The Prevalence of Coronary Artery Disease in Bicuspid Aortic Valve Patients: An Overview of the Literature

Onur B. Dolmaci, MD[1,2]   Tijmen L. Hilhorst, Bsc[2]   Arjan Malekzadeh, PhD[3]   Bart J.A. Mertens, PhD[4]
Robert J.M. Klautz, MD, PhD[1,2]   Robert E. Poelmann, PhD[5,6]   Nimrat Grewal, MD, PhD[1,2,7]

[1] Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands
[2] Department of Cardiothoracic Surgery, Amsterdam University Medical Center, Amsterdam, The Netherlands
[3] Medical Library, Amsterdam University Medical Center, Location University of Amsterdam, Amsterdam, Netherlands
[4] Department of Statistics, Leiden University Medical Center, Leiden, Netherlands
[5] Institute of Biology, Leiden University, Sylvius Laboratory, Leiden, Netherlands

Address for correspondence Nimrat Grewal, MD, PhD, Department of Cardiothoracic Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands (e-mail: N.Grewal@lumc.nl).

[6] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
[7] Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, The Netherlands

Aorta (Stamford)

Abstract

The prevalence of coronary artery disease (CAD) in bicuspid aortic valve (BAV) patients is a debatable topic. Several studies have indicated that BAV patients have a lower prevalence of CAD compared with patients with a tricuspid aortic valve (TAV), but the effects of age and gender have not always been considered. This systematic review provides an overview of articles which report on CAD in BAV and TAV patients. Searches were executed in April 2021 and January 2022 according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines in three online databases: Medline, Embase, and Scopus. Screening and data extraction was done by two investigators separately. Primary and secondary outcomes were compared between BAV and TAV patients; a fixed effects model was used for correcting on confounders. Literature search yielded 1,529 articles with 44 being eligible for inclusion. BAV patients were younger (56.4 ± 8.3 years) than TAV patients (64 ± 10.3 years, $p < 0.001$). All CAD risk factors and CAD were more prevalent in TAV patients. No significant difference remained after correcting for age and gender as confounders. BAV patients have a lower prevalence of CAD and CAD risk factors compared with TAV patients. However, when the age differences between both groups are considered in the analyses, a similar prevalence of both CAD and CAD risk factors is found.

Keywords

► aortic valve stenosis
► atherosclerosis
► bicuspid aortic valve
► coronary artery disease
► tricuspid aortic valve
► coronary revascularization

Introduction

A bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly, with a prevalence of 1 to 2% in the general population.[1,2] Early embryonic defects are held responsible for the development of a BAV and are also associated with the development of thoracic aortopathy in these patients.[3,4] Besides the high risk for developing thoracic aortopathy,[5]

BAV patients are also at risk of developing aortic valve diseases such as an aortic valve stenosis.[1,2] Although both BAV and tricuspid aortic valve (TAV) patients may develop these diseases, the risk in BAV patients is considered much higher with an additional earlier onset of these alterations compared with patients with a TAV.[6]

Aside from the differences in risk and onset of the aortic valve disease, BAV and TAV patients also show differences in pathophysiology and population characteristics, which is best seen in aortic valve stenosis patients. Traditionally, cardiovascular aging (i.e., wear and tear) was considered as the sole contributor to aortic valve calcification (i.e., stenosis). However, recent studies have now shown an important role of cardiovascular risk factors, such as hypertension, hypercholesterolemia, smoking, age, and male sex, in the development of an aortic valve stenosis.[7–11] This multifactorial pathophysiology, which is considered the atherosclerotic disease spectrum, is also the underlying cause of the association of an aortic valve stenosis with coronary artery disease (CAD).[7,12,13] Although these new observations are true for TAV patients, BAV patients do not fit the same profile as TAV patients and the exact pathogenesis of aortic valve stenosis in BAV patients remains unclear. While carrying a higher risk for aortic valve stenosis, the prevalence of cardiovascular risk factors and CAD is found significantly lower in BAV compared with that of TAV patients.[12,13] Furthermore, less calcification and atherosclerotic plaque formation is found in the thoracic aorta of BAV patients, which led to the hypothesis that BAV patients have a lower atherosclerotic disease burden compared with TAV patients. Only a few studies have directly investigated atherosclerosis in BAV patients through imaging (e.g., coronary angiography or computed tomography) or histology. Our knowledge of the role and prevalence of atherosclerosis in BAV patients therefore remains scarce. The literature regarding this subject is also inconsistent, with some sources even suggesting an increased risk for atherosclerosis in BAV individuals.[14] Since direct investigations of atherosclerosis are rare, clinical CAD and coronary revascularization (both indirect markers of atherosclerosis) are often used to compare and evaluate the atherosclerotic disease burden in BAV patients.

This review provides an overview of the studies that reported on CAD in BAV patients. Furthermore, comparisons will be made with TAV patients and the prevalence of cardiovascular risk profiles will be provided as secondary outcomes.

Methods

Study Objectives

The purpose of this analysis is to provide an overview of studies reporting on the prevalence of CAD and CAD risk factors in BAV and TAV patients. Primary outcomes were a prior myocardial infarction, prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG) and concomitant CABG. Secondary outcomes were the CAD risk factors, which included hypertension, hypercholesterolemia, and diabetes mellitus.

Search Strategy and Study Selection

Two delimited searches were executed in April 2021 and January 2022, in line with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[15] Literature search was performed using online databases (Medline [Ovid], Embase [Ovid], and Scopus). The searches contained terms for bicuspid and TAVs, coronary revascularization (e.g., PCI and CABG), myocardial ischemia, and CAD. The search strategy was not restricted by the year of publication. Studies that could not be translated reliably, case reports, reviews, and animal studies were excluded (see ►Supplementary File for full search strategy, available in online version only). Two authors (O.B.D. and T.L.H.) screened all articles independently based on title and abstract using Rayyan.[16] Included articles were then reviewed in full text. In case of conflict in inclusion, discordances were discussed and resolved.

Data Extraction

All studies reporting presence of CAD (including coronary revascularization through CABG or PCI) in BAV and in TAV patients were included and evaluated in this analysis. If a paper was considered eligible, data were extracted. Extracted data included: sample size subdivided into BAV and TAV, demographics, history of CAD (prior myocardial infarction, prior PCI, prior CABG), concomitant CABG, presence of CAD (through coronary imaging), risk factors for CAD (hypertension, hypercholesterolemia, diabetes mellitus, tobacco usage, body mass index), and mortality.

Statistical Analysis (and Risk of Bias Assessment)

Data are presented as absolute number of cases with percentages, means, and standard deviation (reported as mean ± standard deviation) in continuous variables with a normal distribution and as median with the interquartile range in continuous variables without a normal distribution. Normality tests, skewness, and kurtosis were performed for all variables. Normally distributed continuous data were compared using the t-test. In continuous variables without a normal distribution, the Mann–Whitney U test was used, and the Fisher's exact test was used for categorical data. A fixed effects model was developed to correct for the differences in age and gender between the BAV and TAV groups. A p-value of <0.05 was considered to be significant. All statistical analyses were conducted using IBM SPSS for Windows version 25.0.

Results

Literature Search and Outcome

The initial literature search yielded 1,529 studies. ►Fig. 1 shows the overview of the selection process of this systematic review. After selection, a total of 44 articles were eligible for inclusion in this systematic review. The articles reported data on a sum of 60,695 patients, of which 19,934 (32.8%) were patients with a BAV. The articles mainly reported on male subjects ($n = 41,471$, 68.3%) in both groups with a mean age of 60.2 years (± 10 years). BAV patients were younger ($56.4 ± 8.3$ years) compared with
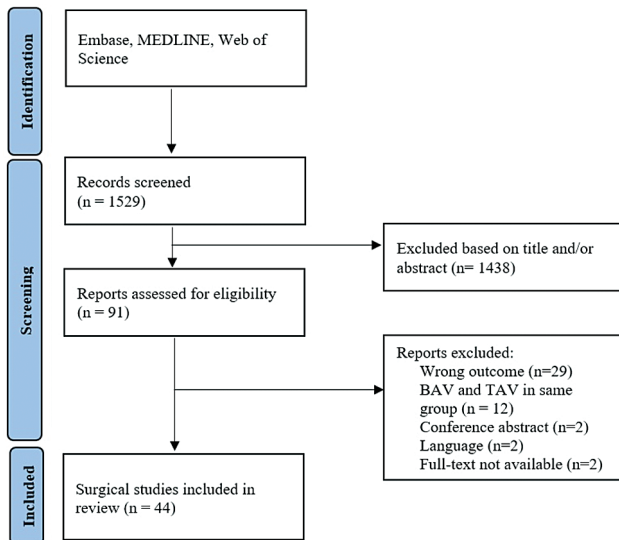
Fig. 1 Selection flowchart.

TAV patients (64 ± 10.3 years, $p < 0.001$). An overview of the outcomes are provided in ►**Tables 1**, **2** and in ►**Fig. 2**.

Coronary Artery Disease

Prior Myocardial Infarction

Nine studies[12,13,17–23] reported on the prevalence of prior myocardial infarction, which included a total of 6,504 patients. Myocardial infarction was reported in 768 (11.8%) of the total group. Of all included BAV patients, 6.9% had a prior myocardial infarction (101 of 1,467 included patients) versus 13.2% of TAV patients (667 of 5,037 included patients), which was a significant difference ($p < 0.001$). No significant difference remained after correcting for the age and gender differences between both groups (odds ratio [OR] = 0.73 [95% confidence interval, CI = 0.43–1.23]; $p = 0.215$).

Prior Percutaneous Coronary Intervention

Six studies[12,13,18,19,21,24] reported on the prevalence of a prior PCI, which included a total of 43,413 patients. A PCI was performed in the past in a total of 2,051 (4.7%) patients. A prior PCI was reported in 409 (2.9%) of 14,247 BAV patients and in 1,642 (5.6%) of 29,166 TAV patients ($p < 0.001$). After correcting for age and gender, a nonsignificant difference was seen between both groups (OR = 0.97 [95% CI = 0.55–1.70]; $p = 0.898$).

Prior Coronary Artery Bypass Grafting

Seven studies[12,13,20,21,24–26] reported on the prevalence of a prior CABG, which included a total of 41,589 patients. Within this group, 1,083 (2.6%) patients had a CABG in their medical history. The prevalence in the BAV group was 151 (1%) of 14,416 and 932 (3.4%) of 27,173 in the TAV group ($p < 0.001$). However, after correction for age and gender, the difference became nonsignificant (OR = 0.34 [95% CI = 0.03–4.38]; $p = 0.366$).

Table 1 Overview of outcomes

Medical history	Bicuspid aortic valve		Tricuspid aortic valve	
	Number of patients with reported outcome (%)	Total patients in studies	Number of patients with reported outcome (%)	Total patients in studies
Prior myocardial infarction	101 (6.9)	1,467	667 (13.2)	5,037
Prior percutaneous coronary intervention	409 (2.9)	14,247	1,642 (5.6)	29,166
Prior coronary artery bypass grafting	151 (1.0)	14,416	932 (3.4)	27,173
Concomitant coronary artery bypass grafting	1,095 (23.1)	4,746	4,486 (39.5)	11,349
Hypertension	10,045 (57.2)	17,560	24,847 (70.5)	35,247
Hypercholesterolemia	730 (27.4)	2,660	2,580 (36.5)	7,061
Diabetes mellitus	2,148 (11.7)	1,8317	6,316 (16.3)	38,703

Abbreviation: CAD, coronary artery disease.
Note: The absolute (uncorrected) prevalence of CAD and CAD risk factors per group and the total number of included patients, of which these outcomes were reported.

Table 2 Fixed effects model (primary outcomes)

Medical history	Coefficient	Standard error	*p*-Value
Prior myocardial infarction	−0.318	0.24	0.215
Prior percutaneous coronary intervention	−0.032	0.24	0.968
Prior coronary artery bypass grafting	−1.094	1.15	0.366
Concomitant coronary artery bypass grafting	−0.192	0.19	0.311

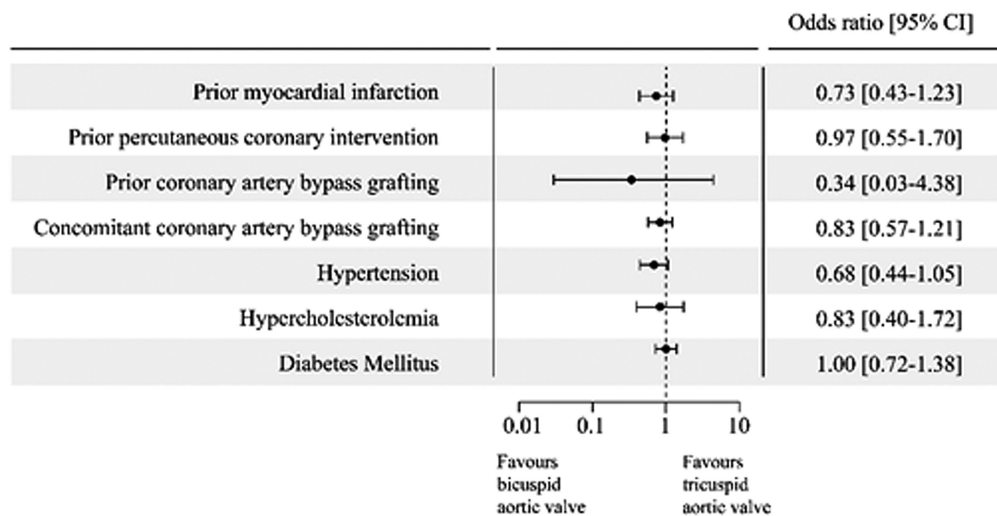Note: Evaluation of the primary outcomes using a fixed effects model.

Fig. 2 Forest plots of the corrected analyses. Figure shows the forest plots of the corrected analyses for each outcome. All outcomes show to be equally prevalent between both groups after correcting for the age and sex differences between the BAV and TAV groups. BAV, bicuspid aortic valve; CI, confidence interval; TAV, tricuspid aortic valve.

Concomitant Coronary Artery Bypass Grafting

Twenty-five studies[7,12,13,18,20,23,26–44] reported on the prevalence of a concomitant CABG, which included a total of 16,095 patients. A concomitant CABG was performed in a total of 5,581 (34.7%) patients. These included 1,095 (23.1%) of 4,746 BAV patients, 4,486 (39.5%) of 11,349 TAV patients ($p < 0.001$). After correction for age and gender, the difference between both groups became nonsignificant (OR = 0.83 [95% CI = 0.57–1.21]; $p = 0.311$).

Cardiovascular Risk Factors

Hypertension

Thirty-five studies[7,12,13,17–26,28,29,32–34,36,39,40,45–58] reported on the prevalence of hypertension, which included 52,807 patients. Hypertension was present in a total of 34,892 (66.1%) patients. These included 10,045 (57.2%) of 17,560 BAV patients and 24,847 (70.5%) of 35,247 TAV patients ($p < 0.001$). After correcting for age and gender, the difference became nonsignificant (OR = 0.68 [95% CI: 0.44–1.05]; $p = 0.082$).

Hypercholesterolemia

Twenty-three studies[12,13,17,18,20,21,23,25,26,28,29,33,39,40,45,47,49–51,55–57,59] reported on the prevalence of hypercholesterolemia, which included a total of 5,240 patients. Within this group, 3,310 (63.2%) had hypercholesterolemia. These included 730 (27.4%) of 2,660 BAV patients and 2,580 (36.5%) of 7,061 TAV patients ($p < 0.001$). After correcting for age and gender, these differences became nonsignificant (OR = 0.83 [95% CI = 0.40–1.72]; $p = 0.602$).

Diabetes Mellitus

Thirty-five studies[7,12,13,17–26,28,29,31–34,36,39,40,45–51,53,55–59] reported on the prevalence of diabetes mellitus, which included a total of 57,020 patients. In a total of 8,464 (14.8%) patients

within this group diabetes mellitus was present. These included 2,148 (11.7%) of 18,317 BAV and 6,316 (16.3%) of 38,703 TAV patients ($p < 0.001$), which was nonsignificant after correction for age and gender (OR = 1.00 [95% CI = 0.72–1.38]; $p = 0.989$).

Discussion

This systematic review aimed to provide an overview of all articles that reported on the prevalence of CAD and risk factors for CAD in BAV patients, and to compare these data with those of TAV patients. These results showed a lower prevalence of CAD and CAD risk factors in BAV patients. However, when corrected for the difference in age between the BAV and TAV patients, no significant differences in the prevalence of both CAD and CAD risk factors remained.

Comparisons between BAV and TAV patients have always been complicated due to the differences in age between both groups at the time of surgery, since BAV patients are on average 7 to 10 years younger than TAV patients at the time of surgery.[6] Especially when focusing on a topic like the prevalence of atherosclerosis, in which age is an important contributing factor in the pathophysiology, it is crucial to consider age as an important confounder. This is also highlighted in the current study, in which all significant differences disappeared after correcting for the age differences. Similar results were seen in a previous systematic review in which age was also an important confounder.[60] This indicates no clinical differences in CAD and coronary revascularization between BAV and TAV patients. Although not significantly different, the prevalence of CAD risk factors was high in both groups, indicating that an individual approach for treating these comorbidities is important for both groups. Clinicians should especially focus on the treatment of hypertension in BAV patients, as both hypertension and a BAV are important risk factors for developing an aortic dissection.

In this review CAD was chosen to study as a marker for atherosclerosis, since papers that directly investigate the presence of atherosclerotic plaque formation (e.g., with coronary imaging or histopathologically) are scarce.[12,13] It is important to point out that CAD is an end-stage disease and coronary revascularization is only advised in patients with coronary stenosis of more than 70%.[61] Only studying CAD as a marker for atherosclerosis would therefore exclude the larger portion of patients with coronary sclerosis that causes less than 70% coronary obstruction.

Previous studies that used different modalities to directly investigate the presence of atherosclerotic plaque formation in BAV patients (e.g., with coronary angiography, computed tomography, and histopathology) indicated that BAV patients have a lower prevalence of CAD (and atherosclerotic plaque formation) when compared with age- and sex-matched TAV patients.[12,13] As mentioned earlier, differences in aortic wall composition between BAV and TAV patients could be an explanation for the lower tendency to develop atherosclerosis in BAV patients. Histopathological studies have revealed a thinner intimal layer of the aortic wall and a phenotypical switch defect of vascular smooth muscle cells characteristic for BAV patients.[3,62,63] Since the vascular smooth muscle cells are important contributors to atherosclerotic plaque formation and the plaques develop in the intima, the abovementioned vascular defects could complicate the formation of plaques within this layer and therefore result in a lower tendency for developing atherosclerosis.

Based on the results of our studies, no conclusions can be drawn about the prevalence of general atherosclerosis in BAV patients. However, this study did show a comparable prevalence of CAD between BAV and TAV patients, as an indirect measure of atherosclerosis. This implies that whether or not a difference in atherosclerosis is present between both groups, it does not cause significant differences clinically regarding CAD and coronary revascularization. This study endorses that age is an important factor in the development and presence of CAD, which could contribute to lesser findings in the preoperative workup of BAV patients. Less invasive coronary imaging techniques (such as computed tomography) could be considered as a good first step in preoperative BAV patients with a low cardiovascular risk profile (e.g., no CAD risk factors and a low age) instead of a traditional coronary angiography.

Limitations

As pointed out before, this review only focused on late (clinical) outcomes of atherosclerosis (CAD with significant coronary occlusion). The conclusions drawn out of this study therefore are only based on the late stages of atherosclerosis and do not include patients with coronary stenosis, which is not significant (as yet). Furthermore, this review included a large proportion of male subjects. Due to the clinical predominance of males within the BAV population, statistical analyses were adjusted for the differences in prevalence. Although these corrections have been made, the interpretation of these results for female subjects still should be done cautiously.

Conclusion

The reported prevalence of CAD and CAD risk factors are comparable between BAV and TAV patients when adjusted for the age and sex differences between both groups.

Conflict of Interest
None declared.

References

1 Ward C. Clinical significance of the bicuspid aortic valve. Heart 2000;83(01):81–85
2 Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55(25):2789–2800
3 Grewal N, Gittenberger-de Groot AC, Lindeman JH, et al. Normal and abnormal development of the aortic valve and ascending aortic wall: a comprehensive overview of the embryology and pathology of the bicuspid aortic valve. Ann Cardiothorac Surg 2022;11(04):380–388
4 Grewal N, Gittenberger-de Groot AC, Thusen JV, et al. The Development of the ascending aortic wall in tricuspid and bicuspid aortic valve: a process from maturation to degeneration. J Clin Med 2020;9(04):908
5 Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation 2002;106(08):900–904
6 Otto CM. Calcification of bicuspid aortic valves. Heart 2002;88 (04):321–322
7 Boudoulas KD, Wolfe B, Ravi Y, Lilly S, Nagaraja HN, Sai-Sudhakar CB. The aortic stenosis complex: aortic valve, atherosclerosis, aortopathy. J Cardiol 2015;65(05):377–382
8 Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90(02):844–853
9 Capoulade R, Clavel MA, Dumesnil JG, et al; ASTRONOMER Investigators. Impact of metabolic syndrome on progression of aortic stenosis: influence of age and statin therapy. J Am Coll Cardiol 2012;60(03):216–223
10 Gotoh T, Kuroda T, Yamasawa M, et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). Am J Cardiol 1995;76(12):928–932
11 Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. J Am Coll Cardiol 1997;29(03): 630–634
12 Dolmaci OB, Driessen AHG, Klautz RJM, Poelmann R, Lindeman JHN, Grewal N. Comparative evaluation of coronary disease burden: bicuspid valve disease is not atheroprotective. Open Heart 2021;8(02):e001772
13 Dolmaci OB, Legué J, Lindeman JHN, et al. Extent of coronary artery disease in patients with stenotic bicuspid versus tricuspid aortic valves. J Am Heart Assoc 2021;10(12):e020080
14 Magni P. Bicuspid aortic valve, atherosclerosis and changes of lipid metabolism: are there pathological molecular links? J Mol Cell Cardiol 2019;129:231–235
15 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535
16 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(01):210
17 Agnese V, Pasta S, Michelena HI, et al. 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. J Mol Cell Cardiol 2019;135:31–39

18 Çelik M, Milojevic M, Durko AP, Oei FBS, Bogers AJJC, Mahtab EAF. Differences in baseline characteristics and outcomes of bicuspid and tricuspid aortic valves in surgical aortic valve replacement. Eur J Cardiothorac Surg 2021;59(06):1191–1199

19 Costopoulos C, Latib A, Maisano F, et al. Comparison of results of transcatheter aortic valve implantation in patients with severely stenotic bicuspid versus tricuspid or nonbicuspid valves. Am J Cardiol 2014;113(08):1390–1393

20 Huntley GD, Thaden JJ, Alsidawi S, et al. Comparative study of bicuspid vs. tricuspid aortic valve stenosis. Eur Heart J Cardiovasc Imaging 2018;19(01):3–8

21 Leone O, Corsini A, Pacini D, et al. The complex interplay among atherosclerosis, inflammation, and degeneration in ascending thoracic aortic aneurysms. J Thorac Cardiovasc Surg 2020;160 (06):1434–1443.e6

22 Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors–a causal relationship? A clinical morphologic study. Clin Cardiol 1991;14(12):995–999

23 Etz CD, von Aspern K, Hoyer A, et al. Acute type A aortic dissection: characteristics and outcomes comparing patients with bicuspid versus tricuspid aortic valve. Eur J Cardiothorac Surg 2015;48(01):142–150

24 Elbadawi A, Saad M, Elgendy IY, et al. Temporal trends and outcomes of transcatheter versus surgical aortic valve replacement for bicuspid aortic valve stenosis. JACC Cardiovasc Interv 2019;12(18):1811–1822

25 Eleid MF, Forde I, Edwards WD, et al. Type A aortic dissection in patients with bicuspid aortic valves: clinical and pathological comparison with tricuspid aortic valves. Heart 2013;99(22): 1668–1674

26 Badiu CC, Eichinger W, Bleiziffer S, et al. Should root replacement with aortic valve-sparing be offered to patients with bicuspid valves or severe aortic regurgitation? Eur J Cardiothorac Surg 2010;38(05):515–522

27 Abdulkareem N, Soppa G, Jones S, Valencia O, Smelt J, Jahangiri M. Dilatation of the remaining aorta after aortic valve or aortic root replacement in patients with bicuspid aortic valve: a 5-year follow-up. Ann Thorac Surg 2013;96(01):43–49

28 Ali A, Patel A, Ali Z, et al. Medium to long-term clinical outcome following stentless aortic valve replacement: comparison between allograft and xenograft valves. Interact Cardiovasc Thorac Surg 2010;11(02):166–170

29 Cozijnsen L, van der Zaag-Loonen HJ, Cozijnsen MA, et al. Differences at surgery between patients with bicuspid and tricuspid aortic valves. Neth Heart J 2019;27(02):93–99

30 Davies MJ, Treasure T, Parker DJ. Demographic characteristics of patients undergoing aortic valve replacement for stenosis: relation to valve morphology. Heart 1996;75(02):174–178

31 Holmgren A, Enger TB, Naslund U, et al. Long-term results after aortic valve replacement for bicuspid or tricuspid valve morphology in a Swedish population. Eur J Cardiothorac Surg 2020;12:12

32 Holubec T, Zacek P, Jamaliramin M, et al. Valve cuspidity: a risk factor for aortic valve repair? J Card Surg 2014;29(05):585–592

33 Kayatta MO, Leshnower BG, McPherson L, Binongo JN, Lasanajak Y, Chen EP. Valve-sparing root replacement provides excellent midterm outcomes for bicuspid valve aortopathy. Ann Thorac Surg 2019;107(02):499–504

34 Kvitting JP, Kari FA, Fischbein MP, et al. David valve-sparing aortic root replacement: equivalent mid-term outcome for different valve types with or without connective tissue disorder. J Thorac Cardiovasc Surg 2013;145(01):117–126, 127.e1–e5

35 Liebrich M, Kruszynski M, Roser D, Doll N, Hemmer W. Aortic valve-sparing reimplantation technique (David-procedure) in different pathologies: long-term clinical and echocardiographic follow-up in 170 patients. A single-center experience. Thorac Cardiovasc Surg 2011;59(Suppl 1)

36 Mautner GC, Mautner SL, Cannon RO III, Hunsberger SA, Roberts WC. Clinical factors useful in predicting aortic valve structure in patients > 40 years of age with isolated valvular aortic stenosis. Am J Cardiol 1993;72(02):194–198

37 Mosala Nezhad Z, de Kerchove L, Hechadi J, et al. Aortic valve repair with patch in non-rheumatic disease: indication, techniques and durability†. Eur J Cardiothorac Surg 2014;46(06): 997–1005, discussion 1005

38 Naito S, Petersen J, Reichenspurner H, Girdauskas E. The impact of coronary anomalies on the outcome in aortic valve surgery: comparison of bicuspid aortic valve versus tricuspid aortic valve morphotype. Interact Cardiovasc Thorac Surg 2018;26(04): 617–622

39 Ouzounian M, Feindel CM, Manlhiot C, David C, David TE. Valve-sparing root replacement in patients with bicuspid versus tricuspid aortic valves. J Thorac Cardiovasc Surg 2019;158(01):1–9

40 Regeer MV, Versteegh MI, Klautz RJ, et al. Effect of aortic valve replacement on aortic root dilatation rate in patients with bicuspid and tricuspid aortic valves. Ann Thorac Surg 2016;102(06): 1981–1987

41 Roberts WC, Ko JM. Weights of operatively-excised stenotic unicuspid, bicuspid, and tricuspid aortic valves and their relation to age, sex, body mass index, and presence or absence of concomitant coronary artery bypass grafting. Am J Cardiol 2003;92(09): 1057–1065

42 Roberts WC, Ko JM, Moore TR, Jones WH III. Causes of pure aortic regurgitation in patients having isolated aortic valve replacement at a single US tertiary hospital (1993 to 2005). Circulation 2006; 114(05):422–429

43 Roberts WC, Roberts CC, Vowels TJ, et al. Effect of coronary bypass and valve structure on outcome in isolated valve replacement for aortic stenosis. Am J Cardiol 2012;109(09):1334–1340

44 Stephan PJ, Henry AC III, Hebeler RF Jr, Whiddon L, Roberts WC. Comparison of age, gender, number of aortic valve cusps, concomitant coronary artery bypass grafting, and magnitude of left ventricular-systemic arterial peak systolic gradient in adults having aortic valve replacement for isolated aortic valve stenosis. Am J Cardiol 1997;79(02):166–172

45 Branchetti E, Bavaria JE, Grau JB, et al. Circulating soluble receptor for advanced glycation end product identifies patients with bicuspid aortic valve and associated aortopathies. Arterioscler Thromb Vasc Biol 2014;34(10):2349–2357

46 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(01):276–282

47 Hwang HY, Shim MS, Park EA, Ahn H. Reduction aortoplasty for the ascending aortic aneurysm with aortic valve disease. Does bicuspid valve matter? Circulation 2011;75(02):322–328

48 Jackson V, Eriksson MJ, Caidahl K, Eriksson P, Franco-Cereceda A. Ascending aortic dilatation is rarely associated with coronary artery disease regardless of aortic valve morphology. J Thorac Cardiovasc Surg 2014;148(06):2973–2980.e1

49 Manjunath CN, Agarwal A, Bhat P, et al. Coronary artery disease in patients undergoing cardiac surgery for non-coronary lesions in a tertiary care centre. Indian Heart J 2014;66(01):52–56

50 Nakamura Y, Ryugo M, Shikata F, et al. The analysis of ascending aortic dilatation in patients with a bicuspid aortic valve using the ratio of the diameters of the ascending and descending aorta. J Cardiothorac Surg 2014;9:108

51 Philip F, Faza NN, Schoenhagen P, et al. Aortic annulus and root characteristics in severe aortic stenosis due to bicuspid aortic valve and tricuspid aortic valves: implications for transcatheter aortic valve therapies. Catheter Cardiovasc Interv 2015;86(02):E88–E98

52 Roberts WC, Vowels TJ, Ko JM. Natural history of adults with congenitally malformed aortic valves (unicuspid or bicuspid). Medicine (Baltimore) 2012;91(06):287–308

53 Rylski B, Desai ND, Bavaria JE, et al. Aortic valve morphology determines the presentation and surgical approach to acute type A aortic dissection. Ann Thorac Surg 2014;97(06):1991–1996, discussion 1996–1997

54 Shen M, Tastet L, Capoulade R, et al. Effect of aortic valve morphology on the hemodynamic and anatomic progression of aortic stenosis. Circulation 2019;140(Suppl 1):A11488

55 Sia CH, Ho JS, Chua JJ, et al. Comparison of clinical and echocardiographic features of asymptomatic patients with stenotic bicuspid versus tricuspid aortic valves. Am J Cardiol 2020; 128:210–215

56 Yalonetsky S, Horlick EM, Osten MD, Benson LN, Oechslin EN, Silversides CK. Clinical characteristics of coronary artery disease in adults with congenital heart defects. Int J Cardiol 2013;164 (02):217–220

57 Yuan SM, Jing H. The bicuspid aortic valve and related disorders. Sao Paulo Med J 2010;128(05):296–301

58 Brown B, Le T, Naeem A, et al. Stentless valves for bicuspid and tricuspid aortic valve disease. JTCVS Open 2021;8:177–188

59 Shen M, Tastet L, Capoulade R, et al. Effect of bicuspid aortic valve phenotype on progression of aortic stenosis. Eur Heart J Cardiovasc Imaging 2020;21(07):727–734

60 Poggio P, Cavallotti L, Songia P, et al. Impact of valve morphology on the prevalence of coronary artery disease: a systematic review and meta-analysis. J Am Heart Assoc 2016;5(05):e003200

61 Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). Circulation 1999;100(13):1464–1480

62 Grewal N, Gittenberger-de Groot AC, Poelmann RE, et al. Ascending aorta dilation in association with bicuspid aortic valve: a maturation defect of the aortic wall. J Thorac Cardiovasc Surg 2014;148(04):1583–1590

63 Grewal N, Velders BJJ, Gittenberger-de Groot AC, et al. A Systematic histopathologic evaluation of type-A aortic dissections implies a uniform multiple-hit causation. J Cardiovasc Dev Dis 2021;8(02):12