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The effect of bicuspid aortic valve versus tricuspid aortic valve as a risk factor for aortic dilatation: a systematic review and meta-analysis

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ABSTRACT

Background: The enlargement of the ascending aorta (AA) is a frequent finding in clinical practice. Age, gender, and body size have been shown to be important determinants of AA diameter. One of the most prevalent congenital heart conditions is bicuspid aortic valve (BAV) disease, which primarily affects male subjects and has a population prevalence of 0.5% to 2.0%. Purely severely stenotic BAVs developed a moderate dilation of the aorta at an early age, while TAVs (Tricuspid Aortic Valves) did not. This study aims to compare BAV and TAV as risk factors for aortic dilatation.

Methods: A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines by using PubMed/Medline, Scopus, and ScienceDirect databases according to PICO. The studies obtained were adjusted to the eligibility criteria. We conducted a journal appraisal assessment using the CASP 2024 tools for the 10 included studies. Meta-analysis was performed using Review Manager 5.4.

Result: Out of 208 studies, 10 studies are included for a systematic review according to eligibility criteria. From the baseline characteristics, BAV with aortic dilatation is often seen at a younger age compared to TAV. 5 studies are analyzed for the incidence risk of aortic dilatation between BAV and TAV group (OR 5.16; 95% CI 2.69, 9.92; p<0.001) and 6 studies are analyzed for the aortic diameter between BAV and TAV group (OR 0.55; 95% CI -1.37, 2.46; p<0.58).

Conclusion: Our systematic review-meta-analysis study found that there is an increase in ithe ncidence risk of aortic dilatation in BAV patients compared to TAV patients. Our study result supports the guideline designed by the American Association for Thoracic Surgery that suggests patients undergoing concurrent heart surgery, concomitant ascending aorta/root repair should be actively performed when the aortic diameter is 45 mm.

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INTRODUCTION

The enlargement of the ascending aorta (AA) is a frequent finding in clinical practice. Age, gender, and body size have been shown to be essential determinants of AA diameter.[1] Ascending aortic dilation is defined as an aortic diameter of ≥4.0 cm, and the risk of aortic dissection significantly increases when the aortic diameter is ≥4.5 cm. Normalized aortic diameters are based on patient height, body surface area, or a cross-sectional aortic area-to-height ratio to define surgical thresholds in patients who are either shorter or taller than average.[2]

One of the most prevalent congenital heart conditions is bicuspid aortic valve (BAV) disease, which primarily affects male subjects and has a population prevalence of 0.5% to 2.0%. Although most individuals experience issues like aortic dilatation and aortic valve malfunction, other people may never experience any symptoms. BAV sufferers' lives may be at risk if their aortic dilatation develops into an aortic aneurysm an aortic dissection, or rupture.[3]

BAV with significant AS is present in the majority of younger patients compared with tricuspid aortic valve (TAV).[4] A study on the aorta dimensions of patients with purely severely stenotic BAVs revealed that these patients developed a moderate dilation of the aorta at an early age, while controls that had TAVs did not.[5]

METHODS

A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Search Strategy

Studies from 2014 - 2024 in Pubmed (incl. MEDLINE), Scopus, and ScienceDirect were searched from databases. We used a combination of aged, bicuspid aortic valve, aortic aneurysm, aortic dilatation, and aortic dissection by using the Boolean operators "AND", "OR", and "NOT".

Eligibility Criteria

Two independent researchers (R.A. and I.D.) screened all citations yielded by the search according to a predefined protocol. Eventual disagreements were discussed and resolved by consensus with a third researcher (D.A). All comparative studies, comparing bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV), also aortic dilatation and no aortic dilatation, were included. In vitro or animal studies were excluded. If studies reported the same set of patients, only the most recent study was included. In order to evaluate risk of bias, we collected information on methodology for every included study (study type, method of patient selection and enrolment, way of outcome retrieval and registration, inclusion and exclusion criteria, and statistical methods). CASP 2024 was used according to the appraisal of each study.

Data Extraction

The following baseline data were extracted from the included papers: patient demographics including gender, age, and body surface area (BSA), and comorbidities including: hypertension, history of smoking, and diabetes. The primary outcome was the incidence of aortic dilatation and the diameter of aortic. The outcome was determined by echocardiography, Cardiac CT, and Cardiac MRI. There is no secondary outcome in our study.

Data Analyses

Primary data were extracted and reported, continuous data in median (interquartile range) or mean (standard deviation), and categorical data in frequency (%). Review Manager Version 5.4 is used in the relevant study for meta-analysis. We used random effect models with generic inverse variance, presenting the risk ratio with a 95% confidence interval. Forest plots were given, and the funnel plot was used for publication bias. Heterogeneity was reported as low (I2 = 0–40%), moderate (I2 = 30–60%), substantial (I2 = 50–90%), and considerable (I2 = 75–100%).

RESULT

Complete search results are shown in Figure 1. Out of 208 studies, 2 studies are excluded for duplication, 149 studies are excluded for irrelevant title, 20 studies are excluded for irrelevant abstract, 12 studies have no full text, and some studies are excluded due to wrong population (3 studies), wrong outcome (9 studies), or wrong study design (3 studies). 10 studies are included for a systematic review according to eligibility criteria.

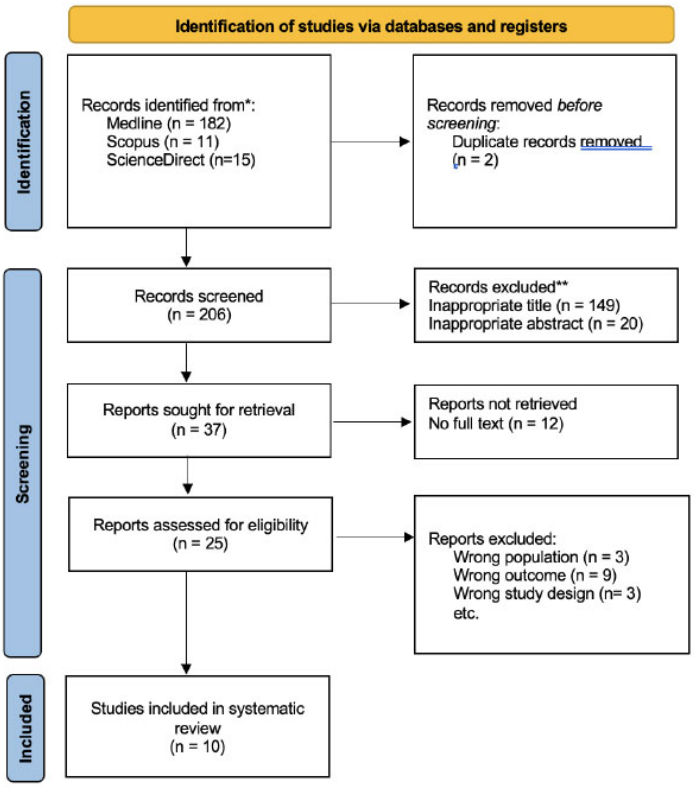

Figure 1. PRISMA 2020 flow diagram.

The baseline characteristics of each study are shown in Table 1. Most of the studies are cohort studies that compare BAV and TAV. Only 2 studies are comparing aortic dilatation and no aortic dilatation.[6,7] BAV patients are often seen at a younger age. All the studies have hypertension as their comorbidities.

Aortic Dilatation

5 studies are analyzed for the incidence risk of aortic dilatation between the BAV and TAV groups. Figure 2 shows the forest plot between the two groups. There is a significant effect to measure the outcome between BAV and TAV for aortic dilatation (OR 5.16; 95% CI 2.69, 9.92; p<0.001). The funnel plot is relatively symmetrical (Figure 3).

Aortic Diameter

6 studies are analyzed for the diameter of aortic between BAV and TAV groups. Figure 4 shows the forest plot between the two groups. There is no significant effect to measure the outcome between BAV and TAV for aortic diameter (OR 0.55; 95% CI -1.37, 2.46; p<0.58). The funnel plot is relatively symmetrical (Figure 5).

DISCUSSION

A bicuspid aortic valve (BAV) is a common congenital heart disease.[8-10] It is observed in 1–2% of the entire population1 and in 31.9% of individuals with aortic valve disorders.[9-12] Aortic dilation begins at an early age in the BAV patients and is usually characterized by "mid-ascending"-type dilation. The dilation process can be observed even in patients with normally functioning BAVs.[13-15]

An aorta diameter of ≥4.0 cm is

Table 1. Baseline Characteristics

Study (Year)	Sample (n)	Population	Male sex (%)		Age (years)		BSA		Hypertension (%)	History of Smoking (%)	Diabetes (%)
			BAV	TAV	BAV	TAV	BAV	TAV			
Heng (2015)[8]	100	Aortic Replacement Surgery	47	19	57.6 ± 10.1	67.48 12.8			63	10	13
Swahn (2023)[6]	70	Aortic Dilatation	77%		59±4		2.1 ± 0.2		47	10	9
Kassis (2020)[7]	1677	Aortic Aneurysm	66.1		80 (71–86)				86		20.5
Boudoulas (2015)[9]	270	Aortic Valve Surgery	71.6	55.4	62±13	71±10			81.1	50	41.4
Nakamura (2014)[10]	76	AS or AR	76.5	52.5	70±7	77±7	1.48 ± 0.40	1.46 ± 0.18	75	39.4	19.7
Fujiwara (2022)[4]	276	AS	60	31	66.0 ± 10.8	75.2 ± 8.0	1.54 ± 0.19	1.60 ± 0.19	58		23
Billaud (2017)[11]	81	Aortic Aneurysm	53	22.2	56±11	64.0 10			71	55	
Jackson (2014)[12]	152	AS	61.1	16.4	61±11	64±12	2.00±0.2	2.03±0.2	45	7	7
Haunschild (2017)[13]	87	Aortic Dilatation	64.8	81.8	60.5 ±13	64.0 ±12	1.95± 0.18	2.05± 0.22	83.9	16.1	21.8
Singh (2019)[14]	169	AS	73%	77.4	64.6 [51.1, 69.7]	71.4 [65.8, 77.3]	1.92 ± 0.20	1.97 ± 0.20	54.4		14.2

Abbreviation in table: BAV: Bicuspid Aortic Valve; TAV: Tricuspid Aortic Valve; BSA: Body Surface Area; AS: Aortic Stenosis; AR: Aortic Regurgitation

considered to be ascending aortic dilatation, and an aortic diameter of ≥4.5 cm considerably raises the risk of aortic dissection. In order to establish surgical thresholds for patients who are either shorter or taller than usual, normalized aortic diameters are determined using the patient's height, body surface area, or a cross-sectional aortic area-to-height ratio.[2]

Age, gender, and body size are known determinants of ascending aortic (AA) diameter.[1] Also, bicuspid aortic valve (BAV) disease and some other hereditary conditions have been associated with AA dilation.[16,17] Prior literature consistently reveals that patients with bicuspid aortic valves are at increased risk for aortic aneurysm and dissection.[5,18,19] Some of these findings suggest that BAV is responsible for the dilatation of the AA as reported in the prior studies.[18,20–22] A study on the aorta dimensions of patients with purely severely stenotic BAVs revealed that these patients developed a moderate dilation of the aorta at an early age, while controls that had TAVs did not.[23]

Aortic dilatation in patients with a bicuspid aortic valve is due to abnormalities in the medial architecture of the aortic wall, where there is a loss of smooth muscle cells and fragmentation of elastin fibers, resulting in progressive aortic dilatation.[24–27] The mechanism of aortic dilation can be caused by several changes. Genetics (different expression of antiapoptotic bcl-2, causes apoptosis of Vascular Smooth Muscle Cells/ VSMCs) causes decreased production of Extracellular Matrix/ECM proteins.[26,28–33] It also produces microvesicles and exosomes that cause calcification.[34,35] Proteoglycan deposition in the aortic wall causes nidus/attachment for calcification.[36,37] Hemodynamic factors cause increased wall shear stress, ECM dysregulation, and finally, aortopathy.[38–47] The environmental cause of aortic dilatation is the response to oxidative stress (versus TAV), lipid peroxidation, which disrupts plasma membrane homeostasis, cell death, especially in VSMC that causes cystic medial degeneration.[11,48–55] These factors as a whole in BAV patients cause hemodynamic/mechanical disturbances in the medial architecture of the aortic

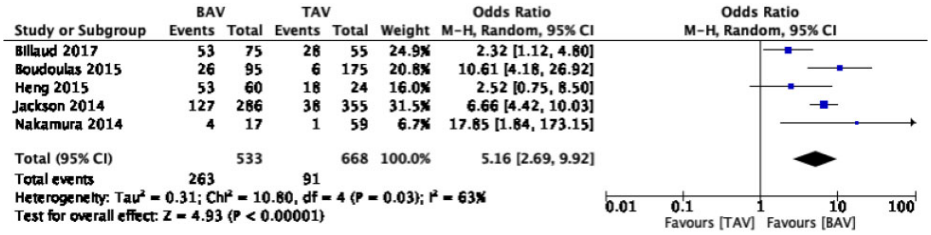

Figure 2. Forest plot of aortic dilatation between the BAV and TAV groups.

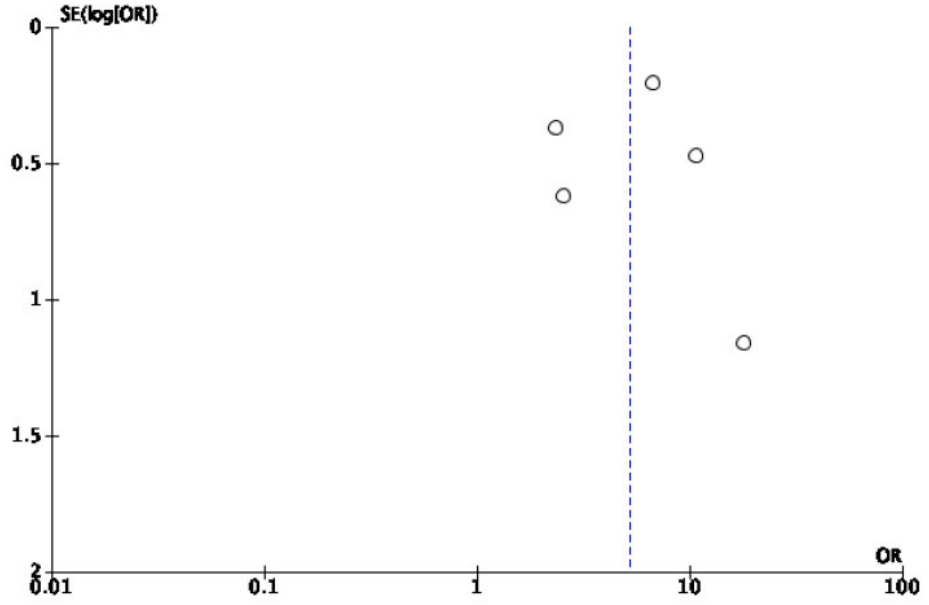

Figure 3. Funnel plot of aortic dilatation between the BAV and TAV groups.

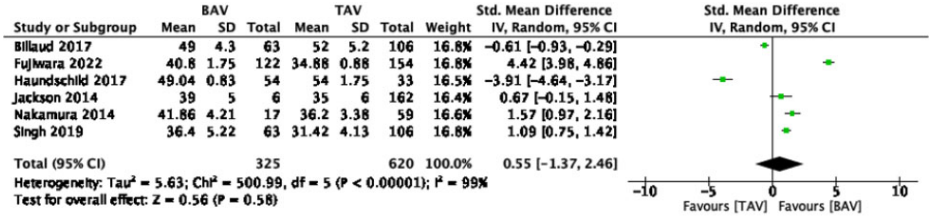

Figure 4. Forest plot of aortic diameter between the BAV and TAV groups.

wall (loss of Smooth Muscle Cells/SMCs and fragmentation of the elastin fibers of the medial layer of the aortic wall), pathological stiffness and decreased elasticity of the aortic wall, which in turn causes aortic stiffness and serve as mechanical driving force for development into aneurysm and remodeling.[36,56–61]

In our study, we found an increase in the incidence risk of aortic dilatation in BAV patients compared to TAV patients (OR 5.16; 95% CI 2.69, 9.92; p<0.001) as depicted in the forest plot (Figure 2). We also found that the standardized mean difference of aortic diameter in BAV patients is higher compared to TAV patients (SMD 0.55; 95% CI -1.37, 2.46; p=0.58), although the result is not statistically significant. Nevertheless, our study concluded to support the idea and findings that BAV tends to cause aortic dilatation more than TAV.

The highlight is that the BAV study population exhibited more aortic valve stenosis than did the TAV group. Theoretically, this fact may give rise to a notion that the BAV group was generally more susceptible to calcifying processes than were the patients with TAV. However, although they cannot rule out this as a possibility per se, they are unaware of pathologic mechanistic studies to support this hypothesis.[13] Approximately 27% of patients with aortic stenosis and a bicuspid aortic valve required concomitant surgery for thoracic aortic aneurysm as compared to only approximately 3% of patients with aortic stenosis and a tricuspid aortic valve. Thus, thoracic aortic aneurysm is mostly seen in patients with a bicuspid aortic valve, while it is unusual in patients with aortic stenosis and a tricuspid aortic valve.[9]

In terms of clinical decision-making, there has always been a debate between active surgical intervention and conservative follow-up.[3] The latest 2018 guidelines from the American Association for Thoracic Surgery (ATS) on BAV-related aortopathy define intervention indications. For patients undergoing concurrent heart surgery, concomitant ascending aorta/root repair should be actively performed when the aortic diameter is 45 mm (class IIa/B). Among patients with moderate aortic root dilatation (4.5–5.0 cm) undergoing concurrent surgery, simultaneous complete aortic root replacement is justified for patients with mechanical valve selection. Most of the current guidelines for the establishment of intervention indications are based on retrospective studies, and there is a lack of large-scale and long-term longitudinal studies to provide support for indications.[62]

The limitations of our study are the number of studies included, the number of samples of each study included, and the lack of subgroup analysis conducted because of the limited time of our research and the inability to retrieve the primary data from the original researcher of each study included in our systematic review and meta-analysis study. Nonetheless, to the best of our knowledge, there has not been a systematic review and meta-analysis study conducted in the same area that we studied. We hope to give new perspectives and evidence of BAV, TAV, and aortic dilatation in their causality as to help in building guidelines and decision-making, especially the consideration for surgery and the basis for future and more detailed research.

CONCLUSION

Bicuspid Aortic Valve (BAV) is one of the most prevalent congenital heart conditions. Many prior studies have tried to identify that BAV has causality relationship with aortic dilatation, more

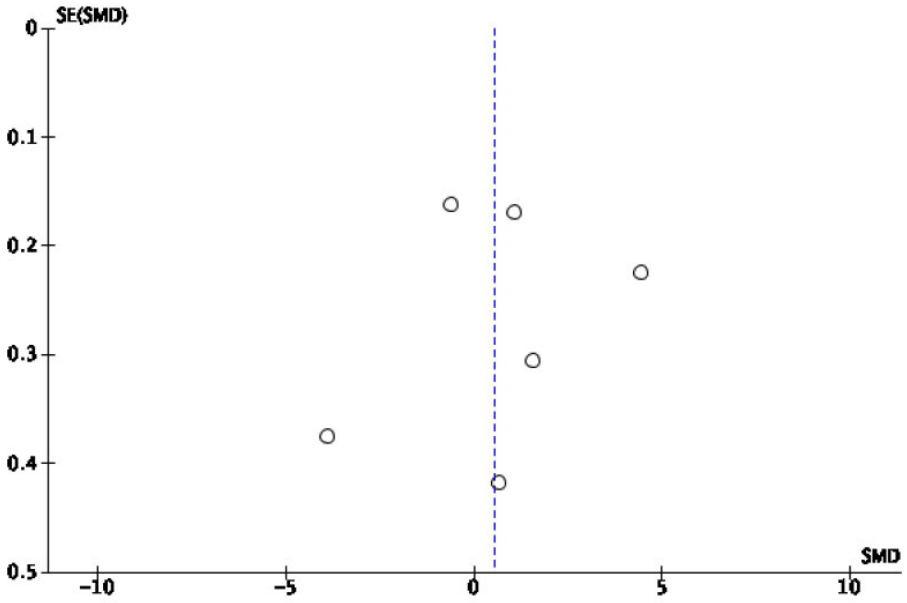

Figure 5. Funnel plot of aortic diameter between the BAV and TAV groups.

often than Tricuspid Aortic Valve (TAV). Our systematic review-metaanalysis study found that there is an increase in the incidence risk of aortic dilatation in BAV patients compared to TAV patients. Our study result supports the guideline designed by the American Association for Thoracic Surgery that suggests patients undergoing concurrent heart surgery, concomitant ascending aorta/root repair should be actively performed when the aortic diameter is 45 mm. There is still a need to be a larger and more detailed study to better identify the causality relationship between BAV, TAV, and aortic dilatation.

CONFLICT OF INTEREST

All author declares there is no conflict of interest regarding the publication of the study.

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None.

AUTHOR CONTRIBUTION

All authors contributed to the manuscript writing and agreed on the final version of the manuscript for publication.

ETHICAL CONSIDERATION

Not mandatory.

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