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Bicuspid aortic valve: long-term morbidity and mortality

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Abstract

Background and Aims Bicuspid aortic valve (BAV) is the most common congenital heart anomaly. Lifetime morbidity and whether long-term survival varies according to BAV patient-sub-groups are unknown. This study aimed to assess lifetime morbidity and long-term survival in BAV patients in the community.

Methods The authors retrospectively identified all Olmsted County (Minnesota) residents with an echocardiographic diagnosis of BAV from 1 January 1980 to 31 December 2009, including patients with typical valvulo-aortopathy (BAV without accelerated valvulo-aortopathy or associated disorders), and those with complex valvulo-aortopathy (BAV with accelerated valvulo-aortopathy or associated disorders).

Results 652 consecutive diagnosed BAV patients [median (IQR) age 37 (22–53) years; 525 (81%) adult and 127 (19%) paediatric] were followed for a median (IQR) of 19.1 (12.9–25.8) years. The total cumulative lifetime morbidity burden (from birth to age 90) was 86% (95% CI 82.5–89.7); cumulative lifetime progression to ≥ moderate aortic stenosis or regurgitation, aortic valve surgery, aortic aneurysm ≥45 mm or z-score ≥3, aorta surgery, infective endocarditis and aortic dissection was 80.3%, 68.5%, 75.4%, 27%, 6% and 1.6%, respectively. Survival of patients with typical valvulo-aortopathy [562 (86%), age 40 (28–55) years, 86% adults] was similar to age-sex-matched Minnesota population ($P = .12$). Conversely, survival of patients with complex valvulo-aortopathy [90 (14%), age 14 (3–26) years, 57% paediatric] was lower than expected, with a relative excess mortality risk of 2.25 (95% CI 1.21–4.19) ($P = .01$).

Conclusion The BAV condition exhibits a high lifetime morbidity burden where valvulo-aortopathy is close to unavoidable by age 90. The lifetime incidence of infective endocarditis is higher than that of aortic dissection. The most common BAV clinical presentation is the typical valvulo-aortopathy with preserved expected long-term survival, while the complex valvulo-aortopathy presentation incurs higher mortality.

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Structured Graphical Abstract

Key question

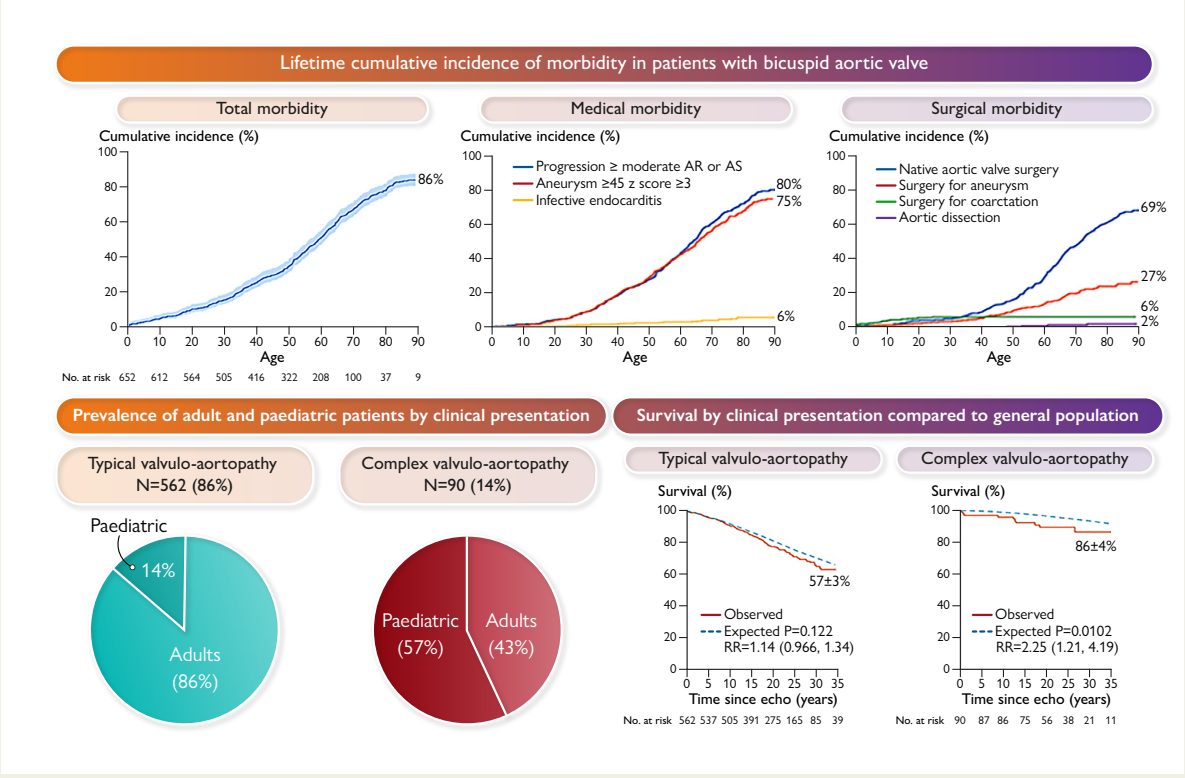
In patients with bicuspid aortic valve diagnosed in the community, what is the lifetime morbidity burden, and is their long-term survival different according to clinical sub-groups?

Key finding

The total cumulative lifetime morbidity burden was 86%, driven by progressive valvulo-aortopathy. The lifetime risk of infective endocarditis was higher than aortic dissection. The most common clinical presentation was the typical valvulo-aortopathy (86%) with preserved expected survival while the complex valvulo-aortopathy (14%) had higher than expected mortality.

Take-home message

In bicuspid aortic valve patients in the community, significant valvulo-aortopathy is close to unavoidable by age 90. The lifetime risk of infective endocarditis is higher than aortic dissection. The most common clinical presentation is the typical valvulo-aortopathy with preserved expected survival.



Top: Lifetime cumulative incidence of medical and surgical morbidity endpoints and all combined. Bottom: Proportion of adults and paediatric patients with typical and complex valvulopathy, and survival of patients with typical and complex valvulopathy compared to the age-sex-matched general population. AR, aortic regurgitation; AS, aortic stenosis.

Keywords Bicuspid aortic valve • Community • Morbidity • Mortality

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect[1] with a population-based prevalence of 0.5%[2] to 0.77%.[3] The congenital BAV condition is a progressive valvulo-aortopathy with significant heterogeneity in anatomic phenotypes, associated disorders,[4] and, therefore, exhibits variable prognosis.[5] Four large contemporary observational cohorts[6–9] demonstrated benign BAV outcomes, with survival similar to age- and sex-matched population, however, it is possible that by virtue of including paediatric patients in some of these studies,[6–8] or due to insufficient follow-up, the outcome appeared artificially benign. Indeed, some tertiary-referral cohorts have reported a survival penalty for patients with BAV[10,11] as compared to the population. Moreover, patients with BAV exhibit a higher incidence of infective endocarditis[12] and aortic dissection[8] compared to the general population, and the need for aortic valve surgery (AVS) has been reported to be as high as 50%.[5] Whether this morbidity results in excess mortality and excess heart failure (HF),[6] remains unproven. To reconcile this outcomes diversity from a nosology perspective, the international BAV nomenclature and classification consensus[13] categorized the BAV clinical-history into three hypothetical prognostic groups: (i) typical valvulo-aortopathy; (ii) complex valvulo-aortopathy,[4] and (iii) undiagnosed or uncomplicated; whether

differences in outcomes exist between these groups is unknown. Furthermore, whether there are differences in survival between adult and paediatric populations is also unknown. Finally, the morbidity associated with BAV is significant but with variable rates of BAV dysfunction and ascending aorta dilatation[5,14] resulting in variable rates of AVS and aorta surgery across studies.[5,14]

To resolve these issues, a critical principle is that the BAV condition is present throughout a person's lifetime, since birth until death. To determine the lifetime clinical history of BAV morbidity, whether patients with BAV incur a higher risk of HF, and whether BAV patients' survival is compromised, a population-based cohort with very long-term follow-up is necessary. In addition, analysis of survival should be performed in adult and paediatric populations separately, as well as within the proposed international BAV consensus prognostic groups.[13]

As compared to tertiary-referral studies, population-based cohorts minimize referral bias, allow ascertainment of disease burden (e.g. prevalence, incidence) and generate observations that are closest to the truth for a specific disease.[15] Olmsted County, Minnesota, provides a geographically defined population with a single echocardiographic laboratory centralizing all diagnoses up to 2010,[16] with all echocardiograms and most cardiac surgeries performed at the same centre. Very long-term follow-up allows for assessment of cumulative lifetime-risk of complications. In this study, we report lifetime risks of morbidity and very long-term mortality in patients with BAV from Olmsted County, Minnesota.

Methods

Study population

Methodology for this study relied upon systematic and comprehensive retrospective identification of all Olmsted County residents diagnosed with BAV via transthoracic echocardiography (TTE) or autopsy, with ascertainment of complications and death from all existing sources.

Between 1 January 1980 and 31 December 2009, Mayo Clinic TTEs were performed in 49,046 individual residents of Olmsted County identified by home-address at the time of TTE. This cohort included 728 patients with possible BAV. Of these, 16 patients who declined research authorization, and 60 patients who were found to have no BAV or non-diagnostic TTE by *de novo* review were excluded, resulting in a final cohort of 652 (1.3% of Olmsted County residents with TTE from 1980 to 2009) patients for analysis, with all BAV diagnoses verified by *de novo* TTE review (Li-Tan Yang (LTY), Hector I Michelena (HIM), Maurice Enriquez-Sarano). This study includes patients gathered from 1980 to 1999 from our previous report.[8]

Echocardiography

Patients underwent comprehensive TTE with Doppler. All baseline TTEs (in tapes or digitalized) were reviewed *de novo* to confirm the presence of BAV (only two commissures and two cusps from short-axis imaging of the aortic valve).[6,13] The fused types were classified as right-left-coronary cusp fusion, right-non-coronary cusp fusion, or left-non-coronary cusp fusion, and the presence of raphe was ascertained *de novo* by two experienced echocardiographers (LTY, HIM). Aortic stenosis (AS) was evaluated by trans-valvular peak velocity, mean pressure gradient, and aortic valve area from continuity equation and/or planimetry,[17] and graded as mild, moderate, moderate-severe, and severe. Aortic regurgitation (AR) was graded by vena contracta, aortic flow reversal, and quantitative measurements, as mild, moderate, moderate-severe, and severe.[18] In patients diagnosed before continuous wave Doppler became available (before 1983),[6] wide valvular opening ascertained absence of AS.[6] Using leading-edge to leading-edge technique,[19] dimensions of sinuses of Valsalva (root) and mid-ascending aorta were measured, and the largest dimension was used for aortopathy analysis. For patients younger than 18 years, *z* scores were calculated. Clinically significant aortic dilatation was defined as maximal dimension ≥45 mm (termed aneurysm)[8] or z-score ≥3.[20]

All comorbid conditions and concomitant congenital defects and associated genetic syndromes, whether cardiac or non-cardiac, were individually abstracted by chart review (paper charts before 1996) and from electronic records (since 1996). The protocol was approved by our Institutional Review Board.

Patients with bicuspid aortic valve diagnosed by autopsy

To identify undiagnosed patients with BAV who were alive during the study period, the Olmsted County coroner's database was searched manually between 1980 and 1992 and electronically from 1992 to 2019 [in order to cover the entire inclusion period (1980–2009) plus the follow-up period]. Cause of death and valve morphology were recorded from autopsy reports.

Complex-presentation vs. typical-presentation valvulo-aortopathy

Patients were classified as having complex-presentation valvulo-aortopathy if they had any of the following: severe aortic coarctation requiring treatment with surgical or endovascular procedures, ≥moderately severe AR/AS before age 30, aortopathy (≥45 mm or *z*-score ≥3) before age 30, associated genetic syndrome, and associated complex congenital heart disease.[13] The rest of the patients were considered typical-presentation valvulo-aortopathy and were permitted to have simple congenital heart disease, mild coarctation not requiring immediate treatment, mild non-cardiac congenital defects, and autoimmune connective tissue diseases.

Endpoints

Morbidity end-points related to BAV were: (i) medical morbidity endpoints: Significant valvular dysfunction (≥moderate AS and/or AR), aortic dilatation (i.e. root and/or mid-ascending ≥45 mm or *Z*-score ≥3), infective endocarditis, and HF (defined by International Classification of Diseases code and/or New York Heart Association class III-IV symptoms); and (ii) surgical morbidity endpoints: AVS (repair or replacement), surgery of the aorta, aortic dissection. All medical and surgical morbidity endpoints utilized date of birth as time 0, except for HF where time 0 was the date of TTE diagnosis of BAV, thereby allowing comparison of the observed HF incidence to the expected Olmsted County HF incidence.

The mortality end-point was all-cause death. The survival status was retrieved from electronic records and by Accurint (LexisNexis, RELX Group, New York, New York), a proprietary resource combining multiple national sources (queried February 2020). For patients not known to be deceased through Accurint, August 2019 was set as their last follow-up date for survival analysis. Paper charts, electronic records (also linked to other institutions), and last available echocardiograms, were all reviewed. All-cause death observed was compared to the general population, and time 0 was the date of BAV TTE diagnosis, to allow for such comparison.

Lifetime risk and estimated incidence by 5-year age groups

Follow-up was considered complete until 2018–19 (mailed survey period), or death. Mailed surveys (Supplementary data online, *Supplemental Survey.pdf*) and telephone interviews were conducted with patients who did not return to our institution after 2018. The cumulative lifetime risk of morbidity events since birth by decade was estimated using all events happening before and after baseline TTE, where time 0 was the patient's date of birth. We also estimated non-cumulative point-incidence of events using 5-year age groups (patients at risk were only those alive during each 5-year period) by sex, to highlight age/sex-related incidence-peaks.

Statistical analysis

Continuous variables, expressed as mean (SD) or median [interquartile range (IQR)], were compared using the Student's *t*-test or Wilcoxon rank sum test as appropriate. Categorical data, presented as percentages, were compared using Pearson χ^2. With the exception of HF, the incidence of surgical and medical endpoints of interest starting at birth were estimated by sex using cumulative incidence curves, accounting for the competing risk of mortality (patients were censored at the last follow-up). These curves were also estimated by sex and were compared using the Fine-Gray hazard ratio and corresponding *P*-value. Kaplan–Meier analysis was used to study associations with mortality and HF, starting at baseline TTE. While mortality analysis started at baseline TTE due to the necessity of patients being alive at that time, HF analyses were started at that baseline TTE due to expected incidence in Olmsted county being available only back to 1980 and not at the time of birth for all subjects. Estimates of expected mortality and incidence of HF were computed based on Olmsted County published rates, matched for age, sex, and time-period,[21,22] using tables of event probabilities broken down by age, sex, and calendar year. Thus, the age, sex, and years under observation for each patient in our sample were used to derive appropriate estimates of mortality given the unique data from each patient. Once these estimates were derived, the data were aggregated to derive the expected curve. Comparison of observed to expected survival was done using one-sample log-rank tests. The observed-to-expected rate ratio (RR) was calculated and the 95% confidence interval (CI) was calculated from the Poisson standard error. Prevalence calculations used patients alive and residing in Olmsted County on 31 December 2010. All statistical analyses were performed using commercially available software (JMP 11 and SAS 9.4, SAS Institute Inc., Cary, North Carolina).

Results

Baseline patient characteristics

Table 1 shows the baseline characteristics of 652 patients divided into adults (≥18 years) and paediatric (<18 years) patients. Of 652 total patients, 525 (81%, age 45 ± 16 years, 70% males) were adults and 127 (19%, age 7 ± 6 years, 70% males) were paediatric patients. The indications for TTE included systolic click or murmur in 307 (47%), a diastolic murmur in 59 (9%), assessment of left ventricular function in 15 (2%), rule-out infective endocarditis in 8 (1%), and other (e.g. cardiac and non-cardiac symptoms, and follow-up studies) in 263 (41%). Adults were more likely to have age-related comorbidities, i.e. hypertension, diabetes, and CAD. Conversely, a higher proportion of paediatric patients had aortic coarctation (20% vs. 4%), congenital heart defects (35% vs. 6%), non-cardiac congenital defects, or associated genetic syndromes (16% vs. 3%) compared to adults. As for valvulo-aortopathy, a higher proportion of adults had AR while prevalence of AS was similar. A higher proportion of adults had raphe (70% vs. 56%),[23] while the prevalences of different fusion types were similar in adults and paediatric patients. For the entire cohort, the prevalence of ≥ moderate AS was higher in raphe-positive patients (11% vs. 6%, $P = .03$), but not so for AR ($P = .52$).

Table 2 presents the baseline characteristics of those with typical and complex valvulo-aortopathy separately. The most common clinical presentation was typical valvulo-aortopathy [562 (86%), age 40 (28–55) years,72% male, 14% paediatric patients] followed by complex valvulo-aortopathy [90 (14%), age 14 (3–26) years, 63% male, 57% paediatric patients] (*Structured Graphical abstract*). Compared to those with typical valvulo-aortopathy, patients with complex valvulo-aortopathy had a higher prevalence of aortic coarctation (44% vs. 0.9%), congenital heart defects (62% vs. 4%), and non-cardiac congenital defects or associated genetic syndromes (18% vs. 4%) (*Table 2*). Typical valvulopathy patients had a higher prevalence of AR. The prevalences of different severities of AS and BAV fusion types were similar in both groups, and a higher proportion of patients with the complex valvulo-aortopathy did not have raphe compared to those with the typical type.

In the typical presentation type ($n = 562$), most common simple congenital heart disease abnormalities found were ventricular septal defect ($n = 7$), atrial septal defect ($n = 3$), patent ductus arteriosus ($n = 4$), mild aortic coarctation ($n = 5$), and mild pulmonic stenosis ($n = 2$). In the complex type ($n = 90$), the most common abnormalities were severe coarctation ($n = 38$), ≥moderate to severe AR/AS in <30-year-olds ($n = 28$), and aneurysm or z-score ≥3 in <30-year-olds ($n = 5$). Genetic syndromes were Turner ($n = 5$), Marfan ($n = 1$), Shone's complex ($n = 3$), velocardiofacial ($n = 1$), Down ($n = 1$), 47 XYY ($n = 1$), 47 XXX ($n = 1$), and DiGeorge ($n = 1$). Complex congenital heart defects included tetralogy of Fallot, atrioventricular (AV) canal, supravalvular, and subvalvular AS.

Prevalence of bicuspid aortic valve

We used Olmsted County population data from 2010 to calculate the prevalence of BAV. The overall prevalence of BAV in Olmsted County was 0.27 (95% CI: 0.25–0.30), 0.39% (95% CI: 0.34–0.43) in males, and 0.16% (95%CI: 0.14–0.20) in females. *Figure 1* shows the TTE-diagnosed BAV prevalence by age group and sex. The prevalence steadily increased in both males and females up to age 75. The prevalence for the age 65–74 group (0.51% overall and 0.76% men) and ≥75 group (0.44% overall and 0.78% men) was similar to the general BAV population prevalence.[2,3] Conversely, the prevalence in younger age groups was lower than that of the general population. The rate of BAV prevalence-increase across different age groups was similar in men and women, with a consistently higher prevalence of men in any age group.

Follow-up

Dead/alive status ascertainment at follow-up was complete 100%. The median follow-up for mortality in the total cohort ($n = 652$) was 20.1 (IQR 14.1–26.6) years (maximum follow-up 39.5 years). The median follow-up for endpoints other than mortality in the total cohort was 19.1 (IQR 12.9–25.8) years. Follow-up was complete (until 2018–19, death, or 25-year follow-up) for 585 (90%) patients. In 67 (10%) patients with incomplete follow-up, the median follow-up for endpoints other than mortality was 10.7 (IQR 4.6–16.4) years. During follow-up, repeat echocardiograms were available in 502 (77%) patients, most performed at Mayo Clinic, and some performed at outside facilities and reports retrieved. The total number of observed events for each outcome overall and by sex is presented in *Table 3*.

Medical endpoints

Progression of valvulopathy to ≥ moderate aortic regurgitation or aortic stenosis

The cumulative lifetime risk of progression to ≥ moderate AS or AR was 80.3% (95%CI: 75.8–85.1) by age 90 (*Figure 2A*). Compared to women, men had a similar cumulative lifetime risk of developing AS (*Figure 3B*-left) with a linear incidence increase across their lifetime, while women's AS incidence peaked between 60 and 75 years of age (*Figure 3B*-right). Conversely, as compared to women, men exhibited a higher lifetime risk of developing AR [hazard ratio (HR), 1.67 (1.17–2.39)], $P = .004$ (*Figure 3C*-left), and the incidence of AR for men peaked between 30 and 50 years of age (*Figure 3C*-right).

Table 1 Baseline characteristics of the entire cohort, paediatric, and adult patients

	Total $n = 652$	Adult $n = 525$	Paediatric $n = 127$
Age, years	37.4 [22.4–52.5]	42.6 [31.6–56.4]	5.9 [1.0–12.9]
Women	193 (29.6)	155 (29.5)	38 (29.9)
Hypertension	191 (29.3)	182 (34.7)	9 (7.1)
Diabetes mellitus	62 (9.5)	61 (11.6)	1 (0.8)
Congestive heart failure	26 (4.0)	20 (3.8)	6 (4.7)
Coronary artery disease/old myocardial infarction	48 (7.4)	48 (9.1)	0 (0)
Prior coronary artery bypass graft surgery	7 (1.1)	7 (1.3)	0 (0)
Prior stroke	16 (2.5)	16 (3)	0 (0)
Prior endocarditis	6 (0.9)	4 (0.8)	2 (1.6)
Connective tissue disease[a]	24 (3.7)	22 (4.2)	2 (1.6)
Aortic dissection at baseline	1 (0.2)	1 (0.2)	0 (0)
Coarctation of aorta	45 (6.9)	20 (3.8)	25 (19.7)
Congenital heart defects[b]	77 (11.8)	32 (6.1)	45 (35.4)
Non-cardiac congenital defects or syndrome[c]	36 (5.5)	16 (3.0)	20 (15.7)
Any symptoms[d]	123 (18.9)	104 (19.8)	19 (15.0)
Total cholesterol ($n = 356/10/346$), mg/dL	200.4 ± 43.2	201.1 ± 43.2	176.1 ± 39.6
Left ventricular ejection fraction, %	62.2 ± 7.8	61.9 ± 7.7	63.5 ± 8.2
Left ventricular end diastolic diameter, mm	49.7 ± 9.6	52.2 ± 7.1	39.0 ± 11.6
Left ventricular end-systolic diameter, mm	31.0 ± 7.7	32.9 ± 6.4	23.4 ± 7.5
Aortic regurgitation			
No	306 (46.9)	213 (40.6)	93 (73.2)
Mild	218 (33.4)	193 (36.8)	25 (19.7)
Moderate	79 (12.1)	74 (14.1)	5 (3.9)
Moderate-severe	28 (4.3)	24 (4.6)	4 (3.1)
Severe	15 (2.3)	15 (2.9)	0 (0)
Missing	6 (0.9)	6 (1.1)	0 (0)
Aortic stenosis			
No	514 (78.8)	410 (78.1)	104 (81.9)
Mild	51 (7.8)	41 (7.8)	10 (7.9)
Moderate	37 (5.7)	29 (5.5)	8 (7.9)
Severe	34 (5.2)	29 (5.5)	5 (3.9)
Missing	16 (2.5)	16 (3.0)	0 (0)
Aortic valve trans-valvular mean pressure gradient, mmHg	16.2 ± 13.8	16.3 ± 13.5	15.6 ± 15.2
Aortic valve peak velocity, m/s	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 1.0
Aortic valve area, cm^2	2.2 ± 1.1	2.4 ± 1.0	1.3 ± 0.9
Fusion type ($n = 646$)			
Left-right	522 (80.1)	426 (81.1)	96 (75.6)
Right-non	110 (16.9)	83 (15.8)	27 (21.3)
Left-non	14 (2.1)	11 (2.1)	3 (2.4)

Continued

Table 1 *Continued*

	Total $n = 652$	Adult $n = 525$	Paediatric $n = 127$
Raphe			
Present	437 (67.0)	366 (69.7)	71 (55.9)
No raphe	191 (29.3)	139 (26.5)	52 (40.9)
Undetermined	24 (3.7)	20 (3.8)	4 (3.1)
Sinus of valsalva, mm	33.0 ± 8.4	35.8 ± 5.8	21.1 ± 7.3
Maximal diameter of aorta, mm ($n = 632$)	34.4 ± 8.9	37.0 ± 6.5	22.5 ± 8.3
Maximal diameter of aorta ≥45 mm ($n = 632$)	60 (9.2)	59 (11.2)	1 (0.7)
Maximal *Z*-score of aorta ($n = 119$)	—	—	1.9 ± 2.0
Maximal *Z*-score of aorta ≥3 ($n = 119$)	—	—	26 (21.8)

Categorical variables are expressed as number (%), continuous variables are expressed as mean (SD), or median (IQR).
[a]Including rheumatoid arthritis, thyroiditis, marfanoid habitus, Marfan syndrome, giant cell arteritis, lichen sclerosus et atrophicus, polyarthritis, psoriatic arthritis, scleroderma, sicca syndrome, and systemic lupus erythematous.
[b]Including coarctation of aorta, pulmonary stenosis/atresia, patent ductus arteriosus, dextrocardia, atrioventricular canal defect, ventricular septal defect, atrial septal defect, Shone's complex, parachute mitral valve, and congenital aortic stenosis.
[c]Including Hirschprung disease, single kidney, supernumerary nipple, Turner's syndrome, camptodactily, thyroglossal cyst, myelomeningocele, pyloric stenosis, DiGeorge syndrome, Down's syndrome, 47XXX syndrome, Sagittal alveolar deficiency, congenital anal stenosis, 47XYY syndrome, velocardiofacial syndrome, HLA-B27 spondyloarthropathy, and hereditary sensory motor neuropathy.
[d]Symptoms include dyspnoea, syncope, palpitation, and typical chest pain.

Aortic dilatation/aneurysm

The lifetime-risk of aortic dilatation was 75.4% (95%CI: 70.6–80.4) by age 90 (*Figure 2C*). Compared to women, men exhibited a higher lifetime cumulative incidence of aneurysm formation up to age 70 and then similar to women after that [HR, 1.30 (1.02–1.65)], $P = .05$ (*Figure 3A*-left) and a linear increase in incidence across their lifetime, while women showed an incidence peak between 60 and 75 years of age (*Figure 3A*-right). However, aortic diameter corrected by body surface area tended to be higher in adult women vs. men (20.9 ± 6.7 vs. 19.7 ± 6.9, $P = .06$).

Infective endocarditis

Infective endocarditis impacted patients throughout their lifetime (age range 9–79 years), with a lifetime-risk of 6% (85%CI:3.8%–9.4%) by age 90 (*Figure 2G*). Men tended to develop endocarditis more than women [HR, 3.81 (0.88–16.53), $P = .07$].

Heart failure

At a median of 12.6 (IQR 6.1–20.7) years after baseline TTE, the 35-year cumulative incidence of HF was 36% (95%CI: 29.8–42.9). As compared to the expected HF incidence in Olmsted County's general population, patients with BAV had higher risk of developing HF [RR, 2.92 (2.45–3.44), $P < .001$, *Figure 4*]. The cause for HF was valvular heart disease in 51% of patients, cardiovascular risk factor-related or ischaemic cardiomyopathy in 25%, rhythm-related in 9%, nonischemic cardiomyopathy in 6%, congenital heart disease in 2%, endocarditis in 2%, and miscellaneous.

Surgical endpoints

Aortic valve surgery

The lifetime risk of AVS was 68.5% (95%CI: 63.1%–74.4%) by age 90 (*Figure 2B*) and similar in both sexes (*Figure 3D*).

There was a steady increase in the lifetime risk of AVS since birth which was driven by coarctation before age 30 (*Figure 2F*) and aneurysms thereafter (*Figure 2D*). The lifetime risk of aorta surgery was 27% (95%CI: 22.2%–32.9%) by age 90(*Figure 2F*). The maximal presurgical aortic diameter was 48 (IQR 26–54) mm. The lifetime risk of isolated aorta AVS was 0.7 ± 0.4% at age 90, suggesting that BAV rarely behaves as isolated aortopathy.

Aortic dissection

Aortic dissection or rupture occurred in a total of six patients since birth, all of whom were male, and BAV was previously diagnosed in five who lacked imaging within 2 years before dissection occurred. Type A in 4, type B in 1, and proximal descending aorta rupture in 1. Dissections occurred between ages 47–74 years. Dissections were confirmed via computed tomography in 2, echocardiography in 2, and via autopsy in 2 [one died of cardiac tamponade, one died of proximal descending aorta rupture (80 mm) involving previous repair site for coarctation of aorta]. Of six patients, three had surgical intervention, one had medical treatment, and two died. The lifetime risk of dissection remained 0 until age 47, and the cumulative lifetime risk was 1.6% (0.6%–4.0%) by age 90 (*Figure 2E*).

Total lifetime morbidity

The combined lifetime total morbidity (medical plus surgical) was 86% (95%CI: 82.5%–89.7%) by age 90 (*Structured Graphical abstract*).

All-cause mortality

All-cause death occurred in 152/652 patients. At 35 years, survival of the adult cohort ($n = 525$) and typical valvulo-aortopathy patients ($n = 562$) was 52 ± 3% and 57 ± 3%, respectively, similar to that expected for age-sex-matched Minnesota population (*Figure 5*). Conversely, the 35-year survival of complex valvulo-aortopathy

Table 2 Patient characteristics of typical- and complex-valvulo-aortopathy

	Typical $n = 562$	Complex $n = 90$	*P*
Age, years	39.9 [27.9–55.4]	13.7 [2.9–26.4]	**<.001**
Women	160 (28.5)	33 (36.7)	.12
Hypertension	171 (30.4)	20 (22.2)	.10
Diabetes mellitus	58 (10.3)	4 (4.4)	.05
Congestive heart failure	20 (3.6)	6 (6.7)	.20
Coronary artery disease/old myocardial infarction	45 (8.0)	3 (3.3)	.08
Prior coronary artery bypass graft surgery	7 (0.7)	0	.60
Prior stroke	16 (2.8)	0	.15
Prior Endocarditis	4 (0.7)	2 (2.2)	.22
Connective tissue disease[a]	22 (3.9)	2 (2.2)	.39
Aortic dissection at baseline	1 (0.2)	0	—
Coarctation of aorta	5 (0.9)	40 (44.4)	**<.001**
Congenital heart defects[b]	21 (3.7)	56 (62.2)	**<.001**
Non-cardiac congenital defects or syndrome[c]	20 (3.6)	16 (17.8)	**<.001**
Any symptoms[d]	106 (18.9)	17 (18.9)	.10
Total cholesterol ($n = 352/342/10$), mg/dL	201.1 ± 43.2	176.1 ± 39.6	.07
Left ventricular ejection fraction, %	62.0 ± 7.5	63.6 ± 9.4	.07
Left ventricular end-diastolic diameter, mm	50.5 ± 8.8	44.7 ± 13.4	**<.001**
Left ventricular end-systolic diameter, mm	31.6 ± 7.3	27.2 ± 8.9	**<.001**
Aortic regurgitation			**.002**
No	260 (46.3)	46 (51.1)	
Mild	195 (34.7)	23 (25.6)	
Moderate	74 (13.2)	5 (5.6)	
Moderate-severe	18 (3.0)	10 (11.1)	
Severe	11 (2.0)	4 (4.4)	
Missing	4(0.7)	2 (2.2)	
Aortic stenosis			.08
No	450 (80.1)	64 (71.1)	
Mild	46 (8.2)	5 (5.6)	
Moderate	28 (5.0)	9 (10.0)	
Severe	26 (4.6)	8 (8.9)	
Missing	12 (2.1)	4 (4.4)	
Aortic valve trans-valvular mean pressure gradient, mmHg	15.7 ± 13.0	19.0 ± 17.7	.11
Aortic valve peak velocity, m/s	2.2 ± 0.9	2.5 ± 1.1	**.01**
Aortic valve area, cm^2	2.2 ± 1.0	1.7 ± 1.4	**.002**
Fusion type ($n = 647$)			.64
Left-right	452 (80.5)	71 (78.9)	
Right-non	93 (16.2)	17 (18.9)	
Left-non	13 (2.3)	1 (1.2)	
Raphe			**.007**
Present	397 (70.6)	40 (44.5)	

Continued

Table 2 ***Continued***

	Typical $n = 562$	Complex $n = 90$	P
No raphe	144 (25.6)	47 (52.2)	
Undetermined	21 (3.7)	3 (3.3)	
Sinus of valsalva, mm ($n = 515$)	34.1 ± 7.4	26.2 ± 10.8	**<.001**
Maximal diameter of aorta, mm ($n = 632$)	35.4 ± 8.0	28.0 ± 11.3	**<.001**
Maximal diameter of aorta ≥45 mm ($n = 632$)	55 (10.1)	5 (5.9)	.20
Maximal Z-score of aorta ($n = 119$)	1.6 ± 1.4	2.3 ± 2.5	.07
Maximal Z-score of aorta ≥3 ($n = 119$)	10 (14.1)	16 (33.3)	.01

Categorical variables are expressed as number (%), continuous variables are expressed as mean (SD), or median (IQR).
[a,d,c,d]Same as *Table 1*.
Bold text represents heading for categorical variables.

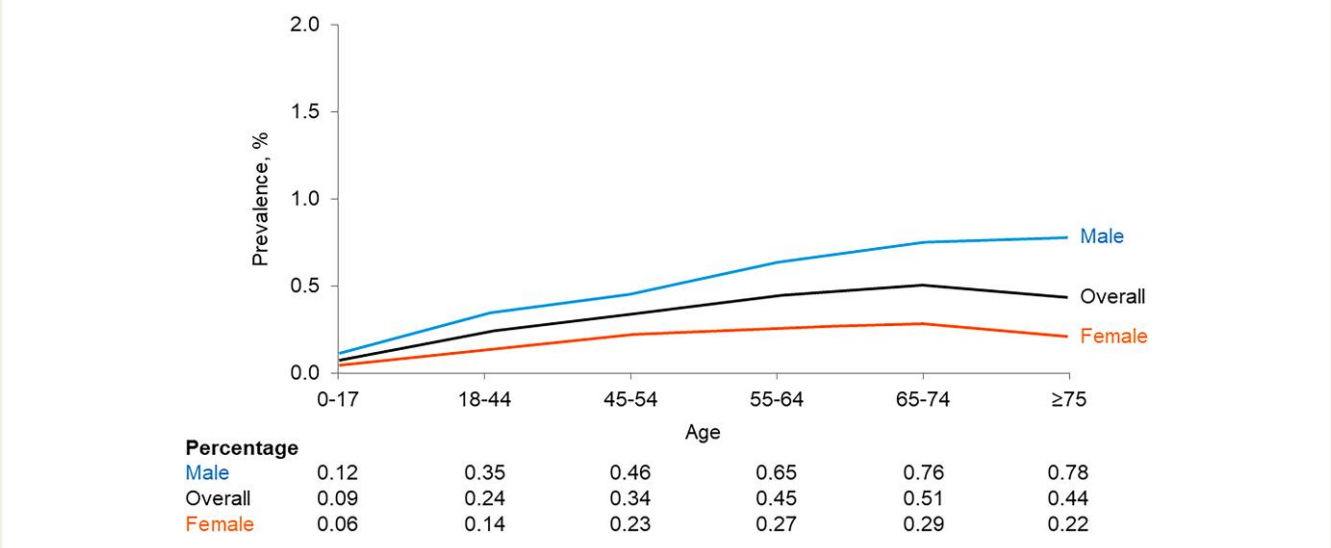


Figure 1 Prevalence of transthoracic echocardiography-diagnosed bicuspid aortic valve by age and by sex.

patients ($n = 90$) was 86 ± 4%, lower than expected for age-sex-matched Minnesota population; excess RR of 2.25 (1.21–4.19), $P = .01$ (*Figure 5*). When analysing the survival of complex valvulo-aortopathy patients excluding genetic syndromes and complex congenital heart disease ($n = 18$), their expected survival ($n = 72$) was not different from the Minnesota population [RR = 1.54 (0.56, 3.35), $P = .29$]. Therefore, when analysing the survival of the paediatric cohort, we excluded patients with genetic syndromes or severe congenital heart disease and demonstrated no survival penalty in the paediatric cohort ($n = 115$) compared to the general population ($P = .51$) (*Figure 5*).

Undiagnosed patients with bicuspid aortic valve

The Supplementary data online, *Table* depicts the characteristics of 12 patients whose BAV status was not identified until autopsy. Four patients had previously unknown severe AS at autopsy and seven patients had ≤ mild valve dysfunction. One patient died of infective endocarditis and another from type A aortic dissection.

Discussion

The principal findings of this community-based very long-term follow-up study are: (i) The lifetime cumulative medical and surgical incidence increased steadily as patients with BAV aged, resulting in a high total morbidity burden of 86% by age 90, driven by high incidence of aortic valve dysfunction requiring AVS and aortic dilatation requiring surgical repair. (ii) The lifetime cumulative risk of infective endocarditis and aortic dissection were relatively low by age 90(6% and 1.6%, respectively) with infective endocarditis risk being approximately four times higher than aortic dissection. (iii) The 35-year HF incidence was higher than that of the general population and driven by valvular heart disease. (iv) The typical valvulo-aortopathy was by far the most common clinical presentation (86% of cases), with adult predominance (86%) and 35-year survival similar to that of the general population. Conversely, the complex valvulo-aortopathy was significantly less

common (14%), with paediatric patient predominance (57%), and decreased 35-year survival as compared to the general population. Adult 35-year survival was similar to the general population. paediatric 35-year survival including patients with severe coarctation and accelerated valvulo-aortopathy but excluding genetic syndromes and complex congenital heart disease was almost identical to the general population.

Table 3 Total number of observed events for each outcome overall and by sex

Outcome	Overall	Males	Females
Mortality	152	120	32
Valvulopathy progression	343	252	91
Native aortic valve surgery	253	188	65
Dilatation of the aorta	330	249	81
Surgery for aneurysm	83	62	21
Aortic dissection or aneurysm	6	6	0
Surgery for aortic coarctation	41	25	16
Infective endocarditis	25	22	3
Heart failure[a]	140	99	41

[a]26 patients with prior HF were excluded from HF analysis which started at baseline transthoracic echocardiography.

Community prevalence of bicuspid aortic valve

The overall BAV prevalence estimate in Olmsted County (0.27%) represents an underestimation as compared to previous reports (0.5%–0.77%).[2,3] This likely results from our inability to perform TTEs in the entire County's population, since our echocardiographic database comprises TTEs that have been physician-requested; indeed, within the County's population with TTEs, the proportion of BAV was 1.3%. In addition, for prevalence calculation, we could not include patients with BAV that had moved from Olmsted County in the numerator, only current residents. Remarkably, the prevalence of TTE-diagnosed BAV increased significantly as BAV complications arose with age (*Figure 1*), so that by age 60–75, the prevalence was reflective of the previously reported, which confirms the progressive nature of the valvulo-aortopathy throughout a lifetime, and demonstrates that the typical valvulo-aortopathy is mostly diagnosed in adults, while a significant amount of BAV paediatric patients come to attention as part of the complex valvulo-aortopathy clinical

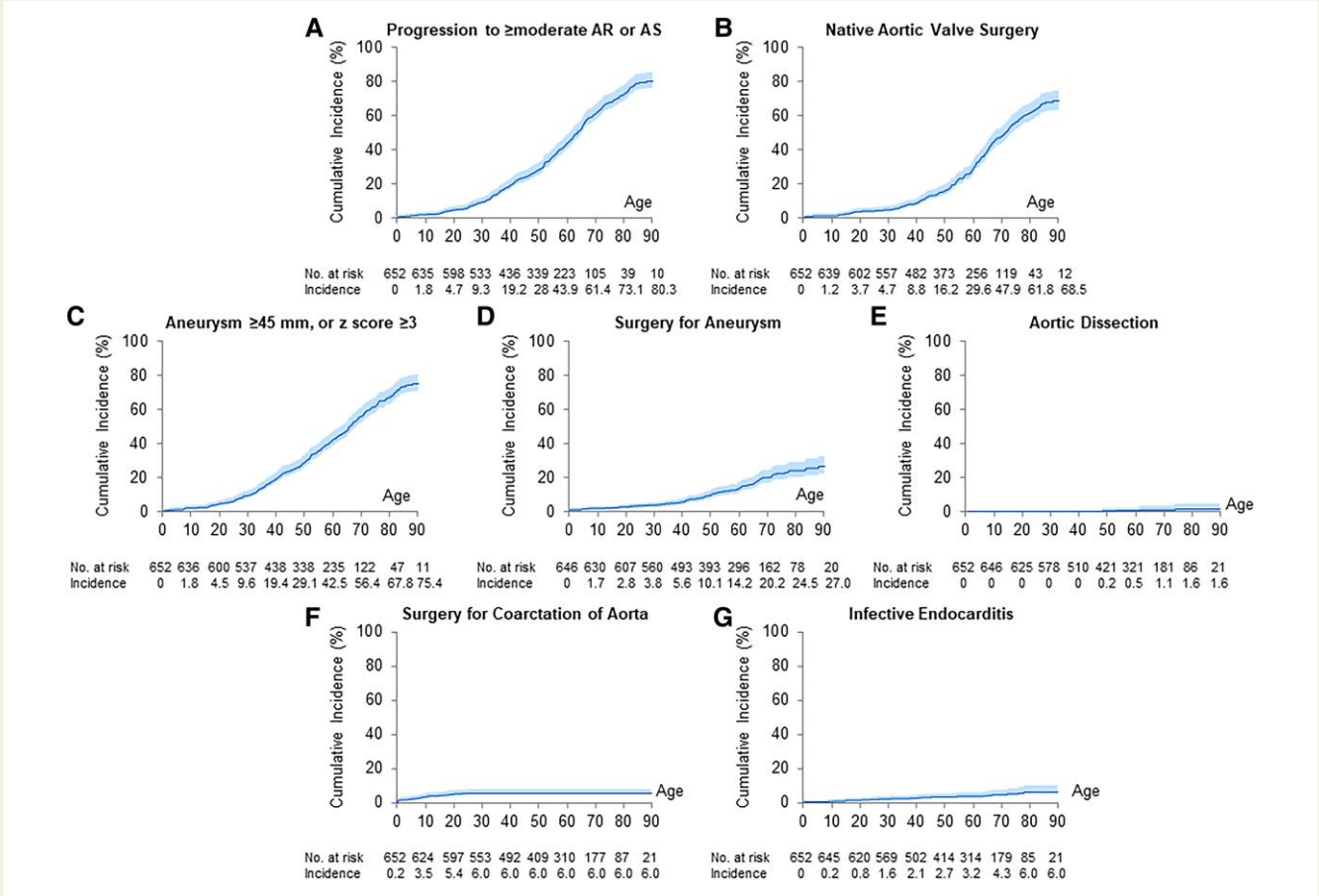


Figure 2 Lifetime (from birth to age 90) cumulative incidence of medical and surgical endpoints. (*A*) *Valvulopathy progression*. AR or AS ≥ moderate or mixed occurred in 343/652 patients since birth. (*B*) *Native AVS* occurred in 253/652 patients since birth. (*C*) *Dilatation of the aorta* occurred in 330/652 patients since birth. (*D*) *Surgery for aneurysm* occurred in 83/652 patients since birth. (*E*) *Aortic dissection or aneurysm* rupture occurred in 6/652 patients since birth. (*F*) *Surgery for aortic coarctation* occurred in 41/652 patients since birth. (*G*) *Infective endocarditis* occurred in 25/652 patients since birth.

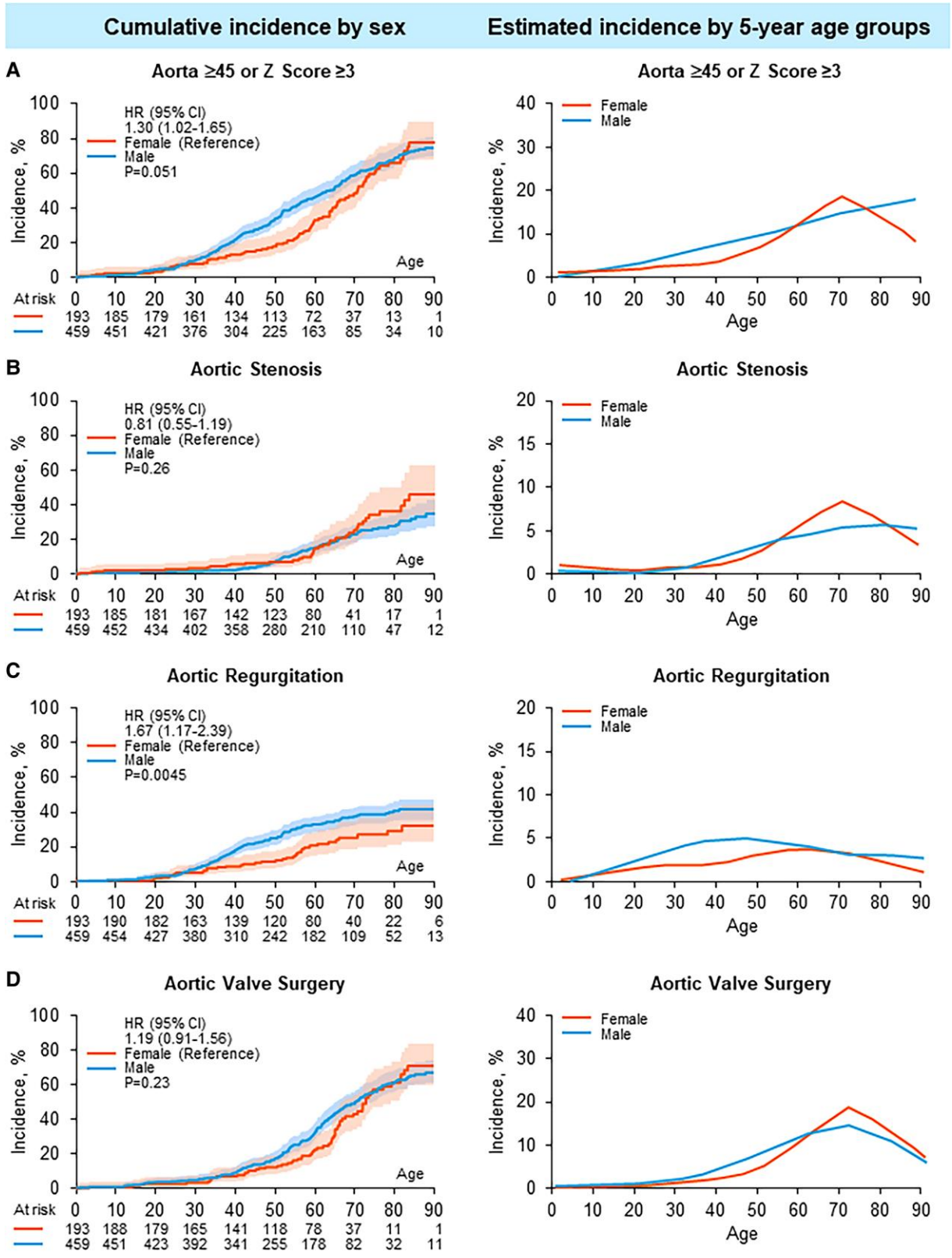


Figure 3 Lifetime valvulo-aortopathy incidence by sex: (*A*) dilatation of the aorta; (*B*) aortic stenosis; (*C*) aortic regurgitation; and (*D*) aortic valve surgery. The left graphs show cumulative lifetime incidence, right graphs show non-cumulative point-incidence of events using 5-year age groups.

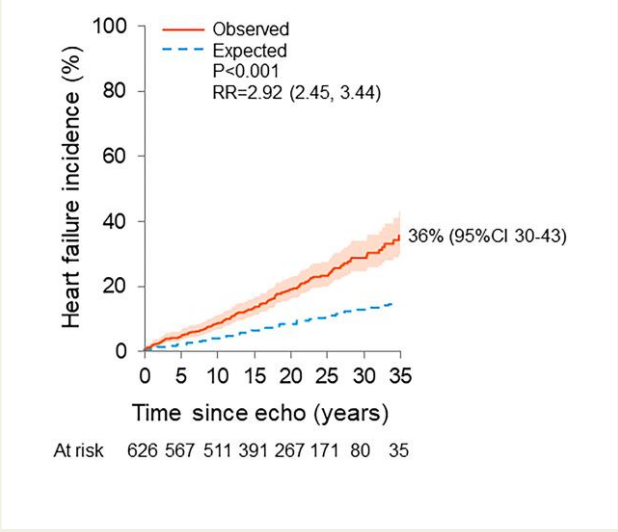


Figure 4 Thirty-five-year cumulative heart failure incidence compared to expected for olmsted county, Minnesota. At the transthoracic echocardiography baseline, 26/652 patients had a history of HF and were excluded from the 35-year incidence analysis, thus *n* at risk = 626.

presentation (*Structured Graphical abstract*), which in turn, is reassuringly uncommon.

Bicuspid aortic valve morbidity patterns and clinical implications

The most important contributor to the high total morbidity burden of patients with BAV was progressive valvulopathy driven by AS,[24] with AR being less common and affecting mostly younger males (*Figure 3*). This resulted in a lifetime risk of AVS of almost 70% (*Figure 2*). Likewise, the lifetime risk of aortic dilatation was high yet it did not result in a prominent risk of aorta surgery, likely because aortopathy progression is slower[25] than valvulopathy, and aortopathy is asymptomatic without significant impact on left ventricular function. Nonetheless, the risk of aorta surgery was not small and was ever-present throughout the lifetime; for coarctation in <30-year-olds and for aneurysm thereafter (*Figure 2*). Our study demonstrates a low incidence of aortic dissection which did not occur in paediatric patients or adults younger than 40, extending this recognized notion[7–10] over very long-term follow-up. Remarkably, infective endocarditis exhibited approximately four times higher lifetime incidence than dissection,[12] in fact, of the 152 total deaths from this cohort, two were from aortic dissection and four from infective endocarditis. Importantly, we demonstrated a higher-than-expected incidence of HF which was driven by valvular heart disease. Finally, the total morbidity of patients with BAV became close to unavoidable by age 90 (*Structured Graphical abstract*).

An obvious implication of these lifetime morbidity patterns is that early diagnosis of the BAV condition (including screening of first-degree relatives of BAV cases) whereby appropriate interval monitoring is instituted to ensure timely interventions is critical. Regular lifelong valvulo-aortopathy monitoring is, therefore, mandatory in patients with BAV. Given that the leading morbidity is AVS for AS,[24] research must focus on the development of medical therapies to prevent AS or halt AS progression. Surveillance of young BAV males with AR is critical for appropriate surgical timing and native BAV conservation should be prioritized through surgical repair. The Ross procedure[26] may also play a role in early AS and AR in order to avoid long-term prosthetic valve use. Prevention of HF must be a goal in the management of patients with BAV, best carried out by regular monitoring of valve function and timely referral for surgical correction, along with endocarditis prevention. Technological advancement in catheter-based endovascular thoracic aorta solutions for ascending aorta aneurysms will be critical, along with research in medical treatment preventing or halting aorta dilatation. Our study suggests that the burden of the life-threatening infective endocarditis complication has been overlooked in the BAV population as it is relatively high; high clinical suspicion for early referral and treatment, as well as research in the prevention of this complication are warranted.

Bicuspid aortic valve nosology and survival variability

Most previous BAV cohorts have combined paediatric (i.e. <18-year olds) and adult populations together.[6–8] In this study, we report for the first time the very long-term survival of paediatric BAV patients exclusively, which is similar to the general population when genetic syndromes and complex congenital heart disease are excluded (*Figure 5*). This paediatric group still exhibits a moderate prevalence of severe coarctation and accelerated valvulo-aortopathy, which does not increase mortality at 35 years, probably because of the very young age at TTE diagnosis [6 (1–13) years, *Table 1*]; however, it is possible that longer follow-up and larger cohorts would reveal decreased survival. In addition, our study demonstrates that in the community, most patients with BAV present with a typical valvulo-aortopathy (93% of total adult BAV diagnoses and 60% of total paediatric diagnoses) and their very long-term outcome is benign. Thus, despite the significant lifetime morbidity burden, there is no significant mortality penalty for the majority of patients with BAV, which is a critical reassuring notion for patients and physicians. This notion is dependent upon appropriate clinical follow-up by experienced cardiologists and rigorous guideline implementation. Conversely, patients with complex valvulo-aortopathy presentation (7% of total adult BAV diagnoses and 40% of total paediatric diagnoses), incur a survival penalty which is mostly related to the presence of genetic syndromes and complex congenital heart disease. Indeed, after excluding genetic syndromes and complex congenital heart disease, the survival penalty in the complex group attenuated. This attenuation could be related to a power limitation due to small patient numbers and young patient age; the presence of severe aortic coarctation and accelerated valvulo-aortopathy could further increase mortality in larger cohorts with longer follow-up (i.e. >35 years). Finally, an undetermined number of patients with BAV remained undiagnosed, some uncovered at autopsy, categorized as 'undiagnosed or uncomplicated',[13] however, although some were clinically silent, others concealed advanced AS and two debuted with fatal complications (see Supplementary data online, *Table*). Therefore, the undiagnosed BAV is not benign. This underscores the importance of screening echocardiography in first-degree relatives of BAV cases and raises the question of whether general BAV screening should be implemented.

Limitations

Our study design was retrospective with its inherent limitations, and although population-based (geographically constrained), it relied on physician-requested echocardiography for BAV diagnoses, therefore, the total number of undiagnosed BAV cases in Olmsted County remains undetermined and overall prevalence was underestimated.

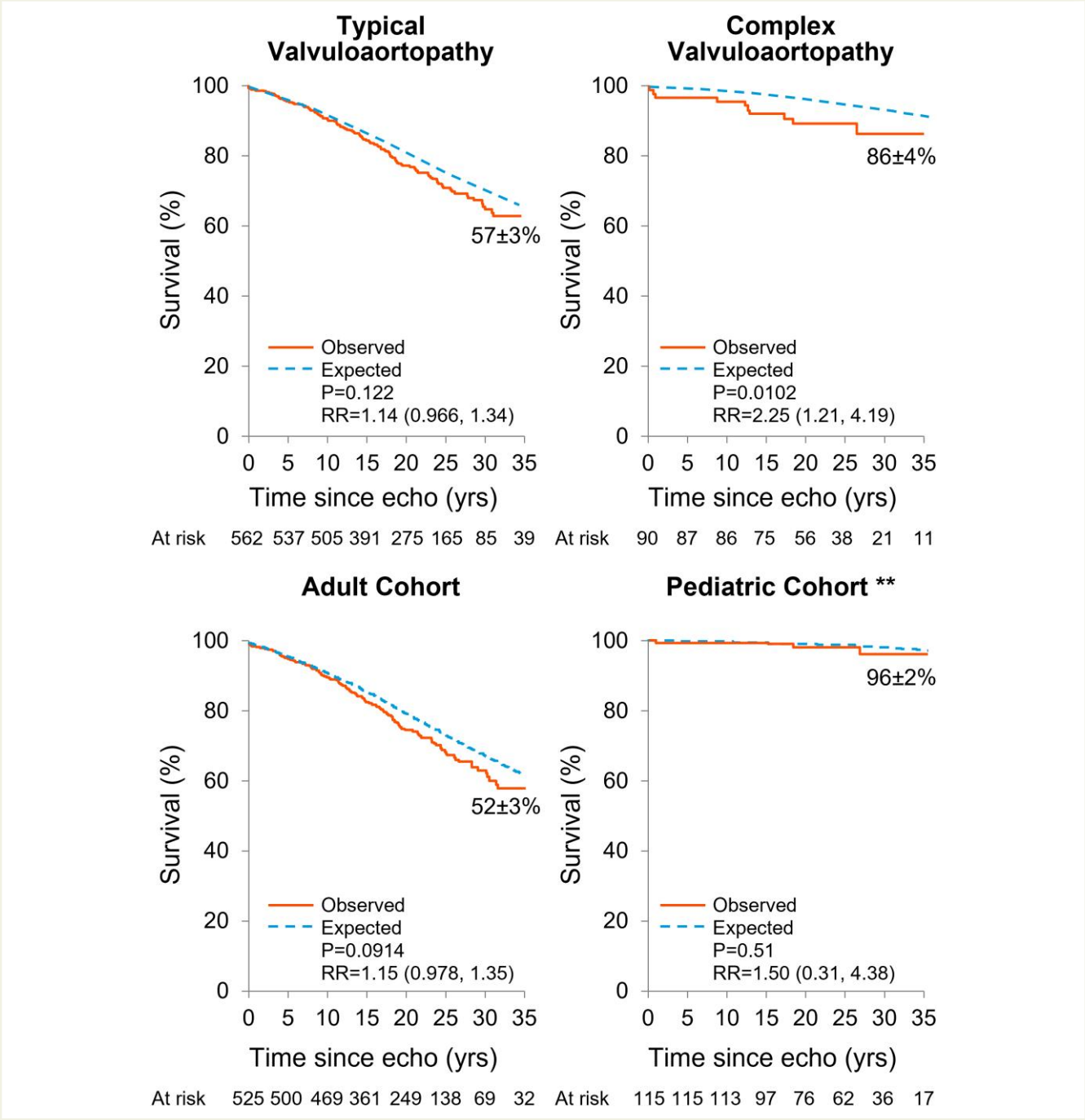


Figure 5 Thirty-five-year survival compared to age-and sex-matched Minnesota population. Typical valvulo-aortopathy, complex valvulo-aortopathy, adult cohort, and paediatric cohort. ** for survival analysis of the paediatric cohort, 18 patients with syndromes and complex congenital heart disease were excluded.

The sensitivity and specificity of TTE for BAV diagnosis are in the order of 80% and 95% respectively, therefore, cases could have been missed. Also, the newly defined forme fruste BAV phenotype was not included in the cohort. In addition, there could have been more undiagnosed patients who died in whom autopsy was not performed and therefore their BAV remained unaccounted, and therefore it remains possible that overall survival could be overestimated. However, our study represents the only available population-based assessment of lifetime morbidity and very long-term survival in patients with an echocardiographic diagnosis of BAV, which is representative of the patients with BAV seen in cardiology practices everywhere (i.e. with echocardiographic diagnosis of BAV). A study based on complete population echocardiographic screening would be significantly costly and would require many decades of prospective follow-up, beyond an investigator's lifetime. Morbidity endpoints could have been missed in patients who moved from the state and survey responses could underestimate ascertainment of events, particularly non-surgical ones (recall bias). However, the total morbidity burden would only increase further

(not decrease) if there was perfect follow-up. The survival penalty associated with the complex valvular aortopathy was driven by associated genetic syndromes and complex congenital heart disease, which were excluded from the paediatric population survival analysis. Although reassuring that paediatric survival was not affected at 35 years, assessment of long-term survival in paediatric BAV patients with severe coarctation and accelerated valvular aortopathy needs to be determined in a larger paediatric cohort with longer follow-up. Women were under-represented in the study given the known male BAV predominance and were less likely to reach an aorta size of 45 mm, thus our definition of aortic aneurysm may underestimate aortopathy in women. Our population was predominantly white and of Northern European descent and race may be a potential disease modifier in BAV.[27] Finally, it is possible that in areas with poor access to health care, there may be a survival penalty for patients with BAV and typical valvulo-aortopathy.

Conclusions

The congenital BAV condition exhibits a significant cumulative morbidity burden beginning at birth and increasing steadily throughout the patient's lifetime so that morbidity is close to unavoidable by age 90, driven by progressive valvulo-aortopathy. Of the life-threatening BAV complications, the lifetime risk of endocarditis is close to four times higher than that of aortic dissection. The most common BAV clinical presentation in the community is by far, the typical valvulo-aortopathy which is associated with good long-term survival, providing critical reassurance for patients and physicians. Conversely, the less common complex valvulo-aortopathy, characterized by a high proportion of paediatric patients, high prevalence of severe aortic coarctation, high incidence of accelerated severe valvulopathy, as well as genetic syndromes and complex congenital heart disease, carries a long-term survival penalty for those patients. Nonetheless, paediatric patients without genetic syndromes or complex congenital heart disease had no survival penalty for up to 35 years. Finally, contrary to the prior assumption that undiagnosed patients with BAV exhibited a silent benign condition, these patients may present with advanced valvulopathy and life-threatening complications.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

There are no related disclosures for this work.

Data Availability

Completely de-identified study data could be made available upon request if such request is considered valid and only with explicit approval of the Mayo Clinic research authority.

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Ethical Approval

This study was approved by the Mayo Clinic institutional review board.

Pre-registered Clinical Trial Number

None.

References

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002;**39**:1890–900. https://doi.org/10.1016/S0735-1097(02)01886-7
2. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicego D, *et al.* An echocardiographic survey of primary school children for bicuspid aortic valve. *Am J Cardiol* 2004;**93**:661–3. https://doi.org/10.1016/j.amjcard.2003.11.031
3. Sillesen AS, Vogg O, Pihl C, Raja AA, Sundberg K, Vedel C, *et al.* Prevalence of bicuspid aortic valve and associated aortopathy in newborns in Copenhagen, Denmark. *JAMA* 2021;**325**:561–7. https://doi.org/10.1001/jama.2020.27205
4. Michelena HI, Vallabhajosyula S, Prakash SK. Nosology Spectrum of the bicuspid aortic valve condition: complex-presentation valvulo-aortopathy. *Circulation* 2020;**142**:294–9. https://doi.org/10.1161/CIRCULATIONAHA.120.046892
5. Michelena HI, Prakash SK, Della Corte A, Bissell MM, Anavekar N, Mathieu P, *et al.* Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the international bicuspid aortic valve consortium (BAVCon). *Circulation* 2014;**129**:2691–704. https://doi.org/10.1161/CIRCULATIONAHA.113.007851
6. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, *et al.* Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation* 2008;**117**:2776–84. https://doi.org/10.1161/CIRCULATIONAHA.107.740878
7. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT, *et al.* Outcomes in adults with bicuspid aortic valves. *JAMA* 2008;**300**:1317–25. https://doi.org/10.1001/jama.300.11.1317
8. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, *et al.* Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA* 2011;**306**:1104–12. https://doi.org/10.1001/jama.2011.1286
9. Cheng C, Bohbot Y, Michelena HI, Rusinaru D, Fay F, Elmkies F, *et al.* Clinical outcomes of adults with bicuspid aortic valve: a European perspective. *Mayo Clin Proc* 2021;**96**:648–57. https://doi.org/10.1016/j.mayocp.2020.04.047
10. Masri A, Kalahasti V, Alkharabsheh S, Svensson LG, Sabik JF, Roselli EE, *et al.* Characteristics and long-term outcomes of contemporary patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg* 2016;**151**:1650–9.e1. https://doi.org/10.1016/j.jtcvs.2015.12.019
11. Michelena HI, Suri RM, Katan O, Eleid MF, Clavel MA, Maurer MJ, *et al.* Sex differences and survival in adults with bicuspid aortic valves: verification in 3 contemporary echocardiographic cohorts. *J Am Heart Assoc* 2016;**5**:e004211. https://doi.org/10.1161/JAHA.116.004211
12. Michelena HI, Katan O, Suri RM, Baddour LM, Enriquez-Sarano M. Incidence of infective endocarditis in patients with bicuspid aortic valves in the community. *Mayo Clin Proc* 2016;**91**:122–3. https://doi.org/10.1016/j.mayocp.2015.10.011
13. Michelena HI, Della Corte A, Evangelista A, Maleszewski JJ, Edwards WD, Roman MJ, *et al.* International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes. *Eur J Cardiothorac Surg* 2021;**60**:448–76. https://doi.org/10.1093/ejcts/ezab038
14. Yang LT, Tribouilloy C, Masri A, Bax JJ, Delgado V, Girdauskas E, *et al.* Clinical presentation and outcomes of adults with bicuspid aortic valves: 2020 update. *Prog Cardiovasc Dis* 2020;**63**:434–41. https://doi.org/10.1016/j.pcad.2020.05.010
15. Sorlie P, Wei GS. Population-based cohort studies: still relevant? *J Am Coll Cardiol* 2011;**58**:2010–3. https://doi.org/10.1016/j.jacc.2011.08.020
16. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ III. History of the Rochester epidemiology project: half a century of medical records linkage in a US population. *Mayo Clin Proc* 2012;**87**:1202–13. https://doi.org/10.1016/j.mayocp.2012.08.012
17. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, *et al.* Echocardiographic assessment of valve stenosis: eAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;**22**:1–23; quiz 101–2. https://doi.org/10.1016/j.echo.2008.11.029
18. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, *et al.* Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802. https://doi.org/10.1016/S0894-7317(03)00335-3
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1–39 e14. https://doi.org/10.1016/j.echo.2014.10.003
20. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr* 2008;**21**:922–34. https://doi.org/10.1016/j.echo.2008.02.006
21. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, *et al.* A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota,

2000 to 2010. *JAMA Intern Med* 2015;**175**:996–1004. https://doi.org/10.1001/jamainternmed.2015.0924
22. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, *et al.* Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;**292**:344–50. https://doi.org/10.1001/jama.292.3.344
23. Yang LT, Enriquez-Sarano M, Michelena HI. The bicuspid aortic valve raphe: an evolving structure. *Eur Heart J Cardiovasc Imaging* 2020;**21**:590. https://doi.org/10.1093/ehjci/jez294
24. Lee G, Chikwe J, Milojevic M, Wijeysundera HC, Biondi-Zoccai G, Flather M, *et al.* ESC/EACTS vs. ACC/AHA guidelines for the management of severe aortic stenosis. *Eur Heart J* 2023;**44**:796–812. https://doi.org/10.1093/eurheartj/ehac803
25. Detaint D, Michelena HI, Nkomo VT, Vahanian A, Jondeau G, Sarano ME. Aortic dilatation patterns and rates in adults with bicuspid aortic valves: a comparative study with marfan syndrome and degenerative aortopathy. *Heart* 2014;**100**:126–34. https://doi.org/10.1136/heartjnl-2013-304920
26. El-Hamamsy I, Toyoda N, Itagaki S, Stelzer P, Varghese R, Williams EE, *et al.* Propensity-Matched comparison of the ross procedure and prosthetic aortic valve replacement in adults. *J Am Coll Cardiol* 2022;**79**:805–15. https://doi.org/10.1016/j.jacc.2021.11.057
27. Chandra S, Lang RM, Nicolarsen J, Gayat E, Spencer KT, Mor-Avi V, *et al.* Bicuspid aortic valve: inter-racial difference in frequency and aortic dimensions. *JACC Cardiovasc Imaging* 2012;**5**:981–9. https://doi.org/10.1016/j.jcmg.2012.07.008