Systematic Review

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

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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

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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 19th 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^2 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^2=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^2=95, 4.3% (95% CI: 2.1–7.2%) I^2=89, and 8.4% (95% CI: 4.8–12.9%) I^2=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^2=97. Aortic stenosis and aortic regurgitation were present in 30.7% (95% CI: 18.6–44.3%) I^2=98 and 44.1% (95% CI: 31.1–57.6%) I^2=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^2=99 and 42.8 mm (95% CI: 40.5–44.6 mm) I^2=99, respectively. Overall pooled incidence of bicuspid valve-related AD events was 0.6% (95% CI: 0.2–1.2%) I^2=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).

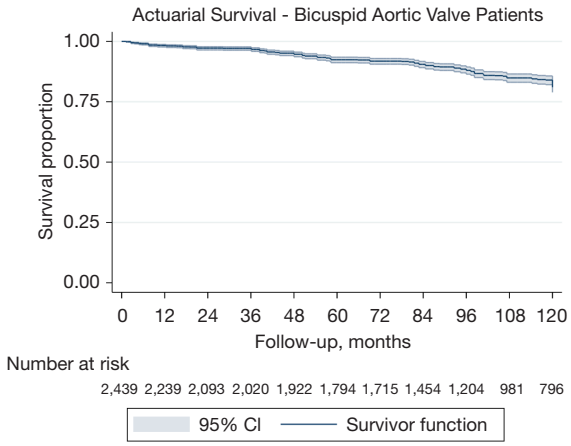

Figure 1 Actuarial survival in bicuspid aortic valve patients with number at risk (failure events).

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.

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Footnote

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

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