



Prognosis of Unrepaired Ascending Aorta after the Surgical Replacement of Bicuspid Aortic Valves

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Background: The surgical threshold for bicuspid aortic valve (BAV)-related aortopathy is a matter of debate due to its uncertain etiology and prognosis. This study investigated the prognosis of unrepaired BAV aortopathy in patients undergoing surgical aortic valve replacement (SAVR).

Methods: We retrospectively analyzed data from 720 patients (age, 60.8±11.5 years; 246 women) who underwent SAVR for BAV disease without aortic repair between 2005 and 2020 at Asan Medical Center. The clinical endpoints were defined as occurrences of sudden death, aortic dissection or rupture, and elective aortic repair. To estimate postoperative changes in the dimensions of the unrepaired aorta, the individual annual aortic expansion rate was calculated. Multiple linear regression models were used to evaluate the risk of aortic expansion.

Results: The mean ascending aortic diameter was 39.5±4.6 mm, and 299 patients (41.5%) had a baseline ascending aorta diameter >40 mm. During 70.0±68.3 months of follow-up, the mean annual aortic expansion rate was 0.39±1.96 mm/yr, no aortic dissection or rupture was observed, and sudden deaths were reported in 12 patients (0.34% per person-year). Linear regression analysis revealed no significant correlation between the baseline ascending aortic diameter and postoperative aortic expansion ($R^2=0.004$, $\beta=-0.84$, $p=0.082$).

Conclusion: In selected patients undergoing SAVR for a BAV (<55 mm), the risk of adverse aortic events was very low. As this observation contradicts current practice guidelines advocating for proactive aortic replacement in dilated ascending aortas measuring >45 mm, the study results need further validation by studies involving larger populations or randomized controlled trials.

Keywords: Bicuspid aortic valve disease, Aortopathy, Prognosis, Aortic valve replacement

Introduction

Individuals with a bicuspid aortic valve (BAV) are prone to develop valvular dysfunction such as aortic regurgitation (AR) and aortic stenosis (AS), as well as aortic wall abnormalities, including ascending aorta dilatation and dissection [1]. The risk of ascending aortic dissection (AD) in BAV patients is estimated to be 8-fold higher than that in the general population [2]. The pathogenesis of aortic dilatation associated with BAV, termed BAV aortopathy, has not yet been clearly elucidated, although genetic and he-

modynamic causes have been referred to as the 2 main possible etiologies [3]. If BAV aortopathy were secondary to a genetic condition, dilatation of the aorta would persist despite aortic valve replacement (AVR), whereas if the main mechanism were hemodynamic in nature, the dilatation would cease after AVR. The current guidelines recommend performing ascending aortic replacement during AVR if the aortic diameter is greater than 45–50 mm in BAV patients [4,5]; however, this would not be necessary in cases of aortic dilatation secondary to a hemodynamic etiology. In accordance with this, a recent clinical study revealed



that a long-term hemodynamic burden is the most important factor contributing to aortic dilatation in BAV, and that isolated AVR is effective in preventing pathologic progression [6-8]. To add supporting evidence to this theory, we evaluated the natural course of an unrepaired ascending aorta in BAV patients at the time of AVR.

Methods

Patients

Between January 2005 and June 2020, 901 BAV patients underwent AVR at the Asan Medical Center (Seoul, Korea). Of these patients, those who underwent aortic root surgery (n=29), aortic valve repair (n=31), and ascending aortic replacement (n=121) were excluded. The final study population comprised 720 patients (age, 60.8 ± 11.5 years; 246 women) with AVR. The decision to perform concomitant aortic procedures was dependent on the aortic size, the expected surgical risk based on left ventricular (LV) function, the discretion of the attending surgeon, and patients' provision of informed consent after education on BAV aortopathy while completing the surgery consent form. This study was approved by the Ethics Committee/Review Board of Asan Medical Center, and the committee waived the requirement for informed consent from individual patients due to the retrospective nature of the study (IRB approval no., 2021-0383).

Data acquisition

The primary outcomes of interest were occurrences of sudden death, AD or aortic rupture, and elective aortic repair. Patients underwent regular postoperative follow-up examinations at the outpatient clinic at 3- to 6-month intervals, and information on their survival status and the occurrence of aortic and cardiovascular events was collected by reviewing electronic medical records. Data were obtained during regular outpatient clinic appointments until December 2020. The date and cause of death were obtained from the institutional electronic database at Asan Medical Center, and to further validate mortality status, the health claims database of the National Health Insurance Service was referenced in December 2020. Early mortality was defined as death occurring within 30 days post-AVR or during the postoperative hospital stay. All deaths were considered of cardiovascular origin unless a non-cardiovascular origin was clinically established. To assess changes in the maximal diameter of the ascending aorta in patients

who underwent AVR, serial postoperative echocardiographic data were reviewed. Postoperative echocardiographic assessments were routinely performed before discharge.

Generally, follow-up echocardiographic evaluations were performed at 6 months, 1 year, and then biennially thereafter. Multiple echocardiographic measurements of the maximal diameter of the proximal ascending aorta from the aortic root through tubular ascending aorta were performed in systole using the parasternal long-axis view, and the maximal diameter was recorded. The difference between aortic diameters before surgery and at the last follow-up was calculated and divided by the follow-up duration to yield the aortic expansion rate (mm/yr).

Statistical analysis

Categorical variables, presented as frequencies and percentages, were compared using the chi-square test. Continuous variables, expressed as mean \pm standard deviation or median with range, were compared using analysis of variance or the Kruskal-Wallis test, as appropriate.

Pearson correlation analysis was conducted to determine the association between the preoperative aortic diameter and the postoperative aortic expansion rate. Multiple linear regression models were applied to evaluate the risk of aortic expansion. All baseline parameters were examined using a univariable linear regression model to evaluate associations with the aortic expansion rate. Subsequently, multivariable linear regression analyses were conducted, including only variables with $p < 0.20$ in the univariable models. A stepwise method was used to exclude covariates with $p < 0.10$ in the final model. Finally, significant predictors of aortic expansion found in the multivariable linear model were further examined using a nonparametric Loess regression model. Time-weighted average data were used in the regression models. All reported p -values were two-sided, and a p -value < 0.05 was considered to indicate statistical significance. PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Baseline characteristics and in-hospital outcomes

The baseline demographic, clinical, and echocardiographic parameters are shown in Table 1. The mean age was 60.8 ± 11.5 years, and 246 patients (34.2%) were women. The dominant aortic valve pathologies were AS (47.1%) and

Table 1. Baseline characteristics of patients (n=720)

Characteristic	Value
Age (yr)	60.8±11.5
Female	246 (34.2)
Body mass index (kg/m ²)	24.7±10.2
Body surface area (m ²)	1.7±0.2
Diabetes mellitus	124 (17.2)
Hypertension	280 (38.9)
Echocardiographic findings	
Predominant pathology	
Stenotic	339 (47.1)
Insufficient	266 (36.9)
Mixed	115 (16.0)
BAV types	
Type 0 (true bicuspid)	26 (3.6)
Type 1 (1 raphe)	689 (95.7)
Type 2 (2 raphes)	5 (0.7)
BAV directions, available data only	426
Anterior-posterior	234 (54.9)
Left-right	192 (45.1)
Ascending aorta diameter (mm)	39.5±4.6
Size categories (mm)	
<40	343 (47.6)
≥40 and <45	295 (41.0)
≥45 and <50	75 (10.4)
≥50	7 (1.0)

Values are presented as mean±standard deviation, number (%), or number. BAV, bicuspid aortic valve.

AR (36.9%). The BAV type was determined based on the Sievers and Schmidtke classification as follows: type 0, no raphe; type 1, 1 raphe; and type 2, 2 raphes. As supplementary characteristics, the spatial position and function were also described [9]. Type 1 BAV was observed in 95.7% of patients, and the BAV direction was anterior-posterior in most cases (54.9%). The mean ascending aortic diameter was 39.5±4.6 mm (Fig. 1), and 377 patients (52.4%) had a dilated ascending aorta (>40 mm). AVR with a mechanical prosthetic valve was performed in 289 patients (40.1%). Concomitant tricuspid annuloplasty, coronary bypass surgery, surgical atrial fibrillation ablation, and ventricular septal defect or patent foramen closure were performed in 22 (3.1%), 49 (6.8%), 38 (5.3%), and 14 (1.9%) patients, respectively. Early mortality occurred in 9 patients (1.3%), due to cardiac output syndrome in 6 patients, alveolar hemorrhage in 1, and multi-organ failure in 2 (Table 2).

Follow-up results

The median follow-up duration was 59.1 months (25th to 75th percentiles: 20.0–97.1 months), and there was a total

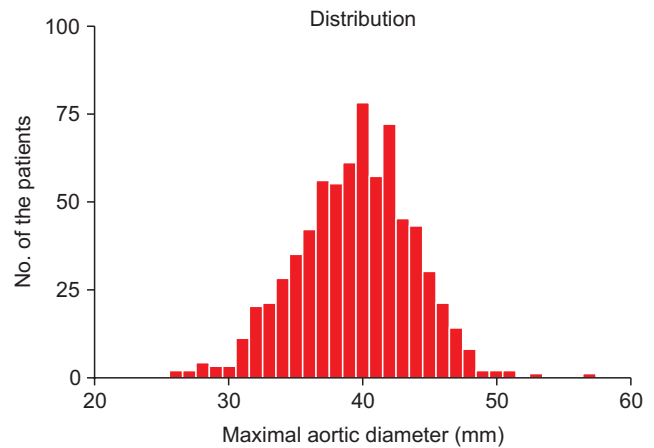


Fig. 1. Frequency distribution of maximal aortic diameter (mm) prior to aortic valve replacement.

Table 2. Details of aortic valve replacement, concomitant procedures, and early mortality (n=720)

Characteristic	No. (%)
Prosthetic valve	
Mechanical	289 (40.1)
Tissue	431 (59.9)
Concomitant procedures	
Tricuspid annuloplasty	22 (3.1)
Coronary bypass surgery	49 (6.8)
Surgical atrial fibrillation ablation	38 (5.3)
Ventricular septal defect or patent foramen closure	14 (1.9)
Early mortality	9 (1.3)
Low cardiac output syndromes	6 (0.8)
Alveolar hemorrhage	1 (0.1)
Multi-organ failure	2 (0.3)

of 3,528 patient-years of follow-up. During follow-up, 91 deaths (2.58% per patient-year) were reported; however, AD and aortic rupture were not reported in any patients. There were 12 cases of sudden death (0.34% per patient-year). Regarding competing event occurrence, there was 1 unknown death (0.03% per patient-year), and no elective aortic surgery was performed. The cumulative mortality rate is shown in Fig. 2.

Aortic expansion rate

Follow-up echocardiographic assessments were available for all surviving patients. The baseline mean ascending aortic diameter in this cohort was 39.5±4.6 mm. To calculate the aortic expansion rate, data from 4,740 echocardiographic assessments were retrieved (6.6 per patient) during a median follow-up of 59.1 months. The mean annual aor-

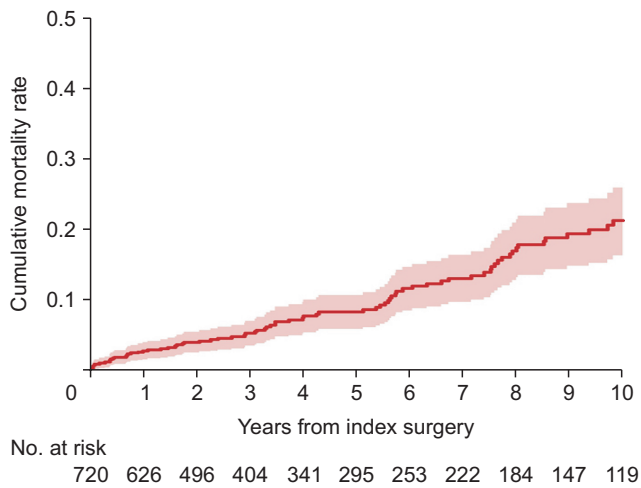


Fig. 2. Cumulative risk of death.

Table 3. Results of univariate and multivariate linear regression analyses exploring the association between baseline variables and the aortic expansion rate

Variable	Univariate analysis (p-value)	Multivariate analysis	
		Odds ratio (95% CI)	p-value
Age	0.18		
Female sex	0.053		
Preoperative aortic size	0.045	0.91 (0.84–0.99)	0.029
Body surface area	0.067		

CI, confidence interval.

tic expansion rate was 0.39 ± 1.96 mm/yr. Eight patients showed an aortic expansion rate >5 mm/yr, in whom the baseline maximal aortic diameter was 32.9 mm (range, 27 to 44 mm) to 40.8 mm (range, 37 to 50 mm) over a mean duration of 11.4 months (mean expansion rate, 8.9 mm/yr). There were no cases of death or aortic reoperation among these patients. In the risk factor analysis, the baseline maximal aortic diameter was found to be a significant preventive factor (hazard ratio, 0.91; 95% confidence interval, 0.84–0.99; $p=0.029$) against aortic expansion (Table 3). However, we investigated the aortic expansion rate of each group categorized by initial aortic size, and the results were not statistically significant ($P=0.160$) (Table 4). The baseline aortic diameter was inversely associated with the aortic expansion rate, although the correlation was not statistically significant ($R^2=0.004$, $\beta=-0.84$, $p=0.082$) (Fig. 3). Multiple linear regression models revealed no significant risk factors for aortic expansion.

Table 4. Aortic expansion rate depending on the baseline aortic diameters (mm/yr)

Variable	Mean \pm SD	p-value
Overall (mm/yr)	0.39 ± 1.96	0.160
Size categories (mm)		
<40	0.53 ± 2.16	
≥ 40 and <45	0.31 ± 1.89	
≥ 45 and <50	-0.03 ± 1.24	
≥ 50	0.86 ± 0.84	

SD, standard deviation.

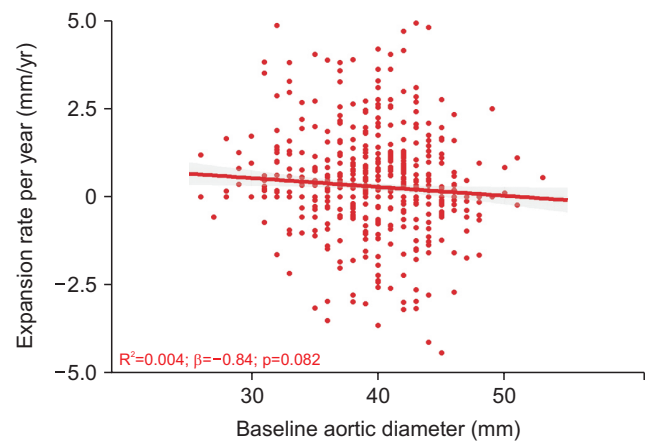


Fig. 3. Association between baseline aortic diameter and aortic expansion rate.

Discussion

The present study had 2 main findings. First, AD and aortic rupture did not occur in any patients during a median follow-up of approximately 5 years after AVR. Second, the aortic expansion rate was inversely related to the baseline aortic diameter, although the correlation was not statistically significant. These findings support the most up-to-date practice recommendations, according to which there is no definite need to perform a procedure for a dilated ascending aorta (40–55 mm) during bicuspid AVR. We previously reported that the aortic expansion rate was not affected by either the morphology of aortic valves (i.e., bicuspid versus tricuspid) or the initial aortic diameter, and AVR alone achieved similar clinical outcomes, showing considerably low risks of adverse aortic events or significant aortic expansion in the dilated ascending aorta [7]. In that study, there were 139 BAV patients out of 362 patients undergoing AVR alone; with an extension of the sample size and the study duration, the present study included 720 BAV patients and showed similar results regarding aortic

events to those of the prior study. According to clinical practice guidelines on the management of the ascending aorta during AVR, patients with an ascending aorta diameter >45–50 mm should be considered for concomitant ascending aorta replacement [4,5]. A literature search for research supporting the prior recommendation advocating a more aggressive threshold of >45 mm for concomitant aortic repair only yielded 1 observational study, in which the authors retrospectively reviewed 201 BAV patients who underwent AVR without aortic replacement and suggested that patients with an ascending aorta diameter ≥ 45 mm should be considered for concomitant aorta replacement [10]. The cutoff value of 45 mm has been accepted as a standard in the management of the ascending aorta during AVR, and this suggestion has also been supported by several studies suggesting “intrinsic aortopathy” in BAV disease [11–14]. In those studies, aortic dilatation was attributed to an intrinsic abnormality of the aortic wall; thus, the aorta was viewed as being likely to expand further, even after the correction of aortic valve disease. These reports derived conclusions based on the hypothesis that BAV is a genetic disease and BAV aortopathy is caused by innate aortic wall weakness. However, the abnormal hemodynamics of BAV have emerged as a potential alternative or coincident etiology [15,16]. Of note, the primary author of a previous report suggesting a genetic etiology for BAV now has a contradicting opinion favoring a hemodynamic etiology [16]. Den Reijer et al. [17] reported significant correlations between the blood flow jet angle, representing a quantitative measurement of misdirected blood flow, and the ascending aorta dimensions at the levels of the sinuses of Valsalva, sinotubular junction, and the tubular part of the ascending aorta, which were evaluated using 3-dimensional velocity-encoded cardiac magnetic resonance imaging. The significant positive correlation revealed that larger angles of misdirected flow at the aortic axis caused greater aortic dimensions and more severe aortic dilatation. In flow loop experiments with phantom models of the aorta, excised BAVs were shown to be associated with abnormal flow patterns and turbulence toward the right anterolateral wall (i.e., convexity) of the aorta. This implies that BAV with good valvular function and without AS or AR can cause abnormal hemodynamic effects in asymmetric aortic dilatation [18]. These effects can cause various types of ascending aortic dilatation, including the aortic root type, due to differences in the spatial relationship of BAV [19,20]. In that study, AR was more common in patients with anterior-posterior orientation and raphe-positive BAV, and AS was more common in patients with right-left orientation

and raphe-negative BAV. In patients with raphe-positive BAV, the diameters of the aortic annulus and the tubular portion of the ascending aorta with reference to the body surface area were larger and smaller, respectively, than those in patients with raphe-negative BAV. These findings promote the hemodynamic theory of BAV aortopathy and imply that subsequent dilatation of the ascending aorta will cease after AVR [6–8].

Regarding the etiology of BAV aortopathy, we have to consider the study by Fernández et al. [21], which reported that fused right and noncoronary leaflets (R-N) and fused right and left leaflets (R-L) BAVs are different etiological entities, and suggested that the factors determining the formation of fused R-N and fused R-L BAVs might also be involved in the occurrence and progression of the pathologies associated with each BAV subtype. However, these findings require confirmation.

Regarding aortic events, the present study showed that AD and aortic rupture did not occur in any patient during a median post-AVR follow-up of 5 years. These findings are consistent with other studies showing that BAV has no significant impact on the risk of AD and/or rupture [22,23]. Girdauskas et al. [23] also reported that AD occurred in 3 patients with tricuspid aortic valves, but not in BAV patients. However, in a subsequent study that included 56 patients with BAV insufficiency and a root diameter of 40–50 mm, the authors reported progressive dilatation of the aortic root and an increased risk of aortic events after isolated AVR. Thus, aggressive aortic surgery was recommended in BAV patients with a “root phenotype” [24]. Another meta-analysis demonstrated a 10-fold higher risk of AD after AVR in patients with BAV insufficiency than in patients with BAV stenosis [25]. In the present study, there were no cases of AD or aortic rupture, even with 37% of the study participants being AR-dominant patients. However, considering a study suggesting that fused R-N and fused R-L BAVs were of different etiologies [21] and another report showing a higher likelihood of the root phenotype in relatively younger male patients [19], we should appraise the possibility of a genetic etiology and monitor similar patterns in patients with BAV insufficiency. The aortic expansion rate after AVR appeared to be inversely related to the baseline aortic diameter, although the difference was not statistically significant. In our previous report [7], aortic expansion rates were not significantly different between bicuspid and tricuspid aortic valves, or among aortic valves with stenosis, regurgitation, or mixed steno-insufficiency. Furthermore, no significant correlation was found between the initial maximal aortic diameter and the aortic expansion

sion rate, in accordance with the results of our previous study.

This study had the limitations inherent to a retrospective analysis of observational data. The performance of aortic procedures was affected by the preoperative conditions and informed decisions of the patients. Aortic size was measured through a transthoracic echocardiographic assessment, which is not the gold standard for aortic size evaluation, particularly due to measurement variations on the distal ascending aorta. Moreover, limited clinical and echocardiographic follow-up durations are important limitations of this study. However, longitudinal echocardiographic assessments in this patient population are inevitably limited owing to a significant proportion of patients who no longer require imaging during follow-up. Additionally, due to the absence of AD or aortic rupture during the follow-up period, risk factors for adverse outcomes were not identified. As for the 12 patients with sudden death, the exact cause of death could not be described due to incomplete medical records.

In conclusion, in selected patients with non-severely dilated BAV aortopathy (<55 mm), an unrepaired ascending aorta was not significantly associated with subsequent aortic expansion, dissection, or rupture. As this observation contradicts current practice guidelines advocating for proactive aortic replacement in cases of dilated ascending aortas of >45 mm as a Class IIa recommendation [4], studies involving larger populations or randomized controlled trials should be conducted for further validation.

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Author contributions

Conceptualization: JBK. Data curation: WKK. Formal analysis: HJS, WKK. Methodology: All authors. Project administration: WKK, DKK. Visualization: WKK, JBK. Writing—original draft: HJS, WKK, JBK. Writing—review & editing: HJS, WKK, JBK. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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References

1. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol* 2010;55:2789-800. <https://doi.org/10.1016/j.jacc.2009.12.068>
2. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA* 2011;306:1104-12. <https://doi.org/10.1001/jama.2011.1286>
3. Sievers HH, Sievers HL. Aortopathy in bicuspid aortic valve disease: genes or hemodynamics? or Scylla and Charybdis? *Eur J Cardiothorac Surg* 2011;39:803-4. <https://doi.org/10.1016/j.ejcts.2011.02.007>
4. Isselbacher EM, Preventza O, Hamilton Black J 3rd, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on clinical practice guidelines. *Circulation* 2022;146:e334-482. <https://doi.org/10.1161/CIR.0000000000001106>
5. Writing Committee Members; Otto CM, Nishimura RA, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol* 2021;77:e25-197. <https://doi.org/10.1016/j.jacc.2020.11.018>
6. Kim YG, Sun BJ, Park GM, et al. Aortopathy and bicuspid aortic valve: haemodynamic burden is main contributor to aortic dilatation. *Heart* 2012;98:1822-7. <https://doi.org/10.1136/heartjnl-2012-302828>
7. Lee SH, Kim JB, Kim DH, et al. Management of dilated ascending aorta during aortic valve replacement: valve replacement alone versus aorta wrapping versus aorta replacement. *J Thorac Cardiovasc Surg* 2013;146:802-9. <https://doi.org/10.1016/j.jtcvs.2013.06.007>
8. Kim MS, Kim JH, Lee SH, et al. Long-term fate of dilated ascending aorta after aortic valve replacement for bicuspid versus tricuspid aortic valve disease. *Am J Cardiol* 2020;129:53-9. <https://doi.org/10.1016/j.amjcard.2020.05.026>
9. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg* 2007;133:1226-33. <https://doi.org/10.1016/j.jtcvs.2007.01.039>
10. Borger MA, Preston M, Ivanov J, et al. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? *J Thorac Cardiovasc Surg* 2004;128:677-83. <https://doi.org/10.1016/j.jtcvs.2004.05.026>

- org/10.1016/j.jtcvs.2004.07.009
11. Keane MG, Wieggers SE, Plappert T, Pochettino A, Bavaria JE, Sutton MG. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. *Circulation* 2000;102(19 Suppl 3):III35-9. https://doi.org/10.1161/01.cir.102.suppl_3.iii-35
 12. Yasuda H, Nakatani S, Stugaard M, et al. Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. *Circulation* 2003;108 Suppl 1:II291-4. <https://doi.org/10.1161/01.cir.0000087449.03964.fb>
 13. Della Corte A, Bancone C, Quarto C, et al. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. *Eur J Cardiothorac Surg* 2007;31:397-405. <https://doi.org/10.1016/j.ejcts.2006.12.006>
 14. McKellar SH, Tester DJ, Yagubyan M, Majumdar R, Ackerman MJ, Sundt TM 3rd. Novel NOTCH1 mutations in patients with bicuspid aortic valve disease and thoracic aortic aneurysms. *J Thorac Cardiovasc Surg* 2007;134:290-6. <https://doi.org/10.1016/j.jtcvs.2007.02.041>
 15. Barker AJ, Markl M. The role of hemodynamics in bicuspid aortic valve disease. *Eur J Cardiothorac Surg* 2011;39:805-6. <https://doi.org/10.1016/j.ejcts.2011.01.006>
 16. Girdauskas E, Disha K, Borger MA, Kuntze T. Relation of bicuspid aortic valve morphology to the dilatation pattern of the proximal aorta: focus on the transvalvular flow. *Cardiol Res Pract* 2012;2012:478259. <https://doi.org/10.1155/2012/478259>
 17. den Reijer PM, Sallee D 3rd, van der Velden P, et al. Hemodynamic predictors of aortic dilatation in bicuspid aortic valve by velocity-encoded cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010;12:4. <https://doi.org/10.1186/1532-429X-12-4>
 18. Robicsek F, Thubrikar MJ, Cook JW, Fowler B. The congenitally bicuspid aortic valve: how does it function?: why does it fail? *Ann Thorac Surg* 2004;77:177-85. [https://doi.org/10.1016/s0003-4975\(03\)01249-9](https://doi.org/10.1016/s0003-4975(03)01249-9)
 19. Kim JS, Ko SM, Chee HK, Shin JK, Song MG, Shin HJ. Relationship between bicuspid aortic valve phenotype, valvular function, and ascending aortic dimensions. *J Heart Valve Dis* 2014;23:406-13.
 20. Shin HJ, Shin JK, Chee HK, Kim JS, Ko SM. Characteristics of aortic valve dysfunction and ascending aorta dimensions according to bicuspid aortic valve morphology. *Eur Radiol* 2015;25:2103-14. <https://doi.org/10.1007/s00330-014-3585-z>
 21. Fernandez B, Duran AC, Fernandez-Gallego T, et al. Bicuspid aortic valves with different spatial orientations of the leaflets are distinct etiological entities. *J Am Coll Cardiol* 2009;54:2312-8. <https://doi.org/10.1016/j.jacc.2009.07.044>
 22. Kim JB, Spotnitz M, Lindsay ME, MacGillivray TE, Isselbacher EM, Sundt TM 3rd. Risk of aortic dissection in the moderately dilated ascending aorta. *J Am Coll Cardiol* 2016;68:1209-19. <https://doi.org/10.1016/j.jacc.2016.06.025>
 23. Girdauskas E, Disha K, Borger MA, Kuntze T. Long-term prognosis of ascending aortic aneurysm after aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Thorac Cardiovasc Surg* 2014;147:276-82. <https://doi.org/10.1016/j.jtcvs.2012.11.004>
 24. Girdauskas E, Disha K, Rouman M, Espinoza A, Borger MA, Kuntze T. Aortic events after isolated aortic valve replacement for bicuspid aortic valve root phenotype: echocardiographic follow-up study. *Eur J Cardiothorac Surg* 2015;48:e71-6. <https://doi.org/10.1093/ejcts/ezv259>
 25. Girdauskas E, Rouman M, Disha K, et al. Aortic dissection after previous aortic valve replacement for bicuspid aortic valve disease. *J Am Coll Cardiol* 2015;66:1409-11. <https://doi.org/10.1016/j.jacc.2015.07.022>