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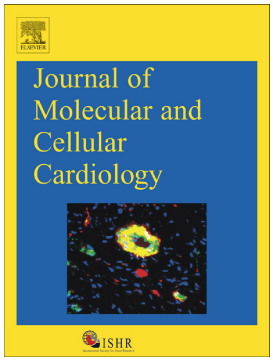

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Patterns of Ascending Aortic Dilatation and Predictors of Surgical Replacement of the Aorta: A Comparison of Bicuspid and Tricuspid Aortic Valve Patients over Eight Years of Follow-Up

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ABSTRACT:

Background: Predictors of thoracic aorta growth and early cardiac surgery in patients with bicuspid aortic valve are undefined. Our aim was to identify predictors of ascending aorta dilatation and cardiac surgery in patients with bicuspid aortic valve (BAV).

Methods: Forty-one patients with BAV were compared with 165 patients with tricuspid aortic valve (TAV). All patients had LV EF > 50%, normal LV dimensions, and similar degree of aortic root or ascending aorta dilatation at enrollment. Patients with more than mild aortic stenosis or regurgitation were excluded. A CT-scan was available on 76% of the population, and an echocardiogram was repeated every year for a median time of 4 years (range: 2 to 8 years). Patterns of aortic expansion in BAV and TAV groups were analyzed by a mixed-effects longitudinal linear model. In the time-to-event analysis, the primary end point was elective or emergent surgery for aorta replacement.

Results: BAV patients were younger, while the TAV group had greater LV wall thickness, arterial hypertension, and dyslipidemia than BAV patients. Growth rate was 0.46 ± 0.04 mm/year, similar in BAV and TAV groups (p=0.70). Predictors of cardiac surgery were aorta dimensions at baseline (HR 1.23, p= 0.01), severe aortic regurgitation developed during follow-up (HR 3.49, p 0.04), family history of aortic aneurysm (HR 4.16, p 1.73), and history of STEMI (HR 3.64, p < 0.001).

Conclusions: Classic baseline risk factors were more commonly observed in TAV aortopathy compared with BAV aortopathy. However, it is reassuring that, though diagnosed with aneurysm on average 10 years earlier and in the absence of arterial hypertension, BAV patients had a relatively low growth rate, similar to patients with a tricuspid valve. Irrespective of aortic valve morphology, patients with a family history of aortic aneurysm, history of coronary artery disease, and those who developed severe aortic regurgitation at follow-up, had the highest chances of being referred for surgery.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality in adults, and is estimated to be present in 0.5% to 1.5% of the population. Though survival among patients with BAV is similar to that of the general population, there is a greater incidence of cardiac and aortic complications in these patients[1-3].

An important non-valvular association with BAV is the development of ascending thoracic aortic dilatation[4,5]. We have shown that hemodynamic factors such as shear stress play a key role in the pathophysiology of aneurysm dilatation[6-8], distinct pathogenetic mechanisms occur with BAV[9]. Moreover, patients with BAV have been shown to have larger aortic diameters than controls[10]. Yet, very few studies have addressed the progression of ascending aortic dilatation in BAV patients with respect to those with a tricuspid aortic valve (TAV) and comparable aortic size at baseline[11].

Therefore, we investigated the progression pattern of ascending aortic dilatation by assessing the influence of predisposing factors, such as aortic valve morphology and its variation at follow-up using both clinical and echocardiographic variables. Specifically, we aimed to test whether growth curve trajectories of the aortic diameter differ in BAV patients versus TAV patients, and to identify independent predictors of surgery for ascending aortic dilatation.

METHODS

Study Population

One thousand three-hundred forty-two consecutive (1,342) patients from our outpatient clinic and referred for elective surgery for ascending aortic dilatation from 2000 to 2017 at our institute were retrospectively reviewed for recruitment. Inclusion criteria were left ventricular ejection fraction (LV-EF) > 50 %, maximal aortic diameter indexed to BSA > 2.1 cm/m^2, and echocardiographic follow-up with at least 2 examinations 1 year apart. Exclusion criteria at

baseline were evidence of uncontrolled stage II/III hypertension (blood pressure > 160/95 mmHg); LV dilatation, as defined by LV end-diastolic diameter ≥ 55 mm; more than moderate mitral or tricuspid valve disease; previous history of cardiac surgery; acute and chronic aortic dissections; aortic dilatation associated with significant congenital or acquired cardiac diseases (i.e., untreated or recurrent aortic coarctation), or genetic screening positive for systemic syndromes (i.e., Marfan, Loeys-Dietz, Ehler-Danlos, Turner). However, a family history of aortic aneurysm was not an exclusion criterion. The study was approved by our Institutional Research Review Board.

After exclusions, a total of 206 patients comprised the study group, with available data at baseline and follow-up. Standard demographic, clinical, and echocardiographic data were collected, as well as chest CT measurements of the aorta when available (N=156, 76%, with no missing data for the echocardiographic imaging) at each follow-up visit.

Echocardiography

Transthoracic echocardiograms were analyzed de novo and then reviewed by a reader blinded to clinical outcomes (D.B.). All echocardiographic examinations were performed with a commercially available instrument (Vivid E90 System; Vingmed, General Electric, Milwaukee, Wisconsin). Standard LV systolic and diastolic parameters from 2D and Doppler echocardiography were acquired and measured, as previously described[12].

Severity of aortic stenosis was graded by integration of Doppler methods, continuity equation, and planimetry. Aortic regurgitation (AR) degree was defined as composite evaluation of proximal jet vena contracta, pressure half-time of the regurgitant jet, diastolic reverse flow duration and end-diastolic maximal velocity in ascending thoracic aorta, and LV end-diastolic dimension[13, 14]. BAV was defined as a systolic fish-mouth appearance of the orifice in parasternal short-axis views[15].

The aorta was measured twice (leading-edge to leading-edge method) by bidimensional imaging[16] in parasternal long-axis views at the root (maximal dilation of the sinuses of Valsalva)

and ascending aorta at the maximal diameter. The tubular tract was routinely visualized at least 2 to 3 cm distal to the sino-tubular junction (STJ).

Outcome measures

Aortic growth rate was defined as the difference between the diameter at presentation and the diameter at baseline in-hospital admission, divided by the follow-up time interval in years. The primary end point was surgical operation of the aorta and/or aortic valve for elective referral as assessed by hospital chart review (100% completeness of data). Patients admitted for emergent aortic surgery or with acute aortic dissection were excluded by study design. Mortality data were obtained from review of medical records or observation of death certificate with subsequent confirmation from a family member. Cardiovascular death due to aortic rupture occurred in one patients while noncardiac deaths were observed in three patients (ie, two malignancies and one hepatitis). Emergent surgical repair of aneurysmal aorta was observed in one patient treated out of our hospital institution.

Statistical Analysis

Initially, two-way repeated measures analysis of variance (time-group interaction) was performed using STATA version 15.1 (Stata-Corp LP, College Station, TX). The two groups stratified according to aortic valve morphology (BAV vs TAV) were the between-subjects factor (group), while the repeated measurements of the aorta during follow-up were the within-subjects factor (time). A Greenhouse–Geisser correction was used for sphericity[17]. This was done for aortic size evaluations as well as demographic, clinical, and echocardiographic measures within and between patients with either BAV or TAV. One-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison tests was done to test change from baseline within each group. Unpaired two-sided Student's t-test or a Fisher's exact test were used to a) compare baseline conditions of BAV versus TAV patients and b) compare groups

stratified according to clinical indication (patients referred for surgery vs. patients not referred to surgery).

Subsequently, linear growth curve parameters of aortic root and ascending aortic dimensions measured yearly by echocardiography were estimated by a random-effects mixed model, implemented in R Software, version 3.3.4 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/)[18]. Model selection was based on Akaike's information criterion[19].

Finally, univariate as well as multivariable time-to-event analysis by Cox proportional-hazards models was done to assess prognostic usefulness of demographic, clinical, and echocardiographic measures in defining risk for surgery. Given the longitudinal design of our study, most of collected variables changed over time during follow-up, and such time-varying (or time-dependent) covariates were accounted for when included in the Cox regression analysis[20]. At the beginning, the proportional hazards assumption was tested by examining the residuals of each model so that, for each time-dependent covariate, two different values of hazard ratio (and relative p-value) were obtained. The first referred to the "main effect," and was therefore the prognostic significance of the covariate considering its value at baseline as in a standard Cox analysis. The second hazard ratio (and p-value) was the "time-varying effect," and was the prognostic significance of the change over time of predictors determining primary outcome[21]. Multivariable survival analysis was done with stepwise mixed (backward and then forward) strategy, including predictors with p-value ≤ 1.0 according to simple survival analysis.

RESULTS

Demographic, Clinical and Echocardiographic Characteristics of the Study Population

Out of 206 patients included in this study, 165 patients (80%) had TAV, while BAV was found in 41 patients (20%). Ascending aortic replacement was performed in 30 patients (15%) at a median follow-up of 5 years in the range of 2-13 years from initial screening.

Patient demographics are summarized in **Table 1**. At baseline hospital admission, BAV patients were significantly younger than TAV patients (57±12 years for BAV, and 69±9 years for TAV, p-value<0.001). Though biometrics, blood pressure, and heart rate were comparable between groups at both baseline and serial evaluations, the baseline measurement of LV wall thickness of the anteroseptum was larger in TAV patients with respect to BAV patients. Prevalence of arterial hypertension, dyslipidemia, and mild-to-moderate mitral regurgitation at enrollment of TAV patients was higher than that of BAV patients. LVEF and LV dimensions/volumes, as well as trans-mitral flow measures were comparable between the groups at both baseline in-hospital admission and surveillance imaging.

With regard to aortic sizes (**Table 2**), initial in-hospital measurements of both aortic root and ascending aortic dimensions were high by study design, but there was no statistically significant difference in the mean values between BAV and TAV patient groups (i.e., 45.3±3.5mm for BAV-related ascending aortic diameter vs. 45.8±3.8mm for TAV-related ascending aortic diameter, p=0.70, and 39.5±6.4mm for BAV-related aortic root diameter vs. 41.4±5.6mm for TAV-related aortic root diameter). During serial evaluation, aortic dilatation increased significantly in both groups similarly, so that interaction of group by time was not significant (**Figure 1**).

Linear Growth Models: Aortic Aneurysm Progression over Time

For the entire study population, a linear mixed model with time as single predictor (as both fixed and random effect) showed that the ascending aorta dilated at a growth rate = 0.46 ± 0.04 mm / year, with an average rate of 1.33 ± 0.04% / year for the whole follow-up time. The actual growth rate per year was high at the first and second year (2.5%) then decreased steadily from third year to end of follow-up as shown by **Table 2** and **Figure 2**. Similar growth rates were found when analysis was repeated for BAV patients versus TAV patients (average growth rate = 1.4% for TAV patients, and 1.2% per year for BAV patients). When considering time, the model with the highest fit to observed data was a quadratic polynomial linear growth model that

included time and squared time (time^2) as both fixed and random effects (**Table 3a**). The inclusion of aortic valve morphology (i.e., grouping variable) did not improve prediction (p-value = 0.44).

When demographic, clinical and echocardiographic variables were added one by one to the unconditional model, ascending aortic dimensions at baseline (p-value < 0.001), development of moderate-to-severe aortic regurgitation during follow-up (β = 3.81 ± 0.67, p-value < 0.001), LV wall thickness of the anteroseptum (β = 0.16 ± 0.06, p-value 0.006), use of a β-blocker (at any effective dosage, β = -0.61± 0.30 p-value 0.03), and use of aspirin (100 mg PO daily, β = 0.60 ± 0.30 p-value 0.04) were all significant predictors of change in aortic dimensions during surveillance.

Finally, according to multivariable analysis done by forcing both time and time^2 into the model, ascending aortic diameter at baseline, development of severe aortic regurgitation during follow-up, and the use of a β-Blocker were the only independent predictors of aortic dimensions over time (Table 3b).

Predictors of Cardiac Surgery

During the study period, aortic replacement was performed in 4 patients (10%) with BAV, and 26 patients with TAV (16%, p-value=0.46).

At baseline, patients referred for surgery had greater aortic dimensions independent of aortic valve morphology at either root level or ascending tubular tract compared with non-surgically-treated patients (**Table 4**). In addition, patients referred for surgery had higher LV end-diastolic dimensions (index), and greater prevalence of moderate-to-severe aortic regurgitation developed during follow-up compared with patients who did not undergo surgery. Surgically-treated patients had also higher proportion of family history of aortic aneurysm, greater prevalence of coronary artery disease (specifically history of ST elevation myocardial infarct) compared with non-surgically treated patients. Most importantly, patients referred for surgery

developed moderate-to-severe mitral regurgitation during follow-up, and used a higher proportion of beta-blocker more frequently than the non-surgical group.

Table 4 shows hazard ratios and p-values for simple (univariate) Cox analysis. BAV patients had a significantly lower risk of being referred for surgery compared with TAV patients, as shown in **Figure 3**. On the other hand, patients with lower body surface area, greater dimensions of aortic root (index), ascending aorta, as well as LV at baseline had the greatest risk of being referred for surgery. Likewise, patients who developed severe aortic regurgitation during follow-up, and those with a family history of aortic aneurysm, ischemic cardiomyopathy, ST elevation myocardial infarct, transitory ischemic attack, or pacemaker / ICD implant, had the highest chances of undergoing surgical repair of dilated aorta. Considering time-varying covariates, change in aortic dimensions during follow-up, as well as change in LV wall thickness or LV dimensions during follow-up did not modify risk of being referred for cardiac surgery.

According to multivariable analysis, independent predictors of cardiac surgery referral for aortic replacement were as follows: aortic root, as well as ascending aorta dimensions at recruitment (HR 1.23, p 0.01 and HR 1.38 p-value < 0.001, respectively), severe aortic regurgitation developed during follow-up (HR 3.49, p-value = 0.04), family history of aortic aneurysm (HR 4.16, p-value = 0.03), and history of ST elevation myocardial infarct (HR 3.64, p-value < 0.001).

DISCUSSION

To the best of our knowledge, this is the first study to describe progression of ascending thoracic aortic aneurysms in stable outpatients with chronic aortic aneurysm to compare differences between BAV and TAV patients and, at the same time, to identify independent factors to consider for referring this population for surgery of dilated aorta.

The principal findings of this investigation are here described: 1) ascending aortic dilatation measurements at baseline and growth rates of aortic size in a time range of 8 years were comparable between TAV and BAV patients; yet, BAV patients were younger and free of

cardiovascular risk factors aortas compared with TAV patients; 2) the aorta dilated primarily in the first 2 years after diagnosis, then reached a plateau, and remained substantially stable over the 8-year follow-up period; 3) β-blocking therapy was associated with the progression of aortic dilatation, apparently reducing growth rate, and 4) aortic dimensions at baseline, family history of aortic aneurysm, and the development of severe aortic regurgitation or an ST elevation myocardial infarct during follow-up, but not the aortic valve morphology itself, were the most important predictors of aortic replacement in the long term.

In healthy adults, aortic diameter does not usually exceed 40 mm, and is variably influenced by several factors, including age, gender, body size, and blood pressure. Overall, the rate of ascending aortic progression in our study population was 0.5 mm per year, that is, slightly more than 1% per year. These data are reassuring, and consistent with previous reports focused on either TAV [22, 23] or BAV patients [11, 24, 25].

High blood pressure is a well-known risk factor for the development of aortic dilatation, and it is not surprising that patients with TAV and aortic aneurysm had increased LV wall thickness compared with dilated aorta with BAV. On the other hand, though BAV patients had aortic enlargement similar to that of TAV at baseline, this was not associated with arterial hypertension, dyslipidemia or other known cardiovascular risk factors. Indeed, the larger aortic diameters in patients with BAV may be a result of longer periods of exposure to increased aortic shear stress in patients born with a congenital anomaly, as opposed to acquired disorders, such as hypertension or atherosclerosis. Looking at growth trajectories grouped according to valve morphology, the aorta expanded in both groups, with a similar trend. However, diagnosis of aortic dilatation in BAV occurred 10 years earlier than in TAV. Therefore, in the BAV group, other factors, including altered hemodynamics secondary to abnormal valve morphology or genetic predisposition leading to a defect in the aortic wall structure may have dramatically influenced the progression of aortic dilatation, and are definitely more influential than standard risk factors[26].

It is also noteworthy that yearly growth rate was highest in the first 2 years (i.e., 2.5% at 1-year follow-up, and 1% at 2-year follow-up), but then decreased substantially from the third year on, reaching a plateau (0.2% and 0.7% at the 8th year for TAV and BAV, respectively), thereby justifying the use of a quadratic polynomial model to best describe the trajectory of aortic enlargement.

This favorable trend is significantly different from that observed in other congenital aortopathies, such as Marfan syndrome or degenerative aortopathy[11], and is likely influenced by several factors, among which a timely established therapy. In fact, according to our analysis, beta-blockers were the only drug to have a significant effect on modifying aortic enlargement over time. This protective effect of beta-blocking has been found in specific groups of patients with aortic aneurysms, for example in the setting of Marfan syndrome[27 28], and though our data seem to confirm the role of beta-blockers in delaying or even preventing aortic expansion independent of aortic valve morphology, at this time a causal effect involving such medication can only be hypothesized, due to the retrospective nature of this study. It is also possible to speculate that the beneficial effect provided by beta-blockers could act differently in TAV patients compared with BAV patients: in the former group, arterial hypertension is a primary risk factor for aneurysm enlargement, and therapy with beta-blockers can help in preventing high blood pressure peaks. Beta-blockers could be beneficial even in younger patients with BAV but without arterial hypertension, providing a well-recognized cardio-protective action and reducing hemodynamic loads induced by the development of valvulopathies during the life course (i.e., aortic stenosis or aortic regurgitation), which are common in these patients.

Considering the predictors of referral for surgery for aortic repair, it is not surprising that aortic dimensions at diagnosis (either at root or at tubular ascending level) were among the most significant and independent determinants of adverse outcome. It is interesting to note that changes in the aortic size at follow-up in our population were negligible; in fact, patients who were not referred for surgical replacement within the first 2 years of diagnosis underwent

cardiac surgery for super-imposed cardiac comorbidities, including the development of severe aortic regurgitation (requiring valve surgery) or coronary artery disease, and STEMI in particular (requiring coronary-artery bypass graft). Once the indication for surgery was given, replacement of the ascending aorta is usually (and understandably) performed to prevent risk of new surgery after some time. This secondary repair of the aorta is quite common, and consistent with most recent guidelines[29]. It is also reassuring that patients with no cardiac pathologies beyond aortic enlargement have a reduced risk of undergoing surgery after the first 2 years from diagnosis. These findings reflect a general change toward a more conservative approach to BAV-associated aortopathy compared with previous guidelines, which stated that such patients should be managed as aggressively as those with connective tissue disorders[30].

Avadhani et al. highlighted the association between aortic valve disease and high growth rate at follow-up, specifically in BAV patients[24]. Furthermore, Della Corte et al. suggested that aortic stenosis would be a protective factor of aortic root enlargement, at the same time exposing the patient to mid-ascending aorta to dilatation[31], while a recent study by Evangelista et al. of 852 patients with BAV found that significant aortic regurgitation at baseline was associated with enlarged aortic root, but not with ascending aorta dilatation[32]. These above-mentioned findings cannot be corroborated by our investigation since by study design our population did not include patients with moderate to severe valvulopathy at baseline. However, as found in Evangelista et al. we can confirm that BAV patients have enlarged ascending aorta at baseline in the absence of significant aortic valve stenosis or regurgitation, and that the development of severe aortic regurgitation at follow-up is an independent predictor of both aortic enlargement during follow-up as well as referral for surgical repair, as reported by Della Corte et al.[25], and in our previous study[33].

Isolated enlargement of the aortic root was reported as an independent predictor of faster aortic expansion, specifically in BAV patients[25]. In our cohort, BAV patients had only a small enlargement of the aortic root compared with the TAV group, and the number of patients with an

isolated dilatation of the aortic root was too small to be analyzed separately. It may be that differences in the aortic root and mid-ascending aortic growths over time apply specifically to patients with a significant valve disease at baseline.

Though family history of an aortic aneurysm in our study population was not a predictor of the expansion rate of the aorta during follow-up, this was an independent predictor of surgery, being associated with a greater enlargement diagnosed at initial in-hospital admission. This finding highlights the significant role of a thorough family history in defining overall risk of surgery in patients with aortic aneurysms, and is consistent with the most recent guidelines[29,34]. Furthermore, we recently demonstrated how epigenetic (micro RNAs profiling) information can be used in this population[35] to discriminate the severity of ascending aortic dilatation from circulating blood. Therefore, we remark that a deeper work-up, including formal genetic and epigenetic screening for known mutations exposing the aorta to severe enlargement should be routinely performed in patients with aortic aneurysm at first diagnosis and, in particular, in those with BAV.

Study Limitations

Our study has several limitations. Baseline measurements of dilated aorta refer to the first echocardiogram (or CT scan) performed to reach a definitive diagnosis, and is therefore necessarily arbitrary. Since growth rates are computed from that specific time point, trajectories can be influenced by the time the patient entered the study. However, since we have completed a long-term follow-up (up to 13 years) the left truncation effect should be negligible. Such a study does not apply to patients with demonstrated genetic causes of aortic aneurysms, such as Marfan, Loeys-Dietz, Ehlers-Danlos, or Turner syndromes since the term “family history of aortic aneurysm” was general and not specific of the type of genetic disorders. Information on the BAV-related phenotype were not included in this study because other reports have demonstrated that leaflet orientation was not helpful in determining rate of aorta expansion[24]; moreover, subsetting groups of BAV patients into additional subgroups would have affected the

statistical power of the study. Though we collected aortic size measurement also by CT scan, these were not available for all patients, and just for one or two time points at follow-up, since echocardiographic surveillance is preferred over CT imaging. Moreover, also considering potential disagreement between the two imaging techniques[36,37], and in order to avoid likely inconsistencies, CT imaging was used solely to identify patients with a diagnosis of aortic aneurysm, but aortic dimensions were measured and analyzed exclusively by echo, either at baseline or at each follow-up visit. Our study was focused on patients with chronic and stable aneurysm of dilated aorta either with a TAV or BAV, who underwent regular follow-up, and were referred (or not) for elective cardiac surgery, so that findings cannot be applied to patients presenting with acute aortic dissection or requiring emergent surgery.

CONCLUSIONS

Pathophysiology of aortic aneurysm in BAV patients is substantially different from that observed in TAV patients, where classic risk factors such as arterial hypertension or dyslipidemia are of utmost importance. Though diagnosed with aneurysm on average 10 years earlier in the absence of arterial hypertension, BAV patients had relatively low growth rates, different from other congenital aortopathies and similar to TAV patients. Irrespective of aortic valve morphology, patients with a family history of aortic aneurysm, history of coronary artery disease, and those who developed severe aortic regurgitation during surveillance had the highest chances of being referred for surgical repair of the dilated aorta. To improve the clinical decision-making process, timely anti-hypertensive therapy in all patients with high blood pressure, preferably including a beta-blocker, specifically in patients with known aortic enlargement is highly recommended. Further prospective studies enrolling a larger sample of BAV patients, randomized to either placebo or beta-blocking therapy are warranted to confirm the protective effect of beta-blockers in this population, even in the absence of arterial hypertension.

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DISCLOSURE

All authors have not any financial or personal relationship that could cause a conflict of interest regarding this article.

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Table 1: Demographic, clinical, and echocardiographic characteristics

Variable	Group I (TAV)	Group II (BAV)	p-values (Repeated Measure ANOVA)			Longitudinal Mixed Effects Models		
Mean ± SD	(N = 165)	(N = 41)	Between Groups	Within Group (Time)	Between * Within	p-values	AIC	p-value per Group
Age (Years)	69 ± 9.4	57 ± 12.2	< 0.001	0.881	0.811	< 0.001	3584.6	0.05
Males (N (%))	139 (84)	34 (83)	0.8150			0.82	3623.5	0.41
Height (cm)	169.93 ± 8.1	172.71 ± 7.3	0.2151	0.968	0.988	0.61	3623.3	0.45
Weight (Kg)	82.32 ± 13.6	82.34 ± 15.2	0.9658	0.413	0.266	0.46	3623.0	0.40
BMI	28.44 ± 3.9	27.48 ± 4	0.3873	0.428	0.496	0.32	3622.5	0.45
BSA	1.92 ± 0.2	1.94 ± 0.2	0.5856	0.180	0.195	0.46	3623.0	0.39
Smoke (N (%))	22 (78.6)	6 (21.4)	0.8020			0.88	3623.5	0.41
Systolic Blood Pressure (mmHg)	130 ± 16.3	128 ± 15.5	0.6861	0.086	0.156	0.97	3623.5	0.41
Diastolic Blood Pressure (mmHg)	73.69 ± 12.3	75.15 ± 12.1	0.4491	0.831	0.556	0.17	3621.6	0.43
Heart Rate (bpm)	69.23 ± 13.9	74.42 ± 14.8	0.3429	0.967	0.891	0.61	3623.3	0.40
Previous Aortic Surgery (N (%))	26 (16)	4 (9.7)	0.4590			< 0.001	3595.1	0.63
Family History of Aortic Aneurysm (N (%))	29 (18)	7 (17)	1.0000			0.91	3623.5	0.41
Atrial Fibrillation (N (%))	11 (7)	1 (2.4)	0.4670			0.88	3623.5	0.40
Ischemic Cardiopathy (N (%))	4 (2)	1 (2.4)	1.0000			0.25	3622.2	0.41
Cardiomyopathy (N (%))	1 (0.6)	0 (0.0)	1.0000			0.11	3620.9	0.44
Chronic Kidney Disease (N (%))	2 (1.2)	0 (0.0)	1.0000			0.71	3623.4	0.42
Chronic Obstructive Pulmnary Disease (N (%)	3 (2)	1 (2.4)	1.0000			0.49	3623.0	0.41
Hypertension (N (%))	139 (87.4)	20 (49)	< 0.001			0.35	3622.7	0.59
Diabetes (N (%))	15 (9.1)	2 (4.4)	0.5340			0.09	3620.7	0.36
Dyslipidemia (N (%))	45 (28)	4 (8.2)	0.0230			0.84	3623.5	0.40
Implantable Cardioverter Defibrillator (N (%))	4 (2)	1 (2.4)	1.0000			0.22	3622.0	0.41
STEMI (N (%))	9 (5.4)	1 (2.4)	0.6900			0.44	3622.9	0.43
Stroke (N (%))	2 (1.2)	0 (0.0)	1.0000			0.75	3623.4	0.42
Statin (N (%))	54 (33)	9 (22)	0.2550			0.28	3622.3	0.45
ACE inhibitor (N (%))	108 (65)	18 (44)	0.0130			0.44	3622.9	0.46
Alpha-blocker (N (%))	9 (5.4)	5 (12)	0.1600			0.77	3623.4	0.42
Antiaggregant (N (%))	16 (9.7)	3 (7.3)	0.7710			0.77	3623.4	0.41
Anticoagulant (N (%))	17 (85.0)	3 (7.3)	0.7700			0.26	3622.3	0.43
Acetylsalicylic acid (N (%))	51 (83.6)	10 (24.4)	0.4520			0.04	3619.3	0.47
Beta blocker (N (%))	63 (87.5)	9 (22)	0.0670			0.03	3619.0	0.34
Calcium channel blocker (N (%))	43 (86.0)	7 (41)	0.3090			0.34	3622.6	0.44
Digoxin (N (%))	1 (0.6)	1 (2.4)	0.3590			0.51	3623.1	0.38
Diuretics (N (%))	27 (16)	4 (8.2)	0.3400			0.62	3623.3	0.42
Transient ischemic attack (N (%))	2 (1.2)	0 (0.0)	1.0000			0.25	3622.2	0.44
Ant-Septum Thickness (mm)	12.15 ± 1.7	10.21 ± 4.3	0.0007	0.656	0.816	0.01	3616.0	0.73
Posterior Wall Thickness (mm)	10.88 ± 3.9	10.43 ± 2.7	0.7336	0.590	0.798	0.52	3623.1	0.40
LV ED Diameter Index (mm/cm2)	24.45 ± 3.1	23.47 ± 3.4	0.5529	0.432	0.572	0.25	3622.2	0.43
LV ED Diameter (mm)	46.74 ± 5.9	45.18 ± 5.4	0.3006	0.484	0.714	0.17	3621.6	0.43
LV ED Volume Index (mL/cm2)	54.02 ± 13.6	53.51 ± 11.4	0.7211	0.087	0.558	0.67	3623.3	0.41
LV ED Volume (mL)	106.45 ± 27.7	103.99 ± 24.6	0.4592	0.169	0.458	0.48	3623.0	0.41
LV ES Volume Index (mL/cm2)	21.53 ± 8.2	21.07 ± 7.8	0.8847	0.093	0.855	0.18	3621.7	0.40
EF (%)	60.97 ± 4.6	60.74 ± 3.7	0.4769	0.337	0.095	0.70	3623.4	0.41
Mitral regurgitation (mild-moderate)	90 (88.2)	12 (11.8)	0.0050			0.98	3623.5	0.41
E wave Velocity (mt/sec)	0.45 ± 5.4	0.98 ± 4.7	0.6300	0.490	0.578	0.41	3622.8	0.42
A Wave Velocity (mt/sec)	0.18 ± 5.4	0.24 ± 5.6	0.9240	0.358	0.459	0.49	3623.0	0.42
E Wave Deceleration Time (msec)	237.48 ± 55.9	238.63 ± 54.5	0.2661	0.507	0.416	0.96	3623.5	0.41
E/A Ratio	1.26 ± 6.3	0.66 ± 2.6	0.7127	0.503	0.893	0.83	3623.5	0.40
Tricuspid regurgitation (mild-moderate) (N (%))	100 (83.3)	20 (16.7)	0.2150			0.14	3621.4	0.43

Table 2: Aortic dimensions by time and group

	Baseline	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	p-values Between Groups	p-values Within Group (Time)	p-values Between * Within
TAV												
Aortic Root	41.4 ± 5.6	42.4 ± 5.3	43 ± 5	43.9 ± 5.1	44.4 ± 4.8	44.6 ± 5.2	46.6 ± 5.1	46.7 ± 3.7		0.144	< 0.001	0.791
Growth Rate (%)		2.9 ± 6.8	1.1 ± 3.0	1.2 ± 2.5	0.7 ± 2.0	0.6 ± 2.9	-0.2 ± 0.8	0.5 ± 1.1				
Ascending Aorta	45.8 ± 3.8	46.8 ± 4.2	46.8 ± 3.6	47 ± 3.5	47.6 ± 3.7	47.7 ± 4.6	47.7 ± 4.4	47.7 ± 4.3		0.702	< 0.001	0.962
Growth Rate (%)		2.4 ± 8.1	1.0 ± 1.8	0.8 ± 1.9	0.7 ± 1.6	0.3 ± 0.7	0.1 ± 0.6	0.1 ± 1.0				
BAV												
Aortic Root	39.5 ± 6.4	40.2 ± 6.5	40.3 ± 6.6	40.2 ± 6.3	41.8 ± 4.7	41.9 ± 5.3	42 ± 5.3	42 ± 5.5	42.1 ± 5.7			
Growth Rate (%)		1.8 ± 3.4	1.6 ± 3.0	0.6 ± 1.7	0.8 ± 2.4	0.5 ± 2.0	0.0 ± 0.0	0.0 ± 0.0	1.9 ± 3.2			
Ascending Aorta	45.3 ± 3.5	46.2 ± 3.6	46.6 ± 3.1	46.9 ± 3.1	46.7 ± 2.7	47.6 ± 2.5	48.5 ± 1.7	48.7 ± 1.4	48.9 ± 1.1			
Growth Rate (%)		2.4 ± 4.6	1.0 ± 1.7	0.7 ± 1.6	0.6 ± 1.5	0.5 ± 1.1	0.5 ± 1.4	0.3 ± 0.8	0.2 ± 1.2			
Indexed values (mm / cm2)												
TAV												
Aortic Root	24.02 ± 2.83	24.6 ± 3.28	24.38 ± 2.71	24.47 ± 2.76	24.2 ± 2.2	24.22 ± 2.31	23.58 ± 1.9	23.19 ± 2.34		0.533	< 0.001	0.773
Ascending Aorta	24.02 ± 2.83	24.6 ± 3.28	24.38 ± 2.71	24.47 ± 2.76	24.2 ± 2.2	24.22 ± 2.31	23.58 ± 1.9	23.19 ± 2.34		0.533	< 0.001	0.773
BAV												
Aortic Root	23.56 ± 2.99	23.92 ± 3.08	24.2 ± 2.92	24.69 ± 3.29	24.27 ± 2.84	24.57 ± 3.03	26.21 ± 2.28	25.8 ± 3.02	26.38 ± 3.49			
Ascending Aorta	23.56 ± 2.99	23.92 ± 3.08	24.2 ± 2.92	24.69 ± 3.29	24.27 ± 2.84	24.57 ± 3.03	26.21 ± 2.28	25.8 ± 3.02	26.38 ± 3.49			

Table 3a: Unconditional Linear Growth Model, Fixed and Random Intercept, Time and Time2

Ascending Aorta Dimensions	β (Std.Err)	[95% Conf. Interval]	p-value
Intercept	45.7 (0.26)	45.16	< 0.001
Timewave	1.12 (0.23)	0.68	< 0.001
Timewavesqr	-0.13 (0.04)	-0.2	0

Table 3b: Final Multivariable Growth Model for Ascending Aorta Dilataton by Time

Predictor	β (Std.Err)	p-value
Aortic dimension at Baseline (mm)	45.68 (0.29)	< 0.001
Time	1.04 (0.15)	< 0.001
$Time^2$	0.05 (0.01)	< 0.001
β-Blockers	-0.6 (0.28)	0.04
Severe Aortic Regurgitation	4.07 (1.9)	0.03

Table 4: Study population characteristics: grouped by cardiac surgery

Variable (Mean ± SD)	No Surgery (N = 177)	Surgery (N = 30)	p-value	Main Effect HR	Main Effect p-value	Time-Varying Effect HR	Time-Varying Effect p-value
Age (years)	66.69 ± 11.04	69.14 ± 11.10	0.271	1.03	0.12		
Height (cm)	171.03 ± 7.96	167.10 ± 7.34	0.014	0.94	0.00		
Weight (kg)	82.78 ± 14.20	79.53 ± 11.92	0.244	0.98	0.09		
BMI	28.22 ± 3.98	28.43 ± 3.44	0.796	1.01	0.92		
BSA	1.93 ± 0.19	1.87 ± 0.16	0.085	0.10	0.02		
Systolic Blood Pressure (mmHg)	131.18 ± 15.85	123.93 ± 16.73	0.025	0.99	0.20		
Diastolic Blood Pressure (mmHg)	74.42 ± 12.19	71.36 ± 12.69	0.214	0.98	0.21		
Heart Rate (bpm)	70.40 ± 13.93	69.39 ± 15.97	0.722	0.99	0.43		
Ascending Aorta	45.36 ± 3.66	47.41 ± 3.78	0.006	1.50	< 0.001	1	0.13
Ascending Aorta Index	23.66 ± 2.78	25.53 ± 2.88	0.001	1.47	< 0.001	1	0.24
Aortic Root	41.17 ± 5.55	40.03 ± 7.25	0.331	1.00	0.93	1	0.98
Aortic Root Index	23.66 ± 2.78	25.53 ± 2.88	0.001	1.47	< 0.001	1	0.93
Ant-Septum Thickness (mm)	11.79 ± 2.74	11.60 ± 1.18	0.719	1.10	0.31	1	0.69
Posterior Wall Thickness (mm)	10.97 ± 3.33	9.73 ± 5.36	0.095	0.97	0.45	1	0.2
LV ED Diameter (mm)	46.26 ± 5.70	47.51 ± 6.38	0.283	1.03	0.33	1	0.42
LV ED Diameter Index (mm / cm2)	24.04 ± 3.00	25.56 ± 3.79	0.016	1.15	0.01	1	0.73
LV ED Volume (mL)	104.49 ± 28.49	101.45 ± 23.65	0.587	0.99	0.39	1	0.35
LV ED Volume Index (mL/cm2)	53.87 ± 13.49	54.18 ± 11.12	0.909	1.00	0.94	1	0.12
LV ES Volume Index (mL/cm2)	21.72 ± 7.72	19.70 ± 10.15	0.215	0.97	0.21	1	0.64
LV Ejection Fraction (%)	60.99 ± 4.32	60.52 ± 4.97	0.594	0.92	0.06	1	0.66
E wave Velocity (mt/sec)	0.76 ± 4.23	-0.66 ± 9.22	0.177	0.98	0.45		
A Wave Velocity (mt/sec)	0.05 ± 4.71	-0.31 ± 8.55	0.742	0.99	0.86		
E Wave Deceleration Time (msec)	239.52 ± 54.12	226.65 ± 63.12	0.248	1.00	0.59		
E/A Ratio	1.02 ± 5.63	1.83 ± 6.46	0.483	1.01	0.72		
Categorical Variables							
Male (N (%))	151 ± 85.8	22 ± 73.3	0.147	0.54	0.14		
Bicuspid Aortic Valve (N (%))	37 ± 21.0	4 ± 13.3	0.467	0.26	0.02		
Aortic Regurgitation (Mild-Moderate)	9 ± 5.1	5 ± 16.7	0.053	4.72	0.01		
Aortic Regurgitation			0.035				
Mild	122 ± 69.3	23 ± 76.7					
Moderate	8 ± 4.5	5 ± 16.7					
Severe	1 ± 0.6	0 ± 0.0					
Familiar (N (%))	25 ± 14.2	11 ± 36.7	0.006	3.08	0.00		
Atrial Fibrillation (N (%))	9 ± 5.1	3 ± 10.0	0.526	1.28	0.69		
Ischemic Cardiopathy (N (%))	2 ± 1.1	3 ± 10.0	0.023	3.03	0.07		
Cardiomiopathy (N (%))	0 ± 0.0	1 ± 3.3	0.314	49.46	< 0.001		
Chronic Kidney Disease (N (%))	1 ± 0.6	1 ± 3.3	0.674	5.85	0.09		
Chronic Obstructive Pulmonary Disease (N (%))	4 ± 2.3	0 ± 0.0	0.906	0.00	1.00		
Hypertension (N (%))	134 ± 76.1	25 ± 83.3	0.527	1.93	0.19		
Diabetes (N (%))	15 ± 8.5	2 ± 6.7	1	1.21	0.80		
Dyslipidemia (N (%))	40 ± 22.7	9 ± 30.0	0.527	1.58	0.24		
Implantable Cardioverter Defibrillator (N (%))	3 ± 1.7	2 ± 6.7	0.322	4.97	0.01		
STEMI (N (%))	4 ± 2.3	6 ± 20.0	<0.001	0.47	< 0.001		
Smoke (N (%))	24 ± 13.6	4 ± 13.3	1	0.55	0.86		
Statin (N (%))	53 ± 30.1	10 ± 33.3	0.889	0.40	0.36		
Stroke (N (%))	2 ± 1.1	0 ± 0.0	1	0.00	1.00		
Transient Ischemic Attack (N (%))	1 ± 0.6	1 ± 3.3	0.674	1.09	0.00		
Mitral Regurgitation (Mild-Moderate)	82 ± 46.6	20 ± 66.7	0.04	0.39	0.35		
Tricuspid Regurgitation (Mild-Moderate) (N (%))	100 ± 56.8	20 ± 66.7	0.417	0.41	0.08		
Ace Inhibitor (N (%))	107 ± 60.8	19 ± 63.3	0.951	0.41	0.37		
Alpha-Blocker (N (%))	13 ± 7.4	1 ± 3.3	0.672	0.74	0.94		
Antiaggregant (N (%))	16 ± 9.1	3 ± 10.0	1	0.61	0.52		
Anticoagulant (N (%))	15 ± 8.5	5 ± 16.7	0.29	0.50	0.20		
Acetylsalicylic Acid (N (%))	49 ± 27.8	12 ± 40.0	0.258	0.38	0.14		
Beta Blocker (N (%))	55 ± 31.2	17 ± 56.7	0.013	0.37	0.06		
Calcium Channel Blocker (N (%))	45 ± 25.6	5 ± 16.7	0.412	0.47	0.72		
Digoxin (N (%))	1 ± 0.6	1 ± 3.3	0.674	1.03	0.07		
Diuretics (N (%))	24 ± 13.6	7 ± 23.3	0.273	0.46	0.18		

Figure Legends

Figure 1: Ascending aorta dimensions (mm) by time in patients with tricuspid or bicuspid aortic valve, according to repeated measures ANOVA.

Figure 2: Trajectories of ascending aorta growth in patients with tricuspid or bicuspid aortic valve. Red line: superimposed polynomial quadratic linear growth model.

Figure 3: Kaplan-Meier survival estimates. Outcome: time to aorta replacement.

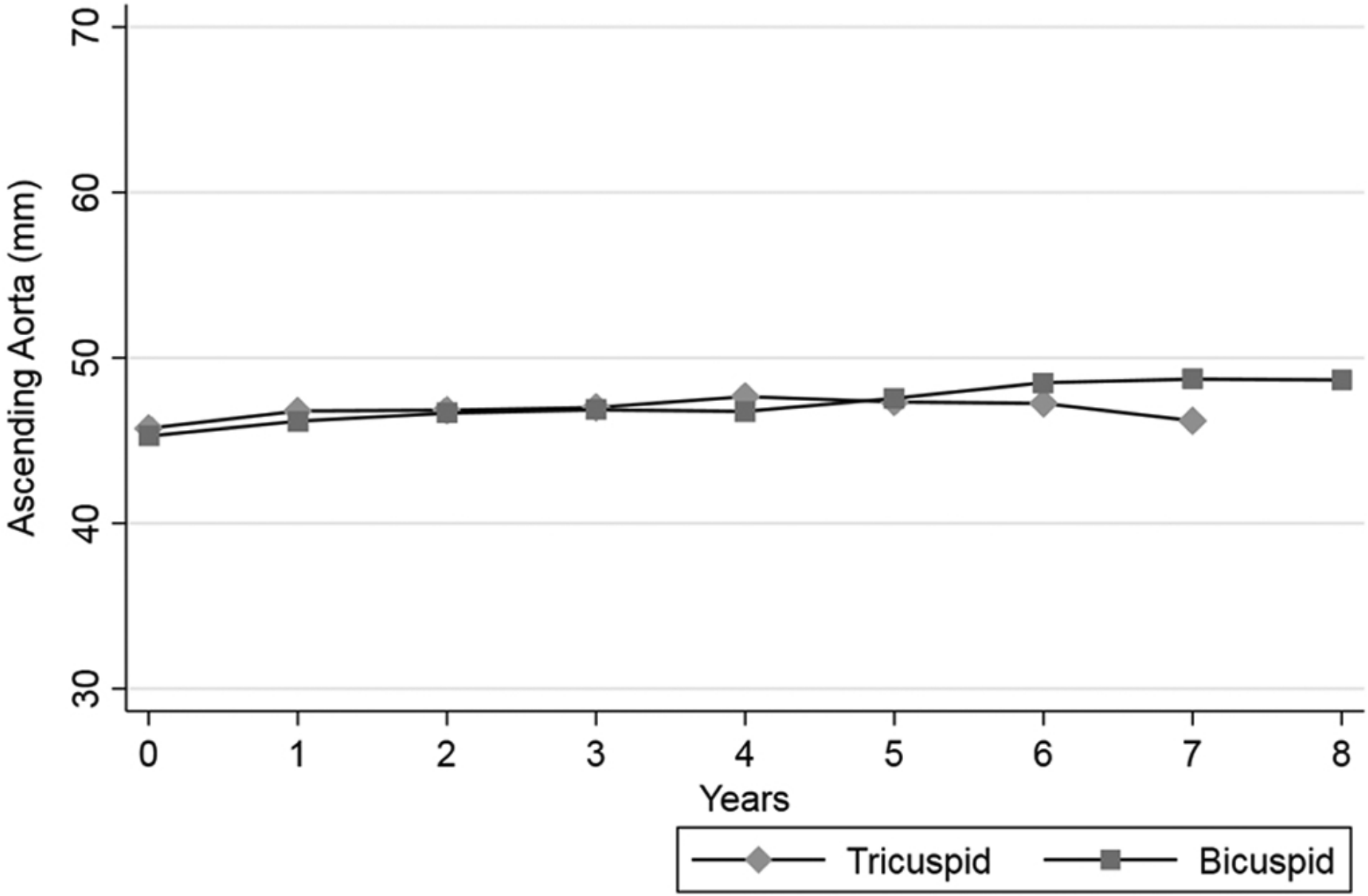
Ascending Aorta (mm)
70
60
50
40
30
0
1
2
3
4
5
6
7
8
Years
Tricuspid
Bicuspid

Figure 1

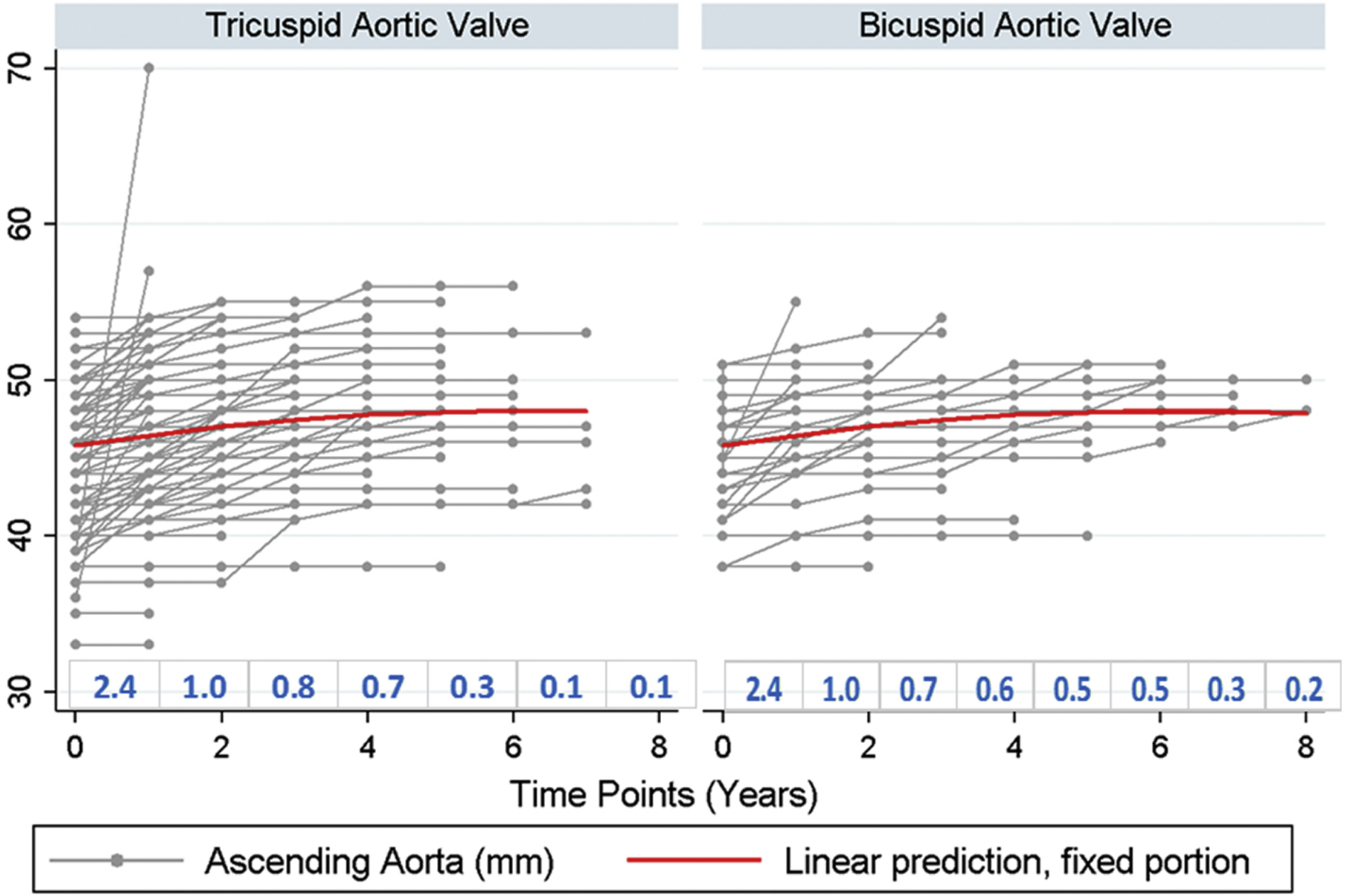
Tricuspid Aortic Valve
Bicuspid Aortic Valve
70
60
50
40
30
2.4 1.0 0.8 0.7 0.3 0.1 0.1
2.4 1.0 0.7 0.6 0.5 0.5 0.3 0.2
0 2 4 6 8
Time Points (Years)
Ascending Aorta (mm)
Linear prediction, fixed portion

Figure 2

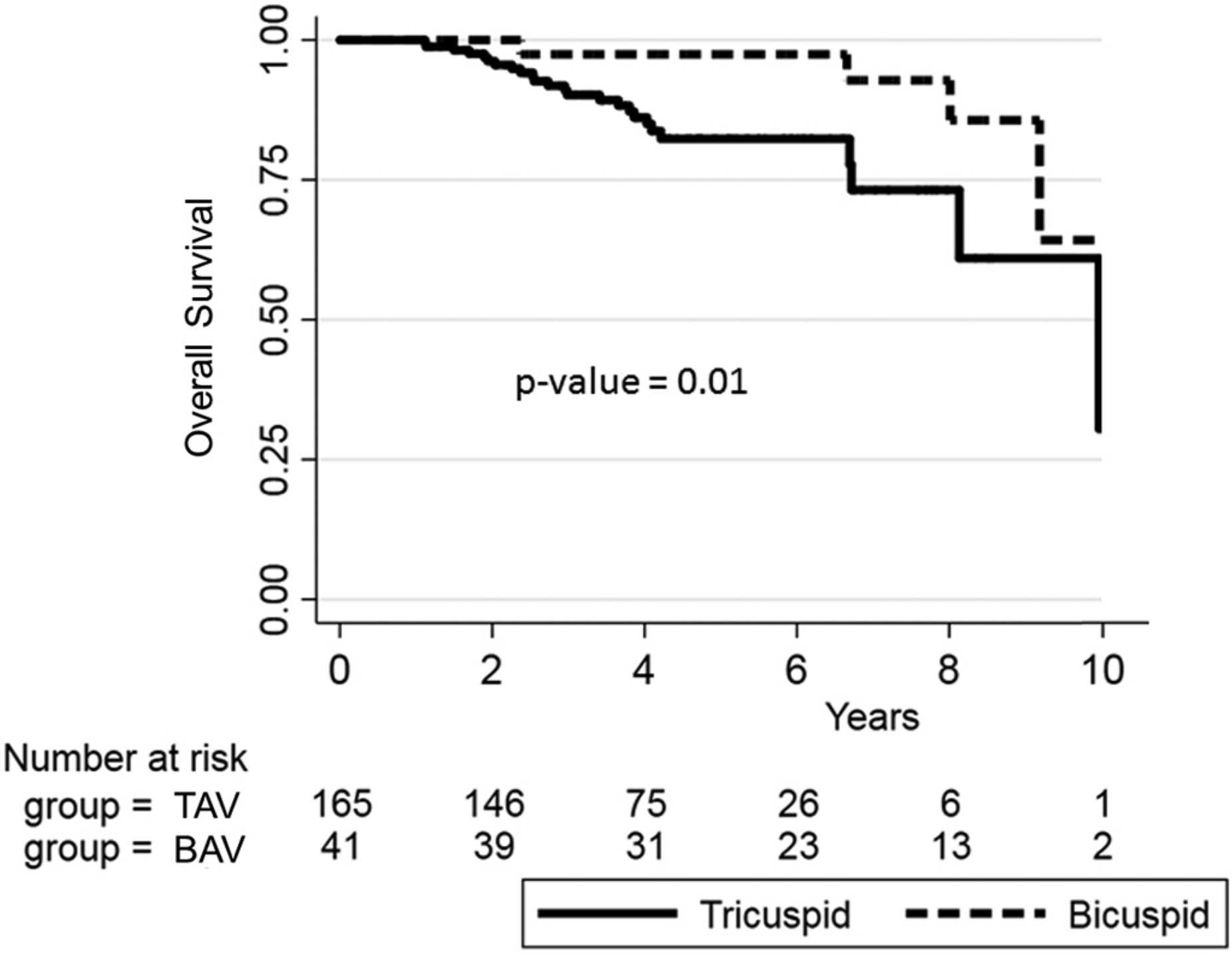
Overall Survival
1.00
0.75
0.50
0.25
0.00
p-value = 0.01
0
2
4
6
8
10
Years
Number at risk
group = TAV 165 146 75 26 6 1
group = BAV 41 39 31 23 13 2
Tricuspid
Bicuspid

Figure 3