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ORIGINAL RESEARCH

Characteristics of Bicuspid Aortic Valve Disease and Stenosis: The National Echo Database of Australia

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BACKGROUND: Bicuspid aortic valve (BAV) is the most common congenital heart disease in adults but is clinically heterogeneous. We aimed to describe the echocardiographic characteristics of BAV and compare patients with BAV with moderate-to-severe aortic stenosis (AS) with those with tricuspid aortic valve (TAV) stenosis.

METHODS AND RESULTS: Using the National Echo Database of Australia, patients in whom BAV was identified were studied. Those with moderate-to-severe AS (mean gradient >20 mm Hg [BAV-AS]) were compared with those with TAV and moderate-to-severe AS (TAV-AS). Of 264 159 adults whose aortic valve morphology was specified, 4783 (1.8%) had confirmed BAV (aged 49.6±17.4 years, 69% men). Of these, 42% had no AS, and 46% had no aortic regurgitation. Moderate-to-severe AS was detected in a greater proportion of patients with BAV with a recorded mean gradient (n=1112, 34%) compared with those with TAV (n=4377, 4%; $P<0.001$). Patients with BAV-AS were younger (aged 55.3±16.7 years versus 77.3±11.0 years; $P<0.001$), and where measured had larger ascending aortic diameters (37±8 mm versus 35±5 mm; $P<0.001$). Age and sex-adjusted mortality risk was significantly lower in patients with BAV-AS (hazard ratio, 0.53; 95% CI, 0.45–0.63; $P<0.001$).

CONCLUSIONS: In this large study of patients across the spectrum of BAV disease, the largest proportion had no significant valvulopathy or aortopathy. Compared with those with TAV-AS, patients with BAV were more likely to have moderate-to-severe AS, have larger ascending aortas, and were over 2 decades younger at the time of AS diagnosis. Despite this, patients with BAV appear to have a more favorable prognosis when AS develops, compared with those with TAV-AS.

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Key Words: aortic stenosis ■ cardiac ultrasound ■ mortality ■ regurgitation

Bicuspid aortic valve (BAV) is the most common congenital heart abnormality.[1] Despite its relatively high prevalence compared with other congenital heart defects, the significant heterogeneity of the clinical manifestations of this condition presents challenges in understanding patient prognosis and optimal management strategies. Before the widespread use of echocardiography in clinical practice, descriptions of BAV populations were mostly based on small autopsy studies.[2,3] More recently, most contemporary studies have focused on patients recruited from tertiary referral centers.[4] This introduces substantial selection biases by predominantly representing those with severe clinical manifestations of BAV and/or those undergoing surgical intervention for valvular or aortic complications.[5,6] To address this important caveat, researchers have undertaken systematic reviews based on smaller heterogeneous study cohorts with BAV.[7] However, in such analyses, those with less severe clinical phenotypes of BAV have been underrepresented, producing significant gaps in our understanding of demographics and clinical consequences of BAV overall.

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CLINICAL PERSPECTIVE

What Is New?

- This large study of patients with bicuspid aortic valve (BAV) provides a contemporary description of the heterogeneity of BAV disease at echo diagnosis.
- Moderate-to-severe aortic stenosis develops in significantly more patients with BAVs than tricuspid aortic valves. These patients are significantly younger, have more mixed aortic valve disease, and have larger ascending aortic dimensions.
- Patients with BAV–aortic stenosis have lower age and sex-adjusted all-cause mortality compared with their tricuspid aortic valve counterparts.

What Are the Clinical Implications?

- Many patients with BAV are free of significant valvulopathy or aortopathy at echo diagnosis.
- Despite the significantly different profiles in patients with BAV–aortic stenosis, it is reassuring that these patients have better mortality outcomes compared with patients with tricuspid aortic valve–aortic stenosis.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AS	aortic stenosis
AV	aortic valve
AVR	aortic valve replacement
BAV	bicuspid aortic valve
MG	mean gradient
NEDA	National Echo Database of Australia
TAV	tricuspid aortic valve

The NEDA (National Echo Database of Australia) is a continuously growing database with currently >1.1 million deidentified echocardiography studies performed in a variety of real-world cardiology practice settings across Australia. This large database provides a unique opportunity to gain a more complete understanding of BAV. Specifically, the NEDA has captured profiling and outcome data on a large cohort of patients with BAV across the broad spectrum of disease states, providing a closer reflection of the contemporary experience of BAV. On this basis, we first aimed to describe the patterns of BAV valvulopathy and aortopathy to gain a deeper understanding of this clinically heterogeneous patient population. Second, based on a recently described mortality threshold for aortic valve (AV) stenosis within the broader NEDA cohort at an AV mean gradient (MG) of >20 mm Hg,[8] and the inherently high risk for developing aortic stenosis (AS) at a younger age among adults with BAV, we specifically compared the profile and outcome of cases identified with AS within the NEDA cohort according to the presence of a BAV versus an anatomically correct tricuspid aortic valve (TAV).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

NEDA Database

A full description of the NEDA methodology has previously been published.[9] At the time of this analysis, echo data had been collected from 23 centers across 6 states of Australia. The database is linked with the National Death Index, provided by the Australian Institute for Health and Welfare, to obtain mortality data for each individual. Vital status was recorded as of May 21, 2019; if patients were alive on this date, they were censored alive. The NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approval for the NEDA study has been obtained from the Sydney Local Health District Human Research Ethics Committee, protocol X15-0387 and 2019/ETH069899, and the study adheres to the Declaration of Helsinki. At the inception of the NEDA, a patient waiver for retrospectively collected data was authorized by the Human Research Ethics Committee for retrospectively acquired echo studies; since 2018, prospective consent has been obtained by verbal script.

Study Population

The study population was identified according to the recorded description of AV morphology (Figure 1). Using a broad list of search terms, specialized text recognition software was used to identify patients in whom the AV morphology had been specified as either bicuspid or tricuspid (from each unique individual's first study in the database). Patients in whom the AV morphology was not specified (n=365 799) or in whom there was discrepant coding for valve morphology (n=1866) were excluded. Distributions of age and sex in patients without AV morphology were statistically different to that of patients with AV morphology recorded (median age, 64 years; interquartile range [IQR], 51–75 years versus 62 years; IQR, 47–74 years; $P<0.001$; and men, 53.3% versus 51.6%; $P<0.001$). However, these differences were

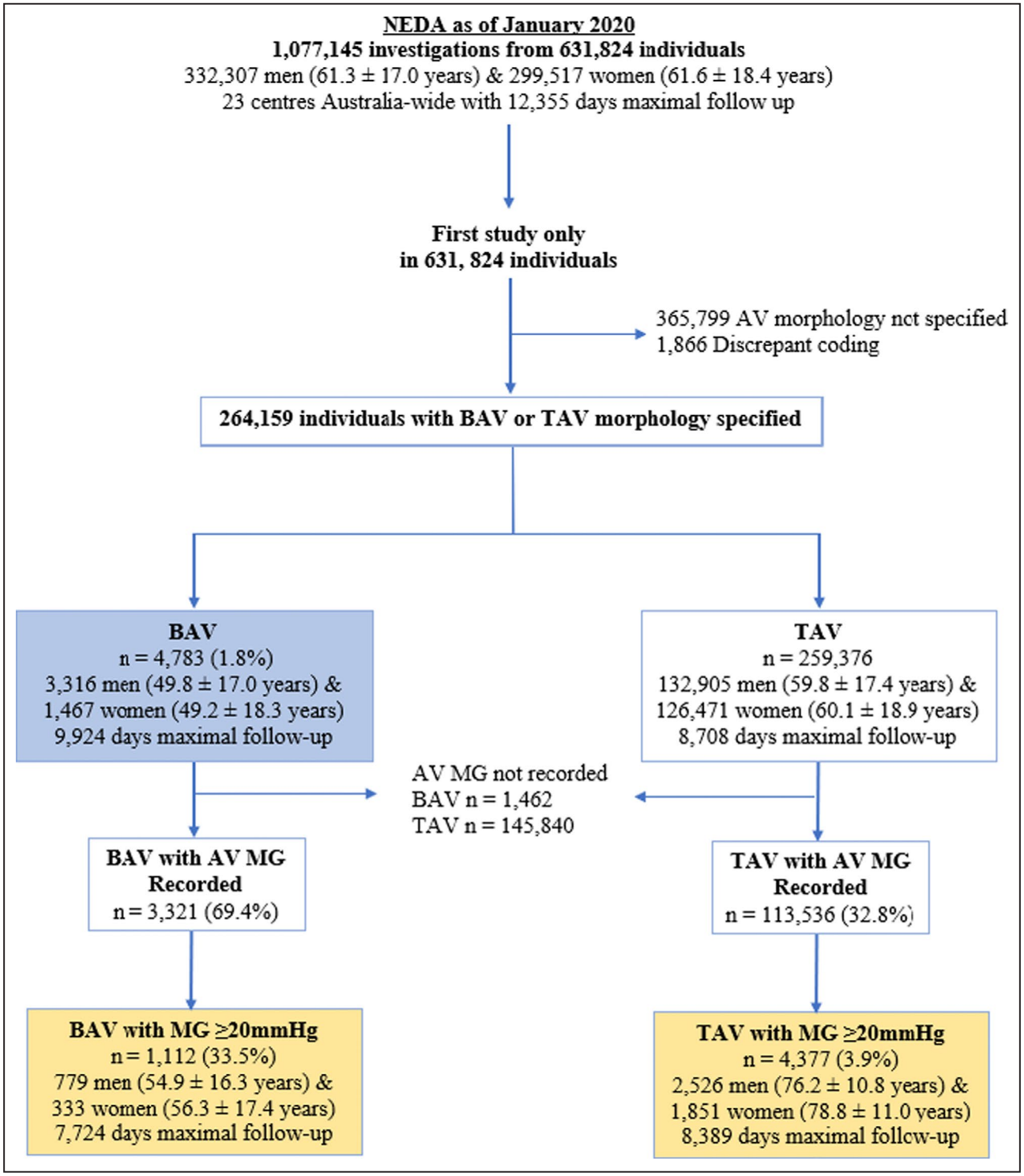

Figure 1. Study flowchart.
This flowchart demonstrates how echo studies were selected from the NEDA, first, for analysis of all patients with BAV (blue box), and second, to compare patients with BAV or TAV and moderate-to-severe aortic stenosis (yellow boxes). AV indicates aortic valve; BAV, bicuspid aortic valve; MG, mean gradient; NEDA, National Echo Database of Australia; TAV, tricuspid aortic valve.

not clinically significant and are unlikely to have introduced significant selection bias.

For the comparison of patients with BAV or TAV with moderate-to-severe AS, we included those in whom the mean AV gradient was recorded; thus, a further 1462 patients with BAV and 145 840 patients with TAV who did not have a mean AV gradient recorded were excluded. Those excluded patients

without an AV MG recorded were marginally younger than patients with an AV MG recorded (median age, 60 years; IQR, 45–72 years versus 65 years; IQR, 51–76 years; *P*<0.001 and men 49.7% versus 54.0%; *P*<0.001). However, age- and sex-adjusted mortality was lower in those without an AV MG recorded (overall mortality hazard ratio [HR], 0.71; 95% CI, 0.70–0.72; *P*<0.001; Table S1). As such, their exclusion is unlikely to have led to any underestimation of mortality risk in this study.

Study Outcomes

The echocardiographic profile of the confirmed patients with BAV is described including the distributions of age, sex, severity of valve dysfunction, and aortic dimensions. In these adults, the presence and severity of AS was determined according to the AV MG and peak velocity (no AS was defined as MG 0.00–9.99 mm Hg and/or peak velocity <2.0 m/s, mild as MG 10.00–19.99 mm Hg and/or peak velocity 2.0–2.9 m/s, moderate as MG 20.00–39.99 mm Hg and/or peak velocity 3.0–3.9 m/s, and severe as MG >40 mm Hg and/or peak velocity >4.0 m/s). In cases where MG and peak velocity were discordant, the patient was classified into the higher of the 2 categories (ie, if MG was 38 mm Hg and the peak velocity was 4.1 m/s, then the patient was classified into the severe AS category). The presence and severity of aortic regurgitation (AR) was determined from qualitative text descriptions (none/trace, mild, moderate, and severe); these were also extracted using specialized text recognition software.

For the comparison between patients with moderate-to-severe AS (AV MG ≥20 mm Hg) and BAV (BAV-AS) or TAV (TAV-AS), the echocardiographic profiles of the groups were reported in the same manner as that for the BAV cohort described above. Additionally, subsequent AV intervention (surgical or transcatheter AV replacement [AVR]) was assessed from subsequent echo studies where available in the NEDA, for the same individuals, noting the presence of a replaced AV. To account for the influence of any concomitant congenital heart conditions, the most commonly associated with BAV being aortic coarctation, we used text recognition software to identify studies in which the presence or absence of aortic coarctation was also reported. Survival comparisons were derived from median follow-up of 6.0 years (IQR, 3.8–9.1 years). Three survival outcomes are reported as actual 1- and 5-year mortality (5466 and 3379 cases, respectively, with complete follow-up at these time points) and then overall survival during the entire follow-up period. Given the significant mean age difference between the BAV-AS and TAV-AS groups, age-specific analyses comparing the clinical profiles and survival outcomes were performed, comparing those with BAV-AS to TAV-AS in patients aged ≤65 years and then in patients aged >65 years.

Statistical Analysis

Descriptive data are expressed as mean±standard deviation, or where nonnormal, as median with IQR. Those with BAV or TAV and moderate-to-severe AS were compared using independent samples *t* tests for continuous variables or Pearson χ^2 tests for categorical variables. Nonnormal distributions were compared using the Mann-Whitney *U* test. Age- and sex-adjusted odds ratios (ORs) with 95% CIs are reported for actual 1- and 5-year mortality using multiple logistic regression (entry model). The Kaplan-Meier method followed by a Cox proportional hazards regression model were used to compare overall survival between the 2 groups. Covariates were entered into the model (entry method) at a univariate *P* value of <0.10 or when clinically important. The proportional hazards assumption was verified by visual assessment of linearity in plots of the log-minus-log survival curves. Given marked age differences between the 2 groups, separate age-specific analyses (above and below the age of 65 years) were also conducted. A 2-tailed value of *P*<0.05 was considered statistically significant. All statistical analysis was performed using SPSS version 25.0 (IBM, Armonk, NY).

RESULTS

Characteristics of Patients With BAV

Of the 264 159 patients in whom AV morphology was specified, 4783 (1.8%) patients were identified to have a BAV (49.6±17.4 years, 69.3% men; Table 1). The proportion of adults in whom ascending aorta dimensions were recorded was relatively low (aortic root 86.1%, sinotubular junction 28.0%, ascending aorta 35.5%), but where measured, the average aortic dimensions were 36±6 mm, 34±7 mm, and 36±8 mm, respectively. Of these, 218 adults (12.8%) had significant ascending aorta dilatation, defined as diameter >45mm. There was a spectrum of valvular dysfunction (Figure 2), with the majority of patients with BAV having no AS (42.2%) and no/trace AR (45.9%). However, 11.2% and 8.8% had severe AS or severe AR, respectively.

Comparison of Patients With BAV or TAV With Moderate-to-Severe AS

Of 113 536 patients with echo-confirmed TAV and a mean AV gradient recorded, 4377 (3.9%) had moderate-to-severe AS. By contrast, of the 3321 patients with BAV and an MG recorded, 1112

Table 1. Echocardiographic Characteristics of Patients With Bicuspid Aortic Valve

	Data points available	Patients with BAV n=4783
Age, y		49.6±17.4
Sex, men		3316 (69.3%)
LVEF	3881/4783 (81.1%)	63±11
Aortic stenosis	4095/4783 (85.6%)	
None		1730 (42.2%)
Mild		1162 (28.4%)
Moderate		744 (18.2%)
Severe		459 (11.2%)
Aortic regurgitation	3353/4783 (70.1%)	
None/trace		1538 (45.9%)
Mild		912 (27.2%)
Moderate		607 (18.1%)
Severe		296 (8.8%)
Aortic dimensions, mm		
LVOT	2632/4783 (55.0%)	23±3
Aortic root	4118/4783 (86.1%)	36±6
Sinotubular junction	1340/4783 (28.0%)	34±7
Ascending aorta	1700/4783 (35.5%)	36±8
Aortic arch (%)	680/4783 (14.2%)	29±6
Ascending aorta >45 mm	1700/4783 (35.5%)	218 (12.8%)

Results are expressed as mean±standard deviation, median (interquartile range), or n (%). BAV indicates bicuspid aortic valve; LVEF, left ventricular ejection fraction; and LVOT, left ventricular outflow tract.

Table 2. Comparison of Patients With BAV and Moderate-to-Severe AS With Those With TAV and Moderate-to-Severe AS

	BAV-AS, n=1112, 33.5%	TAV-AS, n=4377, 3.9%	*P* value
Age, y	55.3±16.7	77.3±11.0	<0.001
Sex, men	779 (70.1%)	2526 (57.7%)	<0.001
LVEF, %	65±12	60±13	<0.001
RVSP, mm Hg	38±12	43±13	<0.001
Aortic regurgitation			<0.001
None	332 (38.8%)	1565 (46.3%)	
Mild	246 (28.8%)	1204 (35.6%)	
Moderate	184 (21.5%)	524 (15.5%)	
Severe	93 (10.9%)	87 (2.6%)	
Aortic stenosis			
MG, mm Hg	32 (25–45)	31 (24 – 42)	<0.001
Peak V, m/s	3.70 (3.27–4.33)	3.65 (3.27 – 4.20)	0.03
Aortic dimensions, mm			
Aortic root	36±6	33±4	<0.001
STJ	35±7	27±4	<0.001
Ascending aorta	37±8	35±5	<0.001
Subsequent AVR	407 (36.6%)	1027 (23.5%)	<0.001

Results are expressed as mean±standard deviation, median (interquartile range), or n (%). For BAV-AS and TAV-AS groups, respectively, data were available for LVEF in 974 (87.6%) and 3518 (80.4%), for RVSP in 621 (55.8%) and 2603 (59.5%), for aortic regurgitation 855 (76.9%) and 3380 (77.2%), for peak velocity 1040 (93.5%) and 4085 (93.3%), for aortic root dimension 945 (85.0%) and 3368 (76.9%), for STJ dimension 388 (34.9%) and 782 (17.9%), and for ascending aorta dimension in 440 (39.6%) and 1748 (39.9%). AS indicates aortic stenosis; AVR, aortic valve replacement; BAV, bicuspid aortic valve; LVEF, left ventricular ejection fraction; MG, mean gradient; RVSP, right ventricular systolic pressure; STJ, sinotubular junction; TAV, tricuspid aortic valve; and V, velocity.

(33.5%) had moderate-to-severe AS (*P*<0.001; Table 2). The degree of AS was similar between the 2 groups (median AV MG, 32; IQR, 25–45 mm Hg for BAV versus 31; IQR, 24–42 mm Hg for TAV; *P*<0.001). However, a higher proportion of patients with BAV-AS had moderate (21.5% versus 15.5%; *P*<0.001) or severe (10.9% versus 2.6%; *P*<0.001) AR compared with TAV-AS. Patients with BAV were

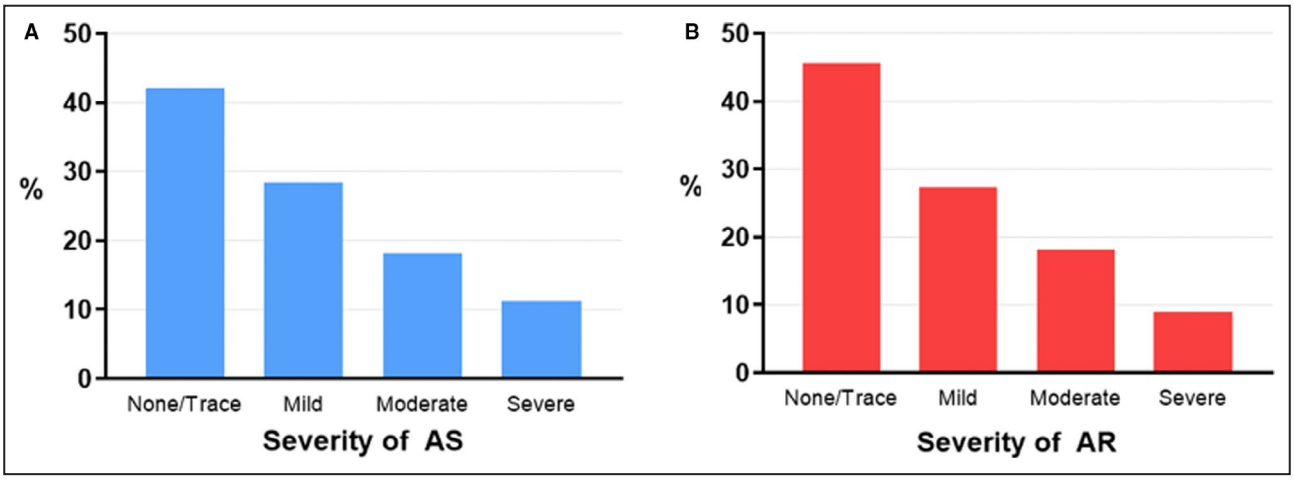

Figure 2. Aortic valve dysfunction in patients with bicuspid aortic valve.
Distribution of grades of (**A**) aortic stenosis and (**B**) aortic regurgitation in patients with bicuspid aortic valve. AR indicates aortic regurgitation; and AS, aortic stenosis.

substantially younger at the time of echo diagnosis (55.3±16.7 years versus 77.3±11.0 years; *P*<0.001). Where aortic dimensions were recorded, the diameters at the aortic root, sinotubular junction, and ascending aorta were significantly larger in patients with BAV-AS compared with TAV-AS (36±6 mm versus 33±4 mm, 35±7 mm versus 27±4 mm, 37±8 mm versus 35±5 mm, respectively; *P*<0.001 in each case). A higher proportion of patients with BAV went on to have subsequent AVR (36.6% versus 23.5%; *P*<0.001).

Mortality

Age- and sex-adjusted 1- and 5-year mortality risk was substantially lower in the BAV-AS cohort (OR, 0.59; 95% CI, 0.48–0.73; *P*<0.001 and OR, 0.52; 95% CI, 0.41–0.66; *P*<0.001, respectively), and this did not significantly change when left ventricular ejection fraction and increasing AR were added to the model. Regarding overall survival, given the patients with BAV were younger at the time of AS diagnosis, the overall age at death was younger for patients with BAV (median age, 76 years; IQR, 66–84 years versus 85 years; IQR, 79–89 years; *P*<0.001). The cause of death was recorded as cardiovascular in similar proportions (45.2% versus 49.7%; *P*=0.272). On an age- and sex-adjusted basis, the overall risk of all-cause mortality was higher in patients with TAV-AS (HR, 0.53; 95% CI, 0.45–0.63; *P*<0.001; Figure 3). Furthermore, when left ventricular ejection fraction and increasing severity of AR was added to the model, the results did not change significantly (Table 3). The higher mortality risk also persisted when right ventricular systolic pressure was further added to the model (HR, 0.53; 95% CI, 0.41–0.69; *P*<0.001).

Given the higher proportion of patients with BAV-AS undergoing subsequent AVR, a sensitivity analysis including only those without subsequent AVR was performed, which demonstrated the same differential in survival (HR, 0.58; 95% CI, 0.48–0.70; *P*<0.001). On the impact of concomitant aortic coarctation, only a small proportion (6.8%) of TAV-AS studies had any comment on the presence or absence of residual aortic coarctation, compared with 31.7% of BAV subjects. When sensitivity analyses were performed with exclusion of all these subjects who were identified to have aortic coarctation, there were no significant changes in any aspect of the reported study results.

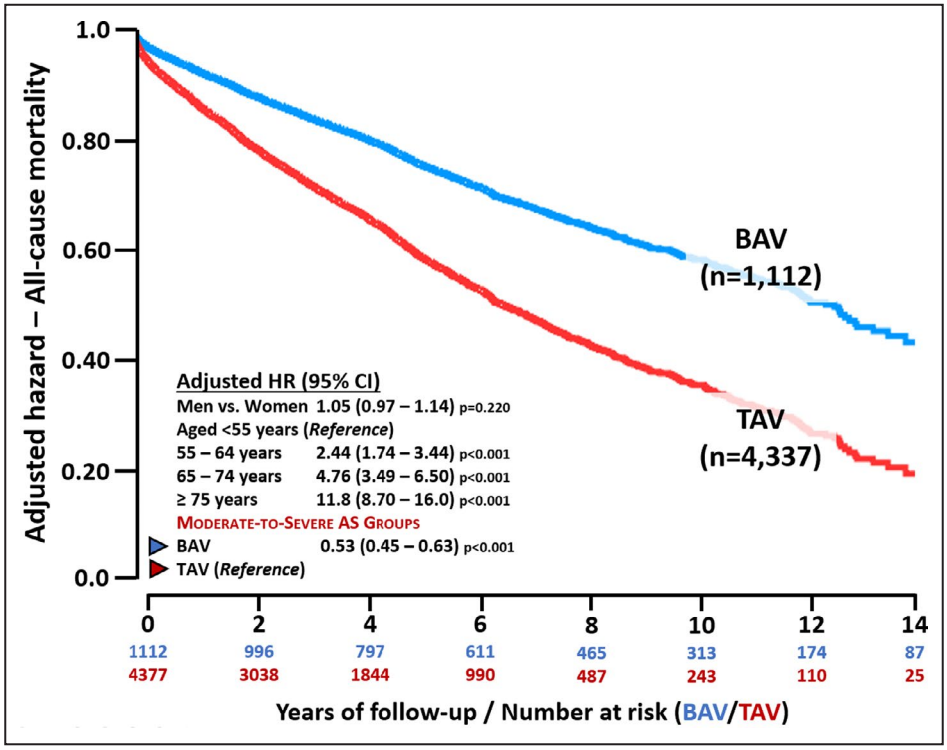

Figure 3. Adjusted survival curves for patients with BAV or TAV and moderate-to-severe AS. Survival curves comparing patients with moderate-to-severe AS and bicuspid (blue) to tricuspid aortic valves (red), adjusted for age and sex. AS indicates aortic stenosis; BAV, bicuspid aortic valve; HR, hazard ratio; and TAV, tricuspid aortic valve.

Table 3. Correlates of Mortality in Patients With BAV or TAV With Moderate-to-Severe Aortic Stenosis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BAV vs TAV	0.19 (0.17–0.22)	<0.001	0.51 (0.41–0.64)	<0.001
Age, y				
<55 (ref)				
55–64	2.74 (1.95–3.85)	<0.001	2.32 (1.53–3.52)	<0.001
65–74	6.50 (4.81–8.77)	<0.001	4.68 (3.21–6.83)	<0.001
>75	17.53 (13.13–23.40)	<0.001	11.54 (7.97–16.71)	<0.001
Sex, men	0.84 (0.78–0.91)	<0.001	0.98 (0.88–1.08)	0.64
Mean gradient	0.998 (0.995–1.000)	0.057	1.000 (0.997–1.003)	0.94
LVEF	0.976 (0.973–0.979)	<0.001	0.981 (0.977–0.984)	<0.001
Increasing AR severity	0.93 (0.89–0.98)	0.006	1.05 (0.99–1.12)	0.13

There are 3494 patients included in the multivariate model (BAV 766, TAV 2728). AR indicates aortic regurgitation; BAV, bicuspid aortic valve; HR, hazard ratio; LVEF, left ventricular ejection fraction; ref, reference; and TAV, tricuspid aortic valve.

Age-Specific Comparisons

Given the significant 22-year mean age difference between the groups, 2 additional age-specific comparisons were performed, first comparing the profiles of BAV-AS to patients with TAV-AS who were aged ≤65 years, and second, comparing the 2 groups including only patients aged >65 years (Table S2**)**. In both subanalyses, the patients with BAV-AS remained younger on average compared with the TAV-AS. However, original age differences narrowed (≤65 years subanalysis: median of 52 years; IQR, 40–59 years versus 60 years; IQR, 53–65 years; *P*<0.001; >65 years subanalysis: median of 72 years; IQR, 68–78 years versus 81 years; IQR, 75–86 years; *P*<0.001). The majority of findings from the original comparisons were replicated, aside from the following: (1) In patients aged ≤65 years, the proportion of patients undergoing subsequent AVR was broadly similar (39% versus 34%; *P*=0.06), potentially reflecting more acceptable surgical risk in the younger cohort. (2) In patients aged >65 years, patients with BAV-AS and TAV-AS had similar rates of AR, and there was no statistically significant difference in mean ascending aorta dimension. The proportion, however, of the original BAV-AS cohort included in the aged >65 years analysis was small (27.4% of BAV-AS compared with 87.9% of TAV-AS). Patients with BAV-AS were therefore relatively underrepresented compared with the patients with TAV-AS, which may account for why these differences were no longer found to be significant in this subanalysis.

The significant difference in mortality risk persisted when the model was applied in age-specific analyses comparing patients with BAV-AS and TAV-AS aged ≤65 years, and then in those aged >65 years (HR, 0.32; 95% CI, 0.21–0.48; *P*<0.001; and HR, 0.69; 95% CI, 0.54–0.88; *P*=0.002; respectively; Table S3), further supporting that patients with BAV-AS have better survival outcomes compared with patients with TAV-AS, independent of age.

DISCUSSION

To our knowledge, this is the largest ever single study of adults with BAV. Using our large national echocardiography database, we studied 4783 BAV subjects across the spectrum of disease severity and describe the wide distribution of aortic and AV characteristics at the time of first echo diagnosis in adulthood, yielding a more comprehensive contemporary description of the heterogeneity of the condition than previous smaller studies with significant selection biases have provided. Furthermore, we demonstrated significantly different profiles and mortality in patients with BAV-AS compared with TAV-AS, with similar degrees of AS.

Characteristics of Patients With BAV

This study enhances our understanding of the epidemiology of this congenital heart disease. The 1.8% incidence of BAV in our cohort is in line with previous estimates from autopsy[1,2] and smaller echo database studies[10]; however, this is likely an underestimate of the true incidence, given that patients who remain undiagnosed throughout their lifetime are not represented. Furthermore, patients who might have died during childhood or before having an echo in adult life at a NEDA center would not have been counted in this sample. There is thus a selection bias here, whereby only those surviving to adult life and those who were referred for a cardiac ultrasound at a participating site were included in this sample. We should also note that just over half of the individuals (n=365 799) had no

report as to whether the AV was bicuspid or tricuspid, raising the possibility of a lower incidence of 0.8% if those excluded studies where valve morphology was not specified represent patients with normal TAVs. These factors therefore introduce possible sources of error into the 1.8% estimate of BAV prevalence in the NEDA registry.

The heterogeneity of BAV disease is well recognized; however, there has been considerable variability in the reported incidences of aortic and AV complications, which is likely a reflection of relatively small study sample sizes and the selection biases arising when those studies with more severe BAV disease have been the most commonly published. In this study, many adults (over 40%) had no significant valvular dysfunction at initial echo diagnosis at a mean age of 50 years. Autopsy studies have similarly observed that a significant proportion of patients have normo-functioning bicuspid valves at the time of death,[3,11] reiterating that a significant proportion of patients with BAV may not ever develop any significant valvular complications. Our future plans to study the individuals in the NEDA, in whom serial studies were performed, may reveal distinguishing characteristics of patients who go on to develop progressive valve dysfunction, compared with those who are spared from progressive disease.

Despite a significant proportion of patients having normal AV function, a wide spectrum of valve dysfunction was observed, with 57.8% and 54.1% of patients manifesting some degree of AS or aortic regurgitation, respectively. Although the proportion of patients with any aortic regurgitation was similar to that found at the time of diagnosis in a small community cohort from Olmsted County[6] (247/416, 59%), the proportion with AS in our patients with BAV was significantly higher than previously reported. Michelena et al found only 23% of their community-based cohort to have any AS at the time of diagnosis, although this difference is almost certainly because of the much younger average age at diagnosis in that study, which was ≈15 years younger than in our cohort.

In this study, we found that the average aortic dimensions at time of BAV diagnosis fell within the normal range. A significant proportion of this relatively young cohort of patients, however, had clinically significant ascending aortic dilatation, with 12.8% of patients having an ascending aortic diameter >45 mm. We note and are concerned by the relatively low proportion of patients with BAV aortic diameter measurements in this database, with only approximately one-third having their proximal ascending aortic dimension recorded, despite a specific identification of a BAV. It is well recognized that BAV disease may be associated with serious sequelae involving not only the AV, but the ascending aorta as well, and so the lack of specified ascending aortic dimensions is surprising. Although it is possible that those studies without aortic dimensions recorded may have been those in whom accurate measurements were not possible because of poor image quality, it is unlikely that this accounts for all cases of underreporting. This is an important and concerning previously undocumented finding on real-world echocardiography practice, and we acknowledge that this significant lack of data completeness may impact the accuracy of our findings.

In addition to the diversity of valvular and aortic sequalae of BAV disease, another feature of the heterogeneity of this condition is the various BAV configurations, commonly termed morphotypes, with differences in cusp number, orientation, and presence and number of raphes. Increasing attention has been given recently to clinical differences between various BAV morphotypes, with certain morphotypes associated with particular patterns of valvular and aortic complications.[12] The real-world nature of the NEDA cohort is such that BAV morphotype data were not routinely available. We speculate that many busy laboratories simply do not record this information routinely, particularly in stenosed valves where the morphology may be difficult to delineate with confidence.

Moderate-to-Severe AS in Patients With BAV Compared With TAV

Clinically significant AS is much more prevalent in patients with BAV than those with TAV, with approximately one-third of patients with BAV having moderate-to-severe AS at the time of diagnosis (compared with ≈4% of those with TAV). We based this cut point of mean AV gradient of ≥20 mm Hg on previously published and widely cited evidence from the NEDA, that this represents an important prognostic inflection point in the severity of AS.[8] The patients with BAV-AS were significantly younger than their TAV counterparts. Although it is already appreciated that valvular dysfunction develops at a younger age in patients with BAV, we found the average age of patients with clinically important AS to be younger than previous reports. In 2242 patients referred for surgical AVR for BAV valvulopathy (88% of whom had AS), Michelena et al found the average age to be 62±14 years[6]; however, this cohort represents only those with severe valvulopathy being referred for intervention. In our study, representing broader community-based patients, the average age was 7 years younger (55±17 years). Accordingly, we also found a much larger age difference (22 years) compared with patients with TAV-AS, than has previously been reported. Davies et al, for example, found in their surgical series that patients with BAV were ≈8 years younger than those with TAV undergoing AVR for AS.[13]

Despite their younger average age, a much higher proportion of patients with BAV-AS in our study had

significant concomitant aortic regurgitation, suggesting that mixed valvular disease may be more prevalent in patients with BAV-AS compared with patients with TAV with a similar degree of AS. This finding has not previously been reported and contrasts with a recent study of 862 patients with mixed AV disease (at least moderate AS and moderate AR), of whom the majority (81.1%) had TAVs.[14] This is an important difference that requires further study, as the presence of mixed AV disease has been shown to have important prognostic implications[15] and a high risk of all-cause mortality that is reduced by AVR.[14]

The mean ascending aortic dimensions in both moderate-to-severe AS groups fell within normal ranges. However, patients with BAV had significantly larger aortic dimensions compared with those with TAV, expanding on previous work in smaller age- and sex-matched populations.[16] This difference existed despite there being a similar severity of AS in the 2 groups. The 2 main hypotheses for the cause of BAV-related aortic disease relate to altered flow characteristics[17–20] and an intrinsic aortic wall abnormality leading to a vulnerability to dilatation. Our observations that BAV aortas were significantly larger than in TAV, despite having similar hemodynamic profiles, may favor the theory of an intrinsic aortic wall abnormality in patients with BAV. Conversely, in favor of the flow-mediated theory is that flow disturbances have been demonstrated in normal-functioning BAVs,[21] and as such, precede the development of stenosis in these patients, exposing the aortas of patients with BAV to more prolonged hemodynamic perturbations compared with patients with TAV. Although we found clear differences in aortic dimensions, the lack of data completeness introduces a potential source of error. Although aortic root dimensions were well reported, sinotubular junction and proximal ascending aortic dimensions were poorly reported in both groups, and so we make these observations with some degree of caution. Overall, the differing echocardiographic profiles in BAV and patients with TAV-AS were mostly replicated in age-specific subanalyses, indicating that these findings are likely to be present independent of the age differential between the 2 groups being studied.

Age- and sex-adjusted 1-year, 5-year, and overall mortality were significantly lower in the BAV-AS cohort, with the difference in overall mortality persisting in age-specific subanalyses, further supporting that this mortality difference is observed independent of age. Previous studies have shown that patients with BAV have similar long-term survival compared with the general population.[22,23] Thus, the significantly increased age-adjusted mortality risk in patients with TAV-AS was disproportionate to that expected. The higher average right ventricular systolic pressure and lower left ventricular ejection fraction of the TAV-AS group were also included as covariates, but despite this, the adjusted mortality risk remained higher in the TAV-AS group. Other than mortality data from the National Death Index linkage, clinical data outside that which is regularly included in echo reports are not available in the NEDA, and as such, we were unable to study the effect of any commonly associated comorbidities. However, we postulate that the higher adjusted mortality risk in the TAV-AS group may be attributed to significant coexisting morbidities, which is expected given their substantially older age. Furthermore, Kang et al recently demonstrated that in patients with severe AS (61% of whom had BAV), early surgery conferred significant operative and cardiovascular mortality benefit compared with a watchful-waiting approach.[24] In our study, a significantly higher proportion of patients with BAV-AS underwent subsequent AVR, and so this higher rate of intervention may also contribute to our finding of better survival in BAV-AS subjects, compared with those with TAV-AS.

Study Limitations

Although a rigorous approach has been taken in this study to use the NEDA with the highest possible accuracy, the nature of this database does introduce some limitations. A significant number of patients were excluded from analysis, first, when AV morphology was not specified, and second, when there was no mean AV pressure gradient recorded. With respect to the former, we were not able to assume that the AV was tricuspid if it was simply not specifically noted to be bicuspid, and consequently, more than half of the echo studies were excluded at this step. However, the age and sex distribution of these excluded patients did not differ in a clinically significant way to the included patients with AV morphology, which provides some reassurances that their exclusion is unlikely to have introduced significant biases. In the BAV versus TAV AS part of the study, a further one-third of patients with BAV and two-thirds of patients with TAV were excluded because of lack of mean AV pressure gradient recording. For this comparison, we believe that exclusion because of lack of MG data is unlikely to have introduced a systematic bias, because this limitation is likely to apply equally to both BAV-AS and TAV-AS groups. Furthermore, these excluded patients, although marginally younger than those who were included, demonstrated lower mortality risks, and as such, their exclusion is unlikely to have introduced any underestimation in mortality outcome analyses. The lack of data on valve morphology and MG does, however,

provide important information about real-world echocardiography practices.

For this study, we analyzed only the first echo study for each patient and excluded information from any serial studies (other than to infer the presence of later AVR). In real-world practice, inter- and intraobserver variability can lead to inconsistent identification of AV morphology, both within single or multiple echo study reports. Furthermore, transthoracic echocardiography has imperfect specificity and sensitivity for diagnosing BAV.[25] In the NEDA, there is no mechanism by which reported valve morphology can be confirmed, and as such, the text extraction process of identifying patients with BAV or TAV may have led to some inaccuracies. To confirm the accuracy of valve morphology identification, we performed a sensitivity analysis limited to high-volume academic centers, because it has been shown that diagnostic accuracy is higher in these settings.[25] Studies from these academic centers comprised 28.5% of the original data set; the percentage of studies in whom AV morphology was specified was slightly lower compared with the original analysis (36.6% compared with 41.8%). However, the proportion of studies in which a BAV was identified was marginally higher, with an estimated incidence of 2.6% (compared with 1.8% in the original analysis). Thus, although our real-world observations suggest that over 60% of studies might not have the AV morphology specified across most clinical settings, the sensitivity analysis supports our estimated incidence of BAV. We also acknowledge that unicuspid AVs may have been incorrectly diagnosed as BAVs and consequently included in our BAV cohort. However, unicuspid valves are rare, with an incidence of just 0.5%,[26] and as such this is unlikely to have significantly affected our main findings.

We acknowledge the limitation of using MG to assess the severity of AS, which may be inaccurate in the presence of left ventricular dysfunction. Of the patients with either a BAV or TAV morphology identified, 81.1% and 84.5% had a left ventricular ejection fraction reported, respectively. The great majority of patients in both groups had normal (>50%) left ventricular ejection fractions (91.3% BAV, 86.8% TAV). Of the remaining patients with left ventricular dysfunction, some with significant AS may have been misclassified and consequently omitted from our analysis. Because the proportion of subjects with good left ventricular systolic function was similar in the BAV and TAV groups, this is unlikely to have introduced any systematic error in our main findings.

On aortic dilatation, as discussed above, there was a significant proportion of patients in whom no aortic dimensions were recorded, especially above the aortic root. Furthermore, as previously discussed, we do not have clinical data on any potential comorbidities in patients, which might have substantially affected their survival. We also have no recorded information concerning commonly associated conditions such as Turner's syndrome, Marfan's syndrome, or hypertension, which could contribute to aortic disease and its complications. The ascertainment of later AVR is incomplete, because it relied on subsequent echocardiograms rather than on national surgical databases. Finally, the NEDA only includes adults who have undergone echocardiography. However, as with all other study methods (with the exception of autopsy studies), patients who are never diagnosed with BAV during their lifetime are not captured in this patient cohort.

CONCLUSIONS

This study, to our knowledge, is the largest series of adults with BAV yet reported and extends our understanding of this complex and heterogeneous disease by providing contemporary insights into the incidence of BAV-related valvulopathy and aortopathy at the time of echo diagnosis, across the broad spectrum of disease severity, and in a large cohort of community-based patients with BAV. Moderate-to-severe AS was significantly more prevalent in adults with BAV compared with TAV. These patients were over 2 decades younger, had a higher prevalence of concomitant aortic regurgitation, and had significantly larger ascending aortas. Despite this, adjusted survival outcomes appeared better in patients with BAV-AS compared with those with TAV and AS.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S3

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Supplemental Material

Table S1. Basic demographics comparing adults with and without an aortic valve mean gradient (AV MG) recorded.

	AV MG recorded n = 116 857	**AV MG not recorded** n = 147 302	
Age (years)	65 (51 - 76)	60 (45 - 72)	< **0.001**
Sex - male	63 072 (54.0%)	73 149 (49.7%)	< **0.001**
1-year mortality		OR 0.81 (0.79 – 0.84)	< **0.001**
5-year mortality		OR 0.72 (0.70 – 0.74)	< **0.001**
Overall Mortality		HR 0.71 (0.70 – 0.72)	< **0.001**

Results are presented as median (interquartile range), n (%), odds ratio (95% confidence interval), or hazard ratio (95% confidence interval). 1-year mortality analysis included 115,992 with AV MG and 145,049 without AV MG recorded. 5-year mortality analysis included 72,178 with AV MG and 89,440 without AV MG recorded. AV – aortic valve, HR – hazard ratio, MG – mean gradient, OR – odds ratio.

Table S2. Age-specific sub-analyses comparing the echocardiographic profiles of BAV-AS to TAV-AS patients aged ≤65 years and those aged >65 years.

	PATIENTS AGED ≤ 65 YEARS			**PATIENTS AGED > 65 YEARS**		
	BAV-AS n = 807	**TAV-AS** n = 529		**BAV-AS** n = 305	**TAV-AS** n = 3848	
Age (years)	52 (40 – 59)	60 (53 – 65)	**< 0.001**	72 (68 – 78)	81 (75 – 86)	**< 0.001**
Sex - Male	585 (72.5%)	352 (66.5%)	**0.02**	194 (63.6%)	2174 (56.5%)	**0.02**
LVEF (%)	65 ± 11	61 ± 13	**< 0.001**	63 ± 14	60 ± 13	**< 0.001**
RVSP (mmHg)	37 ± 12	40 ± 12	**< 0.001**	41 ± 10	43 ± 13	**0.04**
Aortic regurgitation			**0.016**			0.21
None	239 (38.4%)	188 (47.4%)		93 (40.1%)	1377 (46.2%)	
Mild	156 (25.0%)	93 (23.4%)		90 (38.8%)	1111 (37.2%)	
Moderate	140 (22.5%)	79 (19.9%)		44 (19.0%)	445 (14.9%)	
Severe	88 (14.1%)	37 (9.3%)		5 (2.2%)	50 (1.7%)	
Aortic Stenosis						
MG (mmHg)	32 (25 – 44)	31 (24 – 44)	0.09	32 (25 – 46)	31 (24 – 42)	**0.009**
Peak V (m/s)	3.70 (3.29 – 4.30)	3.63 (3.24 – 4.25)	0.26	3.70 (3.20 – 4.41)	3.65 (3.27 – 4.20)	0.31
Aortic Dimensions (mm)						
Aortic Root	35 ± 6	33 ± 5	**< 0.001**	37 ± 6	33 ± 4	**< 0.001**
STJ	34 ± 7	29 ± 4	**< 0.001**	38 ± 7	27 ± 4	**< 0.001**

Ascending Aorta	37 ± 8	35 ± 5	< **0.001**	36 ± 9	35 ± 5	0.09
Subsequent AVR	315 (39.0%)	180 (34.0%)	0.06	92 (30.2%)	847 (22.0%)	**0.001**

Results are expressed as mean ± standard deviation, median (interquartile range), or n (%). For the ≤65 years sub-analysis, in the BAV-AS and TAV-AS groups respectively, data were available for LVEF in 716 (88.7%) and 427 (80.7%), for RVSP in 416 (51.5%) and 215 (40.6%), for aortic regurgitation 623 (77.2%) and 397 (75.0%), for peak velocity 760 (94.2%) and 493 (93.2%), for aortic root dimension 687 (85.1%) and 416 (78.6%), for STJ dimension 289 (35.8%) and 91 (17.2%), and for ascending aorta dimension in 331 (41.0%) and 196 (37.1%). For the >65 years sub-analysis, in the BAV-AS and TAV-AS groups respectively, data were available for LVEF in 258 (84.6%) and 3091 (80.3%), for RVSP in 205 (67.2%) and 2388 (62.1%), for aortic regurgitation 232 (76.1%) and 2983 (77.5%), for peak velocity 280 (91.8%) and 3592 (93.3%), for aortic root dimension 258 (84.6%) and 2952 (76.7%), for STJ dimension 99 (32.5%) and 691 (18.0%), and for ascending aorta dimension in 109 (35.7%) and 1552 (40.3%).

Table S3. Age-specific Cox Proportional Hazards Models in patients aged ≤65 years, and patients aged >65 years.

	Patients aged ≤ 65 years				Patients aged > 65 years			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
BAV vs TAV	0.26 (0.19 – 0.35)	< **0.001**	0.32 (0.21 – 0.48)	**<0.001**	0.47 (0.39 – 0.56)	< **0.001**	0.69 (0.54 – 0.88)	**0.002**
Age (yrs)	1.07 (1.05 – 1.09)	< **0.001**	1.05 (1.02 – 1.07)	**0.001**	1.08 (1.07 – 1.09)	< **0.001**	1.08 (1.07 – 1.09)	**<0.001**
Sex - male	0.92 (0.68 – 1.25)	0.607	0.87 (0.59 – 1.30)	0.51	0.98 (0.90 – 1.07)	0.68	1.08 (0.97 – 1.20)	0.19
Mean gradient	0.993 (0.984 – 1.002)	0.108	0.996 (0.985 – 1.008)	0.51	1.000 (0.997 – 1.003)	0.92	0.999 (0.996 – 1.003)	0.684
Increasing AR severity	0.81 (0.69 – 0.96)	**0.014**	1.00 (0.84 – 1.20)	0.97	1.10 (1.04 – 1.16)	**0.002**	1.06 (0.99 – 1.13)	**0.09**
LVEF	0.987 (0.974 – 0.999)	**0.038**	0.995 (0.981 – 1.009)	0.50	0.978 (0.975 – 0.981)	**<0.001**	0.980 (0.976 – 0.984)	**<0.001**

892 patients (BAV 569, TAV 323) are included in the multivariate analysis of patients aged ≤65 years. 2,602 patients (BAV 197, TAV 2,405) are included in the multivariate analysis of patients aged >65 years. AR – aortic regurgitation, BAV – bicuspid aortic valve, CI – confidence interval, HR – hazard ratio, LVEF – left ventricular ejection fraction, TAV – tricuspid aortic valve.