants and to analyze the Olmsted County community over 20 years to examine and define the complication rates of BAV.

Clinical Perspective p 2784

Methods

Study Subjects

Eligible subjects were residents of Olmsted County (Minn) of all ages in whom BAV was diagnosed and confirmed by echocardiography from 1980 to 1999 who had no cardiovascular symptoms at diagnosis and had normal function or minimal dysfunction of the aortic valve as shown by clinical evaluation confirmed by echocardiography that showed no or at most mild stenosis (wide systolic valvular opening with mean gradient <20 mm Hg in patients who underwent continuous wave Doppler) and no or mild regurgitation (no or mild left ventricular enlargement,¹⁹ no or mild regurgitation by pulsed-wave Doppler of the LV outflow tract and aortic arch or by color flow Doppler) with left ventricular ejection fraction $\geq 50\%$. Olmsted County is the geographic location of the Mayo Clinic, and residents of the county represent the primary care basis of our institution, which provides all cardiovascular consultative services and all echocardiographic services to county residents. Exclusion criteria were severe comorbidity at diagnosis and complex congenital heart disease at diagnosis; prisoners of the Federal Medical Center of Olmsted County also were excluded. The protocol was approved by the Mayo Clinic Institutional Review Board. The study design involved retrospective identification of all patients diagnosed with BAV and the analysis of validated echocardiographic measurements (left ventricular size and function, aortic size, Doppler variables) measured prospectively during the diagnostic study.

Echocardiography

All patients underwent baseline clinical evaluation performed by their personal physician and comprehensive 2-dimensional and

Doppler echocardiographic evaluation with state-of-the-art technology at diagnosis.^{20,21} Left ventricular ejection fraction was assessed with 2-dimensional echocardiography guidance²² and visual estimation.²³ 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 leaflets (Figure 1). Multiple views were obtained with immediate physician review and, if necessary, repeat imaging to confirm the bicuspid valve. BAVs 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).^{24–26} Presence of a raphe and systolic doming of the valve also were recorded. Doppler was used to measure blood velocity, with pulsed Doppler, color Doppler, or both assessing subaortic flow and degree of aortic regurgitation,²⁷ with assessment of flow reversal in the aortic arch, and with continuous-wave Doppler measurement of maximal jet velocity.²⁸ In all patients diagnosed before continuous-wave Doppler became available, wide valvular opening ascertained the absence of valve stenosis. Two-dimensional ascending aorta measurements were made in patients with appropriate aortic visualization in systole at the proximal ascending aorta level.

All baseline echocardiograms were reviewed by experienced observers who were blinded to identification and outcome to evaluate valve degeneration (Figure 1). A baseline 2-dimensional echocardiographic aortic valve degeneration score was calculated. Each component of valve degeneration was graded 0 (normal), 1 (mild alteration), 2 (moderate alteration), or 3 (severe alteration) for thickening, calcification, and reduced mobility. Moderate or severe alterations were localized and did not affect the overall normal hemodynamic function of the valve. A visible raphe was not considered a sign of valve degeneration. These 3 component scores were then summated into a final composite score of degeneration, which ranged potentially from 0 to 9 points. Twenty randomly chosen studies also were graded repeatedly for intraobserver and interobserver agreement of the degeneration score.

Follow-Up and Outcomes

Clinical follow-up was obtained by review of medical records, surveys, and telephone interviews. Cause of death was determined by review of medical records and death certificates. Events used as end points were mortality and cardiovascular medical events, surgical events, and total events. Medical cardiovascular events included

cardiac death, congestive heart failure (CHF), new cardiovascular symptoms (dyspnea, syncope, and anginal pain), stroke, and endocarditis. Surgical events were made up of aortic valve surgery (AVR, repair, or valvulotomy) and surgery of the thoracic aorta (for aortic aneurysm, dissection, or coarctation). Follow-up echocardiography, when available (143 patients), was analyzed for progression of aortic dilatation.

Statistical Analysis

Continuous variables are expressed as mean±SD for continuous variables and percentage for categorical variables. Intraobserver and interobserver agreement of degeneration score was analyzed by use of matched pairs for absolute differences and Pearson correlation coefficients. Survival and event rates were determined with the Kaplan–Meier method and compared between 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. Because full Doppler methods (continuous-wave Doppler and color-flow imaging) were available only after 1985, we analyzed comparability of outcomes before and after 1985. Values of $P<0.05$ were considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Subjects

Between 1980 and 1999, BAV was diagnosed in 5747 patients, of whom 5126 were distantly referred, 621 were from Olmsted County, 373 had moderate or severe valve disease (with or without symptoms or abnormal ventricular function), and 248 had an echocardiographic diagnosis of BAV and a normal or minimally dysfunctional aortic valve. Seven were excluded because of questionable cusp number without BAV confirmation, and 29 were excluded because they presented at diagnosis with severe comorbidity, complex congenital heart disease, symptoms of ongoing cardiovascular disease, or ejection fraction $<50\%$ or could not be involved in research (inmates). The remaining 212 patients responding to eligibility criteria formed the final study group. Baseline characteristics of the 212 eligible patients (65% men) are presented in Table 1. Age at diagnosis was 32 ± 20 years; 154 patients (73%) were ≥ 18 years of age at diagnosis; and the oldest patient diagnosed with a normally functioning BAV valve was 89 years of age. Indications for echocardiography were a systolic ejection murmur in 101 (48%), a systolic click in 32 (15%), a diastolic murmur in 18 (9%), and miscellaneous in the remainder (including assessment of left ventricular function, suspected thoracic aortic disease, palpitations, atypical chest pain, and noncardiac symptoms). Associated congenital cardiac abnormalities were found in 32 patients (15%) and were mostly mild, causing no cardiac symptoms and no heart failure, with the most frequent being aortic coarctation ($n=15$). A typical BAV was present in 182 patients; an atypical BAV was present in 30 (14%). The degeneration score was low (0.80 ± 1.4 ; median, 0) and ranged from 0 to 6. Intraobserver and interobserver correlations for degeneration score were 0.89 and 0.94 (both $P<0.01$) with no systematic difference (both $P>0.50$). One-hundred-eighty-four patients (87%) had no valve degenera-

Table 1. Baseline Characteristics of Olmsted County Community Residents With BAV Overall and Grouped According to the Presence or Absence of Valve Degeneration at Diagnosis (Degeneration Score <3 or ≥ 3) by Echocardiography

Population Variable	Valve Degeneration at Diagnosis			P
	Total (n=212)	Absent (n=184)	Present (n=28)	
Age, y	32±20	28±19	52±16	<0.01
Male, n (%)	138 (65)	117 (64)	21 (75)	0.23
Hypertension, n (%)	43 (20)	31 (17)	12 (43)	0.003
Diabetes mellitus, n (%)	5 (2)	3 (2)	2 (7)	0.13
Smoking, n (%)	56 (26)	45 (24)	11 (39)	0.09
Ejection click, n (%)	71 (33)	67 (36)	4 (14)	0.01
Systolic murmur, n (%)	162 (76)	139 (76)	23 (82)	0.41
Diastolic murmur, n (%)	35 (17)	30 (17)	5 (19)	0.78
Typical BAV, n (%)	182 (86)	157 (85)	25 (89)	0.56
Visible raphe, n (%)	103 (49)	83 (45)	20 (71)	<0.01
Systolic doming, n (%)	108 (51)	96 (52)	12 (43)	0.42
Ejection fraction, %	63±5	64±5	63±5	0.40
LVD, mm	48±9	48±9	50±5	0.42
Aortic regurgitation, n (%)	100 (47)	82 (45)	18 (64)	0.03
Creatinine, mg/dL	1.03±0.4	1.03±0.4	1.06±0.2	0.51
Total cholesterol, mg/dL	198±45	193±42	220±52	0.05

LVD indicates left ventricular end-diastolic dimension.

tion (score <3 ; Figure 1A) and 28 patients (13%) had valve degeneration at diagnosis (score ≥ 3 ; Figure 1C). Their baseline characteristics are compared on the right side of Table 1. Valve degeneration showed the strongest association with older age, and after adjustment for age, its association with hypertension became insignificant ($P=0.80$). However, adjustment for age did not affect the trend for association with cholesterol level ($P=0.05$). A raphe was visualized more frequently in patients with valve degeneration at diagnosis. A systolic click was heard more often in patients without valve degeneration. Diagnosis was made up to 1985 in 50 patients and after 1985 in 162 patients. These subsets had similarly normal LV sizes (49 ± 7 versus 48 ± 10 mm; $P=0.15$), similar ejection fractions ($63\pm 6\%$ versus $63\pm 5\%$; $P=0.92$), and similar prevalences of valve degeneration (12% versus 13.6%; $P=0.83$).

Long-Term Clinical Outcome

Follow-up was complete (for survival and morbid complications) up to July 2005 to July 2006 or death in 196 patients (93%). The remaining 7% in whom last contact was earlier than 2005 were followed up for 11 ± 6 years. Total follow-up was 15 ± 6 years (range, 0.4 to 25 years), during which 14 deaths occurred, 3 related to the aortic valve (endocarditis [$n=1$], aortic stenosis [$n=1$], and aortic regurgitation [$n=1$]). No death was related to ascending aortic or congenital disease complications. Survival was $97\pm 1\%$ and $90\pm 3\%$ at 10 and 20 years after diagnosis and was identical to expected survival of the population matched for age and sex ($P=0.72$; Figure 2). Observed versus expected survival comparison

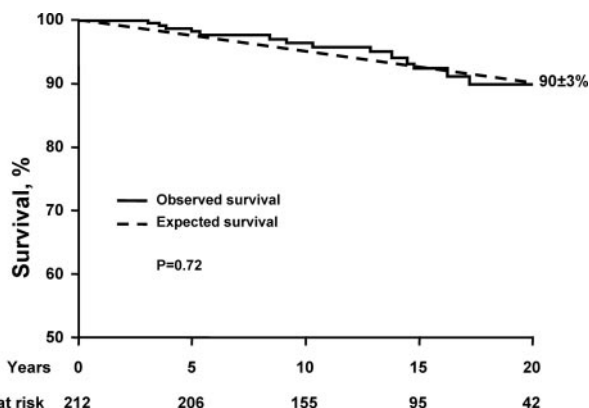


Figure 2. Survival after diagnosis of asymptomatic community members with BAV (solid line) vs expected survival in the same community (dashed line). The numbers at the bottom indicate the patients at risk for each interval. The survival (\pm SE) 20 years after diagnosis is indicated.

stratified by age at diagnosis showed no excess mortality in the <20-year (15 years, 100% versus 99%; $P=0.38$), 20- to 49-year (15 years, 93% versus 96%; $P=0.55$), and ≥ 50 -year (15 years, 64% versus 66%; $P=0.60$) age groups.

During follow-up, CHF occurred in 10 patients ($7\pm 2\%$ at 20 years), and new cardiac symptoms (dyspnea, syncope, or angina) occurred in 41 patients ($26\pm 4\%$ at 20 years; Figure 3). Four patients were diagnosed with bacterial endocarditis (subsequently, 1 died and 3 underwent AVR), and stroke occurred in 5 patients. Thus, the incidence of cardiovascular medical events (cardiac death, heart failure, new symptoms, endocarditis, or stroke) was $33\pm 5\%$ at 20 years after diagnosis (Figure 3).

During follow-up, aortic valve surgery was performed in 39 patients, involving aortic valvotomy in 3 patients, 2 of whom later required reoperation (AVR); thus, AVR was ultimately performed in 38 patients. AVR was indicated for severe aortic stenosis in 26 patients, severe aortic regurgitation in 6 patients, and severe mixed aortic valve disease in 2 patients, whereas moderate valve dysfunction with severe ascending aortic dilatation was present in 3 patients and acute

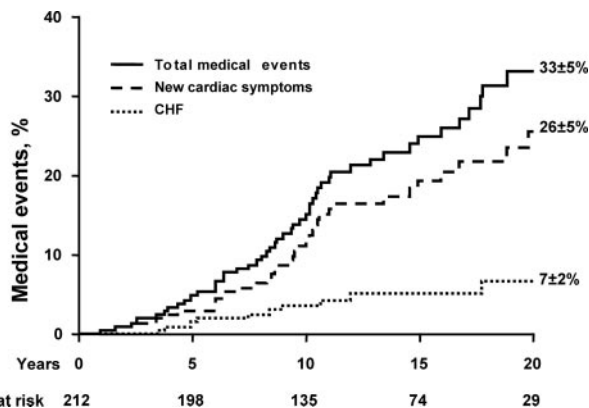


Figure 3. Incidence of total medical events (cardiac death, CHF, new cardiac symptoms, stroke, and endocarditis; solid line), new cardiac symptoms (dyspnea, cardiac chest pain, and syncope; dashed line), and CHF (dotted line). The numbers at the bottom indicate the patients at risk for each interval. The event rates (\pm SE) at 20 years are indicated.

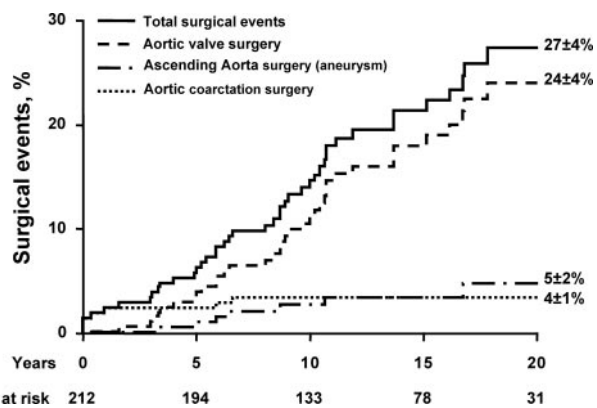


Figure 4. Incidence of total surgical events (aortic valve, ascending aorta, aortic coarctation; solid line), aortic valve surgery (AVR or surgical valvotomy; dashed line), ascending aortic surgery (dashed and dotted line), and aortic coarctation surgery (dotted line). The numbers at the bottom indicate the patients at risk for each interval. The event rates (\pm SE) at 20 years are indicated.

endocarditis was seen in 1 patient. AVR was indicated for new symptoms or heart failure in 26 patients (68%), whereas asymptomatic aortic dilatation or ventricular dysfunction resulting from severe valve dysfunction justified the indication in 7 patients (18%) and patient and/or physician preference justified the indication in 5 patients. The time from diagnosis to valve surgery was 11 ± 6 years, and age at surgery was 49 ± 20 years. Thus, the 20-year aortic valve surgery incidence was $24\pm 4\%$ (Figure 4). Eight patients required surgery for aortic coarctation, leading to a 20-year rate of $4\pm 1\%$, and 8 patients required surgery for ascending aortic dilatation or aneurysm, leading to a 20-year rate of $5\pm 2\%$ (Figure 4). Among the 143 patients who underwent follow-up echocardiography, aortic dilatation increased (diameter progressing from 35.5 ± 6 to 39.4 ± 7 mm [$P<0.001$] in patients initially >18 years of age over 10 ± 6 years of echocardiographic follow-up). Ascending aorta dilatation (>40 mm) was noted in 15% at baseline and 39% at follow-up. No aortic dissection was diagnosed or operated on during follow-up.

Thus, the 20-year rate of surgical events (aortic valve or aorta) was $27\pm 4\%$, and the rate of any cardiovascular event (medical or surgical) was $42\pm 5\%$ (Figure 5). When patients with coarctation were excluded, 20-year rates of cardiovascular medical, surgical, and total events ($35\pm 5\%$, $25\pm 4\%$, $40\pm 5\%$) were unaffected. The patients diagnosed up to 1985 versus after 1985 had similar rates of medical (at 20 years, $33\pm 7\%$ versus $33\pm 7\%$; $P=0.88$) and surgical (at 20 years, $26\pm 7\%$ versus $27\pm 5\%$; $P=0.83$) events.

Comparing cardiovascular events in BAV versus general population is difficult because population age- and sex-specific expected rates of morbid events are not available. With regard to CHF, in our BAV population, the annual incidence rate was 370 per 100 000 subject-years, whereas published overall CHF incidence rates in Olmsted County are between 378 and 280 per 100 000 subject-years for men and women, respectively.²⁹ However, our BAV population was young at diagnosis, so the expected CHF rates for age are very low.³⁰ Importantly, CHF occurred at 62 ± 20 versus

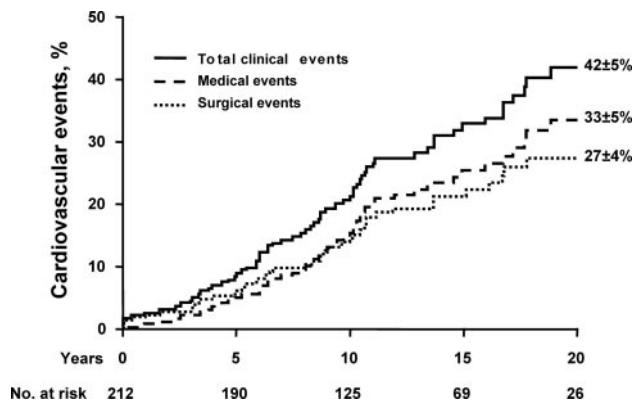


Figure 5. Incidence of any cardiovascular event (total of medical or surgical; solid line), medical events (cardiac death, CHF, new cardiac symptoms, stroke, and endocarditis; dashed line), and surgical events (AVR, surgical valvotomy, ascending aorta surgery, or coarctation surgery; dotted line). The numbers at the bottom indicate the patients at risk for each interval. The event rates (\pm SE) at 20 years are indicated.

76 \pm 12 years of age in the general population ($P=0.0002$), demonstrating that CHF occurs prematurely in BAV compared the general population. With regard to need for AVR, no complete national statistics are available. In Olmsted County, during the period of 1990 to 1999, 190 patients underwent AVR with or without bypass, leading to an estimated incidence rate of 19 per 100 000 subject-years, which contrasts to the rate of 1370 per 100 000 subject-years in our patients with BAV. Furthermore, AVR for BAV was performed at a younger age for BAV than for tricuspid aortic valve in our community (49 \pm 20 versus 67 \pm 16 years; $P<0.0001$), demonstrating that need for AVR occurs prematurely in BAV compared with the general population.

Predictors of Clinical Events

Characteristics noted at diagnosis that were used as candidate predictors of outcome were age, sex, hypertension, ejection fraction, BAV type, presence of aortic regurgitation, total cholesterol, ascending aortic diameter, and degeneration score (Table 2).

For all cardiovascular events (medical and surgical) univariately, the most powerful predictor was older age (hazard ratio, 4.4; 95% confidence interval [CI], 2.4 to 7.9; $P<0.01$).

Table 2. Independent Predictors of Outcome After Diagnosis

End Points		Independent Multivariate Predictors			
		Predictor	HR	95% CI	<i>P</i>
Medical CV events	Cardiac death, CHF, new CV symptoms, stroke, endocarditis	Age \geq 50 y	4.7	2.2–9.6	<0.01
		Valve degeneration	2.6	1.2–5.3	0.016
Surgical CV events	Aortic valve surgery, thoracic aorta surgery	Age \geq 50 y	2.9	1.3–6.2	0.01
		Valve degeneration	4.5	2.1–9.3	<0.01
Aortic valve surgery	Valvotomy or valve replacement	Age \geq 50 y	4.8	2.0–11.6	<0.01
		Valve degeneration	6.9	3.0–15.5	<0.01
Aortic aneurysm surgery		Baseline aorta \geq 40 mm	10.8	1.8–77.3	<0.01
Total events	Medical or surgical events	Age \geq 50 y	3.0	1.5–5.7	<0.01
		Valve degeneration	2.4	1.2–4.5	0.016

HR indicates hazard ratio; CV, cardiovascular.

Although hypertension and ascending aortic diameter were univariately predictive of cardiovascular events (both $P<0.01$), with adjustment for age and sex, these characteristics lost their association with outcome (both $P>0.60$). Baseline systolic or diastolic murmur and echocardiographic presence of aortic regurgitation were not associated with events. Conversely, valve degeneration at diagnosis with a score \geq 3 univariately predicted all cardiovascular events (hazard ratio, 3.6; 95% CI, 1.9 to 6.3; $P<0.01$) and remained so after adjustment for age (as a continuous variable; $P=0.01$) and sex. In the multivariate analysis, baseline predictors of all cardiovascular events were age \geq 50 years (risk ratio, 3.0; 95% CI, 1.5 to 5.7; $P<0.01$) and valve degeneration (risk ratio, 2.4; 95% CI, 1.2 to 4.5; $P=0.016$). The period of diagnosis (up to versus after 1985) did not significantly affect predictors of medical events ($P=0.52$).

For surgical cardiovascular events, age \geq 50 years was independently predictive (2.9; 95% CI, 1.3 to 6.2; $P=0.01$) with valve degeneration (score \geq 3) at diagnosis (4.5; 95% CI, 2.1 to 9.3; $P<0.01$). No other variable was independently predictive of all surgical events. For aortic valve surgery as the surgical end point, age \geq 50 years (4.8; 95% CI, 2.0 to 11.6; $P<0.01$) and valve degeneration (6.9; 95% CI, 3.0 to 15.5; $P<0.01$) also were independently predictive of outcome. Aortic valve surgery incidence according to the presence or absence of valve degeneration at diagnosis at baseline is presented in Figure 6A, showing a steep increase in surgery rate between 5 and 10 years after diagnosis in patients with valve degeneration at baseline. The period of diagnosis (up to versus after 1985) did not significantly affect predictors of surgical events ($P=0.64$).

During follow-up, 8 patients underwent ascending aortic surgery for severe aortic dilatation or aneurysm. Ascending aorta \geq 40 mm at baseline predicted subsequent aorta surgery (10.8; 95% CI, 1.8 to 77.3; $P<0.01$) independently of age and sex. Medical cardiovascular events also were independently predicted by age \geq 50 years (4.7; 95% CI, 2.2 to 9.6; $P<0.01$) and by valve degeneration at baseline (2.6; 95% CI, 1.2 to 5.3; $P=0.016$). Medical cardiovascular events according to the presence or absence of valve degeneration at baseline are presented in Figure 6B, showing a steep increase in event rate between 5 and 10 years after diagnosis with baseline valve degeneration.

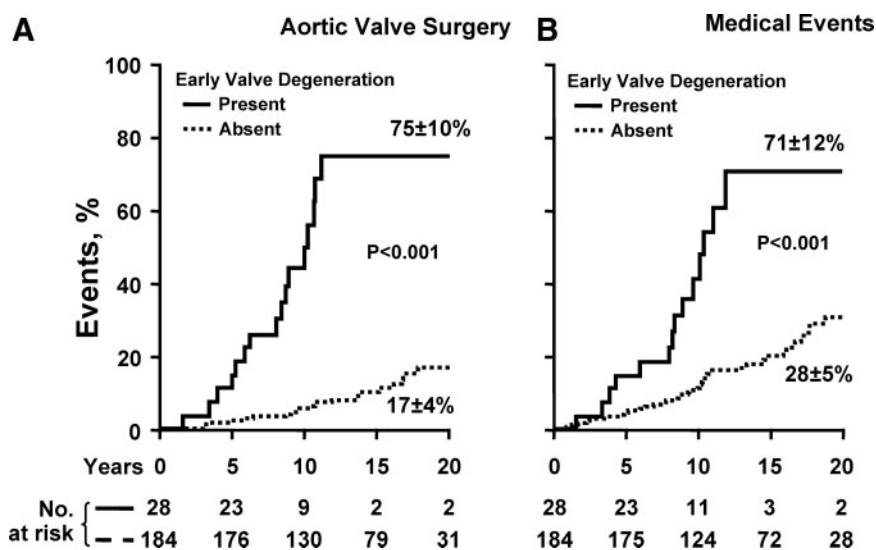


Figure 6. Incidence of events during follow-up according to the presence or absence of valve degeneration at diagnosis (defined as score ≥ 3 or < 3). A, Incidence of aortic valve surgery according to baseline valve degeneration at diagnosis. At 12 years, aortic valve surgery was $75 \pm 10\%$ with and $8 \pm 2\%$ without valve degeneration at diagnosis. B, Medical event rates according to baseline valve degeneration at diagnosis demonstrating the high medical events rate in patients who display valve degeneration at diagnosis at baseline.

Discussion

In this study of 212 asymptomatic community patients with normally functioning or minimally dysfunctional BAV, long-term follow-up for to 20 years can be ascertained and provides both reassurance and reason for concern. In this mostly young population, overall mortality was low and no different from that expected for an age- and sex-matched population. However, cardiovascular morbid events were frequent, affecting ≈ 4 in 10 patients over 20 years. The main surgical event was aortic valve surgery, performed mostly for aortic stenosis and required at a much higher rate and younger age than in the general population. Surgery for aortic dilatation or coarctation was notable but less common, and patients without coarctation had event rates similar to those of the entire series. Medical events were frequent and mostly aortic valve related. Endocarditis was rare but serious. Ascending aortic dilatation increased with time, becoming ≥ 40 mm in ≈ 4 in 10 patients at follow-up. However, an encouraging observation was that no aortic dissection occurred. Apart from age, a major independent predictor of clinical outcome was the presence of valve degeneration at diagnosis by echocardiography, whereas clinical signs were not discriminant. Despite normal valvular function or minimal dysfunction at baseline, valve degeneration at diagnosis was associated with high subsequent event rates ($> 70\%$ at 20 years). Hence, this first community study of BAV allows separating in clinical practice the majority of patients without valve degeneration in whom only episodic follow-up is necessary from the minority with valve degeneration at diagnosis in whom regular assessment and potential clinical trials of progression prevention should be considered.

Natural History of BAVs

The clinical outcome of patients with BAV has been poorly defined. Definite reasons exist for such a gap in knowledge. Symptomatic patients with or without moderate or severe valve disease come to medical attention, and their poor outcome reveals the degree of valve dysfunction rather the original valve deformation.³¹ Asymptomatic patients usually do not come to medical attention.³¹ From that point of view,

our community, in which frequent contact with healthcare providers is the rule,³² offers a particular advantage. In addition, historical studies based solely on auscultatory diagnosis have been at a definitive disadvantage in accurately identifying and ascertaining BAV.¹⁷ Although echocardiography allows reliable BAV identification, referral centers collect mostly referred patients with potential comorbidity and serious valve disease.¹⁸ Therefore, it is not surprising that results reported in the literature are based on small series and are quite discordant. It has been suggested that endocarditis of BAV is the most prevalent complication¹⁷ and is frequent and severe.⁴ Autopsy series painted a bleak picture, with a high frequency of endocarditis and valve dysfunction leading to patients' demise.⁵ Other series touted rapid progression to aortic stenosis,^{6,7} whereas it was also suggested that aortic regurgitation may be the most prominent threat.¹⁸ These discordant and concerning reports are confusing as to what the guidelines for clinical management of patients with BAV presenting with no or minimal hemodynamic abnormalities should be.³³ In our community, frequent population–healthcare provider contacts and high imaging use allow early detection of BAV, thus providing the first large series with long-term outcome of affected community members.

Our study both reassures and raises concerns about the outcome of BAV with no or minimal hemodynamic dysfunction. A favorable result is that no excess mortality was observed 20 years after diagnosis. Later in life, BAV may exert a toll on life expectancy, but within the 20-year span, we can reassure patients with this condition regardless of their age at diagnosis. Another favorable observation regards endocarditis, which may have serious consequences but is infrequent in BAV.

Conversely, morbid events were frequent, and over the 20-year follow-up, 4 patients in 10 incurred a cardiovascular medical or surgical event. The dominant morbid event is progression to aortic stenosis with development of symptoms or heart failure and requirement of AVR.^{6,7} Our comparison with the Olmsted County population shows that AVR is required in subjects with BAV not only at higher rates but also at a younger age. Progression to aortic stenosis is

complex, with similarities to atherosclerosis and, in some studies, association with cholesterol levels.³⁴ More recent studies emphasized a biphasic progression, with atherosclerotic initial lesion and secondary geometric growth of calcifications independent of atherosclerotic risk factors.³⁵ Imaging studies suggesting that valve sclerosis tends to progress³⁶ are consistent with our observations in BAV. Despite quasynormal valve hemodynamics, the presence of valve degeneration, independently of age, portends a negative prognosis on future clinical events related mostly to progression to aortic stenosis. Valve degeneration supersedes the potential impact of BAV morphology (typical versus atypical) on progression, for which previous reports were discordant.^{15,26} Thus, patients with valve degeneration require relatively close follow-up that quasynormal hemodynamics would not suggest a priori. Medical treatment of patients with BAV to prevent progression to aortic stenosis is conjectural. Statins were not effective in preventing the progression of advanced valve lesions, but their role in early valve lesions is still an unanswered question,³⁷ particularly relating to BAV. Mechanisms for the progression to severe aortic regurgitation are poorly understood and deserve future studies to appreciate the factors leading to this less frequent but important complication.

Aortic Complications Associated With BAVs

Aortic complications of BAV are the focus of much controversy. Reports of referral centers suggested aortic dissection risk 5 to 9 times greater in bicuspid than tricuspid valves,^{2,14} whereas others did not notice such an association^{17,18} and a large international registry of aortic dissections denoted a low BAV prevalence (<2%).³⁸ Contradictory data also are reported on aortic dilatation associated with BAV. Although studies with mostly severe valve diseases suggested frequent aortic dilatation,^{11,12} others showed no such association.³⁹ Thus, it remained unclear whether patients with BAV should be managed aggressively to monitor and protect from aortic dilatation and dissection or whether a more lenient approach is in order.

Our study both reassures and raises important issues of follow-up. For aortic dissection, reassurance is in order in patients diagnosed with minimal valvular dysfunction. With severe BAV dysfunction or after AVR, the risk of aortic dissection may be higher.⁴⁰ However, as we previously suspected,¹⁰ accelerated aortic dilatation is real in BAV, even without severe aortic stenosis or regurgitation and without aortic coarctation.^{24,25} Indeed, ≈ 4 in 10 patients develop notable ascending aorta dilatation during follow-up, which then predicts a subsequent need for ascending aortic surgery. Thus, aortic complication risk is notable, often requiring surgical correction, particularly when aortic dilatation is present at baseline. The wide CI relative to the association of aortic dilatation and ascending aortic surgery is due to the relatively small number of events (despite the fact that our series is the largest available) and requires further collaborative and large studies.

Clinical Implications

Overall, patients diagnosed incidentally with BAV should be reassured that their condition is manageable and that major

complications, mortality, endocarditis, and aortic dissection are rare.

Conversely, these patients should be made aware that morbid events directly linked to the BAV are rather frequent and premature. These events are particularly frequent in patients with valve degeneration at diagnosis who, despite quasynormal hemodynamics, are at risk of developing severe valve disease, particularly aortic stenosis, justifying regular assessment during follow-up. In addition, patients with aortic dilatation are at risk of requiring ascending aortic surgery. Those who have neither valve degeneration nor aortic dilatation at baseline are at low risk of complication and can be followed up episodically. A corollary of these findings is the importance of echocardiographic diagnosis of BAV in asymptomatic patients and thus of clinical skills in detecting and interpreting cardiac clicks and murmurs.

Study Limitations

BAV is a congenital valve condition. Although BAV appears in utero, follow-up and analysis of outcome can start only at diagnosis because of potential undiagnosed disease bias. Furthermore, this approach provides clinically useful information on expected outcome after diagnosis in clinical practice. BAV also may be associated with other congenital heart disease. However, exclusion of symptomatic patients with notable comorbidity limited this concern. Even after exclusion of coarctation, event rates were almost unaffected, a reassuring observation.

During the study period, technical Doppler echocardiographic progress allowed marked improvement in the assessment of valve disease severity. However, we believe that adequate techniques were available throughout the study period to detect patients with normal or near-normal valve hemodynamics. Indeed, a wide valve area visible in systole ensures the absence of valve stenosis. Pulsed Doppler examination of the left ventricular outflow tract and/or aortic arch confirms regurgitation. Concordant normal left ventricular size and benign clinical presentation support the absent or minimal hemodynamic valve alteration. In that regard, the identical outcome observed in patients diagnosed up to versus after 1985 reassures that the outcomes described are not biased by undiagnosed moderate or severe valve disease.

BAV diagnosis is not always easy. We excluded patients with questionable cusp numbers by echocardiography. Among those operated on, the cusp numbers could not be determined pathologically in 3 patients, 1 had a unicuspid leaflet mimicking a bicuspid leaflet, and all others had BAV confirmation. Recording a well-oriented short-axis view is essential for appropriate BAV diagnosis. For simplification, BAVs were classified into 2 types because fusion of left and noncoronary cusps is extremely rare.

Diagnosis of valve sclerosis or degeneration previously was only qualitative,³⁶ and the present reproducible scoring system improves echocardiographic assessment. The score is a continuous variable, but different thresholds did not affect our results. Medical events were $70 \pm 10\%$, $71 \pm 12\%$, and $76 \pm 12\%$ with scores of 2, 3, and 4, respectively, and $26 \pm 5\%$, $28 \pm 5\%$, and $29 \pm 5\%$ without, showing that event rates are little affected by selected thresholds. Thus, it is more impor-

tant to underscore reproducible detection of valve degeneration than specific score.

Valve degeneration is linked to age (Table 1), and the predictive power for outcome independently of age is important to confirm. Because of the age overlap between groups with and without degeneration, these results show that degeneration is predictive of outcome independently of age, with the model improved by adding degeneration to age ($P=0.05$). We were able to match for age (51 versus 47 years; $P=0.23$), sex ($P=0.99$), and ejection fraction ($P=0.86$), and for patients with ($n=26$) and without ($n=51$) valve degeneration. We confirmed that those with degeneration, despite similar ages, had higher 15-year cardiovascular event rates ($75\pm 10\%$ versus $35\pm 8\%$; $P=0.018$) in univariate and multivariate analyses (2.3; 95% CI, 1.13 to 4.8; $P=0.02$).

Screening an entire population would provide true prevalence, but resources for such a massive endeavor ($\approx 40\,000$ echocardiograms) are not available,³ although our data obtained from all cases diagnosed in a community give information on outcome, risk factors, and management of community members with BAV. Similarly, assessing changes in valvular degeneration progression rates with changes in risk factors requires large populations in multicenter studies that can now be planned using our outcome data.

Conclusions

Our long-term study with up to 20 years of outcome data on asymptomatic community members with BAV displaying no or minimal hemodynamic deterioration provides both reassurance and reason for concern. Reassuring are the preserved life expectancy and the rarity of endocarditis or aortic dissection. Conversely, concerns are raised by the frequent and premature occurrence of morbid cardiac events. These are dominated by development of symptoms or heart failure resulting from the progression of aortic stenosis and are less frequently due to aortic regurgitation or the development of severe ascending aorta dilatation requiring surgery. Patients with aortic valve degeneration at diagnosis are at higher risk for cardiac events, and those with enlarged aorta are at notable risk for requiring surgery of the aorta, calling for regular assessment in such patients and emphasizing the importance of echocardiographic diagnosis in patients in whom BAV may be suspected.

Disclosures

None.

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CLINICAL PERSPECTIVE

Bicuspid aortic valve, a frequent congenital aortic valve deformation, often allows the valve to function almost normally at birth and often into adult life. Affected subjects have no symptoms and do not require immediate surgery, but we had no information on their future, outcome, and risk factors and on those who are at higher risk and require close follow-up. Thus, for up to 20 years, we followed up 212 patients diagnosed by echocardiography in the community, incidentally or for a murmur, with asymptomatic bicuspid aortic valves functioning normally or close to normally. Our findings are reassuring but uncover patients who need closer follow-up. Reassuringly, we found no excess mortality compared with the general population; valve infections (endocarditis) were rare; and we observed no aortic dissection. Conversely, morbid events directly linked to the bicuspid valve were frequent and premature for age. Approximately 4 in 10 patients incurred morbidity, mostly aortic stenosis leading to symptoms and/or surgery. Echocardiographic early aortic valve degeneration at diagnosis predicted higher subsequent morbidity. Aortic dilatation, also a feature of bicuspid valves, was progressive, sometimes leading to the formation of aneurysms and requiring surgery in a limited number of patients. Aortic dilatation at diagnosis marks patients at risk for aneurysm formation and surgery. Thus, though reassuring in many aspects, our study emphasizes specific risks associated with bicuspid valves, even those apparently normally functioning, and underscores the limited subsets of patients at notable risk (with valve degeneration or aortic dilatation) who need closer follow-up.

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