Clinical and echocardiographic determinants in bicuspid aortic dilatation
Results from a longitudinal observational study

Frederique E.C.M. Peeters, MD, Noreen Van der Linden, MD, Alissa L.L. Thomassen, Harry J.G.M. Crijns, MD, Steven J.R. Meex, PhD, Bas L.J.H. Kietseelaer, MD, PhD

Abstract
Bicuspid aortic valve (BAV) disease is associated with aortic dilatation. Timing of follow-up and surgery is challenging. Hence, there is an unmet clinical need for additional risk stratification. It is unclear whether valve morphology is associated with dilatation rates. Therefore, the objective of this study was to examine the association between clinical and echocardiographic determinants (including valve morphology) and aortic dimension and the progression rate of dilatation.

Aortic dimensions were assessed on serial echocardiographic images between 1999 and 2014 in a population of 392 patients with BAVs in a tertiary care center in the Netherlands. Analyses using mixed linear models were performed.

Mean age of participants was 48±17 years and 69% were male. BAV morphology was associated with aortic dimensions, as well as age, sex, BSA, and valvular dysfunction. Tubular ascending aorta, sinus of Valsalva, and sinotubular junction showed a dilatation rate of 0.32, 0.18, and 0.06 mm/year, respectively. Dilation rate was not associated with valve morphology.

In the present study, there is no association between BAV morphology and aortic dilatation rates. Therefore, morphology is of limited use in prediction of aortic growth. Discovering fast progressors remains challenging.

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association, AoS = aortic valve stenosis, AR = aortic regurgitation, ASE = American Society of Echocardiography, BAV = bicuspid aortic valve, LVOT = left ventricular outflow tract, STJ = sinotubular junction, TA = tubular ascending aorta.

Keywords: aortic dilatation, aortic dilatation rate, aortic dimensions, bicuspid aortic valve, thoracic aorta

1. Introduction
The bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality with an estimated prevalence of 13 per 1000 births in the general population. It is known for its heterogeneous presentation and its association with valvular and vascular complications, including aortic dilatation. Because of the association with aortic dilatation, BAV is considered as an aortopathy rather than a stand-alone valvulopathy. Yet, the natural course of dilatation varies widely, from virtually nonprogressive to rapidly progressive, potentially leading to life-threatening aortic complications. Indication and timing of elective aortic surgical intervention remains challenging at present, as current guidelines recommend variable treatment options based on studies advocating aggressive repair versus a conservative treatment approach.

The exact pathophysiologic mechanisms underlying aortic dilatation in bicuspid aortopathy are not fully elucidated. Two mechanisms are proposed: firstly, the inherited or intrinsic predisposition. Several studies show abnormalities in the matrix, fibrillin, and elastin fragmentation leading to accelerated degeneration of the media. Secondly, the hemodynamic consequences of BAV on aortic tissue by abnormal mechanical (local) stress (overload). Also, BAV morphology and its effect on blood flow in the ascending aorta has been studied as a potential contributing factor for development of aortic complications. Contradictory results exist concerning the possible association of valve morphology and both aortic dilatation and valvular function.

Optimizing the risk stratification of aortic dilatation in BAV patients is desirable, as this could impact timing of clinical follow-up and surgery. Few studies are available regarding dilatation rates and associated risk factors, showing variable outcomes. Therefore, the aim of this study was to analyze the dimensions and dilatation rates of different segments of the ascending aorta and its determinants/risk factors, including BAV morphology.
2. Methods

Patients were identified in a tertiary care center in the Netherlands (Maastricht University Medical Centre, MUMC), by using the electronic database of all echocardiographic records from 1999 to 2014. Eligible patients were at least 18 years old and had a visually confirmed BAV on echocardiographic images. Serial echocardiographic images had to be available, at least 6 months apart. Patients with prior valve replacement surgery or surgery of the ascending aorta were excluded, whereas all degrees of valvular dysfunction were accepted. Clinical information was obtained through review of the available electronic hospital charts. This study was approved by the local institutional review board and ethics committee.

2.1. Echocardiography

Measurements were performed in serial transthoracic echocardiographic images of eligible patients by 2 observers, using a dedicated workstation (Philips Xcelera software Version R3, Philips Medical Systems, Best, the Netherlands). Presence of a BAV was confirmed in a short-axis view and valve morphology was determined. In case of ambiguity, consensus was reached in the presence of a third observer. BAVs were systematically classified during systole, according to Sievers classification,\textsuperscript{[22]} firstly as a raphe-related type 0 (BAV without raphe), type 1 (BAV with presence of 1 raphe) or type 2 (BAV with presence of 2 raphes). Secondly, the exact fusion type was reported by description of the fusion patterns between the right coronary cusp (RCC), left coronary cusp (LCC), and noncoronary cusp (NCC). Echocardiographic Doppler methods were used to assess the function of the aortic valve, in accordance with the American Society of Echocardiography (ASE) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines.\textsuperscript{[5,23]}

Diameters of the left ventricular outflow tract (LVOT), sinus of Valsalva, sinotubular junction (STJ), and the tubular ascending aorta (TA) were measured from inner edge to inner edge in a parasternal long axis view. The LVOT diameter was assessed underneath the hinge points of the leaflets of the aortic valve, the sinus of Valsalva maximal diameter was measured perpendicular to the axis of the proximal aorta. The STJ was measured at the point where the sinus of Valsalva continues to the TA. The tubular aorta was visualized as distally as possible. The maximal diameter perpendicular to the axis of the aorta was taken (Fig. 1).\textsuperscript{[6]}

Figure 1. Schematic overview of measurement of aortic dimensions. 1, LVOT; 2, sinus of Valsalva; 3, sinotubular junction; and 4, ascending aorta.

2.2. Statistical analyses

Statistical analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL). Normally distributed continuous variables were reported as mean ± standard deviation (SD) and non-normal distributed continuous variables as median and interquartile range [IQR]. Categorical data are reported as number (n) and percentage (%). Changes in aortic dimensions over time were modeled using mixed linear model analyses with a random slope and random intercept. Independent variables investigated were age, sex, body surface area (BSA), valve morphology, valvular dysfunction, hypertension, aortic dimension, and time. The final models were also analyzed in the presence of potential confounders (sex, BSA, and age). Dependent variables were LVOT, sinus of Valsalva, STJ, and TA. Potential interactions between time and the other independent variables were also tested. The final models were realized by stepwise elimination using a threshold \( P \)-value of <0.10.

3. Results

3.1. Population characteristics

In this single-center study, 392 patients with a BAV with serial echocardiographic images available were enrolled. Median follow-up (IQR) was 5 (4) years in which patients underwent 3.6 ± 1.6 echocardiographies. Sixty-nine percent of patients were male and mean age was 48 (±17) years with a mean BSA of 1.9 (±0.2)\textsuperscript{m\textsuperscript{2}} during the first echocardiography (Table 1). According to the raphe-related classification,\textsuperscript{[22]} 78% (n = 305) of patients were classified as type 1, 19% (n = 73) as type 0 BAV and 2% (n = 7) as type 2 BAV. When considering the leaflet fusion type within the raphe-related classification type 1, BAV with a raphe between the RCC and LCC (RCC/LCC subtype) was the most common subtype of BAV in 56% of the study population (n = 221), followed by the RCC/NCC subtype in 14% (n = 54). The NCC/LCC subtype of BAV was the least common in this group with 8% (n = 30) of patients (Fig. 2). In 2% (n = 7) of the patients, presence of BAV was confirmed, although exact determination of the morphology was uncertain.

3.2. Associations with aortic dimensions

Aortic dimensions per BAV subtype during the first echocardiography are presented in Fig. 3. Classification using leaflet fusion type showed an association with all aortic segments. The dimension of the sinus of Valsalva was significantly smaller in patients with the BAV subtype NCC/LCC when compared to the other fusion types. Furthermore, the RCC/LCC fusion subtype was significantly larger when compared to the RCC/NCC fusion subtype. As for the STJ dimensions, the NCC/LCC subtype was associated with the smallest dimensions in comparison to the other subtypes and the subtype without a raphe had larger dimensions in comparison to the RCC/NCC subtype. Finally, the NCC/LCC subtype was associated with smaller TA and LVOT dimensions compared to the other subtypes. On the contrary, when patients were classified according to number of raphes, an association between the aortic dimensions with BAV morphology in the model was not found. Presence of an association between aortic dimensions and other biologically plausible parameters was investigated. The significantly associated parameters for all aortic dimensions are listed in Table 2. Dimensions of all segments were significantly larger in males. A high BSA was associated with significantly larger dimensions of the LVOT, STJ, and TA.
3.3. Aortic dilatation rate variation

Serial assessments of aortic dimensions were used to determine the dilatation rates of the aortic segments, employing mixed linear models. Mean aortic dilatation rates differed across aortic segments. The mean (±SD) increase of the STJ was 0.06 (±0.05) mm/year, the mean increase of the sinus of Valsalva was 0.18 (±0.02) mm/year and the TA showed the fastest dilatation rate: 0.32 (±0.03) mm/year. The LVOT did not show significant annual progression of dilatation.

We next investigated which parameters were associated with increased aortic dilatation rates. BAV morphology type was not associated with aortic dilatation in any of the segments mentioned above. This finding is illustrated by similar slopes in Fig. 4, representing growth per morphology type. Baseline dimensions of the TA were associated with dilatation rate of that specific aortic segment but this association could not be found in the other segments. As for the other parameters a significant association with dilatation rates of any of the aortic segments could not be demonstrated. Addition of potential confounders (age, sex, and BSA) to the model did not affect the results (data not shown).

3.4. Monocuspid valves, a special subgroup

Two percent (n=7) of the aortic valves in this study population was monocuspid. Overall, the presence of a monocuspid aortic valve seemed to result in larger dimensions of the aorta in all segments, but did not show morphology-dependent dilatation rates as well. The small number of patients necessitates cautious interpretation of these data, as they may not be representative for the population with a monocuspid aortic valve as a whole.

4. Discussion

The aim of the present study was to elucidate on determinants of dimensions and dilatation rates of ascending aortic segments in a population consisting of 392 patients with a BAV. The main findings of this study are as follows.

First, segments of the proximal ascending aorta showed different dilatation rates. The TA showed the highest dilatation rate of 0.32 mm/year, followed by the sinus of Valsalva with 0.18 mm/year and the STJ with a dilatation rate of 0.06 mm/year. Second, type of BAV morphology showed no association with aortic dilatation rates, regardless of the classification system (raphe-related type or fusion type). The association between valve morphology and aortic dilatation rates has been suggested and contradicted in previous studies and shows a wide dispersion of dilatation rates.[2,21,24] Our study results are in accordance with recent studies, regarding dilatation rates in BAV aortopathy. However, we believe that the results of this study have added value in the confirmation of results of these studies,[19,20] due to group size and the strong method of analyses. Mixed linear models provide an elegant way to overcome different follow-up time intervals and provide a solid basis to underpin the dilatation
rates found in this study by not only taking the first and last measurement of the aortic dimensions into account, but all intermediate measurements as well, leading to a more accurate estimate of the aortic dimensions and dilatation rates over time. Third, morphology types were associated with differences in dimensions of the proximal aorta. The association between BAV morphology and aortic size has been subject of extensive debate, especially since initial studies did not find an association whereas in later studies morphology related significantly to both sinus of Valsalva and TA size. The present findings are in accordance with the latter and support the notion that BAV morphology related hemodynamics may cause aortic dilatation directly, but does not exclude a role for underlying ontogenetic defects or a role of an interplay between both. The involvement of genetic defects and defects in the neural crest cells leading to the development of BAV (calcification) and concomitant abnormalities of the aorta by disruption of the extracellular matrix have been studied in conjunction with hemodynamic patterns in BAV disease. A cross-sectional study by Hope et al. showed an eccentric flow resulting in an abnormal helical flow pattern in a subset of patients with and without aortic dilatation and a BAV with “normal” function. They suggested a role for hemodynamic stress in identifying patients at risk for developing aortic aneurysms, taking into account the alternative hypothesis that presence of intrinsic aortic wall abnormalities predisposes to a greater aortic dilatation in the presence of abnormal hemodynamic stress. Fourth, our modeled analyses show that dimensions of the aortic segments are influenced by sex, age, BSA, and valvular function, whereas dilatation rates are not. The inability to show this association does not aid in optimizing risk stratification in BAV aortopathy. As a result of the unpredictability of dilatation rates, an especially challenging aspect of BAV is the timing of surgical intervention. Verma et al. found significantly different clinical decisions by cardiac surgeons toward optimal timing of surgical intervention. This group recommended a renewed strategy for follow-up and timing of aortic surgical interventions, accepting more dilatation of the aorta (in absence of risk factors). Biological/genetic background might play a more important role in dilatation rates and should probably be taken into account when deciding on timing of

Table 2
Factors associated with dimensions.

|        | LVOT         | Sinus of Valsalva | STJ          | TA           |
|--------|--------------|------------------|--------------|--------------|
| Age    | –0.013 (–0.028; 0.002) | 0.099           | –0.004 (–0.150; 0.151) | 0.122 (0.084; 0.141) | 0.113 (0.084; 0.141) | –0.004 (–0.150; 0.151) |
| Male   | 2.296 (1.735; 2.896)   | <0.001          | 3.355 (2.380; 4.312) | <0.001       | 2.120 (1.090; 3.149) | <0.001       | 2.120 (1.090; 3.149) | <0.001       |
| BSA    | 1.931 (0.966; 2.890)   | <0.001          | 0.921 (–0.317; 2.158) | 0.145        | 2.174 (0.513; 3.838) | 0.010        | 2.174 (0.513; 3.838) | 0.010        |
| AR     | –0.721 (–1.242; –0.200) | 0.007           | –0.801 (–1.744; 0.141) | 0.096        | –0.645 (–1.700; 0.420) | 0.234        | –0.645 (–1.700; 0.420) | 0.234        |
| AoS    | 0.187 (–0.100; 0.473)  | 0.202           | 0.121 (–0.125; 0.456) | 0.481        | 0.038 (–0.448; 0.523) | 0.879        | 0.038 (–0.448; 0.523) | 0.879        |

95% CI = 95% confidence interval, AoS = aortic valve stenosis, AR = aortic valve regurgitation, BSA = body surface area, LVOT = left ventricular outflow tract, STJ = sinotubular junction, TA = tubular ascending aorta.
follow-up and aortic surgery. A positive family history has been described as a denominator of risk as well. For now, it still is a matter of debate whether the timing of surgery in BAV should be based on absolute dimensions. A novel model for timing of follow-up and surgical intervention fed by data from observational studies incorporating the above aspects including genomics may improve surgical care for BAV patients but obviously needs validation in prospective trials.

4.1. Study limitations

Although the study population size was relatively large and the aortic measurements were repeated prospectively by 2 independent observers, some possible limitations merit attention. Despite the size, this study is prone to some bias due to its retrospective observational design. On the other hand, our hospital is a combined regional and tertiary center serving its own population. With that, we assume we evaluated a representative population when compared to populations in exclusively tertiary centers. Another limitation is inherent to the serial echocardiographic measurements. Measurements are dependent on image quality and availability of echocardiographic images. We tried to minimize bias based on image quality by requiring valid measurements from independent observers. Aortic dilatation is a lifelong process, necessitating long-term follow-up in clinical studies. Thus, aortic dilatation is frequently studied in retrospective cohorts. Although the retrospective study design inherently involves some limitations, the current manuscript represents the natural clinical course of BAV patients within our institution. These results have to be interpreted with caution in a population with a tricuspid aortic valve, since this group was not included in the present study and might show another natural clinical course of aortic dilatation when compared to patients with BAV.

Finally, despite the relatively large population size, the group of patients with a monocuspid aortic valve was relatively small and reliability of the analyses considering this group was considered low and was not included in this study.

4.2. Conclusion and clinical implications

The prediction of aortic complications resulting from (asymptomatic) aortic dilatation rates and timing of surgical intervention is a major challenge in patients with BAV, necessitating long-term and costly follow-up. Dilatation rates in BAV aortopathy vary widely among patients with a maximum dilatation rate of the TA, followed by the sinus of Valsalva and the STJ. Dilatation rates are not associated with BAV morphology, and thus BAV morphology should not be used for additional risk stratification. A small group of patients might benefit from a stricter follow-up to determine progression of dilatation at an early stage. Moreover, the risk of developing aortic complications should be determined individually during follow-up echocardiography. Finally, there is an unmet clinical need for improvement of risk stratification in BAV patients. Genomics is expected to gain importance in this field.

References

[1] Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29–322.
[2] Della Corte A, Bancone C, Buonocore M, et al. Pattern of ascending aortic dimensions predicts the growth rate of the aorta in patients with bicuspid aortic valve. JACC Cardiovasc Imaging 2013;6:1301–10.
[3] Michalena HI, Desjardins VA, Averinos JF, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation 2008;117: 2776–84.
[4] Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. JAMA 2008;300:1317–25.
[5] Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440–92.

[6] Hiratzka LF, Bakris GL, Beckman JA, et al. ACCF/AHA/ACE/SCA/SRST/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121:246–39.

[7] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery, Vahanian A, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451–2496.

[8] Erbel R, Aboyans V, Boileau C, et al. ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873–926.

[9] Hiratzka LF, Creager MA, et al. ACCF/AHA/ATS/ACR/ASA/SCA/SCAI/SIR/STS/VSM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease Representative Members and Surgical Acuity for aortic dilation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016;133:680–6.

[10] Verma S, Yanagawa B, Kahr S, et al. Knowledge, attitudes, and practice patterns in surgical management of bicuspid aortopathy: a survey of 100 cardiac surgeons. J Thorac Cardiovasc Surg 2013;146:1033–40.

[11] Nistri S, Sorbo MD, Marin M, et al. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. Heart 1999;82:19–22.

[12] Yasuda H, Nakatani S, Stugaard M, et al. Failure to prevent progressive dilatation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. Circulation 2005;110(suppl 1):I291–4.

[13] Fedak PW, Verma S, David TE, et al. Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation 2002;106:900–4.

[14] Nataatmadja M, West M, West J, et al. Abnormal extracellular matrix protein transport associated with increased apoptosis of vascular smooth muscle cells in Marfan syndrome and bicuspid aortic valve thoracic aortic aneurysm. Circulation 2003;108(suppl 1):I323–34.

[15] Burris NS, Hope MD. Bicuspid valve-related aortic disease: flow assessment with conventional phase-contrast MRI. Acad Radiol 2015;22:690–6.

[16] Hope MD, Hope TA, Meadows AK, et al. Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. Radiology 2010;255:53–61.

[17] Kang JW, Song HG, Yang DH, et al. Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction and bicuspid aortopathy: comprehensive evaluation using MDCT and echocardiography. JACC Cardiovasc Imaging 2013;6:510–61.

[18] Schafer BM, Lewin MB, Stout KK, et al. The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. Heart 2008;94:1634–8.

[19] Avadhanlani SA, Martin-Doyle W, Shaikh AY, et al. Predictors of ascending aortic dilation in bicuspid aortic valve disease: a five-year prospective study. Am J Med 2015;128:647–52.

[20] Detaint D, Michihena HI, Nkomo VT, et al. Aortic dilation patterns and rates in adults with bicuspid aortic valves: a comparative study with Marfan syndrome and degenerative aortopathy. Heart 2014;100:126–34.

[21] Thanassoulis G, Yip JW, Filton K, et al. Retrospective study to identify predictors of the presence and rapid progression of aortic dilation in patients with bicuspid aortic valves. Nat Clin Pract Cardiovasc Med 2008;5:821–8.

[22] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226–33.

[23] Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1–23. quiz 101–102.

[24] Holmes KW, Lehmann CU, Dalal D, et al. Progressive dilation of the ascending aorta in children with isolated bicuspid aortic valve. Am J Cardiol 2007;99:978–83.

[25] Jassal DS, Bhagirath KM, Tam JW, et al. Association of Bicuspid aortic valve morphology and aortic root dimensions: a substudy of the aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study. Echocardiography 2010;27:174–9.

[26] Cecconi M, Nistri S, Quarti A, et al. Aortic dilation in patients with bicuspid aortic valve. J Cardiovasc Med 2006;7:11–20.

[27] Fedak PW, de Sa MP, Verma S, et al. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. J Thorac Cardiovasc Surg 2003;126:797–806.

[28] Fedak PW, Verma S. The molecular fingerprint of bicuspid aortopathy. J Thorac Cardiovasc Surg 2013;145:1334.

[29] Garg V, Muth AN, Ransom JF, et al. Mutations in NOTCH1 cause aortic valve disease. Nature 2005;437:270–4.

[30] Ikonomidis JS, Jones JA, Barbour JR, et al. Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic dilatation. J Thorac Cardiovasc Surg 2003;126:806.

[31] Broberg CS, Therrien J. Understanding and treating aortopathy in Marfan syndrome and degenerative aortopathy. Heart 2014;100:926.

[32] Thanassoulis G, Yip JW, Filton K, et al. Retrospective study to identify predictors of the presence and rapid progression of aortic dilation in patients with bicuspid aortic valves. Nat Clin Pract Cardiovasc Med 2008;5:821–8.

[33] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226–33.

[34] Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1–23. quiz 101–102.

[35] Holmes KW, Lehmann CU, Dalal D, et al. Progressive dilation of the ascending aorta in children with isolated bicuspid aortic valve. Am J Cardiol 2007;99:978–83.

[36] Jassal DS, Bhagirath KM, Tam JW, et al. Association of Bicuspid aortic valve morphology and aortic root dimensions: a substudy of the aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study. Echocardiography 2010;27:174–9.

[37] Cecconi M, Nistri S, Quarti A, et al. Aortic dilation in patients with bicuspid aortic valve. J Cardiovasc Med 2006;7:11–20.

[38] Fedak PW, de Sa MP, Verma S, et al. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. J Thorac Cardiovasc Surg 2003;126:797–806.

[39] Fedak PW, Verma S. The molecular fingerprint of bicuspid aortopathy. J Thorac Cardiovasc Surg 2013;145:1334.

[40] Garg V, Muth AN, Ransom JF, et al. Mutations in NOTCH1 cause aortic valve disease. Nature 2005;437:270–4.

[41] Ikonomidis JS, Jones JA, Barbour JR, et al. Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic aneurysms of patients with bicuspid or tricuspid aortic valves. J Thorac Cardiovasc Surg 2007;133:1028–36.

[42] Broberg CS, Therrien J. Understanding and treating aortopathy in bicuspid aortic valve. Trends Cardiovasc Med 2015;25:445–51.

[43] Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. Circulation 2009;119:880–90.

[44] Frenck M, Pape LA. Changes in size of ascending aorta and aortic valve function with time in patients with congenital bicuspid aortic valves. Am J Cardiol 2013;92:43–6.

[45] Pape LA, Tsai TT, Iselbacher EM, et al. Aortic diameter = 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). Circulation 2007;116:1120–7.