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ORIGINAL RESEARCH

SURGERY

Clinical Outcomes in Patients With Bicuspid Aortic Valves and Ascending Aorta ≥50 mm Under Surveillance

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ABSTRACT

BACKGROUND Clinical outcomes of bicuspid aortic valve (BAV) patients with ascending aortic diameters ≥50 mm who are under surveillance are poorly defined.

OBJECTIVES The purpose of this study was to assess clinical outcomes in BAV patients with ascending aorta ≥50 mm.

METHODS Multicenter retrospective cohort study of BAV adults with ascending aorta diameters ≥50 mm by transthoracic echocardiography (TTE). Patients were categorized into 50 to 54 mm and ≥55 mm groups. Clinical outcomes were aortic dissection (AoD), aorta surgery, surgical mortality, and all-cause death.

RESULTS Of 875 consecutive BAV patients (age 60 ± 13 years, 86% men, aortic diameter 51 mm [interquartile range (IQR): 50-53 mm]), 328 (37%) underwent early surgery ≤3 months from index TTE. Of the remaining 547 patients under surveillance, 496 had diameters 50 to 54 mm and 51 had diameters ≥55 mm and were collectively followed for 7.51 (IQR: 3.98-12.20) years. Of 496 patients with diameters 50 to 54 mm under surveillance, 266 (54%) underwent surgery 2.0 (IQR: 0.77-4.16) years from index TTE. AoD occurred in 9/496 (1.8%) patients for an incidence of 0.4 cases per 100 person-years, surgical mortality was 5/266 (1.9%); and ≥moderate aortic stenosis (but not aorta size) was associated with all-cause death, hazard ratio: 2.05 (95% CI: 1.32-3.20), $P = 0.001$. Conversely, in 547 total patients under surveillance (including 50-54 mm and ≥55 mm), both aorta size and ≥moderate aortic stenosis were associated with all-cause death (both $P \leq 0.027$). AoD rate in patients ≥55 mm under surveillance was 5.9%.

CONCLUSIONS In BAV patients with ascending aorta 50 to 54 mm under surveillance, AoD incidence is low and the overall rates of AoD and surgical mortality are similar, suggesting clinical equivalence between surgical and surveillance strategies. Conversely, patients with aortas ≥55 mm should undergo surgery. Aortic stenosis is associated with all-cause death in these patients. (JACC Adv 2023;2:100626) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AA = tubular ascending aorta

AoD = aortic dissection

AS = aortic valve stenosis

AR = aortic valve regurgitation

BAV = bicuspid aortic valve

CI = confidence interval

HR = hazard ratio

TTE = transthoracic echocardiography

Aortic dilation is common in patients with bicuspid aortic valve (BAV)[1-3] and represents a risk factor for aortic dissection (AoD), which carries high mortality.[4] Although the risk of AoD in BAV patients has been reported ≤1%,[1,2] it is 8 times higher than the general population and increases with larger ascending aortic size.[2,5] Although aortic dimeter has limitations in predicting AoD,[6] current BAV aorta guidelines are mostly size-based.[7-9] The optimal ascending aorta cutoff for prophylactic aorta surgery in BAV has been the subject of debate, initially based on recommendations for Marfan syndrome patients.[10,11] However, compared to Marfan patients, individuals with BAV and aortic dilatation are less likely to develop AoD and have better outcomes, such that the risk of AoD in BAV patients is closer to that of patients with tricuspid aortic valves.[12,13] Therefore, since 2016, the recommended Class I aorta surgery indication cutoff for BAV is the same as the general population;[7,9] the American College of Cardiology/American Heart Association 2016 update and 2022 guidelines[7] defined a diameter of ≥55 mm as a Class I aorta surgery indication and a diameter of 50 to 54 mm as Class II, considering the presence of AoD-related risk factors, patient surgical risk, and expertise of the surgical team/institution. While the cutoff of ≥55 mm is universal,[7-9] the surgical zone between 50 and 54 mm remains the subject of debate and uncertainty,[7-9,14] and there is no data exploring the balance between AoD risk and surgical risk in these patients.

Assessing the clinical value of these diameter cutoffs is a difficult task given the uncommon and deadly nature of AoD, and prospective studies would require large patient samples with many years of follow-up; thus, retrospective cohort studies are important for its assessment.[1,2] The primary goal of our study was to evaluate clinical outcomes of patients within the BAV aorta surgical zone (ie, ≥50 mm), particularly within the Class II zone of surgical uncertainty (50-54 mm) where most debate persists for patients under surveillance. For this purpose, we performed a multicenter study to assess incident AoD, incident aorta surgery, surgical mortality, and all-cause death in BAV patients with ascending aortic diameter ≥50 mm under surveillance.

METHODS

STUDY POPULATION. This is a multicenter study including one entire US health care system, 5 European medical centers, and one Argentinian medical center. Consecutive patients were included by each center; specific years of data inclusion by center are presented in Supplemental Table 1. Inclusion and exclusion criteria are detailed in **Figure 1**. We retrospectively identified 897 consecutive BAV patients with aortic root or tubular ascending aorta (AA) ≥50 mm at index transthoracic echocardiography (TTE) (ie, the first TTE measurement of root or AA diameter ≥50 mm), with native BAV, native aorta (prior coarctation repair accepted), without history of AoD, and without known genetic syndrome. To ascertain outcomes (incident AoD, incident aorta surgery, and death), we required patients to have aorta surgery status and death status available until December 2020. Therefore, we excluded 4 patients with AoD detected at the index TTE, 2 patients with unknown alive/dead status, and 16 patients with unknown aorta surgery status. Therefore, 875 patients were included in the final analysis (732 [84%] from the U.S., 121 [13%] from Europe, and 22 [3%] from Argentina) (Supplemental Table 1). Of them, 154 patients had a diameter ≥55 mm at index TTE, and 721 patients had a diameter 50 to 54 mm at index TTE. Of 721, 225 (31%) patients had aorta surgery ≤3 months from index TTE (early surgery), and 496/721 (69%) remained "under surveillance" and constituted the focus of our main analysis (**Figure 1**). All institutional review boards approved the study.

DATA COLLECTION AND SURGICAL INDICATIONS. All patients underwent comprehensive 2D and Doppler TTE assessment, clinical assessment, and follow-up at their respective institutions. Diagnoses of BAV were made based on parasternal short-axis views by experienced echocardiographers. Cardiac function, valve function, and aorta size were assessed according to published guidelines.[15-17] The root and AA were measured at end-diastole perpendicular to the long axis of the aorta using the leading-edge-to-leading-edge method.[17] Comorbidities, family history of AoD or aortic aneurysm, and medication use were obtained through medical chart review. Indications for aorta surgery were defined by current

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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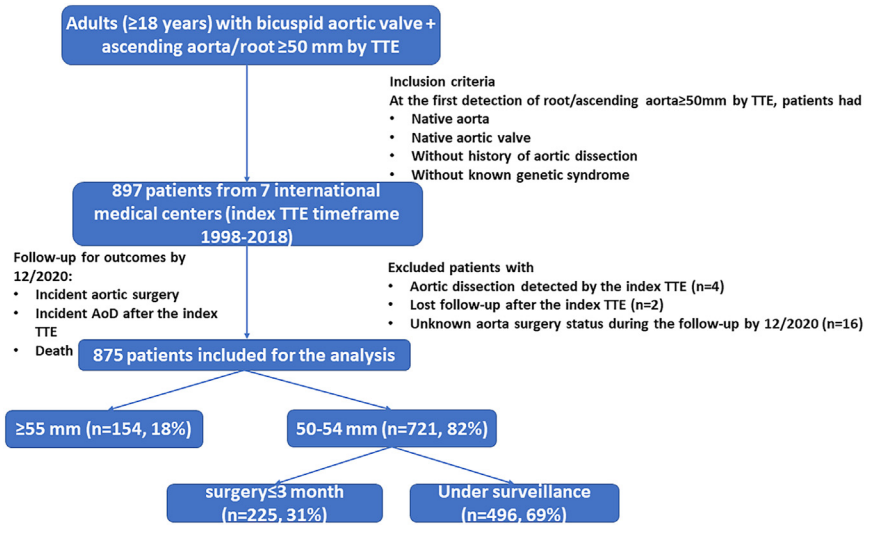
FIGURE 1 Study Flow Chart



AoD = aortic dissection; TTE = transthoracic echocardiography.

recommendations[7-9]: Class I indication if the root or AA diameter was ≥55 mm; and Class II if the root or AA diameter was 50 to 54 mm. In those with diameters 50 to 54 mm, we classified surgical indications as follows: aneurysm only; aneurysm plus severe aortic valve disease; aneurysm plus AoD-related risk factors; aneurysm plus mixed moderate aortic valve disease; and aneurysm plus other cardiac surgery. AoD-related risk factors were uncontrolled hypertension, family history of AoD, personal history of coarctation, aortic dilatation rate >3 mm/year, root ≥50 mm, predominant aortic regurgitation (AR).[7,8] Presurgical TTE aorta measurements were collected to assess presurgical aortic dilatation rates.

OUTCOMES ASCERTAINMENT. Aorta surgery was agreed upon by patient-physician shared decision under existing guidelines at the time. Incident aorta surgery (root and/or AA replacement during follow-up), AoD, and death were ascertained from medical records or death certificates or by phone calls to the patients or relatives. Outcomes were last ascertained in December 2020.

To identify all possible AoD in deceased patients without aorta surgery, we ascertained cause of death in all unoperated patients. AoD was diagnosed by imaging studies, surgery, autopsy, or death certificate. Since AoD is the most common cause of sudden death due to BAV aortopathy and its incidence increases in BAV patients with >45 mm diameters,[2] we considered all sudden deaths as "possible AoD". All-cause and cause-specific death information was ascertained from the medical record and/or death certificates. Surgical mortality was defined as death <30 days after aorta surgery.

STATISTICAL METHODS. Data were expressed as mean (SD) or median (interquartile range [IQR]) for continuous variables and as number (percentages) for categorical variables. Patients were divided into 3 groups based on their maximal aortic diameter and early-surgery or under-surveillance status: 1) maximal aortic diameter ≥55 mm; 2) maximal aortic diameter 50 to 54 mm with early surgery; and 3) maximal aortic diameter 50 to 54 mm under surveillance. Comparisons between groups were assessed by ANOVA t-test or Pearson chi-squared test when appropriate. Cox proportional hazards regression analysis was used to assess risk factors for: 1) aorta surgery; and 2) all-cause death in patients under surveillance. Fine and Gray proportional subdistribution hazards regression model was used to assess risk factors for AoD to account for competing risk of death. No adjustment was made for the analysis of AoD risk due to limited number of AoD events. To assess the incidence of AoD in native aortas, we censored patients at AoD, aorta surgery, last follow-up, or death in unoperated patients. Risk for AoD and all-cause death was calculated as number of

TABLE 1 Clinical and Echocardiographic Characteristics at Index TTE (Total Cohort n = 875)

	Aorta ≥55 mm (n = 154)	Aorta 50-54 mm Early-Surgery (n = 225)	Aorta 50-54 mm Under Surveillance (n = 496)	*P* Value
Clinical characteristics				
Age, y	60 ± 13	57 ± 13	61 ± 13	<0.001
Men	129 (88%)	200 (86%)	423 (85%)	0.60
Body mass index, kg/cm^2 (N = 855)	30.4 ± 6.5	28.7 ± 5.3	28.9 ± 5.6	0.01
Hypertension	71 (49%)	88 (38%)	249 (50%)	0.006
Hypercholesterolemia	50 (34%)	82 (35%)	197 (40%)	0.30
Diabetes mellitus	13 (9%)	20 (9%)	51 (10%)	0.70
Nonsmoker	58 (40%)	118 (51%)	292 (59%)	<0.001
Atherosclerotic cardiovascular disease	23 (16%)	38 (16%)	71 (14%)	0.80
Chronic kidney disease	6 (4%)	11 (5%)	32 (6%)	0.40
History of coarctation	4 (3%)	6 (3%)	12 (2%)	1.00
Family history of aortic aneurysm or aortic dissection	6 (4%)	11 (5%)	34 (7%)	0.30
Medications				
Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blocker	36 (25%)	51 (22%)	160 (32%)	0.008
Beta-blocker	46 (32%)	78 (33%)	157 (32%)	0.90
Statin	35 (24%)	65 (28%)	157 (32%)	0.20
Echocardiographic features				
LV end-diastolic diameter, mm (N = 853)	55 ± 11	54 ± 11	53 ± 8	0.10
LV end-systolic diameter, mm (N = 785)	37 ± 10	35 ± 9	34 ± 7	0.01
LV ejection fraction, % (N = 874)	57 ± 11	61 ± 8	60 ± 10	0.002
Aortic stenosis				<0.001
None	50 (34%)	81 (35%)	234 (47%)	
Mild	41 (28%)	44 (19%)	124 (25%)	
≥Moderate	55 (38%)	108 (46%)	138 (28%)	
Aortic regurgitation				0.07
None/trivial	46 (32%)	70 (30%)	190 (38%)	
Mild	57 (39%)	95 (41%)	198 (40%)	
≥Moderate	43 (29%)	68 (29%)	108 (22%)	
BAV-subtype				0.50
Right-left-fusion	114 (74%)	175 (78%)	394 (79%)	
Right-noncoronary-fusion	25 (16%)	35 (16%)	58 (12%)	
Left-noncoronary-fusion	4 (3%)	3 (1%)	14 (3%)	
Indeterminate	11 (7%)	12 (5%)	30 (6%)	
Tubular ascending aorta diameter, mm (N = 872)	57 ± 5	50 ± 4	50 ± 4	<0.001
Aortic root diameter, mm (N = 859)	47 ± 8	43 ± 6	44 ± 6	<0.001
Maximal aortic diameter, mm	58 ± 4	51 ± 2	51 ± 2	<0.001
Aorta dilatation type at the index TTE				<0.001
Only root ≥50 mm	13 (9%)	25 (11%)	85 (17%)	
Only AA ≥50 mm	102 (66%)	188 (84%)	395 (80%)	
Both root and AA ≥50 mm	39 (25%)	12 (5%)	16 (3%)	
Maximal aortic cross-sectional area/height >10 cm^2/m for root or >13 cm^2/m for AA (N = 855)	143 (95%)	61 (27%)	147 (31%)	<0.001
Maximal aortic diameter/height >32 mm/m	78 (52%)	8 (3%)	25 (5%)	<0.001

Values are mean ± SD or n (%). Atherosclerotic cardiovascular disease: presence of any of coronary artery disease, cerebrovascular disease or peripheral artery disease.
BAV = bicuspid aortic valve; LV = left ventricular; TTE = transthoracic echocardiography.

events per 100 person-years, based on the maximal aortic diameter at index TTE. All tests were 2-sided, with a *P* value of <0.05 considered statistically significant. Data were analyzed using JMP 14 (SAS Institute Inc).

RESULTS

PATIENT CHARACTERISTICS. In a total of 875 patients, mean age was 60 ± 13 years, 86% were men, maximal aorta size was 51 mm [IQR 50-53], and most

(78%) had AA ≥50 mm. **Table 1** depicts clinical and echocardiographic characteristics of patients grouped by surgical triggers (surgical indication class) I vs II and early surgery status: Patients with diameter ≥55 mm, diameter 50 to 54 mm with early surgery, and diameter 50 to 54 mm without early surgery. Patients with diameters 50 to 54 mm undergoing early surgery were the youngest, with least hypertension, and had more ≥moderate aortic stenosis (AS) and more right-left cusp fusion BAV than other groups (all $P \leq 0.006$). In turn, patients with diameter of 50 to 54 mm without early surgery were more likely to be nonsmokers, more frequently had hypertension, and had less ≥moderate aortic stenosis or regurgitation (all $P < 0.001$). In all 3 groups, AA dilatation ≥50 mm was most common (66%-84%). Patients with diameter ≥55 mm at index TTE more often had both root and AA dilatation (25%) than the other groups ($P < 0.001$). Family history of aneurysm, or AoD, and personal history of coarctation were comparable between the 3 groups. Percentages of patients with a maximal aorta size/height >32 mm/m (considered high risk)[18] and maximal aortic cross-sectional area/height >10 cm^2/m for the root or >13 cm^2/m for the AA.[14] were higher in patients with diameter ≥55 mm than the other 2 groups.

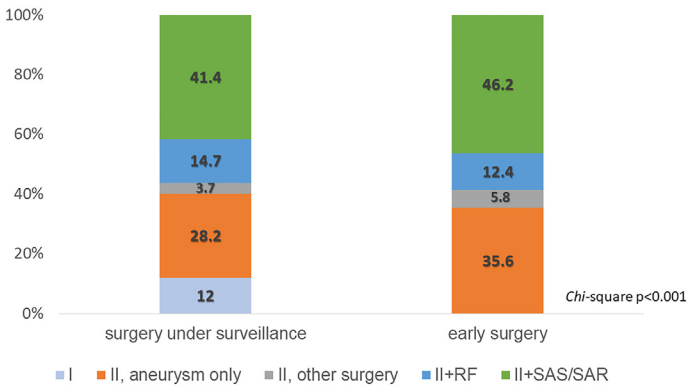
FOLLOW-UP. For the entire cohort (n = 875), follow-up was 7.77 (IQR: 4.20-12.04) years. For 547 total patients under surveillance (including diameters ≥55 mm and 50-54 mm), follow-up was 7.51 (IQR: 3.98-12.20) years. For 496/547 patients with diameters 50 to 54 mm under surveillance, follow-up was 7.26 (IQR: 3.91-12.06) years, and 398/496 patients (80%) had TTE during follow-up.

INCIDENT AORTA SURGERY AND SURGICAL INDICATIONS. For the entire cohort (n = 875), 634/875 (72%) patients underwent early surgery (≤3 months from index TTE) or surgery under surveillance. Frequencies of early surgery were 67% in patients with diameters ≥55 mm and 33% in patients with diameters 50 to 54 mm ($P < 0.0001$). Of 154 patients with diameter ≥55 mm at index TTE, 93% underwent aorta surgery early or under surveillance, and 7% remained unoperated. Of 721 patients with diameters 50 to 54 mm at index TTE, 68% underwent aorta surgery early or under surveillance, and 32% remained unoperated.

Of these 721 patients, 225 underwent early surgery (**Figure 1**), with common surgical indications being aneurysm plus severe AS or AR (46.2%) and aneurysm alone in 35.6% (**Figure 2**). Of 496 patients with diameter 50 to 54 mm under surveillance, 266 (54%) had aorta surgery, median time to surgery 2.0 (IQR: 0.77-4.16) years. Of 266 operated patients, 212 (80%) had presurgery TTE evaluation, and presurgical aorta size was 52.6 ± 4.5 mm. At the time of surgery, 12% of aortic sizes had increased to ≥55 mm and therefore met Class I indications, but the most common indications were similar to the early surgery group: 41.4% aneurysm plus severe AS or AR and 28.2% aneurysm alone (**Figure 2**). A detailed account of surgical triggers in 721 patients with aortas 50 to 54 mm is presented in Supplemental Table 2. Risk factors for aorta surgery in 496 patients (50-54 mm under surveillance) are shown in **Table 2**, and include younger age, larger AA size, ≥moderate AS or AR, aorta dilatation rate >3 mm/year, and being a non-Mayo patient (all $P \leq 0.001$).

INCIDENT AoD VS SURGICAL MORTALITY. Of 496 patients with diameter 50 to 54 mm under surveillance, 5 confirmed AoD occurred during a median follow-up of 3.79 (IQR:1.76-9.43) years: 2 confirmed by both imaging and surgery (both patients survived), 2 confirmed by death certificate, and 1 confirmed by autopsy. Possible AoD (sudden death) occurred in 4

FIGURE 2 Surgical Indications for Patients With Diameters 50 to 54 mm Under Surveillance (n = 266) Vs Early-Surgery (n = 225)



RF = risk factors for aortic dissection; SAS = severe aortic stenosis; SAR = severe aortic regurgitation.

TABLE 2 Risk Factors for Aorta Surgery in Patients With Aorta Size of 50-54 mm Under Surveillance in Multivariable Analysis (n = 496)

	Risk Ratio (95% CI)	*P* Value
Age, y	0.98 (0.97-0.99)	<0.001
Maximal aorta size, mm	1.15 (1.04-1.27)	0.008
≥Moderate aortic stenosis	2.16 (1.64-2.85)	<0.001
Predominant aortic regurgitation	1.75 (1.25-2.45)	0.001
Growth rate>3 mm/y	2.95 (1.98-4.41)	<0.001
Mayo clinic vs non-Mayo clinic	0.61 (0.45-0.81)	<0.001

TABLE 3 Risk Factors for All-Cause Death in Multivariable Analysis

Diameters 50-54 mm	HR (95% CI)	P Value
Age, y	1.04 (1.03-1.07)	<0.001
Body mass index, g/m^2	0.95 (0.90-0.99)	0.033
Aorta surgery	0.23 (0.15-0.38)	<0.001
Nonsmoker	0.50 (0.33-0.76)	<0.001
Atherosclerotic vascular disease	2.04 (1.27-3.23)	0.003
LV ejection fraction	0.98 (0.96-0.99)	0.001
≥Moderate aortic stenosis	2.05 (1.32-3.20)	0.001
Diameters 50-54 mm and ≥55 mm		
Age, y	1.04 (1.02-1.06)	<0.001
Body mass index, g/m^2	0.95 (0.91-0.99)	0.019
Aorta surgery	0.23 (0.15-0.35)	<0.001
Nonsmoker	0.51 (0.34-0.75)	<0.001
Atherosclerotic vascular disease	1.92 (1.23-2.93)	0.003
LV ejection fraction	0.98 (0.96-0.99)	0.002
≥Moderate aortic stenosis	2.07 (1.39-3.10)	<0.001
Aorta size	1.08 (1.00-1.15)	0.027
Diabetes	1.86 (1.04-3.15)	0.028

Upper 496 patients with diameters 50-54 mm under surveillance; lower 547 total patients under surveillance, including those 50-54 mm and ≥55 mm.
LV = left ventricular.

unoperated patients. Therefore, 9 confirmed plus possible AoD occurred in the surveillance 50 to 54 mm group (n = 496), resulting in a total AoD rate of 1.8%. Of 266/496 surgeries under surveillance, 5 patients died <30 days after surgery for a surgical mortality of 1.9%.

When evaluating all patients under surveillance (**Figure 1**), total confirmed plus possible AoD occurred in 12 out of 547 patients (including both ≥55 mm and 50-54 mm groups), for an AoD rate of 2.2%. Of the 306/547 surgeries under surveillance, 6 patients died <30 days after surgery, for a surgical mortality of 2%.

RISK FACTORS FOR AoD. Of 496 patients with diameters 50 to 54 mm under surveillance, 9 patients with confirmed plus possible AoD had no difference in mean aortic size at index TTE vs patients without AoD (51.3 ± 1.5 vs 51.0 ± 1.2 mm, $P = 0.40$), and aorta size and maximal aortic cross-sectional area/height were not associated with AoD (both $P \geq 0.40$). Conversely, of 547 total patients under surveillance (including ≥55 mm and 50-54 mm groups), 12 with confirmed plus possible AoD had larger mean aortic size at index TTE vs patients without AoD (53.4 ± 4.0 mm vs 51.5 ± 2.1 mm, $P = 0.005$). In univariable analysis of these 547 patients, for each mm increase of aorta size, there was 20% increase in AoD risk (HR: 1.20, 95% CI: 1.05-1.38, $P = 0.006$) (Supplemental Figure 1). Lower body mass index (HR: 0.89, 95% CI: 0.81-0.97, $P = 0.008$) and being a non-Mayo patient (HR: 6.25, 95% CI: 1.92-20.0, $P = 0.002$) were associated with increased AoD risk.

RISK FACTORS FOR ALL-CAUSE DEATH. Risk factors for all-cause death in 496 patients with diameters 50 to 54 mm under surveillance were age, surgery, smoking, atherosclerotic heart disease, left ventricular ejection fraction, and ≥moderate AS (**Table 3**), but aortic size and maximal aortic cross-sectional area/height were not associated with all-cause death (both $P \geq 0.10$). In 547 total patients under surveillance (including both ≥55 mm and 50-54 mm), risk factors for all-cause deaths were identical, but diabetes and aortic size became significant (**Table 3**). Specific outcomes for 154 patients with diameter ≥55 mm are depicted in Supplemental Table 3. In 496 patients with AA diameters 50 to 54 under surveillance or 547 patients under surveillance including both 50 to 54 mm and ≥55 mm, Mayo Clinic patients had similar risk for all-cause death compared to non-Mayo Clinic patients ($P = 0.289$ and 0.851, respectively).

AoD AND ALL-CAUSE DEATH RISK BY AORTA SIZE GROUPS. Of 547 total patients under surveillance (including both ≥55 mm and 50-54 mm), 120 died (22%). Total follow-up of patients with native aortas was 2,415.5 person-years. Risk for AoD (per 100 person-years) in 547 patients by diameters 50 to 54 mm, 55 to 59 mm, and ≥60 mm at the index TTE was 0.4 (95% CI: 0.18-0.77), 0.7 (95% CI: 0.02-4.06), and 3.8 (95% CI: 0.46-13.67), respectively, and risk for all-cause death (per 100 person-years) was 4.6 (95% CI: 3.74-5.56), 8.7 (95% CI: 4.51-15.26) and 11.4 (95% CI: 4.17-24.70), respectively (**Figure 3**).

CHARACTERISTICS AND CLINICAL OUTCOMES OF PATIENTS WITH ROOT VS NONROOT ANEURYSM. Of the entire cohort (n = 875), 190 (22%) had root size ≥50 mm at index TTE. Patient characteristics by root vs nonroot aneurysm are presented in Supplemental Table 4. Root aneurysm patients were more commonly men, more frequently had history of coarctation and family history of aortic aneurysm or AoD, and had more ≥moderate AR (all $P \leq 0.03$).

Prevalence of patients with root vs nonroot aneurysms were 43% vs 36% in those receiving early surgery, 26% vs 38% in those receiving surgery under surveillance, and 32% vs 26% in those without surgery ($P = 0.009$). One patient with root ≥50 mm had AoD confirmed by autopsy. In the entire cohort (n = 875), all-cause mortality at 10-years was similar between root vs nonroot aneurysm groups, analyzed separately in operated and unoperated patients (both $P \geq 0.20$). Similarly, root aneurysm was not associated with AoD ($P = 0.17$). Of patients with diameters 50 to 54 mm and under surveillance (n = 496),

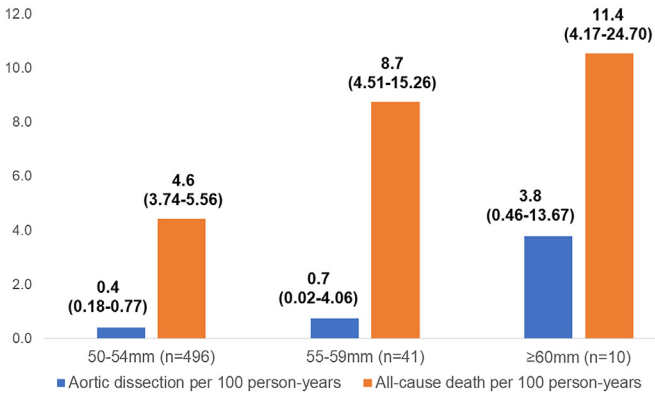
all-cause mortality at 10-years was also similar between root vs nonroot aneurysm, analyzed separately in operated and unoperated groups (both $P \geq 0.30$).

DISCUSSION

To the best of our knowledge, this study addresses for the first time patient-important outcomes in BAV patients with ascending aortas ≥50 mm (surgical zone). Our principal findings in 496 BAV patients with 50 to 54 mm aortic diameters under surveillance are (**Central Illustration**): 1) the most common surgical indications in our study were aneurysm plus severe AS or AR and aneurysm alone; risk factors for aorta surgery were younger age, larger AA size, ≥moderate AS or AR, and aorta dilatation rate; 2) incidence of AoD was low at 0.4 cases per 100 person-years (54% had elective aorta repair with median time-to-surgery of 2 years); 3) in the centers included, AoD rate and aorta surgery mortality were similar at 1.8% and 1.9%, respectively; and 4) ≥moderate AS (but not aortic size) was associated with all-cause death. Principal findings for the entire cohort are: 1) in 547 total BAV patients under surveillance (both diameters ≥55 mm and 50-54 mm), aortic size was associated with risk for AoD, both aortic size and ≥moderate AS were associated with all-cause death; 2) the root aneurysm phenotype was not associated with AoD or all-cause death in unoperated patients, likely related to small dilated-root patient number; and 3) BAV patients with aortas ≥55 mm incurred high rates of AoD.

PREVIOUS STUDIES. In a single-center of excellence study of 1181 BAV patients with AA diameter of 50 ± 0.6 mm and root of 44 ± 0.8 mm followed for 3 years (380 under surveillance),[14] AoD occurred in 5.3%, with probability of AoD increasing at 50 mm (10 cm^2/m) for the root, and 53 mm (13 cm^2/m) for the AA. However, in over 80% of cases the aorta was already dissected at index imaging.[14] AoD may increase aortic size by 30%; [5,18] therefore, it is unknown whether their proposed surgical thresholds are accurate under surveillance. In our study, the maximal aortic cross-sectional area/height >10 cm^2/m for the root or >13 cm^2/m for the AA was not associated with AoD and all-cause death as compared to Wojnarski et al.[14] The reason for this discrepancy may be that the prior study included a wide range of aortic measurements, while our group was limited to 50 to 54 mm. Also, the prior study found an unexpectedly high rate of 5.3% of AoDs in BAV patients. Our study including 496 patients under surveillance with 50 to 54 mm aortas and without dissection at index TTE, demonstrates for the first time a low incidence of AoD in this group (**Figure 3**), with similar overall rates of AoD and surgical mortality of approximately 2% in the real world, that is, multiple community centers and few large centers of excellence. Nonetheless, it is important to recognize that 54% of these patients underwent surgery during surveillance, and this likely reduced the AoD risk. In addition, 80% of these patients had dilatation of 50 to 54 mm of the AA and only 20% of the root, which has been associated with higher risk of AoD.[8,19] Interestingly, our study did not find any association between the root aneurysm and AoD or all-cause death, possibly due to few patients (ie, 20%) with root aneurysm phenotype. Reassuringly, risk factors for aorta surgery under surveillance were clinically rational and consistent with current recommendations,[7-9] **Table 2**. It is also important to recognize that the most common surgical indication within these 496 patients was aneurysm plus severe AS or AR, which highlights the fact that the BAV condition is a valvulo-aortopathy. Indeed, in all patients under surveillance (both diameters ≥55 mm and 50-54 mm), both valvulopathy (ie, ≥moderate AS) and aortic diameter were associated with all-cause death, **Table 3**. Therefore, valvular heart disease guidelines[15,16] should be carefully followed regardless of aortic size, but especially in those with diameters ≥50 mm, to ensure timely surgery.

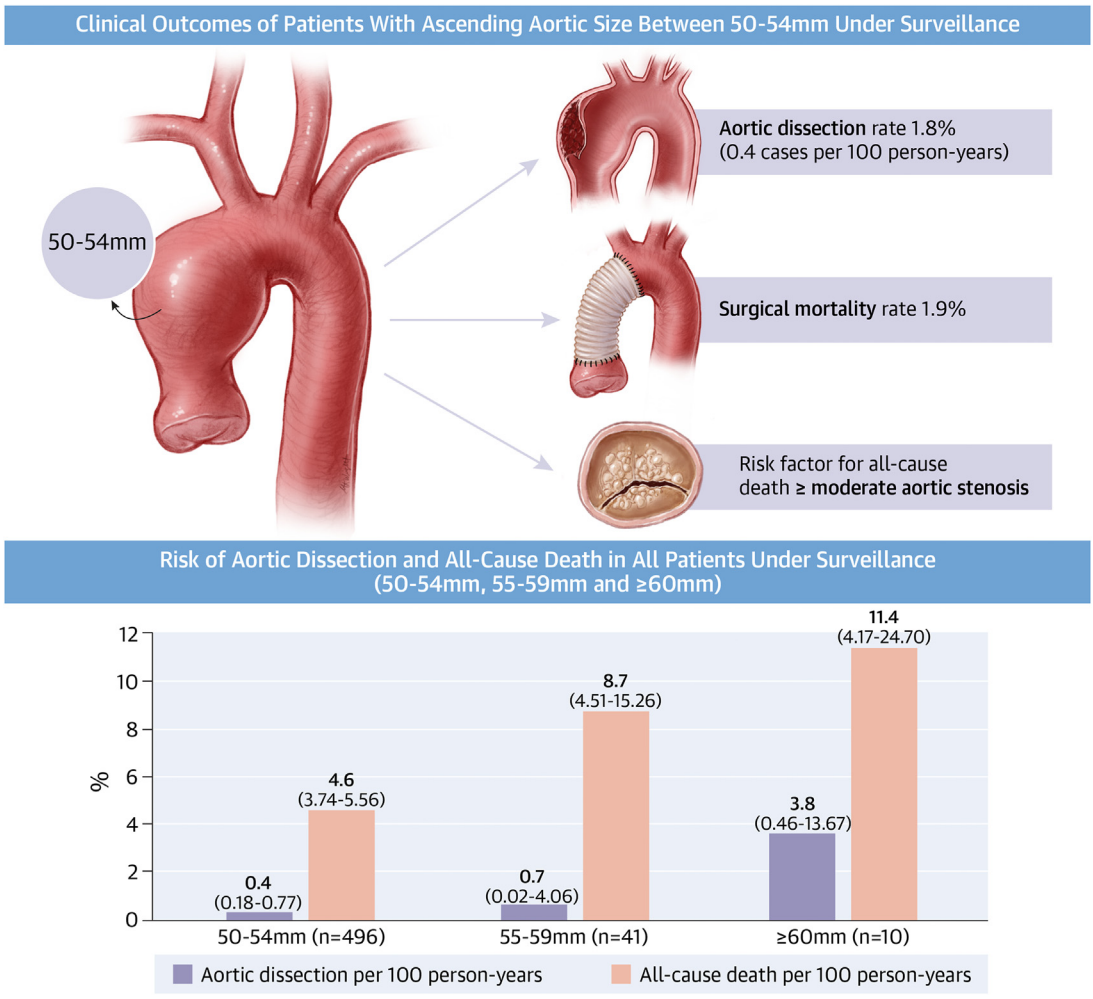
FIGURE 3 Risk of Aortic Dissection and All-Cause Death in 547 Patients Under Surveillance, Grouped by Maximal Aortic Diameters 50 to 54 mm, 55 to 59 mm, and ≥60 mm at Index TTE



Numbers reflect incident rate per 100 person-years (95% CI). TTE = transthoracic echocardiography.

CLINICAL IMPLICATIONS. Taken together, our results suggest that surveillance in BAV patients with ascending diameters of 50 to 54 mm is reasonable, as long as surgery under surveillance is carefully guided by recommended risk factors,[7-9] center-specific

CENTRAL ILLUSTRATION **Clinical Outcomes of BAV Patients With Ascending Aortas 50-54 mm**



Ye Z, et al. JACC Adv. 2023;2(8):100626.

Numbers in the lower panel reflect incident rate per 100 person-years (95% CI).

surgical risk, and valvulopathy progression. The BAV patient with aortic diameters 50 to 54 mm may choose a one-time risk of elective aortic surgery (1.9% operative death in this study) or a yearly risk of AoD (0.4% per person-year in this study) that is accumulative throughout subsequent years and increases with growing aortic size. With a 0.4% per person-year incidence of AoD and similar rates of AoD and surgical mortality (approximately 2% each), it appears that the BAV 50 to 54 mm zone is one of clinical equivalence, where AoD-risk factors and center-specific surgical risk may tilt the balance one way or the other. Definitive confirmation of whether early elective aorta surgery in the 50 to 54 mm zone is equivalent to surveillance in BAV patients requires a randomized trial that excludes patients with AoD-risk factors; the randomized controlled trial for Treatment in Thoracic Aortic Aneurysm: Surgery vs Surveillance (TITAN: SvS [NCT03536312])[20] has begun for that purpose.

STUDY LIMITATIONS. Patients were identified retrospectively, and therefore this study is susceptible to selection bias. Further bias may arise from retrospective adjudication of AoD occurrence; therefore, all centers performed exhaustive investigations into causes of death for each patient, including chart review, telephone calls to family members, and death certificate ascertainment. In addition, we counted both confirmed AoD and all sudden deaths as AoDs;

thus, there is a possibility that AoD cases are even lower than reported, but likely not higher. Due to the limited AoD events, we are not able to adjust AoD risk for confounders. A significant number of patients in this study (84%) came from a large U.S. health system; we included all eligible patients from the Mayo health care system to ensure our cohort was representative of real-world practice and to recruit the largest possible number of patients to be able to draw conclusions, given the uncommon nature of the AoD endpoint. This U.S. health care system included 3 major large referral centers and 31 smaller centers. Likewise, Spain contributed from 1 large referral center and 3 smaller centers. Therefore, the overall findings of this study are likely more representative of the large U.S. health system. The reliance on TTE instead of computed tomography or magnetic resonance represents a limitation of our study since these advanced imaging modalities are considered the gold standard for aorta size assessment.[21] Among 875 total patients with a root or ascending aorta ≥50 mm, 454 (61%) patients had concomitant CT/MR measurements at baseline; 77% had a concordant aortic root size (defined as ≥49 mm), and 80% had a concordant ascending aorta size. The remaining patients had nonconcordant measurements (≤48 mm by CT/MR). This is partly related to our study spanning 20 years, during which the recommendation for verifying large root/ascending aortic sizes with CT/MR were not routine. However, in the development of clinically important surgical thresholds from current guidelines,[7-9] including the 45 mm cutoff (derived from echocardiography data)[5,22] and the 50 mm and 55 mm cutoffs (derived from computed tomography and magnetic resonance but predominantly from echocardiographic data),[2,23,24] echocardiography has played a critical role. Furthermore, reassuringly, measurements of the ascending tubular aorta by TTE and computed tomography have shown excellent correlation and agreement with TTE[25,26] except for the root, which may be underestimated by TTE, particularly in BAV patients with right nonfusion[25,27]. Therefore, it is possible that some root measurements were underestimated in our study. Most of our patients did not have available TTE aorta measurements prior to aorta size reaching 50 mm; therefore, we were unable to ascertain aortic growth rates below 50 mm. The root aneurysm was not predictive of AoD or all-cause death, possibly because few dilatations (22%) ≥50 mm were of the root and because we only included patients with native BAV, and worse root outcomes have been reported after aortic valve replacement[19]. It follows that the results of this study are mostly applicable to patients with dilatation of the AA, which is by far the most common dilatation phenotype in BAV. The surgical mortality of approximately 2% represents multiple U.S. centers, several European centers, and 1 Argentinian center, and some single centers have reported lower risk[14]. Finally, we did not have genetic testing in these patients; hence, we could not identify patients with nonsyndromic heritable thoracic aortic aneurysm and dissection, which could have provided valuable insights into individualized surgical risk stratification.

CONCLUSIONS

In BAV patients with ascending aorta 50 to 54 mm under surveillance, AoD incidence is low (54% had elective aorta repair with median time-to-surgery of 2 years), and the overall rates of AoD and surgical mortality are similar, suggesting clinical equivalence between surgical and surveillance strategies. Conversely, patients with aortas ≥55 mm should undergo surgery. Aortic stenosis is associated with all-cause death in these patients.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In BAV patients with ascending aorta 50 to 54 mm under surveillance, AoD incidence is low and the overall rates of AoD and surgical mortality are similar, suggesting clinical equivalence between surgical and surveillance strategies. Conversely, patients with ascending aortas ≥55 mm should undergo surgery.

TRANSLATIONAL OUTLOOK: Confirmation of these observations requires a randomized trial of BAV patients with ascending aortas 50 to 54 mm randomized to surgery vs surveillance.

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KEY WORDS ascending aorta dilatation, bicuspid aortic valve, surgery, surveillance

APPENDIX For supplemental tables and a figure, please see the online version of this paper.