



# Incidence of bicuspid valve related aortic dissection: a systematic review and meta-analysis

Ashley R. Wilson-Smith<sup>1,2,3,4</sup>, Aditya Eranki<sup>3</sup>, Benjamin Muston<sup>2,5</sup>, Harish Kamalanathan<sup>3</sup>, Amanda Yung<sup>2,6</sup>, Michael L. Williams<sup>2,6</sup>, Prachi Sahai<sup>3</sup>, Caroline Zi<sup>5</sup>, Hector Michelena<sup>5</sup>

<sup>1</sup>The Chris O'Brien Lifehouse Center, Sydney, Australia; <sup>2</sup>The Collaborative Research Group (CORE), Sydney, Australia; <sup>3</sup>The John Hunter Hospital, Newcastle, Australia; <sup>4</sup>Department of Cardiothoracic Surgery, The Hunter Medical Research Institute (HMRI), Newcastle, Australia; <sup>5</sup>Department of Medical Research, The Mayo Clinic, Rochester, MN, USA; <sup>6</sup>Department of Cardiovascular and Thoracic Surgery, The University of Sydney, Sydney, Australia

Correspondence to: Dr. Ashley R. Wilson-Smith. The Collaborative Research Group (CORE), Sydney, Australia; Chris O'Brien Lifehouse, Sydney, Australia; The John Hunter Hospital, Newcastle, Australia. Email: wilsonsmithash597@gmail.com.

**Background:** The true incidence of bicuspid valve-related aortic dissection (AD) is extremely difficult to ascertain. This review aimed to provide the reported cumulative incidence of bicuspid aortic valve (BAV)-related AD in actively monitored study populations.

**Methods:** Four electronic databases were used to perform literature searches. A meta-analysis of proportions or means were performed for categorical and continuous variables, as appropriate. Survival data was calculated from the aggregation of Kaplan-Meier (KM) curves from the included studies, where reported.

**Results:** A total of 4,330 patients were identified in eleven studies. A cumulative incidence of bicuspid valve-related AD of 0.6% across a median follow-up time of 9 years was identified. Actuarial survival across this monitored population at 1, 3, 5 and 10 years was 97.2%, 96.7%, 92.45%, and 81.1%, respectively.

**Conclusions:** This systematic review and meta-analysis identified a low incidence of AD across the examined follow-up period. Large, prospective studies involving early identification of bicuspid valve pathology, recruitment, and follow-up of BAV cohorts with comparison to the baseline population are required to most accurately determine the outcomes of these patients.

**Keywords:** Bicuspid aortic valve (BAV); aortic dissection (AD); cumulative incidence



Submitted May 19, 2022. Accepted for publication Jul 11, 2022.

doi: 10.21037/acs-2022-bav-21

View this article at: <https://dx.doi.org/10.21037/acs-2022-bav-21>

## Introduction

The bicuspid aortic valve (BAV) has long been the focus of academic and surgical inquiry, with its earliest description attributed to Leonardo da Vinci some 400–500 years ago (1). Throughout the 19<sup>th</sup> century, Paget, Peacock, and Osler outlined the proclivity of these aberrant valves to obstruct, become incompetent, and harbor infective endocarditis (2). In the contemporary setting, the BAV has been the source of investigation as to its contribution to almost half of all isolated, severe aortic stenosis requiring intervention, and its association with catastrophic aortic phenomena like aortic dissection (AD) (3). The exact incidence of AD in patients with BAV remains elusive, however, given the impracticality

of carrying out large-scale population screening and follow-up. This is also in part due to the difficulty of detecting valvular abnormalities such as BAV early, given its oft asymptomatic progression throughout childhood and early adulthood. This systematic review and meta-analysis hence aimed to provide the cumulative incidence of bicuspid aortic valve-related AD in actively monitored cohorts.

## Methods

### Literature search strategy

Four electronic databases were used to perform the literature searches, including EMBASE, Ovid MEDLINE,

PubMed, and SCOPUS. These databases were searched from the date of database inception through to October 2021. For examination of the incidence of BAV-related AD, a search strategy using the combination of keywords and Medical Subject Headings (MeSH) including (Bicuspid aortic valve OR BAV) AND (incidence) AND (aortic dissection OR Stanford Type A OR Stanford Type B OR DeBakey) was carried out (Figure S1). Predefined selection criteria were applied to assess for inclusion (see “Inclusion and exclusion criteria”).

### Inclusion and exclusion criteria

Studies were included in the review if they examined the incidence of bicuspid aortic valve-related AD in an as-of-yet untreated (i.e., no previous surgical intervention for their BAV) patient population. Studies were excluded for: non-English reporting, case reports/small case series, registries without recruiting details, combined tricuspid aortic valve (TAV) and BAV populations (such that no statistical differentiation could be made), no mention of BAV-associated AD, if patients were referred for cardiac surgery in the first instance, and predominately pre-2000s cohorts (unless as a part of a consecutive institutional experience). Three reviewers (BM, HK, CZ) independently screened for the title and abstract of all identified records in the library, with a final reviewer (ARWS) completing a concurrent review of all records in isolation. Where the title and/or abstract provided insufficient detail in the determination of relevance for inclusion, a full-text review of the record was carried out in the first instance. The reference lists of the included studies were reviewed at completion of the database search to identify any extra, relevant studies not already included.

### Primary and secondary endpoints

The primary endpoints for analysis were the incidence rates of AD in surveyed populations and their freedom from mortality (all-cause). Secondary endpoints included baseline cohort characteristics, such as comorbid disease (i.e., hypertension, type 2 diabetes mellitus, ischemic heart disease, smoking status, non-BAV valvular disease/dysfunction) and freedom from AD-related mortality, if reported.

### Data extraction and critical appraisal

Two independent reviewers (BM, HK) extracted data

directly from publication texts, tables, and figures. A third reviewer (ARWS) independently reviewed and confirmed all extracted data. Differing opinions between the two main reviewers were resolved through discussion led by the primary investigator. Attempts were made to clarify insufficient/indistinct data from authors of included studies, as required. Data was extracted in a way that each study was effectively treated as a case series, irrespective of underlying design. The Newcastle-Ottawa score was used as the quality assessment tool (4).

### Statistics

A meta-analysis of proportions or means were performed for categorical and continuous variables, as appropriate, by an independent reviewer (MLW). A random effects model was used to account for differing regions, surgeon experience, surgical technique and equipment, and management protocols across the included studies. Means and standard deviations were calculated from the median, where reported, using the methods described by Wan and colleagues (5). Pooled data are presented as N (%) with 95% confidence intervals (CI). For outcome data, heterogeneity amongst studies was assessed using the  $I^2$  statistic. Thresholds for these values were considered as low, moderate, and high heterogeneity as 0–49%, 50–75% and greater than or equal to 75%, respectively. Meta-analysis of proportions or means were performed using Stata (version 17.0, StataCorp, Texas, USA). Survival data was calculated from the aggregation of Kaplan-Meier (KM) curves from the included studies, where reported, by utilizing the methods of Guyot and colleagues (6). Digitization of Kaplan Meier curves was performed using DigitizeIt (version 2.5.9, Braunschweig, Germany) and survival meta-analysis was performed using Stata (version 17.0, StataCorp, Texas, USA). KM curves were not included for aggregation in the instance where the number at risk at each time interval was not reported, or where graph quality was low (to the extent where clear digitizing of the original curve could not take place).

## Results

### Baseline demographic data—incidence population

A total of 4,330 patients were identified in the incidence library, drawn from 11 included studies (refer to Tables S1-S3) (7-17). Male patients accounted for 71.2%

**Table 1** Baseline demographic data and 95% CI

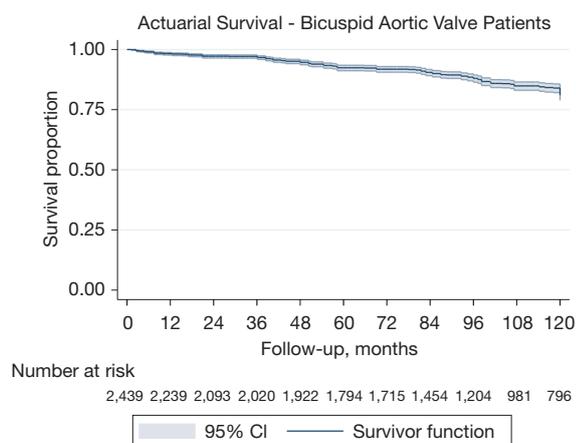
| Variables              | Demographic data + (95% CI) | I <sup>2</sup> value | Total patients* |
|------------------------|-----------------------------|----------------------|-----------------|
| Cohort (n)             | 4,330                       | –                    | 4,330           |
| Males                  | 3,104 (71.2%) (62.3–73.7%)  | 92                   | 4,330           |
| Age, mean ± SD         | 42.5±15.6 (34.4–50.3)       | 66                   | 4,330           |
| Hypertension           | 944 (31.6%) (24.3–39.4%)    | 95                   | 3,846           |
| T2DM                   | 122 (4.3%) (2.1–7.2%)       | 89                   | 3,846           |
| IHD                    | 8.4% (4.8–12.9%)            | 84                   | 1,733           |
| CVA-PD                 | 2.0% (1.2–3.0%)             | 35                   | 1,353           |
| Smoking all pack-years | 506 (19.9%) (10.5–31.4%)    | 97                   | 2,524           |
| Aortic stenosis        | 30.7% (18.6–44.3%)          | 98                   | 3,466           |
| AR                     | 44.1% (31.1–57.6%)          | 98                   | 4,330           |
| SD (pooled mean mm)    | 36.4 (36.1–36.6)            | 99                   | 3,240           |
| AAD (mm)               | 42.8 (40.5–44.6)            | 99                   | 3,618           |
| Congenital disease     | 10.2% (2.3–22.8%)           | 98                   | 3,148           |
| Cumulative iBAV-AD     | 0.6% (0.2–1.2%)             | 66                   | 4,330           |

Note: % all represent pooled values; smoking (all pack-years) represents total smokers without stratification of quantity. Total patients are presented for each variable. \*, flags to readers an explanation of the value presented. CI, confidence interval; n, number; SD, standard deviation; T2DM, type 2 diabetes mellitus; IHD, ischemic heart disease; CVA-PD, Cerebrovascular accidents with permanent deficits; AR, aortic regurgitation; SD, sinus diameter; AAD, ascending aortic diameter; iBAV-AD, incidence of bicuspid valve with aortic dissection.

(95% CI: 62.3–73.7%) I<sup>2</sup>=92 of the patient cohort. Rates of hypertension, type 2 diabetes mellitus, and ischemic heart disease were 31.6% (95% CI: 24.3–39.4%) I<sup>2</sup>=95, 4.3% (95% CI: 2.1–7.2%) I<sup>2</sup>=89, and 8.4% (95% CI: 4.8–12.9%) I<sup>2</sup>=84, respectively. Patients who had previously experienced cerebrovascular accidents with permanent deficits accounted for 2.0% of the cohort. Cumulative smoking status was 19.9% (95% CI: 10.5–31.4%) I<sup>2</sup>=97. Aortic stenosis and aortic regurgitation were present in 30.7% (95% CI: 18.6–44.3%) I<sup>2</sup>=98 and 44.1% (95% CI: 31.1–57.6%) I<sup>2</sup>=98 of the population, respectively. Subgroup differentiation based on classification of stenosis or regurgitation was not possible, as they were not reported. Mean pooled sinus diameter and ascending aortic diameter were 36.4 mm (95% CI: 36.1–36.6 mm) I<sup>2</sup>=99 and 42.8 mm (95% CI: 40.5–44.6 mm) I<sup>2</sup>=99, respectively. Overall pooled incidence of bicuspid valve-related AD events was 0.6% (95% CI: 0.2–1.2%) I<sup>2</sup>=66 across a median follow-up period of 9 years (108 months), with 1 case (0.66) per 100-patient years of follow-up (see

Table 1).

Variables with insufficient reporting for pooling (i.e., reported in ≤50% of studies) include body surface area (BSA, 5 studies), body mass index (BMI, 2 studies), New York Heart Association (NYHA) score (3 studies), Society of Thoracic Surgery (STS) score (0 studies), chronic obstructive pulmonary disease (COPD, 1 studies), heart failure (4 studies), atrial fibrillation (2 studies), transient ischemic events (TIA, 0 studies), prior cardiac surgery (0 studies), ejection fraction (EF, 5 studies), mean gradients (1 study), annulus diameter (3 studies), aortic root diameter (2 studies), sinotubular junction diameter (2 studies), septal defects (3 studies), and mitral valve prolapse (0 studies). The majority of studies were derived from either European (5 studies) or North American (5 studies) centers, with the remainder from an Asian center. Patient enrolment varied from as early as 1980, ranging through to 2019, though all papers were published after the year 2000 as noted in the methodology [2007–2020]. All studies were of moderate (1 study) or high quality (10 studies).



**Figure 1** Actuarial survival in bicuspid aortic valve patients with number at risk (failure events).

### Actuarial survival

Actuarial survival across this monitored population at 1, 3, 5 and 10 years was 97.2%, 96.7%, 92.45%, 81.1%, respectively (see *Figure 1*) (8,10,11,13,16,17).

### Discussion

This systematic review and meta-analysis sort to identify the cumulative, pooled incidence of bicuspid valve-related AD events based on the existing contemporary literature. Overall, the cumulative incidence of 0.6% of bicuspid valve-related AD across a follow-up period of 108 months was identified, with 1 case per 100-patient-years in a cohort of over four thousand patients. Three of eleven studies reported no aortic events throughout their follow-up. Survival across this monitored population at 1, 3, 5 and 10 years was 97.2%, 96.7%, 92.45%, 81.1%, respectively. This reaffirms the outcomes of the most recent meta-analysis on the subject from 2017, which demonstrated an incidence of AD in 0.4% of a total cohort of 6,446 patients, with similar rates of survival. Notably, this paper included all studies reporting outcomes across four decades of follow-up [1980–2017], and included those undergoing surgical intervention (18). These two elements were specifically used as exclusion criteria in this meta-analysis so as to reduce risk of bias and heterogeneity in an already extremely heterogenous cohort.

Additionally, this study corroborates the findings of the largest observational studies that are currently published on bicuspid valve patients. Despite a number

of large cohort studies illustrating significant proportions of aortic valve (AV) stenosis, aortic dilatation and other associated aortopathy in BAV patients, the long-term rates of dissection and mortality are low. These patients, when they do present symptomatically, are far younger than their tricuspid valve counterparts—being in their 40s and 50s—have less comorbid disease, and have worsened aortic dimensions; none of this is new information (19). Based on a literature review of the best available evidence to date, in those that do go on to have AVR and/or aortic surgery, survival is similar to that of the general population. This is noted by Masri *et al.* in their cohort, and in the cohorts presented in the 2018 American Association for Thoracic Surgery's (AATS) consensus guidelines on bicuspid valve-related aortopathy (10,16,17,20,21). It is critical to note that survival in these cohorts were higher in those that did go on to surgery in comparison to those that remained under active surveillance, though there are a multitude of reasons that are not necessarily related to bicuspid disease that could explain this difference. Lacking data on dissection-specific mortality constrains analysis in this respect.

Further, isolated AVRs in bicuspid patients can be safely performed with equivalent outcomes to that of the general population, though earlier surgery to correct the BAV with isolated AVR is not beneficial (22). With respect to those patients have received isolated aortic surgery in the available literature, aside from low rates of mortality and good freedom from reintervention, it should be noted that more conservative strategies of operating (i.e., with ascending diameters >5.5 cm, in the absence of high-risk factors) are not recommended based on the data (15,20). Limited discussion can be made regarding obstetric patients with BAV, other than that some data suggest that in the absence of connective tissue disorders, BAV patients fare no worse than the general population in relation to immediate aortic risk (23). Masri *et al.* make comment of a small cohort of patients they identified which did see rapid increases in rate of aortic dilatation, though this did not translate to increased rates of peri-pregnancy dissection (18). Potentially important contributing factors such as a family history of bicuspid valve disease, root phenotype, the effect of activity levels, and so on, are all incredibly difficult if not impossible to assess, as the literature available simply does not provide this data.

### Limitations

There are several limitations in the present review that must be discussed. Originally, it was intended that a direct

comparison between electively treated bicuspid aortic valves (i.e., in a non-emergent setting) and emergently treated BAV-associated ADs would take place alongside an examination of the incidence of dissection in these patients; however, there are very limited large cohort data on BAV-associated ADs managed emergently in the published literature, and pragmatically, there is not the scope within a single paper to examine both incidence and the outcomes of surgical candidates. Whilst it appears obvious that an emergent surgical population would fare worse than an electively managed cohort, an assessment of the exact differences in outcomes would have been beneficial in solidifying the importance of early detection, radiological surveillance, and prophylactic treatment. This was one of the advantageous features of the recent meta-analyses by Masri *et al.*, though there are methodological issues to note with respect to including surgical cohorts in amongst conservative but actively monitored cohorts (18). Additionally, BAV data is often aggregated in with normal aortic valve patients in some of the largest population-level analyses. Other important demographic and surgical data were consistently not reported, as noted previously. This is particularly surprising, as some of the highest quality papers on this topic clearly outline these variables as contributory to morbidity and mortality, and most are very common conditions within the general population. Whilst the findings presented herein are encouraging, it is critical to note that the patients identified likely represent the lower-risk demographic of those with bicuspid aortic valves; patients who had died from AD who were not identified or eligible for study inclusion would likely negatively skew results—though accounting for these patients is practically impossible.

### Future directions

The establishment of screening clinics and mass population recruitment, despite the seemingly impractical nature of the task, may not be unattainable. Crawford *et al.* has demonstrated the feasibility of surveillance clinics for adolescent patients identified as having BAVs, combining family screening and first-line imaging evaluation (i.e., magnetic resonance angiography, electrocardiogram-gated computational tomography) (24). In an era of progressively individualized surgery, tools such as computational fluid modelling, enabled by the above, presents surgeons with additional options in identifying “grey-zone” patients, and would be particularly useful in identifying those with

features of connective tissue disorders that may not present until critical aortic events. It is evident that repeated clinical and echocardiographic assessment is required to assess the functional state of the valve and the dimensions of the aorta throughout any BAV patient’s clinical journey, and that current guidelines for management appear to be appropriate and are being followed attentively.

### Conclusions

This systematic review and meta-analysis identified a low incidence of AD and good long-term freedom from mortality in surveilled patients with bicuspid aortic valves. To the authors’ knowledge, this is the only publication to present an aggregation of actuarial survival in this important cohort of patients. Large, prospective studies involving early identification, recruitment, thorough investigation and follow-up of BAV cohorts are required to most accurately determine the outcomes of these patients.

### Acknowledgments

*Funding:* None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

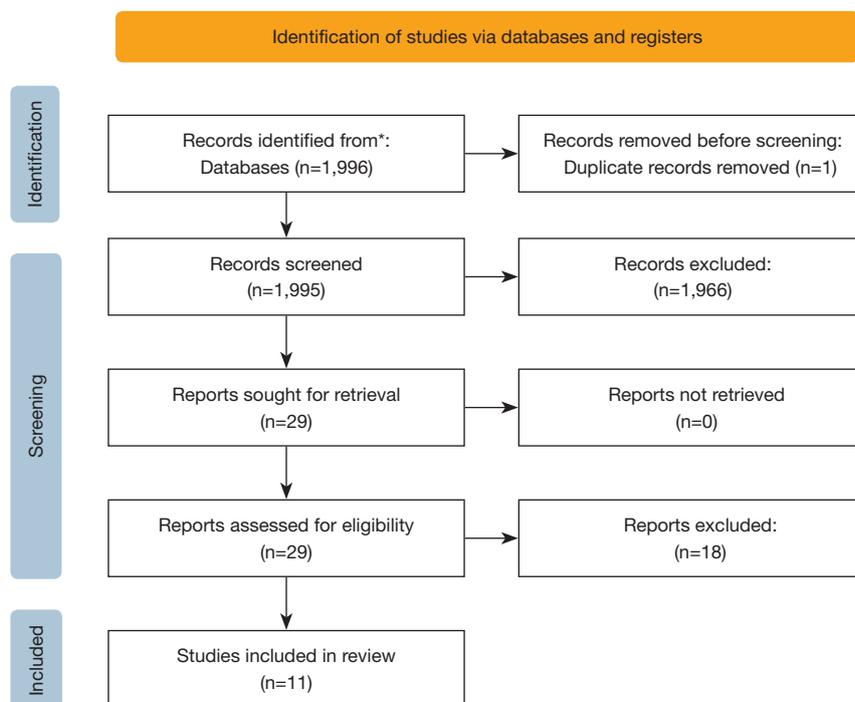
*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

### References

1. Braverman AC, Güven H, Beardslee MA, et al. The bicuspid aortic valve. *Curr Probl Cardiol* 2005;30:470-522.
2. Wauchope GM. The clinical importance of variations in the number of cusps forming the aortic and pulmonary valves. *QJM: An International Journal of Medicine* 1928;os-21: 383-99.
3. Cedars A, Braverman AC. The many faces of bicuspid

- aortic valve disease. *Progress in Pediatric Cardiology* 2012;34:91-6.
4. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
  5. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
  6. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.
  7. Alegret JM, Ligeró C, Vernis JM, et al. Factors related to the need for surgery after the diagnosis of bicuspid aortic valve: one center's experience under a conservative approach. *Int J Med Sci* 2013;10:176-82.
  8. Cheng C, Bohbot Y, Michelena HI, et al. Clinical Outcomes of Adults With Bicuspid Aortic Valve: A European Perspective. *Mayo Clin Proc* 2021;96:648-57.
  9. Duijnhouwer A, van den Hoven A, Merckx R, et al. Differences in Aortopathy in Patients with a Bicuspid Aortic Valve with or without Aortic Coarctation. *J Clin Med* 2020;9:290.
  10. Masri A, Kalahasti V, Alkharabsheh S, et al. Characteristics and long-term outcomes of contemporary patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg* 2016;151:1650-1659.e1.
  11. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA* 2011;306:1104-12.
  12. Oliver JM, Alonso-Gonzalez R, Gonzalez AE, et al. Risk of aortic root or ascending aorta complications in patients with bicuspid aortic valve with and without coarctation of the aorta. *Am J Cardiol* 2009;104:1001-6.
  13. Rodrigues I, Agapito AF, de Sousa L, et al. Bicuspid aortic valve outcomes. *Cardiol Young* 2017;27:518-29.
  14. Sun BJ, Oh JK, Lee SH, et al. Mid-term Clinical Outcomes in a Cohort of Asymptomatic or Mildly Symptomatic Korean Patients with Bicuspid Aortic Valve in a Tertiary Referral Hospital. *J Cardiovasc Imaging* 2019;27:105-18.
  15. Wojnarski CM, Svensson LG, Roselli EE, et al. Aortic Dissection in Patients With Bicuspid Aortic Valve-Associated Aneurysms. *Ann Thorac Surg* 2015;100:1666-73; discussion 1673-4.
  16. Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. *JAMA* 2008;300:1317-25.
  17. Davies RR, Kaple RK, Mandapati D, et al. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. *Ann Thorac Surg* 2007;83:1338-44.
  18. Masri A, Svensson LG, Griffin BP, et al. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart* 2017;103:1323-30.
  19. 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;99:1668-74.
  20. Borger MA, Fedak PWM, Stephens EH, et al. The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve-related aortopathy: Full online-only version. *J Thorac Cardiovasc Surg* 2018;156:e41-74.
  21. Michelena HI, Desjardins VA, Avierinos 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.
  22. Glaser N, Jackson V, Eriksson P, et al. Relative survival after aortic valve surgery in patients with bicuspid aortic valves. *Heart* 2021;107:1167-72.
  23. Toprak B, Szöcs K, Zengin-Sahm E, et al. Marfan Syndrome Versus Bicuspid Aortic Valve Disease: Comparative Analysis of Obstetric Outcome and Pregnancy-Associated Immediate and Long-Term Aortic Complications. *J Clin Med* 2020;9:1124.
  24. Crawford EE, McCarthy PM, Malaisrie SC, et al. Applications of a Specialty Bicuspid Aortic Valve Program: Clinical Continuity and Translational Collaboration. *J Clin Med* 2020;9:1354.

**Cite this article as:** Wilson-Smith AR, Eranki A, Muston B, Kamalanathan H, Yung A, Williams ML, Sahai P, Zi C, Michelena H. Incidence of bicuspid valve related aortic dissection: a systematic review and meta-analysis. *Ann Cardiothorac Surg* 2022;11(4):363-368. doi: 10.21037/acs-2022-bav-21



**Figure S1** PRISMA Flow-chart (incidence cohort). \*, Embase, Ovid MEDLINE, PubMed, SCOPUS.

| Study              | Cohort (n) | Males (n) | BSA  | BMI   | AS  | AV regurg | Annulus diameter (mm) | AR diameter (mm) | Sinus diameter (mm) | STJ diameter (mm) | Root dilatation (mm) | Ascending aorta diameter | Congenital defects | Septal defects | Newcastle Ottawa Scale Score* |
|--------------------|------------|-----------|------|-------|-----|-----------|-----------------------|------------------|---------------------|-------------------|----------------------|--------------------------|--------------------|----------------|-------------------------------|
| Alegret (2013)     | 120        | 96        | 1.84 | –     | 37  | 101       | –                     | 37±7             | –                   | –                 | 58                   | 40±8                     | –                  | –              | 13/16                         |
| Cheng (2021)       | 350        | 249       | 1.98 | –     | 142 | 80        | –                     | NR               | 38±6                | –                 | 167>4                | 38±7                     | –                  | –              | 14/16                         |
| Duijnhouwer (2020) | 499        | 281       | –    | 24.06 | 28  | 89        | –                     | NR               | 33.4±8.9            | –                 | 130>4                | 34.4±7.2                 | 114                | 33             | 12/16                         |
| Masri (2016)       | 972        | 701       | 2.0  | –     | –   | 549       | –                     | 3.4±0.7          | –                   | –                 | –                    | 3.6±0.7                  | 71                 | –              | 14/16                         |
| Michelena (2011)   | 416        | 288       | –    | –     | 94  | 247       | –                     | NR               | –                   | –                 | –                    | 34±9                     | 84                 | –              | 13/16                         |
| Oliver (2009)      | 484        | 334       | –    | –     | –   | 1         | –                     | 33               | –                   | –                 | 4                    | –                        | 0                  | –              | 13/16                         |
| Rodrigues (2017)   | 227        | 101       | –    | –     | 87  | 133       | –                     | –                | 31±6                | –                 | 32                   | 35±11                    | 77                 | 21             | 13/16                         |
| Sun (2019)         | 170        | 117       | 1.74 | –     | 121 | 58        | –                     | –                | 36±5                | 32                | 98                   | 43±7                     | 2                  | 1              | 14/16                         |
| Wojnarski (2015)   | 380        | 310       | 2.1  | –     | –   | 186       | –                     | –                | 43±4.9              | –                 | –                    | 49±3.6                   | 9                  | –              | 13/16                         |
| Tzemos (2008)      | 642        | 437       | –    | 25    | 140 | 132       | –                     | –                | 32.75±6             | –                 | 180 <35              | –                        | N/A                | N/A            | 14/16                         |
| Davies (2007)      | 70         | 52        | 1.99 | –     | 34  | 37        | –                     | –                | –                   | –                 | –                    | –                        | –                  | –              | 13/16                         |

\*, High quality = 13–16; moderate quality 12–13; low quality <12/16 (critical deficiencies in study methodology may influence quality outcome past raw score).

| Study              | Mitral valve prolapse | Overall dissection | Hypertension | T2DM | COPD | Heart failure | IHD | AF  | CVA | TIA | PVD | Prior cardiac surgery | Smoking status | NYHA Class (I, II, III, IV) |
|--------------------|-----------------------|--------------------|--------------|------|------|---------------|-----|-----|-----|-----|-----|-----------------------|----------------|-----------------------------|
| Alegret (2013)     | N/A                   | 0                  | 37           | 10   | N/A  | 120           | 6   | N/A | 2   | –   | N/A | N/A                   | 28             | 114, 2, 4                   |
| Cheng (2021)       | –                     | 0                  | 164          | 48   | –    | –             | 31  | 21  | –   | –   | –   | –                     | –              | 333, Class 3–4 = 17         |
| Duijnhouwer (2020) | –                     | N = 3              | 99           | 10   | –    | –             | –   | –   | –   | –   | –   | –                     | 53             | –                           |
| Masri (2016)       | –                     | N = 2              | 693          | 97   | 70   | –             | –   | 136 | 30  | –   | 29  | 87                    | –              | 826 (I)                     |
| Michelena (2011)   | –                     | 3.1:10000          | 93           | 15   | –    | –             | –   | –   | –   | –   | –   | –                     | 132            | –                           |
| Oliver (2009)      | –                     | n=6                | –            | –    | –    | –             | –   | –   | –   | –   | –   | –                     | –              | –                           |
| Rodrigues (2017)   | –                     | n=2                | 60           | 5    | –    | 7             | 6   | 12  | 6   | –   | –   | 43                    | 34             | –                           |
| Sun (2019)         | –                     | 0                  | 49           | 16   | –    | 95            | 13  | –   | 2   | –   | –   | –                     | 32             | 75, 79, 16                  |
| Wojnarski (2015)   | –                     | n = 10             | 194          | –    | 22   | –             | 35  | –   | 9   | –   | –   | –                     | 139            | –                           |
| Tzemos (2008)      | N/A                   | n=5                | 170          | 12   | –    | –             | –   | –   | –   | –   | –   | –                     | 12             | –                           |
| Davies (2007)      | –                     | n=4                | 35           | 1    | –    | 3             | 18  | –   | 1   | –   | 0   | 0                     | 20             | –                           |

**Table S3** Patient recruiting and identification methodology

| Study              | Recruitment Years    | Patient recruitment method  | Imaging modality to identify BAV                              |
|--------------------|----------------------|---|---|
| Alegret (2013)     | 1998–2012            | Data collected and prospectively followed up all patients (>14 years old) after BAV diagnosis in facility<br>Mean follow-up 86 months   | Transthoracic Echocardiography                                |
| Cheng (2021)       | Jan 2005–Dec 2017    | Consecutive patients (>18 years) diagnosed with BAV prospectively identified and included in electronic database<br>Mean follow-up 80 months  | Short axis view Echocardiography                              |
| Duijnhouwer (2020) | Feb 2003–Feb 2019    | Retrospective study including all BAV patients that visited adult outpatient clinic<br>Mean follow-up 72 months   | Echocardiography, CMR, or surgeon during aortic valve surgery |
| Masri (2016)       | 2003–2007            | Consecutively recruited patients compared to surgical repair cohort   | Echocardiography  |
| Michelena (2011)   | Jan 1980 to Dec 1999 | Community cohort comprised of residents of Olmsted County in whom definite BAV of any type diagnosed from 1980–1999<br>Mean follow-up 192 months  | Echocardiography  |
| Oliver (2009)      | Dec 1989–Jun 2006    | Patients (>15 years old) with BAV were identified within a database of Adult Congenital Heart Disease from La Paz Hospital<br>Mean follow-up 84 months  | Echocardiography or surgical inspection                       |
| Rodrigues (2017)   | 1990 – 2015          | Retrospective study using a database containing referral population of consecutive adults with bicuspid aortic valve assessed at the ambulatory adult congenital heart disease clinic. Mean follow-up 240 months  | Transthoracic echocardiography                                |
| Sun (2019)         | July 2014–Feb 2017   | Patients with BAV over 19 years old who underwent comprehensive echocardiography at institution recruited through web-based platform. Mean follow-up 48 months  | Echocardiography  |
| Wojnarski (2015)   | Jan 1995–Jan 2014    | Patients not immediately undergoing operation, with an aortic diameter $\geq 4.7$ cm at sinus of Valsalva or tubular ascending aorta, that were found to have a BAV on echocardiography and had CT/MRI available for analysis<br>Mean follow-up 36 months | Echocardiography  |
| Tzemos (2008)      | 1994–2001            | Referral population of consecutive adults with BAV assessed at (Toronto) University Health Network ambulatory cardiac clinics and were identified using hospital's echocardiography and congenital cardiac databases<br>Mean follow-up 108 months         | Transthoracic Echocardiography                                |
| Davies (2007)      | 1985–2005            | Institutional database containing information on 1504 patients with thoracic aortic disease had 70 BAV patients that were followed by Yale Centre for Thoracic Aortic Disease between 1985–2005. Mean follow-up 64 months                                 | Echocardiography or intraoperatively                          |