frontiers | Research Topics

Bicuspid aortic valve: From pathophysiological mechanisms, imaging diagnosis to clinical treatment methods

Edited by
Mao Chen, Lars Sondergaard, Darren Mylotte, Nicolo Piazza and Bernard Prendergast

Published in
Frontiers in Cardiovascular Medicine
Frontiers in Genetics

ISSN 1664-8714
ISBN 978-2-8325-2405-3
DOI 10.3389/978-2-8325-2405-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Bicuspid aortic valve: From pathophysiological mechanisms, imaging diagnosis to clinical treatment methods

Topic editors

Mao Chen — Sichuan University, China
Lars Sondergaard — University of Copenhagen, Denmark
Darren Mylotte — University of Galway, Ireland
Nicolo Piazza — McGill University, Canada
Bernard Prendergast — Guy's and St Thomas' NHS Foundation Trust, United Kingdom

Citation

Chen, M., Sondergaard, L., Mylotte, D., Piazza, N., Prendergast, B., eds. (2023). *Bicuspid aortic valve: From pathophysiological mechanisms, imaging diagnosis to clinical treatment methods*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-2405-3

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 28 April 2023
DOI 10.3389/fcvm.2023.1193544

OPEN ACCESS

EDITED AND REVIEWED BY
Elena Aikawa,
Brigham and Women's Hospital and Harvard Medical School, United States

*CORRESPONDENCE
Mao Chen
hmaochen@vip.sina.com

†These authors have contributed equally to this work

RECEIVED 25 March 2023
ACCEPTED 18 April 2023
PUBLISHED 28 April 2023

CITATION
Zhang Y, Xiong T-Y, Sondergard L, Mylotte D, Piazza N, Prendergast B and Chen M (2023) Editorial: Bicuspid aortic valve: from pathophysiological mechanisms, imaging diagnosis to clinical treatment methods. Front. Cardiovasc. Med. 10:1193544. doi: 10.3389/fcvm.2023.1193544

Editorial: Bicuspid aortic valve: from pathophysiological mechanisms, imaging diagnosis to clinical treatment methods

Yi Zhang[1†], Tian-Yuan Xiong[1†], Lars Sondergard[2], Darren Mylotte[3], Nicolo Piazza[4], Bernard Prendergast[5,6] and Mao Chen[1*]

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China, [2]The Heart Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]Department of Cardiology, University Hospital Galway, National University of Ireland, Galway, Ireland, [4]Division of Cardiology, Department of Medicine, McGill University Health Center, Montreal, QC, Canada, [5]Department of Cardiology, St Thomas' Hospital, London, United Kingdom, [6]Cleveland Clinic London, London, United Kingdom

KEYWORDS

bicuspid aortic valve, valvular heart disease, aortopathy, aortic dilatation, transcatheter aortic valve replacement

Editorial on the Research Topic
Bicuspid aortic valve: from pathophysiological mechanisms, imaging diagnosis to clinical treatment methods

This Research Topic, entitled "Bicuspid Aortic Valve: From pathophysiological mechanisms, imaging diagnosis to clinical treatment methods", is created to set a forum for researches that tackle the difference or uniqueness of the BAV entity, from genetic, cellular and pathophysiological mechanisms of BAV and the subsequent bicuspid aortic stenosis, clinical imaging for bicuspid aortic stenosis to unveil its function and anatomy, treatment innovations and strategies tailored for bicuspid aortic stenosis, to clinical outcomes. Herein, we introduce the 13 articles collected in this Research Topic (Table 1).

Genomic issues in congenital BAV

The genetics behind BAV are acknowledged to be different from a normal tricuspid aortic valve (TAV), as patients with BAV may develop aortic malformations, valvular dysfunctions, or symptoms at a younger age. Several genomic mutations have been found to be associated with BAV, such as mutations in *NOTCH1*, *ROBO4*, etc. (1). In this research topic, Jacob Gutierrez et al. identified that patients with Turner syndrome (TS), a rare cytogenetic disorder presenting a 60-fold increased risk of BAV compared to the general population, have differentially methylated regions (DMRs) encompassing *MYRF* and enrichment for genomic targets, including genes in *NOTCH1* and the downstream gene *MYH11* in those with concomitant BAV. These DMRs in TS appeared to contribute to both BAV development and BAV-associated aortopathy, adding evidence in the genomic etiology of congenital BAV.

TABLE 1 Information and highlights of the 13 articles in the research topic.

Authors	Key challenges in the field	Objectives of the study	Highlights of the study
Jacob Gutierrez et al.	Congenital heart defects, particularly left-sided anomalies, including BAV, occur in about 30% of individuals with TS and are the leading cause of premature mortality. Despite the significant prevalence of BAV in TS, there has been limited exploration of the potential role of epigenetic regulation in the development of this condition and in TS.	To identify DNAm alterations associated with TS BAV as well as between TS and euploid females with BAV, and detect possible epigenetic modifications in BAV-associated genes and pathways that may further explain the high incidence of BAV and aortopathy in TS	The current study investigates the genomic contributions to the higher susceptibility to BAV in TS, thereby highlighting the probable involvement of epigenetic regulations in the development of both TS and BAV.
Shinjeong Song et al.	Under echocardiographic surveillance, many BAVs are diagnosed without significant valve dysfunction. However, there is limited data is available regarding the progression and outcomes of non-dysfunctional BAV.	To determine the incidence of aortopathy at initial diagnosis and characterize aortic complications among patients with non-dysfunctional BAV vs. dysfunctional BAV, further assess the progression of valvular dysfunction and aortopathy in non-dysfunctional BAV based on a large Korean BAV registry	This study, conducted in Korea, highlights that a significant proportion of individuals with BAV without any significant valvular dysfunction also exhibit aortopathy, which increases the likelihood of AA dilation and subsequent need for aortic operation compared to those without aortopathy. Moreover, the results suggest that most non-dysfunctional BAVs maintain normal valvular function for up to 6 years, providing evidence to support the clinical management of non-dysfunctional BAVs in terms of valvular replacement.
Constance G. Weismann et al.	BAV is the most common congenital cardiac anomaly and has been linked to aortopathy, increased aortic stiffness, and diastolic dysfunction. However, the underlying mechanisms and the impact of age on BAV-associated complications are not yet fully understood.	To characterize arterial and cardiac function, their correlation, and the effect of age in children and adults with a history of BAV by a multimodal approach	This study highlights that children with BAV can experience diastolic dysfunction, which progressively worsens with age, mainly due to reduced ascending aortic distensibility. As a result, these findings shed light on the mechanisms of vascular and ventricular dysfunction in BAV populations, as well as the effect of age.
Mi Chen et al.	According to the current practice guideline, patients with BAV and significant valve dysfunction should undergo ascending aortic replacement if their aortic diameter exceeds 45 mm. However, it is uncertain whether patients with dilated aortas but without significant valvular dysfunction require concomitant AVR.	To compare the perioperative and follow-up benefits and risks of IR vs. PR for BAV-related aortopathy	This study proposes that IR is a better treatment option than PR for patients with BAV-related aortopathy, suggesting a minimum cutoff of 40 mm of aortic diameter for patients with "valve type" and 52 mm for those with "aorta type." This provides a reference for clinical practice, particularly for patients without significant valvular dysfunction.
Nils Perrin et al.	The impact of BAV morphology on TAVR outcomes remains poorly investigated due to the lack of pivotal randomized trials comparing TAVR with surgery that include BAV. However, data from registries and observational studies that include highly selected patients have shown promising results of TAVR in BAV populations.	To describe anatomical and pathophysiological characteristics of BAV, discuss the main aspects to assess diagnostic imaging modalities, and give an overview of TAVR outcomes and technical considerations specific to BAV morphology in this review	This study provides a review of the anatomical and pathophysiological characteristics of BAV, the main aspects to assess diagnostic imaging modalities, and technical considerations and outcomes specific to BAV morphology with regards to the TAVR procedure.
Giulia Costa et al.	With BAV affecting approximately 1–2% of the population, it is possible that an increasing number of patients with degenerated BAV may eventually require TAVR during the course of their disease. However, BAV presents a challenge due to its unique anatomical features and the absence of consensus on the optimal sizing strategy.	To review the peculiar aspects of BAV and to discuss and compare the currently available sizing methods	This review provides an overview of available sizing methods for the BAV population with regards to the TAVR procedure, as well as ways to optimize procedural outcomes.
Yung-Tsai Lee et al.	According to current guidelines, TAVR should be performed on only selected patients with BAV and AS. However, it is crucial to identify the important factors that affect long-term outcomes in patients with BAV who undergo TAVR.	To identify what the truly important factors are that determine the device success and long-term outcomes in patients with BAV undergoing TAVR	This study provides the first report of the prevalence of BAV referred to TAVR in Taiwan and identifies predictors of prognosis. With the novel sizing method (Wei's Method), safer prosthesis implantation could be achieved when using a balloon-expandable valve.
Jiajun Zhang et al.	Studies on the association of Sievers BAV morphology with conduction disorders after TAVR have not reached consensus.	To pool and analyze about post-TAVR conduction abnormalities and their association with Sievers BAV morphology	This pooled analysis firstly focuses on the association of Sievers BAV morphology with post-TAVR conduction disorders, revealing higher risk of post-TAVR PPI and conduction disorders in type 1 BAV compared with type 0.
Yuchao Guo et al.	NOCDs, including complete left bundle branch block and high-grade atrioventricular block, remain the most common complication after TAVR. However, there is limited data on predictors and strategies to decrease NOCDs in severe AS patients with BAV.	To evaluate the predictors of NOCDs in BAV patients using self-expanding valves and identify modifiable technical factors	This study provides a predictive model for NOCDs after TAVR based on the BAV population receiving self-expandable valves from seven centers in China, providing robust evidence for clinical management to decrease the risk of NOCDs after TAVR.

(*Continued*)

TABLE 1 Continued

Authors	Key challenges in the field	Objectives of the study	Highlights of the study
Gangjie Zhu et al.	SLT is an important sequela that compromises the durability of the bioprosthetic valve of TAVR. Moreover, no studies have compared the SLT detected by CT and its clinical implications and prognoses in patients with BAV and TAV.	To retrospectively assess the SLT defined by the CT in the BAV and TAV stenotic patients	This study presents novel findings indicating a comparable occurrence rate of SLT in BAV patients who received TAVR in a single center, and a similar set of predictors compared to those of TAV patients.
Yi Zhang et al.	The absence of specific guidelines and practical recommendations for TAVR in the BAV population emphasizes the urgent need for a reliable evaluation of the effectiveness and safety of TAVR procedures in these patients.	To conduct a systematic review and meta-analysis of clinical adverse events in patients undergoing TAVR with BAV versus TAV anatomy and the efficacy of BE vs. SE valves stratified into early- and new-generation devices, as well as differences of prosthetic geometry on CT between BAV and TAV and BAV morphological presentations in included studies	This meta-analysis provides an up-to-date synthesis of the most extensive evidence on TAVR in patients with BAV. The findings indicate a higher risk of procedural and 30-day adverse events among BAV patients undergoing TAVR when compared to TAV patients, but a more significant benefit in terms of mortality.
Yu Du et al.	TAVR has achieved satisfactory outcomes in selected patients with BAV, predominately type 1 BAV (~90%). However, there is limited research on the safety and efficacy of TAVR in type 0 BAV.	To compare procedural and 30-day outcomes after TAVR between type 0 and type 1 BAV through a systematic review and meta-analysis	This study conducted the first meta-analysis comparing the procedural and clinical outcomes of TAVR in patients with Sievers type 0 and type 1 BAV, indicating comparable procedural and 30-day outcomes.
Kyu Kim et al.	The population is aging, and in the last two decades, advances in multimodal imaging and transcatheter valve intervention for BAV have been remarkable.	To investigate temporal trends in demographic characteristics, use of multimodal imaging, treatments, and outcomes in patients with BAV from a large Korean registry	This study aims to provide a systematic description of temporal changes and trends in patient characteristics, valvular function, diagnosis, treatment, and outcomes among patients with BAV from a single tertiary center over the past two decades. These findings will be a valuable reference for further diagnostic and treatment advances.

TS, Turner syndrome; BAV, bicuspid aortic valve; DNAm, DNA methylation; AA, ascending aorta; AVR, aortic valve replacement; IR, integrated aortic-valve and ascending-aortic replacement; PR, partial replacement; TAVR, transcatheter aortic valve replacement; AS, aortic stenosis; PPI, permanent pacemaker implantation; NOCD, new-onset conduction disturbance; SLT, subclinical leaflet thrombosis; CT, computed tomography; TAV, tricuspid aortic valve; BE, balloon expandable; SE, self-expanding.

Natural disease course of BAV

With the generalization of echocardiographic surveillance, the diagnosis of non-dysfunctional BAV (BAV without significant aortic stenosis or aortic regurgitation) is increasing. Based on a BAV registry enrolling patients from a single hospital in Seoul, Shinjeong Song et al. found that patients with non-dysfunctional BAV, especially the true BAV, were more likely to be considered as candidates for aortic surgery due to the progression of ascending aortic dilatation. In addition, most non-dysfunctional BAVs could still maintain normal valve function 6 years after their initial diagnosis. In patients with non-dysfunctional BAV, initial BAV function and degree of aorta dilatation might be important factors for disease progression and prognosis.

Concomitant aortic dilatation is present in about 20%–40% of BAV patients, which may be secondary to abnormalities of the aortic media (4, 5). Currently, guideline recommends ascending aortic replacement in dysfunctional BAV with concomitant dilated aorta if the cutoff of 45 mm is reached (6). Mi Chen et al. proposed a classification to describe the BAV-related dilated aortopathy into valve type and aorta type which represents the most dysfunctional part. Integrated aortic-valve and ascending-aortic replacement (IR) was associated with long-term mortality and reoperation benefits compared to partial replacement, with an IR cutoff of 40 mm in the "valve type" and 52 mm in the "aorta type". This finding provides a preliminary exploration of the surgical therapy in BAV with different types of dilated aortopathy, providing a reference for clinical management.

Aortopathy in BAV

Aortopathy is common in the BAV population and may predispose to aortic stiffening, dilation and dissection. Despite controversies, aortic stiffening may lead to heart failure through arterio-ventricular interaction (2, 3). In this research topic, Constance G. Weismann et al. used a multimodal method to reveal that ascending aortic distensibility appears to be the most important predictor of diastolic dysfunction in the BAV population, with increased proximal aortic stiffness and wave reflection in both children and adults. Therefore, timely management of proximal arterial stiffness may be a target to prevent further diastolic dysfunction in the BAV population.

TAVR for BAV

Bicuspid aortic stenosis is one of the most encountered complications in patients with BAV, occurring in >20% of high-risk elderly patients undergoing surgery (7). With the advent of transcatheter aortic valve replacement (TAVR), patients with severe aortic stenosis of any surgical risk have an alternative beneficial therapy. However, bicuspid aortic stenosis has long been regarded as a challenging anatomy. Nils Perrin et al. reviewed the BAV population in the setting of TAVR Apart from the most widely known BAV classification proposed by Sievers, several novel classifications have been updated in aim to achieve better description of the anatomy and prediction of

interventional outcomes (8–10). Despite the technical improvements in imaging modalities, difficulties remain in TAVR planning and execution for BAV due to its distinctive anatomy and hemodynamics. The eccentricity of the opening orifice, the asymmetric heavy burden of calcium deposition in BAV would increase the risk of device malposition and mal-expansion, annular rupture, etc. These suboptimal interactions could further lead to new-onset conduction disturbances (NOCDs) and subclinical leaflet thrombosis (SLT), impeding the durability of the bio-prosthesis and patient prognosis.

In order to achieve better results, several sizing strategies have been proposed. Giulia Costa et al. have discussed and compared the currently available sizing methods for TAVR in terms of BAV population, such as "annular" sizing, "supra-annular" sizing, "balloon-technique" BAV sizing, "raphe-based" sizing, Casper algorithm and LIRA method. A specific prosthesis sizing method, i.e., the Wei's method was proposed by Yung-Tsai Lee et al. which achieved safe implantation and efficacious performance of Sapien 3 in the BAV population. The different sizing techniques that have emerged have not yet been tested in large trials, and therefore a better understanding of BAV sizing is needed, especially with regard to different types of devices. Despite prosthesis iteration, new-onset conduction disturbances (NOCDs) are one of the most common complications of TAVR with an increased risk of mortality and rehospitalization (11). Sievers type 1 BAV morphology seems to have a higher risk of permanent pacemaker implantation (PPI) and NOCDs after TAVR than type 0, as reported by Jiajun Zhang et al. To best predict NOCDs in BAV after TAVR who received self-expanding valves, Yuchao Guo et al. have built a model including age, oversizing ratio on left ventricular outflow tract and Δcoronal membranous septum minus implantation depth. Moderate reduction of the oversizing ratio may be a feasible strategy to reduce conduction disturbances while maintaining good peri-procedural outcomes in heavily calcified bicuspid anatomy with short membranous septum length. Regarding the incidence of SLT in patients undergoing TAVR, comparable data were observed between BAV and TAV at 30 days or 1 year after TAVR, as reported by Gangjie Zhu et al. providing more specific evidence of SLT in the BAV population.

Studies are encouraging in the light of similar outcomes to TAVR for the BAV versus TAV population (12, 13). Yi Zhang et al. and Yu Du et al. have done meta-analyses focused on the prognosis of TAVR in BAV patients, both of which demonstrated similar in-hospital and 30-day post-TAVR mortality not only between BAV and TAV, but also between Sievers type 0 BAV and Sievers type 1 BAV, despite a higher risk of other procedural complications such as conversion to surgery, valve-in-valve, paravalvular leak, device failure, acute kidney injury, PPI, and stroke. BAV patients showed a lower 1-year mortality after TAVR than TAV in the report. As the application of TAVR in patients with BAV becomes more frequently on a day-to-day basis in clinical practice, consensus and studies aim for a standardized protocol on TAVR in BAV are being updated (14, 15). Further randomized trials are needed for guidance and standardization of specific peri-operative techniques of TAVR for heterogeneous BAV anatomies, as well as the prognosis in this population.

Temporal trend of BAV diagnosis and treatment

The demographic characteristics, multimodal imaging, and interventional therapy of BAV have changed over the past two decades. To explore the temporal trends of the aforementioned aspects of the BAV population, Kyu Kim et al. analyzed data from a large Korean registry, and revealed a significant temporal increase in both the age of initial diagnosis and indexed intervention or surgery in the BAV population. Over time, the proportions of non-dysfunctional BAV and significant aortic stenosis increased, while those of significant aortic regurgitation and infective endocarditis decreased. An increase in the use of bioprosthetic valves and TAVR, and survival improvements in BAV were observed.

In summary, the 13 articles in this Research Topic presented the latest advances in the aforementioned aspects of BAV. These discoveries help to better understand and guide clinical practice in this population. However, the conclusions need to be further validated by larger studies and randomized trials in view of the limitations caused by their small size and non-randomized natures.

Author contributions

YZ and T-YX drafted the editorial with guidance and comments from LS, DM, NP, BP, and MC. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, et al. ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. *Nat Genet*. (2019) 51:42–50. doi: 10.1038/s41588-018-0265-y

2. Weismann CG, Lombardi KC, Grell BS, Northrup V, Sugeng L. Aortic stiffness and left ventricular diastolic function in children with well-functioning bicuspid aortic valves. *Eur Heart J Cardiovasc Imaging*. (2016) 17:225–30. doi: 10.1093/ehjci/jev151

3. Lee SY, Shim CY, Hong GR, Seo J, Cho I, Cho IJ, et al. Association of aortic phenotypes and mechanical function with left ventricular diastolic function in subjects with normally functioning bicuspid aortic valves and comparison to subjects with tricuspid aortic valves. *Am J Cardiol*. (2015) 116:1547–54. doi: 10.1016/j.amjcard.2015.08.017

4. Masri A, Svensson LG, Griffin BP, Desai MY. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart*. (2017) 103:1323–30. doi: 10.1136/heartjnl-2016-309916

5. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol*. (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068

6. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European society of cardiology (ESC). *Eur Heart J*. (2014) 35:2873–926. doi: 10.1093/eurheartj/ehu281.

7. Roberts WC, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol*. (2012) 109:1632–6. doi: 10.1016/j.amjcard.2012.01.390

8. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg*. (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039

9. Michelena HI, Della Corte A, Evangelista A, Maleszewski JJ, Edwards WD, Roman MJ, et al. International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes. *J Thorac Cardiovasc Surg*. (2021) 162:e383–414. doi: 10.1016/j.jtcvs.2021.06.019

10. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging*. (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022

11. Faroux L, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, et al. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *Eur Heart J*. (2020) 41:2771–81. doi: 10.1093/eurheartj/ehz924

12. Makkar RR, Yoon SH, Chakravarty T, Kapadia SR, Krishnaswamy A, Shah PB, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke among patients at low surgical risk. *J Am Med Assoc*. (2021) 326:1034–44. doi: 10.1001/jama.2021.13346

13. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol*. (2017) 69:2579–89. doi: 10.1016/j.jacc.2017.03.017

14. Xiong TY, Ali WB, Feng Y, Hayashida K, Jilaihawi H, Latib A, et al. Transcatheter aortic valve implantation in patients with bicuspid valve morphology: a roadmap towards standardization. *Nat Rev Cardiol*. (2023) 20:52–67. doi: 10.1038/s41569-022-00734-5

15. Wang X, De Backer O, Bieliauskas G, Wong I, Bajoras V, Xiong TY, et al. Cusp symmetry and coronary ostial eccentricity and its impact on coronary access following TAVR. *JACC Cardiovasc Interv*. (2022) 15:123–34. doi: 10.1016/j.jcin.2021.11.010

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 11 January 2021
doi: 10.3389/fcvm.2020.603323

Progression and Outcomes of Non-dysfunctional Bicuspid Aortic Valve: Longitudinal Data From a Large Korean Bicuspid Aortic Valve Registry

*Shinjeong Song[1], Jiwon Seo[2], Iksung Cho[2], Geu-Ru Hong[2], Jong-Won Ha[2] and Chi Young Shim[2]**

[1] Division of Cardiology, Department of Internal Medicine, Ewha Womans University Hospital, Ewha Womans University College of Medicine, Seoul, South Korea, [2] Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea

OPEN ACCESS

Edited by:
Magnus Bäck,
Karolinska Institutet (KI), Sweden

Reviewed by:
Salah A. Mohamed,
University Medical Center Schleswig-Holstein, Germany
Tanja Katharina Rudolph,
Heart and Diabetes Center North Rhine-Westphalia, Germany

***Correspondence:**
Chi Young Shim
cysprs@yuhs.ac

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: 06 September 2020
Accepted: 07 December 2020
Published: 11 January 2021

Citation:
Song S, Seo J, Cho I, Hong G-R, Ha J-W and Shim CY (2021) Progression and Outcomes of Non-dysfunctional Bicuspid Aortic Valve: Longitudinal Data From a Large Korean Bicuspid Aortic Valve Registry. Front. Cardiovasc. Med. 7:603323. doi: 10.3389/fcvm.2020.603323

Background: Using echocardiographic surveillance, many patients are diagnosed with bicuspid aortic valve (BAV) without significant valve dysfunction. Limited data are available regarding the progression and outcomes of non-dysfunctional BAV.

Methods and Results: We investigated 1,307 BAV patients (984 male, mean age 56 years) diagnosed from Jan 2003 through Dec 2018 in a single tertiary center. Seven hundred sixty-one patients underwent follow-up echocardiography at ≥1 year post-diagnosis. Non-dysfunctional BAV was defined as BAV without moderate aortic stenosis (AS) or aortic regurgitation (AR). The presence of aortopathy was defined as an ascending aorta diameter >37mm. Progression to significant BAV dysfunction, progression to severe aortopathy (ascending aorta diameter ≥45mm), and incidence of valve or aorta operation were analyzed. One hundred eighty-seven (25%) patients showed non-dysfunctional BAV. Among them, 104 (56%) had mild AS or AR, and 81 (43%) had aortopathy at indexed echocardiography. At 6.0 ± 3.8 years post-diagnosis, 56 (29%) progressed to dysfunctional BAV, 28 (15%) progressed to severe aortopathy, 22 (12%) underwent valve operation, and 19 (10%) experienced aorta operation. Eighty-nine percent of patients with normal BAV function and 61% of patients with mild AS or AR maintained non-dysfunctional BAV. More patients with aortopathy progressed to severe aortopathy (35 vs. 0% without aortopathy, p <0.001), with a higher incidence of aorta operation (21 vs. 2%, p < 0.001).

Conclusions: In patients with non-dysfunctional BAV, initial BAV function and degree of aorta dilatation might be important for progression and outcomes. Patients without any dysfunction or aortopathy tend to maintain good structure and function for 6 years.

Keywords: bicuspid aortc valve, valve function, aortopathy, progression, outcomes

INTRODUCTION

Bicuspid aortic valve (BAV) is known as the most common congenital heart valve disease. Patients with BAV exhibit significant heterogeneity in various clinical aspects, including the type and degree of valve dysfunction or aortopathy (1–3). As echocardiographic surveillance has recently been carried out in the general population, the diagnosis of non-dysfunctional BAV, in which BAV has no significant aortic stenosis (AS) or aortic regurgitation (AR), is increasing.

It is well-established that patients with clinically significant AS or AR incur serious outcome consequences, whether they have bicuspid or tricuspid valves (4, 5). However, limited data are available regarding patients with normally functioning or minimally dysfunctional BAV at initial diagnosis (6, 7).

Our objective was to determine the incidence of aortopathy at initial diagnosis and characterize aortic complications among patients with non-dysfunctional BAV compared with dysfunctional BAV. We also used a large Korean BAV registry to assess the progression of valvular dysfunction and aortopathy in patients with non-dysfunctional BAV.

METHODS

Study Population

We retrospectively reviewed the echocardiographic database and medical records of patients with BAVs diagnosed from January 2003 to December 2018 at Severance Cardiovascular Hospital (Yonsei University College of Medicine, Seoul, South Korea). During this period, 1,307 patients with BAVs were identified and included in our BAV registry. Among them, 761 patients had undergone follow-up echocardiography at a minimum of 1 year post-diagnosis.

Significant AS and significant AR were detected via transthoracic echocardiograms; significant AS was defined as at least moderate AS, and significant AR was defined as at least moderate AR, using the guidelines in place (8, 9). Non-dysfunctional BAV was defined as BAV without significant AS or AR. Presence of aortopathy was defined as an ascending aorta (AA) diameter >37 mm (10, 11). We excluded 574 patients with significant AS or AR at the indexed echocardiogram in this study. Among 574 patients with dysfunctional BAVs, 354 showed severe AS or severe AR. During the mean follow-up of 5.9 years, 409 (71%) patients underwent operations (281 isolated BAV operation, 122 both BAV and aorta surgery and six isolated aorta surgery). One hundred eighty-seven non-dysfunctional BAV patients were classified according to valve function and aortopathy. For valve function, the patients were divided into the normal valve function group and the mild AS or AR group. In addition, they were divided into two groups according to presence of aortopathy (**Figure 1**).

The Institutional Review Board of Severance Hospital approved the present study, which was conducted in compliance with the Declaration of Helsinki.

Echocardiographic Assessments

Standard two-dimensional and Doppler measurements were performed following the current guidelines (12). A congenital BAV was diagnosed when only two cusps were unequivocally identified in systole and diastole in the short-axis view, with a clear "fish mouth" appearance during systole, as previously described (13). Anatomical types of BAV were identified according to a classification system suggested by Schaefer and colleagues (14). Type 1 exhibits congenital fusion of the right and left coronary cusp. Type 2 has a congenital fusion of the right and non-coronary cusp. Type 3 exhibits a congenital fusion of the non-coronary and left coronary cusp. Type 0 has no raphe and is also called "true type BAV." The severity of AS or AR was assessed using an integrated approach (9, 15). All measurements of the aorta were performed according to recommendations on the QRS complex of the electrocardiogram (12). The dimensions of the Valsalva sinuses were measured perpendicularly to the right and left (or non-) aortic sinuses. The sinotubular junction was measured where the aortic sinuses met the tubular aorta. The AA was measured $\sim$2 cm distal to the sinotubular junction, as described previously (13). Echocardiographic data were gathered and analyzed by experienced echocardiographers who were blinded to each patient's clinical data.

Statistical Analysis

Continuous variables are expressed as a mean $\pm$ standard deviation. Categorical variables are expressed as a number (percentage). Comparisons between groups were performed using standard chi-square tests for categorical variables and student *t*-tests for continuous variables. Multiple regression analysis was performed to determine the association between clinical and echocardiographic variables at the initial diagnosis and progression to BAV dysfunction or receiving aortic valve surgery. Similarly, multiple regression analysis was applied to find factors associated with the progression to severe aortopathy or receiving aorta surgery. The variables selected for entry into the multivariate analysis were those with a p-value <0.1 in the univariate analysis as well as other important variables. All statistical analyses were performed using SPSS Statistics, version 23.0 (IBM, Armonk, NY, USA). P-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics According to Valve Function and Aortopathy

Among 761 BAV patients in the registry, 187 (25%) patients showed non-dysfunctional BAV. Among these, 104 (56%) patients had mild AS or AR, and 81 (43%) had aortopathy at indexed echocardiography. The baseline characteristics of the subjects according to their baseline aortic valve function or presence of aortopathy were largely comparable (**Table 1**). Patients with aortopathy had a higher mean age and a higher use rate of beta blockers than those without aortopathy. However, the distribution of comorbidities, including hypertension, was similar between comparison groups. The most common BAV morphology was the type 1 morphology of fusion of the left

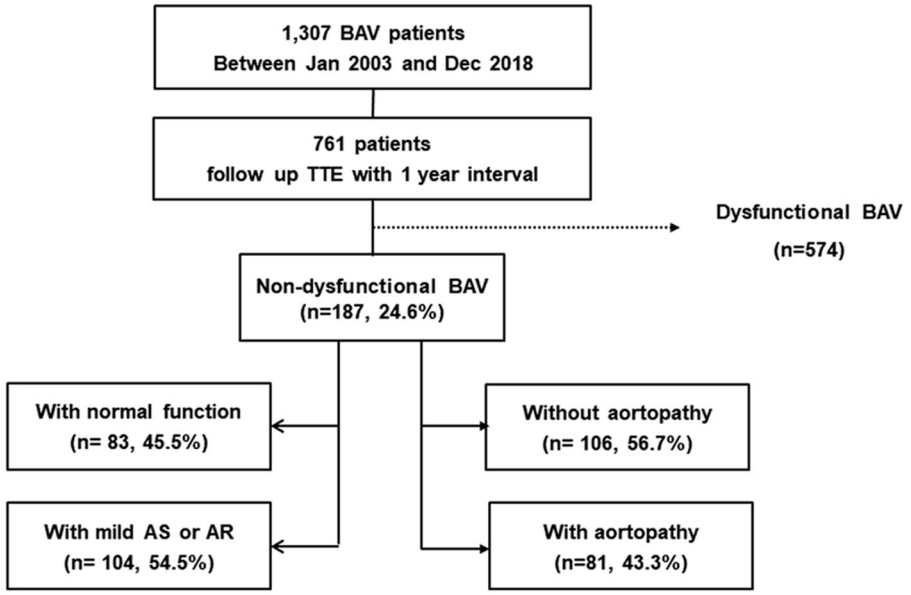


FIGURE 1 | Flow chart of the study.

TABLE 1 | Baseline characteristics.

	Normal function ($n = 83$)	Mild AS or AR ($n = 104$)	Without aortopathy ($n = 106$)	With aortopathy ($n = 81$)
Age, y	52 ± 13	55 ± 13	51 ± 13	58 ± 11†
Male sex	64 (74.4)	81 (77.9)	82 (74.5)	63 (77.8)
BMI, kg/m^2	24.4 ± 3.3	23.8 ± 3.1	23.8 ± 3.0	24.5 ± 3.5
Systolic BP, mmHg	125.9 ± 17.8	126.0 ± 16.2	127.0 ± 17.6	124.4 ± 16.1
Diastolic BP, mmHg	78.6 ± 11.4	79.0 ± 13.0	78.6 ± 12.3	79.1 ± 12.2
Comorbidities				
Hypertension	38 (44.7)	52 (50)	54 (49.1)	36 (44.4)
Diabetes mellitus	23 (27.1)	22 (21.2)	27 (24.5)	18 (22.2)
Chronic kidney disease	4 (4.6)	8 (7.7)	9 (8.2)	3 (3.7)
Dyslipidemia	34 (40.0)	30 (28.8)	36 (32.7)	28 (34.6)
Coronary artery disease	26 (30.6)	23 (22.1)	28 (25.5)	21 (25.9)
Medications				
RAAS blocker	27 (33.3)	32 (30.8)	29 (26.4)	30 (37.0)
Beta blocker	20 (24.7)	21 (20.2)	17 (15.5)	24 (29.6)†
Calcium channel blocker	19 (23.5)	23 (22.1)	27 (24.5)	15 (18.5)
Diuretics	10 (13.3)	15 (14.4)	31 (28.2)	13 (16.0)
Statin	25 (30.9)	26 (25.0)	12 (10.9)	20 (24.7)

Data are shown as Mean ± SD or n (%).
P < 0.05 compared with the normal function group, †compared with the group without aortopathy.*
AS, aortic stenosis; AR, aortic regurgitation; BP, blood pressure; RAAS, renin angiotensin aldosterone system.

and right coronary cusps in all groups, and the patients with aortopathy revealed a higher incidence of type 0 morphology than those without aortopathy (27.2 vs. 14.2%, $p = 0.019$) (**Table 2**). Patients with aortopathy showed a significantly larger aorta dimension than the other groups. Also, patients with aortopathy revealed a lower e' velocity than those without aortopathy.

Progression to BAV Dysfunction and Incidence of Aortic Valve Operation

In the normally functioning BAV group, 87% maintained non-dysfunctional BAV after follow-up (mean follow-up duration: 5.8 yrs). However, in the group with mild AS or AR, 61% did not show progression to significant valve dysfunction (mean follow-up duration; 6.2 yrs) (**Figure 2A**). The follow-up echocardiographic characteristics and detailed information for the operation were presented in **Supplementary Tables 1 and 2**. Also, aortic valve operation tended to be more frequent in the group with mild AS or AR, but this did not meet statistical significance (12.5 vs. 6.0%, $p = 0.068$) (**Table 3**). In the analysis for progression of valve dysfunction according to BAV morphology, the ratio of progression maintained with non-dysfunction was similar regardless of the presence of true type BAV (75 vs. 72%, $p = 0.172$) (**Figure 3A**). However, true type BAV showed a tendency of a higher incidence of valve operation than other types (19 vs. 10%, $p = 0.112$) (**Figure 3B**). In multivariate analysis, the presence of mild AS and initial aorta dimension were independently associated with the progression to non-dysfunctional BAV or receiving aortic valve operation (**Table 4**).

Progression to Severe Aortopathy and Incidence of Aorta Operation

Patients with BAV were subdivided into two groups according to the presence of aortopathy. Compared to patients without

aortopathy, the aortopathy group showed a tendency for faster progression, but this was not statistically significant (0.42 ± 0.85 mm vs. 0.32 ± 0.66 mm, $p = 0.22$) (**Table 5**). None of the patients without aortopathy experienced a progression of >45 mm in aorta diameter during follow-up (mean 6.0 years), whereas 34.6% of patients with aortopathy had an increase in aorta diameter of >45 mm (**Figure 2B**). Furthermore, 9.9% of the patients with aortopathy had an increase of >50 mm. Also, in the group with aortopathy, the rate of surgery was significantly higher (21.0 vs. 1.8% without aortopathy, $p < 0.001$) during the follow-up period (mean 6.0 years). The progression of aortopathy was analyzed according to BAV morphology. The rate of progression to severe aortopathy or the rate of aorta operation was higher in true type BAV than in other types of BAV (**Figures 3C,D**). However, in multivariate analysis, initial aorta dimension was the single independent predictor for the progression to severe aortopathy or receiving aorta operation (**Table 6**).

TABLE 2 | Echocardiogram characteristics.

	Normal function ($n = 83$)	Mild AS or AR ($n = 104$)	Without aortopathy ($n = 106$)	With aortopathy ($n = 81$)
BAV morphology				
Type 1	48 (57.8)	69 (66.3)	69 (65.1)	48 (59.3)
Type 2	14 (16.9)	17 (16.3)	20 (18.9)	11 (13.6)
Type 3	1 (1.2)	1 (1.0)	2 (1.8)	0 (0)
Type 0	20 (24.1)	17 (16.3)	15 (14.2)	22 (27.2)†
BAV function				
Normal	83 (100)	0 (0) *	50 (47.2)	33 (40.7)
Mild AR	0 (0)	51 (49.0)*	31 (29.2)	20 (24.7)
Mild AS	0 (0)	36 (34.6)*	17 (16.0)	19 (23.5)
Mild ASR	0 (0)	17 (16.3)*	8 (7.5)	9 (11.1)
Aorta dimension, mm	39.3 ± 5.8	38.5 ± 5.1	32.4 ± 3.5	44.3 ± 6.3†
Annulus, mm	20.0 ± 3.3	20.8 ± 3.3	19.3 ± 2.6	21.9 ± 3.7†
Sinus of Valsalva, mm	34.3 ± 6.4	34.0 ± 9.7	32.0 ± 5.7	36.8 ± 6.6†
Sinotubular junction, mm	30.1 ± 6.0	30.2 ± 5.1	27.6 ± 3.4	33.6 ± 6.0†
LVEDD, mm	49.7 ± 5.9	50.7 ± 6.1	49.6 ± 5.9	51.2 ± 6.1
LVESD, mm	33.7 ± 5.7	33.8 ± 7.0	33.1 ± 6.4	34.6 ± 6.3
LVEF, %	63.1 ± 9.1	64.5 ± 10.2	65.0 ± 8.9	62.7 ± 10.7
LV mass index, g/m^2	92.8 ± 27.0	99.6 ± 28.8	95.9 ± 24.8	99.4 ± 32.4
LA volume index, ml/m^2	25.0 ± 10.7	29.1 ± 14.0	28.6 ± 13.9	25.5 ± 10.7
e' velocity, cm/s	7.1 ± 2.4	6.8 ± 2.4	7.5 ± 2.4	6.2 ± 2.2†
S' velocity, cm/s	7.1 ± 1.5	7.0 ± 1.5	7.1 ± 1.6	6.9 ± 1.4
E/e'	10.6 ± 4.9	10.7 ± 4.7	10.5 ± 4.5	11.1 ± 5.2
RVSP, mmHg	24.8 ± 6.2	24.5 ± 5.5	24.7 ± 6.3	24.6 ± 5.1

Data are shown as Mean ± SD or n (%).
*P < 0.05 *compared with the normal function group, †compared with the group without aortopathy.*
AS, aortic stenosis; AR, aortic regurgitation; BAV, bicuspid aortic valve; ASR, aortic stenosis with regurgitation; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrium; e', early diastolic mitral annular; S', systolic mitral annular; E/e', the ratio of early diastolic mitral inflow and early diastolic mitral annular; RVSP, right ventricular systolic pressure.

DISCUSSION

The principal findings in the present study are that (1) aortopathy was quite common in patients with BAV, even in the absence

TABLE 3 | Progression of BAV dysfunction and incidence of aortic valve operation.

	Normal function ($n = 83$)	Mild AS or AR ($n = 104$)
Progression to dysfunctional BAV		
Moderate dysfunction	5 (6.0)	24 (23.1)*
Severe dysfunction	1 (1.2)	4 (3.8)
Aortic valve operation, *n* (%)	5 (6.0)	13 (12.5)
Severe dysfunction at operation	3 (3.6)	5 (4.8)
Non-severe dysfunction at operation	2 (2.4)	8 (5.7)
Coronary artery bypass graft	0 (0)	1 (0.9)
Graft replacement of ascending aorta	2 (2.4)	7 (6.7)
Follow-up duration, years	5.8 ± 3.6	6.2 ± 3.9

Data are shown as Mean ± SD or n (%).
P < 0.05 compared with the normal function group.
AS, aortic stenosis; AR, aortic regurgitation; BAV, bicuspid aortic valve.

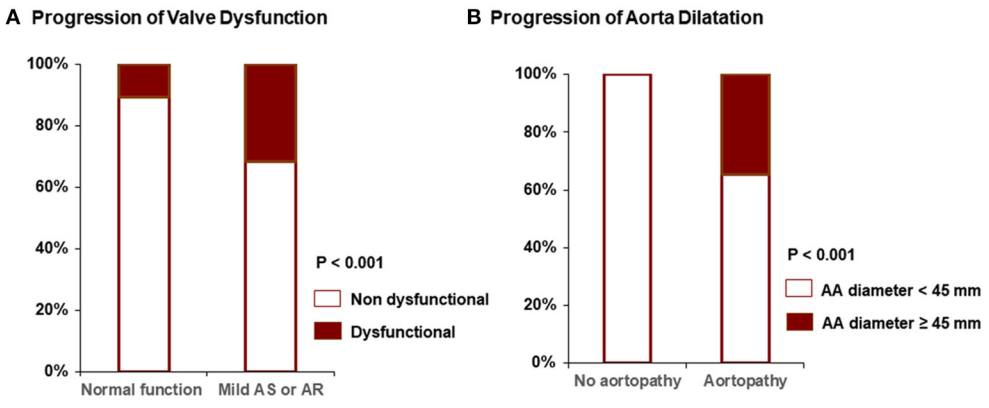


FIGURE 2 | Progression to valve dysfunction **(A)** and aorta dilatation **(B)** between groups.

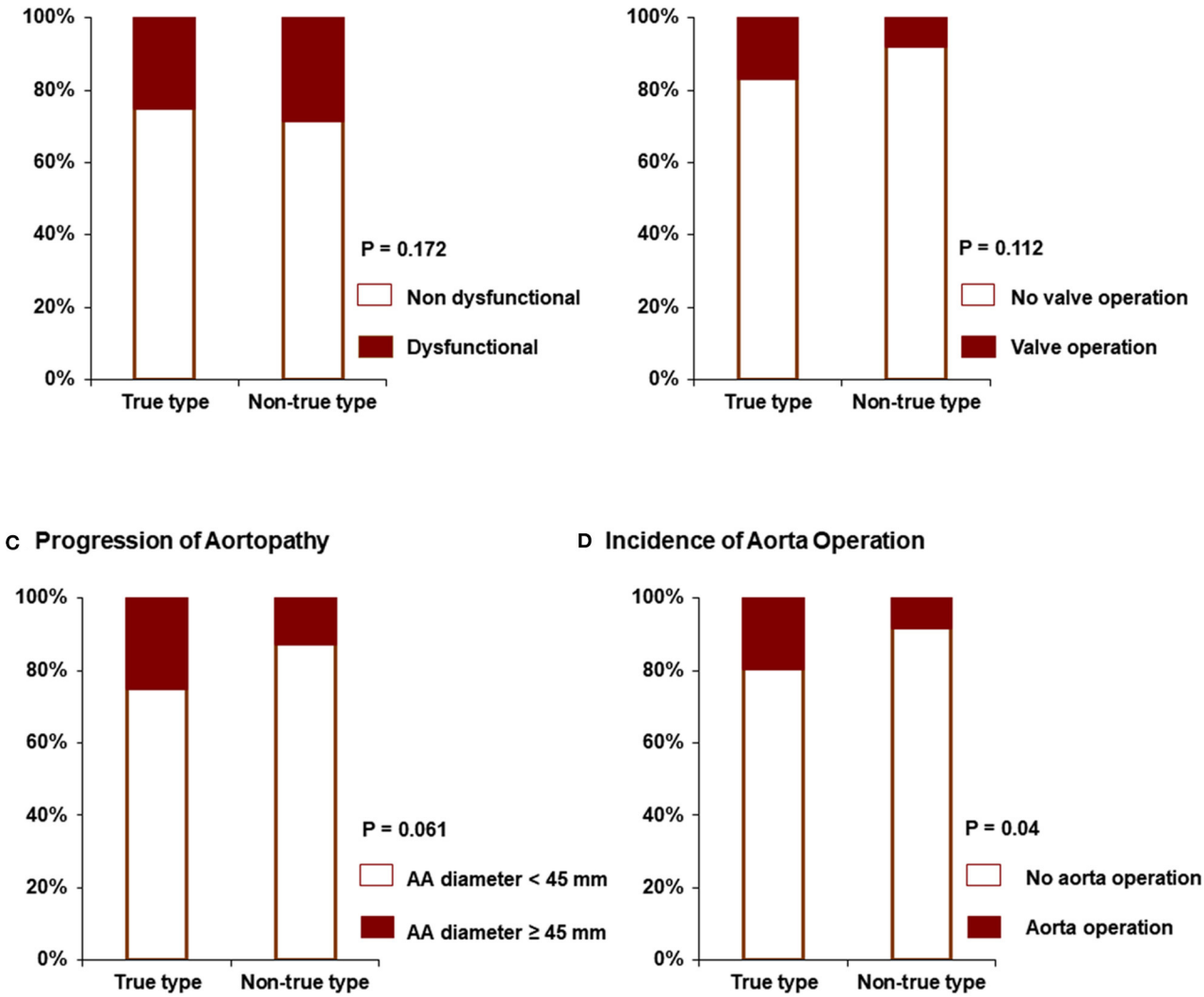


FIGURE 3 | Progression to valve dysfunction **(A)**, the incidence of valve operation **(B)**, the progression to severe aortopathy **(C)**, and incidence of aorta operation **(D)** according to BAV morphology.

of significant valvular dysfunction, (2) the progression of AA dilatation that met the requirements for aorta operation was more common in BAV patients with aortopathy at initial diagnosis than in those without aortopathy, (3) 89% maintained non-dysfunctional BAV after 6 years of follow-up when BAV patients were diagnosed with normal valve function. However, only 61% maintained non-dysfunctional BAV in patients with mild dysfunction, and (4) the rate of progression to severe aortopathy or the rate of aorta operation was higher in true type BAV than in other types of BAV.

The ratio of aortopathy to valvulopathy varies in patients with BAVs. The results of the present study also allow for the interpretation that the proportion of aortopathy is significant in the absence of valvulopathy (16–19). Our findings support previous studies suggesting that BAV is associated with intrinsic aortopathy, as well as with valve function-related pathology (16–19). We found that the association with the initial degree of BAV aortopathy was important in determining the incidence of aorta operation. Interestingly, when patients with initial normal valve function with advanced aortopathy (>45 mm, 28 patients) were followed up for 6.1 years, 14 (50.0%) patients underwent aorta and valve surgery. Four of the 14 patients underwent aortic valve replacement and aorta surgery for severe AS or severe AR, and 10 patients underwent aortic valve replacement with aorta operation, even though BAV function was normal or mildly dysfunctional. Thus, the aortopathy predominant patients with non-dysfunctional BAVs experienced aortopathy-associated clnical events during about 6 years. Because there was no adequate information on the natural history of existing BAV, additional aortic valve replacement was considered. However,

TABLE 4 | Factors associated with the progression to non-dysfunctional BAV or receiving aortic valve operation.

$R = 0.438$	β	T	*P*-value
Age	−0.075	−0.926	0.356
Male sex	−0.077	−1.068	0.287
Hypertension	0.041	0.498	0.619
Diabetes mellitus	0.039	0.493	0.623
Chronic kidney disease	−0.004	−0.047	0.962
RAAS blocker use	−0.027	−0.328	0.744
Beta blocker use	−0.041	−0.515	0.607
Statin use	0.014	0.177	0.860
Presence of mild AR	0.046	0.641	0.523
Presence of mild AS	0.305	4.228	<0.001
True type BAV	−0.054	−0.748	0.456
Initial aorta dimension, mm	0.314	3.997	<0.001

RAAS, renin angiotensin aldosterone system; AR, aortic regurgitation; AS, aortic stenosis, BAV, bicuspid aortic valve.

TABLE 5 | Progression of aortopathy and incidence of aorta operation.

	Without aortopathy ($n = 106$)	With aortopathy ($n = 81$)
Progression rate, mm/year	0.32 ± 0.66	0.42 ± 0.85
Initial AA diameter, mm	32.3 ± 3.5	42.0 ± 6.3*
Final AA diameter, mm	34.1 ± 3.6	44.0 ± 5.1*
Progression to severe aortopathy		
AA diameter ≥ 45 mm	0	28 (34.6)*
AA diameter ≥ 50 mm	0	8 (9.9)*
Aorta operation	2 (1.8)	17 (21.0)*
Follow-up duration, years	6.0 ± 3.5	6.1 ± 4.1

Data are shown as Mean ± SD or n (%).
**P < 0.05 compared with the group without aortopathy.*
AA, ascending aorta.

TABLE 6 | Factors associated with the progression to severe aortopathy or receiving aorta operation.

$R = 0.782$	β	T	*P*-value
Age	−0.006	−0.114	0.909
Male sex	−0.30	−0.606	0.545
Hypertension	−0.076	−1.320	0.189
Diabetes mellitus	0.012	0.226	0.821
Chronic kidney disease	−0.007	−0.144	0.886
RAAS blocker use	−0.065	−1.134	0.258
Beta blocker use	0.078	1.397	0.164
Statin use	−0.054	−1.000	0.319
Presence of mild AR	−0.064	−1.270	0.206
Presence of mild AS	0.022	0.445	0.657
True type BAV	−0.007	−0.140	0.889
Initial aorta dimension, mm	0.749	13.724	<0.001

RAAS, renin angiotensin aldosterone system; AR, aortic regurgitation; AS, aortic stenosis; BAV, bicuspid aortic valve.

according to our study, overall 71% of patients with non-dysfunctional BAVs maintained non-dysfunctional BAVs at 6 years follow-up. In young female patients of childbearing age, warfarin would be indicated for a long time in operations performed with mechanical valves. Therefore, when performing aorta operation in patients with non-dysfunctional BAVs, the decision of concomitant aortic valve replacement should be made cautiously in considering the individual's risk and benefits.

In general, degenerative changes in BAV patients occur earlier than in tricuspid AV patients. Recently, the diagnosis of normally functioning BAV in patients without valve dysfunction and aortopathy is increasing. There have been studies on factors that determine valve dysfunction in BAV patients (20–22) or progression in BAV patients with significant valvular dysfunction (4). Previous studies have also examined how these factors affect left ventricular diastolic function, according to BAV morphology (13). Moreover, a previous report from the Korean BAV cohort also demonstrated mid-term clinical outcome in asymptomatic or mildly symptomatic patients with BAVs including both non-dysfunctional BAVs and dysfunctional BAVs (23).

However, there have been few studies on the natural course of normally functioning BAV patients, and in the real world, patients may wonder about their prognosis and when to perform a follow-up echocardiogram. As a result, we expect our research to serve as a reference. Although the mean follow-up duration was not long enough (about 6 years), ∼89% of patients with normal valvular functional BAV at the time of diagnosis had no surgical treatment during the follow-up period, and 71% of the patients maintained mild valve dysfunction during the follow-up period. Even for non-dysfunctional BAV patients, if the aorta is over 37 mm at the time of diagnosis, or if there is mild BAV dysfunction, if true type BAV, the progression of aortopathy or BAV dysfunction should be regularly examined by echocardiography.

Studies of BAV have increased rapidly during recent years. An international BAV consortium has identified knowledge gaps and risen to the challenge regarding BAV (24). Also, the American Association for Thoracic Surgery published consensus guidelines on BAVs (25). Genetic studies on BAV have been published, some groups have broadened the scope of transcatheter aortic valve replacement to focus on BAV (26). However, few natural history data are based on long-term observations. In particular, the Olmsted county study is an ideal community-based study, whereas our BAV registry is affected by several sources of bias because we included a referral cohort. The patients in the Olmsted County study were obtained by screening through auscultation revealed that 27% had aortic valve- or aorta-related surgery within a 20-year follow-up period (27). Similar to our registry, Olmsted's study also constructed a cohort in normal or mild aortic valve disease patients. In Olmsted study, the results for detailed follow up-echocardiography were missing, the rate of surgery was shown. Compared to the olmsted study, it is noteworthy that the rate of surgery of our study after mean 6 years follow-up is similar. In comparison, our study has the advantage of including detailed echocardiographic follow-up data for valve function and aorta dimensions as well as

clinical outcomes over 6 years in patients with non-dysfunctional BAV. The present study provides additional information to help clinicians predict which patients will progress and worsen clinical outcomes.

LIMITATIONS

The present study had several limitations. First, this retrospective study included only Korean BAV subjects from a single tertiary referral center, which may result in bias. Therefore, multi-center, prospective studies are needed to evaluate the prevalence of aortopathy in normal valvular BAV and progression of aortic valve function in BAV. Since the follow-up period for valve dysfunction is different for each patient, it is limited in its use for quantitative evaluation of the progression of valve dysfunction. However, we believe that this study is a meaningful study that has reported on the prevalence of aortopathy and valve progression in a large Korean registry using comprehensive reviews. Additionally, the median follow-up duration was only 6 years, which is insufficient to analyze the long-term natural history of early BAV disease. Second, data were lacking regarding common genetic backgrounds in BAV patients. Third, aortic diameters were measured based on echocardiographic imaging alone, because only some BAV subjects underwent computed tomography or cardiac magnetic resonance imaging.

CONCLUSIONS

In patients with non-dysfunctional BAV, initial BAV function and degree of aorta dilatation might be important for progression and outcomes. Patients without any dysfunction or aortopathy tend to maintain good structure and function for 6 years.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Severance Hospital, Yonsei University College of Medicine. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

SS and CS are the gurantors of the entire manuscript. CS and G-RH contributed to the study conception and design, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. JS, IC, and J-WH contributed to the data acquisition, analysis, and interpretation. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported in part by a faculty research grant of Yonsei University College of Medicine (6-2014-0153).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2020.603323/full#supplementary-material

REFERENCES

1. Ward C. Clinical significance of the bicuspid aortic valve. *Heart.* (2000) 83:81–5. doi: 10.1136/heart.83.1.81
2. Prakash SK, Bossé Y, Muehlschlegel JD, Michelena HI, Limongelli G, Corte AD, et al. and BAVCon Investigators. A roadmap to investigate the genetic basis of bicuspid aortic valve and its complications: insights from the international BAVCon (Bicuspid Aortic Valve Consortium). *J Am Coll Cardiol.* (2014) 64:832–9. doi: 10.1016/j.jacc.2014.04.073
3. Jeong H, Shim CY, Kim D, Choi JY, Choi KU, Lee SY, et al. Prevalence, characteristics, and clinical significance of concomitant cardiomyopathies in subjects with bicuspid aortic valve. *Yonsei Med J.* (2019) 60:816–23. doi: 10.3349/ymj.2019.60.9.816
4. Beppu S, Suzuki S, Matsuda H, Ohmori F, Nagata S, Miyatake K. Rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves. *Am J Cardiol.* (1993) 71:322–7. doi: 10.1016/0002-9149(93)90799-I
5. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation.* (1997) 95:2262–70. doi: 10.1161/01.CIR.95.9.2262
6. Mills P, Leech G, Davies M, Leathan A. The natural history of a non-stenotic bicuspid aortic valve. *Br Heart J.* (1978) 40:951–7. doi: 10.1136/hrt.40.9.951
7. Pachulski RT, Chan KL. Progression of aortic valve dysfunction in 51 adult patients with congenital bicuspid aortic valve: assessment and follow up by Doppler echocardiography. *Br Heart J.* (1993) 69:237–40. doi: 10.1136/hrt.69.3.237
8. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* (2003) 16:777–802. doi: 10.1016/S0894-7317(03)00335-3
9. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* (2009) 22:1–23; quiz 101–2. doi: 10.1016/j.echo.2008.11.029
10. Beroukhim RS, Kruzick TL, Taylor AL, Gao D, Yetman AT. Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. *Am J Cardiol.* (2006) 98:828–30. doi: 10.1016/j.amjcard.2006.04.022
11. Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M, et al. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. *Eur J Cardiothorac Surg.* (2007) 31:397–404. doi: 10.1016/j.ejcts.2006.12.006
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* (2015)16:233–70. doi: 10.1093/ehjci/jev014
13. Lee SY, Shim CY, Hong GR, Seo J, Cho I, Cho IJ, et al. Association of aortic phenotypes and mechanical function with left ventricular diastolic function

in subjects with normally functioning bicuspid aortic valves and comparison to subjects with tricuspid aortic valves. *Am J Cardiol*. (2015)116:1547–54. doi: 10.1016/j.amjcard.2015.08.017
14. Schaefer BM, Lewin MB, Stout KK, Gill E, Prueitt A, Byers PH, et al. The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. *Heart*. (2008) 94:1634–8. doi: 10.1136/hrt.2007.132092
15. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Scientific document committee of the european association of cardiovascular imaging. recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. (2013) 14:611–44. doi: 10.1093/ehjci/jet105
16. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, et al. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA*. (2011) 306:1104–12. doi: 10.1001/jama.2011.1286
17. Hahn RT, Roman MJ, Mogtader AH, Devereux RB. Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. *J Am Coll Cardiol*. (1992)19:283–8. doi: 10.1016/0735-1097(92)90479-7
18. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, Sutton MG. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. *Circulation*. (2000)102(19 Suppl 3):III35–9. doi: 10.1161/01.CIR.102.suppl_3.III-35
19. Yasuda H, Nakatani S, Stugaard M, Tsujita-Kuroda Y, Bando K, Kobayashi J, et al. Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. *Circulation*. (2003)108(Suppl 1):II291–4. doi: 10.1161/01.cir.0000087449.03964.fb
20. Lee SY, Shim CY, Hong GR, Cho IJ, Chang HJ, Ha JW, et al. Determinants and prognostic significance of symptomatic status in patients with moderately dysfunctional bicuspid aortic valve. *PLoS ONE*. (2017) 12:e0169285. doi: 10.1371/journal.pone.0169285
21. Lee SY, Shim CY, Kim D, Cho I, Hong GR, Ha JW, et al. Factors determining aortic valve dysfunction in Korean Subjects with a bicuspid aortic valve. *Am J Cardiol*. (2017) 110:2049–55. doi: 10.1016/j.amjcard.2017.03.038
22. Kim D, Chae D, Shim CY, Cho IJ, Hong GR, Park K, et al. Predicting disease progression in patients with bicuspid aortic stenosis using mathematical modeling. *J Clin Med*. (2019) 8:1302. doi: 10.3390/jcm8091302
23. Sun BJ, Oh JK, Lee SH, Jang JY, Lee JH, Lee S, 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. doi: 10.4250/jcvi.2019.27.e19
24. Michelena HI, Prakash SK, Corte AD, Bissell MM, Anavekar N, Mathieu P, et al. BAVCon Investigators. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). *Circulation*. (2014) 129:2691–704. doi: 10.1161/CIRCULATIONAHA.113.007851
25. Borger MA, Fedak PWM, Stephens EH, Gleason TG, Girdauskas E, Ikonomidis JS, 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. doi: 10.1016/j.jtcvs.2018.02.115
26. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging*. (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
27. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*. (2008) 117:2776–84. doi: 10.1161/CIRCULATIONAHA.107.740878

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 23 March 2021
doi: 10.3389/fcvm.2021.643900

Multimodal Assessment of Vascular and Ventricular Function in Children and Adults With Bicuspid Aortic Valve Disease

Constance G. Weismann[1], Sara Ljungberg[1], Anna Åkesson[2] and J Hlebowicz[3]*

[1] Division of Pediatric Cardiology, Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden, [2] Clinical Studies Sweden – Forum South, Skåne University Hospital, Lund, Sweden, [3] Department of Cardiology, Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden

OPEN ACCESS

Edited by:
Giovanni Battista Luciani, University of Verona, Italy

Reviewed by:
Alessandra Cristofaletti, Integrated University Hospital Verona, Italy
Federico Gutierrez-Larraya, University Hospital La Paz, Spain

****Correspondence:***
Constance G. Weismann
constance.weismann@med.lu.se
orcid.org/0000-0001-7477-7283

Specialty section:
This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *19 December 2020*
Accepted: *25 February 2021*
Published: *23 March 2021*

Citation:
Weismann CG, Ljungberg S, Åkesson A and Hlebowicz J (2021) Multimodal Assessment of Vascular and Ventricular Function in Children and Adults With Bicuspid Aortic Valve Disease. Front. Cardiovasc. Med. 8:643900. doi: 10.3389/fcvm.2021.643900

Background: Bicuspid aortic valve (BAV), the most common congenital cardiac anomaly, has been associated with an aortopathy, increased aortic stiffness and diastolic dysfunction. The involved mechanisms and impact of age remain unclear. It was the aim of this study to characterize arterial and cardiac function, their correlation, and the effect of age in children and adults with a history of BAV.

Methods: Multimodal cardiovascular assessment included echocardiography, ascending aortic distensibility, common carotid intima media thickness [cIMT], parameters of wave reflection [central (cAIx75) and peripheral (pAIx75) augmentation index corrected to a heart rate of 75/min, aging index (AI)], carotid-femoral pulse wave velocity [cfPWV], and endothelial function (EndoPAT). Multivariable linear regression and correlation analyses were performed.

Results: We included 47 BAV patients and 84 controls (age 8–65 years). Ascending aortic stiffness, pulse wave reflection (cAIx75, pAIx75, and AI) and central blood pressure were significantly increased in patients with BAV. However, PWV, cIMT, and endothelial function were not significantly different from controls. BAV patients had marginally reduced diastolic (E': $\beta = -1.5$, $p < 0.001$) but not systolic function compared to controls. Overall, all parameters of arterial stiffness had moderate-strong correlations with diastolic dysfunction and age. In the BAV group, ascending aortic distensibility had the strongest correlation with diastolic dysfunction.

Conclusions: BAV is associated with increased proximal arterial stiffness and wave reflection. However, PWV and cIMT are not increased, and endothelial function is preserved. This suggests that the mechanism of arterial and cardiac stiffening is different from patients with acquired heart diseases.

Keywords: bicuspid aortic valve, aortic stiffness and distensibility, augmentation index, pulse wave velocity, intima media thickness, endothelial function, diastolic function, congenital heart disease

INTRODUCTION

Bicuspid aortic valve (BAV) is one of the most common congenital cardiac malformations, existing in 1–2% of the population. Due to its high prevalence, it may cause more morbidity and mortality than all other congenital heart defects combined (1). BAV has a wide spectrum of clinical presentations ranging from the neonate with critical aortic stenosis to the asymptomatic adult. The disease is, however, not confined to the aortic valve, but rather associated with a congenital aortopathy which is thought to predispose to ascending aortic stiffening, dilation and even dissection (2–4). Furthermore, diastolic and systolic dysfunction have been described in BAV patients even without significant valvular impairment (3, 5, 6). The cause for diastolic and/or systolic myocardial dysfunction without significant valve dysfunction remains unclear, but could be due to (1) abnormal intraventricular flow dynamics in the setting of an asymmetrically opening valve, (2) intrinsic myocardial abnormalities, or (3) be the result of arterio-ventricular interaction (i.e., the impact of arterial stiffening on ventricular function). Arterio-ventricular interaction as a cause of diastolic heart failure appears to be an important mechanism in adults with heart failure and preserved ejection fraction (7). There, arterial stiffness increases late systolic afterload, which in turn affects thick-thin myofilament interaction and crossbridge dissociation, leading to impaired cardiac relaxation during diastole (7). However, the published data on arterio-ventricular interaction specific to congenital heart disease and BAV in particular are limited and controversial to date (3, 6, 8).

We hypothesized that patients with BAV have abnormalities in vascular characteristics that extend from the large to small arteries, and that aortic stiffness correlates with left ventricular diastolic function. The secondary hypothesis was that arterial and ventricular stiffening are present in childhood and are further increased at older age. We tested these hypotheses using a multimodal approach on children and adults with a history of BAV, aiming to enhance insights into the pathophysiological mechanisms involved in BAV disease. The methods chosen aimed to cover anatomical and physiological aspects ranging from the ascending aorta to peripheral arteries.

METHODS

Study Population

This is a prospective cross-sectional observational study comparing cardiovascular function in patients with a history of a BAV to healthy controls. The study was approved by the local ethics committee (#2017/243) and conducted 2017-2019.

BAV patients were recruited through SWEDCON (Swedish national registry on congenital heart disease) and control patients were recruited through advertisement. Inclusion criteria for the BAV group were a history of BAV including patients who have undergone aortic surgery such as commissurotomy, aortic valve or ascending aortic replacement. Exclusion criteria were associated congenital heart disease (e.g., aortic coarctation), severe aortic stenosis or insufficiency, cardiac surgery within the last 3 months, diabetes, rheumatological, hematological, or oncological disorders. Control group specific exclusion criteria were a personal history of heart disease or a family history of a 1st degree relative with known thoracic aortic aneurysm.

Baseline characteristics such as gender, age, weight, height, body surface area, body mass index, blood pressure and heart rate were recorded. For the BAV group, prior cardiac interventions were documented if applicable. Patients were examined after at least 4 h of fasting and a minimum 10 h abstinence from caffeine and nicotine. The exams were performed in a quiet room with dampened light at a room temperature set to 22°C. Patients were in a supine position for at least 5 min prior to vascular examinations.

Ultrasound

Echocardiograms and common carotid artery ultrasound evaluations were performed using the EPIQ7 (Philips Healthcare, Netherlands). Probe frequency (X5-1, X7-2, L15-7io) was selected as appropriate for patient size. Echocardiograms were performed using 2-dimensional, color, spectral, and tissue Doppler (TDI) as previously described (9). For TDI measurements, averages of septal and lateral E' velocities [cm/s] were used. Four-dimensional analysis of left ventricular systolic function included ejection fraction (EF). Four beat acquisitions were obtained at a frame rate of at least 30 Hz.

As previously described, two-dimensional measurements of the ascending aorta in peak systole (SD) and end-diastole (DD) were obtained from a high parasternal long axis view at the level of the right pulmonary artery to calculate distensibility, stiffness index, and strain (9, 10). Patients who had undergone prior ascending aortic replacement were excluded for ascending aortic elasticity measurements. Mean common carotid intima media thickness (cIMT) was measured semi-automatically in end-diastole over a distance of 1 cm, using a 15 MHz transducer.

Measurements were performed offline (Philips Intellispace and QLAB Cardiac Analysis, Philips Healthcare, Netherlands; 4D LV-Analysis, Tomtec Imaging Systems, Unterschleissheim, Germany). All measurements were performed by one of two experienced congenital echocardiographers (B.G., C.W.).

Arterial Function

Carotid-femoral arterial pulse wave velocity (PWV), a surrogate parameter of large arterial stiffness, was determined using SphycmoCor XCEL (AtCor, Australia) (11). Path length was measured according to guidelines, using the direct method * 0.8 (12). CfPWV was recorded over a period of 10 s. Averages of two separate measurements were used for analyses. Only measurements that passed the internal Quality Control were used.

Using the same device, pulse wave analysis was performed, which uses a transfer function to derive a central from a brachial pulse wave form. Cuff size was selected according to arm circumference. Using the central wave form, central blood pressure and augmentation index (cAIx) corrected to a heart rate of 75 beats per minute (cAIx75) were determined. AIx is defined as the difference between the reflected wave (P2) and the forward wave (P1), divided by the pulse pressure. A higher cAIx75 corresponds to a relatively increased wave reflection and stiffer

arteries. Following two consecutive right arm blood pressure measurements, pulse wave analysis was performed and averaged over 10 s. The protocol was repeated and average measurements were used for analyses.

Digital pulse wave analysis with photoplethysmography (DPA; Meridian, South Korea) provides a digital pulse curve as well as its second derivative that represents accelerations and decelerations of the blood flow (Acceleration Plethysmography) (13). Aging index (AI) is derived from the acceleration curve and has previously been shown to correlate strongly with AIx75 measured by the SphygmoCor device (13). A higher, less negative AI is consistent with aging (i.e., stiffer arteries). The second derivative of the pulse curve in the right index finger was analyzed continuously over 1 min. Averages of two separate measurements were used for analyses.

Endothelial function was assessed using EndoPAT 2000 (Itamar Medical, Israel) (14, 15). The reactive hyperaemic response in the right index finger was measured following a 5 min period of right arm occlusion in relation to baseline and contralateral peripheral arterial tone (reactive hyperemia index, RHI) (16). From the baseline recording, the peripheral augmentation index [(P2-P1)/P1] corrected to a heart rate of 75 beats per minute (pAIx75) was derived.

TABLE 1 | Comparison of demographic characteristics between BAV patients and controls.

Demographic characteristics	BAV ($n = 47$)	Controls ($n = 84$)	p
Age [years]	36 (19–46)	27 (20–40)	0.125
Female gender	14 (30 %)	42 (50%)	0.025
Height [cm]	176 (170–182)	171 (160–180)	0.079
Weight [kg]	74 (62–86)	70 (58–80)	0.139
Body mass index [kg/m^2]	23 (21–25)	23 (21–27)	0.623
Heart rate [beats per minute]	61 (56–69)	60 (54–68)	0.308
Brachial systolic blood pressure [mmHg]	123 (116–135)	118 (112–123)	0.013
Brachial diastolic blood pressure [mmHg]	77 (69–84)	70 (64–77)	0.003
Nicotine use	9 (19%)	12(15%)	0.506

Values expressed as median (interquartile range). Significance was tested with Mann-Whitney U-test. P-value of <0.05 was considered significant.

Statistics

For statistical analyses, continuous variables were expressed as median and inter-quartile range (IQR). Categorical variables were expressed as frequency and compared by the Chi square or Fisher exact test as appropriate. Linear regression analyses were carried out correcting for the covariates age and sex. Additional covariates were included in the model as appropriate and specified in **Tables 2–4**. If necessary, logarithmic transformation was used (stiffness index). Variables were associated using Pearson's correlation coefficient (r).

TABLE 2 | Descriptive statistics and linear regression model comparing outcome variables of BAV patients to controls.

	BAV ($n = 47$)	Controls ($n = 84$)	β (95% CI)	p
Diastolic and systolic cardiac function				
E' [cm/s]	11.8 (9.6–13.1)	13.6 (11.8–15.1)	−1.5 (−2.2 to −0.8)	<0.001
E/E' ratio	7.6 (6.3–9.2)	5.8 (5.1–6.7)	2.0 (1.4 – 2.7)	<0.001
Ejection fraction [%]	60.9 (55.9–63.7)	62.3 (59.9–64.5)	−1.5 (−3.2 – 0.2)	0.084
Left ventricular mass Index [g/m^2]	83.2 (61.7–98.9)	65.96 (49.4–75.4)	19.1 (11.0 – 27.3)	<0.001
Proximal arterial characteristics by ultrasound				
Ascending aortic dimension [cm]	3.4 (2.9–4.1)	2.9 (2.5–3.1)	0.7 (0.5 – 0.9)	<0.001
AscAo distensibility [10^{-6}cm^2/dyn]	2.2 (1.6–3.4)	5.2 (4.2–7.1)	−2.3 (−3.0 to −1.6)	<0.001
AscAo stiffness index	9.0 (6.4–14.4)	4.1 (3.1–5.4)	2.7 (2.5 – 2.9)	<0.001
AscAo strain [%]†	5.6 (3.6–7.8)	12.3 (9.2–17.2)	−5.9 (−7.7 to −4.2)	<0.001
cIMT [mm]	0.5 (0.4–0.6)	0.5 (0.4–0.6)		0.939
Central blood pressure, arterial, endothelial and microcirculatory function				
Central systolic pressure [mmHg]	110.5 (103.5–120.3)	102.5 (95.8–109.0)	5.6 (1.8–9.4)	0.004
Central diastolic pressure [mmHg]	77.5 (70.0–82.3)	70.8 (65.0–77.1)	3.7 (0.6–6.8)	0.020
cAIx75%§	10.1 (−1.3–23.3)	−6.3 (−14.47–6.82)	15.1 (9.9–20.1)	<0.001
pAIx75%§	−1.00 (−13.00–15.00)	−18.00 (−27.00 to −3.75)	13.8 (8–19.5)	<0.001
Aging index*§	−0.50 (−0.73 to −0.13)	−0.73 (−0.94 to −0.58)	0.2 (0.1–0.3)	<0.001
Pulse wave velocity [m/s]*§	6.2 (5.1–7.6)	6.6 (4.9–7.2)		0.182
Reactive hyperemia index	2.3 (1.8–2.6)	2.2 (1.7–2.6)		0.748

Ascending aortic parameters excluded subjects who have undergone ascending aortic replacement. Continuous variables are presented as median (interquartile range), linear regression results as β (95% confidence interval). Beta values adjusted for age and sex, and their significance level (p) are provided if $p < 0.1$. Parameter specific additional covariates are marked as: †central mean pressure, §height, *heart rate.

AscAo, ascending aorta; cIMT, common carotid artery intima media thickness; cAIx75, central augmentation index corrected to a heart rate of 75/min; pAIx75, peripheral augmentation index corrected to a heart rate of 75/min.

TABLE 3 | Subgroup analysis of BAV patients with native aortic valves (i.e., excluding 15 patients who have undergone prior aortic valve replacements) compared to controls.

	β	P
Diastolic and systolic cardiac function		
E' [cm/s]	−1.4	<0.001
E/E' ratio	1.7	<0.001
Ejection fraction [%]		0.572
LV mass index [g/m^2]	12.6	0.003
Central blood pressure and proximal arterial characteristics by ultrasound		
Ascending aortic dimension [cm]	0.7	<0.001
AscAo distensibility	−2.4	<0.001
AscAo stiffness index	2.9	<0.001
AscAo strain [%]†	−5.8	<0.001
CCA IMT [mm]		0.133
Arterial, endothelial and microcirculatory function		
Central systolic pressure [mmHg]	5.2	0.008
Central diastolic pressure [mmHg]	3.7	0.033
cAIx75%§	17.0	<0.001
pAIx75%§	15.4	<0.001
Aging index*§	0.3	<0.001
Pulse wave velocity [m/s] *§		0.292
Reactive hyperemia index		0.928

*Linear regression model adjusting for age, sex, and parameter specific additional variables marked as: †central mean pressure, §height, *heart rate. β is provided if $p < 0.1$.*

A p-value of <0.05 was considered statistically significant. Where appropriate, Bonferroni correction of alpha level was used to adjust for multiple comparisons. Data were stored using REDCap electronic data capture tools hosted at Lund University. Statistical analysis was performed using Statistical Package for Social Sciences, version 25 (IBM SPSS, Chicago, IL).

RESULTS

We prospectively recruited 47 patients with a history of BAV and 88 controls. Of the controls, three were excluded due to pre-existing cardiovascular disease, and one was excluded due of technical difficulties. Thus, 84 controls were included in the study. The median age was 29 (range 8–65) years. Eleven patients were under 18 years of age.

BAV Cohort Description

The majority of the patients had never required an intervention for BAV. Twenty (43.6%) of the 47 subjects had at least one intervention. Eight (17%) had undergone surgical commissurotomy. Fifteen (32.0%) had prosthetic aortic valves (five mechanical, two bioprosthetic, five Ross procedures) whereof six (12.8%) also had ascending aortic grafts. No one had been operated for aortic dissection. At the time of the study visit, four (8.5%) patients had moderate aortic stenosis with mean gradients between 20 and 30 mmHg, and two (4.3%) had moderate aortic insufficiency associated with BAV. Only 12 (25.5%) of the patients with BAV were taking medications (anticoagulants: $n = 7$, 14.9%; antihypertensives: $n = 3$, 6.4%).

TABLE 4 | Subgroup analysis comparing BAV patients with native well-functioning valves (BAV_1; $n = 22$) and BAV with prior intervention (BAV_2; $n = 19$) to controls.

	BAV_1 vs. Control		BAV_2 vs. Control		BAV1_vs. BAV_2	
	β	P	β	p	β	p
E' [cm/s]	−1	0.096	−1.3	0.045		1
AscAo distensibility	−2.2	<0.001	−2.5	<0.001		1
cAIx75%§	13.5	<0.001	15.1	0.001		1

Linear regression model with Bonferroni correction, adjusting for age and sex. Parameter specific additional variables marked as: §height, β is provided if $p < 0.1$.

Demographics BAV vs. Control

There was no difference between the BAV group and the control group regarding age, weight, height, BMI, HR and nicotine use. However, the BAV group had significantly higher proportion of males as well as higher systolic and diastolic brachial blood pressures (**Table 1**). Following correction for age and sex though, systolic blood pressure no longer significantly elevated ($p = 0.233$), while diastolic blood pressure was significantly elevated ($\beta = 3.4$, $p = 0.032$).

Cardiac Function

Left ventricular mass index was significantly greater and diastolic function was significantly impaired compared to healthy controls following adjustment for age and sex (**Table 2**). This was evidenced by a lower E' velocity by TDI and a higher E/E' ratio. The difference in diastolic function (E') remained statistically significant when adding moderate aortic stenosis ($b = -1.2$, $p = 0.001$), LV mass index ($b = -1.4$, $p < 0.001$), or central blood pressure ($b = -1.4$, $p < 0.001$), as covariates. In the BAV group, diastolic function correlated negatively with LV mass index ($r = -0.36$, $p = 0.015$), but not with left ventricular outflow tract gradient ($p = 0.788$). In addition, E' corrected for ascending aortic distensibility was not significantly different between the BAV and control groups ($p = 0.399$). Systolic function described by 4-dimensional EF was not significantly different between the groups. Above findings on cardiac structure and function were sustained when excluding BAV patients who have undergone prior aortic valve replacement (**Table 3**).

Arterial Characteristics

Multimodal assessment of arterial function consistently revealed pathologic changes of proximal arterial characteristics and wave reflection in the BAV group (**Table 2**). The proximal large arteries were characterized by decreased ascending aortic elasticity (increased stiffness index, decreased distensibility, and strain). CIMT, by contrast, was not significantly different from controls. Central blood pressure and arterial wave reflection measured by three different methods (cAIx75 by SphygmoCor XCEL, pAIx75 by EndoPAT, and AI by DPA) was significantly increased in BAV patients compared to controls. In spite of clearly increased proximal arterial stiffness and increased peripheral

TABLE 5 | Correlations between average E' (diastolic function) and cardiovascular characteristics for all patients as well as group-wise analysis for controls and BAV patients.

Diastolic function	*R* for All*	*p*	*R* for BAV*	*p*	*R* for Control	*p*
	N = 131		*N* = 47		*N* = 84	
Proximal arterial characteristics by ultrasound						
AscAo Distensibility [10^{-6}cm^2/dyn]†	0.59	<0.001*	0.63	<0.001*	0.48	<0.001*
Ascending aortic dimension [cm]†	−0.54	<0.001*	−0.37	0.016	−0.58	<0.001*
cIMT [mm]	−0.59	<0.001*	−0.53	<0.001*	−0.65	<0.001*
Arterial wave reflection and pulse wave velocity						
Central systolic blood pressure [mmHg]	−0.54	<0.001*	−0.34	0.031	−0.61	<0.001*
cAIx75%	−0.47	<0.001*	−0.23	0.149	−0.54	<0.001*
pAIx75%	−0.40	<0.001*	−0.17	0.301	−0.45	<0.001*
Aging Index	−0.42	<0.001*	−0.38	0.031	−0.40	<0.001*
Pulse Wave Velocity [m/s]	−0.56	<0.001*	−0.47	0.002*	−0.63	<0.001*

*Pearson's correlation coefficient R and p-values are listed. *Significant following Bonferroni correction for multiple comparisons with significance level at 0.006.*
AscAo, ascending aorta; cIMT, common carotid artery intima media thickness; cAIx75, central augmentation index corrected to a heart rate of 75/min; pAIx75, peripheral augmentation index corrected to a heart rate of 75/min.
*† six patients with aortic prostheses excluded. *Partial correlations adjusting for moderate aortic stenosis.*

wave reflection, cfPWV – representing arterial stiffness between the carotid and femoral arteries—was not significantly different between patients and controls (**Table 2**). Further, RHI, which describes endothelial function, revealed no difference between the BAV and Control groups. Above findings on arterial characteristics were sustained when excluding BAV patients who have undergone prior aortic valve replacement (**Table 3**).

Arterial and Cardiac Stiffening Independent of Prior Intervention

In order to identify risk factors for worse diastolic function (average E'), ascending aortic distensibility or cAIx75we performed multivariate linear regression analyses within the BAV group. Independent variables included age, sex, central systolic pressure, LV mass index, aortic valve morphology, moderate aortic stenosis, history of prior aortic valve intervention, aortic valve prosthesis, and prior ascending aortic replacement. Except for age (see above) none of the other factors met statistical significance (data not shown).

In an effort to evaluate potential differences in diastolic or arterial function that are secondary to prior surgery, we performed subgroup analyses comparing BAV patients with at most mild valve dysfunction and no prior aortic procedure (BAV_1; $n = 22$) to BAV patients who have had an aortic procedure (BAV_2; $n = 19$) to controls. Following Bonferroni correction for multiple comparisons, differences in diastolic function (average E') were no longer significant between the BAV subgroups and controls (**Table 4**). By contrast, group differences in ascending aortic distensibility (in those with native ascending aortas) and cAIx75 prevailed, but there was no significant difference in arterial parameters between the BAV subgroups (**Table 4**).

Arterio-Ventricular Interaction

Next, we evaluated whether diastolic cardiac function correlates with arterial characteristics, correcting for the effect of aortic stenosis (**Table 5**, **Figure 1**). Across all study subjects, there were moderate-strong and highly significant correlations between diastolic function and absolute values of arterial parameters.

We then evaluated correlations between arterial parameters and diastolic function group-wise. In decreasing order, the control group had moderate strong and highly significant negative correlations of diastolic function with cIMT, PWV, central systolic pressure, ascending aortic dimension, cAIx75, inverse ascending aortic distensibility, pAIx75 and AI ($|r| = 0.4–0.65$). In the BAV group, by contrast, diastolic function had significant correlations (in decreasing order) only with ascending aortic distensibility, cIMT and PWV ($|r| = 0.47–0.63$), while central systolic pressure, ascending aortic dimension, cAIx75, pAIx75, and AI did not meet statistical significance following Bonferroni correction. Ascending aortic dimension corrected for distensibility, age and sex did not reveal significant correlations with diastolic function or cAIx75 in either group.

Arterial and Cardiac Stiffening With Advancing Age

All arterial parameters tested had strong and highly significant correlations with age in the control group (**Table 6**, **Figure 2**). In the BAV group, however, inverse ascending aortic distensibility, cIMT, central systolic pressure, and PWV correlated strongly ($r > 0.7$, $p < 0.001$), and AI moderately with age. CAIx75, pAIx75 and ascending aortic dimension did not have significant correlations with age in the BAV group following Bonferroni correction for multiple comparisons.

Diastolic function (average E') was decreasing with age in both groups, while a trend toward decreasing systolic function (EF) was seen only in the BAV group (**Table 6**, **Figure 2D**).

DISCUSSION

This multimodal study of children and adults with a history of BAV disease demonstrates increased proximal aortic stiffness and

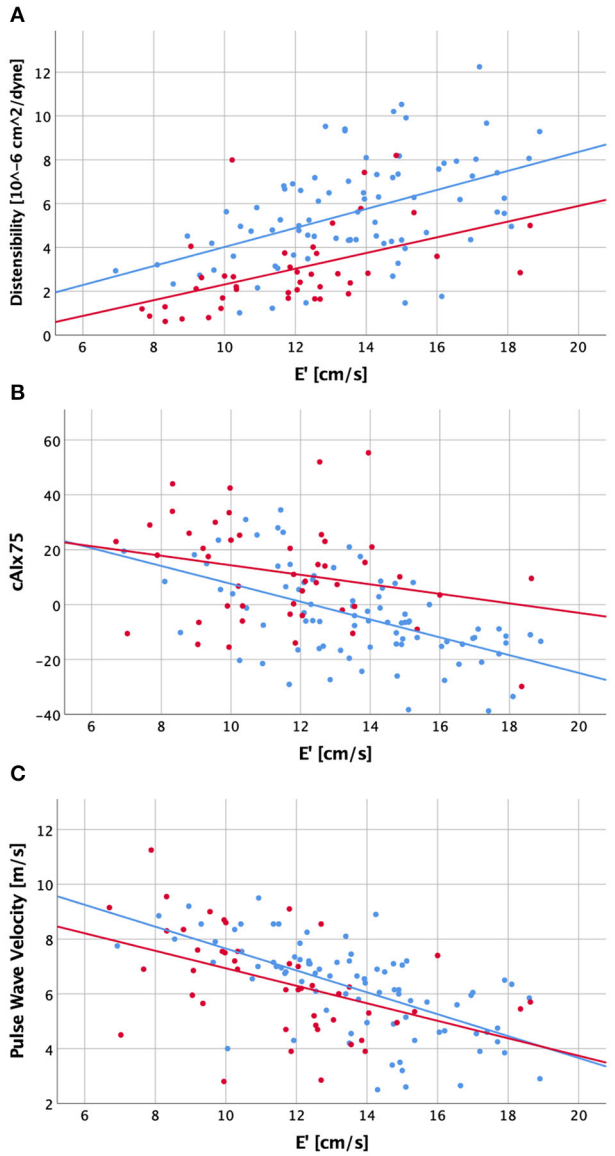


FIGURE 1 | Scatter plot visualizing correlations between diastolic function (E') and ascending aortic distensibility **(A)**, central augmentation index corrected to a heart rate of 75/min [cAIx75; **B**] and carotid-femoral pulse wave velocity **(C)** for patients with a history of bicuspid aortic valve (red dots and regression line) and healthy controls (blue dots and regression line).

wave reflection while there is no evidence of generally increased arterial stiffness, or endothelial dysfunction. Ascending aortic distensibility and diastolic function correlate with each other, are reduced already at young age, and decline further with advanced age. Arterial wave reflection, by contrast, is abnormal already at young age, does not worsen significantly with advanced age and does not correlate significantly with diastolic function. Overall, diastolic function appears only marginally decreased—though statistically highly significant—compared to controls, and can likely be attributed to decreased ascending aortic distensibility.

Proximally increased aortic stiffness has been described previously in children and adults with BAV, suggesting that impaired aortic elasticity may be congenital (3, 4, 17). In addition, Lee et al. have previously shown increased AIx75 in BAV disease (18). Most recently, we demonstrated in patients with repaired aortic coarctation, that those with associated BAV har particularly elevated Aix75 (19). In the study presented herein, multimodal assessment of vascular function revealed that vascular impairment appears indeed limited to the proximal aorta. The underlying mechanism of increased proximal wave reflection (as evidenced by increased cAIx75, pAIx75, and AI) may be due to a combination of eccentric flow across the BAV, ascending aortic dilation and increased ascending aortic stiffness. This hypothesis is supported by a recent cardiac magnetic resonance imaging study where BAV was associated with higher viscous energy loss compared with healthy controls (20).

By contrast, arterial abnormalities that are usually seen with arteriosclerotic changes, were not detected in our BAV cohort. First, cfPWV was not increased compared to controls. Both, increased as well as normal cfPWV have previously been described in BAV with dilated compared to non-dilated aortas (18, 21). Secondly, cIMT was not increased in patients with BAV. Similarly, Goudot et al. recently found no altered carotid artery stiffness compared to healthy controls when measuring carotid distensibility, maximal rate of systolic distension, and local PWV (22). Interestingly—as in our cohort—these patients did have increased ascending aortic stiffness. This supports the notion that the stiffness of the aorta in BAV is not due to arteriosclerotic changes. Third, we found no evidence of endothelial dysfunction in the small arteries (EndoPAT). Endothelial dysfunction, assessed by flow mediated dilatation (FMD) in the brachial artery, however, has been described in patients with BAV (17, 21). Thus, endothelial function may be affected in the brachial artery but not in smaller vessels.

There has been conflicting data about whether or not aortic stiffness correlates with diastolic function in BAV patients (3, 6, 8, 18). The current study was unique in that we used multiple modalities to answer this question. While diastolic function in the control group correlated moderately-strongly with all arterial parameters, the only significant correlations in the BAV group—controlling for aortic stenosis—were seen with ascending aortic distensibility, cIMT and cfPWV. In absolute terms, diastolic impairment in the BAV group was at most modest following adjustment for aortic stenosis. In fact, E' corrected for ascending aortic distensibility was not significantly different between the BAV and control groups ($p = 0.399$), suggesting that changes in E' across BAV patients and controls can be attributed to changes in ascending aortic distensibility. These findings argue against an intrinsically increased myocardial stiffness.

Systolic function was overall preserved in patients with BAV, but there was a trend toward a lower EF with increasing age. In an earlier study, EF has been described to be lower in patients with BAV compared to controls (5). Our study population was larger and did not show a significant difference in EF compared to controls. Thus, we cannot confirm that there is significant cardiac dysfunction in BAV disease.

TABLE 6 | Correlations between age and cardiovascular characteristics for all patients as well as group-wise analysis for BAV patients and controls.

AGE	*R* for All	*p*	*R* for BAV (Control)	*p*	*R* for Control	*p*
	N = 131		*N* = 47		*N* = 84	
Proximal arterial characteristics by ultrasound						
AscAo Distensibility [10^{-6}cm^2/dyn]†	−0.60	<0.001*	−0.75	<0.001*	−0.57	<0.001*
Ascending aortic dimension [cm]†	0.45	<0.001*	0.33	0.038	0.66	<0.001*
cIMT [mm]	0.75	<0.001*	0.79	<0.001*	0.71	<0.001*
Arterial wave reflection and pulse wave velocity						
Central systolic blood pressure [mmHg]	0.60	<0.001*	0.61	<0.001*	0.58	<0.001*
cAIx75	0.51	<0.001*	0.33	0.025	0.62	<0.001*
pAIx75	0.48	<0.001*	0.34	0.024	0.55	<0.001*
Aging Index	0.52	<0.001*	0.47	0.001*	0.55	<0.001*
Pulse Wave Velocity [m/s]	0.71	<0.001*	0.72	<0.001*	0.70	<0.001*
Cardiac function						
E' [cm/s]	0.70	<0.001*	−0.66	<0.001*	−0.72	<0.001*
Ejection fraction [%]	−0.20	0.026	−0.36	0.015	−0.02	0.833

*Pearson's correlation coefficient R and p-values are listed. *Significant following Bonferroni correction for multiple comparisons with significance level at 0.005.*
AscAo, ascending aorta; cIMT, common carotid artery intima media thickness; cAIx75, central augmentation index corrected to a heart rate of 75/min; pAIx75, peripheral augmentation index corrected to a heart rate of 75/min.
†six patients with aortic prostheses excluded.

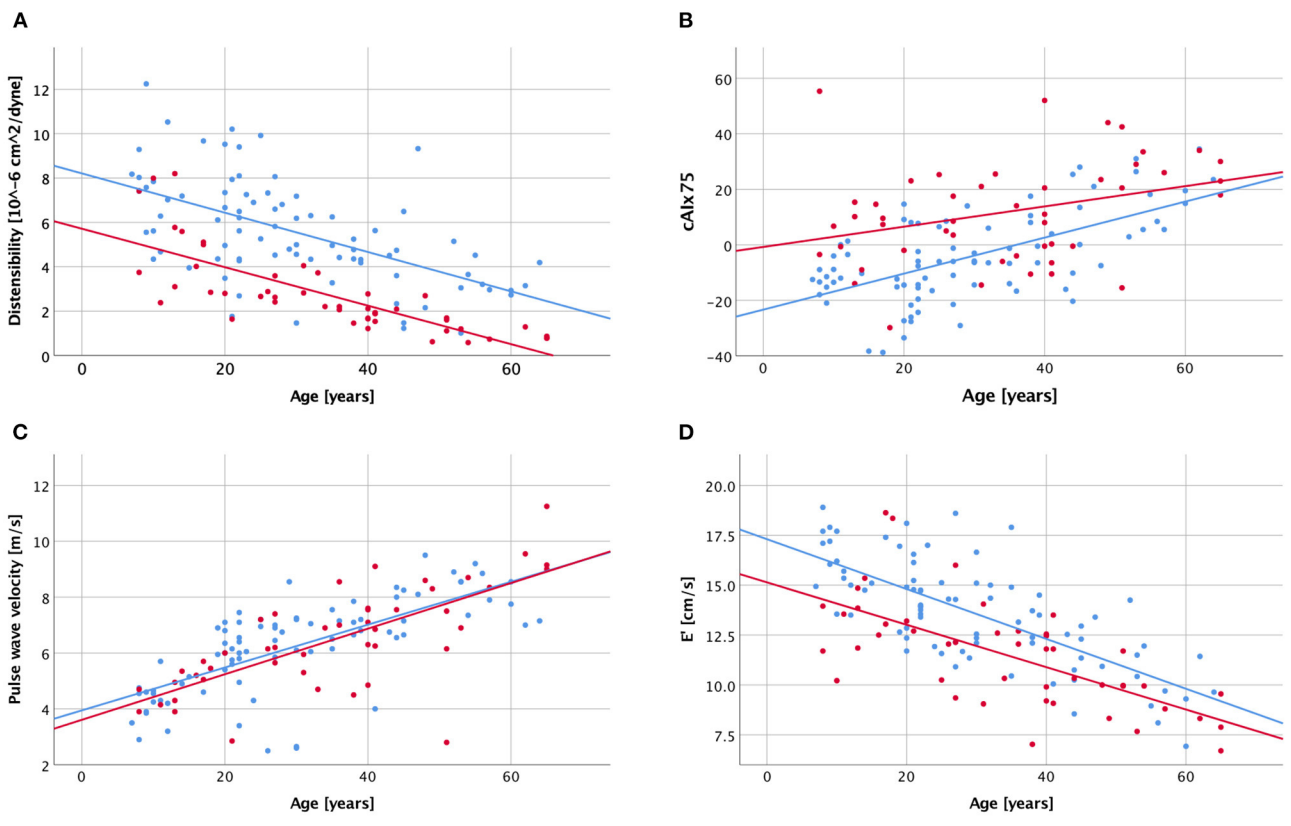


FIGURE 2 | Scatter plot visualizing correlations between age and ascending aortic distensibility **(A)**, central augmentation index corrected to a heart rate of 75/min [cAIx75; **B**], carotid-femoral pulse wave velocity **(C)**, and diastolic function [E'; **D**] with a history of bicuspid aortic valve (red dots and regression line) and healthy controls (blue dots and regression line).

All arterial parameters correlated moderately-strongly with age in both groups. While ascending aortic distensibility correlated particularly strong with age in the BAV group, there was no significant correlation for cAIx75 and pAIx75. However, both were abnormal in BAV patients even at young age. This is consistent with earlier findings of impaired ascending aortic elasticity in children with BAV (3). We conclude therefore that proximal arterial stiffness is increased already in childhood and progresses further with age, leading to advanced "arterial age." PWV and cIMT correlated to the same degree with age in both groups. We therefore propose that these parameters can be used to monitor for cardiovascular risk factors due to arteriosclerosis.

A limitation of this study is that some patients had already undergone aortic surgery including valve replacement. However, prior valve replacement was not associated with any of the parameters analyzed. In addition, the moderate size of our study population in combination with a wide age range may have led to a type II error, especially when performing subgroup-analyses. In the future, we plan longitudinal follow-up of patients who participated in this study.

The clinical impact of this study is that ascending aortic distensibility appears to be the most important predictor of diastolic function in BAV disease. As such, we suggest that clinicians include ascending aortic distensibility in their assessment. Whether pharmacologic amelioration of ascending aortic stiffening and diastolic function is possible should be the subject of future randomized controlled trials.

CONCLUSION

Arterial dysfunction in BAV disease is characterized by ascending aortic stiffening, increased wave reflection and central blood pressure. We did not observe general aortic stiffening, cIMT increase or endothelial dysfunction, indicating that arterial stiffening in BAV disease is due to other mechanisms than those seen in acquired heart diseases. Diastolic function appears to correlate best with ascending aortic distensibility in BAV, but overall diastolic function is only marginally decreased. Systolic function is not abnormal either. This argues against an intrinsic myocardial abnormality and for a potentially modifiable interplay between ascending aortic distensibility and diastolic function.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was reviewed and approved by Lund University ethics committee. Written informed consent to participate in this study was provided by the particiant and/or the participants' legal guardian.

AUTHOR CONTRIBUTIONS

CW: study design, funding acquisition, data acquisition, analysis, and writing and editing manuscript. SL: patient recruitment, data acquisition, and writing and editing of manuscript. AÅ: statistical analyses and review of manuscript. JH: patient recruitment, reviewing, and editing of manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Swedish Heart-Lung Foundation (#20170397; CW), Avtal om Läkarutbildning och Forskning (ALF; CW), and Hjärtebarnsfonden (Swedish Pediatric Heart Foundation).

ACKNOWLEDGMENTS

Many thanks to sonographer Bernhard S. Grell, and research nurses Elin Friberg and Annika Maxedius.

REFERENCES

1. Ward C. Clinical significance of the bicuspid aortic valve. *Heart.* (2000) 83:81–5. doi: 10.1136/heart.83.1.81
2. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068
3. Weismann CG, Lombardi KC, Grell BS, Northrup V, Sugeng L. Aortic stiffness and left ventricular diastolic function in children with well-functioning bicuspid aortic valves. *Eur Heart J Cardiovasc Imaging.* (2016) 17:225–30. doi: 10.1093/ehjci/jev151
4. Goudot G, Mirault T, Bruneval P, Soulat G, Pernot M, Messas E. Aortic wall elastic properties in case of bicuspid aortic valve. *Front Physiol.* (2019) 10:299. doi: 10.3389/fphys.2019.00299
5. Demir M. Left ventricular systolic and diastolic function in subjects with a bicuspid aortic valve without significant valvular dysfunction. *Exp Clin Cardiol.* (2013) 18:e1–4.
6. Bilen E, Akcay M, Bayram NA, Kocak U, Kurt M, Tanboga IH, et al. Aortic elastic properties and left ventricular diastolic function in patients with isolated bicuspid aortic valve. *J Heart Valve Dis.* (2012) 21:189–94.
7. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Heart Fail Clin.* (2008) 4:23–36. doi: 10.1016/j.hfc.2007.10.001
8. Kocabay G, Karabay CY, Kalkan S, Kalayci A, Efe SC, Akgun T, et al. Relationship between left ventricular diastolic function and arterial stiffness in patients with bicuspid aortic valve. *J Heart Valve Dis.* (2014) 23:279−88.
9. Lombardi KC, Northrup V, McNamara RL, Sugeng L, Weismann CG. Aortic stiffness and left ventricular diastolic function in children following early repair of aortic coarctation. *Am J Cardiol.* (2013) 112:1828–33. doi: 10.1016/j.amjcard.2013.07.052
10. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J.* (1990) 11:990–6. doi: 10.1093/oxfordjournals.eurheartj.a059639
11. Butlin M, Qasem A. Large artery stiffness assessment using SphygmoCor technology. *Pulse.* (2017) 4:180–92. doi: 10.1159/000452448
12. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens.* (2012) 30:445–8. doi: 10.1097/HJH.0b013e32834fa8b0

13. von Wowern E, Ostling G, Nilsson PM, Olofsson P. Digital photoplethysmography for assessment of arterial stiffness: repeatability and comparison with applanation tonometry. *PLoS ONE.* (2015) 10:e0135659. doi: 10.1371/journal.pone.0135659
14. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J.* (2010) 31:1142–8. doi: 10.1093/eurheartj/ehq010
15. Hamburg NM, Keyes MJ, Larson MG, Vasan RS, Schnabel R, Pryde MM, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. *Circulation.* (2008) 117:2467–74. doi: 10.1161/CIRCULATIONAHA.107.748574
16. Axtell AL, Gomari FA, Cooke JP. Assessing endothelial vasodilator function with the Endo-PAT 2000. *J Vis Exp.* (2010) 44:2167. doi: 10.3791/2167
17. Ali OA, Chapman M, Nguyen TH, Chirkov YY, Heresztyn T, Mundisugih J, et al. Interactions between inflammatory activation and endothelial dysfunction selectively modulate valve disease progression in patients with bicuspid aortic valve. *Heart.* (2014) 100:800–5. doi: 10.1136/heartjnl-2014-305509
18. Lee SY, Shim CY, Hong GR, Seo J, Cho I, Cho IJ, et al. Association of aortic phenotypes and mechanical function with left ventricular diastolic function in subjects with normally functioning bicuspid aortic valves and comparison to subjects with tricuspid aortic valves. *Am J Cardiol.* (2015) 116:1547–54. doi: 10.1016/j.amjcard.2015.08.017
19. Weismann CG, Maretic A, Grell BS, Akesson A, Hlebowicz J, Liuba P. Multimodal assessment of vascular and ventricular function in children and adults with repaired aortic coarctation. *Int J Cardiol.* (2020) 323:47–53. doi: 10.1016/j.ijcard.2020.08.095
20. Elbaz MSM, Scott MB, Barker AJ, McCarthy P, Malaisrie C, Collins JD, et al. Four-dimensional virtual catheter: noninvasive assessment of intra-aortic hemodynamics in bicuspid aortic valve disease. *Radiology.* (2019) 293:541–50. doi: 10.1148/radiol.2019190411
21. Tzemos N, Lyseggen E, Silversides C, Jamorski M, Tong JH, Harvey P, et al. Endothelial function, carotid-femoral stiffness, and plasma matrix metalloproteinase-2 in men with bicuspid aortic valve and dilated aorta. *J Am Coll Cardiol.* (2010) 55:660–8. doi: 10.1016/j.jacc.2009.08.080
22. Goudot G, Mirault T, Khider L, Pedreira O, Cheng C, Poree J, et al. Carotid stiffness assessment with ultrafast ultrasound imaging in case of bicuspid aortic valve. *Front Physiol.* (2019) 10:1330. doi: 10.3389/fphys.2019.01330

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 04 November 2021
doi: 10.3389/fcvm.2021.766430

Temporal Trends in Diagnosis, Treatments, and Outcomes in Patients With Bicuspid Aortic Valve

*Kyu Kim, Dae-Young Kim, Jiwon Seo, Iksung Cho, Geu-Ru Hong, Jong-Won Ha and Chi Young Shim**

Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: The population is aging and advances in multimodal imaging and transcatheter valve intervention have been prominent in the past two decades. This study investigated temporal trends in demographic characteristics, use of multimodal imaging, treatments, and outcomes in patients with bicuspid aortic valve (BAV).

Methods and Results: A total of 1,497 patients (male 71.7%, 57 ± 14 years old) first diagnosed with BAV between January 2003 and December 2020, in a single tertiary center were divided into three groups according to year of diagnosis: group 1 (2003–2008, $n = 269$), group 2 (2009–2014, $n = 594$), and group 3 (2015–2020, $n = 634$). The patients' demographic characteristics, comorbidities, BAV morphology, BAV function, BAV-related disease, use of multimodal diagnostic imaging, treatment modality for BAV, and clinical outcomes were compared among the three groups. The ages at diagnosis and at the time of surgery/intervention increased considerably from group 1 to 3. The patients' comorbidity index also increased progressively. The proportion of non-dysfunctional BAV and significant AS increased, while that of significant AR decreased. The frequency of infective endocarditis as an initial presentation significantly decreased over time. Additionally, the use of multimodal imaging increased markedly in the most recent group. The results also indicated increasing trends in the use of bioprosthetic valves and transcatheter aortic valve replacement. Overall and cardiovascular survival rates improved from group 1 to 3 (log rank $p < 0.001$).

Conclusions: For the past two decades, remarkable temporal changes have occurred in patient characteristics, use of multimodal diagnostic imaging, choice of treatment modality, and clinical outcomes in patients with BAV.

Keywords: bicuspid aortic valve, trend, diagnosis, imaging, treatment, outcome

OPEN ACCESS

Edited by:
Mao Chen,
Sichuan University, China

Reviewed by:
Dhrubajyoti Bandyopadhyay,
New York Medical College, United States
Sungmin Ko,
Wonju Severance Christian Hospital, South Korea

****Correspondence:***
Chi Young Shim
cysprs@yuhs.ac

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *29 August 2021*
Accepted: *13 October 2021*
Published: *04 November 2021*

Citation:
Kim K, Kim D-Y, Seo J, Cho I, Hong G-R, Ha J-W and Shim CY (2021) Temporal Trends in Diagnosis, Treatments, and Outcomes in Patients With Bicuspid Aortic Valve. Front. Cardiovasc. Med. 8:766430. doi: 10.3389/fcvm.2021.766430

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital heart valve disease, and the burden of BAV disease is greater than for other congenital anomalies (1–3). BAV can present in diverse spectrum and affect valve function from non-dysfunctional to severe aortic stenosis (AS) or severe aortic regurgitation (AR) (4–6). In addition, BAV often is accompanied by aortopathy, other congenital defects, cardiomyopathies, or infective endocarditis (IE) (7–9). In

the past two decades, echocardiographic surveillance of asymptomatic subjects has increased, and multimodality imaging has been developed and applied in heart valve diseases (10, 11). Recently, transcatheter aortic valve replacement (AVR) has been expanded to young age and low risk groups, and treatment methods in BAV patients have diversified (12–14). In addition, the incidence of IE as a first manifestation in BAV patients is expected to decrease as socioeconomic status improves (15). Therefore, this study aimed to investigate temporal trends in demographic characteristics, use of multimodal imaging, treatment modality, and clinical outcomes in patients with BAV from a large Korean registry.

METHODS

Study Population

We systemically analyzed a single-center Korean registry that consisted of 1,497 consecutively enrolled BAV patients 19 years of age or older. This retrospective and prospective registry contains echocardiographic data and clinical information from medical records of the patients from January 2003 to December 2020, in Severance Cardiovascular Hospital, Seoul, Korea. All patients were diagnosed with BAV through transthoracic echocardiography, and additional diagnostic imaging was performed according to the clinical judgement of the physician. When there was discrepancy between imaging tests, we determined exclusion after comprehensive consideration of all imaging studies and intraoperative findings. There were 14 exclusions in this study. The Institutional Review Board of Severance Hospital approved this study, which was conducted in compliance with the Declaration of Helsinki. The need for informed consent was waived.

Patient Data

Baseline characteristics at the time of diagnosis were age, sex, height, weight, body mass index, and comorbidities. The Charlson comorbidity index was calculated to determine patient risk (16). All participants in the study population underwent comprehensive transthoracic echocardiography. All echocardiographic studies were performed using commercially available equipment and were analyzed retrospectively without knowledge of the clinical data. Standard 2-dimensional and Doppler measurements were performed, and the severity of BAV dysfunction was assessed based on the American Society of Echocardiography guidelines (17, 18).

Congenital BAV was diagnosed when only two cusps were identified unequivocally in systole and diastole in the short-axis view, with a clear "fish-mouth" appearance during systole, as previously described (5–8). Type 1 was confirmed based on congenital fusion of the right and left coronary cusps; Type 2 was confirmed based on a congenital fusion of the right and non-coronary cusps; Type 3 was confirmed based on a congenital fusion of the non-coronary and left coronary cusps; Type 0 was confirmed for cases without raphe, which also is referred to as "true type" BAV. The severity of AS and AR was assessed using an integrated approach (17, 18). Patients that had at least moderate AS or moderate AR were classified as significant AS or significant AR, respectively, and others were classified with non-dysfunctional BAV (5, 6).

All measurements of the aorta were performed on the QRS complex of the electrocardiogram according to recommendations (19). The dimensions of the Valsalva sinuses were measured perpendicularly to the right and left (or non-) aortic sinuses. The sinotubular junction was measured where the aortic sinuses met the tubular aorta. The AA was measured 2 cm distal to the sinotubular junction. The presence of aortopathy was defined as an ascending aorta diameter $\geq$37 mm (6, 7, 20). A maximum dimension of the ascending aorta $\geq$45 mm was defined as severe aortopathy (6). Concomitant congenital defects including ventricular septal defect, atrial septal defect, patent foramen ovale, and patent ductus arteriosus were investigated. Concomitant cardiomyopathy was defined as specific cardiomyopathies such as hypertrophic cardiomyopathy, noncompaction cardiomyopathy, and idiopathic dilated cardiomyopathy (8). A diagnosis of IE was determined according to modified Duke criteria (21).

We investigated whether transesophageal echocardiography (TEE) and MDCT were performed in addition to transthoracic echocardiography. Diagnostic multimodal imaging was performed based on the clinician's judgement. Surgery or intervention was conducted according to the guidelines at time of diagnosis, based on patient symptoms, cardiac function, and BAV function and clinician decision. Eligibility for transcatheter AVR was determined by a multidisciplinary heart team.

The study population was divided into three groups according to year of diagnosis with six-year increments: group 1 (2003–2008, $n = 269$), group 2 (2009–2014, $n = 594$), and group 3 (2015–2020, $n = 634$). The baseline characteristics, ages at diagnosis and at the time of surgery or intervention, use of multimodality imaging, number of surgeries or interventions, and survival from all-cause death and cardiovascular death were compared among the groups.

The index date was the time of the first BAV diagnosis. Death information was collected by medical records. Cardiovascular death was defined as death due to worsening heart failure, acute coronary syndrome, cerebrovascular accidents, or sudden cardiac death. The cause of death was determined based on the death certificate.

Statistical Analysis

Categorical variables are expressed as percentage or frequency and compared using the χ^2 test or Fisher's exact test. Continuous variables are expressed as mean $\pm$ standard deviation. The Cochran–Armitage and Jonckheere–Terpstra methods were used to test trends in nominal and categorical variables across time periods. Survival from all-cause death and cardiovascular death was estimated using the Kaplan–Meier method and compared by Log-rank test. A probability value (P-value) <0.05 was considered statistically significant. Statistical analyses were

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; BAV, bicuspid aortic valve; IE, infective endocarditis; MDCT, multidetector computed tomography; TEE, transesophageal echocardiography.

TABLE 1 | Demographic, clinical, and imaging characteristics in the three groups.

	Group 1 (*n* = 269)	Group 2 (*n* = 594)	Group 3 (*n* = 634)	*P* value	*P* for trend
Age at diagnosis, year	53.2 ± 15.1	56.7 ± 14.3	57.8 ± 13.8	<0.001	<0.001
Male sex, *n* (%)	201 (74.7)	423 (71.2)	450 (71.0)	0.290	0.290
Body mass index, kg/m^2	23.6 ± 3.1	24.0 ± 4.0	24.2 ± 3.9	0.063	0.036
Comorbidities, *n* (%)					
Hypertension	76 (28.1)	275 (46.6)	289 (44.2)	<0.001	<0.001
Diabetes mellitus	46 (17.1)	123 (20.7)	113 (17.8)	0.314	0.862
Coronary artery disease	45 (16.7)	125 (21.0)	121 (19.1)	<0.001	0.667
Atrial fibrillation	33 (12.3)	102 (17.2)	92 (14.5)	0.148	0.732
Dyslipidemia	55 (20.4)	171 (28.8)	229 (36.1)	<0.001	<0.001
Chronic kidney disease	12 (4.5)	36 (6.1)	34 (5.4)	0.624	0.764
Liver cirrhosis	3 (1.1)	16 (2.7)	11 (1.7)	0.252	0.870
Chronic pulmonary disease	12 (4.5)	36 (6.1)	34 (5.4)	0.624	0.764
History of CVA	10 (3.7)	12 (2.0)	18 (2.8)	0.323	0.699
History of cancer	18 (6.7)	58 (9.8)	48 (7.6)	0.219	0.968
Charlson comorbidity index	1.8 ± 1.6	2.2 ± 1.8	2.2 ± 1.7	0.013	0.029
BAV morphology, *n* (%)					
Type 1, R-L fusion	161 (59.9)	364 (61.3)	374 (59.0)	0.547	0.627
Type 2, R-N fusion	40 (14.9)	96 (16.2)	113 (17.8)	0.750	0.254
Type 3, L-N fusion	14 (5.2)	27 (4.5)	24 (3.8)	0.771	0.312
Type 0, No raphe	54 (20.0)	107 (18.0)	123 (19.4)	0.716	0.969
BAV function, *n* (%)					
Non-dysfunctional AV	68 (25.3)	214 (36.0)	199 (31.4)	0.006	0.039
Significant AS	112 (41.6)	277 (46.6)	313 (49.4)	0.102	0.039
Significant AR	119 (44.2)	153 (25.8)	192 (30.3)	<0.001	0.002
Significant ASR	30 (11.2)	50 (8.4)	70 (11.0)	0.246	0.698
BAV-associated disease, *n* (%)					
Presence of aortopathy	119 (44.2)	315 (53.0)	300 (47.3)	0.030	0.913
Severe aortopathy	58 (21.6)	177 (29.8)	160 (25.2)	0.027	0.666
Coarctation of aorta	3 (1.1)	2 (0.3)	7 (1.1)	0.262	0.676
Infective endocarditis	13 (4.8)	17 (2.9)	11 (1.7)	0.027	0.010
Concomitant cardiomyopathy	10 (3.7)	17 (2.9)	24 (3.8)	0.640	0.768
Congenital defects	7 (2.6)	22 (3.7)	44 (6.9)	0.005	0.002
Multimodal imaging, *n* (%)					
TEE	60 (22.3)	210 (35.4)	245 (38.6)	<0.001	<0.001
MDCT	6 (2.2)	61 (10.3)	215 (33.9)	<0.001	<0.001
Both TEE and MDCT	4 (1.5)	42 (7.1)	126 (19.9)	<0.001	<0.001
CMR	3 (1.1)	30 (5.1)	8 (1.3)	<0.001	0.281

AS, aortic stenosis; AR, aortic regurgitation; ASR, aortic stenosis and regurgitation; BAV, bicuspid aortic valve; TEE, transesophageal echocardiography; MDCT, multidetector computed tomography; CMR, cardiac magnetic resonance.

conducted using R version 4.1.0 (The R Foundation for Statistical Computing; www.R-project.org).

RESULTS

Temporal Trends in Characteristics of Patients With BAV

During the study period, a total of 1,497 patients (male 71.7%, 56.5 ± 14.3 years old) was diagnosed with BAV. The absolute numbers of patients diagnosed with BAV in groups 1, 2, and 3 were 269, 594, and 634, respectively. Baseline characteristics of the study population are shown in **Table 1**.

Patient demographics indicated that age at diagnosis increased significantly from group 1 to group 3 (P for trend < 0.001), and sex distribution was not significantly different between groups according to diagnosis year, with males accounting for more than 70% of all groups. From group 1 to 3, a tendency for an increase in body mass index was observed (P for trend $= 0.036$). Analysis of patient comorbidities indicated that the more recent patients experienced more frequent hypertension and dyslipidemia, and the Charlson comorbidity index increased in this group (P for

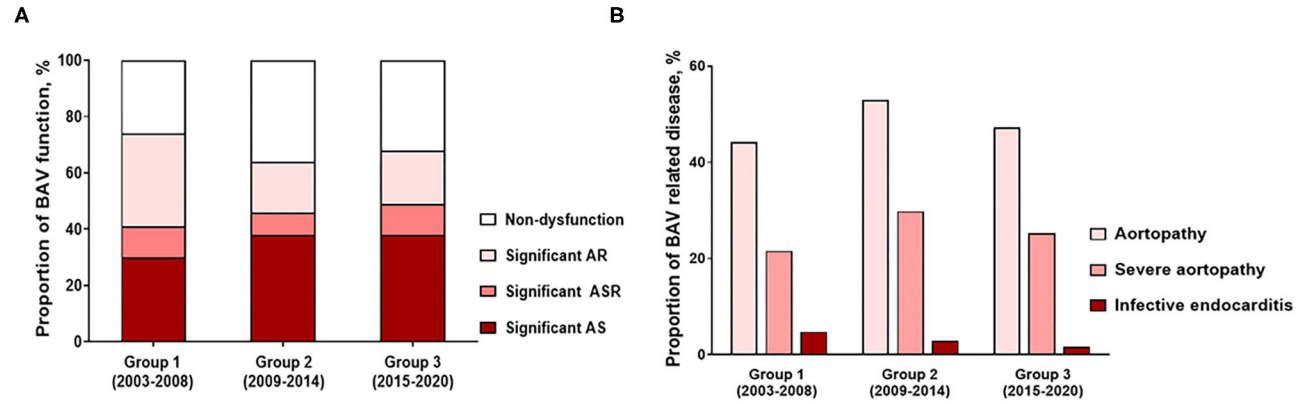


FIGURE 1 | Temporal trends of **(A)** proportion of BAV function and **(B)** proportion of BAV-related disease.

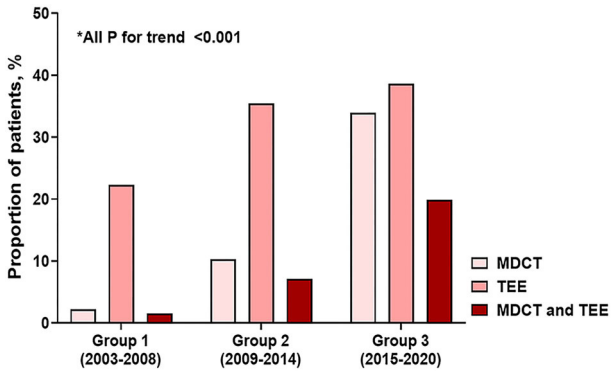


FIGURE 2 | Temporal trends in the use of additional diagnostic imaging.

trend = 0.029). Analysis of BAV morphology indicated that type 1 was dominant in all groups, and there was no difference according to group. In terms of BAV function, the diagnosis of non-dysfunctional BAV increased in groups 2 and 3 compared to group 1 (*P* for trend=0.039), the proportion of significant AR decreased (*P* for trend = 0.002), and the significant AS increased steadily (*P* for trend = 0.039; **Figure 1A**). In terms of BAV-associated disease, about half of the patients had aortopathy, and about one-quarter had severe aortopathy, with no significant trends observed over time (**Figure 1B**). From group 1 to 3, the prevalence of infective endocarditis significantly decreased (*P* for trend = 0.010; **Figure 1B**). Detection of congenital defects increased (*P* for trend = 0.002) and likely was attributable to the increased use in additional diagnostic imaging from groups 1 to 3. In group 3, TEE and MDCT were used in 38.6 and 33.9% of patients, respectively (**Figure 2**).

Temporal Trends for Treating BAV-Related AV Disease

Table 2 shows treatment characteristics for the three groups of the study population. There was an increasing trend in age at surgery or intervention between groups (*P* for trend < 0.001; **Figure 3A**). The mean age at surgery or intervention in group 1 was 55 years, while that in group 3 was 62 years. The proportion of patients older than 70 years at surgery or intervention remarkably increased (*P* for trend = 0.003) and reached about 25% in groups 2 and 3. In terms of indications for surgery or intervention, surgery due to severe AR or infective endocarditis decreased over time (*P* for trend = 0.024, 0.027, respectively).

As age at surgery increased from group 1 to 3, surgical AVR using bioprosthetic valves significantly increased (*P* for trend = 0.002). In addition, transcatheter AVR gradually increased over time (*P* for trend = 0.024; **Figure 3B**). The results indicate that there were more frequent concomitant surgeries such as coronary artery bypass for patients diagnosed and treated more recently (*P* for trend = 0.002). During the 3.8 years (interquartile range 1.0–6.9 years) of follow-up, all-cause death and cardiovascular death significantly decreased from group 1 to group 3 (both log-rank *P* < 0.001; **Figure 4**).

DISCUSSION

The principal findings of this study were as follow: (1) a significant temporal increase was observed in both age at the time of diagnosis and age at the time of surgery or intervention; (2) over time, the proportions of non-dysfunctional BAV and significant AS increased and significant AR decreased in patients with BAV; (3) a temporal change in the incidence of infective endocarditis was observed in patients with BAV; (4) surgical AVR using bioprosthetic valve and transcatheter AVR increased; (5) the frequency of additional diagnostic imaging, such as TEE or MDCT, remarkably increased in patients with BAV; and (6) there was a recent significant improvement in all-cause and cardiovascular death among all patients diagnosed with BAV. Understanding these temporal changes and trends in patient characteristics, BAV function, diagnosis, treatment, and outcome will be important for further diagnostic and treatment advances.

TABLE 2 | Treatment approaches in the three groups.

	Group 1 (*n* = 269)	Group 2 (*n* = 594)	Group 3 (*n* = 634)	*P* value	*P* for trend
Surgery/intervention, *n* (%)	123 (45.7)	281 (47.3)	315 (49.7)	0.498	0.309
Age at surgery/intervention, years	54.5 ± 12.8	59.7 ± 12.7	61.7 ± 12.0	<0.001	<0.001
<30, *n* (%)	6 (2.2)	5 (0.8)	5 (0.8)	0.123	0.094
30–49, *n* (%)	30 (11.2)	47 (7.9)	37 (5.8)	0.021	0.006
50–69, *n* (%)	75 (27.9)	156 (26.3)	195 (30.8)	0.213	0.218
≥70, *n* (%)	12 (4.5)	73 (12.3)	78 (12.3)	0.001	0.003
Indications for surgery/intervention					
Severe AS, *n* (%)	97 (36.1)	204 (34.3)	232 (36.6)	0.702	0.731
Severe AR, *n* (%)	64 (23.8)	92 (15.5)	103 (16.2)	0.008	0.024
Severe ASR, *n* (%)	13 (4.8)	4 (1.3)	17 (2.7)	0.010	0.311
Severe aortopathy, *n* (%)	58 (21.6)	177 (29.8)	169 (25.2)	0.027	0.666
Infective endocarditis, *n* (%)	10 (3.7)	16 (2.7)	9 (1.4)	0.086	0.027
Surgical AVR or repair, *n* (%)	119 (44.2)	271 (45.6)	298 (47.0)	0.731	0.448
Bioprosthetic valve	28 (10.4)	96 (16.2)	99 (15.6)	0.071	0.105
Mechanical valve	89 (33.1)	175 (29.5)	199 (31.4)	0.536	0.809
Aortic valve repair	2 (0.7)	3 (0.5)	3 (0.5)	0.871	0.646
Surgery for aorta, *n* (%)	27 (10.0)	98 (16.5)	112 (17.7)	0.012	0.009
Isolated aorta surgery	4 (1.5)	4 (0.7)	6 (0.9)	0.516	0.605
Concomitantly with AV surgery	23 (8.6)	94 (15.8)	106 (16.7)	0.005	0.003
Concomitant surgery, *n* (%)	2 (0.7)	18 (3.0)	68 (10.7)	<0.001	<0.001
Coronary artery bypass	2 (0.7)	8 (1.3)	19 (3.0)	0.032	0.012
Other surgery*	0 (0.0)	10 (1.7)	52 (8.2)	<0.001	<0.001
Transcatheter AVR, *n* (%)	0 (0.0)	6 (1.0)	11 (1.7)	0.074	0.024

*AS, aortic stenosis; AR, aortic regurgitation; ASR, aortic stenosis and regurgitation; AVR, aortic valve replacement; AV, aortic valve. *Other surgery included patch repair of ventricular or atrial septal defect, direct closure of patent foramen ovale, and patent ductus arteriosus ligation.*

Temporal Trends in Patient Characteristics, Diagnosis, and Treatment

BAV is the most common adult congenital heart defect and has associated increased risk for severe AS or AR, thoracic aortic disease or acquired complications such as IE (1–4, 22, 23). Because BAV is congenital, BAV-related diseases typically manifest at an early age. Therefore, the majority of previous studies has reported a mean age of about 40 years (24). Significant bicuspid AS usually occurs earlier than tricuspid AS and is reported in their 50s and 60s (25). In patient with BAV, AR is more common at a young age, whereas AS usually presents later in life (26). In this study, the mean age at diagnosis was 56.5 years, and the mean age increased over about two decades. Furthermore, the mean age at surgery or intervention was 61.6 years, and 24.5% of patients in the more recent group were older than 70 years. In addition, as the global burden of calcified aortic valve disease increased, the proportion of significant AR decreased while that of significant AS increased from group 1 to 3, likely related to the increase in age for the general population (27). As ages of patients at diagnosis and at surgery or intervention increased, the treatment strategy for BAV dysfunction also changed. In this study, 35.6% of patients in group 3 underwent AVR with bioprosthetic valves. Increased use of bioprosthetic valves was an expected finding because of the increasing aging trend in patient with BAV. In addition, as the comorbidities of patients increased, the surgical risk also increased, as did the demand for transcatheter AVR. This study showed increasing trend of transcatheter AVR in BAV patients after its launch in 2011, in Korea.

The diagnosis of non-dysfunctional BAV had increased in this study. In Korea, the number of TTE as screening tool is continuously increasing (28). The increased number of exam might enable early diagnosis of BAV and related disease in general population.

The present study also showed a decreasing trend for prevalence of IE as the first manifestation of BAV disease. The rate of IE was 1.7% in group 3, and the incidence of IE in BAV has been reported around 2%, which was comparable to our results (9, 24). A recent report from the United States showed decreasing trend of native valve endocarditis but that of increased prosthetic valve and device-related endocarditis (15). These trends might be derived from increased echocardiographic surveillance for BAV and improved socioeconomic status over time.

Temporal Trends for Multimodal Imaging in BAV Patients

Multimodality imaging has become increasingly important because BAV is not only a valve disease, but also is associated with other diseases such as aortopathy and cardiomyopathies (6–8, 10). The first diagnostic tool of choice to evaluate heart

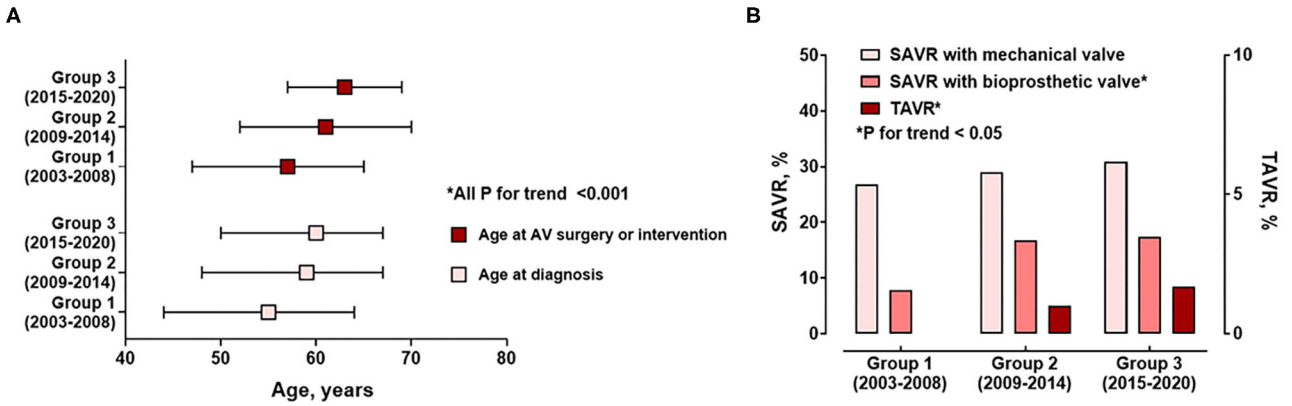


FIGURE 3 | Temporal trends of **(A)** ages at diagnosis and AV surgery or interventions and **(B)** treatment methods.

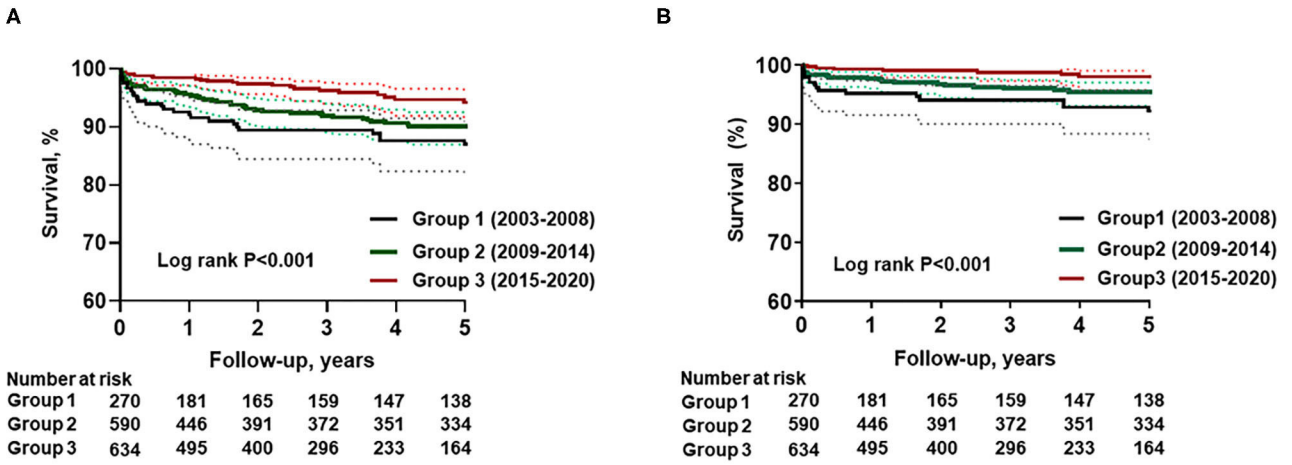


FIGURE 4 | Temporal trends in clinical outcomes: **(A)** survival from all-cause death, **(B)** survival from cardiovascular death.

valves was transthoracic echocardiography because it is easy to use and noninvasive. Recently, MDCT has been used as a complement to echocardiography for diagnosing heart valve disease and preoperative evaluation (18, 29, 30). In patients with BAV, MDCT can provide accurate information about the BAV and adjacent structural abnormalities including the aorta, concomitant anomalies, or combined coronary artery disease (10, 11). Furthermore, in the era of transcatheter AVR, the use of multimodal imaging is becoming an increasingly essential part of routine clinical practice, particularly for BAV patients with significant AS (10, 31). The patients with BAV had chance of concomitant cardiomyopathies. They had different flow dynamics from the patients with tricuspid aortic valve (32). Furthermore, myocardial fibrosis has been reported as important prognostic factor in BAV related disease such as AS or AR (33, 34). Cardiac magnetic resonance might be useful in patients with BAV and related disease (8, 35). The results of this study indicate that the use of multimodal imaging has increased, and that this approach can detect concomitant disease such as congenital defects based on the overall trends in diagnostic imaging in patients with BAV.

Temporal Trends of Clinical Outcomes in BAV Patients

This study also showed clinical outcome improvements in the more recent group despite an increase in mean age with a higher comorbidity index. There are several factors that could impact these results. Notably, as the proportion of non-dysfunctional BAV increased in group 3, it is possible that fewer clinical events were diagnosed because those events likely were attributable to previously undetected non-dysfunctional BAV in patients. In addition, recent advances in diagnostic imaging, surgical techniques (36), medical systems such as a multidisciplinary approach, and application of transcatheter AVR in patients with high surgical risk might influence the improved clinical outcomes in patients with BAVs.

Study Limitations

Our study had several limitations. First, this study was conducted at a single tertiary center by comprehensively reviewing retrospective and prospective data; therefore, selection and referral bias were inevitable, and our results could not be generalized. The proportions of significant BAV dysfunction and severe aortopathy were higher than reported in previous studies (24, 26). The clinical follow-up duration for the study population was relatively short. Seconds, the study subjects were diagnosed based on TTE, so there might be inevitable limitations and bias for the morphologic evaluation of BAV, particularly severely calcified aortic valve. However, as this study had additional imaging studies performed by clinician's judgement and consisted of a large-scale population, we believe this potential bias would not change our main findings. Additionally, it is difficult to generalize and apply these temporal trends to other societies or countries because if differing social and medical environmental factors. Despite these limitations, we believe that the data from this large Korean registry will be helpful to understand the characteristics, diagnosis, treatment, and outcomes for BAV patients over the past two decades. Further, some of the temporal trends might be applicable to other societies.

CONCLUSIONS

In past two decades, there have been remarkable temporal changes in patients with BAV. Patient characteristics, proportion of BAV dysfunction, diagnosis, and treatment strategy have changed, and the demand for bioprosthetic valves has increased. Temporal trends were observed with improvements of clinical outcomes in patients with BAV.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Severance Hospital, Yonsei University College of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KK and CS contributed to the conception, design of the work, and drafted the manuscript. D-YK, JS, and IC assisted in data collection and analysis. G-RH and J-WH contributed to the review and revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported from the Korean Cardiac Research Foundation (202103-02).

REFERENCES

1. Ward C. Clinical significance of the bicuspid aortic valve. *Heart.* (2000) 83:81–5. doi: 10.1136/heart.83.1.81
2. Sillesen AS, Vogg O, Pihl C, Raja AA, Sundberg K, Vedel C, et al. Prevalence of bicuspid aortic valve and associated aortopathy in newborns in Copenhagen, Denmark. *JAMA.* (2021) 325:561–7. doi: 10.1001/jama.2020.27205
3. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068
4. Braverman AC, Guven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. *Curr Probl Cardiol.* (2005) 30:470–522. doi: 10.1016/j.cpcardiol.2005.06.002
5. Lee SY, Shim CY, Kim D, Cho I, Hong GR, Ha JW, et al. Factors determining aortic valve dysfunction in Korean subjects with a bicuspid aortic valve. *Am J Cardiol.* (2017) 119:2049–55. doi: 10.1016/j.amjcard.2017.03.038
6. Song S, Seo J, Cho I, Hong GR, Ha JW, Shim CY. Progression and outcomes of non-dysfunctional bicuspid aortic valve: longitudinal data from a large korean bicuspid aortic valve registry. *Front Cardiovasc Med.* (2020) 7:603323. doi: 10.3389/fcvm.2020.603323
7. Lee SY, Shim CY, Hong GR, Seo J, Cho I, Cho IJ, et al. Association of aortic phenotypes and mechanical function with left ventricular diastolic function in subjects with normally functioning bicuspid aortic valves and comparison to subjects with tricuspid aortic valves. *Am J Cardiol.* (2015) 116:1547–54. doi: 10.1016/j.amjcard.2015.08.017
8. Jeong H, Shim CY, Kim D, Choi JY, Choi KU, Lee SY, et al. Prevalence, characteristics, and clinical significance of concomitant cardiomyopathies in subjects with bicuspid aortic valves. *Yonsei Med J.* (2019) 60:816–23. doi: 10.3349/ymj.2019.60.9.816
9. Zegri-Reiriz I, de Alarcon A, Munoz P, Martinez Selles M, Gonzalez-Ramallo V, Miro JM, et al. Infective endocarditis in patients with bicuspid aortic valve or mitral valve prolapse. *J Am Coll Cardiol.* (2018) 71:2731–40. doi: 10.1016/j.jacc.2018.03.534
10. Galian-Gay L, Rodriguez-Palomares J, Guala A, Michelena HI, Evangelista A. Multimodality imaging in bicuspid aortic valve. *Prog Cardiovasc Dis.* (2020) 63:442–51. doi: 10.1016/j.pcad.2020.06.003
11. Kim D, Shim CY, Kim YJ, Nam K, Hong GR, Lee SH, et al. Differences in flow-gradient patterns between severe bicuspid aortic stenosis and severe tricuspid aortic stenosis- mechanistic insight from multimodal imaging. *Circ J.* (2019) 84:119–26. doi: 10.1253/circj.CJ-19-0702
12. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* (2019) 380:1706–15. doi: 10.1056/NEJMoa1816885
13. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* (2019) 380:1695–705. doi: 10.1056/NEJMoa1814052
14. Tarantini G, Fabris T. Transcatheter aortic valve replacement for bicuspid aortic valve stenosis: a practical operative overview. *Circ Cardiovasc Interv.* (2021) 14:e009827. doi: 10.1161/CIRCINTERVENTIONS.120.009827
15. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York State, 1998-2013. *JAMA.* (2017) 317:1652–60. doi: 10.1001/jama.2017.4287
16. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in registry-based research. *Methods Inf Med.* (2017) 56:401–6. doi: 10.3414/ME17-01-0051
17. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the american society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr.* (2017) 30:303–71. doi: 10.1016/j.echo.2017.01.007

18. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the european association of cardiovascular imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr.* (2017) 30:372–92. doi: 10.1016/j.echo.2017.02.009
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* (2015) 28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
20. Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M, et al. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. *Eur J Cardiothorac Surg.* (2007) 31:397–404; discussion 404–5. doi: 10.1016/j.ejcts.2006.12.006
21. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* (2000) 30:633–8. doi: 10.1086/313753
22. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med.* (2014) 370:1920–9. doi: 10.1056/NEJMra1207059
23. Kiyota Y, Della Corte A, Montiero Vieira V, Habchi K, Huang CC, Della Ratta EE, et al. Risk and outcomes of aortic valve endocarditis among patients with bicuspid and tricuspid aortic valves. *Open Heart.* (2017) 4:e000545. doi: 10.1136/openhrt-2016-000545
24. Masri A, Svensson LG, Griffin BP, Desai MY. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart.* (2017) 103:1323–30. doi: 10.1136/heartjnl-2016-309916
25. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation.* (2005) 111:920–5. doi: 10.1161/01.CIR.0000155623.48408.C5
26. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT, et al. Outcomes in adults with bicuspid aortic valves. *JAMA.* (2008) 300:1317–25. doi: 10.1001/jama.300.11.1317
27. Coffey S, Roberts-Thomson R, Brown A, Carapetis J, Chen M, Enriquez-Sarano M, et al. Global epidemiology of valvular heart disease. *Nat Rev Cardiol.* (2021). doi: 10.1038/s41569-021-00570-z
28. Chung SH, Lee HJ, Kim HS, Oh J-Y. Health insurance benefit criteria and quality assurance policies of diagnostic ultrasound services in other countries. *Health Policy Manag.* (2014) 24:109–19. doi: 10.4332/KJHPA.2014.24.2.109
29. Choi JY, Suh YJ, Seo J, Choi KU, Hong GR, Lee S, et al. Structural and functional characteristics of mitral paravalvular leakage identified by multimodal imaging and their implication on clinical presentation. *J Clin Med.* (2021) 10:222. doi: 10.3390/jcm10020222
30. Kim IC, Chang S, Hong GR, Lee SH, Lee S, Ha JW, et al. Comparison of cardiac computed tomography with transesophageal echocardiography for identifying vegetation and intracardiac complications in patients with infective endocarditis in the era of 3-dimensional images. *Circ Cardiovasc Imaging.* (2018) 11:e006986. doi: 10.1161/CIRCIMAGING.117.006986
31. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodes-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
32. Hope MD, Meadows AK, Hope TA, Ordovas KG, Reddy GP, Alley MT, et al. Images in cardiovascular medicine. Evaluation of bicuspid aortic valve and aortic coarctation with 4D flow magnetic resonance imaging. *Circulation.* (2008) 117:2818–9. doi: 10.1161/CIRCULATIONAHA.107.760124
33. Bing R, Cavalcante JL, Everett RJ, Clavel MA, Newby DE, Dweck MR. Imaging and impact of myocardial fibrosis in aortic stenosis. *JACC Cardiovasc Imaging.* (2019) 12:283–96. doi: 10.1016/j.jcmg.2018.11.026
34. Malahfji M, Senapati A, Tayal B, Nguyen DT, Graviss EA, Nagueh SF, et al. Myocardial scar and mortality in chronic aortic regurgitation. *J Am Heart Assoc.* (2020) 9:e018731. doi: 10.1161/JAHA.120.018731
35. Bohbot Y, Renard C, Manrique A, Levy F, Marechaux S, Gerber BL, et al. Usefulness of cardiac magnetic resonance imaging in aortic stenosis. *Circ Cardiovasc Imaging.* (2020) 13:e010356. doi: 10.1161/CIRCIMAGING.119.010356
36. Masri A, Kalahasti V, Alkharabsheh S, Svensson LG, Sabik JF, Roselli EE, et al. Characteristics and long-term outcomes of contemporary patients with bicuspid aortic valves. *J Thorac Cardiovasc Surg.* (2016) 151:1650–9.e1. doi: 10.1016/j.jtcvs.2015.12.019

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 05 November 2021
doi: 10.3389/fcvm.2021.771789

Transcatheter Aortic Valve Implantation in Sievers Type 0 vs. Type 1 Bicuspid Aortic Valve Morphology: Systematic Review and Meta-Analysis

*Yu Du, Zhijian Wang, Wei Liu, Yonghe Guo, Wei Han, Hua Shen, Shuo Jia, Yi Yu, Kangning Han, Dongmei Shi, Yingxin Zhao and Yujie Zhou**

Beijing Key Laboratory of Precision Medicine of Coronary Atherosclerotic Disease, Department of Cardiology, Clinical Center for Coronary Heart Disease, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

Background: Transcatheter aortic valve implantation (TAVI) has achieved satisfactory outcomes in the selected patients with bicuspid aortic valve (BAV), predominately type 1 BAV (~90%). However, there are few reports about the safety and efficacy of TAVI in type 0 BAV. Therefore, in the current study, we aimed to compare procedural and 30-day outcomes after TAVI between type 0 and type 1 BAV.

Methods: Studies comparing the outcomes of TAVI in Sievers type 0 vs. type 1 BAV were retrieved from PubMed, EMBASE, Cochrane Library, and Web of Science from inception to May 2021. The data were extracted regarding the study characteristics and outcomes. The odds ratios (ORs) with 95% CIs were pooled for procedural and 30-day outcomes.

Results: Six observational studies were included with determined type 0 BAV in 226 patients and type 1 BAV in 902 patients. The patients with type 0 BAV were slightly younger, had larger supra-annular structure, and more frequently implanted self-expanding prosthesis compared with type 1 BAV. In the pooled analyses, the patients with type 0 BAV had a similar incidence of procedural death (OR = 2.6, 95% CI 0.7–10.3), device success (OR = 0.6; 95% CI 0.3–1.3), and ≥ mild (OR = 0.8; 95% CI 0.4–1.6) or moderate (OR = 0.9, 95% CI 0.4–1.8) paravalvular leak, whereas significantly higher mean aortic gradient (mean difference = 1.4 mmHg, 95% CI 0.03–2.7) and increased coronary compromise risk (OR = 7.2; 95% CI 1.5–34.9), compared with type 1 BAV. Meanwhile, the incidence of death (OR = 1.2; 95% CI 0.5–3.1), stroke (OR = 0.5; 95% CI 0.1–2.4), and new pacemaker (OR = 0.6; 95% CI 0.2–2.2) at 30 days were not significantly different between the BAV morphologies ($p > 0.05$). The treatment effect heterogeneity across the studies for the above outcomes were low.

Conclusions: The patients with type 0 BAV appear to have similar short-term outcomes after TAVI compared with type 1 BAV. Whereas, TAVI for type 0 BAV aortic stenosis might lead to an elevated coronary obstruction risk and suboptimal aortic valvular hemodynamics.

Keywords: transcatheter aortic valve implantation, Sievers type 0, outcomes, meta-analysis, bicuspid aortic valve

OPEN ACCESS

Edited by:
Martin Swaans,
St. Antonius Hospital, Netherlands

Reviewed by:
Jef Van den Eynde,
University Hospitals Leuven, Belgium
Konstantinos Stathogiannis,
Stanford University, United States

****Correspondence:***
Yujie Zhou
azzyj12@163.com

Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *07 September 2021*
Accepted: *06 October 2021*
Published: *05 November 2021*

Citation:
Du Y, Wang Z, Liu W, Guo Y, Han W, Shen H, Jia S, Yu Y, Han K, Shi D, Zhao Y and Zhou Y (2021) Transcatheter Aortic Valve Implantation in Sievers Type 0 vs. Type 1 Bicuspid Aortic Valve Morphology: Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 8:771789. doi: 10.3389/fcvm.2021.771789

INTRODUCTION

Transfemoral transcatheter aortic valve implantation (TAVI) is confirmed as a safe and effective alternative to surgical aortic valve replacement (SAVR) for symptomatic, elderly patients with severe aortic stenosis (AS), regardless of the estimated surgical risk (1). However, for selected severe patients with AS and bicuspid aortic valve (BAV), TAVI has only presented a class 2b guidelines recommendation since these patients were excluded from the previous randomized controlled trials (1). Different reasons to exclude the patients with BAV in the prior trials include young age, low surgical risk, and the challenging aortic valvular complex anatomies (e.g., fused calcified raphe, asymmetric leaflet calcification, and coexisting aortopathy) (2). Recently, due to the newest generation devices and refined techniques, TAVI in the selected patients with BAV has become more prevalent, and achieved optimal procedural and short-term outcomes, except for a small, but notable, stroke and paravalvular leak (PVL) risk compared with the tricuspid aortic valves (3, 4). Meanwhile, the US Food and Drug Administration has removed the precaution from commercial labeling regarding TAVI in the patients with BAV using SAPIEN-3 (Edwards Lifesciences Inc., CA, USA) or Evolut-R/Pro (Medtronic Inc., Dublin Ireland) (5, 6).

However, BAV can present different morphologies. According to the Sievers classification, the BAV phenotypes are categorized by the raphe number (0, 1, and 2), with BAV type 1 as the most common (2, 7). The Sievers type 0 BAV morphology, with the two commissures opening in a significant elliptical fashion, was under-represented (∼10%) in the previous multicenter analyses (8–10). Thus, the questions regarding the procedural and mid-term outcomes of TAVI in type 0 BAV remain unanswered. Therefore, in the present systematic review and meta-analysis, we aimed to investigate whether BAV morphology (e.g., Sievers type 0 vs. type 1) can affect the TAVI results.

METHODS

This study was performed following the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) protocol (11) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (12).

Search Strategy, Study Selection, and Eligibility Criteria

According to the Population, Interventions, Comparison, Outcome and Study Design (PICOS) strategy, the studies were enrolled if the following criteria were met: (1) the population consisted of the patients with BAV that underwent TAVI; (2) there was an exposure (or intervention) group with Sievers type 0 BAV; (3) there was an exposure (or comparator) group with Sievers type 1 BAV; (4) the outcomes of interest included in-hospital, 30-day and 1-year outcomes; and (5) the comprehended observational studies. We searched for the published studies in PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science from inception to May 2021. We used the Medical Subject Headings terms and free text to describe the following keywords: (1) "Transcatheter Aortic Valve Implantation" or "Transcatheter Aortic Valve Replacement," (2) "Bicuspid Aortic Valve" or "Bicuspid Aortic Valve Disease," (3) "Aortic Valve Stenosis" or "Aortic Stenosis," and (4) "Bicuspid Aortic Valve Stenosis" or "Bicuspid Aortic Stenosis." The search strings included: (1) AND (2), (1) AND (2) AND (3), and (1) AND (4). Some studies could have used different BAV morphological classification systems [e.g., (13, 14)] and we only included those in which the BAV classification could be translated to Sievers and Schmidtke (7). We excluded the case reports, animal studies, or studies published in non-English languages. The eligibility and quality of each study were assessed by the two independent investigators, and the discrepancies were solved by consensus.

Data Extraction, Outcomes, and Bias Risk Assessment

We collected the following data from each study: study design, the patient characteristics, the imaging findings, the procedural details, and in-hospital, 30-day, and 1-year outcomes. The primary outcome of this study was 30-day mortality. The secondary outcomes consisted of other 30-day outcomes [stroke, life-threatening bleeding, major vascular complication, acute kidney injury (AKI) stage 2–3, and new permanent pacemaker (PPM)]; 1-year outcomes (mortality, cardiac mortality, and stroke); and in-hospital outcomes [procedural death, need of > 1 transcatheter heart valve (THV), cardiac tamponade, aortic root injury, coronary compromise, conversion to surgery, post-dilatation, new PPM, device success, and ≥ mild or moderate PVL at discharge echocardiography]. The outcomes were defined in line with the Valve Academic Research Consortium 2 (VARC-2) criteria (15). It is worth mentioning that the outcomes data were extracted only from the patients with an established Sievers type 0 or type 1 BAV anatomy. The bias risk of each study was systematically assessed using the Newcastle-Ottawa scale criteria (16).

The Statistical Analyses

Effect summary measures are presented as the mean differences (MDs) or odds ratios (ORs) with their 95% CIs. We combined the summary measures using the random-effects Mantel–Haenszel method (17). The χ^2 and I^2 tests were used to assess the heterogeneity, with a $p < 0.1$ indicating statistical significance for heterogeneity and $I^2 > 50\%$ for important heterogeneity (18). The subgroup analyses were performed in studies (1) reporting cardiac death or disabling stroke, (2) using early-generation THV (e.g., SAPIEN, SAPIEN XT, and CoreValve) vs. new-generation THV (e.g., SAPIEN-3, Evolut-R, and Evolut-Pro), and (3) using self-expanding valve (SEV) + balloon-expandable valve (BEV) vs. SEV. A sensitivity analysis was performed by removing each study from the pooled analysis in turn and examining if there was a change in the pooled results. A two-tailed $p < 0.05$ was considered statistically significant. The statistical analyses were performed using the Review Manager software (version 5.3. Cochrane Collaboration; Copenhagen, Denmark).

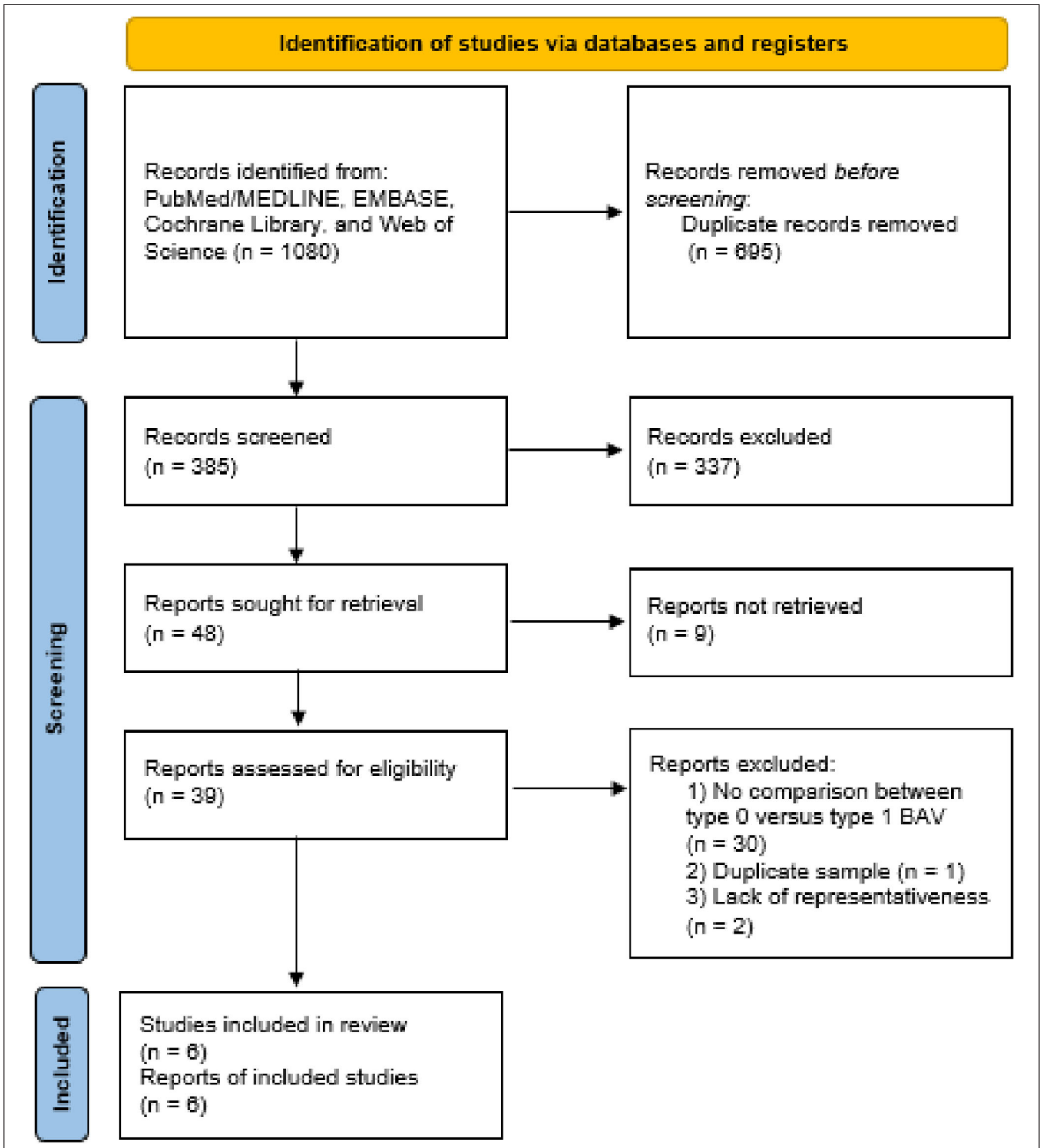


FIGURE 1 | Study inclusion flowchart. BAV, bicuspid aortic valve.

RESULTS

The inclusion flow chart of the current study is shown in **Figure 1**. Six studies (1,239 patients) were enrolled to compare the procedural and clinical outcomes of TAVI between the Sievers type 0 and type 1 BAV (8, 13, 19–22). The bias risk of the enrolled studies was generally low based on the Newcastle-Ottawa scale criteria (**Table 1**). Multi-detector CT (MDCT) was

TABLE 1 | The risk of bias of each study by the Newcastle-Ottawa scale criteria.

	Jilaihawi et al. (13)	Yoon et al. (8)	Liao et al. (19)	Fan et al. (20)	Forrest et al. (23)	Ielasi et al. (22)
Selection						
-Representativeness (1)	1	1	1	1	0	1
-Non-exposed cohort (1)	1	1	1	1	1	1
-Exposure (1)	1	1	1	1	1	1
-Outcome (1)	1	1	1	1	1	1
Comparability						
-Most important factor (1)	0	0	0	0	0	0
-Additional factor (1)	0	0	0	0	0	0
Outcome						
-Assessment (1)	1	0	0	1	1	0
-Follow-up (1)	1	1	1	1	1	1
-% Follow-up (1)	1	1	1	1	1	1
Overall	7	6	6	7	6	6

used for BAV diagnosis in most of the patients, with 226 patients with determined Sievers type 0 BAV and 902 patients with type 1 BAV (**Table 2**).

The Baseline and Procedural Characteristics Between Sievers Type 0 and Type 1 BAV

The clinical and imaging characteristics were available for 116 patients with the Sievers type 0 BAV and 455 with type 1 BAV (**Tables 3**, **4**). Briefly, the mean overall age of patients was 75.7 years and 39% were female. Most of the patients had New York Heart Association (NYHA) functional class III–IV (62.5%) and low society of thoracic surgeons predicted the risk of mortality (mean score of 3.7%). The patients with type 0 BAV were slightly younger (MD = −1.4 years, $p = 0.08$) and had slightly lower ejection fraction (MD = −3.9%, $p = 0.08$) compared with type 1 BAV. Notably, the patients with type 0 BAV had markedly smaller aortic valve area (MD = −0.07 cm^2, $p < 0.01$), larger sino-tubular junction (STJ) diameter (MD = 1.9 mm, $p < 0.01$), and height (MD = 2.4 mm, $p < 0.01$), as well as larger ascending aorta diameter at 40 mm from the annulus (MD = 1.7 mm, $p < 0.01$), compared with type 1 BAV. Meanwhile, the patients with type 0 BAV had larger left (MD = 1.6 mm, $p < 0.01$) and right (MD = 1.2 mm, $p = 0.04$) coronary take-offs compared with type 1 BAV.

The TAVI procedural details were available for 156 patients with Sievers type 0 BAV and 790 with type 1 BAV (**Table 5**). Overall, the conscious sedation (68.9%) and balloon pre-dilation (73.0%) were commonly used. Most of the patients (90.0%) had transfemoral access and nearly half (50.8%) implanted SEV. It is worth noting that, compared with type 1 BAV, the patients with type 0 BAV were less likely to implant BEV (OR = 0.5, 95% CI 0.2–0.9), and numerically more frequently received SEV (OR = 2.2, 95% CI 0.9–4.8).

The Procedural and Clinical Outcomes Between Sievers Type 0 and Type 1 BAV

Outcome data were available for 226 patients with Sievers type 0 BAV and 902 with type 1 BAV (**Table 6**). Regarding the in-hospital outcomes, no significant difference was observed for the patients with Sievers type 0 vs. type 1 BAV that underwent TAVI: procedural death (OR = 2.6, 95% CI 0.7–10.3), THV embolization (OR = 1.1, 95% CI 0.11–9.4), > 1 THV (OR = 1.6, 95% CI 0.8–3.4), cardiac tamponade (OR = 1.6, 95% CI 0.2–11.9), aortic root injury (OR = 1.8, 95% CI 0.4–8.1), conversion to surgery (OR = 3.4, 95% CI 0.5–25.3), balloon post-dilation (OR = 0.95, 95% CI 0.4–2.2), new PPM (OR = 0.6, 95% CI 0.4–1.1), device success (OR = 0.6, 95% CI 0.3–1.3), ≥ mild (OR = 0.8, 95% CI 0.4–1.6), or ≥ moderate PVL (OR = 0.9, 95% CI 0.4–1.8) (**Figure 2**). It is worth mentioning that, compared with type 1 BAV, TAVI for the patients with type 0 BAV was associated with significant higher mean aortic gradient (MD = 1.35 mmHg, 95% CI 0.03–2.7) and increased coronary compromise risk (OR = 7.2; 95% CI 1.5–34.9). The treatment effect heterogeneity was low across the studies for the above outcomes, except for balloon post-dilation among the four studies with a borderline heterogeneity ($p = 0.11$, $I^2 = 50\%$).

Regarding the 30-day outcomes (**Figure 3**), we did not found significant differences in TAVI for patients with type 0 vs. type 1 BAV: all-cause death (OR = 1.2, 95% CI 0.5–3.1), cardiac death (OR = 1.1, 95% CI 0.1–9.5), stroke (OR = 0.5, 95% CI 0.1–2.4), disabling stroke (OR = 0.96, 95% CI 0.1–8.2), life threatening bleeding (OR = 0.5, 95% CI 0.1–4.0), major vascular complication (OR = 0.6, 95% CI 0.1–5.3), AKI stage 2–3 (OR = 0.7, 95% CI 0.1–6.0) or new PPM (OR = 0.6, 95% CI 0.2–2.2). No significant treatment effect heterogeneity was found among the studies for these outcomes. Additionally, the pooled results were almost unchanged in the sensitivity analysis.

One-year outcomes were available in only one study (22), showing no difference in all-cause mortality, cardiac mortality, and stroke between the two BAV phenotypes ($p > 0.05$).

The Subgroup Analyses Between the Sievers Type 0 and Type 1 BAV

No significant differences in the procedural and 30-day outcomes between TAVI in the patients with type 0 and type 1 BAV were observed using either early-generation THV (e.g., SAPIEN, SAPIEN XT, and CoreValve) or new-generation THV (e.g.,

TABLE 2 | Overview of included BAV studies.

	Jilaihawi et al. (13)	Yoon et al. (8)	Liao et al. (19)	Fan et al. (20)	Forrest et al. (23)	Ielasi et al. (22)
Inclusion period	Apr 2005—Oct 2014	Apr 2005—May 2016	Apr 2012—Feb 2017	Dec 1—Dec 31, 2016	Dec 2018—Oct 2019	Jun 2013—Oct 2018
Location	14 centers from US, Canada, Europe and Asia	33 centers from Europe, North America and the Asia-Pacific region	1 center from China	1 center from China	25 centers from US	18 centers from Europe
Main exclusion criteria	NA	Missing data, degenerated bioprosthesis	THV neither CoreValve nor Venus-A	Absence of baseline (e.g., contraindication) or post-procedural MRI (e.g., in-hospital death, conversion to SAVR), recent stroke or TIA	STS PROM score ≥3.0%, aortopathy, age <60 yrs, prohibitive LVOT Calcium	Type 2 BAV, undeterminable BAV type
Number of patients–no.	130	546	87	83	150	243
BAV diagnosis by MDCT–no. (%)	91 (70.0)	NA	86 (98.9)	83 (100)	150 (100)	243 (100)
BAV morphology	Tricommisural BAV ($n = 24$); Bicommissural BAV (Non-raphe, $n = 21$; Raphe, $n = 74$; Undetermined, $n = 4$); Unknown ($n = 7$)	Type 0 ($n = 61$); Type 1 ($n = 409$); Type 2 ($n = 8$); Undetermined ($n = 68$)	Type 0 ($n = 49$); Type 1 ($n = 38$)	Type 0 ($n = 56$); Type 1 ($n = 27$)	Type 0 ($n = 14$); Type 1 ($n = 136$)	Type 0 ($n = 25$); Type 1 ($n = 218$)
Type of THV						
–Balloon expandable	Sapien or Sapien XT ($n = 62$), Sapien 3 ($n = 8$)	Sapien XT ($n = 155$), Sapien 3 ($n = 160$)	0	Sapien XT or Sapien 3 ($n = 3$)	0	Sapien 3 ($n = 170$)
–Self-expanding	CoreValve ($n = 60$)	CoreValve ($n = 165$), Evolut R ($n = 23$)	Corevalve ($n = 25$), Venus-A ($n = 59$)	CoreValve, Venus-A, VitaFlow or TaurusOne ($n = 80$)	Evolut R ($n = 64$) or Evolut PRO ($n = 85$)	Evolut R or Evolut PRO ($n = 73$)
–Others	$n = 0$	Lotus ($n = 43$)	$n = 0$	$n = 0$	$n = 0$	$n = 0$
Mortality (%)						
-Procedural	1.5	1.3	NA	0	0.7	0.8
-Thirty-day	3.8	3.7	9.2	0	0.7	4.0
-One-year	NA	11.4	NA	NA	NA	9.8

BAV, bicuspid aortic valve; LVOT, left ventricular outflow tract; MRI, magnetic resonance imaging; MDCT, multi-detector computed tomography; NA, not applicable; SAVR, surgical aortic valve replacement; STS PROM, society of thoracic surgeons predicted risk of mortality; THV, transcatheter heart valve; TIA, transient ischemic attack.

SAPIEN-3, Evolut-R, and Evolut-Pro) (**Table 7**), and using either SEV + BEV or SEV (**Table 8**).

DISCUSSION

To our knowledge, this study comprehended the first meta-analysis comparing the procedural and clinical outcomes of TAVI in the patients with Sievers type 0 vs. type 1 BAV. Our main findings were: (1) the incidence of most procedural outcomes was similar between the type 0 vs. type 1 BAV (i.e., procedural death, THV embolization, > 1 THV, cardiac tamponade, aortic root injury, conversion to surgery, balloon post-dilation, new PPM, device success, ≥ mild PVL, or ≥ moderate PVL). However, the patients with type 0 BAV were associated with markedly higher mean aortic gradient before discharge and increased coronary compromise risk compared with type 1 BAV. (2) No marked differences between the two BAV configurations were found for the following 30-day outcomes: death, cardiac death, stroke, disabling stroke, life-threatening bleeding, major vascular complication, AKI stage 2–3, or new PPM. Importantly, the treatment effect heterogeneity was consistently low across the studies for procedural and 30-day outcomes. (3) The subgroup analyses in the patients using different THV generations, different THV types, and different hard endpoints definitions were consistent with the aforementioned procedural and 30-day outcomes.

Bicuspid aortic valve is the most common congenital heart disease (1∼2% of the population) and represents the main AS cause in the patients under 65 years of age (24, 25). Given the indications of TAVI expanding to the young patients

TABLE 3 | Clinical characteristics.

	Jilaihawi et al. (13)		Yoon et al. (8)	Liao et al. (19)	Fan et al. (20)		Forrest et al. (23)		Ielasi et al. (22)		MD or OR	95% CI	*P*-value
BAV morphology	**Type 0** ***n*** **= 21**	**Type 1[#]** ***n*** **= 74**	**Not specified** ***n*** **= 546**	**Not specified** ***n*** **= 87**	**Type 0** ***n*** **= 56**	**Type 1** ***n*** **= 27**	**Type 0** ***n*** **= 14**	**Type 1** ***n*** **= 136**	**Type 0** ***n*** **= 25**	**Type 1** ***n*** **= 218**			
Age (yrs)	74.4 ± 7.3	76.1 ± 10.8	77.2 ± 8.2	73.4 ± 6.4	75.0 ± 6.8	77.7 ± 3.1	70.6 ± 4.1	70.3 ± 5.6	77.8 ± 9.3	79.1 ± 7.8	−1.4	−2.9, 0.1	0.08
Male–no. (%)	11 (52.4)	46 (62.2)	343 (62.8)	50 (57.5)	33 (58.9)	16 (59.3)	5 (35.7)	73 (53.7)	19 (76.0)	144 (66.1)	0.9	0.5, 1.5	0.65
STS PROM score (%)	4.2 ± 1.6	5.1 ± 3.6	4.6 ± 4.6	7.9 ± 4.0	5.6 ± 3.6	5.8 ± 3.8	1.4 ± 0.5	1.4 ± 0.6	3.4 ± 1.8	4.5 ± 3.0	−0.5	−1.2, 0.2	0.15
NYHA class III-IV–no. (%)	18 (85.7)	60 (81.1)	439 (80.4)	80 (92.0)	51 (91.1)	24 (88.9)	2 (14.3)	39 (28.6)	17 (68.0)	146 (67.3)	1.0	0.5, 1.8	0.98
Prior PCI–no. (%)	4 (19.0)	8 (10.8)	121 (22.2)	7 (8.0)	3 (5.4)	5 (18.5)	1 (7.1)	10 (7.4)	6 (24.0)	54 (24.8)	0.9	0.4, 1.9	0.73
Prior CABG–no. (%)	1 (4.8)	8 (10.8)	62 (11.4)	NA	0 (0)	0 (0)	2 (14.3)	0 (0)	2 (8.0)	18 (8.3)	2.1	0.2, 21.2	0.54
CKD–no. (%)	1 (5.0)*	19 (29.7)*	NA	10 (16.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lung disease–no. (%)	6 (28.6)	31 (41.9)	98 (17.9)	50 (57.5)	13 (23.2)	6 (22.2)	2 (15.4)	24 (17.9)	7 (28)	52 (23.9)	0.9	0.5, 1.6	0.72
Stroke or TIA–no. (%)	3 (14.3)	9 (12.2)	77 (14.1)	13 (14.9)	0 (0)	1 (3.7)	0 (0)	10 (7.4)	4 (16.0)	27 (12.4)	1.0	0.5, 2.3	0.95
Atrial fibrillation or flutter—no. (%)	6 (28.6)	24 (32.4)	NA	19 (21.8)	5 (18.5)	11 (13.3)	0 (0)	11 (8.1)	6 (25.0)	54 (25.5)	0.5	0.2, 1.3	0.16
Prior PPM—no. (%)	2 (9.5)	12 (16.2)	NA	NA	NA	NA	0 (0)	4 (2.9)	2 (8.0)	20 (9.2)	0.9	0.2, 3.4	0.87

Values are mean ± SD, median (interquartile range) or n (%).

*[#]Functional (or tricommisural) BAV not included; *indicated statistically significant difference ($P < 0.05$) between type 0 and type 1 within the study.*

BAV, bicuspid aortic valve; CI, Confidence Interval; CABG, coronary artery bypass graft; CKD, chronic kidney disease; MD, Mean Difference; NYHA, New York Heart Association; NA, not applicable; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS PROM, society of thoracic surgeons predicted risk of mortality; TIA, transient ischemic attack.

TABLE 4 | Imaging findings.

	Jilaihawi et al. (13)		Yoon et al. (8)	Liao et al. (19)	Fan et al. (20)		Forrest et al. (23)		Ielasi et al. (22)		MD or OR	95% CI	*P*-value
BAV morphology	**Type 0** ***n*** **= 21**	**Type 1[#]** ***n*** **= 74**	**Not specified** ***n*** **= 546**	**Not specified** ***n*** **= 87**	**Type 0** ***n*** **= 56**	**Type 1** ***n*** **= 27**	**Type 0** ***n*** **= 14**	**Type 1** ***n*** **= 136**	**Type 0** ***n*** **= 25**	**Type 1** ***n*** **= 218**			
Echocardiography													
Mean aortic gradient (mmHg)	50.3 ± 14.3	50.8 ± 15.9	49.7 ± 17.7	65.4 ± 20.1	56.3 ± 25.7	51.7 ± 12.5	48.1 ± 9.7	50.0 ± 16.0	46.0 ± 10.4	49.2 ± 16.8	−1.3	−4.3, 1.7	0.39
AVA (cm^2)	0.60 ± 0.24	0.67 ± 0.19	0.70 ± 0.20	NA	0.50 ± 0.18	0.57 ± 0.23	0.70 ± 0.10	0.80 ± 0.20	0.67 ± 0.22	0.69 ± 0.23	−0.07	−0.12, −0.03	**<0.01**
Moderate/severe AR—no. (%)	NA	NA	NA	12 (13.8)	6 (10.7)	5 (18.5)	NA	NA	4 (16.0)	46 (21.1)	0.6	0.3, 1.5	0.28
Ejection fraction (%)	NA	NA	51.6 ± 15.0	55.0 ± 19.6	55.2 ± 15.2	58.1 ± 9.2	NA	NA	48.8 ± 15.5	54.2 ± 13.2	−3.9	−8.0, 0.1	0.06
MDCT													
Aortic root angle (degree)	50.1 ± 10.6	50.8 ± 11.4	NA	NA	52.8 ± 9.8	52.7 ± 8.4	NA	NA	NA	NA	−0.2	−3.4, 3.0	0.90
Calcium score (mm^3)	546.3 ± 645.6	391.3 ± 283.5	NA	654.8 ± 406.1	995.1 ± 781.4	919.2 ± 343.4	491.5 ± 425.2	817.2 ± 563.8	NA	NA	−36.7	−332.0, 258.7	0.81
Moderate/severe aortic valve calcium—no. (%)	NA	NA	NA	NA	NA	NA	NA	NA	13 (52.0)*	155 (71.1)*	NA	NA	NA
Annulus area (mm^2)	434.4 ± 92.7*	505.0 ± 93.3*	NA	459.3 ± 136.4	462.0 ± 118.8	442.1 ± 75.2	NA	NA	547.2 ± 133.2	509.2 ± 107.3	−5.0	−71.0, 60.9	0.88
Annular perimeter (mm)	75.0 ± 8.1*	80.9 ± 7.5*	NA	78.0 ± 9.5	77.8 ± 9.6	76.3 ± 5.9	NA	NA	83.4 ± 10.8	81.4 ± 8.9	−0.8	−5.8, 4.2	0.75
STJ diameter (mm)	33.5 ± 6.0	32.0 ± 4.2	NA	30.8 ± 3.9	31.8 ± 3.7	28.7 ± 4.1	NA	NA	31.0 ± 3.6	30.0 ± 4.3	1.9	0.5, 3.2	**<0.01**
STJ height (mm)	26.4 ± 5.1	24.4 ± 4.8	NA	NA	24.5 ± 5.4	21.8 ± 5.3	NA	NA	NA	NA	2.4	0.6, 4.1	**<0.01**
AAo diameter at 4 cm (mm)	38.8 ± 5.8	37.7 ± 5.0	NA	NA	38.9 ± 3.4	37.1 ± 2.3	NA	NA	NA	NA	1.7	0.6, 2.8	**<0.01**
Max AAo diameter (mm)	42.5 ± 6.4	40.5 ± 6.5	NA	NA	43.9 ± 4.0	39.2 ± 2.8	NA	NA	36.6 ± 4.0	36.8 ± 5.4	2.2	−1.2, 5.6	0.21
Left coronary height (mm)	15.5 ± 4.3	14.5 ± 3.6	NA	14.1 ± 3.5	17.2 ± 3.9	15.3 ± 2.0	NA	NA	NA	NA	1.6	0.6, 2.7	**<0.01**
Right coronary height (mm)	17.9 ± 2.9	17.1 ± 3.7	NA	15.3 ± 3.1	17.5 ± 4.3	15.8 ± 3.5	NA	NA	NA	NA	1.2	0.1, 2.3	**0.04**

Values are mean ± SD, median (interquartile range) or n (%).

*[#]Functional (or tricommisural) BAV not included; *indicated statistically significant difference (P < 0.05) between type 0 and type 1 within the study.*

AVA, aortic valve area; AR, aortic regurgitation; AAo, ascending aorta; BAV, bicuspid aortic valve; CABG, coronary artery bypass graft; CI, Confidence Interval; CKD, chronic kidney disease; MD, Mean Difference; NYHA, New York Heart Association; NA, not applicable; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STJ, sino-tubular junction; STS PROM, society of thoracic surgeons predicted risk of mortality; TIA, transient ischemic attack. Bold values indicated statistically significant difference (P < 0.05) between type 0 and type 1 in pooled analysis.

TABLE 5 | Procedural details.

	Jilaihawi et al. (13)	Yoon et al. (8)		Liao et al. (19)	Fan et al. (20)		Forrest et al. (23)		Ielasi et al. (22)		MD or OR	95% CI	*P*-value
BAV morphology	**Not specified *n* = 130**	**Type 0 *n* = 61**	**Type 1 *n* = 409**	**Not specified *n* = 87**	**Type 0 *n* = 56**	**Type 1 *n* = 27**	**Type 0 *n* = 14**	**Type 1 *n* = 136**	**Type 0 *n* = 25**	**Type 1 *n* = 218**			
Conscious sedation—no. (%)	NA	NA	NA	4 (4.6)	47 (83.9)	24 (88.9)	9 (64.3)	86 (63.2)	20 (80.0)	198 (90.8)	0.6	0.3, 1.3	0.20
Transfemoral access—no. (%)	114 (87.7)	50 (82.0)	360 (88.0)	83 (95.4)	NA	NA	14 (100)	133 (98.5)	25 (100)	193 (88.5)	1.0	0.3, 3.7	0.97
Pre-dilation—no. (%)	116 (91.3)	NA	NA	81 (93.1)	56 (100)	27 (100)	14 (100)	123 (90.4)	11 (44.0)	78 (35.8)	1.50	0.7, 3.4	0.32
THV type—no. (%)													
–Self-expanding	60 (46.2)	32 (52.4)*	113 (27.6)*	84 (96.5)	56 (100)	24 (88.9)	14 (100)	135 (100)	9 (36.0)	64 (29.4)	2.2	0.9, 4.8	0.06
–Balloon expandable	70 (53.8)	25 (41.0)*	260 (63.6)*	0 (0)	0 (0)	3 (11.1)	0 (0)	0 (0)	16 (64.0)	154 (70.6)	0.5	0.2, 0.9	**0.03**
–Mechanically expandable	0 (0)	4 (6.6)*	36 (8.8)*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA

**indicated statistically significant difference (P < 0.05) between type 0 and type 1 within the study.*
BAV, bicuspid aortic valve; CI, Confidence Interval; MD, Mean Difference; NA, not applicable; THV, transcatheter heart valve 0.591–1,163.
Bold values indicated statistically significant difference (P < 0.05) between type 0 and type 1 in pooled analysis.

with AS, more patients with BAV can be encounter in the contemporary pre-TAVI workup. However, little is known about the correlation between the Sievers BAV phenotypes and the clinical manifestations and outcomes after TAVI. Data from a large international, multicenter registry (n = 2,118) showed that, compared with BAV with raphe, the patients with BAV without raphe (i.e., type 0 BAV) referring for cardiac surgery were younger, less likely to have dysfunctional aortic valves, whereas had similar Valsalva sinus, STJ, and ascending aorta diameters by ECGs (26). In contrast, we found, in 571 patients with BAV that underwent TAVI for severe AS, that patients with type 0 BAV were only slightly younger and had numerically lower ejection fraction compared with type 1 BAV. The patients with BAV in the present study appeared much older (75.7 vs. 47.0 years) and to have more frequently severe AS (100 vs. 19.6%) than the aforementioned surgical registry (26). Meanwhile, we found a significantly larger STJ diameter and height, as well as ascending aorta diameter at 40 mm from the annulus. In addition, Jilaihawi et al. showed that the mean Valsalva sinus diameter was larger in the type 0 BAV than type 1 (13). Consistently, these findings demonstrated that type 0 BAV was associated with a larger supra-annular structure than type 1 BAV.

Regarding the TAVI procedure, the balloon pre-dilation proportion was high whereas varied among the different centers [93.1∼100% in two Chinese centers (19, 20) and 36.6% in an international registry mainly compromising the European centers (22)]. Balloon valvuloplasty for BAV-AS is supposed to facilitate the TAVI delivery system crossing, improve prosthesis expansion, and judge prosthesis size selection and coronary obstruction risk in combination with aortography (2). However, routine balloon pre-dilation might increase procedural stroke (20), and the benefit of deploying a cerebral embolic protection device remains to be established in this scenario. In our present pooled analysis, the 30-day stroke risk was similar between the type 0 and type 1 BAV, although no patient had a 30-day stroke in the type 0 BAV group (8, 13, 22, 23). Consistent with these findings, Fan et al. demonstrated a similar number and total volume of cerebral ischemic lesions in diffusion-weighted MRI after TAVI between the two BAV categories (20).

Interestingly, the patients with type 0 BAV seemed more likely to implant SEV than BEV. This might be explained by the fact that TAVI for BAV-AS using BEV was associated with more than a five-time higher annulus rupture risk than SEV (2.5% vs. 0, $p < 0.001$) (27). Moreover, type 0 BAV is uncommon in clinical practice, where the physicians might not be well-experienced with this specific aortic morphology and thus tend to frequently use SEV. Although TAVI for BAV-AS using SEV, compared with BEV, was associated with a higher tolerable error rate, it might also lead to an increased moderate or severe PVL risk, probably due to the decreased radial force of SEV (28). Moderate or severe PVL is a major concern in the early trials of performing TAVI in BAV (incidence ranging from 8 to 20%) (8, 13). Fortunately, its incidence significantly decreased (<4%) due to a more precise aortic valve sizing by MDCT and the use of new-generation THV with an extra sealing skirt or re-capture property (22, 23). In our analysis, although the mean aortic gradient on pre-discharge echocardiography was markedly higher in type 0 compared with type 1 BAV, this small difference on aortic gradient (MD = 1.35 mmHg) did not lead to the significant differences in the ≥ mild or ≥ moderate PVL incidence between the two BAV groups. It

TABLE 6 | In-hospital and 30-day outcomes.

	Jilaihawi et al. (13)		Yoon et al. (8)		Liao et al. (19)		Fan et al. (20)		Forrest et al. (23)		Ielasi et al. (22)	
BAV morphology	**Type 0** ***n* = 21**	**Type 1[#]** ***n* = 74**	**Type 0** ***n* = 61**	**Type 1** ***n* = 409**	**Type 0** ***n* = 49**	**Type 1** ***n* = 38**	**Type 0** ***n* = 56**	**Type 1** ***n* = 27**	**Type 0** ***n* = 14**	**Type 1** ***n* = 136**	**Type 0** ***n* = 25**	**Type 1** ***n* = 218**
In-hospital outcomes—no. (%)												
Procedural death	2 (9.5)*	0 (0)*	1 (1.6)	6 (1.5)	NA	NA	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	2 (0.9)
Prosthesis embolization	0 (0)	2 (2.7)	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	2 (0.9)
Need of > 1 prosthesis	2 (9.5)	2 (2.7)	4 (6.6)	18 (4.4)	9 (18.4)	4 (11.8)	NA	NA	0 (0)	5 (3.7)	0 (0)	9 (4.1)
Cardiac tamponade	1 (4.8)	1 (1.4)	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	6 (2.8)
Aortic root injury	1 (4.8)	1 (1.4)	0 (0)	8 (2.0)	0 (0)	0 (0)	NA	NA	NA	NA	1 (4.0)	3 (1.4)
Coronary compromise	0 (0)	0 (0)	2 (3.3)	3 (0.7)	NA	NA	NA	NA	1 (7.1)	0 (0)	NA	NA
Conversion to surgery	1 (4.8)	1 (1.4)	1 (1.6)	8 (2.0)	NA	NA	0 (0)	0 (0)	1 (7.1)	0 (0)	NA	NA
Post-dilation	4 (19.0)	16 (22.2)	NA	NA	NA	NA	38 (67.9)	15 (55.6)	1 (7.1)	54 (40.0)	7 (28.0)	49 (22.5)
New PPM	NA	NA	7 (11.5)	56 (14.4)	9 (18.4)	12 (31.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.0)	33 (15.5)
Device success	NA	NA	51 (83.6)	350 (85.6)	NA	NA	NA	NA	NA	NA	18 (72.0)	189 (86.7)
Pre-discharge echocardiography												
≥ mild PVL—no. (%)	12 (60.0)	49 (68.1)	NA	NA	19 (38.8)	15 (41.2)	NA	NA	NA	NA	NA	NA
≥ moderate PVL—no. (%)	3 (15.0)	14 (19.4)	5 (8.2)	44 (10.8)	NA	NA	6 (10.7)	0 (0)	0 (0)	0 (0)	1 (4.0)	9 (4.1)
Mean aortic gradient (mmHg)[§]	10.0 (7.0–14.0)	9.5 (7.8–13.0)	12.0 ± 7.2	10.4 ± 5.1	NA	NA	NA	NA	NA	NA	11.5 ± 6.7	9.4 ± 4.7
Thirty-day outcomes–no. (%)												
All-cause mortality	2 (9.5)	2 (2.7)	1 (1.6)	17 (4.2)	5 (10.2)	3 (7.9)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	9 (4.4)
-Cardiac mortality	NA	NA	NA	NA	NA	NA	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	8 (3.9)
Stroke	0 (0)	3 (4.2)	0 (0)	13 (3.2)	NA	NA	NA	NA	0 (0)	6 (4.4)	0 (0)	3 (1.5)
-Disabling	NA	NA	0 (0)	8 (2.1)	NA	NA	NA	NA	0 (0)	1 (0.7)	NA	NA
-Non-disabling	NA	NA	0 (0)	5 (1.3)	NA	NA	NA	NA	0 (0)	5 (3.7)	NA	NA
Life threatening bleeding	NA	NA	0	8 (2.0)	NA	NA	NA	NA	0 (0)	6 (4.4)	NA	NA
Major vascular complication	NA	NA	0	14 (3.4)	NA	NA	NA	NA	0 (0)	2 (1.5)	NA	NA
AKI stage 2–3	NA	NA	1 (1.6)	9 (2.2)	NA	NA	NA	NA	0 (0)	0 (0)	NA	NA
New PPM	4 (22.2)	16 (26.7)	NA	NA	NA	NA	NA	NA	0 (0)	22 (16.7)	NA	NA
One-year outcomes–no. (%)												
All-cause mortality	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (9.1)	18 (9.8)
-Cardiac mortality	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (9.1)	13 (7.1)
Stroke	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (5.6)	7 (7.6)

Values are mean ± SD, median (interquartile range) or n (%).

*[#]Functional (or tricommisural) BAV not included; *indicated statistically significant difference ($P < 0.05$) between type 0 and type 1 within the study; §Mean difference between type 0 and type 1 BAV of 1.35 [0.03–2.66], $I^2 = 0\%$, $P = 0.05$.*

AKI, acute kidney injury; BAV, bicuspid aortic valve; NA, not applicable; PPM, permanent pacemaker; PVL, paravalvular leak.

is worth mentioning that the impact of prosthesis selection (BEV vs. SEV or early- vs. new-generation) on the procedural outcomes should be treated as hypothesis-generating at this time since we did not observe these impacts in our subgroup analysis.

Although the patients with type 0 BAV tended to have larger supra-annular structures and higher coronary take-offs, we found that TAVI for type 0 BAV was associated with a significantly higher coronary compromise risk compared with type 1. Traditionally, the coronary obstruction predictors during TAVI include low coronary take-off, small Valsalva sinus and STJ, long aortic leaflet, and bulky calcification close to the coronary ostium. Recently, Heitkemper et al. found that the distance ratio from cusp to coronary ostium to coronary artery diameter (< 0.7) was superior to coronary ostium height (< 14 mm) and Valsalva

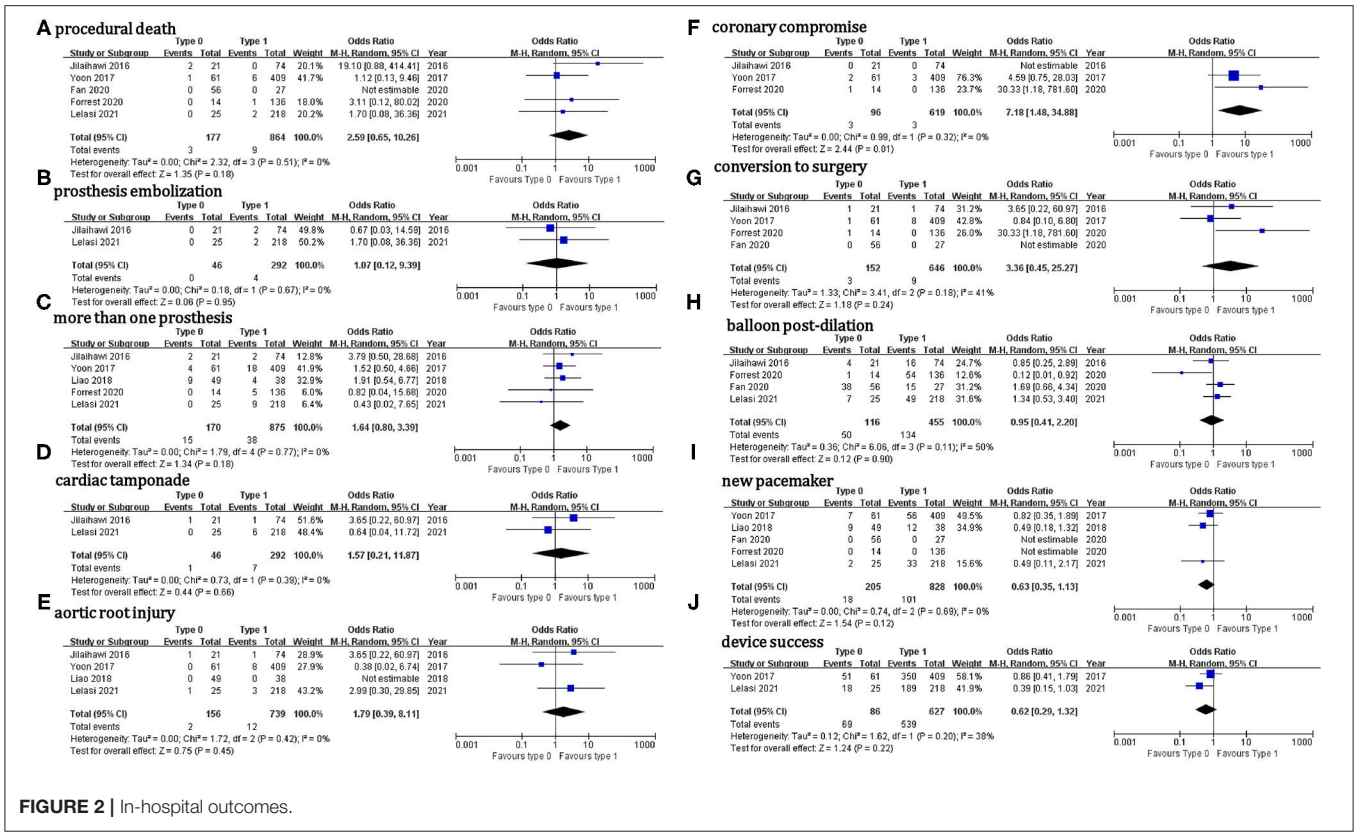


FIGURE 2 | In-hospital outcomes.

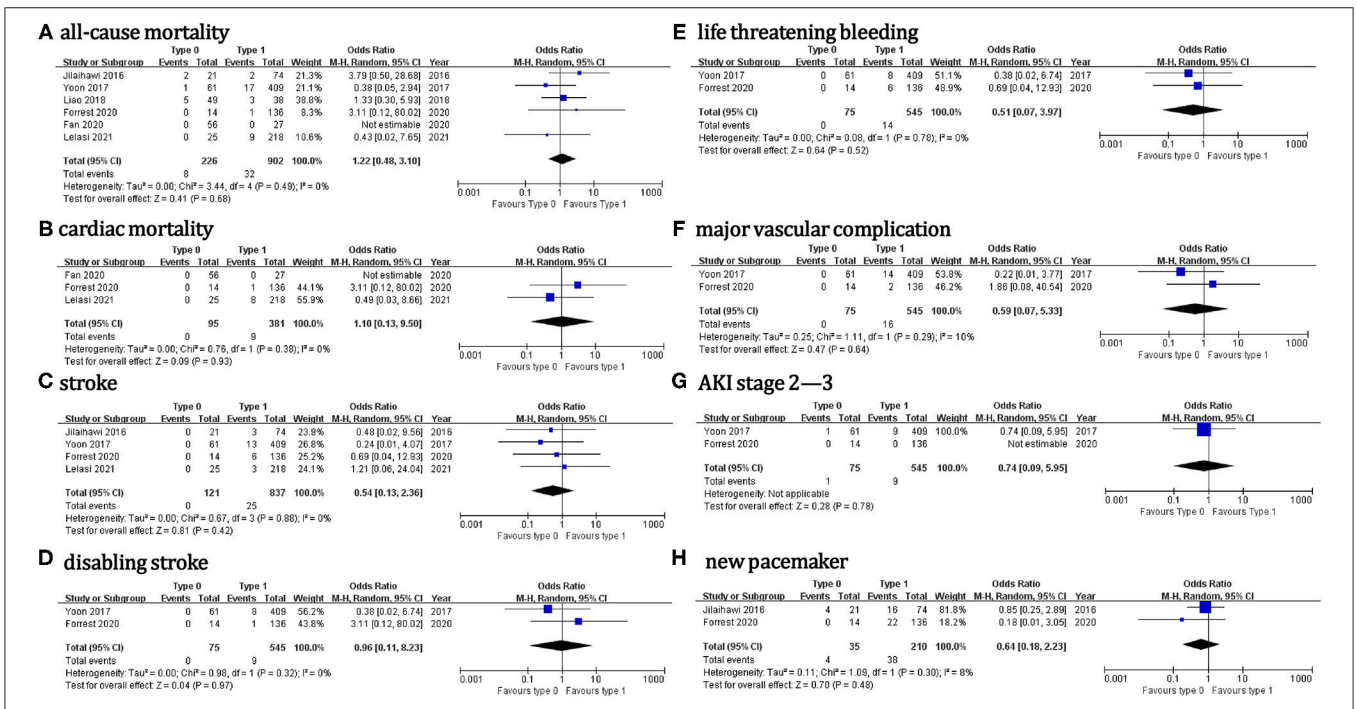


FIGURE 3 | The 30-day outcomes.

TABLE 7 | Subgroup analyses of different generations of prosthesis*.

	Early-generation prosthesis				New-generation prosthesis			
	Sapien, Sapien XT, CoreValve				Sapien 3, Evolut R, Evolut PRO			
	OR	95% CI	I^2	*P*-value	OR	95% CI	I^2	*P*-value
30-day outcomes								
Death	1.9	0.6–6.4	0	0.29	1.0	0.1–8.9	0	0.98
Stroke	NA	NA	NA	NA	0.9	0.1–7.4	0	0.93
In-hospital outcomes								
Procedural death	19.1	0.9–414.4	NA	0.06§	2.3	0.2–21.0	0	0.47
>1 prosthesis	2.3	0.8–6.8	0	0.12	0.6	0.1–4.6	0	0.62
Aortic root injury	3.7	0.2–61.0	NA	0.37§	NA	NA	NA	NA
Conversion to surgery	3.7	0.2–61.0	NA	0.37§	NA	NA	NA	NA
Post-dilation	1.3	0.6–2.8	0	0.48	0.5	0.04–5.7	80%	0.55
Pacemaker	0.5	0.2–1.3	NA	0.16§	0.5	0.1–2.2	NA	0.35§
Perivalvular leak ≥ moderate	1.6	0.2–14.5	52%	0.69	1.0	0.1–8.0	NA	0.98§

**The study by Yoon et al. (8) was not included in either of the two subgroups because 58.6 and 41.4% of patients used early- and new-generation prosthesis, respectively.*
§Two studies were eligible for pool analysis, whereas in one study, no event occurred in type 0 or type 1 BAV.
CI, confidence interval; OR, odds ratio.

TABLE 8 | Subgroup analyses of different types of prosthesis.

	SEV+BEV				SEV			
	OR	95% CI	I^2	*P*-value	OR	95% CI	I^2	*P*-value
30-day outcomes								
Death	1.0	0.2–4.7	33%	0.95	1.54	0.4–6.0	0	0.53
Stroke	0.5	0.1–2.7	0	0.43	NA	NA	NA	NA
In–hospital outcomes								
Procedural death	2.6	0.5–13.7	14%	0.26	3.1	0.1–80.0	NA	0.49§
>1 prosthesis	1.6	0.6–4.1	0	0.31	1.7	0.5–5.4	0	0.38
Aortic root injury	1.8	0.4–8.1	0	0.45	NA	NA	NA	NA
Coronary compromise	4.6	0.8–28.0	NA	0.10§	NA	NA	NA	NA
Conversion to surgery	1.4	0.3–7.6	0	0.69	30.3	1.2–781.6	NA	0.04§
Post-dilation	1.1	0.5–2.4	0	0.73	0.5	0.03–8.0	83%	0.63
Pacemaker	0.7	0.4–1.5	0	0.38	0.5	0.2–1.3	NA	0.16§
Perivalvular leak ≥ moderate	0.8	0.4–1.6	0	0.46	7.1	0.4–130.4	NA	0.19§

§Two studies were eligible for pool analysis, whereas in one study, no event occurred in type 0 or type 1 BAV.
BEV, balloon expandable valve; SEV, self-expanding valve; CI, confidence interval; OR, odds ratio.

sinus diameter (< 30 mm) to predict coronary obstruction in TAVI, with 100% sensitivity and 95.7% specificity (29). Thus, predicting coronary obstruction during TAVI can be difficult, in particular, for the challenging BAV anatomies. Meanwhile, coronary access post-TAVI is important considering that the patients with BAV-AS are generally young and at low surgical risk. In this case, BEV with an intra-annular and lower-frame design can be more friendly than SEV allowing easier coronary access (30, 31).

Regarding hard endpoints after TAVI in type 0 vs. type 1 BAV, the data are scarce and inconsistent. Jilaihawi et al. found that the patients with bicommissural non-raphe-type (i.e., type 0) BAV had higher procedural mortality than bicommissural raphe-type (i.e., "anatomical" type 1) BAV (9.5% vs. 0, $p = 0.047$), although no significant difference was detected at 30 days (13). Similarly, Yousef et al. showed that type 1 BAV with left and right cusp fusion was associated with markedly lower procedural, 30-day, and 1-year mortality, compared with other valve variants ($p \leq 0.05$) (9). However, these mortality differences were driven by just several cases from the above early small-scale studies. Conversely, no significant differences in procedural or 30-day mortality were detected between the Sievers type 0 vs. type 1 BAV in the other five enrolled studies (8, 19–22). Notably, three of them reported no procedural death or 30-day death for the patients with Sievers type 0 BAV (20–22). Consistently, a similar mortality up to 5 years was demonstrated between the two BAV subsets in the patients receiving SAVR after adjusting for age, diabetes, and left ventricular ejection fraction (26). In line with these findings, we did not found marked differences in procedural death, 30-day all-cause death, or 30-day cardiac death

between the two BAV morphologies in the pooled analysis.

In addition, our study has some limitations. The trials included were either small feasibility studies or large retrospective registries, with inconsistent inclusion and exclusion criteria, thus the selection bias was hardly avoidable. Most of the enrolled studies did not report calcification distribution on raphe or leaflet, or aortic annulus elliptic shape, unfavorable anatomies for TAVI in type 1, and 0 BAV (2, 32). The absence of these data precluded further subgroup analyses. Additionally, TAVI prosthesis might be constrained and under expanded in the patients with BAV with an asymmetrical aortic valvular complex, followed by accelerated deteriorating over time (24). However, bioprosthesis durability after TAVI in type 0 vs. type 1 BAV remained unknown due to the short-term follow-up.

CONCLUSION

In the elderly severe AS population with low surgical risk, the patients with Sievers type 0 BAV seem to have higher mean aortic gradient and increased coronary obstruction risk, but otherwise similar procedural and 30-day outcomes after TAVI compared with type 1 BAV. However, the current patients with BAV that underwent TAVI were highly selected, and future studies should identify the BAV related optimal anatomies, refine sizing strategies, and best implantation techniques for TAVI.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YD, YZha, and YZho proposed the idea for the study and finished the study design. YY and SJ retrieved studies, collected and extracted data with disagreements resolved by YG and WH. YD, HS, and KH performed the meta-analysis and drafted the manuscript with a complete review by ZW and WL. All have authors read and approved the final manuscript.

FUNDING

The National Key Research and Development Program of China (2017YFC0908800), the Beijing Municipal Administration of Hospitals' Mission plan (SML20180601), the Capital's Funds for Health Improvement and Research (FH 2020-2-2063) (KM200910025012), the Beijing Municipal Natural Science Foundation (7202041), and the Beijing Municipal Health Commission (jing19-15).

REFERENCES

1. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. (2021) 77:e25–197. doi: 10.1161/CIR.0000000000000932
2. Vincent F, Ternacle J, Denimal T, Shen M, Redfors B, Delhaye C, et al. Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. *Circulation.* (2021) 143:104361. doi: 10.1161/CIRCULATIONAHA.120.048048
3. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, et al. Association between transcatheter aortic valve replacement for bicuspid vs. tricuspid aortic stenosis and mortality or stroke. *JAMA*. (2019) 321:2193–202. doi: 10.1001/jama.2019.7108
4. Halim SA, Edwards FH, Dai D, Li Z, Mack MJ, Holmes DR, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the society of thoracic surgeons/American college of cardiology transcatheter valve therapy registry. *Circulation.* (2020) 141:1071–9. doi: 10.1161/CIRCULATIONAHA.119.040333
5. U.S. Food and Drug Administration. Approval for modifying the labeling to remove the precaution regarding patients with a congenital bicuspid aortic valve for Medtronic CoreValve Evolut R System, Medtronic CoreValve Evolut PRO System, And Medtronic Evolut PRO+ System. (2020).
6. U.S. Food and Drug Administration. Approval for modifying the labeling to remove the precaution regarding patients with a congenital bicuspid aortic valve for Sapien 3 And Sapien 3 Ultra Transcatheter Heart Valves. (2020).
7. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
8. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol.* (2017) 69:2579–89. doi: 10.1016/j.jacc.2017.03.017
9. Yousef A, Simard T, Webb J, Rodés-Cabau J, Costopoulos C, Kochman J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: A patient level multi-center analysis. *Int J Cardiol.* (2015) 189:282–8. doi: 10.1016/j.ijcard.2015.04.066
10. Mangieri A, Tchetchè D, Kim WK, Pagnesi M, Sinning JM, Landes U, et al. Balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis: insights from the BEAT international collaborative registrys. *Circ Cardiovasc Interv.* (2020) 13:e008714. doi: 10.1161/CIRCINTERVENTIONS.119.008714
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71
13. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR Era. *JACC Cardiovasc Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
14. Michelena HI, Prakash SK, Della Corte A, Bissell MM, Anavekar N, Mathieu P, et al. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). *Circulation.* (2014) 129:2691–704. doi: 10.1161/CIRCULATIONAHA.113.007851
15. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol.* (2012) 60:1438–54. doi: 10.4244/EIJV8I7A121
16. 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. doi: 10.1007/s10654-010-9491-z

17. Jackson D, Law M, Stijnen T, Viechtbauer W, White IR. A comparison of seven random-effects models for meta-analyses that estimate the summary odds ratio. *Stat Med.* (2018) 37:1059–85. doi: 10.1002/sim.7588
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557
19. Liao YB, Li YJ, Xiong TY, Ou YW, Lv WY, He JL, et al. Comparison of procedural, clinical and valve performance results of transcatheter aortic valve replacement in patients with bicuspid versus tricuspid aortic stenosis. *Int J Cardiol.* (2018) 254:69–74. doi: 10.1016/j.ijcard.2017.12.013
20. Fan J, Fang X, Liu C, Zhu G, Hou CR, Jiang J, et al. Brain injury after transcatheter replacement of bicuspid versus tricuspid aortic valves. *J Am Coll Cardiol.* (2020) 76:2579–90. doi: 10.1016/j.jacc.2020.09.605
21. Forrest JK, Ramlawi B, Deeb GM, Zahr F, Song HK, Kleiman NS, et al. Transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis. *JAMA Cardiol.* (2021) 6:50–57. doi: 10.1001/jamacardio.2020.4738
22. Ielasi A, Moscarella E, Mangieri A, Giannini F, Tchetchè D, Kim WK, et al. Procedural and clinical outcomes of type 0 versus type 1 bicuspid aortic valve stenosis undergoing trans-catheter valve replacement with new generation devices: Insight from the BEAT international collaborative registry. *Int J Cardiol.* (2021) 325:109–114. doi: 10.1093/ehjci/ehaa946.2626
23. Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, et al. Transcatheter aortic valve replacement in bicuspid versus tricuspid aortic valves from the STS/ACC TVT registry. *JACC Cardiovasc Interv.* (2020) 13:1749–59. doi: 10.1016/j.jcin.2020.03.022
24. Tchetche D, de Biase C, van Gils L, Parma R, Ochala A, Lefevre T, et al. Bicuspid aortic valve anatomy and relationship with devices: the BAVARD multicenter registry. *Circ Cardiovasc Interv.* (2019) 12:e007107. doi: 10.1161/CIRCINTERVENTIONS.118.007107
25. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068
26. Kong WK, Delgado V, Poh KK, Regeer MV, Ng AC, McCormack L, et al. Prognostic implications of raphe in bicuspid aortic valve anatomy. *JAMA Cardiol.* (2017) 2:285–92. doi: 10.1001/jamacardio.2016.5228
27. Sá M, Simonato M, Van den Eynde J, Cavalcanti LRP, Alsagheir A, Tzani A, et al. Balloon versus self-expandable transcatheter aortic valve implantation for bicuspid aortic valve stenosis: A meta-analysis of observational studies. *Catheter Cardiovasc Interv.* (2021). doi: 10.1002/ccd.29538
28. Yoon SH, Lefèvre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. *J Am Coll Cardiol.* (2016) 68:1195–205. doi: 10.1016/j.jacc.2016.06.041
29. Heitkemper M, Hatoum H, Azimian A, Yeats B, Dollery J, Whitson B, et al. Modeling risk of coronary obstruction during transcatheter aortic valve replacement. *J Thorac Cardiovasc Surg.* (2020) 159:829–38.e3. doi: 10.1016/j.jtcvs.2019.04.091
30. Tarantini G, Nai Fovino L, Le Prince P, Darremont O, Urena M, Bartorelli AL, et al. Coronary access and percutaneous coronary intervention up to 3 years after transcatheter aortic valve implantation with a balloon-expandable valve. *Circ Cardiovasc Interv.* (2020) 13:e008972. doi: 10.1161/CIRCINTERVENTIONS.120.008972
31. Tarantini G, Fabris T, Cardaioli F, Nai Fovino L. Coronary access after transcatheter aortic valve replacement in patients with bicuspid aortic valve: lights and shades. *JACC Cardiovasc Interv.* (2019) 12:1190–1. doi: 10.1016/j.jcin.2019.03.031
32. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, et al. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol.* (2020) 76:1018–30. doi: 10.1016/j.jacc.2020.07.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 29 November 2021
doi: 10.3389/fcvm.2021.757190

The Predictors of Conduction Disturbances Following Transcatheter Aortic Valve Replacement in Patients With Bicuspid Aortic Valve: A Multicenter Study

Yuchao Guo[1†], Dao Zhou[1†], Mengqiu Dang[1], Yuxing He[1], Shenwei Zhang[2], Jun Fang[3], Shili Wu[4], Qiong Huang[5], Lianglong Chen[3], Yiqiang Yuan[5], Jiaqi Fan[1], Hasan Jilaihawi[6], Xianbao Liu[7] and Jian'an Wang[7*]*

[1] Department of Cardiology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2] Department of Cardiology, Zhengzhou Cardiovascular Hospital (The Seventh People' Hospital of Zheng Zhou), Zhengzhou, China, [3] Department of Cardiology, Fujian Heart Medical Center, Fujian Institute of Coronary Heart Disease, Fujian Medical University Union Hospital, Fuzhou, China, [4] Department of Cardiology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China, [5] Department of Cardiology, Henan Provincial Chest Hospital, Zhengzhou, China, [6] Heart Valve Center, NYU Langone Health, New York City, NY, United States, [7] Department of Cardiology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

OPEN ACCESS

Edited by:
Paolo Denti,
San Raffaele Hospital (IRCCS), Italy

Reviewed by:
Marco Ancona,
San Raffaele Hospital (IRCCS), Italy
Gidon Yehuda Perlman,
Hadassah Medical Center, Israel

***Correspondence:**
Xianbao Liu
liuxb@zju.edu.cn
Jian'an Wang
wangjianan111@zju.edu.cn

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: 11 August 2021
Accepted: 15 October 2021
Published: 29 November 2021

Citation:
Guo Y, Zhou D, Dang M, He Y, Zhang S, Fang J, Wu S, Huang Q, Chen L, Yuan Y, Fan J, Jilaihawi H, Liu X and Wang J (2021) The Predictors of Conduction Disturbances Following Transcatheter Aortic Valve Replacement in Patients With Bicuspid Aortic Valve: A Multicenter Study. Front. Cardiovasc. Med. 8:757190. doi: 10.3389/fcvm.2021.757190

Objective: To evaluate the predictors of new-onset conduction disturbances in bicuspid aortic valve patients using self-expanding valve and identify modifiable technical factors.

Background: New-onset conduction disturbances (NOCDs), including complete left bundle branch block and high-grade atrioventricular block, remain the most common complication after transcatheter aortic valve replacement (TAVR).

Methods: A total of 209 consecutive bicuspid patients who underwent self-expanding TAVR in 5 centers in China were enrolled from February 2016 to September 2020. The optimal cut-offs in this study were generated from receiver operator characteristic curve analyses. The infra-annular and coronal membranous septum (MS) length was measured in preoperative computed tomography. MSID was calculated by subtracting implantation depth measure on postoperative computed tomography from infra-annular MS or coronal MS length.

Results: Forty-two (20.1%) patients developed complete left bundle branch block and 21 (10.0%) patients developed high-grade atrioventricular block after TAVR, while 61 (29.2%) patients developed NOCDs. Coronal MS <4.9 mm (OR: 3.08, 95% CI: 1.63–5.82, $p = 0.001$) or infra-annular MS <3.7 mm (OR: 2.18, 95% CI: 1.04–4.56, $p = 0.038$) and left ventricular outflow tract perimeter <66.8 mm (OR: 4.95 95% CI: 1.59–15.45, $p = 0.006$) were powerful predictors of NOCDs. The multivariate model including age >73 years (OR: 2.26, 95% CI: 1.17–4.36, $p = 0.015$), Δcoronal MSID < 1.8 mm (OR: 7.87, 95% CI: 2.84–21.77, $p < 0.001$) and prosthesis oversizing ratio on left ventricular outflow tract >3.2% (OR: 3.42, 95% CI: 1.74–6.72, $p < 0.001$)

showed best predictive value of NOCDs, with c-statistic = 0.768 (95% CI: 0.699–0.837, $p < 0.001$). The incidence of NOCDs was much lower (7.5 vs. 55.2%, $p < 0.001$) in patients without Δcoronal MSID < 1.8 mm and prosthesis oversizing ratio on left ventricular outflow tract >3.2% compared with patients who had these two risk factors.

Conclusion: The risk of NOCDs in bicuspid aortic stenosis patients could be evaluated based on MS length and prosthesis oversizing ratio. Implantation depth guided by MS length and reducing the oversizing ratio might be a feasible strategy for heavily calcified bicuspid patients with short MS.

Keywords: bicuspid aortic stenosis, conduction disturbances, TAVR–transcatheter aortic valve replacement, membranous septum, oversizing ratio

INTRODUCTION

New-onset conduction disturbances (NOCDs) such as complete left bundle branch block and high-grade atrioventricular block are common complications after transcatheter aortic valve replacement (TAVR), which may result in permanent pacemaker implantation (PPMI). Despite rapid advances in procedure techniques and new generation prosthesis, the rates of new-onset complete left bundle branch block (10.5–52.3%) and PPMI (2.3–36.1%) after TAVR remain high, especially in TAVR with self-expanding valve (1–4). NOCDs and PPMI were previously believed to mainly impair mid-term improvement of left ventricular remodeling or left ventricular ejection fraction after TAVR (4, 5). However, a recent pooled analysis suggested that new-onset persistent left bundle branch block and permanent pacemaker implantation were associated with the increased risks of 1-year heart-failure rehospitalization and all-cause mortality (3).

The pre-procedural NOCDs risk assessment before TAVR is crucial for procedural planning both for elder patients prone to conduction disturbances or younger recipients with long life expectancy. Baseline conduction disturbances, such as pre-existing right bundle branch block and left bundle branch block, are traditional predictors of NOCDs (2). More recently, studies have suggested that anatomy and procedural factors regarding membranous septum length (MS), device landing zone calcification, and implantation depth are associated with NOCDs. In a recent study, Jilaihawi et al. (6) provided a useful prediction model and procedural strategy to minimize PPMI in patients with tricuspid aortic valve who underwent self-expanding TAVR. Nevertheless, data on predictors and strategies to reduce NOCDs in severe aortic stenosis patients with bicuspid aortic valve (BAV) are limited (7). A recent propensity-matched study from Hamdan et al. (7) reported that MS length was shorter in BAV patients and associated with increased risk of conduction disturbances. On the other hand, over the past few years, undersizing of prosthesis especially in highly calcified bicuspid patients has been a topic. Several supra-annular sizing methods have been raised to select a smaller prosthesis with few paravalvular leakage and high device success (8–10), which might theoretically lower the incidence of conduction disturbances. Consequently, we performed this study to evaluate predictors of NOCDs in BAV patients using self-expanding valve.

Abbreviations: BAV, Bicuspid aortic valve; TAVR, Transcatheter aortic valve replacement; NOCDs, New-onset conduction disturbances; CLBBB, Complete left bundle branch block; ID, Implantation depth; MS, Membranous septum; LVOT, Left ventricular outflow tract; MSID, Membranous septum minus Implantation depth; PPMI, Permanent pacemaker implantation.

MATERIALS AND METHODS

Study Population and Procedure

A total of 520 consecutive patients who underwent TAVR for severe aortic stenosis in 5 centers in China were retrospectively included from February 2016 to September 2020. Two hundred forty-four BAV patients were identified by two experienced cardiologists (YH and QZ) and were confirmed by two authors (YG and DZ) following Jilaihawi's classification (11, 12). In this study, the term "Type 0" was equivalent to "bicommissural non-raphe-type," and "Type 1" was considered same as "bicommissural raphe-type," while the term "Tricommissural BAV (T-BAV)" was equally used to describe Tricommissural raphe-type BAV (11). After excluding 35 patients based on the following exclusion criteria: 1) with prior pacemaker implantation ($n = 3$); 2) needed urgent transfer to open surgery ($n = 5$); 3) with poor pre-operative CT imaging quality ($n = 2$); 4) using balloon-expandable valve or mechanically-expandable valve ($n = 23$); 5) suffering perioperative death ($n = 1$), a total of 209 BAV patients were included in our study (**Figure 1**). Written informed consent was obtained from each participant. The study was approved by the local ethics committee and complied with the Declaration of Helsinki.

In our study, pre-operative electrocardiography was performed in all patients. Holter monitoring was performed in high risk patients to identify potential pre-operative cardiac arrhythmia. The decision to perform TAVR was made by a multidisciplinary heart team. Most TAVR procedures were completed through transfemoral access under general anesthesia. self-expanding valves including Venus A (Venus Medtech, Hangzhou, China), Vitaflow (Microport, Shanghai, China), TaurusOne (Peijia Medical, Suzhou, China), and their series were used in this study. The selection of valve size was made by the heart team based on preoperative cardiac computed tomography (CT) analysis and the fluoroscopy during balloon

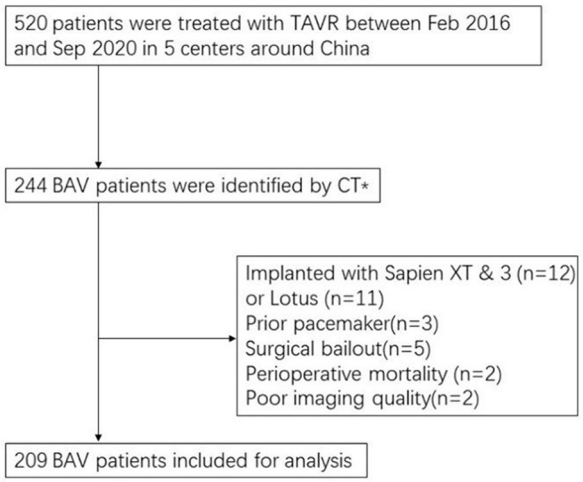


FIGURE 1 | Flow chart of study population. TAVR, Transcatheter aortic valve replacement. *CT classification: bicuspid patients were classified into "bicommissural non-raphe-type," "bicommissural raphe-type," and "tricommissural raphe-type BAV" according to pre-procedural multislice computed tomography.

valvuloplasty. A modified Supra-annular structure assessment method by balloon sizing was recommended for all operators in this study (8). Patients underwent balloon valvuloplasty with a Z-Med balloon (NuMED, Hopkinton, NY). The Z-med balloon size was determined based on the lowest range of annulus perimeter driven diameter. For example, a 20-mm Z-Med balloon was used in annulus perimeter driven diameter range of 20–23 mm. Smaller balloon size was recommended in case of potential risk of annular rupture. If waist sign on the balloon and less than mild regurgitation were simultaneously observed with a contrast injection, a smaller prosthesis other than manufacturer recommendation was chosen based on the balloon size.

Post-procedural electrocardiogram monitoring or remote monitoring was routinely used. Echocardiography and electrocardiography were performed before discharge and at 1 months' follow-up. Also, cardiac contrast-enhanced electrocardiography-gated CT was performed before discharge or at 1-month examination in most patients. Left bundle branch block and high-grade atrioventricular block in our study were defined as reported in a previous study (13). Patients with NOCDs were defined as patients with new-onset persistent complete left bundle branch block or with high-grade atrioventricular block before discharge.

Image Aquasition and Analysis

Cardiac contrast-enhanced electrocardiography-gated multidetector computed tomography (MDCT) was performed on PHILIPS Brilliance iCT 256 or GE Revolution CT using collimation of 0.6 or 0.8 mm, 100 or 120 kV. Fluoroscopy was recorded with a classic coplanar view after valve final deployment to assess final prosthesis depth at NCC (non-coronary cusp). CT or fluoroscopy imaging were analyzed by two authors (YG and DZ) applying a single-blind method, with CT's measurement on 3 mensio Valves software version 9.1/10.0 (Bilthoven, the Netherlands) and fluoroscopy on RadiAnt DICOM Viewer Software version 2020.1 (Medixant, Poznan, Poland). A tertiary researcher (YH) analyzed the imaging separately in the situation of great difference on image analysis.

The length of infra-annular MS was measured as the distance from the annulus to the vertex of the muscular ventricular septum on stretch vessel imaging close to the tricuspid valve insertion point. Coronal MS lengths were measured in the coronal view, as previously described (6, 14). Device's implantation depth (ID) was measured on post-operative CT from the plane where the prosthesis metal stent disappeared (in line with the MS) to the annulus. Implantation depth measured on post-release fluoroscopy was also evaluated on NCC direction (6, 15) (**Figure 2**). The ΔMSID or Δcoronal MSID was calculated by subtracting implantation depth from infra-annular MS or coronal MS length. The severity of valve calcification was classified as grade 1 to 4, and the calcification of LVOT plane was described in a qualitative fashion and graded as none, mild, moderate, or severe, as described in previous studies (16, 17). The oversizing ratio was calculated using device geometrical data from manufacturers by the following formulas: *oversizing by area (%) = (prosthesis inflow nominal area/measured area − 1) × 100%*, and *oversizing by perimeter (%) = (prosthesis inflow nominal perimeter/measured perimeter − 1) × 100%* (18–20).

Statistical Analysis

Category variables were presented as numbers (%) and were tested by Chi-square or Fisher exact test. Continuous variables were expressed as mean ± standard deviation or median [interquartile range (IQR)] and were compared with Student's *t*-test or Mann Whitney *U*-test based on distribution type tested by Shapiro-Wilk test. Correlation analysis was conducted on prosthesis depth measured on CT and fluoroscopy, coronal MS and infra-annular MS, as well as ΔMSID and coronal ΔMSID using Spearman correlation test. A 2-tailed $P < 0.05$ was considered as a significant difference. The optimal cut-off values of continuous variables were determined by receiver operating characteristic (ROC) analysis. The variables with a $P < 0.05$ in univariate regression analyses were entered into multivariate logistic regression models with forward likelihood ratio method, which contained pre-operative variables or included both pre- and post-operative variables. All statistical analyses were performed using SPSS software version 20.0 (IBM, Armonk, New York).

RESULTS

Patients' Baseline Characteristics

Baseline clinical characteristics and CT measurement results are shown in **Tables 1**, **2**. The mean age of the population was 75.12 ± 6.79, and the median Society of Thoracic Surgeons (STS) score was 5.487 (3.626–9.052). Among 209 patients, 99 (47.4%) had type 0, 79 (37.8%) had type 1 and 31 (14.8%) had tricommissural BAV. Most baseline characteristics were similar between three

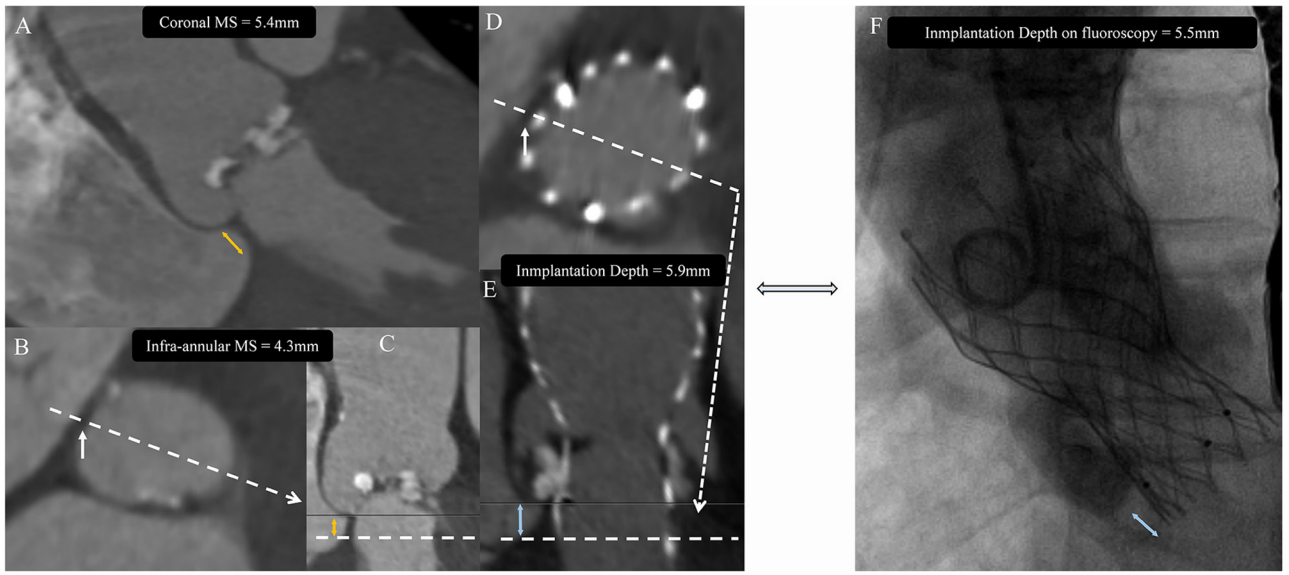


FIGURE 2 | Image analysis protocol. The membranous septum (MS) was measured on coronal view **(A)** as coronal MS or on stretched vessel view **(C)** as infra-annular MS at the tricuspid insertion point **(B)**. Device's implantation depth (ID) was measured on post-operative CT **(D,E)** and was compared with the measurement on post-releasing fluoroscopy **(F)**. Yellow double arrow indicates membranous septum length (MS). White arrow indicates tricuspid insertion point. Blue double arrow indicates prosthesis implantation depth (ID).

different types of BAV except for some differences in anatomy measurement (**Supplementary Tables 1A–C**).

Procedural Characteristics and Relevant Outcomes

Most patients (205, 98.1%) underwent TAVR through transfemoral access, and the remaining 4 patients through transcarotid access. First-generation self-expanding valves were used in 174 (83.3%) patients, while next-generation valve with recapturable features was used in 35(16.7%) patients. One hundred fifty-eight (75.6%) patients received undersized prosthesis based on supra-annular balloon sizing. A total of 204 (97.6%) patients received pre-dilatation and 150 (71.8%) patients underwent post-dilatation. The overall pre-discharge mortality rate was 0.5%; in-hospital stroke rate was 1%, and the rate of second prosthesis implantation was 8.1%. Forty-two (20.1%) patients developed complete left bundle branch block and 21 (10.0%) patients developed high-grade atrioventricular block after TAVR, while 61 (29.2%) patients developed NOCDs. Sixteen (7.7%) patients received pacemaker implantation during the hospital stay, and 1 patient needed pacemaker implantation for high-grade atrioventricular block after discharge (10 days after discharge). The detailed pre- and post- operative arrhythmic characteristics of patients with new-onset high-grade atrioventricular block are described in **Supplementary Table 2**. In a single center analysis of 161 patients recruited in Second Affiliated Hospital Zhejiang University School of Medicine. The VARC-2 device success rate (absence of procedural mortality AND correct positioning of a single valve AND mean gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe regurgitation) was 84.5%, with 13 (8.1%) cases of moderate PVL. Mean post-procedural gradient was 12.5 ± 6.8 mmHg.

MS Length: Reproducibility

The reproducibility of coronal MS and infra-annular MS length measurement was assessed by comparing repeated measures of 18 randomly selected consecutive cases, which were performed by two experienced observers (YG and DZ). The paired samples correlation coefficient of interobserver measurements of coronal MS and infra-annular MS length was 0.855 ($p < 0.001$), 0.976 ($p < 0.001$), respectively. The paired difference was 0.383 mm [95% confidence interval (CI): −0.050–0.818 mm, $p = 0.080$), 0.206 mm (95% CI: −0.012–0.423 mm, $P = 0.063$), respectively. For intraobserver measurements, the paired samples correlation coefficient was 0.883 ($p < 0.001$), 0.982 ($p < 0.001$) and the paired difference was 0.278 mm (95% CI: −0.109–0.665 mm, $p = 0.148$), −0.167 mm (95% CI: −0.356–0.022 mm, $p = 0.082$), respectively.

Membranous Septum and Implantation Depth Measurement Results

The overall median coronal MS was 5.7 [Interquartile range (IQR): 4.7–7.0] mm and the median infra-annular MS was 2.3 (IQR: 1.2–3.9) mm. In the intergroup analysis, Type 0 BAV patients had a shorter coronal MS compared with Type 1 BAV and T-BAV (5.58 ± 1.92 vs. 6.31 ± 2.25 mm, $p = 0.022$; 5.58 ± 1.92 vs. 6.44 ± 2.04 mm, $p = 0.046$) while no difference could be found in infra-annular MS between three groups (**Supplementary Table 1C**). Besides, correlations between coronal MS and infra-annular MS were moderate ($R = 0.515$; $P < 0.01$, **Supplementary Figure 1A**). The mean implantation depth on fluoroscopy or CT was 6.84

TABLE 1 | Baseline clinical characteristics of bicuspid aortic stenosis patients and NOCDs.

	Total ($n = 209$)	No NOCDs ($n = 148$)	NOCDs ($n = 61$)	p-value
Baseline clinical variables				
Age, yrs	75.12 ± 6.79	74.41 ± 6.83	76.85 ± 6.41	**0.017**
Male	128 (61.2%)	96 (64.9%)	32 (52.5%)	0.094
Body mass index, kg/m^2	22.53 ± 3.11	22.66 ± 3.19	22.23 ± 2.89	0.364
Diabetes mellitus	41 (19.6%)	24 (16.2%)	17 (27.9%)	0.054
Hypertension	100 (47.8%)	68 (45.9%)	32 (52.5%)	0.391
Chronic obstructive pulmonary disease	43 (20.6%)	30 (20.3%)	13 (21.3%)	0.866
Chronic kidney disease stage 4–5	4 (1.9%)	4 (2.7%)	0 (0%)	0.324
NYHA classification				0.562
II	24 (11.5%)	15 (10.1%)	9 (14.8%)	
III	105 (50.2%)	77 (52%)	28 (45.9%)	
IV	80 (38.3%)	56 (37.8%)	24 (39.3%)	
STS score, %	5.487 (3.626–9.052)	5.485 (3.697–9.295)	5.487 (3.425–8.882)	0.632
Baseline electrocardiographic variables				
Atrial fibrillation/flutter	32 (15.3%)	22 (14.9%)	10 (16.4%)	0.780
Pre-existing LBBB	18 (8.6%)	18 (12.2%)	0 (0%)	–
Pre-existing RBBB	17 (8.1%)	9 (6.1%)	8 (13.1%)	0.101
Baseline echocardiographic variables				
Mean gradient, mmHg	56.0 (43.0–70.5)	56.5 (43.0–72.5)	53.0 (42.0–70.0)	0.428
Max velocity, m/s	4.90 (4.25–5.52)	4.89 (4.24–5.42)	4.90 (4.25–5.53)	0.970
Aortic regurgitation grade				0.747
None	43 (20.6%)	30 (20.3%)	13 (21.3%)	
Mild	104 (49.8%)	71 (48.0%)	33 (54.1%)	
Moderate	43 (20.6%)	32 (21.6%)	11 (18%)	
Severe	19 (9.1%)	15 (10.1%)	4 (6.6%)	
LVEF, %	57.0 (46.0–63.4)	55.9 (42.3–63.0)	58.8 (50.9–64.5)	0.127

Values are presented as mean ± SD or median (Quartile1–Quartile3) or n (%). p-values in bold are statistically significant.
NOCDs, new-onset conduction disturbances; NYHA, New York heart association; LBBB, left bundle branch block; RBBB, right bundle branch block; STS, society of thoracic surgeons; LVEF, left ventricular ejection fraction.

± 4.36 or 6.37 ± 4.11 mm, respectively. There was a significant positive correlation between implantation depth measured by fluoroscopy and by CT ($R = 0.761$; $P < 0.01$, **Supplementary Figure 1B**).

Patients and Procedural Predictors of Conduction Disturbances and PPMI

Baseline predictors of NOCDs were advanced age and smaller aortic root anatomy, including LVOT and ascending aorta (**Tables 1**, **2**). Notably, patients who developed NOCDs had a significantly shorter coronal MS [5.1 (IQR: 4.1–6.3) mm vs. 6.0 (IQR: 5.0–7.2) mm, $p < 0.001$] compared with no NOCDs patients while no difference of infra-annular MS length could be found between two groups [2.3 (IQR: 1.5–3.4) mm vs. 2.3 (IQR: 1.0–4.1) mm, $p = 0.747$]. However, the proportion of infra-annular MS length <3.7 mm was higher in the NOCDs group (82.0 vs. 67.6%, $p = 0.036$) with the optimal cut-off determined by ROC curve. More patients with coronal MS length <4.9 mm could also be found in NOCDs groups (45.9 vs. 21.6%, $p < 0.001$). Besides, after dividing coronal MS into four quartiles, we found a significant inverse distribution of NOCDs between the four groups. Twenty-four (39.3%) out of 61 NOCDs and 8 (50.0%) out of 16 PPMI occurred in coronal ≤4.7 mm (less than the first quartile, Q1) while 7 (11.5%) NOCDs and 0 (0.0%) PPMI occurred in coronal MS >7 mm (more than the third quartiles) (**Figure 3**). When considering the procedural factors, we found that oversizing ratio by annulus or LVOT, implantation depth, ΔMSID, and Δcoronal MSID were predictors of NOCDs (**Table 3**).

Univariate and Multivariate Predictors of New-Onset Conduction Disturbances

Table 4 shows multivariate analysis results of predictors of NOCDs. The preprocedural multivariate logistic regression models revealed that age >73 years old, LVOT perimeter <66.8 mm, and Coronal MS <4.9 mm or infra-annular MS <3.7 mm were independent predictors of NOCDs. When taking post-procedural variables into consideration, the multivariate model including age, Δcoronal MSID, and oversizing by LVOT perimeter showed the best predictive value of NOCDs, with c-statistics = 0.768 (95% CI: 0.699–0.837, p < 0.001). Besides, age > 73 years old, ΔMSID <-2.9 mm and oversizing by LVOT perimeter >3.2% were independent predictors of NOCDs in another model, which also had a good predictive value

TABLE 2 | Computed tomography characteristics of bicuspid aortic stenosis patients and NOCDs.

	Total (n = 209)	No NOCDs (n = 148)	NOCDs (n = 61)	p-value
BAV classification				0.652
Type 0	99 (47.4%)	70 (47.3%)	29 (47.5%)	
Type 1	79 (37.8%)	58 (39.2%)	21 (34.4%)	
T-BAV	31 (14.8%)	20 (13.5%)	11 (18.0%)	
Valve calcification grade, class III or IV	177 (84.7%)	127 (85.8%)	50 (82.0%)	0.483
Annulus area, mm^2	457.3 (408.3–525.8)	466 (405.4–549.4)	440.5 (408.7–509.4)	0.077
Annulus area derived diameter, mm	24.1 (22.8–25.9)	24.4 (22.7–26.5)	23.7 (22.9–25.5)	0.082
Annulus perimeter, mm	77.2 (73.2–82.9)	77.6 (73.2–84.5)	75.7 (73.2–81.2)	0.072
Annulus perimeter derived diameter, mm	24.6 (23.3–26.4)	24.7 (23.3–26.9)	24.1 (23.3–25.8)	0.065
Annular eccentricity index	0.23 ± 0.07	0.23 ± 0.07	0.23 ± 0.07	0.819
LVOT area, mm^2	488.9 (400.2–602.8)	496.6 (412.6–611.4)	461.5 (389.8–564.7)	**0.041**
LVOT area derived diameter, mm	25.0 (22.6–27.7)	25.2 (22.9–27.9)	24.2 (22.3–26.9)	**0.041**
LVOT perimeter, mm	83.8 (75.4–92.7)	84.6 (76.5–94.1)	80.9 (73.9–88.3)	**0.032**
LVOT perimeter derived diameter, mm	26.4 (23.9–29.1)	26.8 (23.9–29.3)	25.1 (23.7–28.5)	0.058
LVOT eccentricity index	0.31 ± 0.08	0.31 ± 0.09	0.32 ± 0.08	0.372
LVOT calcification	36 (17.2%)	30 (20.3%)	6 (9.8%)	0.069
LVOT/annulus perimeter ratio	1.06 ± 0.17	1.07 ± 0.17	1.03 ± 0.17	0.139
LVOT/annulus area ratio	1.04 ± 0.10	1.05 ± 0.10	1.03 ± 0.10	0.316
SOV mean diameter, mm	32.97 ± 3.53	33.15 ± 3.63	32.55 ± 3.25	0.268
STJ average diameter, mm	31.4 (29.0–34.4)	31.6 (29.0–34.8)	30.7 (28.7–33.5)	0.287
STJ height, mm	22.6 (20.0–26.1)	22.8 (20.4–26.3)	21.6 (19.5–25.0)	0.115
Ascending aorta diameter, at 40 mm	38.85 ± 3.88	39.06 ± 3.83	38.33 ± 4.00	0.221
Ascending aorta diameter, Max	42.62 ± 4.68	43.02 ± 4.68	41.63 ± 4.55	**0.050**
RCA height, mm	16.9 (14.9–19.4)	17.2 (15.1–19.8)	16.3 (14.1–19.0)	0.069
LCA height, mm	15.4 (13.3–18.4)	15.7 (13.2–18.3)	14.9 (13.3–18.9)	0.717
Aortic root angulation	52.82 ± 10.49	53.18 ± 9.96	51.93 ± 11.71	0.435
Infra-annular MS length, mm	2.3 (1.2–3.9)	2.3 (1.0–4.1)	2.3 (1.5–3.4)	0.747
Infra-annular MS length < 3.7 mm	150 (71.8%)	100 (67.6%)	50 (82.0%)	**0.036**
Coronal MS length, mm	5.7 (4.7–7.0)	6.0 (5.0–7.2)	5.1 (4.1–6.3)	**<0.001**
Coronal MS length < 4.9 mm	60 (28.7%)	32 (21.6%)	28 (45.9%)	**<0.001**

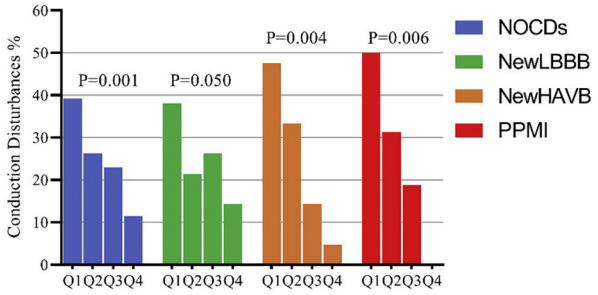
Values are presented as mean ± SD or median (Quartile1–Quartile3) or n (%). p-values in bold are statistically significant. BAV, bicuspid aortic valve; T-BAV, tricommissural bicuspid aortic valve; LVOT, left ventricular outflow tract; SOV, sinus of Valsalva; STJ, sinotubular junction; LCA, left coronary height; RCA, right coronary artery; MS, membranous septum; other abbreviations as in ***Table 1****.*

with c-statistics = 0.752 (95% CI: 0.679–0.824, $p < 0.001$). The detail comparison between predictive models was shown in **Supplementary Table 3**, which suggested a better predictive value of the model including MS measured on coronal view. According to our pre-operative multivariate model, patients could be classified as low, intermediate and high risk of NOCDs with the prevalence rates of 19.9, 46.8, 66.7% (**Figure 4**). When considering implantation depth and oversizing ratio by LVOT perimeter which could be mediated by operators, low, intermediate and high risk patients had rates of NOCDs of 7.5, 23.4, 55.2% (**Figure 4**).

Subgroup Analysis of New High-Grade Atrioventricular Block or Implantation Depth Deeper Than MS Group

We also conducted a subgroup analysis focusing on new-onset high-grade atrioventricular block. The patients in new-onset high-grade atrioventricular block group had a higher rate of pre-existing right bundle branch block (33.3 vs. 5.3%, $p < 0.001$), shorter coronal MS [4.8 (IQR: 4.1–5.5) vs. 5.9 (IQR: 4.8–7.1), $p = 0.003$] and larger oversizing ratio by LVOT perimeter (4.59 ± 12.89 vs. −1.89 ± 12.82, $p = 0.029$) compared with the control group (**Supplementary Table 4A**). In univariate logistic regression analysis, coronal MS, pre-existing right bundle branch block, pre-dilatation and oversizing by LVOT perimeter were independent predictors of high-grade atrioventricular block, while pre-existing right bundle branch block (OR: 8.36, 95% CI: 2.50–27.89, $p = 0.001$), coronal MS < 5.5 mm (OR:5.78, 95% CI: 1.75–19.12, $p = 0.004$) and oversizing ratio by LVOT perimeter >6.4% (OR: 3.80, 95% CI: 1.38–10.50, $P = 0.010$) remained powerful predictors in multivariate regression model with c-statistics = 0.805 (95% CI: 0.699–0.911, $p < 0.001$, **Supplementary Table 4B**).

In a subgroup analysis of patients with implantation depth larger than infra-annular MS, diabetes mellitus, older age,



Quartile rang	Q1	Q2	Q3	Q4	P for Trend
Coronal MS(mm)	≤4.7	4.7~5.7	5.7~7	> 7	
NOCDs	39.3%	26.2%	23.0%	11.5%	0.001
New LBBB	38.1%	21.4%	26.2%	14.3%	0.050
New HAVB	47.6%	33.3%	14.3%	4.8%	0.004
PPMI	50.0%	31.3%	18.8%	0.0%	0.006

FIGURE 3 | Incidence of NOCDs according to quartiles of coronal MS. MS, membranous septum; LBBB, left bundle branch block; HAVB, high-grade.

smaller aortic root morphology, and the larger oversizing ratio of prosthesis might contribute to new conduction disturbances (**Supplementary Table 5A**). We found that in this population, ΔMSID (OR: 0.97, 95% CI: 0.89–1.05, $p = 0.968$) was no longer an independent predictor. In multivariate logistic analysis, only age (OR: 1.07, 95% CI: 1.01–1.12, $p = 0.020$) and prosthesis oversizing ratio of LVOT perimeter (per 1%, OR: 1.05, 95% CI: 1.02–1.08, $p = 0.001$) remained strong predictors for new conduction disturbances (**Supplementary Table 5B**).

DISCUSSION

The main findings of the present study are following: 1) a model including age, LVOT perimeter, and coronal MS yielded best pre-procedural predictive value for NOCDs, while a model that included age, oversizing ratio by LVOT perimeter, and Δcoronal MSID had a best predictive value of NCODs; 2) the risk of NOCDs in BAV patients could be evaluated before TAVR

TABLE 3 | Procedural characteristics and conduction abnormalities.

	Total ($n = 209$)	No NOCDs ($n = 148$)	NOCDs ($n = 61$)	*p*-value
Oversizing by annulus perimeter, %	4.9 ± 8.7	3.8 ± 9	7.7 ± 7.2	**0.003**
Oversizing by annulus area, %	15.8 ± 19.4	13.4 ± 20.1	21.6 ± 16.6	**0.005**
Oversizing by LVOT perimeter, %	−1.2 ± 12.9	−3.1 ± 12.5	3.2 ± 13.0	**0.001**
Oversizing by LVOT area, %	9.1 (−7.8, 29.6)	7.0 (−10.0,26.1)	18.6 (2.6, 37.3)	**0.002**
Pre-dilatation	204 (97.6%)	145 (98%)	59 (96.7%)	0.630
Post-dilatation	150 (71.8%)	106 (71.6%)	44 (72.1%)	0.941
Second valve implantation	17 (8.1%)	10 (6.8%)	7 (11.5%)	0.273
Post-conduction disturbances				
Post-new LBBB	42 (20.1%)	0 (0%)	42 (68.9%)	
Post-new RBBB	6 (2.9%)	5 (3.4%)	1 (1.6%)	
Post-new HAVB	21 (10.0%)	0 (0.0%)	21 (34.4%)	
Post-PPMI	16 (7.7%)	0 (0.0%)	16 (26.2%)	
Implant depth, mm	6.3 (3.9, 9.0)	5.4 (3.7, 8.8)	7.3 (5.1, 10.2)	**0.005**
ΔMSID, mm	−4.0 (−6.6, −1.3)	−3.0 (−6.5, −0.6)	−5.1 (−7.3, −3.1)	**0.006**
Implant depth > Infra-annular MS length	173 (82.8%)	116 (78.4%)	57 (93.4%)	**0.009**
Δcoronal MSID, mm	−0.86 ± 4.85	−0.17 ± 5.07	−2.56 ± 3.78	**<0.001**

Values are presented as mean ± SD or median (Quartile1, Quartile3) or n (%). P-values in bold are statistically significant.
*HAVB, high-grade atrioventricular block; PPMI, permanent pacemaker implantation; ΔMSID, infra-annular MS length minus implantation depth on CT; Δcoronal MSID, coronal MS length minus implantation depth on CT; other abbreviations as in **Tables 1**, **2**.*

TABLE 4 | Multivariate logistic regression for predictors of new-onset conduction disturbances.

	Multivariate analysis					
	Pre-procedural				Pre- and post-procedural	
	p-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)
Age > 73 yrs	0.024	2.18 (1.11–4.28)	0.019	2.29 (1.15–4.56)	0.002	3.07 (1.49–6.31)
LVOT perimeter <66.8 mm	0.013	4.39 (1.37–14.00)	0.019	4.09 (1.26–13.32)	–	–
Infra-annular MS < 3.7 mm	0.040	2.22 (1.04–4.77)	–	–	–	–
Coronal MS < 4.9 mm	–	–	0.001	3.14 (1.61–6.10)	–	–
Δcoronal MSID < 1.8 mm	–	–	–	–	<0.001	7.87 (2.84–21.77)
Oversizing by LVOT perimeter >3.2%	–	–	–	–	<0.001	3.42 (1.74–6.72)

Multivariate logistic regression included parameters with a $p < 0.05$ without significant multicollinearity using forward Likelihood Ratio method.
*OR, odds ratio; CI, confidence interval; other abbreviations as in **Tables 1**–**3**.*

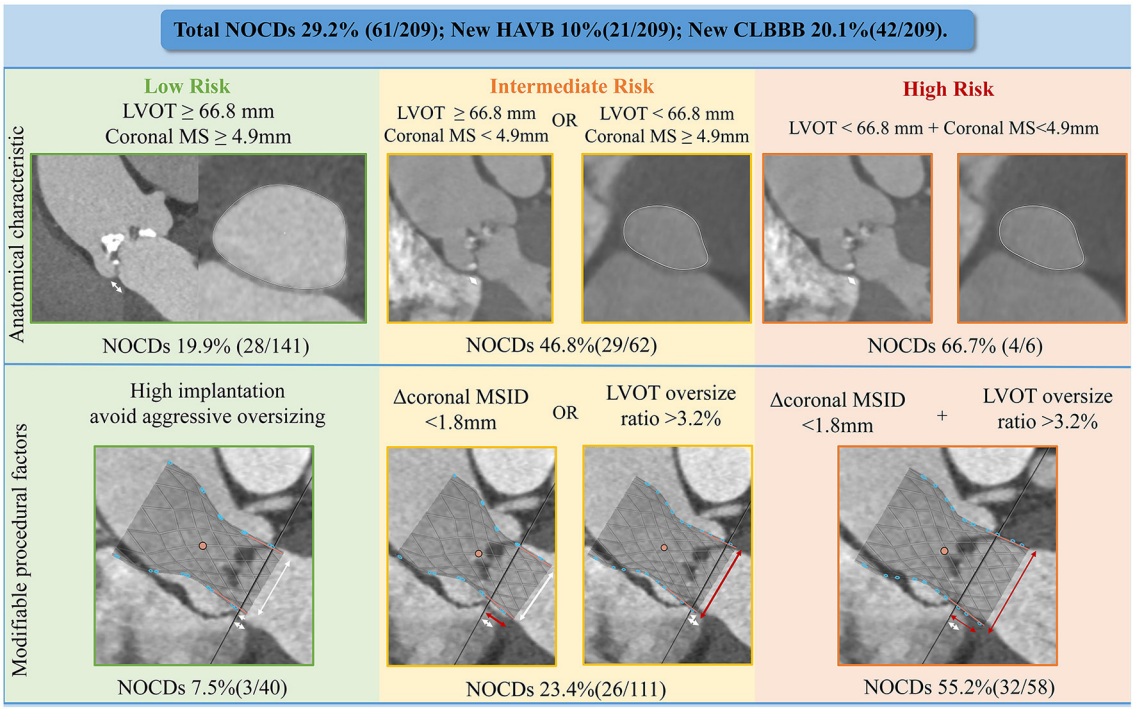


FIGURE 4 | Predictive model of NOCDs. NOCDs, new-onset conduction disturbances; HAVB, high-grade atrioventricular block; CLBBB, complete left bundle branch block; LVOT, left ventricular outflow tract; Δcoronal MSID, coronal MS length minus implantation depth on CT.

procedure based on MS length and LVOT perimeter 3) MS length guide implantation with reduced size valve could be a feasible way to reduce the risk of NOCDs for BAV patients with short MS.

The clinical impact of PPMI and new-onset left bundle branch block after TAVR remains unclear. However, Faroux L's meta-analysis highlighted the adverse clinical impact of NOCDs (3). Recent data also indicated that the incidence of PPMI was still high and highly variable (21–24). The bicuspid aortic valve, previously thought of as a contraindication for TAVR owing to its anatomy, was gradually considered safe and feasible for TAVR (25–27). The rates of BAV in the normal population have been reported to be 0.5–2%, while BAV was quite common in patients who underwent surgical aortic valve replacement for aortic stenosis with the prevalence rate of almost 50% (28, 29). In our study, 244 out of 520 (46.9%) patients were consecutive BAV patients (6, 12) (**Supplementary Tables 1A–C**). Besides, BAV patients were often younger, which means they had more chance of suffering the adverse impact of NOCDs (30). Previous studies also suggested higher or similar risks of PPMI in BAV patients (31–33). In addition, self-expanding valves were widely used in clinical practice and were considered to have a significantly higher risk of PPMI than balloon-expandable valves (34). Nonetheless, the data presented here showed a postoperative new-onset high-grade atrioventricular block rate of 10.0% and a complete left bundle branch block rate of 20.1% in BAV patients, which suggested the acceptable NOCDs risks in our BAV populations. Accordingly, the present study aimed to identify predictors of NOCDs in BAV patients treated with SEV and potentially minimizing strategy. To the best of our knowledge, this is the first multicenter study that evaluated the predictors of NOCDs in a population with BAV using the self-expanding valve.

The Membranous Septum and Implantation Depth

The relationship between NOCDs and anatomy factors, especially the membranous septum, has received increasing attention over recent years. It has been reported that the bundle was located at the edge of the membranous septum, then emerging as a left bundle branch near or beneath the LVOT (35). Different types of NOCDs occurred when corresponding bundle of his branches were oppressed and damaged by prosthesis metal stent or tissue edema (35).

The left bundle branch was vulnerable with a short MS. In our study, both infra-annular and coronal MS lengths were measured. The overall coronal MS 5.7 (IQR 4.7–7.0) mm and infra-annular MS 2.3(IQR: 1.2–3.9) mm were numerical shorter than previously reported tricuspid population, which was in accordance with Hamdan A's finding (6, 7, 36). The high predictive value of coronal MS suggested that clinicians should evaluate BAV patients' coronal MS length before TAVR procedure, which could be measured directly on Picture Archiving and Communication Systems. In addition to MS length, the distance between the membranous septum and implantation depth was a more important predictor of

NOCDs. We found a Δcoronal MSID of 1.8 mm had the best discriminating abilities for NOCDs. The lower rate of NOCDs (8.5 vs. 37.3%, $p < 0.001$) in the group with Δcoronal MSID $\geqq$ 1.8 mm revealed a satisfactory result in self-expanding TAVR for BAV patients. The conduction disturbance incidence in these patients was as low as or even lower than published data in tricuspid patients (1–4). It suggested that releasing prosthesis at a proper height based on MS length was an effective method to reduce the risk of NOCDs. Besides, MS guided prosthesis implantation avoided blindly higher implantation. Individualized implantation depth guided by MS not only minimized NOCDs risk but also reduce the risk of coronary occlusion or valve migration.

Prosthesis Oversizing Ratio and Conduction Disturbances

In our study, smaller aortic root anatomy, especially the LVOT perimeter, had the best negative predictive value for NOCDs. A smaller LVOT perimeter represented higher risks of the larger oversizing ratio by LVOT perimeter, which could cause higher radial forces on the conduction system. All multivariate regression models revealed the importance of LVOT perimeter or oversizing by LVOT perimeter. Jilaihawi's study suggested that it was possible to minimize implantation depth guided by infra-annular membranous septum depth to reduce PPMI (6). Optimal implantation depth of bicuspid patients hasn't been established yet. The manufacturer recommendation of implantation depth was 3–5 mm in Evolut series self-expanding valve and 4–6 mm in Venus series self-expanding valve. With the help of cusp overlap technique, aiming for 3 mm of implantation depth in tricuspid patients can minimize the risk of conduction disturbances (37). However, the cusp overlap view can't be reached in type 0 patients and is often extreme in Type 1 L-R fusion patients. In most heavily calcified bicuspid patients, a tapered anatomy with small supra-annular structure allows the prosthesis to be deployed at a supra-annular positioning. Aiming for <3 mm based on individual MS length may be reasonable in bicuspid patients with a median infra-annular MS of 2.3 mm. However, excessively high implantation (<1 mm below annular plane) increased the risks of "Pop-out" and coronary occlusion.

In some bicuspid patients with extremely short MS, the contact of the conduction system is inevitable. Thus, we conducted a subgroup analysis of patients with infra-annular MS depth less than implantation depth. The multivariate regression model revealed that the oversizing ratio by LVOT was the only independent predictor, which could be mediated by operators. This suggested that reducing the oversizing ratio could serve as another feasible strategy to reduce conduction disturbances and avoid incomplete prosthesis expansion, annular injury or paravalvular regurgitation. BAV patients had more calcification deposition compared with tricuspid patients, which provided a supra-annular anchor position and made it possible to reduce the oversizing ratio (12). In our single center analysis, the TAVR outcome in bicuspid patients was feasible with high device success rate of 84.5% and good performance even with first generation devices. Several recent studies have also suggested the safety and effectiveness of prosthesis undersizing based on supra-annular sizing methods (8, 10, 38, 39). LIRA method, known as Level of Implantation at the RAphe (LIRA) method, was applicated in 20 raphe-type BAV patients. Undersizing prosthesis were chosen based on LIRA method, known as Level of Implantation at the Raphe method, achieved 100% device success in 20 raphe-type BAV patients. In another CASPER study (Calcium Algorithm Sizing for bicusPid Evaluation with Raphe), 70% of prosthesis were undersized according to a new algorithm and no cases of moderate or severe PVL were found (9). Now the authors are expanding the indication of CASPER algorithm in type 0 patients (NCT04817735). To sum up, reducing the oversizing ratio was a feasible strategy to reduce conduction disturbances and maintained good procedural outcome in heavily calcified bicuspid anatomy with short MS length.

Subgroup Analysis of High-Grade Atrioventricular Block

In a subgroup analysis based on whether developed new-onset high-grade atrioventricular block, pre-existing right bundle branch block emerged as a strong predictor of new-onset high-grade atrioventricular block while coronal MS and oversizing by LVOT perimeter remained as independent predictors (**Supplementary Tables 4A,B**). High-grade atrioventricular block can occur when both the left bundle branch and the right bundle branch are affected. This explained the high risk of high-grade atrioventricular block and PPMI if new-onset left bundle branch block occurred in patients with pre-existing right bundle branch block. Thus, strict electrocardiography monitoring should be carried out to detect bradycardia events in this population.

Measurement of Implantation Depth on CT or Fluoroscopy

The prosthesis implantation depth was mainly measured by fluoroscopy on NCC direction during the procedure (40, 41). However, the feasibility of this method has not been proved in BAV patients. As the coplanar view is slightly different in BAV patients. The true position of MS is between right and non-coronary leaflets in most tricuspid patients. Logically, MS measurement on fluoroscopy might be inaccurate in BAV population especially in patients under extreme projection angle in type 0 with anteroposterior cusps or Type 1 with N-L fusion. However, in our study, we found a high linear relationship between the ID measurement on CT and fluoroscopy (**Supplementary Figure 1B**). This suggested ID measured on fluoroscopy could also be used during procedural implantation.

STUDY LIMITATION

The major limitation was related to the use of the first-generation device without recapturable features in the early procedure. The implantation depth was relatively lower, and MSID was numerically larger, which increased the risk of

NOCDs and should be avoided in future clinical practice. However, low rates of PPMI and NOCDs in this situation highlighted the effectiveness of reducing the oversizing ratio to lower the risk of PPMI. Moreover, the study included a small population with relatively low NOCDs and PPMI rates. Thus, reported results need to be further verified in future studies. Besides, this study was unable to encompass the entire TAVR population, which made a comparison with tricuspid patients impossible.

CONCLUSION

There would be more bicuspid aortic stenosis patients undergoing TAVR with the extension of indication and thus the risk of NOCDs would be highlighted for their young age compared with tricuspid aortic stenosis patients. Our study provides a practical predictive model based on MS length and LVOT perimeter. More importantly, we demonstrate the crucial role of operators and procedural strategy. It is suggested that implantation depth should be guided by MS length. Besides, reducing the oversizing ratio might be a feasible strategy to reduce conduction disturbances and maintained good procedural outcome in heavily calcified bicuspid anatomy with short MS length. Moreover, a prospective, multicenter, randomized, superiority clinical trial (NCT04722796) is ongoing to further explore the procedural strategy of BAV patients, which can verify the finding in this study. In all, appropriate individualized procedure strategy based on bicuspid aortic stenosis patients' anatomy might lead to a low incidence of NOCDs even comparable to surgery.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Second Affiliated Hospital, Zhejiang University School of Medicine; Zhengzhou Cardiovascular Hospital; Fujian Medical University Union Hospital; The First Affiliated Hospital of Bengbu Medical College; Henan Provincial Chest Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YG and DZ conceived and designed the study and wrote the paper. MD, YH, and JFan helped collected data and analyzed the result. SZ, JFang, SW, QH, LC, and YY provided the data and interpreted the results. HJ, XL, and JW reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This paper was supported by following foundations: Natural Science Foundation of Zhejiang Province of China (LQ21H020005), Henan Province Scientific and technological project (Grant No. 192102310062), Zhengzhou Scientific and technological beneficial project (2019KJHM0006), and Anhui Provincial Key research and development project (201904a07020017).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.757190/full#supplementary-material

REFERENCES

1. van Rosendael PJ, Delgado V, Bax JJ. Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. *Eur Heart J.* (2018) 39:2003–13. doi: 10.1093/eurheartj/ehx785
2. Siontis GC, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol.* (2014) 64:129–40. doi: 10.1016/j.jacc.2014.04.033
3. Faroux L, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, et al. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *Eur Heart J.* (2020) 41:2771–81. doi: 10.1093/eurheartj/ehz924
4. Chamandi C, Barbanti M, Munoz-Garcia A, Latib A, Nombela-Franco L, Gutiérrez-Ibanez E, et al. Long-Term outcomes in patients with new-onset persistent left bundle branch block following TAVR. *JACC Cardiovasc Interv.* (2019) 12:1175–84. doi: 10.1016/j.jcin.2019.03.025
5. Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol.* (2012) 60:493–501. doi: 10.1016/j.jacc.2012.03.054
6. Jilaihawi H, Zhao Z, Du R, Staniloae C, Saric M, Neuburger PJ, et al. Minimizing permanent pacemaker following repositionable self-expanding transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* (2019) 12:1796–807. doi: 10.1016/j.jcin.2019.05.056
7. Hamdan A, Nassar M, Schwammenthal E, Perlman G, Arow Z, Lessick J, et al. Short membranous septum length in bicuspid aortic valve stenosis increases the risk of conduction disturbances. *J Cardiovasc Comput.* (2020) 15:339–47. doi: 10.1016/j.jcct.2020.10.002
8. Liu X, He Y, Zhu Q, Gao F, He W, Yu L, et al. Supra-annular structure assessment for self-expanding transcatheter heart valve size selection in patients with bicuspid aortic valve. *Catheter Cardiovasc Interv.* (2018) 91:986–94. doi: 10.1002/ccd.27467
9. Petronio AS, Angelillis M, De Backer O, Giannini C, Costa G, Fiorina C, et al. Bicuspid aortic valve sizing for transcatheter aortic valve implantation: development and validation of an algorithm based on multi-slice computed tomography. *J Cardiovasc Comput Tomogr.* (2020) 14:452–61. doi: 10.1016/j.jcct.2020.01.007

10. Iannopollo G, Romano V, Buzzatti N, Ancona M, Ferri L, Russo F, et al. Supra-annular sizing of transcatheter aortic valve prostheses in raphe-type bicuspid aortic valve disease: the LIRA method. *Int J Cardiol.* (2020) 317:144–51. doi: 10.1016/j.ijcard.2020.05.076
11. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
12. Vincent F, Ternacle J, Denimal T, Shen M, Redfors B, Delhaye C, et al. Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. *Circulation.* (2021) 143:1043–61. doi: 10.1161/CIRCULATIONAHA.120.048048
13. Rodés-Cabau J, Ellenbogen KA, Krahn AD, Latib A, Mack M, Mittal S, et al. Management of conduction disturbances associated with transcatheter aortic valve replacement: JACC scientific expert panel. *J Am Coll Cardiol.* (2019) 74:1086–106. doi: 10.1016/j.jacc.2019.07.014
14. Hamdan A, Guetta V, Klempfner R, Konen E, Raanani E, Glikson M, et al. Inverse relationship between membranous septal length and the risk of atrioventricular block in patients undergoing transcatheter aortic valve implantation. *JACC Cardiovasc Interv.* (2015) 8:1218–28. doi: 10.1016/j.jcin.2015.05.010
15. Mazzella AJ, Sanders M, Yang H, Li Q, Vavalle JP, Gehi A. Predicting need for pacemaker implantation early and late after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* (2020) 97:E588–96. doi: 10.1002/ccd.29239
16. Maeno Y, Abramowitz Y, Yoon SH, Israr S, Jilaihawi H, Watanabe Y, et al. Relation between left ventricular outflow tract calcium and mortality following transcatheter aortic valve implantation. *Am J Cardiol.* (2017) 120:2017–24. doi: 10.1016/j.amjcard.2017.08.018
17. Tops LF, Wood DA, Delgado V, Schuijf JD, Mayo JR, Pasupati S, et al. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovasc Imaging.* (2008) 1:321–30. doi: 10.1016/j.jcmg.2007.12.006
18. Kim U, Blanke P, Windecker S, Kasel AM, Schäfer U, Walters D, et al. Computed tomography-based oversizing and incidence of paravalvular aortic regurgitation and permanent pacemaker implantation with a new-generation self-expanding transcatheter heart valve. *Eurointervention.* (2018) 14:e511–8. doi: 10.4244/EIJ-D-17-01040
19. Maeno Y, Abramowitz Y, Yoon SH, Jilaihawi H, Raul S, Israr S, et al. Transcatheter aortic valve replacement with different valve types in elliptic aortic annuli. *Circ J.* (2017) 81:1036–42. doi: 10.1253/circj.CJ-16-1240
20. Blanke P, Weir-McCall JR, Achenbach S, Delgado V, Hausleiter J, Jilaihawi H, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/Transcatheter aortic valve replacement (TAVR): an expert consensus document of the society of cardiovascular computed tomography. *JACC Cardiovasc Imaging.* (2019) 12:1–24. doi: 10.1016/j.jcmg.2018.12.003
21. Yerasi C, Tripathi B, Wang Y, Forrestal BJ, Case BC, Khan JM, et al. National trends and 30-day readmission rates for next-day-discharge transcatheter aortic valve replacement: an analysis from the nationwide readmissions database, 2012-2016. *Am Heart J.* (2021) 231:25–31. doi: 10.1016/j.ahj.2020.08.015
22. Alperi A, Muntané-Carol G, Freitas-Ferraz AB, Junquera L, Del VD, Faroux L, et al. Overcoming the transcatheter aortic valve replacement achilles heel: conduction abnormalities-a systematic review. *Ann Cardiothorac Surg.* (2020) 9:429–41. doi: 10.21037/acs-2020-av-40
23. Kawsara A, Sulaiman S, Alqahtani F, Eleid MF, Deshmukh AJ, Cha YM, et al. Temporal trends in the incidence and outcomes of pacemaker implantation after transcatheter aortic valve replacement in the united states (2012-2017). *J Am Heart Assoc.* (2020) 9:e16685. doi: 10.1161/JAHA.120.016685
24. Lilly SM, Deshmukh AJ, Epstein AE, Ricciardi MJ, Shreenivas S, Velagapudi P, et al. 2020 ACC expert consensus decision pathway on management of conduction disturbances in patients undergoing transcatheter aortic valve replacement: a report of the american college of cardiology solution set oversight committee. *J Am Coll Cardiol.* (2020) 76:2391–411. doi: 10.1016/j.jacc.2020.08.050
25. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JR, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *J Am Coll Cardiol.* (2021) 77:450–500. doi: 10.1161/CIR.0000000000000932
26. Forrest JK, Ramlawi B, Deeb GM, Zahr F, Song HK, Kleiman NS, et al. Transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis. *Jama Cardiol.* (2021) 6:50–7. doi: 10.1001/jamacardio.2020.4738
27. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. *JAMA.* (2019) 321:2193–202. doi: 10.1001/jama.2019.7108
28. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068
29. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation.* (2005) 111:920–5. doi: 10.1161/01.CIR.0000155623.48408.C5
30. Halim SA, Edwards FH, Dai D, Li Z, Mack MJ, Holmes DR, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the society of thoracic surgeons/American college of cardiology transcatheter valve therapy registry. *Circulation.* (2020) 141:1071–9. doi: 10.1161/CIRCULATIONAHA.119.040333
31. Majmundar M, Kumar A, Doshi R, Shah P, Arora S, Shariff M, et al. Meta-Analysis of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valve. *Am J Cardiol.* (2021) 145:102–10. doi: 10.1016/j.amjcard.2020.12.085
32. Radermecker MA, Sprynger M, Hans G. TAVR for stenotic bicuspid aortic valve: feasible, continuously improving results with another red flag. *J Am Coll Cardiol.* (2020) 76:2591–4. doi: 10.1016/j.jacc.2020.10.001
33. Perlman GY, Blanke P, Webb JG. Transcatheter aortic valve implantation in bicuspid aortic valve stenosis. *Eurointervention.* (2016) 12:Y42–5. doi: 10.4244/EIJV12SYA10
34. Bisson A, Bodin A, Herbert J, Lacour T, Saint EC, Pierre B, et al. Pacemaker implantation after balloon- or self-expandable transcatheter aortic valve replacement in patients with aortic stenosis. *J Am Heart Assoc.* (2020) 9:e15896. doi: 10.1161/JAHA.120.015896
35. van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, et al. New conduction abnormalities after TAVI–frequency and causes. *Nat Rev Cardiol.* (2012) 9:454–63. doi: 10.1038/nrcardio.2012.58
36. Tretter JT, Mori S, Anderson RH, Taylor MD, Ollberding N, Truong V, et al. Anatomical predictors of conduction damage after transcatheter implantation of the aortic valve. *Open Heart.* (2019) 6:e972. doi: 10.1136/openhrt-2018-000972
37. Ben-Shoshan J, Alosaimi H, Lauzier PT, Pighi M, Talmor-Barkan Y, Overtchouk P, et al. Double S-Curve versus cusp-overlap technique: defining the optimal fluoroscopic projection for TAVR with a self-expanding device. *JACC Cardiovasc Interv.* (2021) 14:185–94. doi: 10.1016/j.jcin.2020.10.033
38. Zhao ZG, Feng Y, Liao YB, Li YJ, Xiong TY, Ou YW, et al. Reshaping bicuspid aortic valve stenosis with an hourglass-shaped balloon for transcatheter aortic valve replacement: a pilot study. *Catheter Cardiovasc Interv.* (2020) 95 (Suppl. 1):616–23. doi: 10.1002/ccd.28726
39. Xiong TY, Li YJ, Feng Y, Liao YB, Zhao ZG, Mylotte D, et al. Understanding the interaction between transcatheter aortic valve prostheses and supra-annular structures from post-implant stent geometry. *JACC Cardiovasc Interv.* (2019) 12:1164–71. doi: 10.1016/j.jcin.2019.02.051
40. Binder RK, Webb JG, Toggweiler S, Freeman M, Barbanti M, Willson AB, et al. Impact of post-implant SAPIEN XT geometry and position on conduction disturbances, hemodynamic performance, and paravalvular regurgitation.

JACC Cardiovasc Interv. (2013) 6:462–8. doi: 10.1016/j.jcin.2012.12.128

41. Maeno Y, Abramowitz Y, Kawamori H, Kazuno Y, Kubo S, Takahashi N, et al. A highly predictive risk model for pacemaker implantation after TAVR. *JACC Cardiovasc Imaging*. (2017) 10:1139–47. doi: 10.1016/j.jcmg.2016.11.020

Conflict of Interest: HJ has been a consultant to Edwards Lifesciences and Venus Medtech and has received grant/research support from Medtronic and Abbott Vascular.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 22 December 2021
doi: 10.3389/fcvm.2021.790069

Subclinical Leaflets Thrombosis After Transcatheter Replacement of Bicuspid vs. Tricuspid Aortic Valve

Gangjie Zhu[1,2†], Jiaqi Fan[1†], Dao Zhou[1,2], Hanyi Dai[1,2], Qifeng Zhu[1], Yuxin He[1], Yuchao Guo[1], Lihan Wang[1], Xianbao Liu[1,2] and Jian'an Wang[1,2]*

[1] Department of Cardiology, Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China, [2] Zhejiang University School of Medicine, Hangzhou, China

Background: Subclinical leaflet thrombosis (SLT) is an important sequela that compromises the durability of the bioprosthetic valve.

Objectives: To better determine the effect of SLT in bicuspid aortic valve (BAV), we performed a retrospective assessment of CT-defined SLT in BAV and tricuspid aortic valve (TAV) stenotic patients.

Methods: We consecutively collected patients undergoing the TAVR between August 2015 and March 2020 in our center. A total of 170 BAV and 201 TAV cases were enrolled. Multidetector computed tomography was performed within 30 days and at 1-year.

Results: Twenty cases in the BAV group and 19 cases in the TAV group had hypoattenuated leaflet thickening (HALT) in 30 days (12.5 vs. 9.9%, $p = 0.449$), and 52 cases in BAV and 61 cases in TAV had the HALT (34.9 vs. 36.7%, $p = 0.733$) at 1-year follow-up. The mean aortic gradient (MAG) and effective orifice areas (EOA) values were comparable between the two groups at 30 days (HALT vs. no HALT; 10.8 ± 4.8 vs. 11.3 ± 6.0, $p = 0.638$; 1.6 ± 0.4 vs. 1.6 ± 0.3, $p = 0.724$), and still, no difference was observed in the MAG at 1-year (11.5 ± 5.6 vs. 10.6 ± 5.1, $p = 0.164$). However, the EOA at 1-year was statistically different between the two groups (1.5 ± 0.3 vs. 1.6 ± 0.4, $p = 0.004$). The multivariate logistic regression analysis demonstrated the anticoagulation and age as independent predictors both in the BAV and TAV groups at 1-year. There was no difference in clinical events between the HALT and no HALT group in relevant to BAV or TAV at 1-year follow-up.

Conclusions: The presence of subclinical leaflet thrombosis defined by the CT was comparable between the BAV and TAV in the first year after the TAVR procedure. Age and anticoagulation were the independent predictors of the subclinical leaflet thrombosis at 1 year after the TAVR. There was no difference in relevant clinical events between the BAV and TAV groups at 1-year follow-up.

Keywords: transcatheter aortic valve replacement, subclinical leaflet thrombosis, bicuspid aortic valve, tricuspid aortic valve, hypoattenuated leaflet thickening

OPEN ACCESS

Edited by:
Mao Chen,
Sichuan University, China

Reviewed by:
Francesco Sturla,
IRCCS Policlinico San Donato, Italy
Mara Gavazzoni,
University Hospital Zürich, Switzerland

***Correspondence:**
Xianbao Liu
liuxb@zju.edu.cn

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *06 October 2021*
Accepted: *03 December 2021*
Published: *22 December 2021*

Citation:
Zhu G, Fan J, Zhou D, Dai H, Zhu Q, He Y, Guo Y, Wang L, Liu X and Wang J (2021) Subclinical Leaflets Thrombosis After Transcatheter Replacement of Bicuspid vs. Tricuspid Aortic Valve. Front. Cardiovasc. Med. 8:790069. doi: 10.3389/fcvm.2021.790069

INTRODUCTION

In elderly patients with symptomatic aortic stenosis (AS), transcatheter aortic valve replacement (TAVR) is a less invasive heart procedure to replace the stenotic valve with a favorable prognosis. As the use of the TAVR for the indication of the AS expands to younger and low-risk patients, the goal of developing the durable bioprosthetic valve has been particularly focused on. Subclinical leaflet thrombosis (SLT) is a critical occurrence that jeopardizes the durability of the bioprosthetic valve. Hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RELM), as detected by multidetector computed tomography (MDCT) were hallmarks of the subclinical leaflet thrombosis (1–4). The occurrence of the SLT in transcatheter valve replacements is about 10–40% (3–7).

Due to severe and asymmetric calcification in the native aortic valves and the deformation of the bioprosthetic frames after the TAVR, the SLT in the bicuspid aortic valve (BAV) is very concerned (8). At present, there is no study to compare the SLT viewed by computed tomography (CT) and its clinical sequelae and prognosis between the BAV and tricuspid aortic valve (TAV). To better explore the SLT in the BAV, this study aimed to retrospectively assess the SLT defined by the CT in the BAV and TAV stenotic patients.

METHODS

Study Population

This study was a retrospective observational analysis. We consecutively collected patients undergoing the TAVR between August 2015 and March 2020 in our center. Exclusion criteria: (1) Cases lacking the pre-procedure CT to define aortic valve type including quadricuspid valve; (2) Patients received bioprosthetic implant before the TAVR procedure; (3) Patients with contrast agents contraindicated, allergies, and severe renal dysfunction (estimated glomerular filtration rate of $\leq$ 30 ml/min); (4) Patients lost to follow up; (5) Patients with incomplete or inconclusive CT series.

The morphological type of aortic valve was classified into BAV (including type 0, type 1, and type 2) or TAV according to the Sievers classification (9). The study was approved by the local Ethical Committee and was in accordance with the principles of the Declaration of Helsinki.

TAVR Procedure and Antithrombotic Regimen

The TAVR procedures were performed in a hybrid operating room. Unfractionated heparin was used (50–70 U/kg) to maintain an activated clotting time (ACT) of >250 s during all procedures. Adopting general anesthesia or local anesthesia with sedation was decided by anesthetists. Transfemoral or non-transfemoral access was used based on the pre-procedure assessment. The majority of cases were implanted with self-expanding valves, and the rest of the patients were implanted with balloon-expandable or mechanically expanding valves. Post-dilatation was employed based on surgeons' discretion. A large proportion of the patients were prescribed dual antiplatelet therapy (DAPT) following the procedures. Oral anticoagulants (OAC) were recommended if the patients had indications of anticoagulation.

Echocardiography and Laboratory Tests

Transthoracic echocardiography (TTE) was performed before the TAVR procedure, before discharge, and at 30-day and 1-year follow-up. The mean aortic gradient (MAG), effective orifice area (EOA), left ventricular end-diastolic diameter (LVEDd), left atrium diameter, left ventricular ejection fraction (LVEF), and pulmonary arterial systolic pressure (PASP) were measured by the TTE. The results of the TTE were analyzed by experienced echocardiographers. The levels of the D-dimer and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) were tested at each follow-up visit.

MDCT Acquisition and Analysis

Cardiac contrast-enhanced ECG-gated multidetector computed tomography (MDCT) was performed using Philips Brilliance iCT 256 (Philips Corporation, Amsterdam, Netherlands) or GE revolution CT (GE Healthcare, Chicago, IL, USA) with collimation of 0.6 or 0.8 mm, 100 or 120 kV for imaging.

Patients routinely underwent MDCT scanning before the procedure, before discharge or at 30 days after implantation (first CT) and at 1-year follow-up (second CT). Full phase CT imaging was acquired and analyzed by using 3mensio workstation (Pie Medical Imaging, Maastricht, Netherlands). Two authors (Dao Zhou and Hanyi Dai) evaluated the CT scans independently and one author (Gangjie Zhu) reviewed the data.

HALT and RELM

The HALT was evaluated in cardiac diastole. The area and thickness of hypoattenuation were measured in a cross-sectional 2D multiplanar reconstruction (MPR) view and corresponding 2D longitudinal MPR view, respectively. If the HALT was found, the RELM had been evaluated in cardiac systole with the 3D or 4D CT. According to the severity of the leaflet reduced motion, the RELM was graded as mild (<50%), moderate ($\geq$50%, <70%), and severe ($\geq$70%) (10). The moderate and severe RELM were denoted as hypoattenuation affecting motion (HAM) (10).

%RELM = (width of hypoattenuation/ (1/2 diameter of the bioprosthesis in the section)·100%.

Follow-Up and Clinical Adverse Events

Despite this study was a retrospective analysis, patients who underwent the TAVR procedure, were routinely followed up before discharge, and at 30 days and 1 year after the procedure. Clinical adverse events were defined according to the VARC-3 criteria (11).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25.0.0 (International Business Machines Corporation, Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). Continuous variables are presented as mean $\pm$ SD or median [interquartile range (IQR)] and were analyzed by Student's *t*-test or Mann-Whitney *U*-test. Categorical variables

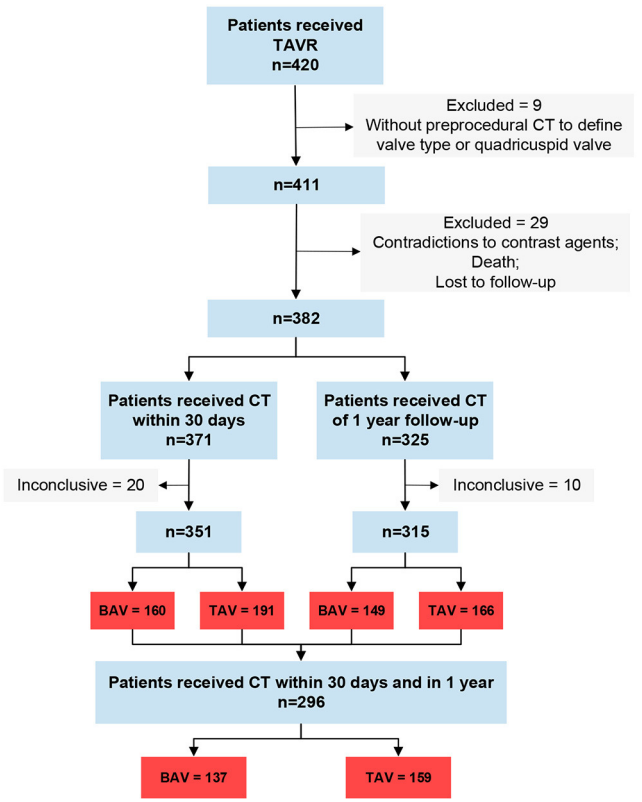


FIGURE 1 | Study flow. Inconclusive, CT can't be analyzed; BAV, icuspid aortic valve; TAV, tricuspid aortic valve.

TABLE 1 | Baseline demographics and clinical characteristics.

	BAV $n = 170$	TAV $n = 201$	*P*-value
Age, yrs	75.1 ± 6.6	76.9 ± 6.7	0.013
Male	97 (57.1)	120 (59.7)	0.607
BMI, kg/m^2	22.4 ± 3.3	22.6 ± 3.6	0.541
STS PROM, %	6.0 ± 3.7	7.1 ± 5.1	0.010
Smoking	24 (14.1)	32 (15.9)	0.629
Dyslipidemia	29 (17.1)	41 (20.4)	0.413
Hypertension	91 (53.5)	121 (60.2)	0.196
Diabetes mellitus	38 (22.4)	44 (21.9)	0.915
Syncope	20 (11.8)	12 (6.0)	0.048
NYHA functional class			
I - II	20 (11.8)	22 (10.9)	0.804
III	84 (49.4)	84 (41.8)	0.142
IV	66 (38.8)	95 (47.3)	0.102
Previous MI	1 (0.6)	5 (2.5)	0.225
Prior PCI	12 (7.1)	23 (11.4)	0.209
Prior CABG	0 (0)	3 (1.5)	0.253
Prior stroke	6 (3.5)	13 (6.5)	0.676
Prior pacemaker	4 (2.4)	5 (2.5)	1.000
Atrial fibrillation/flutter	29 (17.1)	38 (18.9)	0.645
PVD	18 (10.6)	33 (16.4)	0.104
COPD	35 (20.6)	50 (24.9)	0.328
LVEF, %	52.7 ± 14.8	54.9 ± 13.7	0.261

Values are mean ± SD or number (%).
BMI, body mass index; CABG, coronary artery bypass grafting; COPD, Chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PROM, Predicted Risk of Mortality; PVD, peripheral vascular diseases; STS, Society of Thoracic Surgeons.

are presented as count (percentage). And Pearson's chi-squared test or Fisher exact test were used to analyze the categorical variables. Multivariate logistical regression was used to identify predictors of the HALT, which included co-variables with the $p < 0.10$ in the univariable logistical regression. Statistical significance was defined at the $p < 0.05$ with two-tailed tests.

RESULTS

Patients Characteristics

A total of 420 patients underwent the TAVR procedure between August 2015 and March 2020. Among them, 9 patients were excluded because of lacking pre-procedure CT or having a quadricuspid valve, and 29 patients were excluded because of contradictions to contrast agents, death, or loss to follow-up (**Figure 1**). A total of 371 patients had CT within 30 days post TAVR procedure, of which 20 CT scans were inconclusive because of poor imaging quality. Three hundred and twenty-five patients received CT at 1-year follow-up but 10 CT scans were inconclusive. Finally, 160 patients with BAV involvement and 191 patients with TAV involvement were included for the first CT (within 30 days post the procedure) images analysis. A total of 149 BAVs and 166 TAVs were included for the second CT (at 1-year follow-up; BAV vs. TAV, 12.3 ± 1.1 vs. 12.6 ± 1.9 months) images analysis. A total of 137 BAVs and 159 TAVs had completed CT scans within 30 days and 1-year follow-up.

Baseline demographic and clinical characteristics are summarized in **Table 1**. A total of 170 BAV cases and 201 TAV cases were enrolled for this study. Patients in BAV group were younger and had a lower risk than patients in TAV group (age: 75.1 ± 6.6 vs. 76.9 ± 6.7, $p = 0.013$; STS: 6.0 ± 3.7% vs. 7.1 ± 5.1%, $p = 0.010$). Syncope occurred more frequent in the BAV than the TAV (11.8 vs. 6.0%, $p = 0.048$).

TAVR Procedure

Procedural details were listed in **Table 2**. There was a higher proportion of local anesthesia (90.0 vs. 78.6%, $p = 0.003$), transfemoral access (97.1 vs. 86.6%, $p < 0.001$) and post-dilatation (62.9 vs. 41.8%, $p < 0.001$) in the BAV group. Many BAV patients were implanted with 23–26 mm valve devices compared with the TAV patients (62.9 vs. 41.8%, $p < 0.001$). And a higher percentage of 26–29 mm valve devices were implanted in the patients with the TAV (15.3 vs. 31.8%, $p < 0.001$). No case was converted to surgery of both valves in the BAV and TAV groups.

HALT and RELM

A total of 20 cases in the BAV group and 19 cases in the TAV group had HALT in 30 days (12.5 vs. 9.9%, $p = 0.449$) (**Table 3**; **Figure 2**). Among them, involvement of one leaflet, two leaflets, and three leaflets were 70.0 vs. 84.2% ($p = 0.901$), 15.0 vs. 10.5% ($p = 0.663$), and 10.0 vs. 5.3% ($p = 0.335$) in the BAV and TAV groups, respectively. The occurrence of the RELM in BAV and TAV was 11.9 and 9.4% ($p = 0.456$) in 30 days. The occurrence of the HAM in BAV and TAV was 5.6 and 2.6% ($p = 0.152$), respectively. Severe RELM was rare in both groups (1.9 vs. 1.0%, $p = 0.663$). Maximal leaflet thickness, maximal area of hypoattenuation, and total area of hypoattenuation were comparable in two groups (**Table 3**).

At 1-year follow-up, there were 52 cases in BAV and 61 cases in TAV with HALT (34.9 vs. 36.7%, $p = 0.733$), and 51 cases in BAV and 56 cases in TAV with RELM (34.2 vs. 33.7%, $p = 0.926$) (**Table 3**; **Figure 2**). There was no statistical difference with HAM, maximal leaflet thickness, maximal area of hypoattenuation, and total area of hypoattenuation between BAV and TAV.

To eliminate the impact of the device type, we excluded balloon-expandable and mechanically expanding valves. We found the occurrence of HALT was still comparable between the BAV and TAV group within 30 days or at 1 year (BAV vs. TAV, 11.8 vs. 11.6%, $p = 0.959$; 33.3 vs. 34.8%, $p = 0.800$) (**Supplementary Table 1A**). We also compared the occurrence of HALT in the supra-annular bioprostheses (self-expanding valves) and the inter-annular bioprostheses (balloon-expandable and mechanically expanding valves) group (**Supplementary Table 1B**). The outcomes were still comparable between the self-expanding valves and the balloon-expandable/mechanically expanding valves groups within 30 days or at 1 year (**Supplementary Table 1B**).

TABLE 2 | Procedural details.

	BAV $n = 170$	TAV $n = 201$	*P*-value
Procedural time, min	71.3 ± 35.2	68.4 ± 41.8	0.494
Local anesthesia	153 (90.0)	158 (78.6)	0.003
Access			
Transfemoral	165 (97.1)	174 (86.6)	<0.001
Non-transfemoral	5 (2.9)	27(13.4)	<0.001
Transcatheter valve type			
Self-expanding valve	150 (88.2)	164 (81.2)	0.077
Balloon-expandable valve	7 (4.1)	28 (13.9)	0.001
Mechanically expanding valve	13 (7.6)	9 (4.5)	0.198
Bioprosthetic valve size, mm			
≤23	31 (18.2)	40 (19.9)	0.685
>23, ≤26	107 (62.9)	84 (41.8)	<0.001
>26, ≤29	26 (15.3)	64 (31.8)	<0.001
> 29	6 (3.5)	13 (6.5)	0.201
Postdilation	107 (62.9)	84 (41.8)	<0.001
Implantation of >1 valve	13 (12.1)	9 (4.5)	0.198
Conversion to surgery	0 (0)	0 (0)	–

Values are mean ± SD or number (%).

HALT/RELM Evolution

A total of 137 patients with BAV and 159 patients with TAV were evaluated for the evolution of HALT/RELM. Fifty cases in the BAV group and 59 cases in the TAV group (36.5 vs. 37.1%, $p = 0.914$) had the evolution of HALT/RELM in 30 days or 1 year (**Figure 3**). Among them, 5 cases in BAV and 7 cases in TAV regressed; 6 cases in BAV and 8 cases in TAV remained stable; most cases in BAV and TAV (78.0 vs. 74.6%, $p = 0.879$)

TABLE 3 | HALT/RELM within 30 days or at 1-year.

	30 days			1-year		
	BAV $n = 160$	TAV $n = 191$	*P*-value	BAV $n = 149$	TAV $n = 166$	*P*-value
HALT	20 (12.5)	19 (9.9)	0.449	52 (34.9)	61 (36.7)	0.733
One leaflet involved	14 (70.0)	16 (84.2)	0.901	26 (50.0)	38 (62.3)	0.231
Two leaflets involved	3 (15.0)	2 (10.5)	0.663	20 (38.5)	18 (29.5)	0.483
Three leaflets involved	3 (15.0)	1 (5.3)	0.335	6 (11.5)	5 (8.2)	0.624
RELM	19 (11.9)	18 (9.4)	0.456	51 (34.2)	56 (33.7)	0.926
<50%	10 (52.6)	13 (72.2)	0.834	26 (51.0)	34 (60.7)	0.494
≥50%, <70%	6 (30.0)	3 (16.7)	0.310	23 (45.1)	19 (33.9)	0.298
≥70%	3 (15.0)	2 (11.1)	0.663	2 (3.9)	3 (5.4)	1.000
HAM	9 (5.6)	5 (2.6)	0.152	25 (16.8)	22 (13.3)	0.381
Maximal leaflet thickness, mm	3.6 ± 1.9	3.2 ± 2.1	0.513	4.5 ± 2.0	4.0 ± 1.9	0.169
Maximal area of hypoattenuation, mm^2	42.9 ± 16.2	42.4 ± 21.8	0.935	46.2 ± 19.6	44.9 ± 18.3	0.607
Total area of hypoattenuation, mm^2	53.6 ± 31.8	47.9 ± 31.9	0.586	71.1 ± 49.3	63.0 ± 37.8	0.229

Values are mean ± SD or number (%).

BAV, bicuspid aortic valve; HALT, hypoattenuated leaflet thickening; HAM, hypoattenuation affecting motion; RELM, reduced leaflet motion; TAV, tricuspid aortic valve.

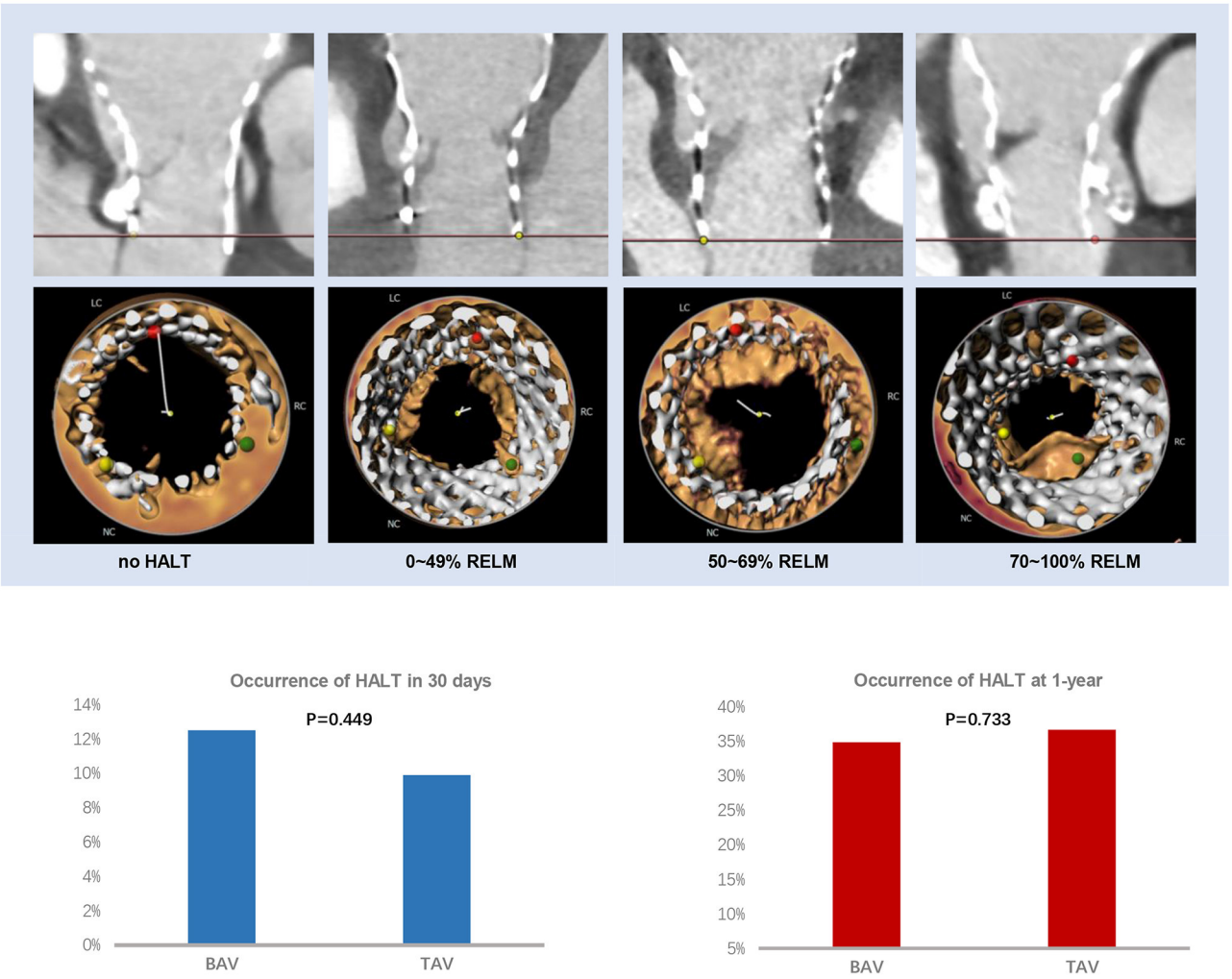


FIGURE 2 | HALT and RELM in BAV and TAV. According to the severity of the leaflet reduced motion, the RELM was graded as mild (<50%), moderate (≥50%, <70%), and severe (≥70%). There was no difference of HALT between the BAV and TAV group within 30 days (12.5 vs. 9.9%, $p = 0.449$) or at 1-year (34.9 vs. 36.7%, $p = 0.733$) follow-up. BAV, bicuspid aortic valve; HALT, hypoattenuated leaflet thickening; RELM, reduced leaflet motion; TAV, tricuspid aortic valve.

progressed. Specific data regarding the evolution of HALT/RELM were given in **Figure 3**; **Table 4**.

Echocardiographic Valve Assessment

In comparison with the HALT group, the no HALT group had a higher percentage of aortic paravalvular leak of ≥ moderate at 30 days (0 vs. 6.7%) and 1-year (3.5 vs. 11.4%, $p = 0.006$) follow-up (**Table 5**). The MAG and EOA values were comparable between the two groups at 30 days (HALT vs. no HALT; 10.8 ± 4.8 vs. 11.3 ± 6.0, $p = 0.638$; 1.6 ± 0.4 vs. 1.6 ± 0.3, $p = 0.724$), and still, no difference was observed in the MAG value at 1 year (HALT vs. no HALT; 11.5 ± 5.6 vs. 10.6 ± 5.1, $p = 0.164$) (**Table 5**; **Figure 4**). However, the EOA at 1 year was statistically different between the two groups (HALT vs. no HALT; 1.5 ± 0.3 vs. 1.6 ± 0.4, $p = 0.004$). Overall, the hemodynamic status was comparable between the HALT and no HALT group at 30 days, but the HALT group had smaller EOA values at 1 year.

Predictors of HALT in BAV and TAV

From the univariate logistical regression, age, body mass index (BMI), Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), New York Heart Association (NYHA) functional class III/IV, use of anticoagulation, aortic paravalvular leak of ≥ moderate, access, bioprosthetic valve type and D-dimer entered the multivariable logistical regression modeling (**Supplementary Table 2**). The multivariable logistical regression demonstrated that the anticoagulation and age were independent predictors of both BAV and TAV groups at 1-year (**Supplementary Table 3**). We didn't find any predictors in the BAV group in 30 days analysis. Transfemoral access and high BMI were protective factors for HALT in the TAV group at 30 days and 1-year, respectively.

Clinical Events

There was no death during the follow-up, including all-cause and cardiovascular mortality in all groups (**Table 6**). Four cases (3

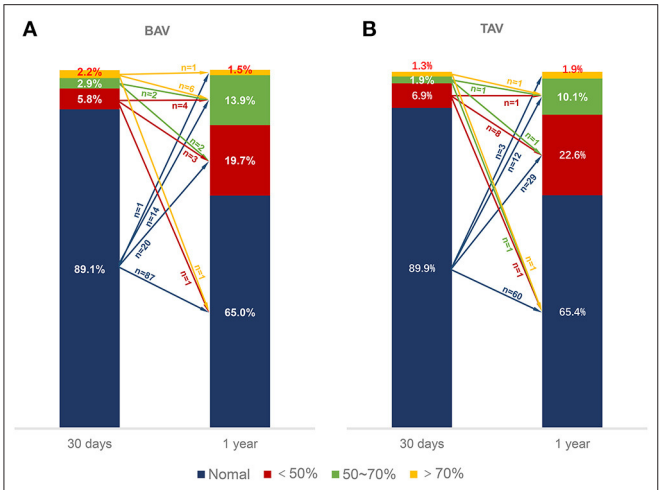


FIGURE 3 | Evolution of RELM. The different color bars represented normal leaflets, <50% RELM, ≥50%, <70% RELM and ≥70% RELM respectively. The different color arrows represented evolution of RELM form 30 days to 1-year follow-up. The numbers upon the color arrows represented the number of patients. BAV, bicuspid aortic valve; RELM, reduced leaflet motion; TAV, tricuspid aortic valve.

TABLE 4 | Regression or progression of RELM.

	BAV $n = 137$	TAV $n = 159$	*P*-value
RELM in 30 days	15 (10.9)	16 (10.1)	0.804
RELM in 1 year	48 (35.0)	55 (34.6)	0.936
RELM in 30 days or 1 year	50 (36.5)	59 (37.1)	0.914
Regression of RELM	5 (10.0)	7 (11.9)	0.743
Progression of RELM	39 (78.0)	44 (74.6)	0.879
No change of RELM	6 (12.0)	8 (13.6)	0.792

Values are number (%). BAV, bicuspid aortic valve; RELM, reduced leaflet motion; TAV, tricuspid aortic valve.

in BAV and 1 in TAV) had strokes and one case in BAV had a myocardial infarction. Rehospitalization for any reason was comparable in all four groups (**Table 5**). There was no statistical difference in the NYHA functional class III/IV, bleeding, and new fibrillation/flutter between the HALT and no HALT groups both in the BAV and TAV during the follow-up. In laboratory tests, D-dimer, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) were not associated with the HALT both in the BAV and TAV. No matter in which group, there was a strong correlation between the HALT and use of anticoagulation at 1-year, but not at 30 days.

DISCUSSION

This study demonstrated that (1) subclinical leaflet thrombosis in BAV and TAV patients was comparable within 30 days or at 1-year; (2) It seemed that the EOA of bioprothesis was different between the HALT and non-HALT group at 1-year follow-up; (3) use of anticoagulation and age were independent predictors both in BAV and TAV; (4) relevant clinical events were similar between the HALT and no HALT groups in BAV and TAV groups.

As the TAVR has been frequently performed in younger and lower-risk patients, the durability of the bioprosthetic valves became a concern in the past years. The SLT was an important cause of bioprosthetic valve dysfunction and compromised the durability of bioprosthetic valves (12). Fortunately, the SLT could be treated and reversed by anticoagulants in many cases (1, 5). Therefore, it may be important to diagnose and treat the SLT to maintain the durability of bioprosthetic valves. At present, some studies have evaluated the leaflet thrombosis of bioprosthetic valves in the TAVR and SAVR procedures, which showed no difference in leaflet thrombosis between the two groups at 1 year (6, 7). Except for durability, Szilveszter et al. found that the SLT was associated with impaired reverse remodeling of left ventricle after the TAVR (13).

Among those younger and lower risk AS patients, the BAV accounted for a large proportion due to the earlier onset in BAV patients. Besides, severe and asymmetric BAV stenosis had some anatomical variations, such as heavily calcified leaflet and the presence of raphe (14), which might have caused under-expansion and malformation of the TAVR stent frame. Those characteristics have increased the concern about leaflet thrombosis and durability in BAV. Waksman et al. found 10.2% HALT from 61 low-risk BAV patients with TAVR at 30 days (8). In this study, the results regarding HALT in BAV patients within 30 days were in line with that previous study. Besides, we explored the differences of HALT between the BAV and TAV groups at early and medium-term follow-up.

In this study, the occurrence of HALT was similar to the outcomes of the prior studies (3, 5, 6). However, we found no difference in HALT between BAV and TAV at early-term (within 30 days) or medium-term (1 year) follow-up. Those anticipated effects of SLT didn't appear to play a role.

In line with the previous studies (15, 16), the MAG value in the HALT or no HALT group was comparable in 1-year follow-up. However, we found that the EOA in the HALT group was smaller than in the no HALT group at 1-year. Of note, MAG in the HALT group was higher than in the no HALT group, although the difference was not significant (HALT vs. no HALT; 11.5 ± 5.6 vs. 10.6 ± 5.1, $p = 0.164$). As is well-known, there was a high correlation between the EOA and MAG. But the difference of the EOA between the HALT and no HALT group might be enlarged by the square calculation. Therefore, it was reasonable to suppose that the MAG might be significantly higher in the HALT group with a longer follow-up.

Except for the age, the use of anticoagulants was an independent predictor for HALT, regardless of in BAV or TAV. The GALILEO-4D study demonstrated that rivaroxaban reduced the risk of RELM in TAVR patients significantly (5). However, this phenomenon wasn't observed within 30 days in this present study. There might be two reasons: (1) almost all patients who needed anticoagulation received warfarin, which required some time to reach a targeted international normalized ratio (INR); (2) more than 90% of

TABLE 5 | Transthoracic echocardiography at 30 days and 1-year.

	30 days			1-year		
	HALT ***n*** **= 39**	**No HALT** ***n*** **= 312**	***P*-value**	**HALT** ***n*** **= 149**	**No HALT** ***n*** **= 201**	***P*-value**
Aortic paravalvular leak ≥ moderate	0 (0)	21 (6.7)	0.148	4 (3.5)	26 (11.4)	0.006
Mean aortic gradient, mmHg	10.8 ± 4.8	11.3 ± 6.0	0.638	11.5 ± 5.6	10.6 ± 5.1	0.164
Effective orifice areas, cm^2	1.6 ± 0.4	1.6 ± 0.3	0.742	1.5 ± 0.3	1.6 ± 0.4	0.004
Transvalvular regurgitation ≥ moderate	0 (0)	2 (0.6)	1.000	1 (0.9)	1 (0.5)	1.000
LVEDd, mm	4.7 ± 0.7	4.7 ± 0.8	0.662	4.5 ± 0.7	4.6 ± 0.7	0.362
LA, mm	3.9 ± 0.7	4.0 ± 0.6	0.122	4.0 ± 0.7	4.1 ± 0.6	0.127
LVEF, %	57.1 ± 12.1	58.4 ± 10.3	0.471	61.1 ± 9.4	61.8 ± 9.2	0.541
Mitral regurgitation ≥ moderate	2 (5.1)	29 (9.3)	0.554	10 (8.8)	17 (8.5)	0.924
Tricuspid regurgitation ≥ moderate	1 (2.6)	26 (8.3)	0.337	13 (11.4)	21 (10.4)	0.793
PASP, mmHg	30.4 ± 6.8	32.1 ± 9.6	0.382	33.1 ± 9.4	32.6 ± 8.8	0.671

Values are mean ± SD or number (%).
HALT, hypoattenuated leaflet thickening; LA, left atrium; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure.

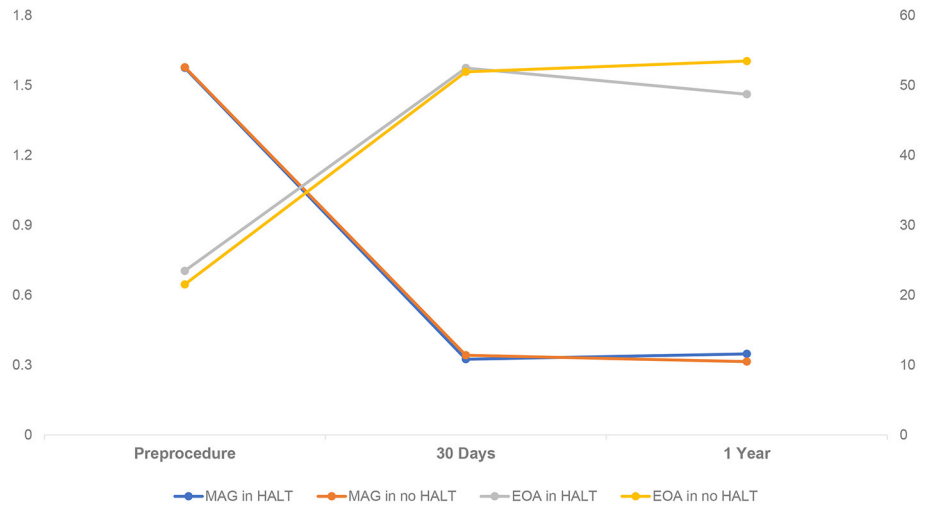


FIGURE 4 | Hemodynamic Change in Patients with HALT or no HALT. There was statistical difference between HALT and no HALT in EOA at 1-year follow-up (1.5 ± 0.3 vs. 1.6 ± 0.4, $p = 0.004$), but not in MAG (11.5 ± 5.6 vs. 10.6 ± 5.1, $p = 0.164$). There was no difference between HALT and no HALT in hemodynamic status at 30 days follow-up. EOA, Effective Orifice Areas; HALT, hypoattenuated leaflet thickening; MAG, mean aortic gradient.

the patients completed first CT scan before discharge so that anticoagulation might not have worked at all. We found the transfemoral access was a protective factor for HALT in the TAV group at 30 days. There was a possible reason involved. Almost patients of non-transfemoral access were received the transapical access, which might affect myocardial contractility due to the surgical trauma during the perioperative period. Low ejection fraction of left ventricle was associated with high occurrence of HALT (2). In this study, we also found that the high BMI was associated with the low occurrence of HALT in the TAV group at 1-year follow-up. We didn't know the nature behind this phenomenon. In previous studies, Abhishek Sharma et al. found patients with higher BMI had better outcomes after TAVR (17). In addition, the aortic paravalvular leak may have been a potential protective factor on SLT (**Table 5**; **Supplementary Table 3**), which could have changed the hemodynamic status near the bioprosthesis. This result needs to be confirmed by the studies with the larger sample size.

In previous studies, resolution or regression of the HALT/RELM was observed in half of the patients with HALT from 30 days to 1-year follow-up (6, 7). The rate of resolution or regression of the HALT/RELM was low in the present study. A possible reason was that higher occurrence of HALT/RELM at 30-day follow-up was observed in their studies. However, almost all patients in this study completed the first CT scan before discharge. Lars Sondergaard et al. found regression was more likely to be observed if the first CT scan was obtained at >3months after TAVR (3).

TABLE 6 | Clinical outcomes in 30 days and 1-year.

	BAV						TAV					
	HALT in 30 days *n* = 25	**No HALT in 30 days *n* = 140**	***P*-value**	**HALT in 1-year *n* = 52**	**No HALT in 1-year *n* = 97**	***P*-value**	**HALT in 30 days *n* = 19**	**No HALT in 30 days *n* = 172**	***P*-value**	**HALT in 1-year *n* = 62**	**No HALT in 1-year *n* = 104**	***P*-value**
All-cause mortality	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Cardiovascular mortality	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–
All stroke	0 (0)	1 (0.7)	1.000	1 (1.9)	1 (1.0)	1.000	0 (0)	1 (0.6)	1.000	0 (0)	0 (0)	–
Disabling stroke	0 (0)	1 (0.7)	1.000	1 (1.9)	0 (0)	0.349	0 (0)	1 (0.6)	1.000	0 (0)	0 (0)	–
Rehospitalization	1 (5.0)	10 (7.1)	0.723	8 (15.4)	17 (17.5)	0.739	0 (0)	10 (5.8)	0.602	7 (11.3)	13 (12.5)	0.817
Myocardial infarction	0 (0)	1 (0.7)	1.000	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Valve endocarditis	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–
NYHA functional class III/IV	7 (35.0)	35 (25.0)	0.342	5 (9.6)	9 (9.3)	0.946	6 (31.6)	54 (31.4)	0.987	9 (14.5)	19 (18.3)	0.532
Bleeding	0 (0)	4 (2.9)	1.000	3 (5.8)	4 (4.1)	0.695	0 (0)	2 (1.2)	1.000	2 (3.2)	2 (1.9)	0.630
Major bleeding	0 (0)	1 (0.7)	1.000	2(3.8)	1 (1.0)	0.279	0 (0)	1 (0.6)	1.000	0 (0)	1 (1.0)	1.000
New fibrillation/flutter	0 (0)	2 (1.4)	1.000	1 (1.9)	0 (0)	0.349	0 (0)	1 (0.6)	1.000	0 (0)	3 (2.9)	0.294
D-dimer, ug/L	1575.0 ± 1421.3	1489.1 ± 2092.2	0.203	864.1 ± 560.0	832.7 ± 1058.3	0.844	1053.2 ± 1027.4	1538.7 ± 2050.1	0.324	1093.6 ± 1010.1	844.7 ± 738.1	0.080
NT-ProBNP, pg/ml	868.3 ± 777.4	1190.4 ± 1301.7	0.295	608.4 ± 707.0	725.1 ± 1207.6	0.530	1801.7 ± 1767.0	2218.5 ± 5284.8	0.685	846.6 ± 1026.9	834.2 ± 1433.6	0.954
Use of anticoagulation*	3 (15.0)	29 (20.7)	0.767	7 (13.5)	31 (32.0)	0.014	6 (31.6)	45 (26.2)	0.613	9 (14.5)	35 (33.7)	0.007
Warfarin	3 (15.0)	29 (20.7)	0.767	5 (9.6)	31 (32.0)	0.002	6 (31.6)	45 (26.2)	0.613	7 (11.3)	34 (32.7)	0.002
Rivaroxaban	0 (0)	0 (0)	–	2 (3.8)	0 (0)	0.120	0 (0)	0 (0)	-	2 (3.2)	1 (1.0)	0.556

*Values are mean ± SD or number (%). *Number was counted at the day of pre-CT procedure.*

BAV, bicuspid aortic valve; HALT, hypoattenuated leaflet thickening; NT-ProBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TAV, tricuspid aortic valve.

In this study, only a few clinical adverse events were observed. There was no difference between the HALT and no HALT groups in BAV or TAV involvement. Some studies showed a higher rate of stroke, transient ischemic attack (TIA), and thromboembolic complications or stroke, and the TIAs were higher in patients with the HALT than in patients with no HALT (2, 6). However, the relationship between the SLT and clinical adverse events still needs a larger sample size trials to confirm.

There were some limitations in this study. First, this was a retrospective study that couldn't avoid some bias, for example, selective bias. Second, the time point of the CT scan was not the exact timepoint of the SLT occurrence. Third, the sample size was not large enough to assess the differences of clinical adverse events.

CONCLUSION

The presence of subclinical leaflet thrombosis defined by the CT was comparable between the BAV and TAV in the first year after the TAVR procedure. Age and anticoagulation were the independent predictors of the subclinical leaflet thrombosis at 1 year after the TAVR.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Second Affiliated Hospital Zhejiang University School of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GZ: collection, analysis and explanation of data, and drafting of the manuscript. JF: collection, analysis and explanation of data, and revising of the manuscript. DZ, HD, QZ, YH, and YG: collection and analysis of data. XL: conception, design, and revising of the manuscript. JW: conception. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Zhejiang Province Science and Technology Department Key R&D Program (2021C03097).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.790069/full#supplementary-material

REFERENCES

1. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med.* (2015) 373:2015–24. doi: 10.1056/NEJMoa1509233
2. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet.* (2017) 389:2383–92. doi: 10.1016/S0140-6736(17)30757-2
3. Sondergaard L, De Backer O, Kofoed KF, Jilaihawi H, Fuchs A, Chakravarty T, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. *Eur Heart J.* (2017) 38:2201–7. doi: 10.1093/eurheartj/ehx369
4. Yanagisawa R, Hayashida K, Yamada Y, Tanaka M, Yashima F, Inohara T, et al. Incidence, predictors, and Mid-term outcomes of possible leaflet thrombosis after TAVR. *J Am Coll Cardiol Img.* (2016) 9:S1936-878X(16)30897-X. doi: 10.1016/j.jcmg.2016.11.005
5. De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med.* (2020) 382:130–9. doi: 10.1056/NEJMoa1911426
6. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol.* (2020) 75:3003–15. doi: 10.1016/j.jacc.2020.04.043
7. Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, et al. Bioprosthetic aortic valve leaflet thickening in the evolut low risk sub-study. *J Am Coll Cardiol.* (2020) 75:2430–42. doi: 10.1016/j.jacc.2020.03.022
8. Waksman R, Craig PE, Torguson R, Asch FM, Weissman G, Ruiz D, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe bicuspid aortic valve stenosis. *JACC Cardiovasc Interv.* (2020) 13:1019–27. doi: 10.1016/j.jcin.2020.02.008
9. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
10. Jilaihawi H, Asch FM, Manasse E, Ruiz CE, Jelnin V, Kashif M, et al. Systematic CT methodology for the evaluation of subclinical leaflet thrombosis. *J Am Coll Cardiol Img.* (2017) 10:461–70. doi: 10.1016/j.jcmg.2017.02.005
11. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol.* (2021) 77:2717–46. doi: 10.1016/j.jacc.2021.02.038
12. Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* (2017) 38:3382–90. doi: 10.1093/eurheartj/ehx303
13. Szilveszter B, Oren D, Molnár L, Apor A, Nagy AI, Molnár A, et al. Subclinical leaflet thrombosis is associated with impaired reverse remodelling after transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging.* (2020) 21:1144–51. doi: 10.1093/ehjci/jez256
14. Yoon SH, Webb JG, Leon MB, Makkar R. Transcatheter aortic valve replacement in bicuspid aortic valve stenosis.

Prog Cardiovasc Dis. (2020) 63:482–7. doi: 10.1016/j.pcad.2020.06.007

15. Hein M, Minners J, Jander N, Breitbart P, Stratz C, Pache G, et al. Haemodynamic prosthetic valve performance in patients with early leaflet thrombosis after transcatheter aortic valve implantation. *Clin Res Cardiol.* (2019) 108:1017–24. doi: 10.1007/s00392-019-01429-7
16. Khan JM, Rogers T, Waksman R, Torguson R, Weissman G, Medvedofsky D, et al. Hemodynamics and subclinical leaflet thrombosis in low-risk patients undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Imaging.* (2019) 12:e009608. doi: 10.1161/CIRCIMAGING.119.009608
17. Sharma A, Lavie CJ, Elmariah S, Borer JS, Sharma SK, Vemulapalli S, et al. Relationship of body mass index with outcomes after transcatheter aortic valve replacement: results from the national cardiovascular -STS/ACC TVT registry. *Mayo Clin Proc.* (2020) 95:57–68. doi: 10.1016/j.mayocp.2019.09.027

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 22 December 2021
doi: 10.3389/fcvm.2021.771346

Integrated Aortic-Valve-And-Ascending-Aortic Replacement vs. Partial Replacement in Bicuspid Aortic Valve-Related Aortopathy

Mi Chen[1,2†], Wangli Xu[3†], Yan Ding[1], Honglei Zhao[1], Pei Wang[3], Bo Yang[1], Huanyu Qiao[1], Wei Zhang[1], Chenyang Zhou[1], Junnan Jia[4], Tao Bai[1], Jinrong Xue[1], Junming Zhu[1], Yongmin Liu[1], Weimin Li[4] and Lizhong Sun[1]**

[1] Department of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, [2] Department of Cardiac Surgery, University Hospital of Zurich, University of Zurich, Zurich, Switzerland, [3] Center for Applied Statistics and School of Statistics, Renmin University of China, Beijing, China, [4] National Tuberculosis (TB) Clinical Lab, Beijing Chest Hospital, Capital Medical University, Beijing, China

Objective: We sought to evaluate the outcomes of integrated aortic-valve and ascending-aortic replacement (IR) vs. partial replacement (PR) in patients with bicuspid aortic valve (BAV)-related aortopathy.

Methods: We compared long-term mortality, reoperation incidence, and the cumulative incidence of stroke, bleeding, significant native valve or prosthetic valve dysfunction, and the New York Heart Association (NYHA) functional classes II-IV between inverse probability-weighted cohorts of patients who underwent IR or PR for BAV-related aortopathy in a single center from 2002 to 2019. Patients were stratified into different aortic diameter groups ("valve type" vs. "aorta type").

Results: Among patients with "valve type," aortic valve replacement in patients with an aortic diameter > 40 mm was associated with significantly higher 10-year mortality than IR compared with diameter 35–40 mm [17.49 vs. 5.28% at 10 years; hazard ratio (HR), 3.22; 95% CI, 1.52 to 6.85; $p = 0.002$]. Among patients with "aorta type," ascending aortic replacement in patients with an aortic diameter 52–60 mm was associated with significantly higher 10-year mortality than IR compared with diameter 45–52 mm (14.49 vs. 1.85% at 10 years; HR, 0.04; 95% CI, 1.06 to 85.24; $p = 0.03$).

Conclusion: The long-term mortality and reoperation benefit that were associated with IR, as compared with PR, minimizing to 40 mm of the aortic diameter among patients with "valve type" and minimizing to 52 mm of the aortic diameter among patients with "aorta type."

Trial Registration: Treatment to Bicuspid Aortic Valve Related Aortopathy (BAVAo Registry): ChiCTR.org.cn no: ChiCTR2000039867.

Keywords: bicuspid aortic valve, aortopathy, bicuspid aortic valve-related aortopathy, aneurysm, aortic dilatation

OPEN ACCESS

Edited by:
Antonio Miceli,
Istituto Clinico Sant'Ambrogio, Italy

Reviewed by:
Guglielmo Saitto,
San Camillo-Forlanini Hospital, Italy
Okan Yurdakok,
Dr. Siyami Ersek Chest Cardiovascular Surgery Training and Research Hospital, Turkey

***Correspondence:**
Lizhong Sun
lizhongsun@foxmail.com
Weimin Li
kwm_18@aliyun.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Heart Surgery, a section of the journal Frontiers in Cardiovascular Medicine

Received: *06 September 2021*
Accepted: *23 November 2021*
Published: *22 December 2021*

Citation:
Chen M, Xu W, Ding Y, Zhao H, Wang P, Yang B, Qiao H, Zhang W, Zhou C, Jia J, Bai T, Xue J, Zhu J, Liu Y, Li W and Sun L (2021) Integrated Aortic-Valve-And-Ascending-Aortic Replacement vs. Partial Replacement in Bicuspid Aortic Valve-Related Aortopathy. Front. Cardiovasc. Med. 8:771346. doi: 10.3389/fcvm.2021.771346

INTRODUCTION

Bicuspid aortic valve (BAV) disease is the most common congenital cardiac disorder, being present in 1–2% of the general population (1). Associated aortopathy, the dilatation of the aortic sinuses, and ascending aorta are present in ∼20–40% of patients with BAV (2). Evidence of phenotypic heterogeneity of BAV and BAV aortopathy has emerged in the last decades. The classification of Sievers is most widely adopted to describe the morphology of BAV, namely the valvular phenotype (3). For aortopathy, the ascending phenotype vs. root phenotype has been proposed to require individualized surgical approaches (4, 5). Although evidence supporting treatment of BAV and aortopathy as separate entity has increased, data on the combined (valve and aorta) pathological phenotypes remain scarce. A comprehensive understanding of the interaction between morphologic features and functional characteristics of the BAV and aortopathy along with transvalvular hemodynamics is required. In particular, the 2 long-debated hypotheses with respect to the pathogenesis of BAV-related aortopathy—namely, the genetic and the hemodynamic theories—may contribute to differing causative factors. Previous data from mixed BAV cohorts resulted in a broad spectrum of surgical treatment methods being suggested, ranging from very conservative approaches to very aggressive recommendations (6). Currently, among patients with BAV with significant valve dysfunction, the practice guideline recommended cutoff for concomitant ascending aortic replacement is 45 mm (7, 8). However, there is a lack of evidence to clarify the need for concomitant aortic valve replacement among patients with dilated aorta, but without significant BAV dysfunction. As etiologic hypotheses based on the phenotypic heterogeneity of BAV and aortopathy continue to be discussed, specific surgical approaches and timing may be required. The aim of this study was to compare the perioperative and follow-up benefits and risks of integrated aortic-valve-and-ascending-aortic replacement (IR) vs. partial replacement (PR) for BAV-related aortopathy.

METHODS

Study Design

In this single-center inverse probability-weighted cohort study, we examined data from patients with BAV-related aortopathy who underwent IR or PR from January 1, 2002 to December 31, 2019 to evaluate the effect of surgical treatment on all-cause mortality and reoperation and the incidence of stroke, bleeding, significant native valve or prosthetic valve dysfunction, and the New York Heart Association (NYHA) functional class II-IV. This study was approved by an Institutional Review Board and the Institutional Review Board waived the need for a written informed consent of the patient. This study was registered with chictr.org.cn (ChiCTR2000039867, Methods in **Supplementary Material**). The patients were followed at 3 months, 6 months, and 1-year interval. Study investigators verified and validated investigation outcomes from the institutional database and standardized telephonic interviews (**Figure 1A** and Methods in **Supplementary Material**).

Study Population and Pathophysiologic Classification

Patients were included in this study if they were diagnosed as BAV and underwent IR or PR. Decisions on IR or PR were based on the practical guidelines (6–10). Stepwise heart team approaches were taken by single unit (guidelines-based decision), multiunit approach, multidisciplinary approach, and heart center approach when symptoms and frailty, the burden of comorbidities, and technical aspects of patients necessitated further evaluation (**Figure 1B**). In particular, a risk factor of dissection (family history of aortic dissection, if the rate of increase in diameter is $\geq$ 0.3 cm per year or uncontrollable hypertension) and relatively low body surface area would be taken into consideration in the heart team to decide whether to perform a concomitant ascending aortic replacement; moderate aortic stenosis/aortic regurgitation (AS/AR), morphology of BAV, the diameter of the aorta, and the prognosis with untreated BAV would be taken into consideration in heart team to decide whether to perform a concomitant aortic valve replacement.

Based on emerging phenotypic heterogeneity of BAV-related aortopathy (3–5), we propose a simple nomenclature classification to include the valve and aorta together. We propose the terms "valve type" and "aorta type" to represent the most dysfunctional part among BAV-related aortopathy. Criteria for "valve type" included: (1) significant aortic valve dysfunction and (2) with or without aortic dilatation. Criteria for "aorta type" included: (1) without significant aortic valve dysfunction and (2) aortic diameter (aortic sinuses or ascending aorta) > 40 mm (**Figure 1C**).

Among patients with "valve type," aortic valve replacement, as PR, was compared with IR. Among "aorta type," ascending aortic replacement, as PR, was compared with IR. IR was defined as surgical treatment including aortic valve replacement and ascending aortic replacement.

Patients undergoing either the Bentall procedure (with coronary artery ostia reimplantation) or the Wheat procedure (11) (without coronary artery ostia reimplantation) were included as IR. Patients with concomitant coronary artery bypass graft (CABG), atrial fibrillation ablation (AFA), or tricuspid valve plasty (TVP) were included to improve statistical power. Exclusion criteria were concomitant mitral valve repair or replacement, aortic valve repair, ascending aortic repair, and descending aortic replacement, given that double valve replacement is associated with worse ventricular function and increased risk of bleeding.

Echocardiographic Evaluation

Transthoracic echocardiography and transesophageal echography play key roles to screen pathophysiologic types. Function and morphology of BAV were verified and re-evaluated by the echocardiographic core laboratory based on the 2020 American College of Cardiology/American Heart Association (ACC/AHA) guideline (12). The criteria to evaluate the severity of aortic valve dysfunction were as follows: (1) severe AS was defined as aortic Vmax $\geq$ 4 m/s or mean $\Delta P \geq 40$ mm Hg; (2) moderate AS was defined as 20 mm Hg < mean ΔP < 40 mm

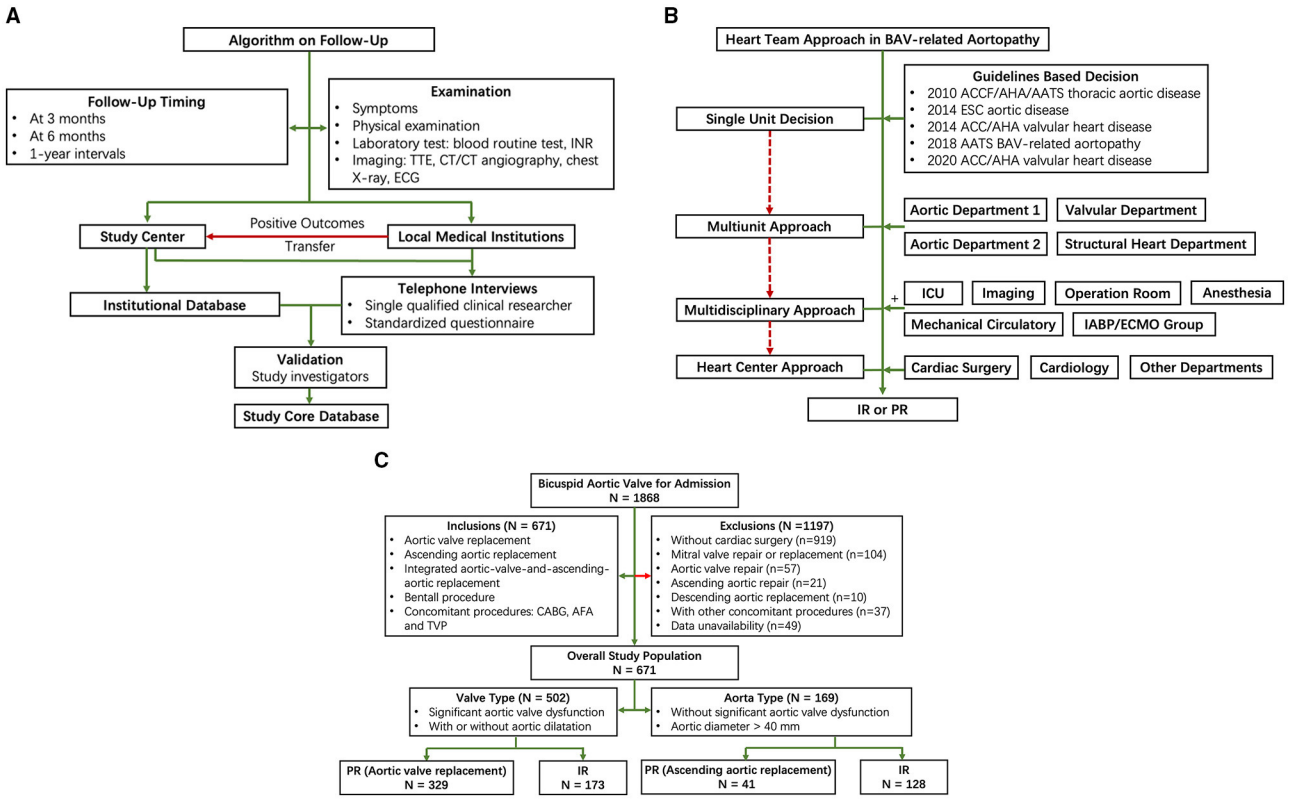


FIGURE 1 | Flow diagram of study design. **(A)** Follow-up; **(B)** Heart team approach; and **(C)** Patient selection. AFA, atrial fibrillation ablation; CABG, coronary artery bypass graft; ICU, intensive care unit; INR, international normalized ratio; IR, integrated aortic-valve-and-ascending-aortic replacement; PR, partial replacement; TTE, transthoracic echocardiography; TVP, tricuspid valve plasty.

Hg; (3) severe AR was defined as vena contracta $>$ 0.6 cm or effective regurgitant orifice (ERO) $\geq$ 0.3 cm^2; (4) moderate AR was defined as 0.3 cm $<$ vena contracta $<$ 0.6 cm; and (5) mild stenosis and regurgitation were regarded as normal valve function. Accordingly, severe AS or severe AR was regarded as significant aortic valve dysfunction. The remaining valve function was regarded as BAV without significant dysfunction. Based on the classification described by Sievers et al. (3), BAV morphology was classified into type 0 without raphe, type 1 with 1 raphe, and type 2 with 2 raphes (also called unicuspid aortic valve) according to the presence and number of raphes.

The aortic evaluation included the diameter of aortic sinuses and the ascending aorta by echocardiography. The aortic diameter was defined as the largest of the 2 diameters measured at the aortic sinus and the ascending aorta.

Stratification Workflow

Stratification was based on the ascending aortic diameter. First, we stratified the study patients with 5-mm intervals roughly according to the current guidelines (9). For "valve type," the stratification categories were: (1) 35–40 mm group and $>$ 40 mm group and (2) 35–45 mm group and $>$ 45 mm group. For "aorta type," the stratification categories were: (1) 45–50 mm group and $>$ 50 mm group and (2) 45–55 mm group and $>$ 55 mm group.

Second, based on the results of the Cox proportional-hazards model, a 1-mm interval was taken to modify the trial categories. Equivalent dimension intervals were taken in two cohorts to achieve appropriate study power assessment if a 1-mm interval was needed.

Study Endpoints

The primary endpoints were mortality and reoperation. Secondary endpoints included the cumulative incidence of stroke, bleeding, significant native valve or prosthetic valve dysfunction, and the NYHA functional classes II-IV. Safety endpoints included the freedom of cumulative incidence of death, reoperation for complications, non-elective cardiovascular surgery for adverse events, and deep wound infection within 1 month.

Statistical Analysis

This study was designed to have a power of at least 90%, at an alpha level of 0.05, to detect a between-group hazard ratio of 3.5 for the analysis of mortality among patients with "valve type" with ascending aortic diameter of $>$ 40 mm at 10 years and among patients with "aorta type" with ascending aortic diameter of $>$ 55 mm at 10 years. Patients with smaller or larger diameters were included as

contrast (13). We predicted IR that was associated with lower mortality in larger ascending aortic diameter and PR that was associated with lower mortality in smaller ascending aortic diameter.

We used inverse probability weighting to limit confounding by indication, particularly for the Sievers classification, valve function, and aortic phenotype (Methods section in the **Supplementary Material**). In each diameter group, non-parsimonious logistic regression was used to estimate probability of each patient to undergo IR or PR. Stabilized weights were calculated by dividing the marginal probability of the observed procedure by propensity score for the treatment received. The balance between the treatment groups was assessed with the use of standardized mean differences. A standardized mean difference of 10% or less was deemed to be the ideal balance and a standardized mean difference of 20% or less was deemed to be an acceptable balance.

The Cox proportional-hazards model with a robust variance estimator was used to compare long-term mortality between the groups. Separate analyses of the weighted population were adjusted for sinus diameter or included surgeon as a random effect. To address non-proportional hazards, the restricted mean survival time was estimated to describe the overall effect of treatment during the study period. Subdistribution hazards in the weighted populations were estimated with the method of Fine and Gray. SEs were estimated with the use of 500 bootstrap replicates.

To explore the diameter-dependent effect of different procedures on death and reoperation, the Cox proportional-hazards model was fit to the entire weighted study population with the use of an interaction term for aortic diameter and procedure. SEs were calculated from 1,000 bootstrap replicates. All the tests of treatment effect were two-tailed with an alpha threshold of 0.05. Statistical analyses were performed with the use of R software, version 4.0.3 (R Foundation) and data management was performed with the use of SPSS software, version 24 (SPSS Incorporation, Chicago, Illinois, USA). Additional details with respect to the statistical analysis are provided in the Methods section in the **Supplementary Material**.

RESULTS

Of 1,868 patients who were diagnosed as BAV for admission during the study period, 671 patients were eligible for inclusion in

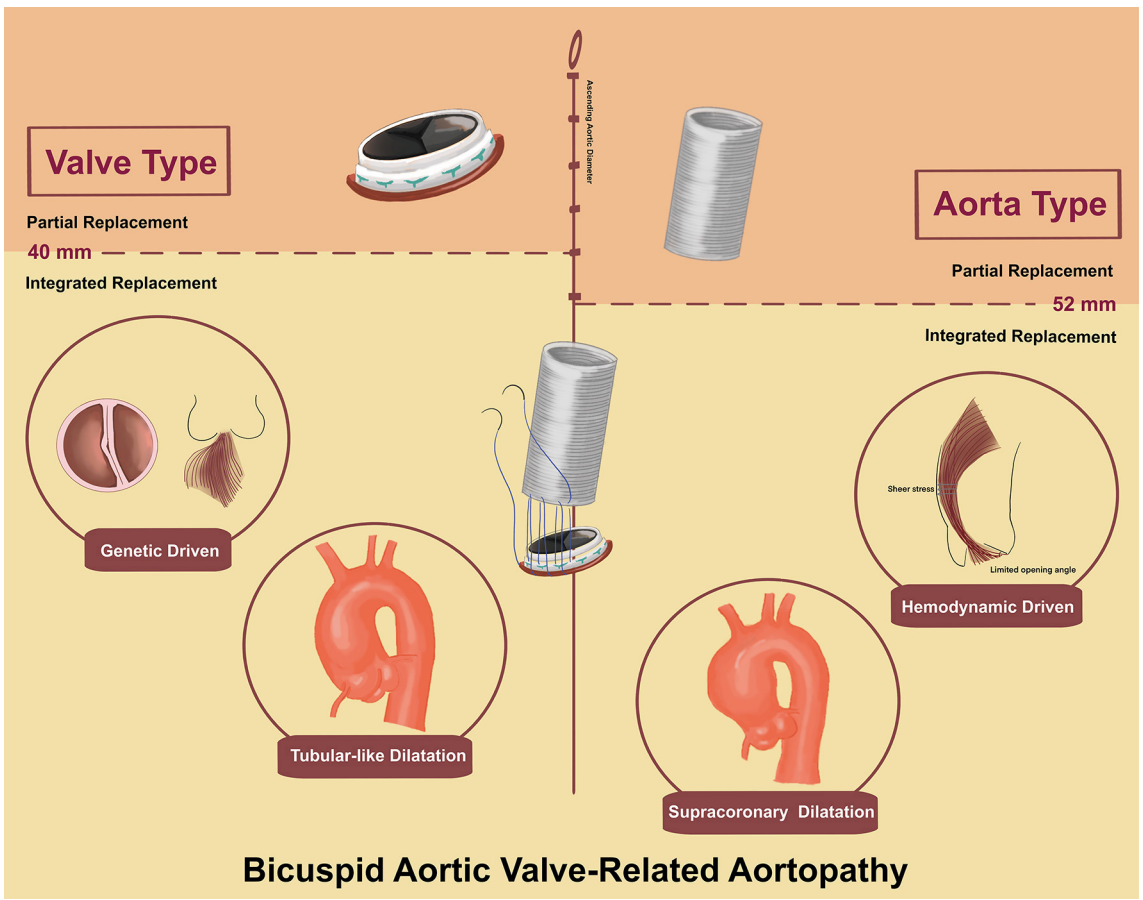


FIGURE 2 | BAV-related Aortopathy.

this study. A total of 502 patients and 169 patients were included in "valve type" and "aorta type," respectively (**Figure 1C**). Among patients with "valve type," the median follow-up was 4.92 years in the PR cohort and 4.75 years in the IR cohort. Among patients with "aorta type," the median follow-up time was 3.33 years in the PR cohort and 4.58 years in the IR cohort.

Clinical Characteristics of "Valve Type" and "Aorta Type"

Different aortic diameter distribution and the aortic valve function and morphology emerged in "valve type" vs. "aorta type" (**Supplementary Figures 5, 6**, **Supplementary Tables**).

In terms of valve function, among "valve type," a similar percentage of severe AS and AR was showed (47.4 vs. 47.8%), while among "aorta type," moderate stenosis had a higher incidence than moderate regurgitation (18.3 vs. 11.8%). With respect to valve morphology, Sievers' type 1 was dominant in both the "valve type" and "aorta type" (51.2 vs. 60.4%), whereas type 0 had a higher percentage in "valve type" and the distribution of the Sievers classification was significantly different ($p = 0.03$).

Concerning the aortic dimensions, the "valve type" had an overall smaller dimension in aortic diameter (43.2 ± 8.2 vs. 53.6 ± 6.9 mm, $p < 0.01$), sinus diameter (35.6 ± 7.5 vs. 38.0 ± 7.7 mm, $p < 0.01$), and ascending aortic diameter (42.3 ± 8.4 vs. 52.9 ± 7.8 mm, $p < 0.01$). However, "aorta type" showed a higher ascending sinuses ratio than "valve type" (1.4 ± 0.3 vs. 1.2 ± 0.3 mm, $p < 0.01$), which was associated with supracoronary dilatation vs. tubular dilation (**Figure 2**).

Inverse Probability Weighting Cohorts

Baseline and operative characteristics before inverse probability weighting are shown in **Table 1**. After using inverse probability weighting, the study population consisted of 333.3 vs. 178.7 in "valve type" and 47.4 vs. 132.4 in "aorta type," which were not necessarily integers owing to inverse probability weighting. The standardized mean differences indicated an adequate match between PR and IR in both the types. Baseline characteristics of the cohorts were more balanced (standardized mean differences < 15%) with considerable objectives reserved to enhance power (**Supplementary Tables 3, 4**).

Primary Endpoints in "Valve Type"

Among diameter group of > 40 mm, IR was associated with a significantly lower cumulative incidence of all-cause mortality and reoperation than PR [11.98 vs. 4.65% at 5 years; 17.49 vs. 5.28% at 10 years; hazard ratio (HR), 3.22; 95% CI, 1.52 to 6.85; $p = 0.002$], but the difference was not significant among 35 to 40 mm diameter of the aorta (**Table 2** and **Figures 3A,B**). These relationships were unaffected by multivariable adjustment or incorporation of the first operator as a random effect. Despite evidence of non-proportional hazards, the results of the comparisons of the restricted mean survival time (RMST) at 10 years were consistent with the marginal HRs but not at 5 years (**Table 2**). At 10-year RMST, PR gained−11.3 (95% CI,−19.6 to−3.0) additional months than IR ($p = 0.007$). Until 10 years, the ratio of life lost was 2.65 (1.3–5.6; $p = 0.01$) between PR and IR. When aortic diameter was examined as a continuous variable, the relative mortality benefits were associated with PR until ∼40 mm of aortic diameter (**Figure 4A**). The individual endpoint of all-cause mortality was consistent with the co-endpoint, while reoperation showed no difference in IR vs. PR (**Supplementary Material**).

Secondary Endpoints in "Valve Type"

Among 35–40 mm of aortic diameter, the co-secondary endpoints occurred less frequently among PR than IR (HR, 0.39; 95% CI, 0.15 to 1.0; $p = 0.05$), but the difference was not significant among diameter > 40 mm. Concerning the freedom from the NYHA function classes II-IV, the difference was not significant in both the 35–40 mm group and > 40 mm group. Safety endpoints were not significantly different in PR vs. IR (**Supplementary Material**).

Primary Endpoints in "Aorta Type"

Among diameter group of 52–60 mm, PR was associated with a significantly higher cumulative incidence of mortality and reoperation than IR (14.49 vs. 1.85% at 5 years; 14.49 vs. 1.85% at 10 years; HR, 9.52; 95% CI, 1.06 to 85.24; $p = 0.04$), but the difference was not significant among 45–52 mm diameter of the aorta (**Table 3** and **Figures 3C,D**). These relationships were unaffected by multivariable adjustment or incorporation of the first operator as a random effect. The results of the comparisons of the restricted mean survival time were not significant at 5 and 10 years. When aortic diameter was examined as a continuous variable, the relative mortality benefits were associated with PR until ∼52 mm of aortic diameter (**Figure 4B**). The individual endpoint of all-cause mortality was consistent with the co-endpoint, while reoperation showed no difference in IR vs. PR (**Supplementary Material**).

Secondary Endpoints in "Aorta Type"

The occurrence of co-secondary endpoints was not significantly different in the 45–52 mm group (HR, 2; 95% CI, 0.69–5.76; $p = 0.2$) and the 52–60 mm group (HR, 2.04; 95% CI, 0.76–5.46; $p = 0.16$). The NYHA functional class II-IV was lower among PR than IR (HR, 3.55; 95% CI, 0.99–12.72; $p = 0.05$) among the 52–60 mm group, whereas the difference was not significant among the 45–52 mm group.

Safety endpoints were shown no difference in PR vs. IR (**Supplementary Material**).

DISCUSSION

The main findings of this study are as follows: (1) A simple nomenclature classification can be used to describe the valve-and-aorta phenotype in BAV-related aortopathy; (2) IR was associated with long-term mortality and reoperation benefits compared with PR; and (3) The cutoff for IR was 45 mm in the "valve type" and 52 mm in the "aorta type."

Entity: Valve and Aorta

The prevalence of dilation of the ascending aorta among patients with BAV has been highly variable with reports ranging from 20 to 84% (14). Since the 1990s, these findings have generated

TABLE 1 | Baseline and operative characteristics before inverse probability weighting.

Characteristic	Valve type			Aorta type		
	PR (*N* = 329)	IR (*N* = 173)	Effect size	PR (*N* = 41)	IR (*N* = 128)	Effect size
Age (years)	48.7 ± 14.4	50.0 ± 12.1	−0.1	52.3 ± 9.0	50.4 ± 12.1	0.17
Year of surgery	2015 ± 3.1	2015.2 ± 3.1	−0.06	2016.4 ± 2.5	2015.2 ± 2.8	0.44
Study period			0.041			0.242
2002–2007	3 (0.9%)	1 (0.6%)		0	0	
2008–2013	94 (28.6%)	48 (27.7%)		7 (17.1%)	40 (31.2%)	
2014–2020	232 (70.5%)	124 (71.7%)		34 (82.9%)	88 (68.8%)	
Female sex			0.296			0.425
Male	228 (69.3%)	144 (83.2%)		25 (61.0%)	106 (82.8%)	
Female	101 (30.7%)	29 (16.8%)		16 (39.0%)	22 (17.2%)	
Valvular disease			0.204			0.556
Severe AS	166 (50.5%)	72 (41.6%)		-	-	
Severe AR	151 (45.9%)	89 (51.4%)		-	-	
Severe AS + AR	12 (3.6%)	12 (7.0%)		-	-	
Moderate AS	-	-		3 (7.3%)	34 (26.6%)	
Moderate AR	-	-		0	18 (14.1%)	
Moderate AS + AR	-	-		0	8 (6.3%)	
Mild or None AS/AR	-	-		38 (92.7%)	68 (53.1%)	
Severe AS						
Aortic V_{max} (m/s)	504.0 ± 76.1	500.4 ± 70.9	0.048	-	-	
Mean ΔP	63.3 ± 21.2	60.5 ± 19.0	0.137	-	-	
Severe AR						
ERO (mm^2)	45.2 ± 15.7	52.4 ± 19.6	0.419	-	-	
Vena Contracta (mm)	7.6 ± 1.7	8.0 ± 1.2	0.258	-	-	
Severe AS +AR						
Aortic V_{max} (m/s)	504 ± 75.7	455.3 ± 41.5	0.737	-	-	
Mean ΔP (mm Hg)	70.1 ± 31.4	49.2 ± 7.2	0.81	-	-	
ERO (mm^2)	43.0 ± 10.8	41 ± 13.5	0.169	-	-	
Vena Contracta (mm)	7.4 ± 0.9	7.4 ± 1.1	0			
Aortic valve diameter (mm)	23.3 ± 3.1	25.6 ± 4.0	0.668	22.7 ± 2.0	24.0 ± 2.4	−0.56
Aortic sinuses diameter (mm)	33.1 ± 5.4	40.3 ± 8.6	1.077	36.0 ± 4.4	38.6 ± 8.4	−0.339
Ascending aortic diameter (mm)	38.5 ± 5.8	49.6 ± 7.7	1.701	53.7 ± 4.5	52.7 ± 8.6	0.127
Aortic diameter (mm)*	39.2 ± 5.4	50.9 ± 7.2	1.922	53.7 ± 4.5	53.6 ± 7.5	0.014
Sievers's BAV type			0.159			0.014
Type 0	162 (49.2%)	71 (41.0%)		17 (41.5%)	50 (39.1%)	
Type 1	160 (48.6%)	97 (56.1%)		24 (58.5%)	78 (60.9%)	
Type 2	7 (2.1%)	5 (2.9%)		0	0	
Coexisting condition						
Hypertension	81 (24.6%)	57 (32.9%)	0.169	15 (36.6%)	47 (36.7%)	0
Diabetes mellitus	23 (7.0%)	14 (8.1%)	0.024	0	6 (4.7%)	0.143
Coronary artery disease	34 (10.3%)	15 (8.7%)	0.039	8 (19.5%)	17 (13.3%)	0.112
Peripheral vascular disease	7 (2.1%)	3 (1.7%)	0	1 (2.4%)	2 (1.6%)	0
Cerebrovascular disease	10 (3.0%)	5 (2.9%)	0	2 (4.9%)	6 (4.7%)	0.007
Congestive heart failure	159 (48.3%)	78 (45.1%)	0.053	12 (29.3%)	46 (35.9%)	0.091
Atrial fibrillation	9 (2.7%)	3 (1.7%)	0.035	1 (2.4%)	4 (3.1%)	0
COPD	2 (0.6%)	1 (0.6%)	0	0	0	
SBE	23 (7.0%)	2 (1.2%)	0.237	0	0	
Chronic kidney disease	1 (0.3%)	2 (1.2%)	0.051	0	3 (2.3%)	0.048
Renal dialysis	0	0		0	1 (0.8%)	0
Liver disease	8 (2.4%)	10 (5.8%)	0.149	3 (7.3%)	3 (2.3%)	0.156

(Continued)

TABLE 1 | Continued

Characteristic	Valve type			Aorta type		
	PR (*N* = 329)	IR (*N* = 173)	Effect size	PR (*N* = 41)	IR (*N* = 128)	Effect size
Cancer	2 (0.6%)	0	0.025	2 (4.9%)	0	0.261
History of smoking	98 (29.8%)	58 (33.5%)	0.068	13 (31.7%)	51 (39.8%)	0.116
Dissection	1 (0.3%)	3 (1.7%)	0.106	0	7 (5.5%)	0.167
Obesity	15 (4.6%)	11 (6.4%)	0.058	2 (4.9%)	13 (10.2%)	0.111
Concomitant procedure						
CABG	18 (5.5%)	13 (7.5%)	0.063	2 (4.9%)	14 (10.9%)	0.131
TVP	0	0		0	0	
AFA	3 (0.9%)	1 (0.6%)	0	0	0	
Bentall procedure	0	129 (74.6%)		0	91 (71.1%)	
Prosthetic type			0.34			
Mechanical	271 (82.4%)	164 (94.8%)		-	122 (95.3%)	
Biological	58 (17.6%)	9 (5.2%)		-	6 (4.7%)	

**Aortic diameter was defined as the maximum diameter between aortic sinuses and ascending aorta.*

ΔP, pressure gradient between the LV and aorta; AFA, atrial fibrillation ablation; AR, aortic regurgitation; AS, aortic stenosis; BAV, bicuspid aortic valve; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ERO, effective regurgitant orifice; IR, integrated aortic-valve-and-ascending-aortic replacement; PR, partial replacement; SBE, subacute bacterial endocarditis; TVP, tricuspid valve plasty; V_{max}, maximum velocity.

TABLE 2 | Diameter-group differences in primary endpoints in "valve type*".

Variable	35–40 mm			>40 mm		
	PR (*N* = 130.1)	IR (*N* = 20.7)	*p*-value	PR (*N* = 126.5)	IR (*N* = 158.9)	*p*-value
Hazard ratio (95% CI)						
Weighted PH model	1.19 (0.14–9.80)	Reference	0.87	3.22 (1.52–6.85)	Reference	0.002
Weighted PH model, with multivariable adjustment†	0.91 (0.14–5.86)	Reference	0.92	3.22 (1.51–6.84)	Reference	0.002
Weighted PH model, with surgeon as random effect	0.38 (0.10–1.42)	Reference	0.15	3.21 (1.49–6.89)	Reference	0.003
5 years						
Incidence (%)	5.48	7.04	0.78	11.98	4.65	0.02
RMST 5 years (95% CI)						
Difference (months)	0.95 (-4.96–6.85)	Reference	0.75	−2.15 (-5.18–0.88)	Reference	0.17
Ratio	1.02 (0.92–1.13)	Reference	0.76	0.96 (0.91–1.02)	Reference	0.17
Ratio of RMSL	0.68 (0.09–5.31)	Reference	0.72	1.96 (0.76–5.04)	Reference	0.16
10 years						
Incidence (%)	7.7%	7.04%	0.9	17.49%	5.28%	0.001
RMST (95% CI)‡						
Difference—months	−2.3 (-16.2–11.6)	Reference	0.74	−11.3 (-19.6−3.0)	Reference	0.007
Ratio	0.98 (0.87–1.11)	Reference	0.74	0.89 (0.83–0.97)	Reference	0.009
Ratio of RMSL	1.34(0.18–9.8)	Reference	0.77	2.65(1.3–5.6)	Reference	0.01

**The overall numbers of patients in each group are not necessarily integers owing to inverse probability weighting.*

† The analysis was adjusted for sinuses diameter.

‡The RMST is the average duration of survival in a cohort over a prespecified follow-up period (5 and 10 years were reported here), as estimated by the area under the curve. The difference in the RMST is the average number of additional months gained in the treatment group (i.e., IR group minus PR group). The RMTL refers to the average number of days of life lost over a prespecified follow-up period; a ratio of more than 1.00 indicates that the treatment increased events incidence (or decreased the survival rate).

IR, integrated aortic-valve-and-ascending-aortic replacement; RMST, restricted mean survival time; RMTL, restricted mean time lost; PH, proportional hazards; PR, partial replacement.

two etiological hypotheses, "genetic" vs. "hemodynamic," which remain debated. Supporters of the "genetic hypothesis" claim that a strong genetic role contributes to BAV-related aortopathy and more aggressive surgical intervention should be recommended, equivalent to Marfan syndrome (6, 15). Conversely, supporters of the "hemodynamic hypothesis" claim

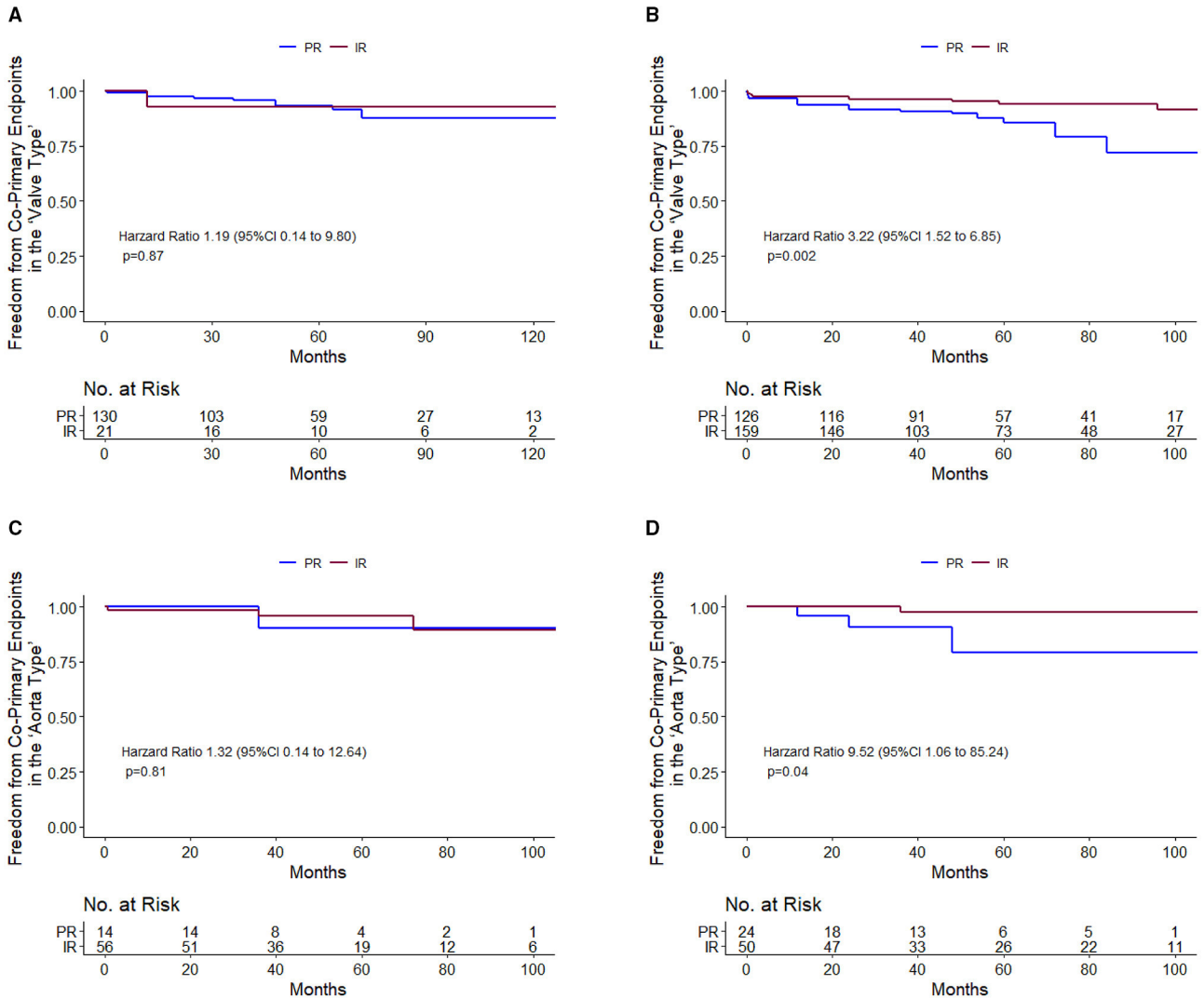


FIGURE 3 | Primary endpoint survival curves for freedom from death and reoperation. 35–40 mm in valve type **(A)**; >40 mm in valve type **(B)**; 45–52 mm in aorta type **(C)**; and 52–60 mm in aorta type **(D)**.

that abnormal flow patterns and asymmetrically increased wall stress resulting from BAV lead to proximal aortopathy and are less dangerous than described in the "genetic hypothesis" (16, 17). However, the marked heterogeneity of BAV-related aortopathy suggests more complex pathogenesis than simply "genetically determined" or "hemodynamically driven," contributing to the increasing recognition of the entity of BAV and aortopathy complex.

"Valve Type" and "Aorta Type"

The currently proposed phenotypes only focus on the valvular part (the Sievers classification) or aortic part (ascending phenotype vs. root phenotype) separately (4, 5). Based on the confirmed phenotype heterogeneity, we proposed a simple nomenclature, "valve type" and "aorta type," in order to include valve and aorta equivalently. The proposed classification is easily instituted by the cardiologist and cardiac surgeon with high precision and generalizability. This classification not only assists in diagnosing BAV-related aortopathy as an entity, but may also improve preprocedural planning and provide long-term benefit. Using this classification may allow cardiac surgeons to follow a phenotype-determined intervention timing.

Notably, the high incidence of Sievers' type 0 and AR in "valve Type" was associated with more instinct abnormality in the light of "genetic hypothesis." In contrast, "aorta type" with a supraannular dilation was associated with the "hemodynamic hypothesis," which was consistent with Barker et al. (16) who reported BAV causing regional aortic wall shear stress due to abnormal BAV-related ascending aortic flow jet patterns. Therefore, our simple nomenclature may connect the two main hypotheses to clinical manifestation.

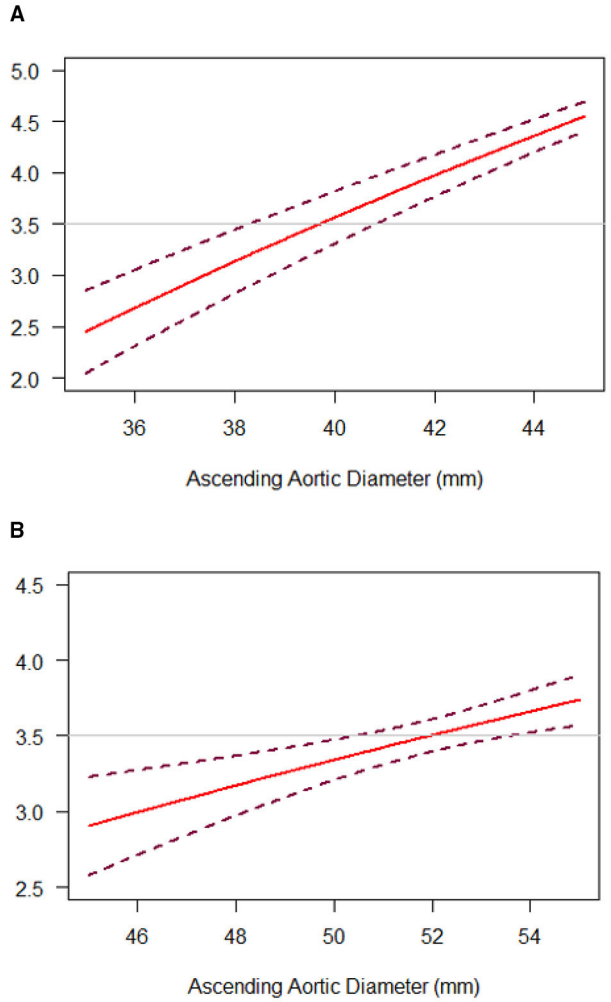


FIGURE 4 | Diameter-dependent hazard of death and reoperation with IR, as compared with PR, in the "Valve Type" **(A)** or "Aorta Type" **(B)** groups. The hazard ratio (HR) for death and reoperation with IR, as compared with PR, was plotted against ascending aortic diameter as a continuous variable (solid lines). Dashed lines representing the 95% CI were obtained from bootstrap resampling. The horizontal line at 3.5 was consistent with reported HR.

Integrated Replacement vs. PR in the "Valve Type"

Several previous guidelines have addressed the management of BAV-related aortopathy from aggressive recommendations to a more conservative set of recommendations (6, 12). However, referred study concluded the cutoff based on isolated aortic valve replacement with different aortic dimensions, a lack of IR cohort in contrast (18). We compared our cohorts with IR vs. PR to evaluate both the long-term feasibility and perioperative safety. Optimally, surgery should be recommended as soon as the risk of watchful waiting exceeds the risk of surgical intervention. To conclude an effective cutoff of a mortality benefit, we chose a HR of 3.5 in our continuous variable line to predict the approximate aortic diameter, given that Michelena et al. (13) reported aorta diameter $\geq$ 40 mm was a predictor of aneurysm formation with a HR of 3.4. These study findings are also adopted generally in aortic aneurysm management.

What Should Be the Determinant for Integrated Replacement in the "Aorta Type"?

For "aorta type" without significant dysfunction, no related studies showed the optimal timing and indication for IR. Factors that need to be considered include aortic diameter, valve function, and presence of surgical risk factors. Given that calcific AS usually presents between the 5th and 7th decades (19), optimal timing for IR may be recommended even without significant aortic valve dysfunction. In this study, a supracoronary dilatation was shown in the "aorta type," which demonstrated the dysfunction order. Based on the "hemodynamic hypothesis," we assumed that the restricted opening angle of the BAV leaflets would result in more severe aortic wall shear stress. However, the related BAV function could be normal or only mildly dysfunctional and the evaluation of the precise opening angle of leaflets could be challenging, which means the BAV itself cannot adequately predict the prognosis. The dilated aorta, however, could play a role as an indicator of the harm dealt by the BAV, given that the abnormal BAV leaflets may continue dilating the native or artificial aorta without valve replacement. Therefore, rather than valve function or sinus diameter, we stratified the study patients according to ascending aortic diameter. A 52-mm was showed as the cutoff for IR, which was more aggressive than the current guideline recommendations for PR (55 or 50 mm in patients with risk factors); evidence for IR is lacking (7). However, such guideline recommendations are based on the observation that 60 mm represents a definite inflection point in the risk of aortic complications in both the BAV and tricuspid aortic valve (TAV), but with a lack of BAV-specific evidence to support this conclusion (20). It is worthwhile noting that operative risk plays a lesser role for experienced aortic surgeons nowadays. The aggressive treatment using advanced cardiac surgical techniques may show prophylactic benefit.

LIMITATIONS

This study is limited by its retrospective and observational design. As numerous confounders exist in cardiac surgery studies, we used inverse probability weighting with well-balanced results to eliminate valve phenotype, aortic phenotype, and the other confirmed confounding factors between compared cohorts. Along with a limited study population, rather than propensity score pair matching, the use of inverse probability weighting reserved the maximal study population to enhance the generalizability and interpretability of study. Given a single-center study with a span of 20 years, we introduced the instrumental variables and selected "operator" as a strong variable to contrast the study outcomes. However, the utility of this classification and

TABLE 3 | Diameter-group differences in primary endpoints in "aorta type*."

Variable	45–52 mm			52–60 mm		
	PR (*N* = 15.7)	IR (*N* = 59.5)	*p*-value	PR (*N* = 25.9)	IR (*N* = 51.5)	*p*-value
Hazard ratio (95% CI)						
Weighted PH model	1.32 (0.14–12.64)	Reference	0.81	9.52 (1.06–85.24)	Reference	0.04
Weighted PH model, with multivariable adjustment†	1.3 (0.15–11.44)	Reference	0.81	10.18 (1.32–78.76)	Reference	0.03
Weighted PH model, with surgeon as random effect	4.86 (0.41–57.54)	Reference	0.21	13.54 (1.12–163.26)	Reference	0.04
5 years						
Incidence (%)	6.93%	3.43%	0.56	14.49%	1.85%	0.03
RMST 5 years (95% CI)						
Difference (months)	−0.77 (-5.79–4.25)	Reference	0.76	−4.74 (-10.83–1.36)	Reference	0.13
Ratio	0.99 (0.9–1.08)	Reference	0.76	0.92 (0.82–1.03)	Reference	0.14
Ratio of RMSL	1.47 (0.14–15.22)	Reference	0.75	8.1 (0.88–74.97)	Reference	0.07
10 years						
Incidence (%)	6.93%	5.16%	0.79	14.49%	1.85%	0.03
RMST 10 year (95% CI)‡						
Difference—months	−6.97 (-19.89–5.96)	Reference	0.29	−14.37 (-32.2–3.46)	Reference	0.11
Ratio	0.94 (0.84–1.06)	Reference	0.3	0.88 (0.74–1.04)	Reference	0.14
Ratio of RMSL	2.63 (0.56–12.25)	Reference	0.22	7.16 (0.8–64.04)	Reference	0.08

**The overall numbers of patients in each group are not necessarily integers owing to inverse probability weighting.*

† The analysis was adjusted for sinuses diameter.

‡The RMST is the average duration of survival in a cohort over a prespecified follow-up period (5 and 10 years were reported here), as estimated by the area under the curve. The difference in the RMST is the average number of additional months gained in the treatment group (i.e., IR group minus PR group). The RMTL refers to the average number of days of life lost over a prespecified follow-up period; a ratio of more than 1.00 indicates that the treatment increased events incidence (or decreased the survival rate).

BAV, bicuspid aortic valve; IR, integrated aortic-valve-and-ascending-aortic replacement; RMST, restricted mean survival time; RMTL, restricted mean time lost; PH, proportional hazards; PR, partial replacement.

the timing of surgical intervention deserve future multicenter prospective trials.

CONCLUSION

A simple classification, "valve type" and "aorta type," could be used in BAV-related aortopathy to identify the surgical timing. In "valve type," the long-term mortality benefit was associated with IR (valve and aortic replacement) when aortic diameter is larger than 40 mm, as compared with PR (valve replacement). In "aorta type," the long-term mortality benefit was associated with IR (valve and aortic replacement) when aortic diameter is larger than 52 mm, as compared with PR (aortic replacement). The utility of this classification and the timing of surgical intervention deserve future international prospective trials to ensure unbiased race inclusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Anzhen Hospital Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MC conceived and designed the study. WX, WL, and PW performed statistical design and analysis. MC, YD, HZ, BY, HQ, WZ, JX, and TB acquired the data. WL and JJ were in charge of the follow-up. MC and PW drafted the manuscript. LS and WL handled funding and supervision. LS, WL, WX, YL, and JZ made critical revision of the manuscript for key intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. ZYLX201503) and the Beijing Municipal Natural Science Foundation (No. 7202038).

ACKNOWLEDGMENTS

We thank Carlos Mestres and Jonathan Michel for their review expertise and all the institutional heart team members in the last 20 years.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.771346/full#supplementary-material

REFERENCES

1. Hoffman J, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol.* (2002) 39:1890–900. doi: 10.1016/S0735-1097(02)01886-7
2. Masri A, Svensson LG, Griffin BP, Desai MY. Contemporary natural history of bicuspid aortic valve disease: a systematic review. *Heart.* (2017) 103:1323–30. doi: 10.1136/heartjnl-2016-309916
3. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
4. Fedak PW, Verma S. Bicuspid aortopathy and the development of individualized resection strategies. *J Thorac Cardiovasc Surg.* (2014) 148:2080–1. doi: 10.1016/j.jtcvs.2014.09.059
5. Detaint D, Michelena HI, Nkomo VT, Vahanian A, Jondeau G, Sarano ME. Aortic dilatation patterns and rates in adults with bicuspid aortic valves: a comparative study with Marfan syndrome and degenerative aortopathy. *Heart.* (2014) 100:126–34. doi: 10.1136/heartjnl-2013-304920
6. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation.* (2010) 121:e266–369. doi: 10.1213/ANE.0b013e3181dd869b
7. Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* (2014) 35:2873–926. doi: 10.1093/eurheartj/ehu281
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwim JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* (2014) 63:2438–88. doi: 10.1016/j.jacc.2014.02.537
9. Borger MA, Fedak PWM, Stephens EH, Gleason TG, Girdauskas E, Ikonomidis JS, 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. doi: 10.1016/j.jtcvs.2018.02.115
10. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* (2021) 77:e25–197. doi: 10.1161/CIR.0000000000000932
11. Wheat MW Jr, Wilson JR, Bartley TD. Successful replacement of the entire ascending aorta and aortic valve. *J Am Med Assoc.* (1964) 188:717–9. doi: 10.1001/jama.1964.03060340015004
12. Otto CM, Nishimura RA, Bonow RO, Carbello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol.* (2020) 77:e25–197. doi: 10.1016/j.jacc.2020.11.018
13. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, et al. Incidence of aortic complications in patients with bicuspid aortic valves. *J Am Med Assoc.* (2011) 306:1104–12. doi: 10.1001/jama.2011.1286
14. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med.* (2014) 370:1920–9. doi: 10.1056/NEJMra1207059
15. Fedak PW, David TE, Borger M, Verma S, Butany J, Weisel RD. Bicuspid aortic valve disease: recent insights in pathophysiology and treatment. *Expert Rev Cardiovasc Ther.* (2005) 3:295–308. doi: 10.1586/14779072.3.2.295
16. Barker AJ, Markl M, Bürk J, Lorenz R, Bock J, Bauer S, et al. Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. *Circul Cardiovasc Imag.* (2012) 5:457–66. doi: 10.1161/CIRCIMAGING.112.973370
17. Girdauskas E, Borger MA, Secknus MA, Girdauskas G, Kuntze T. Is aortopathy in bicuspid aortic valve disease a congenital defect or a result of abnormal hemodynamics? A critical reappraisal of a one-sided argument. *Eur J Cardiothorac Surg.* (2011) 39:809–14. doi: 10.1016/j.ejcts.2011.01.001
18. Borger MA, Preston M, Ivanov J, Davierwala P, Armstrong S, David TE, et al. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? *J Thorac Cardiovasc Surg.* (2004) 128:677–83. doi: 10.1016/S0022-5223(04)00984-5
19. Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. *Mayo Clin Proc.* (1999) 74:14–26. doi: 10.4065/74.1.14
20. Paruchuri V, Salhab KF, Kuzmik G, Gubernikoff G, Fang H, Rizzo JA, et al. Aortic size distribution in the general population: explaining the size paradox in aortic dissection. *Cardiology.* (2015) 131:265–72. doi: 10.1159/000381281

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

MINI REVIEW
published: 27 January 2022
doi: 10.3389/fcvm.2021.770924

Bicuspid Valve Sizing for Transcatheter Aortic Valve Implantation: The Missing Link

Giulia Costa[†], *Marco Angelillis*[†] *and Anna Sonia Petronio*[*]

Cardiothoracic and Vascular Department, Pisa University Hospital, Pisa, Italy

Transcatheter aortic valve implantation (TAVI) is a well-recognized and established therapy for severe aortic stenosis, with expanding indications toward younger patients with low surgical risk profile. As bicuspid aortic valve (BAV) affects ∼1–2% of the population, it may be speculated that an increasing number of patients with degenerated BAV may eventually need TAVI during the course of the disease. On the other hand, BAV represents a challenge due to its peculiar anatomical features and the lack of consensus on the optimal sizing strategy. The aim of this paper is to review the peculiar aspects of BAV and to discuss and compare the currently available sizing methods. Special attention is given to the role of pre-procedural imaging, mostly with multislice computed tomography, and to the aspects that operators should evaluate in order to ensure an optimal procedural planning and avoid procedural-related complications.

Keywords: aortic stenosis, bicuspid aortic valve, multi-slice computed tomography, sizing, transcatheter aortic valve implantation

OPEN ACCESS

Edited by:
Mao Chen,
Sichuan University, China

Reviewed by:
Ernesto Greco,
Sapienza University of Rome, Italy
Alessandro Iadanza,
University of Siena, Italy

***Correspondence:**
Anna Sonia Petronio
as.petronio@gmail.com

[†]*These authors have contributed equally to this work and share first authorship*

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *05 September 2021*
Accepted: *27 December 2021*
Published: *27 January 2022*

Citation:
Costa G, Angelillis M and Petronio AS (2022) Bicuspid Valve Sizing for Transcatheter Aortic Valve Implantation: The Missing Link. Front. Cardiovasc. Med. 8:770924. doi: 10.3389/fcvm.2021.770924

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been widely recognized as a safe and effective treatment for aortic stenosis (AS) in patients who cannot undergo surgical aortic valve replacement (SAVR) or are at high or intermediate surgical risk (1–4). Increased operator experience and improved device systems have led to an expanded use of TAVI in lower surgical risk populations (5, 6) and in other pathologies such as bicuspid AS (7, 8). Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, affecting 1–2% of the population, and is the cause of a significant proportion of aortic valve disease in young adults (9). However, when the progression of the disease is slow, SAVR may be required in older age groups at higher surgical risk due to the age itself and coexistent comorbidities (10, 11). Furthermore, considering the growing expansion of TAVI indications toward younger patients with higher prevalence of bicuspid AS, the clinical outcomes of TAVI in BAV warrant special attention (12). BAV is a challenge for TAVI owing to its complex anatomy with different morphological phenotypes. Peculiar features such as larger dimensions of the aortic valve components, higher calcium burden, presence of a heavily calcified raphe, and associated aortopathy represent some pitfalls when treating BAV patients with TAVI. For these peculiarities and the higher rates of paravalvular leak (PVL), new permanent pacemaker (PPM), need for a second transcatheter heart valve (THV), risk of annulus rupture or aortic dissection, and brain injury (13–15) BAV patients have been initially excluded from the randomized trials. Currently, the use of new-generation devices and the growing attention toward a careful pre-procedural planning have led to an improvement of procedural results, with outcomes nowadays comparable to tricuspid valves (16, 17). However, the unique morphological features of BAV and the lack of consensus on the optimal sizing technique pose a challenge when offering TAVI to such patients.

The aim of this review is to analyze different sizing methods currently used in the real world, taking into account the anatomical features of BAV.

ANATOMICAL FEATURES

The different morphologies of BAV have been initially classified on the basis of cusps size and number and raphe presence and position. The Sievers and Schmidtke classification (18) divides BAV in three major types: type 0 (no raphe, two leaflets), type 1 (one raphe, fusion of the left coronary cusp with either the right or the non-coronary cusp), and type 2 (two raphes, fusion of the left coronary cusp with both the right and the non-coronary cusp). Whilst this classification was based on the analysis of surgical specimens, in 2014 the BAV Consortium proposed a classification based on transthoracic echocardiography (19). BAVs were classified as type 1 (right-left coronary cusp fusion), type 2 (right-non coronary cusp fusion), and type 3 (left-non coronary cusp fusion). In this classification the raphe can be complete, incomplete or absent. Type 1 BAV without raphe was also indicated as true BAV, corresponding to Sievers' type 0. Finally, Jilaihawi et al. (20) proposed a new classification for BAV based on multi-slice computed tomography (MSCT) imaging, taking in account the increasing role of TAVI in such patients. This new "TAVI-oriented" classification includes three BAV morphologies: tricommissural (the "functional" or "acquired" BAV), bicommissural raphe type, and bicommissural non-raphe type. Leaflet orientation was simplified as coronary cusp fusion or mixed coronary and non-coronary cusp fusion. Interestingly, BAV morphology has been linked to TAVI outcomes, with the presence of a calcified raphe and excessive leaflet calcifications being associated with increased risk of aortic root injury, moderate-to-severe PVL and 30-day mortality (21).

BAV-ASSOCIATED AORTOPATHY

BAV is strongly associated with aortic dilatation and subsequent complications (22), affecting a high percentage of BAV patients and whose pathogenesis is still uncertain. The so-called "BAV-associated aortopathy" has been classified considering the presence or absence of dilatation and the specific location of the aortic disease (23, 24). The different phenotypes have been linked to the presence of either aortic valve stenosis or regurgitation and to the risk of disease progression, with the highest risk related to aortic root dilation (25). Moreover, BAV-associated aortopathy is notoriously associated with an increased risk of aortic dissection compared to the general population, especially with a regurgitant valve (26). The factors that come into play that can affect the development of aortic dilatation in BAV patients are a genetic predisposing milieu (especially mutations involving the TGF-beta signaling pathway) (27) and the chronic hemodynamic overload due to aortic valve disease (28).

Abbreviations: AS, aortic stenosis; BAV, bicuspid aortic valve; MSCT, multi-slice computed tomography; PVL, paravalvular leak; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve.

BAV SIZING TECHNIQUES

Precise annular sizing based on MSCT imaging is a key step for successful TAVI (29). This is increasingly true in BAV, which displays particular and challenging anatomical characteristics. In BAV, two planes can be identified: the annulus plane and the supra-annular one, where the so-called inter-commissural distance (ICD) is identified. MSCT-based sizing theories take into consideration these two planes, either in a separate or combined fashion. The balloon-sizing method relies on the intra-procedural evaluation of the BAV during predilation. Finally, sizing methods based on the role of the raphe have been proposed.

"Annular" BAV Sizing

This sizing method is the same used for tricuspid valves, as previously described (30), and identifies the level of the virtual basal ring by connecting the three hinge points at the bottom of the aortic sinuses. The annulus surface area is manually traced, and the geometric mean annulus diameter is then derived. The valve is chosen according the relative sizing chart of each device. The circular shape of the prosthesis is expected to adapt to the aortic annulus, relying on device radial force and on the possibility of raphe fracture. One of the potential limitations of this method is that the unique morphological features of BAV - such as the raphe or the ICD- are not considered. Furthermore, the elliptical shape of the annulus requires some degree of oversizing in order to prevent PVL (31). A possible complication is therefore an excessive oversizing, with increasing risk of annular rupture. This complication is more related to heavily calcified valves or type 1 BAV, where the fibrotic and/or calciphied raphe prevents valve expansion. Yoon et al. (32) in a series of 108 patients treated with balloon-expandable devices reported a rate of 0.9% of annulus rupture and 6.5% of more than moderate PVL. In the experience of Mylotte et al. (33), balloon-expandable valves had a rate of annulus rupture of 0.7%, whereas a more than moderate final PVL was reported in 6% of patients.

"Supra-Annular" BAV Sizing

To identify the commissures by MSCT, the plane is scrolled in the sagittal view from the annulus to the sinuses, in order to identify the distribution of the leaflets. Then, the position of the commissures is marked and therefore scrolled down to 4 mm above the annulus. The measurement is performed from the middle of one commissure to the middle of the opposite one. The distance of 4 mm has been empirically identified as the reference standard for the measurement of the ICD. The size of the prosthesis is chosen based on the mean perimeter-derived diameter of the annulus and the ICD. The minimal value is used to select the device size, based on the current sizing charts. Currently, this method has been directly investigated only in the BAVARD retrospective registry (34). Briefly, the authors identified three possible aortic configurations: the tubular one, where the mean aortic annulus diameter matches the ICD and can be used for sizing; the flared one, in which the mean aortic annulus diameter is smaller than the ICD; lastly, the tapered one (mean perimeter-derived diameter of the annulus greater than ICD). In this configuration the ICD

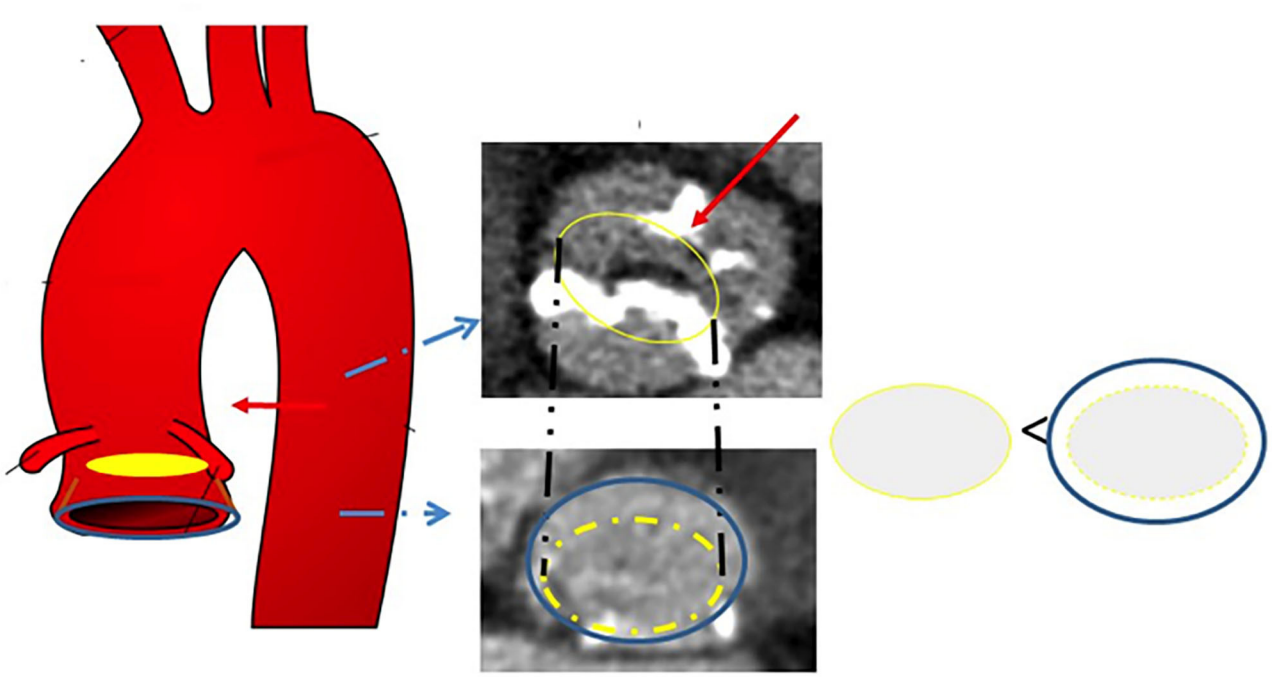


FIGURE 1 | Schematic representation of the effects of the raphe on THV accommodation. The blue circle indicates the annulus, whereas the yellow circle represents the ideal space at the level of the raphe able to accommodate the prosthesis. THV, transcatheter heart valve.

could be integrated for sizing, as an annulus-based sizing would lead to the selection of a THV too large for the patient. In this registry, annulus-based sizing was applicable to 88% of the patients.

Annular vs. Supra-Annular Sizing

Randomized comparisons between different sizing methods are currently lacking. In 2019, Kim et al. (35) published a retrospective, single-center analysis of 217 BAV patients treated with TAVI, with annular sizing being the default method for all patients. Overall, no significant differences where found between ICD and annulus measurements, despite some intra-individual differences. Supra-annular sizing would have resulted in a divergent size selection in more than one-third of patients. On the basis of these results, the authors concluded that supra-annular sizing might have a role in few cases with annular sizing errors, but might also lead to improper THV selection in a considerable percentage of patients. Accordingly, Weir-McCall et al. (36) analyzed a series of 44 patients treated with balloon-expandable THV. Annulus-based device sizing displayed substantial agreement with the chosen THV, whereas a much weaker reproducibility was obtained by supra-annular sizing (performed by generating a circle defined by the ICD).

Overall, supra-annular sizing methods are widely varied, with no consistent recommendation on which height(s) to measure and no consistent tools or techniques on how to measure. Moreover, there is a lack of prospective evidence comparing clinical results to basal plane annulus measurement results.

"Balloon-Technique" BAV Sizing

When the virtual ring measurements falls into a borderline range, the correct prosthesis sizing might be assessed referring to the relationship between the inflated balloon during balloon pre-dilatation and the Valsalva sinuses. A pigtail catheter is placed at the bottom of the right coronary cusp and the C-arm is moved until the coaxial implantation view is obtained using the described "right cusp rule" (37). A contrast injection is performed to achieve optimal visualization of the three cusps, assuming that the distance between the non-coronary and left cusp hinge points correlates to the annulus diameter. A balloon is placed across the virtual aortic annulus and fully expanded under rapid pacing. If the balloon reaches the hinge points, the size of balloon corresponds to the valve size. Otherwise, a larger THV can be chosen. Moreover, the presence of contrast backflow into the left ventricle during valvuloplasty or excessive movement of the inflated balloon suggests that there is insufficient coverage of the annulus, and therefore that a larger THV is recommended. While this method is easy to apply in tricuspid valves, it can be more challenging in BAV because of the asymmetrical distribution of the cusps.

In 2018, Liu et al. (38) described a sizing method for BAV using balloon pre-dilatation based on the so-called "waist sign." Sequential balloon aortic pre-dilatations beginning with the smaller size of 18 mm were performed, with 2 mm

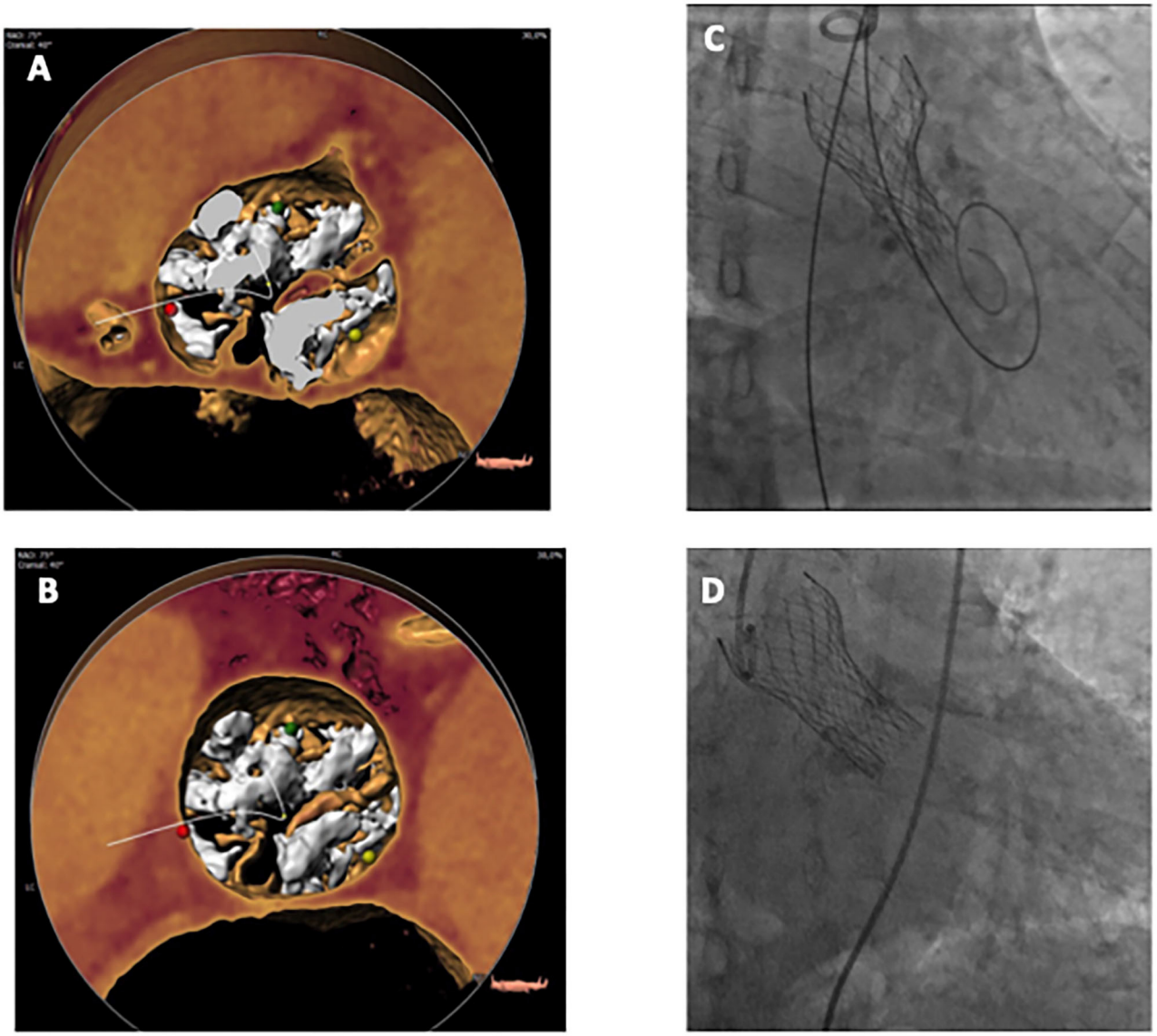


FIGURE 2 | 3D Volume Rendering MSCT view of a BAV at annulus level **(A)** and raphe level **(B)**, in this case at 10.4 mm from annulus plane. Constrained THV right after release **(C)** and final result after post-dilatation **(D)**. BAV, bicuspid aortic valve; MSCT, multislice computed tomography; THV, transcatheter heart valve.

increments until the "waist sign" occurred with less than mild regurgitation during contrast injection. This method has been used in a case series of 12 patients obtaining a downsizing of the THV compared to the MSCT in 91.7% of patients. No aortic ruptures and no residual moderate or severe PVL were reported.

"Raphe-Based" Sizing

These methods are based on the assumption that the raphe plays a pivotal role in the accommodation of the THV in BAV, as this structure is often stiff and heavily calcified, impairing proper valve expansion. **Figures 1**, **2** display the impact of the raphe on the actual space able to accommodate the THV.

Casper Algorithm

Recently, we proposed a new algorithm for BAV sizing (39). This algorithm takes into account both the annulus plane and the supra-annular one. It has been developed from MSCT measurements before and after TAVI in a series of patients with type 1 BAV. This algorithm is based on three main factors: (1) Raphe length is related to incomplete valve expansion; (2) Calcium burden and distribution are associated with lower valve expansion; (3)

Raphe length is the most reliable measure with high inter-observer reproducibility. Starting from the annulus-derived diameter, several millimeters (up to 2.5) are subtracted taking into account the presence of heavy calcium burden, raphe length and calcium distribution. This method has been applied to 21 patients, obtaining 100% procedural success and excellent THV performance.

Lira Method

The method described by Iannopollo et al. (40) aims to recognize the plane where valve anchoring is assumed. For BAV type 1, the prosthesis should anchor at the level of the raphe. Therefore, the LIRA plane is identified as the plane that encounters the raphe at its maximum protrusion. In type 2 BAV, the prosthesis should anchor at the level of the major raphe -defined as the larger one, with the greater amount of calcium. The LIRA plane represents a "neo-virtual basal ring" where the perimeter traces the internal border of the leaflets, excluding all the structures encountered at this level (fused commissures, heavy calcification, etc.). This sizing method has been evaluated in a cohort of 20 patients, with excellent THV performance.

Table 1 resumes the principal characteristics of the currently available sizing methods.

TABLE 1 | Principal characteristics of the currently available sizing methods for BAV.

	Annular sizing	Supra-annular sizing	Balloon sizing	Raphe-based sizing
Undersizing	No	Yes/no	Yes/no	Yes/no
Raphe evaluation	No	No	Yes/no	Yes
Applicability to all THV	Yes	Yes	Yes	Yes
Reproducibility	Yes	Yes/no	No	Yes
Calcium evaluation	No	No	No	Yes

DISCUSSION AND CONCLUSIONS

BAV is improperly believed to be a relatively rare aortic valve abnormality, with BAV type I as the most frequent subtype. Nowadays, a higher number of AS patients with BAV are reported. This increasing trend can be also related to the extensive use of MSCT in pre-procedural planning. Recent studies and registries described encouraging results in this subset of patients, demonstrating that newer generation THV can offer better results than the first generation ones (8, 12, 14, 16, 17, 41). As a consequence, the balloon-expandable (Sapien 3^{TM}, Edwards Lifesciences, CA, USA) and self-expandable (Evolut R/PRO^{TM}, Medtronic, MN, USA) THV have received US Food and Drug Administration and European Conformity approval for all categories of surgical risk regardless of anatomy.

Nevertheless, this abnormal morphology in aortic stenosis entails possible complications such as higher rate of new PPM, moderate to severe PVL, prosthesis embolization and annulus rupture. As BAV is more frequent in younger patients, the foreseen utilization of TAVI in these patients necessitates a need for consensus on procedural and device planning. The strong association between BAV and aortopathy may pose a challenge when addressing such patients to TAVI, considering the risk of progression of the aortic disease. Even if robust data on the evolution of aortic disease in BAV patients treated with TAVI are currently lacking, data from surgical series show that the correction of hemodynamic overload may slow the progression of the disease (28); this might be extrapolated and applied also to TAVI patients. Moreover, a small study on 67 BAV patients treated with TAVI and with aortic diameter <50 mm showed no significant progression of the aortic disease at a median follow-up of 398 days (42). It is as well uncertain if BAV-associated aortopathy may lead to an increased risk of aortic injury during TAVI; with this in mind, the use of flexible devices and avoidance of prosthesis oversizing and aggressive dilation may be advocated.

The different features in BAV compared to tricuspid aortic valves and the variety of subtypes rise the question if BAV have to be measured like tricuspid valves or if a new method of measurement is warranted. As the choice of the THV size is modulated by the presence or absence of some features, instead of referring to sizing techniques such as oversizing or undersizing operators should aim to a *tailored* sizing. The different techniques that have emerged have not been yet tested in large series of patients, and therefore it appears mandatory to better understand the correct method for BAV sizing. It should be underlined that different devices might need different sizing techniques. Currently, data on THV durability in the setting of BAV are lacking, despite encouraging results from early and mid-term outcomes (16, 17). In BAV, some degree of asymmetry is expected due to the presence of raphe and heavy calcifications. As eccentricity and non-circularity have been related to unfavorable valve hemodynamics and a theoretic impact on THVs durability (43), correct sizing is of paramount importance in this setting, especially in younger populations.

Several registries are currently investigating the results of different sizing methods. The BIVOLUT X registry (Bicuspid aortic stenosis with Evolut platform international experience, NCT03495050) is the first international registry of BAV with the attempt to evaluate different sizing methods by means of an imaging-based approach using a pre and a post-MSCT analysis. Moreover, the CASPER registry (NCT04817735) is currently investigating the safety and efficacy of BAV sizing based on calcium burden and raphe length (the CASPER algorithm). Larger, prospective, and randomized trials are expected in order to evaluate mid and long-term follow up of these patients, with possible comparison between SAVR and TAVI results in this setting.

BAV represents a challenge for TAVI operators, both for its peculiar anatomic features and because the progressive shift toward younger patients with low surgical risk and high life expectancy, where optimal procedural results are expected. Careful pre-procedural planning and standardized sizing methods are warranted in order to guarantee a tailored approach and the best possible outcomes.

AUTHOR CONTRIBUTIONS

GC, MA, and AP equally contributed in conception and design of the manuscript, drafting of the manuscript or revising it critically for important intellectual content, and final approval of the manuscript submitted. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic valve replacement in high-risk patients. *N Engl J Med.* (2011) 364:2187–98. doi: 10.1056/NEJMoa1103510
2. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* (2014) 370:1790–8. doi: 10.1056/NEJMoa1400590
3. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* (2016) 374:1609–20. doi: 10.1056/NEJMoa1514616
4. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* (2017) 376:1321–31. doi: 10.1056/NEJMoa1700456
5. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* (2019) 380:1706–15. doi: 10.1056/NEJMoa1816885
6. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* (2019) 380:1695–705. doi: 10.1056/NEJMoa1814052
7. Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol.* (2015) 65:2184–94. doi: 10.1016/j.jacc.2015.03.014
8. Forrest JK, Ramlawi B, Deeb GM, Zahr F, Song HK, Kleiman NS, et al. Transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis. *JAMA Cardiol.* (2021) 6:50–7. doi: 10.1001/jamacardio.2020.4738
9. Michelena HI, Della Corte A, Prakash SK, Milewicz DM, Evangelista A, Enriquez-Sarano M. Bicuspid aortic valve aortopathy in adults: incidence, etiology, and clinical significance. *Int J Cardiol.* (2015) 201:400–7. doi: 10.1016/j.ijcard.2015.08.106
10. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation.* (2005) 111:920–5. doi: 10.1161/01.CIR.0000155623.48408.C5
11. Roberts WC, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol.* (2012) 109:1632–6. doi: 10.1016/j.amjcard.2012.01.390
12. Costopoulos C, Latib A, Maisano F, Testa L, Bedogni F, Buchanan L, 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) 113:1390–3. doi: 10.1016/j.amjcard.2014.01.412
13. Pasic M, Unbehaun A, Buz S, Drews T, Hetzer R. Annular rupture during transcatheter aortic valve replacement: classification, pathophysiology, diagnostics, treatment approaches, and prevention. *J Am Coll Cardiol Intv.* (2015) 8:1–9. doi: 10.1016/j.jcin.2014.07.020
14. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol.* (2017) 69:2579–89. doi: 10.1016/j.jacc.2017.03.017
15. Fan J, Fang X, Liu C, Zhu G, Hou CR, Jiang J, et al. Brain injury after trans catheter replacement of bicuspid versus tricuspid aortic valves. *J Am Coll Cardiol.* (2020) 76:2579–90. doi: 10.1016/j.jacc.2020.09.605
16. Yoon SH, Lefèvre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. *J Am Coll Cardiol.* (2016) 68:1195–205. doi: 10.1016/j.jacc.2016.06.041
17. Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, et al. Transcatheter aortic valve replacement in bicuspid versus tricuspid aortic valves from the STS/ACC TVT registry. *J Am Coll Cardiol Intv.* (2020) 13:1749–59. doi: 10.1016/j.jcin.2020.03.022
18. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
19. Michelena HI, Prakash SK, Della Corte A, Bissell MM, Anavekar N, Mathieu P, et al. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). *Circulation.* (2014) 129:2691–704. doi: 10.1161/CIRCULATIONAHA.113.007851
20. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A Bicuspid Aortic Valve Imaging Classification for the TAVR Era. *J Am Coll Cardiol Img.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
21. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, et al. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol.* (2020) 76:1018–30. doi: 10.1016/j.jacc.2020.07.005
22. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med.* (2014) 370:1920–29. doi: 10.1056/NEJMra1207059
23. Fazel SS, Mallidi HR, Lee RS, Sheehan MP, Liang D, Fleischman D, et al. The aortopathy of bicuspid aortic valve disease has distinctive patterns and usually involves the transverse aortic arch. *J Thorac Cardiovasc Surg.* (2008) 135:901–7, 907.e1–2. doi: 10.1016/j.jtcvs.2008.01.022
24. Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M, et al. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. *Eur J Cardiothorac Surg.* (2007) 31:397–404; discussion 404–5. doi: 10.1016/j.ejcts.2006.12.006
25. Sievers HH, Stierle U, Hachmann RM, Charitos EI. New insights in the association between bicuspid aortic valve phenotype, aortic configuration and valve haemodynamics. *Eur J Cardiothorac Surg.* (2016) 49:439–46. doi: 10.1093/ejcts/ezv087
26. Wang Y, Wu B, Li J, Dong L, Wang C, Shu X. Impact of aortic insufficiency on ascending aortic dilatation and adverse aortic events after isolated aortic valve replacement in patients with a bicuspid aortic valve. *Ann Thorac Surg.* (2016) 101:1707–14. doi: 10.1016/j.athoracsur.2015.10.047
27. Folkersen L, Wågsäter D, Paloschi V, Jackson V, Petrini J, Kurtovic S, et al. Unraveling divergent gene expression profiles in bicuspid and tricuspid aortic valve patients with thoracic aortic dilatation: the ASAP study. *Mol Med.* (2011) 17:1365–73. doi: 10.2119/molmed.2011.00286
28. Kim YG, Sun BJ, Park GM, Han S, Kim DH, Song JM, et al. Aortopathy and bicuspid aortic valve: haemodynamic burden is main contributor to aortic dilatation. *Heart.* (2012) 98:1822–27. doi: 10.1136/heartjnl-2012-302828
29. Buzzatti N, Maisano F, Latib A, Cioni M, Taramasso M, Mussardo M, et al. Computed tomography-based evaluation of aortic annulus, prosthesis size and impact on early residual aortic regurgitation after transcatheter aortic valve implantation. *Eur J Cardiothorac Surg.* (2013) 43:43–50; discussion 50–1. doi: 10.1093/ejcts/ezs155

30. Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA, et al. expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). *J Cardiovasc Comput Tomogr.* (2012) 6:366–80. doi: 10.1016/j.jcct.2012.11.002
31. Blanke P, Willson AB, Webb JG, Achenbach S, Piazza N, Min JK, et al. Oversizing in transcatheter aortic valve replacement, a commonly used term but a poorly understood one: dependency on definition and geometrical measurements. *J Cardiovasc Comput Tomogr.* (2014) 8:67–76. doi: 10.1016/j.jcct.2013.12.020
32. Yoon SH, Sharma R, Chakravarty T, Kawamori H, Maeno Y, Miyasaka M, et al. Clinical outcomes and prognostic factors of transcatheter aortic valve implantation in bicuspid aortic valve patients. *Ann Cardiothorac Surg.* (2017) 6:463–72. doi: 10.21037/acs.2017.09.03
33. Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol.* (2014) 64:2330–9. doi: 10.1016/j.jacc.2014.09.039
34. Tchetche D, de Biase C, van Gils L, Parma R, Ochala A, Lefevre T, et al. Bicuspid aortic valve anatomy and relationship with devices: the BAVARD multicenter registry. *Circ Cardiovasc Interv.* (2019) 12:e007107. doi: 10.1161/CIRCINTERVENTIONS.118.007107
35. Kim WK, Renker M, Rolf A, Fischer-Rasokat U, Wiedemeyer J, Doss M, et al. Annular versus supra-annular sizing for TAVI in bicuspid aortic valve stenosis. *EuroIntervention.* (2019) 15:e231–8. doi: 10.4244/EIJ-D-19-00236
36. Weir-McCall JR, Attinger-Toller A, Blanke P, Perlman GY, Sellers SL, Wood D, et al. Annular versus supra-annular sizing for transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Cardiovasc Comput Tomogr.* (2020) 14:407–13. doi: 10.1016/j.jcct.2020.01.008
37. Kasel AM, Cassese S, Leber AW, von Scheidt W, Kastrati A. Fluoroscopy-guided aortic root imaging for TAVR: "follow the right cusp" rule. *J Am Coll Cardiol Img.* (2013) 6:274–5. doi: 10.1016/j.jcmg.2012.06.014
38. Liu X, He Y, Zhu Q, Gao F, He W, Yu L, et al. Supra-annular structure assessment for self-expanding transcatheter heart valve size selection in patients with bicuspid aortic valve. *Catheter Cardiovasc Interv.* (2018) 91:986–94. doi: 10.1002/ccd.27467
39. Petronio AS, Angelillis M, De Backer O, Giannini C, Costa G, Fiorina C, et al. Bicuspid aortic valve sizing for transcatheter aortic valve implantation: development and validation of an algorithm based on multi-slice computed tomography. *J Cardiovasc Comput Tomogr.* (2020) 14:452–61. doi: 10.1016/j.jcct.2020.01.007
40. Iannopollo G, Romano V, Buzzatti N, Ancona M, Ferri L, Russo F, et al. Supra-annular sizing of transcatheter aortic valve prostheses in raphe-type bicuspid aortic valve disease: the LIRA method. *Int J Cardiol.* (2020) 317:144–51. doi: 10.1016/j.ijcard.2020.05.076
41. Mi C, Michel J, Kasel AM. Application of balloon-expandable transcatheter heart valve in bicuspid aortic valve. *JACC Asia.* (2021) 1:147–61. doi: 10.1016/j.jacasi.2021.07.012
42. Jung JH, Kim HK, Park JB, Lee SP, Koo BK, Kim YJ, et al. Progression of ascending aortopathy may not occur after transcatheter aortic valve replacement in severe bicuspid aortic stenosis. *Korean J Intern Med.* (2021) 36:332–41. doi: 10.3904/kjim.2019.089
43. Tseng EE, Wisneski A, Azadani AN, Ge L. Engineering perspective on transcatheter aortic valve implantation. *Interv Cardiol.* (2013) 5:53–70. doi: 10.2217/ica.12.73

Conflict of Interest: AP is a consultant and received fund from Medtronic, Boston and ABBOTT.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

REVIEW
published: 08 February 2022
doi: 10.3389/fcvm.2021.798949

Bicuspid Aortic Valve Stenosis: From Pathophysiological Mechanism, Imaging Diagnosis, to Clinical Treatment Methods

Nils Perrin[1,2], *Réda Ibrahim*[1], *Nicolas Dürrleman*[1], *Arsène Basmadjian*[1], *Lionel Leroux*[3], *Philippe Demers*[1], *Thomas Modine*[3] *and Walid Ben Ali*[1]*

[1] *Structural Heart Intervention Program, Montreal Heart Institute, Montreal, QC, Canada,* [2] *Cardiology Division, Geneva University Hospitals, Geneva, Switzerland,* [3] *Service Médico-Chirurgical, Valvulopathies-Chirurgie Cardiaque-Cardiologie Interventionelle Structurelle, Hôpital Cardiologique de Haut Lévèque, CHU Bordeaux, Bordeaux, France*

Bicuspid aortic valve (BAV) is the most frequent congenital anomaly and has a natural evolution toward aortic regurgitation or stenosis due to the asymmetrical valve function associated with an evolutive ascending aortopathy. Several BAV classifications exist describing the presence and number of raphe, amount and location of calcium, and the symmetry of the functional cusps. The impact of BAV morphology on transcatheter aortic valve implantation (TAVI) outcomes still remains little investigated. Pivotal randomized trials comparing TAVI with surgery have excluded BAV until yet. However, data from registries and observational studies including highly selected patients have shown promising results of TAVI in BAV. With this review, we aimed at describing anatomical and pathophysiological characteristics of BAV, discussing the main aspects to assess diagnostic imaging modalities, and giving an overview of TAVI outcomes and technical considerations specific to BAV morphology.

Keywords: bicuspid aortic valve stenosis bicuspid aortic valve, nomenclature, transcatheter aortic valve implantation, sizing approaches, review

OPEN ACCESS

Edited by:
Mao Chen,
Sichuan University, China

Reviewed by:
Nicolas Amabile,
L'Institut Mutualiste Montsouris, France
Adel Aminian,
Centre Hospitalier Universitaire de Charleroi, Belgium

***Correspondence:**
Walid Ben Ali
dr.walidbenali@gmail.com

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *20 October 2021*
Accepted: *28 December 2021*
Published: *08 February 2022*

Citation:
Perrin N, Ibrahim R, Dürrleman N, Basmadjian A, Leroux L, Demers P, Modine T and Ben Ali W (2022) Bicuspid Aortic Valve Stenosis: From Pathophysiological Mechanism, Imaging Diagnosis, to Clinical Treatment Methods. Front. Cardiovasc. Med. 8:798949. doi: 10.3389/fcvm.2021.798949

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the standard of care for patients with symptomatic severe aortic stenosis at intermediate and high surgical risk, especially if suitable from a transfemoral approach, and is considered as a valuable option for patients at low surgical risk (1–6). However, in pivotal randomized trials comparing TAVI with surgery, bicuspid aortic valve stenosis (BAV), either congenital or acquired, has been excluded until yet. BAV is the most frequent congenital anomaly and is found in up to 2.25% of the general population. Its natural evolution toward aortic regurgitation and/or stenosis is mainly due to the asymmetrical valve function associated with an evolutive ascending aortopathy. Moreover, BAV was described in >20% of high-risk elderly patients undergoing surgical aortic valve replacement for aortic stenosis (7). This category of patients would largely be considered for TAVI nowadays. In an analysis from the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry regarding transcatheter heart valve off-label use, Hira et al. reported that about 2% of patients treated for BAV (8). A higher prevalence of BAV was demonstrated in the Chinese TAVR registries (up to 5.8%) (9). In addition to a possible impact of ethnicity difference

in BAV prevalence, the younger and lower risk population included in the Chinese BAV studies may lead to interpretation bias. In the worldwide current trend toward younger patients treated by TAVI, transcatheter heart valve operators will face an increasing number of patients with BAV.

With this review, we aimed at describing anatomical and pathophysiological characteristics of BAV, discussing the main aspects to assess with diagnostic imaging modalities, and giving an overview of TAVI outcomes and technical considerations specific to BAV morphology.

NOMENCLATURE

The BAV is defined by the presence of 2 functional commissures with <3 zones of parallel apposition between them (10). The presence and orientation of the commissural fusion and raphe are highly variable among the population. Fused commissures can be either congenital or acquired through the development of a rheumatological valvular disease or progression of age-related atherosclerosis. In theory, all degrees and combinations of fused cusps can be possible. Most BAV classifications reported in the literature were derived from the surgical analysis yet. Fused commissures most often involve the right and left coronary cusps (80% of the cases), followed by the right and non-coronary cusps and, rarely, the left and non-coronary cusps (10). Sievers is the most widely known and used classification of BAV describing the number and orientation of the raphe based on surgical models (10). Briefly, type 0 has no raphe with 2 normal functioning symmetrical cusps. Type 1 presents one raphe connecting two underdeveloped cusps. Finally, type 2 has two raphes with two underdeveloped cusps and commissures, and one fully developed cusp and commissure. The 2014 International BAV Consortium (BAVCon) adopted a similar but simplified classification system according to the 2 fused cusps. All 3 types (type 1: right-left cusp fusion; type 2: right-non fusion; and type 3: left-non fusion) may or may not have a raphe (11). De Kerchove et al. suggested a classification system assessing the surgical repairability of the BAV, such as commissural orientation (varying from symmetrical to very asymmetrical cusp angles), length of fusion, and non-functional commissure height (12). Very recently, a new international consensus statement on the nomenclature of BAV has been developed with a simple and comprehensive classification system based on imaging modalities (echocardiographic, CT, and MRI) and anatomical surgical pathology (**Figure 1**) (13). The authors described 3 types of BAV: the fused (similar to Sievers type 1), the 2-sinus (latero-lateral and antero-posterior phenotypes), and the partial-fusion types. The fused-type is thereafter subclassified according to the symmetry of the functional cusps and commissure angle of the non-fused cusp. The present descriptive classification derives from a multidisciplinary consortium and aims at better identifying anatomical features of BAV that best predict the surgical valve replacement or repair success and TAVI outcomes.

Jilaihawi et al. adapted the traditional Sievers classification to better address the transcatheter heart valve interaction with the aortic root (14). BAV morphologies were defined as bicommissural non-raphe (equivalent to Sievers type 0), bicommissural raphe (equivalent to Sievers type 1), and tricommissural (sharing characteristics between Sievers type 1 and tricuspid valves) types (**Figure 2**). In an early exploratory study, 30-day mortality, cerebrovascular events, and new pacemaker implantation across the BAV morphologies were similar (14). Interestingly, the intercommissural distance (for bicommissural bicuspids) was associated to ≥moderate paravalvular leak, with respect to the limited power of the study ($n = 130$).

In contrast with the STS Surgical Database Form who started to collect specific anatomical characteristics of BAV in 2017, the large STS/ACC TVT registry does not provide information on BAV sub-type classification. The impact of BAV morphology on TAVI outcomes still remains little investigated yet. In an international multicenter BAV TAVI registry, BAV were classified according to a modified Sievers nomenclature differentiating a calcified raphe to a non-calcified raphe type 1 morphology. Death at 1 year increased significantly between type 0 (no raphe), type 1 with a non-calcified raphe, and type 1 with a calcified raphe (2.4, 4.8, and 9.5%, $p = 0.006$ between the groups, respectively). Moreover, patients with both calcified raphe and excess leaflet calcifications presented significantly higher 2-year mortality and ≥ moderate paravalvular regurgitation in comparison with patients with one or none of these characteristics (15).

PATHOPHYSIOLOGICAL CHARACTERISTICS

In comparison with tricuspid valves, BAV has different localization and excess calcification of the aortic valve (16). Asymmetrical BAV leaflet motion and a higher leaflet coaptation point increase the shear stress through the valve leading to a calcification process starting already at a young age. As another consequence of the shear stress, patients with BAV develop progressive aortic root and ascending aorta dilatation. Larger annular and sinus of Valsalva dimensions have been reported among the patient undergoing TAVI for BAV vs. tricuspid valves, respectively (annulus mean area-derived diameter 26.3 ± 3.0 vs. 23.2 ± 1.9 mm, $p < 0.01$ and sinus of Valsalva 930.0 vs. 866.6 mm^2, $p = 0.005$) (17). Recent MRI blood flow analysis was able to confirm the increased aortic wall shear stress, namely, induced by eccentric jets (11). A small cohort study reported an increased aortic growth associated with the degree of the aortic jet angle (18). Interestingly, other blood flow imaging analysis has suggested a different degree of flow abnormality severity according to the BAV type, thus it remains preliminary investigations (19).

Concomitant congenital anomalies of coronary origin are more frequent with the congenital BAV in comparison with tricuspid aortic valves (7 vs. 3%, $p = 0.001$), affecting mainly anomalous origin of the right coronary artery (20). Whereas, the similar prevalence of anomalous origin of the left main has been observed between BAV and tricuspid valves, the absence of the left main with separate left anterior descending and circumflex artery ostia has been more frequently reported in BAV than

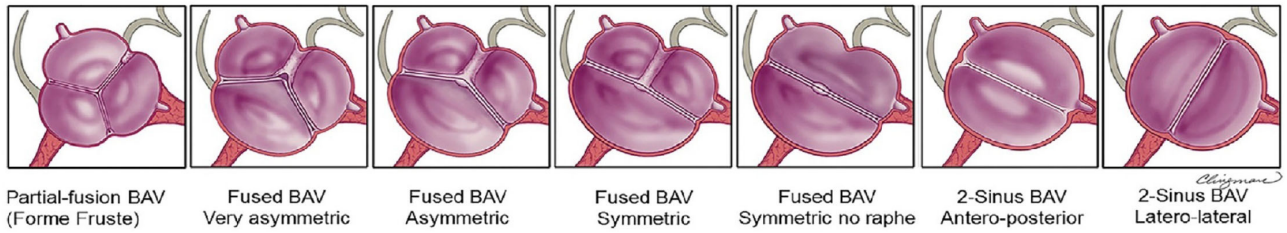


FIGURE 1 | The 2021 international consensus statement on nomenclature and classification of BAV (13).

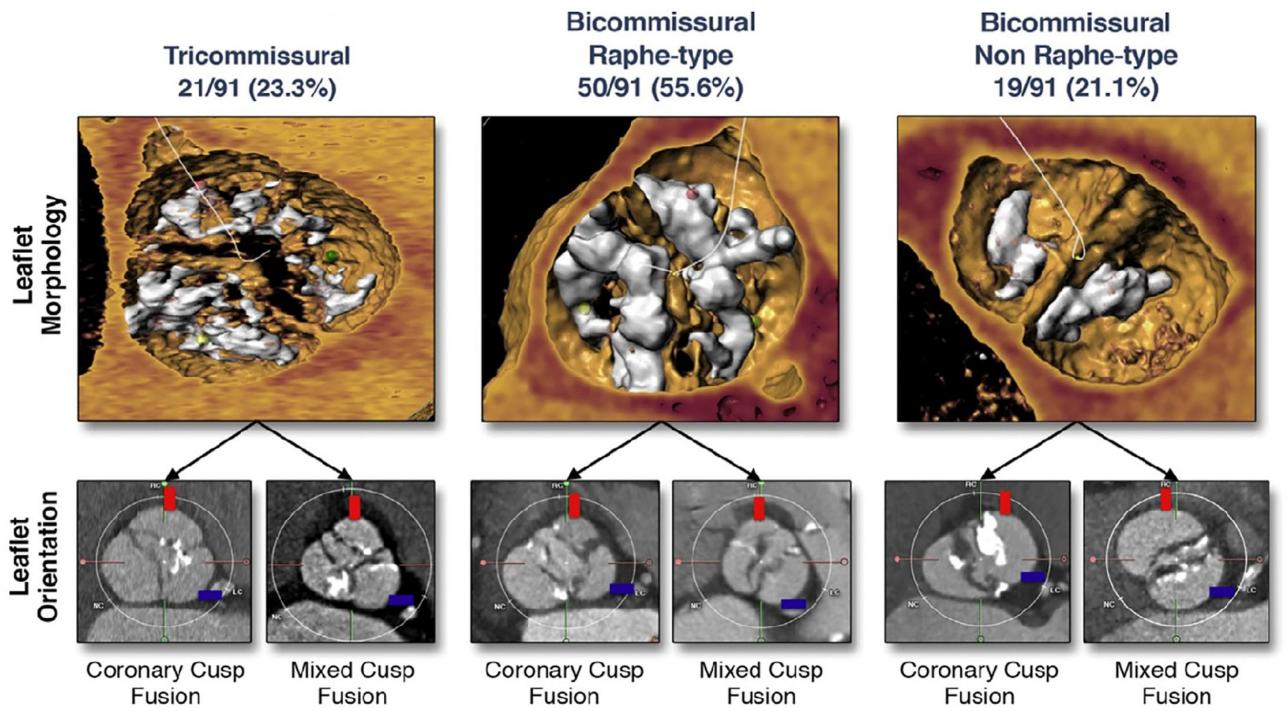


FIGURE 2 | Bicuspid aortic valve classification in the TAVI era (14).

tricuspid valves (21). Moreover, from a TAVI perspective, a higher distance from the aortic annulus to coronary ostia has been reported in BAV (22). As discussed later in this review, the origin and height of coronary ostia will be a specific parameter to assess the pre-procedural multislice CT (MSCT).

IMAGING

Echocardiography

Transthoracic (TTE) and transesophageal echocardiography (TEE) remain the first-line imaging for BAV diagnosis and commissural morphology classification. However, inpatient candidates for TAVI, the important calcification burden of aortic root may limit acoustic windows and participation in misclassification (23). Echocardiography has the best accuracy for aortic valve function analysis. Quantification of BAV aortic stenosis severity is similar to the tricuspid valve and should follow the latest guidelines for valvular heart disease of the European Society of Cardiology (ESC) (24). However, in BAV, maximal velocity flows are most of the time measured at the right parasternal window due to eccentricity of the aortic jet (25). In cases of very eccentric jets, misalignment of the beam leads to maximal velocity underestimation. On the other hand, aortic valve regurgitation severity is more difficult to assess since laminar flow may be falsely assumed at the sinotubular junction leading to inaccurate regurgitation volume calculations. Integration of several parameters, such as aortic holodiastolic retrograde flow velocity, may help to address these limitations. Since BAV is frequently associated with the ascending aorta dilatation, echocardiography often offers favorable visualization of the initial part of the proximal part of the ascending aorta and is thus preferentially used in the clinical practice for patient follow-up.

Multislice CT

In the current TAVI era, MSCT has an integral part in procedural planning investigations. MSCT has the best accuracy for BAV

morphological analysis (26). Detailed analysis of amount and location of aortic root calcification as well as precise aortic and surrounding structures measurements play a pivotal role for prosthesis choice. In comparison with tricuspid valves, BAV has a larger annulus and sinus of Valsalva diameters. In addition, BAV has less elliptical aortic annulus with more eccentric calcifications (27).

Prosthesis Sizing

Prosthesis sizing is mainly dependent on annular diameter measurement in tricuspid valves. A certain degree of prosthesis oversizing (5–20 and 12–25% for balloon- and self-expandable devices, respectively) is recommended to limit the paravalvular leak and prosthesis embolization (28, 29). Calcified and fibrotic leaflets as well as commissural fusion with or without raphe modify the aortic root anatomy and increase the challenge of valve sizing in BAV. Interaction and interference of the prosthesis with the aortic root can occur from the level of the left ventricular outflow tract to above the sinotubular junction according to the prosthesis design. Balloon sizing with waste measurements and sequential aortography has been suggested by some operators for valve sizing in BAV but has never been meticulously investigated by studies (30). The behavior of calcified leaflets and raphe with respect to the surrounding structures (such as coronary ostia) may also be appreciated during balloon inflation.

Initial evidence from post-TAVI MSCT studies has shown that the maximal stent frame interaction with aortic root in BAV anatomies occurred rather at the supra-annular than annular level, typically between 4 and 8 mm above the annulus (31, 32). Perimeters and area at the supra-annular level will have to be circumscribed by taking into account the border of the leaflets and commissural fusions. Unlike tricuspid valves where the virtual basal ring is easily defined by 3 anatomic distinct hinge points at the nadir part of the cusps, defining the virtual basal ring in BAV is challenging and may lead to inaccurate prosthesis sizing.

Prosthesis sizing according to the level of estimated prosthesis anchoring at a supra-annular plane in raphe-type BAV has been recently suggested by a multicenter MSCT study (33). The so-called level of implantation at the raphe (LIRA) plane is identified where the plane cuts the raphe at the level of its maximum protrusion. The perimeter around the internal border of the leaflet is then traced excluding fused commissures or heavy calcifications. The smallest perimeter between the LIRA plane and the virtual basal ring is then chosen for prosthesis sizing (33). The Calcium Algorithm Sizing for bicusPid Evaluation with Raphe (CASPER) algorithm adapted the perimeter/area derived annulus diameter according to 3 main characteristics: raphe length/annulus diameter ratio, calcium score, and prevalence of calcium distribution on raphe site (34). According to the algorithm, operators detracted 0–2 mm from the area/perimeter derived mean annular diameter for valve sizing. In a validation cohort ($n = 21$), Petronio et al. reported 100% VARC-2 defined procedural success (34).

Even though prosthesis maximal constraint seems to occur at a supra-annular level in imaging studies, the Bicuspid Aortic Valve Anatomy and Relationship with Devices (BAVARD) retrospective registry reported a tapered aortic root configuration (intercommissural distance < annular diameter) in only 13.8% of the BAV raising the question whether supra-annular or annular measurements should be best used for prosthesis sizing (22). Importantly, in this registry, the intercommissural distance was systematically measured 4 mm above the annulus for standardization purposes, leading to a possible higher proportion of tapered configuration according to the level of prosthesis maximal constraints. Tubular (intercommissural distance = annular diameter) and flared (intercommissural distance > annular diameter) configuration accounted for 33.7 and 52.5% of the BAV. According to the BAVARD algorithm, size of the prosthesis should best be chosen according to the smallest measure between the annulus diameter (tubular or flared configuration) or the intercommissural distance (tapered configuration) (22).

The specific anatomical particularities of BAV highlight the importance of detailed aortic root analysis taking into account supra-annular structures (including calcification and raphe) in the prosthesis sizing process (**Figure 3**). A possible trend toward the prosthesis down-sizing according to standard measurements at the annulus level is to be considered, particularly in cases of tapered aortic root configuration. All these sizing algorithms need, however, further validation, namely, with special regards to the clinical outcomes according to different BAV morphologies (35).

Evaluation of Coronary Obstruction Risk

Bicuspid aortic valve is associated with the higher coronary ostia take-off and larger sinuses of Valsalva (36). While these characteristics would rather prevent coronary obstruction, other specific characteristics of BAV have to be considered before TAVI. Excessive raphe calcification between the non-coronary cusp and the left or right coronary cusp may lead to the prosthesis displacement after deployment in the opposite direction obstructing either the left main or right coronary ostium. Furthermore, coronary ostia have been described closer to commissures leading to an increased risk of coronary obstruction, especially when leaflets are very asymmetrical or bulky (36). In case of a borderline situation despite the pre-procedural MSCT imaging analysis, balloon inflation with simultaneous aortography may identify aortic root at risk for coronary obstruction. Overall, the risk of coronary obstruction in BAV after TAVI of well-selected patients remains, however, low and similar to tricuspid valves (37). In the case of BAV anatomies at high risk for coronary obstruction, a similar to tricuspid valves approach is recommended, going from simple coronary pre-procedural wiring to chimney technique or Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during TAVR.

AORTIC VALVE REPLACEMENT IN BAV STENOSIS

Surgery

Comparison between TAVI and surgery for BAV relies on propensity-matched studies as no randomized trial exists yet.

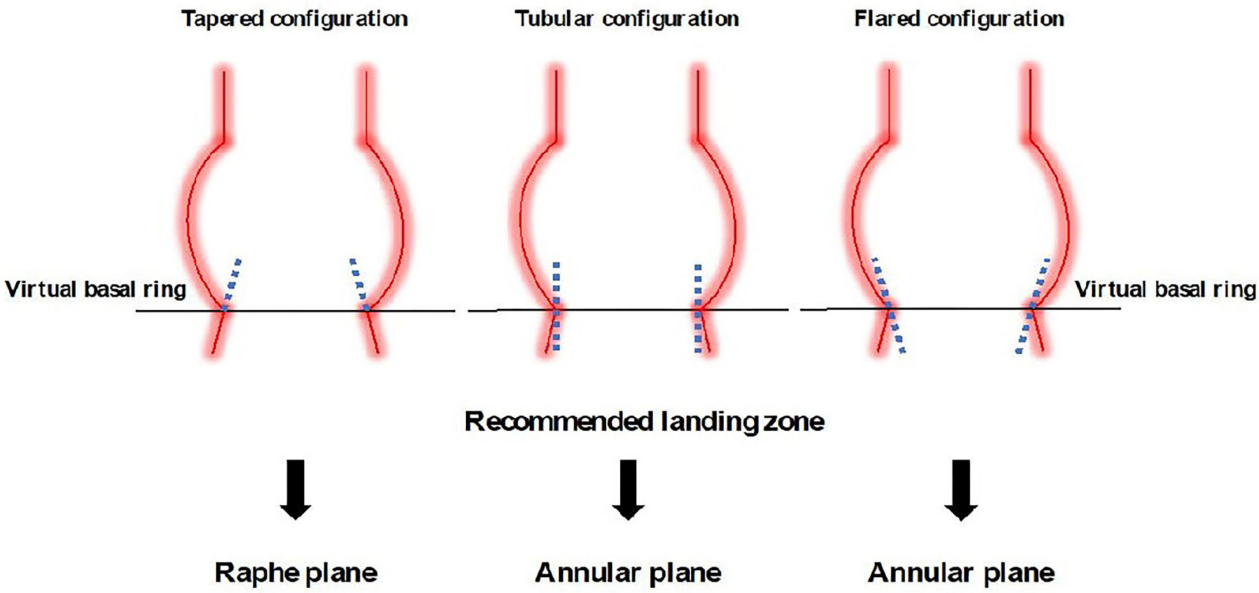


FIGURE 3 | Recommended prosthesis sizing according to the aortic root morphology in BAVs.

BAV stenosis was considered as an exclusion criterion in existing randomized studies comparing TAVI with surgery. Using Medicare data, Mentias et al. compared 699 matched pairs of BAV patients undergoing TAVI and surgery (38). In-hospital mortality and stroke rate were similar between TAVI and surgery (2.2 vs. 2.3%, $p = 0.90$/2.9 vs. 2.7%, $p = 0.90$/2.7 vs. 2.9%, $p = 0.90$, respectively). Thirty-day mortality and 1-year mortality were similar between both groups. Patients undergoing TAVI presented, however, a higher rate of new permanent pacemaker implantation in comparison with surgery (12.2 vs. 7.6%, $p = 0.009$, respectively). Interestingly, clinical outcomes remained similar after excluding patients undergoing concomitant coronary artery bypass graft or aortic root replacement surgery (38). A similar propensity-score matched study was conducted by Elbadawi et al. analyzing patients undergoing TAVI and isolated surgery for BAV ($n = 975$ pairs). Data were retrospectively collected from the US National Inpatient Sample database. After matching, in-hospital mortality and stroke rate were similar between TAVI and surgery (3.1 vs. 3.1 and 2.6 vs. 2.1%, respectively). Here again, patients undergoing TAVI had a higher permanent pacemaker implantation rate. The results of these 2 propensity-matched score studies are encouraging in the light of similar outcomes than studies randomizing patients with tricuspid valves to TAVI or surgery. However, dedicated randomized trials including patients with BAV still need to be designed. As TAVI indication has been progressively extended to younger patients, an increasing number of TAVI will be performed in BAV stenosis. Strong evidence is still lacking since patients with BAV were largely excluded from pivotal randomized trials. Registries of TAVI in BAV have reported excellent outcomes, though result interpretation is limited by significant selection bias related to registries. Before considering TAVI instead of surgery for most BAV stenosis, direct comparison between surgery and TAVI is mandatory, particularly when considering the excellent result of surgery in BAV. In addition, long-term outcomes will be needed with respect to the younger age of patients with BAV but data over 10 years are challenging to collect. In the latest and very recent ESC valvular heart guidelines (2021), the role of TAVI in BAV stenosis remains a gap of evidence, though the consensus paper considers a BAV as an unfavorable anatomical characteristic for TAVI (24). Interestingly, the U.S. FDA approved Edwards Sapien valve and Medtronic Corevalve for patients with aortic stenosis at low surgical risk patients in August 2019. At the same time, the Corevalve Evolut TAVI system obtained the approval for the treatment of BAV deemed at intermediate or greater risk for surgery followed by CE Mark and Health Canada approval, respectively, in June 2020 and January 2021.

TRANSCATHETER AORTIC VALVE IMPLANTATION

Outcomes

Data reporting performances of TAVI in patients with BAV rely mainly on comparative retrospective and small prospective studies. Currently, the BAV stenosis candidates for TAVI are highly selected. Moreover, their younger age and reduced risk profile may definitively bias the comparison with tricuspid valve patients. The challenges raised by the non-standardized BAV patient selection process for TAVI may impact the procedural and clinical outcomes in-between the studies. **Table 1** summarizes

TABLE 1 | Summarizes major published studies including >100 patients treated for bicuspid aortic valve (BAV) severe stenosis with the current generation of transcatheter heart valves.

	N	Prosthesis	Aortic rupture, %	Conversion to surgery, %	≥ Moderate PVL, %	PPM, %	Stroke, %	All-Cause mortality, %
Yoon et al. (9)	102	S3 89% Lotus 11%	1	1	0	16.7	2	3.9
Yoon et al. (37)	226	S3 70.8% Lotus 19% Evolut R 10.2%	NA	1.3	2.7	16.4	3.2	3.7
Tchetche et al. (22)	101	S3 65.3% Evolut R 19.2% Lotus 9.9% Accurate neo 5.8% Other 1.9%	NA	NA	0 (severe)	13	2 (disabling)	0
Kim et al. (35)	184	S3 58.2% Accurate neo 26% Evolut R 7.1% Portico 6.5% Lotus 2.2%	1.1	1.6	4.3	14.5	4.3	3.2
Makkar et al. (39)	2691	S3 100%	0.3	0.9	2.1	9.1	2.5	2.6
Halim et al. (40)	3705	S3 86.7% Evolut R 13.3%	NA	0.7	2.4	NA	2	1.6 (in-hospital)
Forrest et al. (41)	932	Evolut R/PRO 100%	NA	0.6	7.7	15.4	3.4	2.6
Mangieri et al. (42)	353	S3 68.6% Evolut R/PRO 31.4%	1.1	NA	4	16.1	1.6	4.3
Yoon et al. (15)	1034	S3 71.6% Evolut R/PRO 18.2% Lotus 4.5% Accurate neo 3.9% Protico 1.8%	1.7	0.9	3.2	12.2	2.7	2
Forrest et al. (43)	150	Evolut R/PRO 100%	0	0.7	0	15.1	4	0.7

NA, not available; PPM, permanent pacemaker; PVL, paravalvular leak.

main studies reporting outcomes of TAVI in BAV using current generation devices (9, 15, 22, 35, 37, 39–43).

The largest report comes from the STS/ACC TVT registry (40). BAV stenosis represented 3.2% of the 170,959 TAVI procedures performed between 2011 and 2018. Patients with BAV were younger (74 vs. 82 years old, $p < 0.001$, respectively) with a lower risk profile in comparison with those with tricuspid valves. Although the device success (using only current-generation devices) was slightly lower in BAV than tricuspid valves with a higher incidence of ≥ moderate aortic regurgitation, 1-year mortality and stroke risk were not affected. Indeed, patients with BAV had a lower 1-year adjusted mortality [hazard ratio (*HR*), 0.88 (95% CI, 0.78–0.99)] with similar adjusted stroke rate [*HR*, 1.14 (95% CI, 0.94–1.39)] in comparison with patients with a tricuspid valve (40). Caution should be paid when interpreting the results in light of a statistically significant difference in prosthesis type used in BAV and tricuspid valves. Indeed, the Sapien 3 (Edwards Lifesciences, CA, USA) prosthesis was more frequently used in BAV (73 vs. 69%, $p < 0.001$, respectively), but remained the most used prosthesis in both groups (40).

A second analysis from the STS/ACC TVT registry analyzed data from all patients treated with the third-generation Sapien 3 prosthesis (Edwards Lifesciences) between 2015 and 2018. Similar 30-day [2.6 vs. 2.5% (95% CI, 0.74–1.47), respectively], and 1-year mortality [10.5 vs. 12.0% (95% CI, 0.73–1.10), respectively], were reported among 2,691 matched pairs of BAV and tricuspid valves (39). Stroke rate was, however, higher [2.5 vs. 1.6% (95% CI, 1.06–2.33)] and patients with BAV required more frequent open heart surgery conversion in comparison with tricuspid valves [0.9 vs. 0.4%, respectively, absolute risk difference 0.5% (95% CI, 0–0.9%)]. No difference in ≥ moderate aortic regurgitation was, however, reported at 30 days between both groups (39). More recent results of this registry were presented at the EuroPCR congress 2021 reporting outcomes of the same 3,168 propensity match pairs. Authors confirmed similar adjusted 1-year mortality (12 vs. 10.5%, $p = 0.31$) between BAV and tricuspid valves. Even though the stroke rate was higher at 30 days in the BAV group (2.4 vs. 1.6%, $p = 0.02$, respectively for BAV and tricuspid valves), the difference was no longer true when considering adjusted results. One-year stroke rate was similar among matched patients (3.4 vs. 3.1%, $p = 0.16$, respectively) (44).

Similarly, Forrest et al. analyzed data from all patients treated with the Evolut R or PRO valves (Medtronic) included in the STS/ACC TVT registry between 2015 and 2018. One-year all-cause mortality and stroke rate were similar between 1,858 matched pairs of BAV and tricuspid valves (10.4 vs. 12.4%, $p = 0.63$ and 3.9 vs. 4.4%, $p = 0.93$, respectively) (41).

Interestingly, patients with BAV had higher rate of ≥ moderate aortic regurgitation post-procedure (5.6 vs. 2.1%, $p < 0.001$) but this difference was no longer significant at 1-year follow-up (4.7 vs. 3.9%, $p = 0.60$) (41).

A recent large meta-analysis compared outcomes between BAV and tricuspid valve among 17 studies and 181,433 patients undergoing TAVI, including 6,669 patients with BAV (0.27%). While the device success and 1-year mortality were similar between BAV and tricuspid valves in the matched population (97 vs. 94%, $p = 0.55$ and 91 vs. 91%, $p = 0.22$, respectively), patients had higher incidence of cerebral ischemic events (2.4 vs. 1.6%, $p = 0.015$) as well as moderate to severe aortic regurgitation (relative risk 1.42, $p < 0.0001$). Patients treated for BAV presented more frequent procedural complications with higher rate of annular rupture ($p = 0.014$) or conversion to surgery ($p = 0.018$) (45).

Finally, at the 2021 TVT structural heart summit, data from PARTNER 3 TAVI BAV registry were presented comparing 148 matched pairs of patients with BAV and tricuspid valves. No difference in terms of death, stroke, or rehospitalization were reported at 1 year between both anatomies (10.9 vs. 10.2%, $p = 0.8$, respectively, for BAV vs. tricuspid valves) (46).

Substantial iterative technical development of TAVI devices, in addition to the increasing experience and better preprocedural planning of operators, allowed for outcome improvement in BAV patients treated with current-generation devices. Indeed, in the STS/ACC TVT registry, the use of current-generation devices translated into device success increase and aortic regurgitation decline (40). A similar increase in device success and decrease in the paravalvular leak was already described in an earlier but smaller bicuspid TAVI international registry comparing outcomes of early- vs. new-generation devices (47). In a propensity score-matched study ($n = 546$ pairs) by Yoon et al. comparing TAVI in BAV vs. tricuspid valves, device success as well as mortality up to 2 years (17.2 vs. 19.4%, $p = 0.28$, respectively), was similar in patients receiving current generation devices (37).

Whereas, most of TAVI procedural complications and clinical outcomes in tricuspid aortic valve stenosis have significantly improved over time to reach non-inferiority if not superiority in comparison with surgery, high-grade conduction disorders remain a major issue post-TAVI. Several predictors of new permanent pacemaker implantation in tricuspid valves have been identified. Patient (such as baseline conduction disorders and aortic annulus anatomical characteristics) and procedural (such as, prosthesis oversizing, type, and implantation depth) characteristics are associated with an increased risk of high-grade conduction disorders (48, 49). The impact of valve morphology (BAV vs. tricuspid valves) on the new permanent pacemaker implantation rate is still controversial with conflicting results. Shorter membranous septum or asymmetrical radial forces of the prosthesis compressing the conduction system in BAV have been suggested as risk factors for conduction disorders (50). In the large STS/ACC TVT registry, permanent pacemaker implantation rate was slightly but significantly higher among the BAV matched to tricuspid valve patients (7.3 vs. 5.9%, $p = 0.05$, respectively), treated by the third generation Sapien 3 (Edwards Lifesciences) prosthesis (39). The difference became higher (9.1 vs. 7.5%, $p = 0.03$) in the recent up-to-date data presented at the 2021 EuroPCR congress (44). These results are in opposition to a recent meta-analysis including 19 studies (4,040 BAV vs. 8,084 tricuspid valves) where authors reported similar new permanent pacemaker implantation rates between both groups [risk ratio 1.06 (95% CI, 0.93–1.20)] (51). Device type (self-expandable vs. balloon-expandable) seems not to influence the pacemaker implantation rate among new-generation devices. Indeed, in the BEAT (balloon vs. self-expandable valve for the treatment of bicuspid aortic valve stenosis) international registry, BAV treated with self-expandable Evolut R/PRO ($n = 111$), or balloon-expandable Sapien 3 ($n = 242$) prosthesis were compared. The rate of permanent pacemaker was similar in both groups (16.0 vs. 16.1%, $p = 0.98$, respectively, for self- vs. balloon-expandable devices) (42). Interestingly, results remained similar after propensity-score matching. Higher rates of permanent pacemaker implantation were reported by Jilaihawi but, here again, with similar rates between self- and balloon-expandable devices (26.9 vs. 25.5%, $p = 0.83$, respectively) (14).

Technical Considerations for TAVI in BAV

Specific technical considerations related to the different valve morphology and physiopathology in BAV are considered when considering TAVI. BAV opening orifice eccentricity increases the difficulty of retrograde valve crossing in case of severe stenosis. Fine analysis of MSCT pre-procedural imaging may help to identify the fused cusps and predict the location of wire crossing. A step-by-step approach has been suggested by Frangieh and Kasel starting from the non-fused cusp and rotating the catheter clockwise or counter-clockwise in case of left-right or non-right types, respectively (52). In case of no raphe type, no specific rule exists. When retrograde valve crossing remains impossible, transseptal puncture with anterograde aortic valve crossing can be performed.

Asymmetrical and increased burden of calcium deposition, and non-circular shape of BAV increase the risk of device malpositioning during the prosthesis deployment as well as the risk of annular rupture. Non-circular or valve underexpansion has been documented by imaging studies in BAV treated with both self- and balloon-expandable devices (53, 54). Use of the 2 orthogonal views after prosthesis implantation helps to identify the stent frame underexpansion that may be missed with a single fluoroscopic projection. The impact of prosthesis eccentricity on long-term valve function remains unestablished yet with no difference in hemodynamic parameters at short-term (17). In the BIVOLUT-X registry, systematic pre-dilatation (87% of the cases) and post-dilatation according to the angiography appearance of the prosthesis (55%) in BAV have shown favorable ellipticity index (1.2) with encouraging hemodynamic parameters of the self-expandable prosthesis at 30 days (mean gradient of 7.3 mmHg and ≥moderate paravalvular leak in 2% of the patients) (55). However, these anatomical challenges are to be better targeted in light of the higher rate of second valve implanted in BAV vs. tricuspid valves in the large STS/ACC TVT registry (40). The use of a recapturable device may here be a special interest in case of predicted challenging prosthesis deployment.

Pre- and post-dilatation may help in optimizing the prosthesis landing zone at the price of an increased risk of annular rupture and stroke. In different analyses of the STS/ACC registry, the rate of conversion to open surgery was higher in BAV vs. tricuspid valves when a balloon-expandable device was used (0.9 vs. 0.4%, $p = 0.03$, respectively), whereas no significant difference was reported with self-expandable devices (0.6 vs. 0.2%, $p = 0.29$, respectively) (39, 41). When comparing self- to balloon-expandable devices in BAV, the BEAT registry reported higher rate of pre- and post-dilatation with self-expandable prosthesis (pre-dilatation: 57.3 vs. 37.9%; post-dilatation: 42.7 vs. 14.3%; $p < 0.001$ for both) (42). Balloon post-dilatation should be limited to cases with significant prosthesis dysfunction, including more than the mild paravalvular leak or mean gradient >15 mmHg. Indication for post-dilatation of non-circular valve geometry without a hemodynamic impact needs further investigations with long-term data on valve performances and leaflet thrombosis.

A horizontal aorta is frequently associated with BAV and may interfere with both retrograde valve crossing and prosthesis deployment (27). Although different techniques have been described to facilitate the valve crossing or delivery system orientation (56, 57), alternative accesses (transcarotid or axillary as the first alternative choices) can be decided at the time of pre-procedural planning (58).

Coronary re-access following TAVI in BAV is of particular interest according to the younger age of patients developing severe aortic stenosis in BAV in comparison with the tricuspid valve. However, similarly to tricuspid valves, no clear recommendation on commissural alignment during the prosthesis deployment exists yet. Eccentric coronary ostia in the leaflet as well as anomalous coronary origin may significantly complicate commissural alignment and thus coronary re-access in the future.

FUTURE PERSPECTIVES AND CONCLUSIONS

Data coming from specific designed randomized studies are needed to confirm the results of registries. To date, the NOTION-2 trial (NCT02825134) is randomizing low-risk patients with severe aortic stenosis to surgery or TAVI, such as BAV. A Chinese randomized non-inferiority trial (NCT03163329) comparing long-term results of TAVI and surgery in BAV is ongoing and results are expected by the middle of 2024. Long-term data assessing prosthesis hemodynamic performances over time are still lacking. Incomplete stent expansion or prosthesis distortion may influence the prosthesis durability and follow-up studies focusing on the structural valve failure and valve thrombosis become primordial with respect to the low-risk population of patients with BAV. **Figure 4** suggests a treatment algorithm of patients with symptomatic severe BAV stenosis.

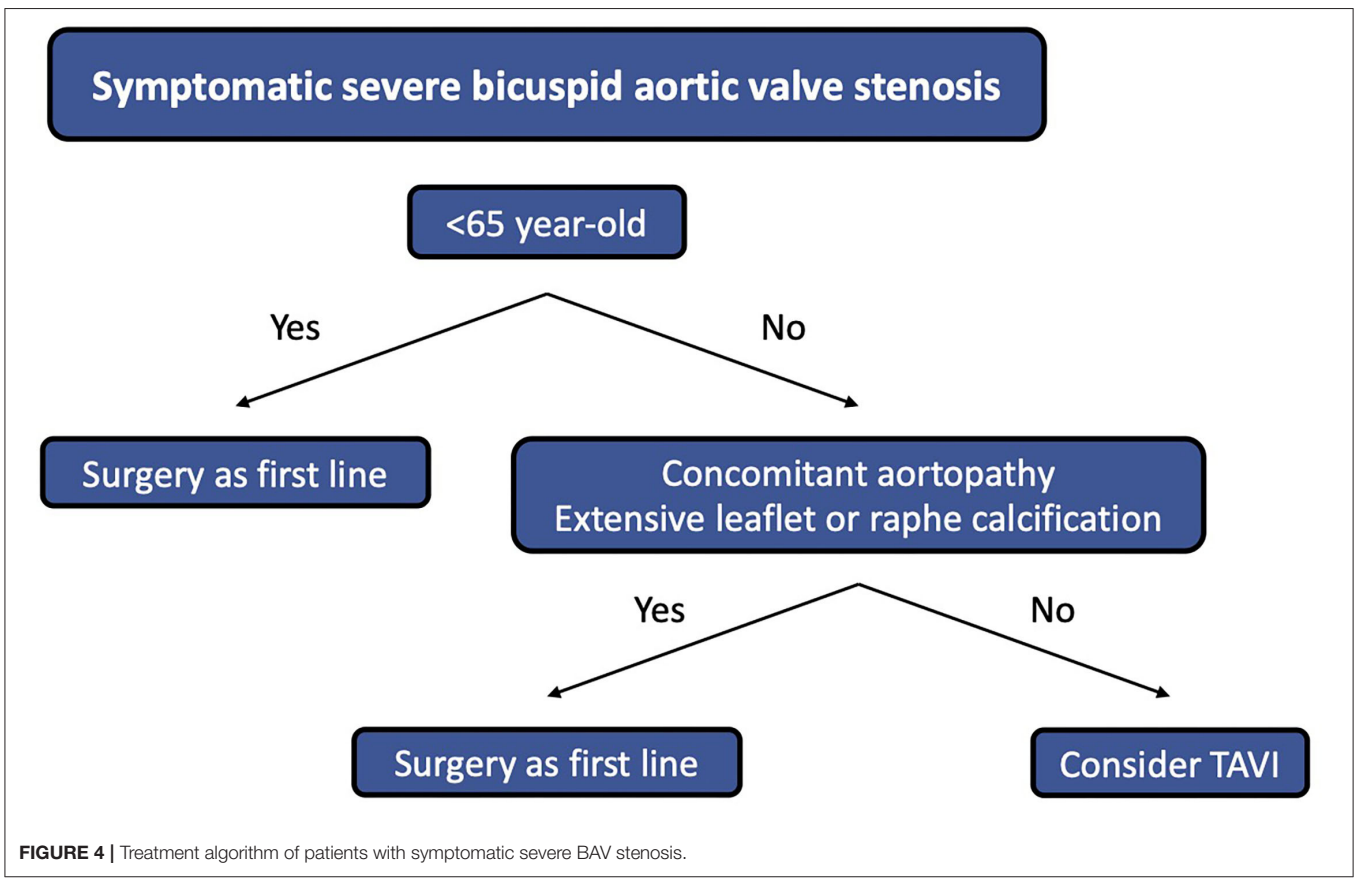


FIGURE 4 | Treatment algorithm of patients with symptomatic severe BAV stenosis.

Bicuspid aortic valve is frequently associated with ascending aortopathy, such as aortic root and proximal ascending aorta dilatation. Currently, TAVI addresses only BAV stenosis and surgery remains the only option to treat the associated ascending aortopathy. The recent ESC guidelines recommend aortic root/proximal ascending aorta replacement in case of a diameter $\geq$ 45 mm when surgery is planned for BAV severe stenosis (24). If those patients are deemed inoperable, TAVI may be considered for the aortic stenosis, taking into account the higher risk of aortic dissection in this setting (59, 60). Whereas, it is well-known that aortic root dilatation progresses with time in BAV, the rate of progression after TAVI remains unknown. Protheses treating aortic valve and ascending aortopathy simultaneously (Endo-Bentall) are under development with encouraging first-in-man cases, however, reserved for compassionate use yet (61).

In conclusion, BAV stenosis has distinct anatomical characteristics in comparison with tricuspid valves leading to specific aortic root distortion. Several sub-types classifications have been developed over time to better address the therapeutic options. When TAVI is considered for BAV, pre-procedural MSCT imaging is essential to assess the number of cusps, presence of a raphe, and location of calcifications. Aortic root, such as supra-annular structures, should be integrated in the device selection and sizing process as prosthesis interaction with the aortic root can occur from the level of the left ventricular outflow tract to above the sinotubular junction. Favorable clinical and safety outcomes have been reported from large international registries with similar outcomes in comparison with tricuspid valves. However, data from randomized trials are needed.

AUTHOR CONTRIBUTIONS

NP contributed to the design of the review and writing of the manuscript. RI, ND, AB, LL, PD, and TM revised the manuscript. WB contributed to the design of the review and reviewed critically the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

NP has received research support from the Swiss National Science Foundation (P400PM_194483) and the Geneva University Hospitals.

REFERENCES

1. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* (2014) 371:967–8. doi: 10.1056/NEJMc1408396
2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* (2010) 363:1597–607. doi: 10.1056/NEJMoa1008232
3. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* (2019) 380:1695–705. doi: 10.1056/NEJMoa1814052
4. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-Year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med.* (2020) 382:799–809. doi: 10.1056/NEJMoa1910555
5. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* (2019) 380:1706–15. doi: 10.1056/NEJMoa1816885
6. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* (2017) 376:1321–31. doi: 10.1056/NEJMoa1700456
7. Roberts WC, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol.* (2012) 109:1632–6. doi: 10.1016/j.amjcard.2012.01.390
8. Hira RS, Vemulapalli S, Li Z, McCabe JM, Rumsfeld JS, Kapadia SR, et al. Trends and outcomes of off-label use of transcatheter aortic valve replacement: insights from the NCDR STS/ACC TVT registry. *JAMA Cardiol.* (2017) 2:846–54. doi: 10.1001/jamacardio.2017.1685
9. Yoon SH, Ahn JM, Hayashida K, Watanabe Y, Shirai S, Kao HL, et al. Clinical outcomes following transcatheter aortic valve replacement in asian population. *JACC Cardiovasc Interv.* (2016) 9:926–33. doi: 10.1016/j.jcin.2016.01.047
10. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
11. Michelena HI, Prakash SK, Della Corte A, Bissell MM, Anavekar N, Mathieu P, et al. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the international bicuspid aortic valve consortium (BAVCon). *Circulation.* (2014) 129:2691–704. doi: 10.1161/CIRCULATIONAHA.113.007851
12. de Kerchove L, Mastrobuoni S, Froede L, Tamer S, Boodhwani M, van Dyck M, et al. Variability of repairable bicuspid aortic valve phenotypes: towards an anatomical and repair-oriented classification. *Eur J Cardiothorac Surg.* (2019) 56:351–9. doi: 10.1093/ejcts/ezz033
13. Michelena HI, Della Corte A, Evangelista A, Maleszewski JJ, Edwards WD, Roman MJ, et al. International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes. *J Thorac Cardiovasc Surg.* (2021) 162:e383–414. doi: 10.1016/j.jtcvs.2021.06.019
14. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodes-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR Era. *JACC Cardiovasc Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
15. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, et al. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol.* (2020) 76:1018–30. doi: 10.1016/j.jacc.2020.07.005
16. van Rosendael PJ, Kamperidis V, Kong WK, van Rosendael AR, Marsan NA, Bax JJ, et al. Comparison of quantity of calcific deposits by multidetector computed tomography in the aortic valve and coronary arteries. *Am J Cardiol.* (2016) 118:1533–8. doi: 10.1016/j.amjcard.2016.08.021
17. Kawamori H, Yoon SH, Chakravarty T, Maeno Y, Kashif M, Israr S, et al. Computed tomography characteristics of the aortic valve and the geometry of SAPIEN 3 transcatheter heart valve in patients with bicuspid aortic valve disease. *Eur Heart J Cardiovasc Imaging.* (2018) 19:1408–18. doi: 10.1093/ehjci/jex333
18. Hope MD, Wrenn J, Sigovan M, Foster E, Tseng EE, Saloner D. Imaging biomarkers of aortic disease: increased growth rates with eccentric systolic flow. *J Am Coll Cardiol.* (2012) 60:356–7. doi: 10.1016/j.jacc.2012.01.072
19. Bissell MM, Hess AT, Biasiolli L, Glaze SJ, Loudon M, Pitcher A, et al. Aortic dilation in bicuspid aortic valve disease: flow pattern is a major contributor and differs with valve fusion type. *Circ Cardiovasc Imaging.* (2013) 6:499–507. doi: 10.1161/CIRCIMAGING.113.000528
20. 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) 26:617–22. doi: 10.1093/icvts/ivx396
21. Michalowska IM, Hryniewiecki T, Kwiatek P, Stoklosa P, Swoboda-Rydz U, Szymanski P. Coronary artery variants and anomalies in patients with bicuspid aortic valve. *J Thorac Imaging.* (2016) 31:156–62. doi: 10.1097/RTI.0000000000000205
22. Tchetche D, de Biase C, van Gils L, Parma R, Ochala A, Lefevre T, et al. Bicuspid aortic valve anatomy and relationship with devices: the BAVARD multicenter registry. *Circ Cardiovasc Interv.* (2019) 12:e007107. doi: 10.1161/CIRCINTERVENTIONS.118.007107
23. Cramer PM, Prakash SK. Misclassification of bicuspid aortic valves is common and varies by imaging modality and patient characteristics. *Echocardiography.* (2019) 36:761–5. doi: 10.1111/echo.14295
24. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J.* (2021) ehab395. doi: 10.1093/eurheartj/ehab395. [Epub ahead of print].
25. Michelena HI, Chandrasekaran K, Topilsky Y, Messika-Zeitoun D, Della Corte A, Evangelista A, et al. The bicuspid aortic valve condition: the critical role of echocardiography and the case for a standard nomenclature consensus. *Prog Cardiovasc Dis.* (2018) 61:404–15. doi: 10.1016/j.pcad.2018.11.003
26. Tanaka R, Yoshioka K, Niinuma H, Ohsawa S, Okabayashi H, Ehara S. Diagnostic value of cardiac CT in the evaluation of bicuspid aortic stenosis: comparison with echocardiography and operative findings. *AJR Am J Roentgenol.* (2010) 195:895–9. doi: 10.2214/AJR.09.3164
27. Philip F, Faza NN, Schoenhagen P, Desai MY, Tuzcu EM, Svensson LG, 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:E88–98. doi: 10.1002/ccd.25948
28. Blanke P, Willson AB, Webb JG, Achenbach S, Piazza N, Min JK, et al. Oversizing in transcatheter aortic valve replacement, a commonly used term but a poorly understood one: dependency on definition and geometrical measurements. *J Cardiovasc Comput Tomogr.* (2014) 8:67–76. doi: 10.1016/j.jcct.2013.12.020
29. Dvir D, Webb JG, Piazza N, Blanke P, Barbanti M, Bleiziffer S, et al. Multicenter evaluation of transcatheter aortic valve replacement using either SAPIEN XT or CoreValve: degree of device oversizing by computed-tomography and clinical outcomes. *Catheter Cardiovasc Interv.* (2015) 86:508–15. doi: 10.1002/ccd.25823
30. Liu X, He Y, Zhu Q, Gao F, He W, Yu L, et al. Supra-annular structure assessment for self-expanding transcatheter heart valve size selection in patients with bicuspid aortic valve. *Catheter Cardiovasc Interv.* (2018) 91:986–94. doi: 10.1002/ccd.27467
31. Xiong TY, Feng Y, Li YJ, Zhao ZG, Liao YB, Ou Y, et al. Supra-Annular sizing for transcatheter aortic valve replacement candidates with bicuspid aortic valve. *JACC Cardiovasc Interv.* (2018) 11:1789–90. doi: 10.1016/j.jcin.2018.06.002
32. Xiong TY, Li YJ, Feng Y, Liao YB, Zhao ZG, Mylotte D, et al. Understanding the interaction between transcatheter aortic valve prostheses and supra-annular structures from post-implant stent geometry. *JACC Cardiovasc Interv.* (2019) 12:1164–71. doi: 10.1016/j.jcin.2019.02.051
33. Iannopollo G, Romano V, Buzzatti N, De Backer O, Sondergaard L, Merkely B, et al. A novel supra-annular plane to predict TAVI prosthesis anchoring in raphe-type bicuspid aortic valve disease: the LIRA plane. *EuroIntervention.* (2020) 16:259–61. doi: 10.4244/EIJ-D-19-00951
34. Petronio AS, Angelillis M, De Backer O, Giannini C, Costa G, Fiorina C, et al. Bicuspid aortic valve sizing for transcatheter aortic valve implantation: development and validation of an algorithm based on multi-slice computed tomography. *J Cardiovasc Comput Tomogr.* (2020) 14:452–61. doi: 10.1016/j.jcct.2020.01.007
35. Kim WK, Renker M, Rolf A, Fischer-Rasokat U, Wiedemeyer J, Doss M, et al. Annular versus supra-annular sizing for TAVI in bicuspid aortic valve stenosis. *EuroIntervention.* (2019) 15:e231–8. doi: 10.4244/EIJ-D-19-00236
36. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068
37. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol.* (2017) 69:2579–89. doi: 10.1016/j.jacc.2017.03.017
38. Mentias A, Sarrazin MV, Desai MY, Saad M, Horwitz PA, Kapadia S, et al. Transcatheter versus surgical aortic valve replacement in patients with bicuspid aortic valve stenosis. *J Am Coll Cardiol.* (2020) 75:2518–9. doi: 10.1016/j.jacc.2020.02.069
39. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. *JAMA.* (2019) 321:2193–202. doi: 10.1001/jama.2019.7108
40. Halim SA, Edwards FH, Dai D, Li Z, Mack MJ, Holmes DR, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the society of thoracic surgeons/American college of cardiology transcatheter valve therapy registry. *Circulation.* (2020) 141:1071–9. doi: 10.1161/CIRCULATIONAHA.119.040333
41. Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, et al. Transcatheter aortic valve replacement in bicuspid versus tricuspid aortic valves from the STS/ACC TVT registry. *JACC Cardiovasc Interv.* (2020) 13:1749–59. doi: 10.1016/j.jcin.2020.03.022
42. Mangieri A, Tchetche D, Kim WK, Pagnesi M, Sinning JM, Landes U, et al. Balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis: insights from the BEAT international collaborative registrys. *Circ Cardiovasc Interv.* (2020) 13:e008714. doi: 10.1161/CIRCINTERVENTIONS.119.008714
43. Forrest JK, Ramlawi B, Deeb GM, Zahr F, Song HK, Kleiman NS, et al. Transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis. *JAMA Cardiol.* (2021) 6:50–7. doi: 10.1001/jamacardio.2020.4738
44. Makkar R. *Outcomes of Transcatheter Aortic Valve Replacement for Bicuspid Aortic Valve Stenosis in the Low-Surgical Risk Population*. Paris: EuroPCR (2021).
45. Montalto C, Sticchi A, Crimi G, Laricchia A, Khokhar AA, Giannini F, et al. Outcomes after transcatheter aortic valve replacement in bicuspid versus tricuspid anatomy: a systematic review and meta-analysis. *JACC Cardiovasc Interv.* (2021) 14:2144–55. doi: 10.1016/j.jcin.2021.07.052
46. Webb J, Williams M. *The PARTNER 3 Bicuspid Registry for SAPIEN 3 TAVR in Low-risk Patients.* Miami: TVT structural heart (2021).
47. Yoon SH, Lefevre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. *J Am Coll Cardiol.* (2016) 68:1195–205. doi: 10.1016/j.jacc.2016.06.041
48. Husser O, Pellegrini C, Kessler T, Burgdorf C, Thaller H, Mayr NP, et al. Predictors of permanent pacemaker implantations and new-onset conduction abnormalities with the SAPIEN 3 balloon-expandable transcatheter heart valve. *JACC Cardiovasc Interv.* (2016) 9:244–54. doi: 10.1016/j.jcin.2015.09.036
49. Siontis GC, Juni P, Pilgrim T, Stortecky S, Bullesfeld L, Meier B, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol.* (2014) 64:129–40. doi: 10.1016/j.jacc.2014.04.033
50. Hamdan A, Nassar M, Schwammenthal E, Perlman G, Arow Z, Lessick J, et al. Short membranous septum length in bicuspid aortic valve stenosis increases the risk of conduction disturbances. *J Cardiovasc Comput Tomogr.* (2021) 15:339–47. doi: 10.1016/j.jcct.2020.10.002
51. Majmundar M, Kumar A, Doshi R, Shah P, Arora S, Shariff M, et al. Meta-Analysis of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valve. *Am J Cardiol.* (2021) 145:102–10. doi: 10.1016/j.amjcard.2020.12.085
52. Frangieh AH, Kasel AM. TAVI in bicuspid aortic valves 'made easy'. *Eur Heart J.* (2017) 38:1177–81. doi: 10.1093/eurheartj/ehx167
53. Himbert D, Pontnau F, Messika-Zeitoun D, Descoutures F, Detaint D, Cueff C, et al. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. *Am J Cardiol.* (2012) 110:877–83. doi: 10.1016/j.amjcard.2012.04.064
54. Perlman GY, Blanke P, Dvir D, Pache G, Modine T, Barbanti M, et al. Bicuspid aortic valve stenosis: favorable early outcomes with

a next-generation transcatheter heart valve in a multicenter study. *JACC Cardiovasc Interv*. (2016) 9:817–24. doi: 10.1016/j.jcin.2016.01.002

55. De Biase C, on behalf ot the Bivolut-X registry. *Transcatheter Treatment of Bicuspid Valves With the Evolut Platform: Interim Analysis From the BIVOLUT-X Registry*. London: PCR London Valves (2019).
56. Noble S, Roffi M. Retrograde aortic valve crossing of the CoreValve prosthesis using the buddy balloon technique. *Catheter Cardiovasc Interv*. (2014) 84:897–9. doi: 10.1002/ccd.25215
57. Sarkar K, Ussia GP, Tamburino C. Trans catheter aortic valve implantation with core valve revalving system in uncoiled (horizontal) aorta. Overcoming anatomical and technical challenges for successful deployment. *Catheter Cardiovasc Interv*. (2011) 78:964–9. doi: 10.1002/ccd.23133
58. Perrin Nils GB, Leroux L, Ibrahim R, Modine T, Ben Ali W. transcatheter aortic valve implantation: all transfemoral? *Front Cardiovasc Med*. (2021) 8:747583. doi: 10.3389/fcvm.2021.747583
59. Jacobzon E, Wolak A, Fink D, Silberman S. Delayed aortic dissection and valve thrombosis after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv*. (2019) 93:E391–3. doi: 10.1002/ccd.27994
60. Rylski B, Szeto WY, Bavaria JE, Walsh E, Anwaruddin S, Desai ND, et al. Transcatheter aortic valve implantation in patients with ascending aortic dilatation: safety of the procedure and mid-term follow-updagger. *Eur J Cardiothorac Surg*. (2014) 46:228–33; discussion 33. doi: 10.1093/ejcts/ezt594
61. Gaia DF, Bernal O, Castilho E, Ferreira CBND, Dvir D, Simonato M, et al. First-in-Human endo-bentall procedure for simultaneous treatment of the ascending aorta and aortic valve. *JACC Case Rep*. (2020) 2:480–5. doi: 10.1016/j.jaccas.2019.11.071

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 16 March 2022
doi: 10.3389/fcvm.2022.794850

Patients With Bicuspid Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

Yi Zhang[1†], Tian-Yuan Xiong[1†], Yi-Ming Li[1], Yi-Jun Yao[1], Jing-Jing He[1], Hao-Ran Yang[1], Zhong-Kai Zhu[1], Fei Chen[1], Yuanweixiang Ou[1], Xi Wang[1], Qi Liu[1], Xi Li[1], Yi-Jian Li[1], Yan-Biao Liao[1], Fang-Yang Huang[1], Zhen-Gang Zhao[1], Qiao Li[1], Xin Wei[1], Yong Peng[1], Sen He[1], Jia-Fu Wei[1], Wen-Xia Zhou[1], Ming-Xia Zheng[1], Yun Bao[1], Xuan Zhou[2], Hong Tang[1], Wei Meng[3], Yuan Feng[1] and Mao Chen[1]**

[1] Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China, [2] Department of Radiology, West China Hospital, Sichuan University, Chengdu, China, [3] Department of Cardiovascular Surgery, West China Hospital, Sichuan University, Chengdu, China

OPEN ACCESS

Edited by:
Luca Testa,
IRCCS San Donato Polyclinic, Italy

Reviewed by:
Antonio Lio,
San Camillo-Forlanini Hospital, Italy
Marco Ancona,
San Raffaele Hospital (IRCCS), Italy

***Correspondence:**
Mao Chen
hmaochen@vip.sina.com
Yuan Feng
fynotebook@hotmail.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: 14 October 2021
Accepted: 07 February 2022
Published: 16 March 2022

Citation:
Zhang Y, Xiong T-Y, Li Y-M, Yao Y-J, He J-J, Yang H-R, Zhu Z-K, Chen F, Ou Y, Wang X, Liu Q, Li X, Li Y-J, Liao Y-B, Huang F-Y, Zhao Z-G, Li Q, Wei X, Peng Y, He S, Wei J-F, Zhou W-X, Zheng M-X, Bao Y, Zhou X, Tang H, Meng W, Feng Y and Chen M (2022) Patients With Bicuspid Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:794850. doi: 10.3389/fcvm.2022.794850

Objective: We sought to conduct a systematic review and meta-analysis of clinical adverse events in patients undergoing transcatheter aortic valve replacement (TAVR) with bicuspid aortic valve (BAV) vs. tricuspid aortic valve (TAV) anatomy and the efficacy of balloon-expandable (BE) vs. self-expanding (SE) valves in the BAV population. Comparisons aforementioned will be made stratified into early- and new-generation devices. Differences of prosthetic geometry on CT between patients with BAV and TAV were presented. In addition, BAV morphological presentations in included studies were summarized.

Method: Observational studies and a randomized controlled trial of patients with BAV undergoing TAVR were included according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Results: A total of 43 studies were included in the final analysis. In patients undergoing TAVR, type 1 BAV was the most common phenotype and type 2 BAV accounted for the least. Significant higher risks of conversion to surgical aortic valve replacement (SAVR), the need of a second valve, a moderate or severe paravalvular leakage (PVL), device failure, acute kidney injury (AKI), and stroke were observed in patients with BAV than in patients with TAV during hospitalization. BAV had a higher risk of new permanent pacemaker implantation (PPI) both at hospitalization and a 30-day follow-up. Risk of 1-year mortality was significantly lower in patients with BAV than that with TAV [odds ratio (OR) = 0.85, 95% CI 0.75–0.97, $p = 0.01$]. BE transcatheter heart valves (THVs) had higher risks of annular rupture but a lower risk of the need of a second valve and a new PPI than SE THVs. Moreover, BE THV was less expanded and more elliptical in BAV than in TAV. In general, the rates of clinical adverse events were lower in new-generation THVs than in early-generation THVs in both BAV and TAV.

Conclusions: Despite higher risks of conversion to SAVR, the need of a second valve, moderate or severe PVL, device failure, AKI, stroke, and new PPI, TAVR seems to be a viable option for selected patients with severe bicuspid aortic stenosis (AS), which demonstrated a potential benefit of 1-year survival, especially among lower surgical risk population using new-generation devices. Larger randomized studies are needed to guide patient selection and verified the durable performance of THVs in the BAV population.

Keywords: transcatheter aortic valve replacement (TAVR), meta-analysis, bicuspid aortic valve (BAV), aortic stenosis (AS), systematic review

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is now a well-established treatment option for patients with symptomatic severe aortic stenosis (AS) in all spectrums of surgical risk (1). According to surgical experience, bicuspid aortic valve (BAV) anatomy may comprise up to 50% of low-risk patients (2). Therefore, when expanded to patients of lower risks and younger age, TAVR procedures are anticipated to treat more patients with BAV. However, all pivotal randomized controlled trials comparing TAVR with surgical aortic valve replacement (SAVR) excluded patients with BAV due to a higher risk of procedural complications, such as paravalvular leakage (PVL), stroke, new permanent pacemaker implantation (PPI), and annular rupture (3). Anatomical features such as the nontubular shape from the annulus to the leaflet tips and heavier calcification in patients with BAV often result in more common malposition of transcatheter heart valves (THVs) than patients with tricuspid aortic valve (TAV), as well as in conduction disturbances or PVL (4, 5). Previous meta-analyses of cohort studies have reported that, compared to patients with TAV, patients with BAV were at a higher risk of procedural complications, such as the conversion to SAVR, the implantation of a second valve, a moderate or severe PVL, and the device failure (6). In addition, new-generation devices were reported to have a lower risk of adverse events compared to early-generation devices in BAV, while balloon-expandable (BE) valves were associated with the lower need of a second valve and a new PPI than self-expanding (SE) valves (6).

With the accumulation of experience and an iteration of prosthesis, TAVR is now used more frequently for patients with BAV (7–10), enabling detailed comparisons to be updated. Because of the lack of the corresponding guideline and normative practical guidance for TAVR in the BAV population, pressing the need for a reliable assessment on the efficacy and safety of TAVR procedures in patients with BAV existed. Therefore, we systematically reviewed related researches and hereby summarized the BAV morphological presentations, clinical adverse events of TAVR in patients with BAV vs. TAV, as well as the efficacy of BE vs. SE valves in patients with BAV. Comparisons of early- vs. new-generation devices were performed where available. Moreover, the geometry of THV on CT after TAVR was compared between patients with BAV and TAV.

METHOD

Search Strategy, Selection Criteria, and Data Extraction

The composition of this current review was in line with an evidence-based set of items in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11). Associated checklist is presented in **Supplementary Table S9**. The search of original articles was conducted by two independent investigators, YZ and TYX, on Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), conference proceedings for the Scientific Sessions of the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, EuroPCR, and Transcatheter Valve Therapeutics. Search code included TAVI OR TAVR OR "percutaneous aortic valve" OR "transcatheter aortic valve") AND (bicuspid OR BAV) on Medline, Embase and conference proceedings; #1 TAVI, #2 TAVR, #3 percutaneous aortic valve, #4 transcatheter aortic valve, #5 bicuspid, #6 BAV, #7 (#1 OR #2 OR #3 OR #4) AND (#5 OR #6) on CENTRAL. The search was last updated on September 22, 2021. Exclusion criteria were: (1) duplicate publication; (2) articles without primary data; and (3) non-English research. Inclusion criteria were one of the followings: (1) a comparison of clinical adverse events of TAVR between BAV and TAV, or a comparison of BE and SE valve outcomes in patients with BAV; (2) a comparison of THV geometry on CT after TAVR between BAV and TAV; both with the availability of binary primary outcome data. The assessment of article quality and extraction of relevant data were done by YZ and YML independently. Data extracted from the included studies and used for all analyses in the review are presented in **Supplementary Material**.

The aim of this study was set to answer: (1) the proportion of different phenotypes of BAV in the included studies; (2) a comparison of clinical outcomes and procedural complications after TAVR in patients with BAV vs. TAV, including a subgroup analysis stratified by early- and new-generation devices; (3) a comparison of clinical outcomes and procedural complications in patients with BAV after TAVR between BE and SE valves, including a subgroup analysis stratified into early- and new-generation devices; and (4) differences of BE and SE THV geometry on CT after TAVR in patients with BAV.

Early-generation TAVR devices included Sapien (Edwards Lifesciences), Sapien XT (Edwards Lifesciences), CoreValve (Medtronic), and Venus A-Valve (Venus MedTech Inc.). New-generation devices included Sapien 3 (Edwards Lifesciences), Lotus (Boston Scientifics), Evolut R and Pro (Medtronic), Acurate Neo (Boston Scientific), and Portico (Abbott). BE devices included Sapien, Sapien XT, and Sapien 3 valves (Edwards Lifesciences); SE devices included CoreValve, Evolut R and Pro (Medtronic), Accurate Neo (Boston Scientifics), Portico (Abbott), Venus A-Valve (Venus MedTech), and Lotus (Boston Scientifics). The year of publication, study design, the number of enrolled centers, countries, the mean or median age of population, the mean or median score of surgical risks, and the number of enrolled patients were collected from each study. Overlapping population of the included articles was screened. The publication of a smaller sample size in studies with overlapping population was then excluded from the subsequent meta-analysis. Discrepancies in the selection of relevant studies and data extraction were solved by a discussion with a third evaluator (YML).

Outcomes of Interest

Bicuspid aortic valve was subclassified as type 0, type 1 (grouped by left–right coronary cusp fusion, left noncoronary cusp fusion, and right noncoronary cusp fusion), and type 2 according to Sievers' classification (12). The proportions of each subtype were compared among regions grouped into the USA, Europe, China, and multiregional areas (data from multicenter studies including Europe, North America, and other Asia-Pacific regions).

Transcatheter aortic valve replacement-specific outcomes were defined according to the Valve Academic Research Consortium 3 (VARC-3), while study-specific definitions remained as they were based on the corresponding articles (13). Adverse events of interest at hospitalization included the conversion to SAVR, coronary obstruction, the need of a second valve, device failure (procedural mortality, the incorrect positioning of a single prosthetic heart valve into the proper anatomical location, prosthesis-patient mismatch, mean aortic valve gradient $>$ 20 mmHg, peak velocity $>$ 3 m/s, or moderate/severe prosthetic valve regurgitation), annular rupture, new-onset atrial fibrillation (NO-AF), life-threatening or major bleeding, major vascular complications, acute kidney injury (AKI), myocardial infarction (MI), a moderate or severe PVL, stroke, a new PPI, MI, and mortality; adverse events of interest at a 30-day follow-up included life-threatening or major bleeding, major vascular complications, AKI, and MI; and adverse events of interest at a 1-year follow-up included a moderate or severe PVL, stroke, a new PPI, MI, and mortality.

Transcatheter heart valve geometry and position were demonstrated by: (1) THV expansion, i.e., (the observed THV external area/device labeled size) $\times$ 100% at inflow, annulus, and the outflow of the valve frame; (2) THV eccentricity index = [1–(minimum external THV diameter/maximum external THV diameter)] $\times$ 100%; and (3) THV implantation depth, i.e., the distance from the inflow of the prosthesis to the floor of right, left, and non-coronary cusps.

Statistical Analysis

The results of meta-analysis were summarized as odds ratios (ORs) or mean difference (MD) and 95% CIs. Heterogeneity across studies was tested by the Cochran's Q statistic and Higgins' and Thompson's I^2 statistics (14). The Freeman–Tukey Double Arcsine method were used for each pooled event rate (%) according to valve generations and aortic valve morphologies. $I^2 > 50\%$ and $p \leq 0.1$ was considered to be a significant heterogeneity, where random-effect models were used. Otherwise, fixed-effect model was used for an analysis. $p < 0.05$ was considered as statistically significant for other results. All analyses were conducted using Review Manager version 5.3 (available from http://tech.cochrane.org/revman).

Quality Assessment

All included studies [except one (15)] were non-randomized studies, so study qualities were evaluated by the ROBINS-I tool (16). Publication bias was presented in funnel plots. The conduction and composition of this review were conformed to the PRISMA 2020 guideline (17).

RESULTS

The study flow is presented as the PRISMA 2020 flow diagram (**Figure 1**). A total of 22 studies (2,546 patients with BAV) were included for the analysis of BAV phenotypes (8, 10, 18–37). A total of 35 studies (including 139,058 patients: 15,700 BAV and 123,358 TAV) were analyzed for comparisons between BAV and TAV (7–10, 15, 18–30, 38–54), while 10 studies (including 1,294 patients: 805 BE and 489 SE) were analyzed for the difference of BE vs. SE in patients with BAV after TAVR (32–38, 40, 55). In addition, four studies (including 551 patients: 149 patients with BAV and 402 patients with TAV) were analyzed for the difference of THV geometry between BAV and TAV after TAVR (21, 31, 41, 53).

Proportion of the Different Types of BAV in the Included Studies

Type 1 BAV accounted for 74.5% (1,897/2,546) of patients, being the most frequently encountered BAV subtype (**Figure 2A**). The predominance of type 1 BAV was presented in Europe, the USA, and multiregional studies, accounting for 78.7% (829/1,053), 72.4% (197/272), and 74.1% (829/1,119) of patients, respectively. However, Chinese patient population demonstrated a different distribution, with 58.8% (60/102) of type 0 and 41.2% (42/102) of type 1 BAV. In addition, type 2 BAV was least commonly seen in all studies with a proportion of 2.5% (64/2,546) in total, 4.4% (49/1,119), 0.9% (9/1,053), 1.8% (5/272), and 0, respectively, in multiregional studies, Europe, the USA, and China. A total of 398 patients with type 1 BAV were included for further analysis of fusion patterns (**Figure 2B**). The L-R coronary cusp fusion was the most common pattern with a proportion of 76.6% (305/398), and the L-N coronary cusp fusion was the least common pattern with a proportion of 5.8% (23/398). Similar distributions of the L-R and L-N fusion was presented in type 1 BAV from Europe, the USA, and multiregional studies.

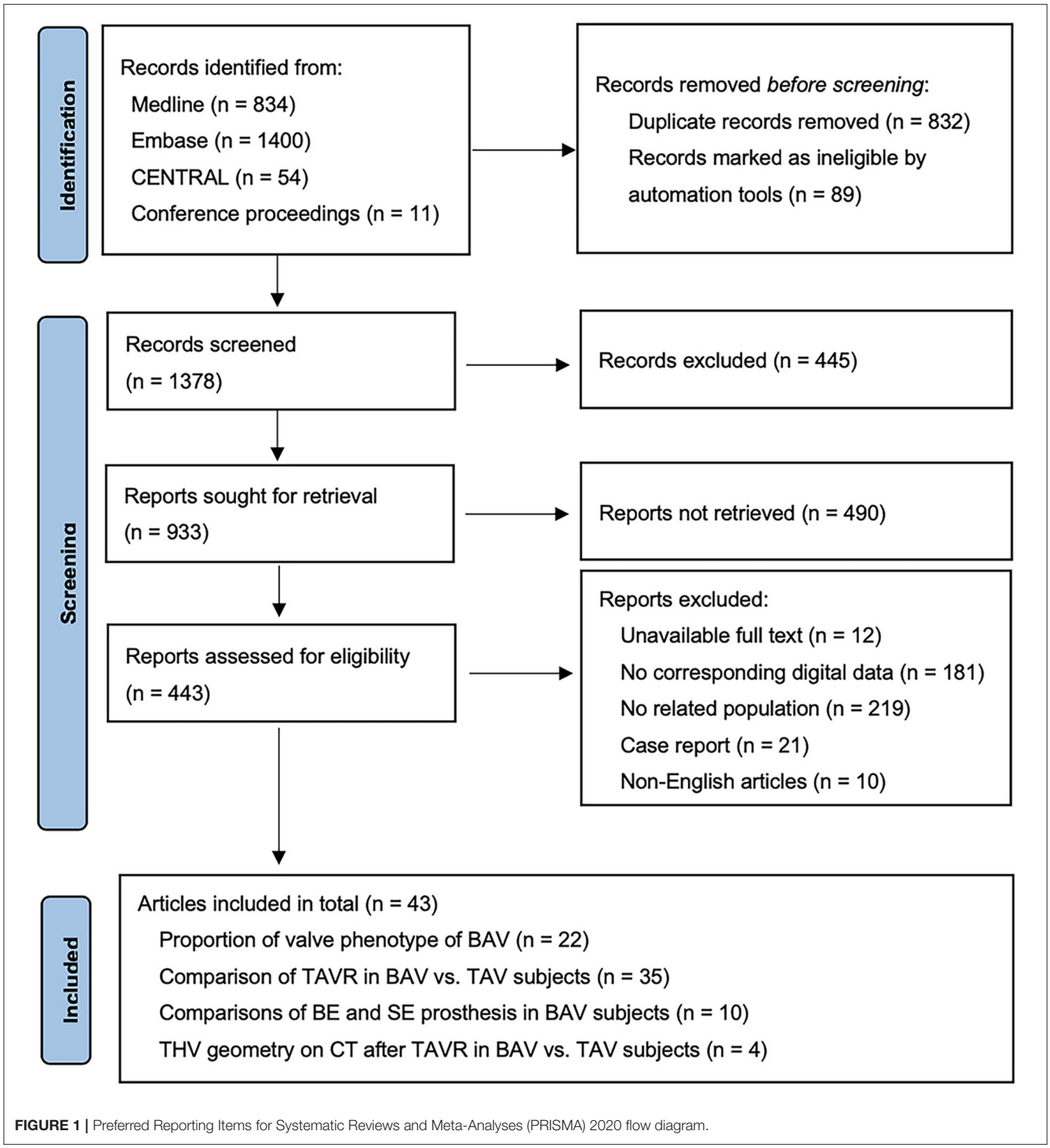


FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram.

Comparisons Between BAV and TAV

Baseline of patients and the characteristics of the included studies are summarized in **Supplementary Table S1**. In-hospital, 30-day and 1-year procedural complications and outcomes are presented in **Figures 3A–C**, respectively. All original records of meta-analysis are presented in **Supplementary Figure S1**. In terms of in-hospital analysis, patients with BAV treated by TAVR were at a higher risk of the need of a second valve (OR = 2.31, 95% CI 1.67–3.19, $p < 0.00001$) and a moderate or severe PVL (OR = 1.50, 95% CI 1.17–1.93, $p = 0.002$) than patients with TAV, with consistent results stratified by early- and new-generation devices. Moreover, patients with BAV were at an increased risk of the

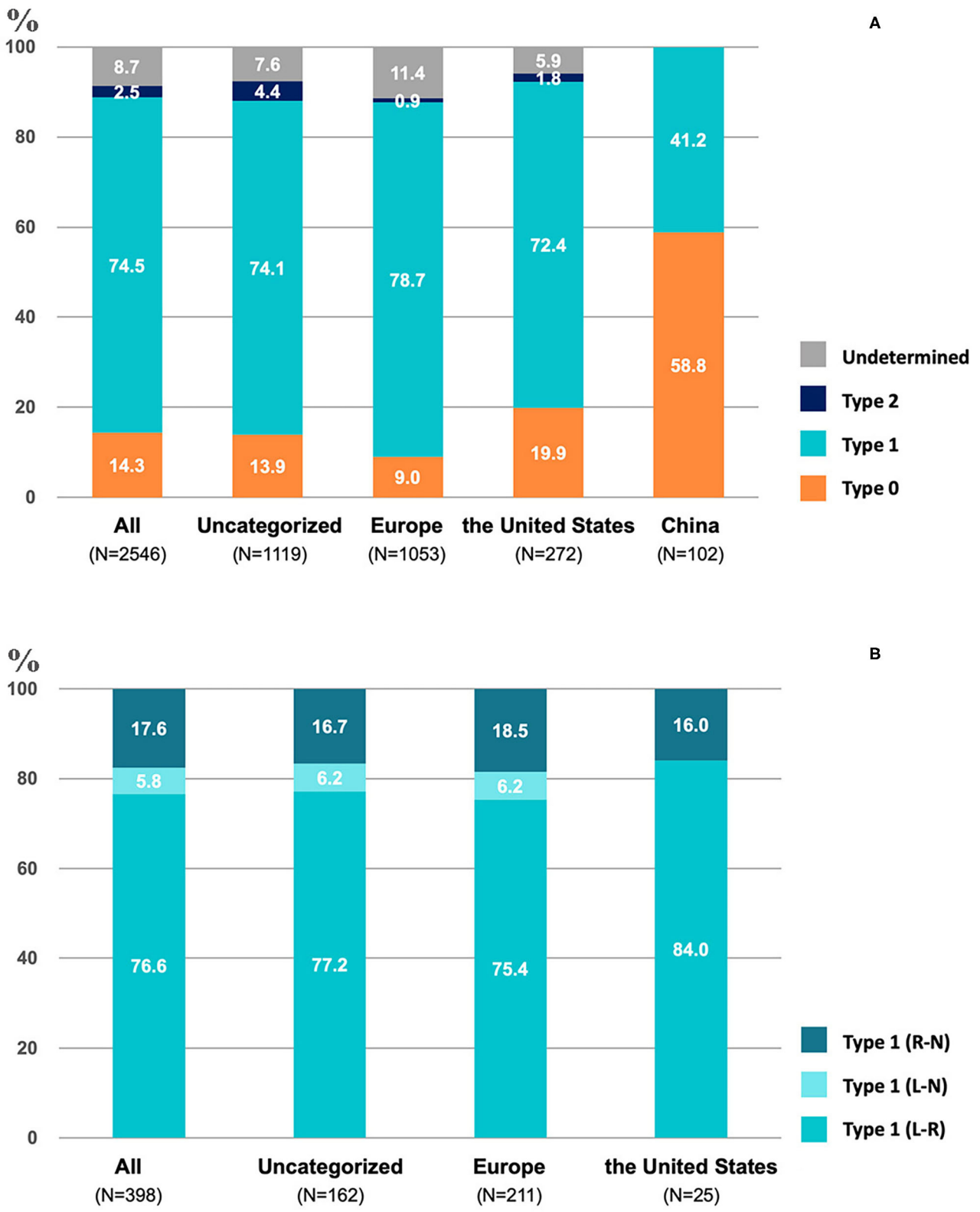


FIGURE 2 | The proportion of different valve phenotypes of bicuspid aortic valve (BAV) **(A)** and type-1 **(B)** in included studies.

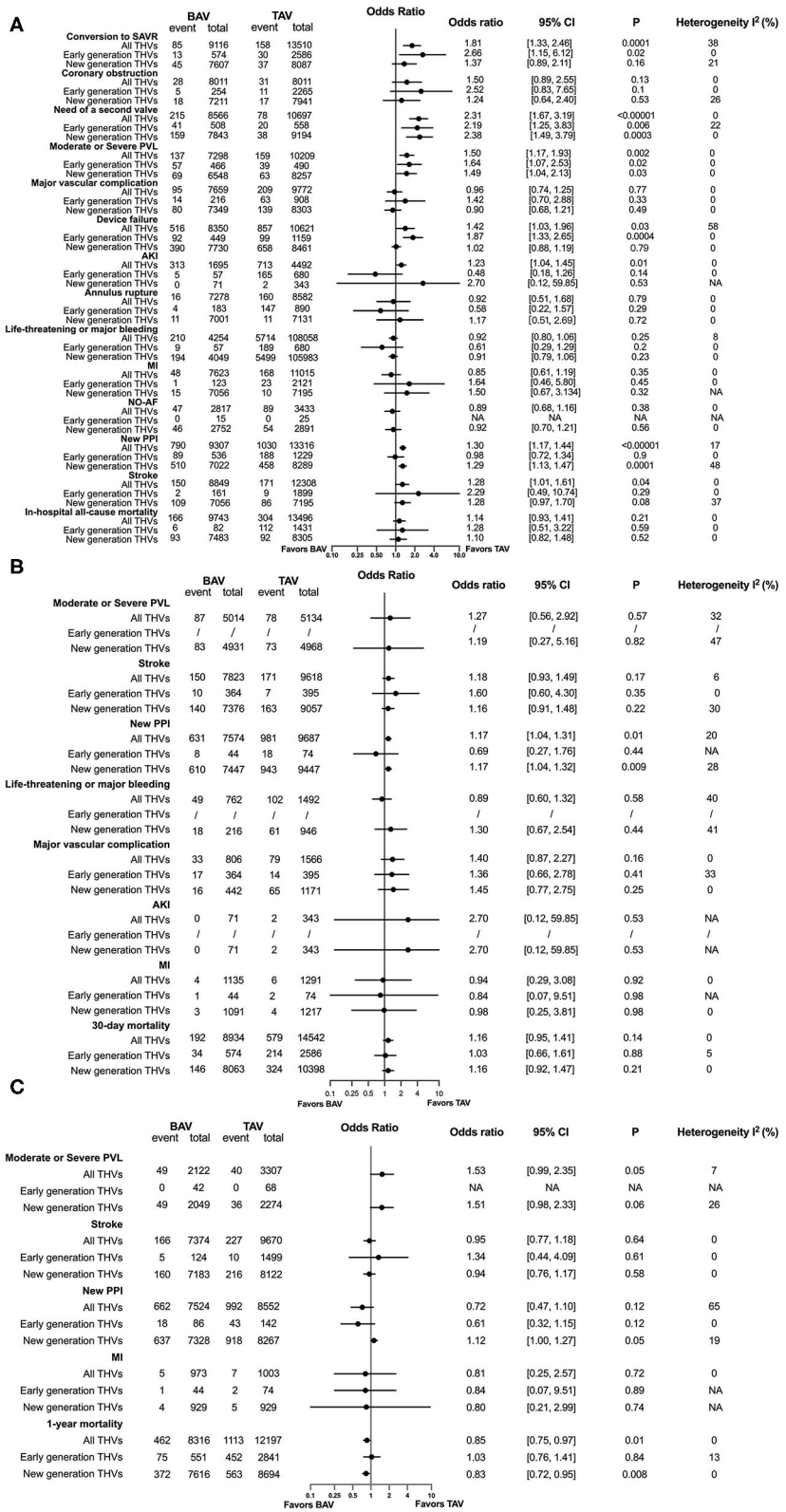


FIGURE 3 | Procedural complications and outcomes between BAV and tricuspid aortic valve (TAV) at in-hospital time **(A)**, in a 30-day **(B)**, and in a 1-year **(C)** follow-up. SAVR, surgical aortic valve replacement; PVL, paravalvular leakage; AKI, acute kidney injury; MI, myocardial infarction; NO-AF, new-onset atrial fibrillation; PPI, permanent pacemaker implantation.

conversion to SAVR (OR = 1.81, 95% CI 1.33–2.46, $p = 0.0001$) and device failure (OR = 1.42, 95% CI 1.03–1.96, $p = 0.03$), with a consistent result in patients receiving early-generation devices. A new PPI (OR = 1.30, 95% CI 1.17–1.44, $p < 0.00001$) was more common in patients with BAV than patients with TAV, as well as in new-generation devices receivers. Patients with BAV were at a higher risk of AKI (OR = 1.23, 95% CI 1.04–1.45, $p = 0.01$) and stroke (OR = 1.28, 95% CI 1.01–1.61, $p = 0.04$) than patients with TAV, but no significant differences were observed when stratified into early and new-generation devices. At 30-day post TAVR, the new PPI (OR = 1.17, 95% CI 1.04–1.31, $p = 0.01$) tended to be more common in BAV than in TAV, with the results in accordance with new-generation devices (OR = 1.17, 95% CI 1.04–1.32, $p = 0.009$). In addition, no differences were observed in 30-day mortality (OR = 1.16, 95% CI 0.95–1.41, $p = 0.14$). At a 1-year follow-up, patients with BAV demonstrated a lower mortality rate than patients with TAV (OR = 0.85, 95% CI 0.75–0.97, $p = 0.01$), with consistent results presented in patients using early-generation devices (OR = 0.83, 95% CI 0.72–0.95, $p = 0.008$).

Rates of complications and adverse outcomes were generally higher in population using early-generation devices than using new-generation devices, including the conversion to SAVR, the need for a second valve, a moderate or severe PVL, major vascular complications, the device failure, AKI, life-threatening or major bleeding, MI, a new PPI, stroke, and mortality in hospital; stroke, major vascular complications, mortality at a 30-day follow-up; stroke, new PPI, mortality at a 1-year follow-up in BAV and TAV subjects, in addition with an in-hospital coronary obstruction, a new 30-day PPI, a 30-day MI in the BAV population (**Figures 4A,B**, **Supplementary Tables S7, S8**). A significant heterogeneity existed in the analysis of in-hospital device failure in all THVs ($I^2 = 58\%, p = 0.003$) and a 1-year new PPI in all THVs ($I^2 = 65\%, p = 0.006$) between patients with BAV and TAV. The risk of bias of the included studies is summarized in **Supplementary Table S2**, and publication bias is presented as a funnel plot in **Supplementary Figure S3**.

Comparisons Between BE and SE Valves in Patients With BAV

The characteristics of the included studies and baseline of patients in the subanalysis of the efficacy of BE vs. SE in patients with BAV are presented in **Supplementary Table S3**. The in-hospital and follow-up results are presented in **Figures 5A,B**, respectively. Patients with BAV using BE THVs were at a lower risk of the need of a second valve (OR = 0.35, 95% CI 0.17–0.70, $p = 0.003$) than SE THVs, and the consistent trend was also observed in early-generation devices (OR = 0.18, 95% CI 0.05–0.70, $p = 0.01$). A new PPI tended to be less common only in the early generation of BE THVs than SE THVs (OR = 0.53, 95% CI 0.29–0.98, $p = 0.04$), while a moderate or severe PVL was less common in only new-generation BE THVs than SE THVs (OR = 0.07, 95% CI 0.02–0.31, $p = 0.0005$). However, patients with BAV were at a higher risk of annular rupture in BE THVs than in SE THVs (OR = 4.84, 95% CI 1.39–16.85, $p = 0.01$), similarly in early-generation devices (OR = 8.11, 95% CI 1.34–49.18, $p = 0.02$). In addition, the 30-day (OR = 0.96, 95% CI 0.53–1.76, $p = 0.9$) and 1-year mortality (OR = 1.11, 95% CI 0.73–1.71, $p = 0.62$) between BE and SE THVs were not different. All original records of the meta-analysis are presented in **Supplementary Figure S2**. The pooled results of meta-analyses of in-hospital moderate or severe PVL in all THVs ($I^2 = 78\%, p = 0.001$), vascular complications in all THVs and first-generation THVs ($I^2 = 54\%, p = 0.11$; $I^2 = 85\%, p = 0.009$), device failure in all THVs and new-generation THVs ($I^2 = 51\%, p = 0.13$; $I^2 = 74\%, p = 0.05$), and a life-threatening or major bleeding one in new-generation THVs ($I^2 = 55\%, p = 0.13$) between BE and SE THVs in patients with BAV had a significant heterogeneity. The risk of bias of the included studies is summarized in **Supplementary Table S4**, and publication bias is presented as a funnel plot in **Supplementary Figure S4**.

THV Geometry After TAVR in Patients With BAV vs. TAV

The characteristics of studies and baseline of patients for the subanalysis of THV geometry are summarized in **Supplementary Table S5**, and the results of meta-analysis are presented in **Figure 6**. The mean BE THV expansion after TAVR at the annulus (MD −2.15, 95% CI −4.03 to −0.28, $p = 0.02$) and outflow level (MD −2.14, 95% CI −4.21 to −0.08, $p = 0.04$) was significantly smaller in patients with BAV than in patients with TAV. According to one original article (41), the mean SE THV expansion of the BAV population on CT at the inflow (MD −13.00, 95% CI −25.84 to −0.16, $p = 0.05$), annulus (MD −15.60, 95% CI −29.37 to −1.83, $p = 0.03$), and outflow level (MD −16.60, 95% CI −27.89 to −5.31, $p = 0.004$) was smaller than that of the TAV population. Moreover, BE THV eccentricity index was larger in patients with BAV than in patients with TAV at the inflow (MD 1.93, 95% CI 1.06–2.79, $p < 0.0001$), annulus (MD 2.35, 95% CI 1.14–3.55, $p = 0.0001$), and outflow level (MD 2.08, 95% CI 0.81–3.36, $p = 0.01$). No significant differences were witnessed in SE THV. In addition, BE THV implantation depth was not different between the two groups. No significant heterogeneity was observed in the pooled analysis. The risk of bias of the included studies is summarized in **Supplementary Table S6**, and the publication bias is presented as a funnel plot in **Supplementary Figure S5**.

DISCUSSION

This meta-analysis represents the up-to-date pooling of most extensive evidence of TAVR in patients with BAV. The major findings are: (1) type 1 BAV accounted for the largest proportion of BAV subtypes in multiregional studies and studies in Europe and the USA, while type 0 was more prevalent than type 1 in China. type 2 BAV was the least common finding in all regions. In terms of type 1 morphology, L-R coronary cusp fusion was the most common pattern while L-N coronary cusp fusion was the least common pattern. (2) Patients with BAV were at a higher risk of the conversion to SAVR, the need of a second valve, a moderate or severe PVL, the device failure, AKI, a new PPI, and stroke during hospitalization than TAV. A new PPI remained more

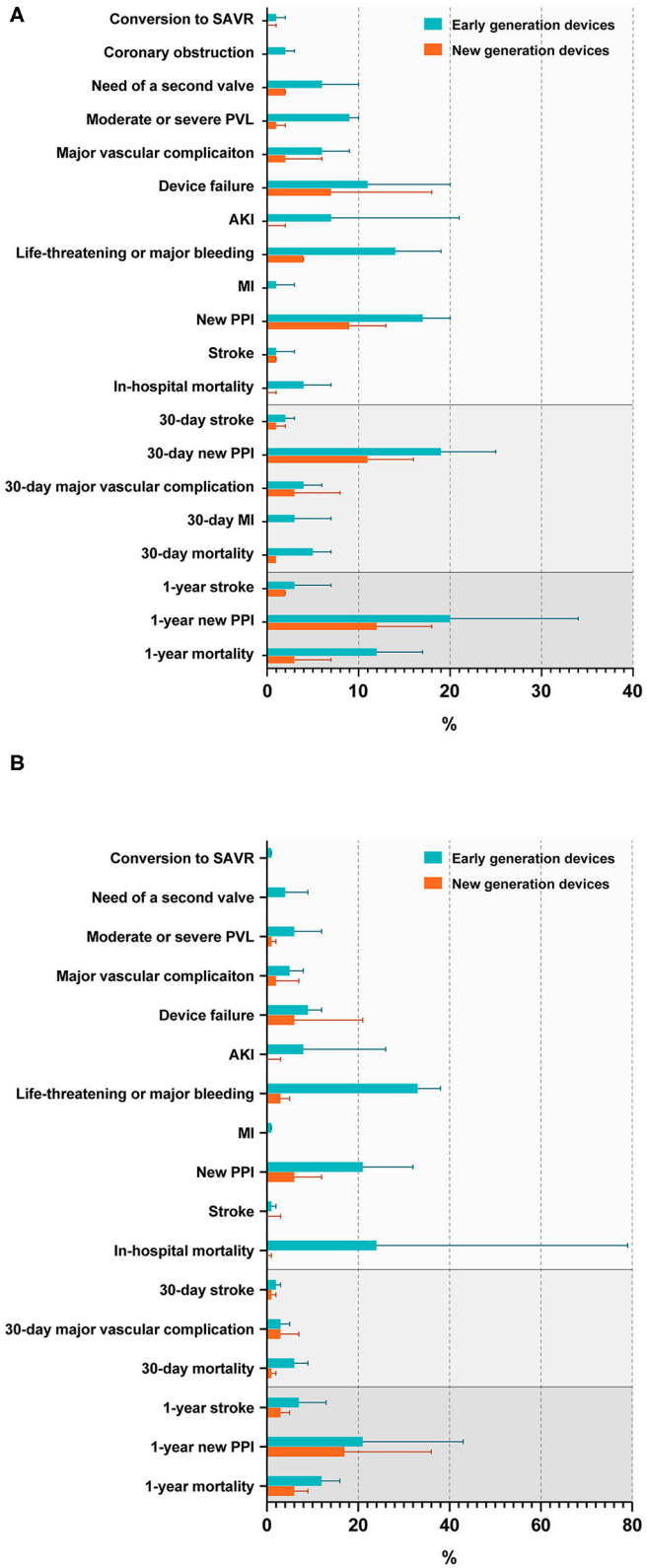


FIGURE 4 | Rates of procedural complications and outcomes in patients with BAV **(A)** and TAV **(B)**. SAVR, surgical aortic valve replacement; PVL, paravalvular leakage; AKI, acute kidney injury; MI, myocardial infarction; PPI, permanent pacemaker implantation.

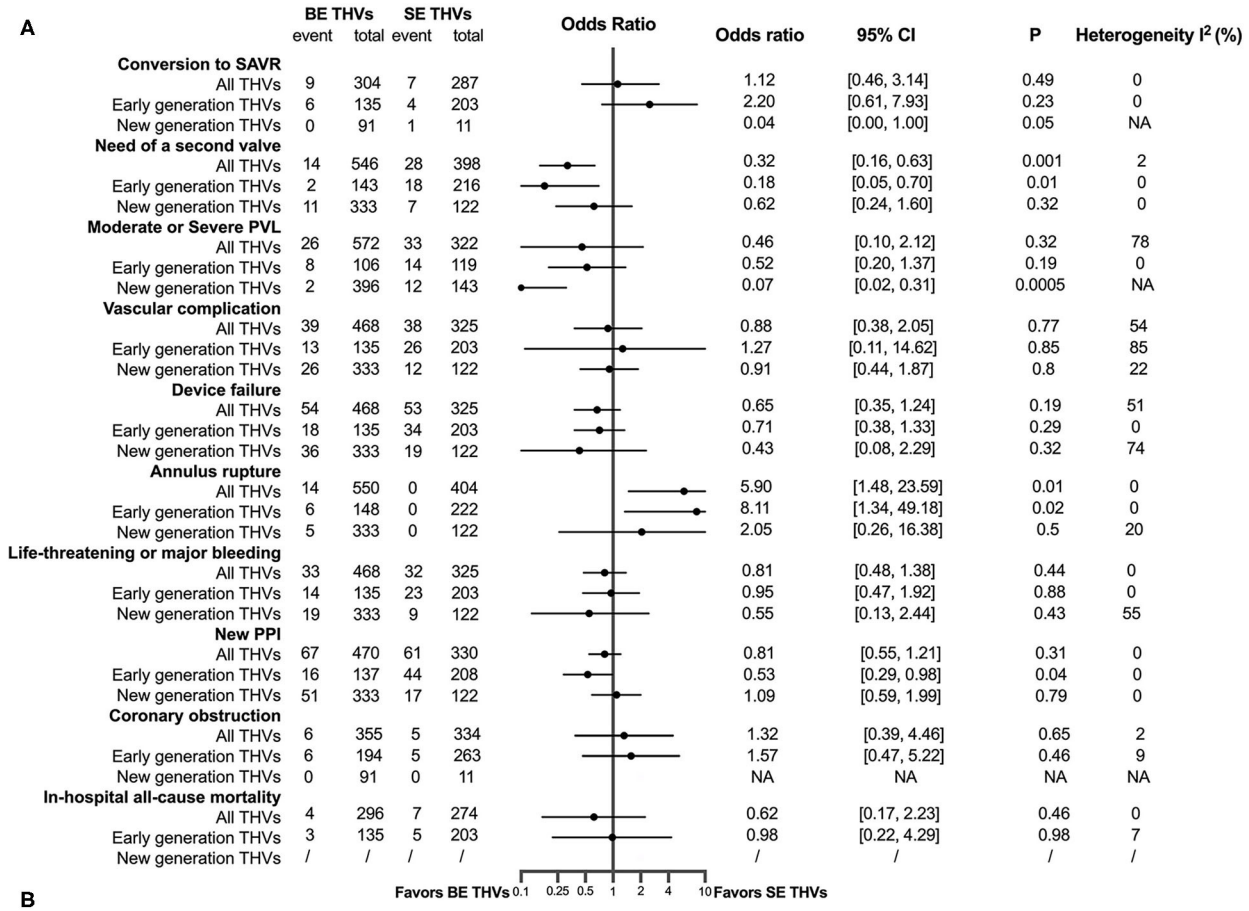


FIGURE 5 | A comparison between balloon-expandable (BE) and self-expanding (SE) valves in patients with BAV at in-hospital time **(A)**, and in a 30-day and a 1-year **(B)** follow-up. SAVR, surgical aortic valve replacement; PVL, paravalvular leakage; PPI, permanent pacemaker implantation.

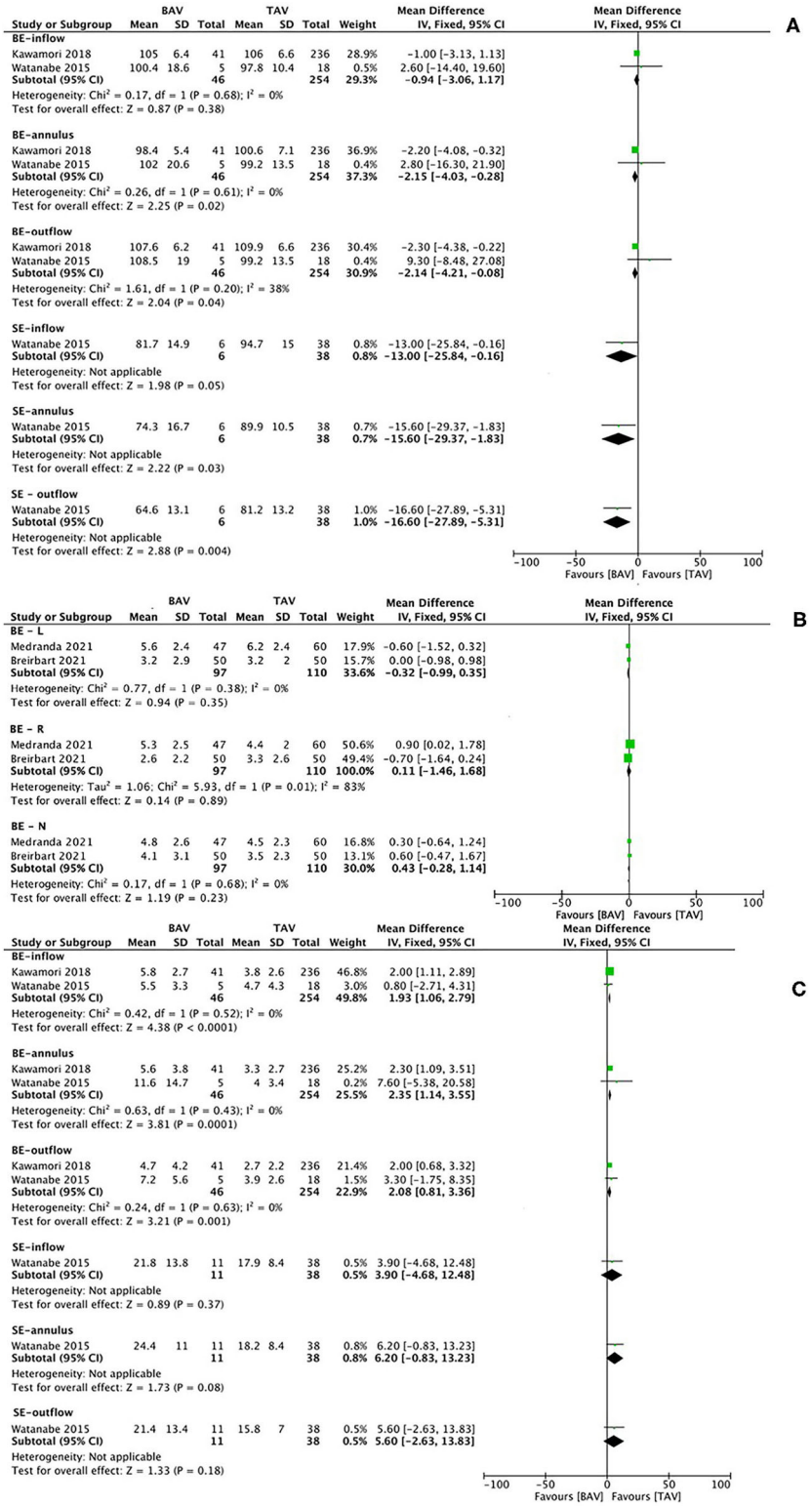


FIGURE 6 | Transcatheter heart valve (THV) expansion **(A)**, implantation depth **(B)**, and eccentricity index **(C)** on CT at different levels after TAVI in patients with BAV vs. TAV. CT image analysis of THVs, dividing into balloon-expandable and SE valves, in terms of the expansion at the inflow, annulus, and outflow level **(A)**; implantation depth below left, right and none coronary sinus **(B)**, and the eccentricity index at the inflow, annulus, and outflow level **(C)**. BE, balloon-expandable; SE, self-expanding; BE-L, balloon-expandable valve—left coronary sinus; BE-R, balloon-expandable valve—right coronary sinus; BE-N, balloon-expandable valve—non-coronary sinus.

common among patients with BAV than among patients with TAV at a 30-day follow-up. Both in-hospital and 30-day mortality between the two groups were not different, but 1-year mortality was lower in patients with BAV than in patients with TAV. (3) BE THVs were at a higher risk of annular rupture but the lower need for a second valve than SE THVs for patients with BAV. In addition, the incidence of a new PPI was higher in BE THVs than in SE THVs only in case of early-generation valves. (4) In terms of BE THV, it was less expanded at the annular and outflow level in BAV than in TAV, while more elliptical in BAV than in TAV at the inflow, annular, and outflow level. The implantation depth of BE THV was similar in the two morphologies. (5) Adverse events were less in new-generation devices than in early-generation devices in general, for patients with both BAV and TAV.

Bicuspid aortic valve is the most common isolated cause of AS among patients aged 50–70 years (56). Now that a series of randomized controlled trials demonstrate noninferior or superior outcomes of TAVR vs. SAVR irrespective of risk profiles, TAVR is expected to expand its utilization and more and more younger patients with bicuspid AS would become the candidates for TAVR. In addition, the latest guideline for valvular heart disease has recommended TAVR as an alternative to SAVR in patients with symptomatic BAV having severe AS despite no solid evidence (1). However, patients with BAV remain challenging for TAVR given its complex anatomical features such as heavy calcification with or without raphe and a concomitant dilatation of the ascending aorta, thus are still at a high risk of device malposition, underexpansion, and other procedural complications even using new-generation devices (19, 34). Thus, in this meta-analysis, we updated current evidence in TAVR for BAV while exploring regional differences in BAV subtypes, device performance, and THV geometry.

According to the number of cusps and presence of raphes, Sievers et al. have classified BAV into different phenotypes (12). The proportion of type 0 BAV seems to be higher in China than in western countries, which was confirmed by our pooled analysis. Although a previous study on Asian patients has shown a prevalence of type 1 BAV, the differences in imaging modality (i.e., MSCT vs. echocardiography), targeting patient population (i.e., AS being evaluated for TAVR vs. BAV being diagnosed with echocardiography), and the enrollment without Chinese centers might explain the divergence from our result (57–59). Type 0 morphology can pose additional challenges to TAVR. Difficulties exist in determining the virtual annulus with only two hinge points (60). A lower rate of VARC-2 defined device success (72% vs. 86.7%; $p = 0.07$) and a higher rate of mean trans-prosthetic gradient $\geq$ 20 mmHg (24% vs. 6%, $p = 0.007$) was reported in type 0 BAV than in type 1 (57). Such regional disparities might be a hint for underlying ethnic issues in the development of BAV, while also suggesting the need to consider BAV subtypes when interpreting TAVR results from different countries.

The in-hospital and 30-day mortality between patients with BAV and TAV receiving TAVR were not different, but patients with TAV ($n = 12{,}197$) seemed to have 1-year mortality higher than patients with BAV ($n = 8{,}316$), as well as in patients with TAV ($n = 8{,}694$) and BAV ($n = 7{,}616$) who received new-generation devices. The significance of survival risk differences in all THV receivers was presented when verified by fixed- (as presented in our results) and random-effect models (OR = 0.86, 95% CI = 0.76–0.98, $p = 0.02$; $I^2 = 0\%$, $p = 0.80$), which indicated the validity of the result. Most patients included in this analysis were from a latest propensity score matched research (including 6,995 BAV and 6,995 TAV; weighted 74.5% in overall meta-analysis), which analyzed consecutive patients undergoing TAVR with third-generation SAPIEN 3 and fourth-generation SAPIEN 3 Ultra valve in the STS/TVT Registry from June 2015 to October 2020, with a relatively low STS-PROM (4.0 ± 3.7 in BAV and 4.0 ± 3.5 in TAV) (54). Although the result in the original research did not show significant differences in 1-year survival (HR = 0.90, 95% CI = 0.78–1.04), the 1-year mortality of BAV (8.6%, 357/6,995) was numerically lower than that of TAV (9.8%, 417/6,995). Consequently, patients with BAV showed better 1-year survival than patients with TAV in the pooled results, indicating the potential survival benefit of the latest BE THVs applied in relatively low-risk patients with TAVR.

Although the rates of procedural complications decreased significantly with the improvement of devices, patients with BAV were still at a higher risk of the conversion to SAVR, the need of a second valve, a moderate or severe PVL, the device failure, AKI, stroke, and a new PPI. Anatomical features (i.e., longer leaflets, more severe valve calcification, and unequal-sized leaflets) and practical challenges (i.e., difficulty in valve sizing and determining the virtual annulus with only two hinge points) in BAV As subjects might bring the THV eccentricity and an incomplete prosthesis expansion during the procedure, as shown in our results, resulting in THV malposition or even aortic root injury (61). Therefore, there were higher risks of the implantation of two valves, PVL and urgent conversion to SAVR, consequently leading to a higher device failure. More AKIs in patients with BAV might be related to the volume of contrast used and the longer procedural time (7). A higher risk of stroke in patients with BAV was demonstrated during hospitalization but not at a 30-day and 1-year follow-up. This might be related to a heavier calcium burden in BAV and more usage of balloon pre-dilation during the procedure. Therefore, the cautious usage of balloon pre-dilation and limitation of the dilation times might be considered during the TAVR procedure in BAV subjects to achieve lower risk of stroke. In addition, a new PPI in hospital and in a 30-day follow-up were more common in patients with BAV than in patients with TAV, particularly in subjects receiving new-generation THVs, which might be caused by the compression on the conduction system beneath the membranes part of interventricular septum by the inflow stent of THVs, leading to conduction disturbances. Newly developed retrievable new-generation devices seemed to be invalid in lowering the risk of a new PPI in patients with BAV even with a potential advantage of implanting in the target landing zone. However, clinical adverse events were comprehensively reduced when devices were iterated into new generations, in both BAV and TAV population, indicating the importance of an improvement in the device design.

The need of a second valve were higher in self-expanding valves than in BE valves. The anchoring of BE THVs is achieved by actively pushing away native structures through balloon

dilatation, which is easier to be implanted in the target landing zone. However, the SE THVs are more likely to be malpositioned because of the passive adaptation of native valve structures. New generations of SE valves have largely overcome malposition by the ability of recapturing and repositioning. Additionally, BE THVs demonstrated a higher risk of annular rupture than SE THVs, which indicated the preference of SE THVs in patients with BAV with risk factors for annular rupture such as asymmetric calcification. Moreover, less aggressive inflating of balloons should be taken into consideration in these patients if BE THV is used. A new PPI was more common in the early generation of SE THVs than BE THVs in BAV but not in new generations of devices, which was related to an inherent difference of the designation of SE and BE THVs. However, the risk of a moderate and severe PVL still seemed to be higher in SE than in BE THVs in BAV even with new-generation devices in one study (36). Valve sizing (i.e., discretion of supra-annular sizing vs. annular sizing) for patients with BAV undergoing TAVR is important, which is frequently encountered in clinical practice. Further analysis in this aspect was not conducted because of limited original articles. There was one published meta-analysis elucidating the outcomes of supra-annular sizing for TAVR in the BAV population (62).

Our result updated new findings of higher risks of AKI and a 30-day new PPI in patients with BAV than in patients with TAV undergoing TAVR when compared with previous meta-analyses. Moreover, 1-year mortality was firstly demonstrated to be significantly higher in TAV than in BAV TAVR receivers. We also identified a higher risk of in-hospital new PPI in patients with early-generation SE THVs than BE THVs in patients with BAV. In addition, the pooled results for the proportion of BAV subtypes being treated by TAVR in different regions and the THV geometry on CT in patients with BAV vs. TAV were displayed, which were not covered previously. Although the use of TAVR in BAV is promising, to further expand indications for TAVR in bicuspid AS, large randomized trials comparing TAVR and SAVR in this population are needed, especially for low-risk patients. So far, the only RCT enrolling low-risk patients with BAV treated by TAVR is "Notion-2 trial" (NCT02825134). A good practice of patient selection, preprocedural planning, intraprocedural techniques, and the prevention of complications are still prerequisites to achieve good outcomes. Advances in device design and treatment strategies should further improve the results of TAVR in patients with BAV.

LIMITATIONS

There were some limitations in this article. Firstly, the majority of the included studies were not randomized trials in design, neither had core laboratory adjudications. The choice of prosthesis was not randomized but up to the operator's discretion. A significant heterogeneity existed in some analyses. Secondly, although consecutive patients were enrolled, a plenty of articles did not use propensity score matching to eliminate an inherent baseline difference. Patients with BAV with different anatomical phenotypes and a varying degree of calcification might lead to disparate outcomes but was not further delineated in many studies. Thirdly, the absence of long-term survival and hemodynamic results of patients with BAV makes it difficult to explore some questions of interest, e.g., THV durability. Fourthly, patients with BAV in our included population were not representable enough for all symptomatic patients with BAV because those who were not suitable for TAVR had already been excluded. Moreover, some studies only enrolled patients with BAV using BE or SE THVs alone were not included. Both resulted in a selection bias in our report. Fifthly, although we have been cautious in overlapping population, it may still present in our result when single-center data were reported both alone and among multicenter studies. Sixthly, we divided the Lotus valve into self-expandable THVs when analyzing although they are mechanically expandable valves academically. However, the sample size is small (about 11 patients). Seventhly, in 37 of 49 funnel plots of our meta-analyses, the number of original studies was < 10, leading to insufficient power of test of the funnel plots. Finally, we only screened the articles in English.

CONCLUSION

Despite higher risks of conversion to SAVR, the need of a second valve, moderate or severe PVL, device failure, AKI, stroke and new PPI, TAVR seems to be a viable option for selected patients with bicuspid severe AS, which had a potential benefit of 1-year survival, especially among lower surgical risk population using new-generation devices. Larger randomized studies were needed to guide candidate selection and verified the durable performance of THVs in the BAV population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ, T-YX, Y-ML, and MC participated in the design of the study. YZ, T-YX, and Y-ML were responsible for the coordination and acquisition of the data. YZ and T-YX performed the statistical analysis. All authors contributed to the preparation, critical review, and approved the final manuscript.

ACKNOWLEDGMENTS

We thank Liu YANG (Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, P. R. China) for her assistance and advice in data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.794850/full#supplementary-material

REFERENCES

1. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg.* (2021) 162:e183–353. doi: 10.1161/CIR.0000000000000923
2. Ward C. Clinical significance of the bicuspid aortic valve. *Heart.* (2000) 83:81–5. doi: 10.1136/heart.83.1.81
3. Vincent F, Ternacle J, Denimal T, Shen M, Redfors B, Delhaye C, et al. Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. *Circulation.* (2021) 143:1043–61. doi: 10.1161/CIRCULATIONAHA.120.048048
4. Sherif MA, Abdel-Wahab M, Stöcker B, Geist V, Richardt D, Tölg R, et al. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. *J Am Coll Cardiol.* (2010) 56:1623–9. doi: 10.1016/j.jacc.2010.06.035
5. Almeida JG, Ferreira SM, Fonseca P, Dias T, Guerreiro C, Barbosa AR, et al. Association between implantation depth assessed by computed tomography and new-onset conduction disturbances after transcatheter aortic valve implantation. *J Cardiovasc Comput Tomogr.* (2017) 11:332–7. doi: 10.1016/j.jcct.2017.08.003
6. Ueshima D, Nai Fovino L, Brener SJ, Fabris T, Scotti A, Barioli A, et al. Transcatheter aortic valve replacement for bicuspid aortic valve stenosis with first- and new-generation bioprostheses: a systematic review and meta-analysis. *Int J Cardiol.* (2020) 298:76–82. doi: 10.1016/j.ijcard.2019.09.003
7. Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, et al. Transcatheter aortic valve replacement in bicuspid versus tricuspid aortic valves from the STS/ACC TVT Registry. *JACC Cardiovasc Interv.* (2020) 13:1749–59. doi: 10.1016/j.jcin.2020.03.022
8. Blackman DJ, Van Gils L, Bleiziffer S, Gerckens U, Petronio AS, Abdel-Wahab M, et al. Clinical outcomes of the lotus valve in patients with bicuspid aortic valve stenosis: an analysis from the RESPOND study. *Catheter Cardiovasc Interv.* (2019) 93:1116–23. doi: 10.1002/ccd.28120
9. Forrest JK, Ramlawi B, Reardon MJ, Ito S, Huang J, Deeb GM. Comparison of 1-Year outcomes after transcatheter aortic valve replacement between low-risk patients with severe bicuspid and tricuspid aortic stenosis. *JAMA Cardiol.* (2021) 6:50–7. doi: 10.1001/jamacardio.2020.4738
10. Williams MR, Webb JG. The PARTNER 3 Bicuspid Registry for SAPIEN 3 TAVR in Low-risk Patients. Florida: TVT 2021 Structural Heart Summit (2021).
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
12. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
13. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *Eur Heart J.* (2021) 42:1825–57. doi: 10.1093/eurheartj/ehaa799
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* (2002) 21:1539–58. doi: 10.1002/sim.1186
15. Kochman J, Huczek Z, Scisło P, Dabrowski M, Chmielak Z, Szymański P, et al. Comparison of one- and 12-month outcomes of transcatheter aortic valve replacement in patients with severely stenotic bicuspid versus tricuspid aortic valves (results from a multicenter registry). *Am J Cardiol.* (2014) 114:757–62. doi: 10.1016/j.amjcard.2014.05.063
16. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol.* (2013) 66:408–14. doi: 10.1016/j.jclinepi.2012.09.016
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71
18. Liu XB, Jiang JB, Zhou QJ, Pu ZX, He W, Dong AQ, et al. Evaluation of the safety and efficacy of transcatheter aortic valve implantation in patients with a severe stenotic bicuspid aortic valve in a Chinese population. *J Zhejiang Univ Sci B.* (2015) 16:208–14. doi: 10.1631/jzus.B1500017
19. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol.* (2017) 69:2579–89. doi: 10.1016/j.jacc.2017.03.017
20. Sannino A, Cedars A, Stoler RC, Szerlip M, Mack MJ, Grayburn PA. Comparison of efficacy and safety of transcatheter aortic valve implantation in patients with bicuspid versus tricuspid aortic valves. *Am J Cardiol.* (2017) 120:1601–6. doi: 10.1016/j.amjcard.2017.07.053
21. Kawamori H, Yoon SH, Chakravarty T, Maeno Y, Kashif M, Israr S, et al. Computed tomography characteristics of the aortic valve and the geometry of SAPIEN 3 transcatheter heart valve in patients with bicuspid aortic valve disease. *Eur Heart J Cardiovasc Imaging.* (2018) 19:1408–18. doi: 10.1093/ehjci/jex333
22. Liao YB, Li YJ, Xiong TY, Ou YW, Lv WY, He JL, et al. Comparison of procedural, clinical and valve performance results of transcatheter aortic valve replacement in patients with bicuspid versus tricuspid aortic stenosis. *Int J Cardiol.* (2018) 254:69–74. doi: 10.1016/j.ijcard.2017.12.013
23. Mangieri A, Chieffo A, Kim WK, Stefanini GG, Rescigno G, Barbanti M, et al. Transcatheter aortic valve implantation using the ACURATE neo in bicuspid and tricuspid aortic valve stenosis: a propensity-matched analysis of a European experience. *EuroIntervention.* (2018) 14:e1269–75. doi: 10.4244/EIJ-D-18-00281
24. De Biase C, Mastrokostopoulos A, Philippart R, Desroche LM, Blanco S, Rehal K, et al. Aortic valve anatomy and outcomes after transcatheter aortic valve implantation in bicuspid aortic valves. *Int J Cardiol.* (2018) 266:56–60. doi: 10.1016/j.ijcard.2018.01.018
25. Aalaei-Andabili SH, Beaver TM, Petersen JW, Anderson RD, Karimi A, Thoburn E, et al. Early and midterm outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valves. *J Card Surg.* (2018) 33:489–96. doi: 10.1111/jocs.13775
26. Tchetche D, De Biase C, Van Gils L, Parma R, Ochala A, Lefevre T, et al. Bicuspid aortic valve anatomy and relationship with devices: the BAVARD multicenter registry. *Circ Cardiovasc Interv.* (2019) 12:e007107. doi: 10.1161/CIRCINTERVENTIONS.118.007107
27. Waksman R, Craig PE, Torguson R, Asch FM, Weissman G, Ruiz D, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe bicuspid aortic valve stenosis. *JACC Cardiovasc Interv.* (2020) 13:1019–27. doi: 10.1016/j.jcin.2020.02.008
28. Pineda AM, Rymer J, Wang A, Banks AZ, Koweek LH, Plichta R, et al. Transcatheter aortic valve replacement for patients with severe bicuspid aortic stenosis. *Am Heart J.* (2020) 224:105–12. doi: 10.1016/j.ahj.2020.02.003
29. Hamdan A, Nassar M, Schwammenthal E, Perlman G, Arow Z, Lessick J, et al. Short membranous septum length in bicuspid aortic valve stenosis increases the risk of conduction disturbances. *J Cardiovasc Comput Tomogr.* (2021) 15:339–47. doi: 10.1016/j.jcct.2020.10.002
30. Kim WK, Bhumimuang K, Renker M, Fischer-Rasokat U, Möllmann H, Walther T, et al. Determinants of paravalvular leakage following transcatheter aortic valve replacement in patients with bicuspid and tricuspid aortic stenosis. *Eur Heart J Cardiovasc Imaging.* (2021). doi: 10.1093/ehjci/jeab011. [Epub ahead of print].
31. Breitbart P, Minners J, Czerny M, Hein M, Neumann FJ, Ruile P. Prosthesis position after TAVI with balloon-expandable SAPIEN 3 in bicuspid aortic valves. *J Clin Med.* (2021) 10:2561. doi: 10.3390/jcm10122561
32. Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol.* (2014) 64:2330–9. doi: 10.1016/j.jacc.2014.09.039
33. Yousef A, Simard T, Webb J, Rodés-Cabau J, Costopoulos C, Kochman J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: a patient level multi-center analysis. *Int J Cardiol.* (2015) 189:282–8. doi: 10.1016/j.ijcard.2015.04.066
34. Yoon SH, Lefèvre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. *J Am Coll Cardiol.* (2016) 68:1195–205. doi: 10.1016/j.jacc.2016.06.041

35. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
36. Mangieri A, Tchetchè D, Kim WK, Pagnesi M, Sinning JM, Landes U, et al. Balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis: insights from the BEAT international collaborative registrys. *Circ Cardiovasc Interv.* (2020) 13:e008714. doi: 10.1161/CIRCINTERVENTIONS.119.008714
37. Husso A, Airaksinen J, Juvonen T, Laine M, Dahlbacka S, Virtanen M, et al. Transcatheter and surgical aortic valve replacement in patients with bicuspid aortic valve. *Clin Res Cardiol.* (2021) 110:429–39. doi: 10.1007/s00392-020-01761-3
38. Hayashida K, Bouvier E, Lefèvre T, Chevalier B, Hovasse T, Romano M, et al. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. *Circ Cardiovasc Interv.* (2013) 6:284–91. doi: 10.1161/CIRCINTERVENTIONS.112.000084
39. Bauer T, Linke A, Sievert H, Kahlert P, Hambrecht R, Nickenig G, et al. Comparison of the effectiveness of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valves (from the German TAVI Registry). *Am J Cardiol.* (2014) 113:518–21. doi: 10.1016/j.amjcard.2013.10.023
40. Costopoulos C, Latib A, Maisano F, Testa L, Bedogni F, Buchanan L, 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) 113:1390–3. doi: 10.1016/j.amjcard.2014.01.412
41. Watanabe Y, Chevalier B, Hayashida K, Leong T, Bouvier E, Arai T, et al. Comparison of multislice computed tomography findings between bicuspid and tricuspid aortic valves before and after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* (2015) 86:323–30. doi: 10.1002/ccd.25830
42. Arai T, Lefèvre T, Hovasse T, Morice MC, Romano M, Benamer H, et al. The feasibility of transcatheter aortic valve implantation using the Edwards SAPIEN 3 for patients with severe bicuspid aortic stenosis. *J Cardiol.* (2017) 70:220–4. doi: 10.1016/j.jjcc.2016.12.009
43. Xu Q, Liu X, Jiang J, He Y, Zhu Q, Gao F, et al. Transcatheter aortic valve replacement in atypical valve anatomy using the lotus valve: a Chinese single-center experience. *Herz.* (2021) 46:63–70. doi: 10.1007/s00059-018-4778-z
44. Nagaraja V, Suh W, Fischman DL, Banning A, Martinez SC, Potts J, et al. Transcatheter aortic valve replacement outcomes in bicuspid compared to trileaflet aortic valves. *Cardiovasc Revasc Med.* (2019) 20:50–6. doi: 10.1016/j.carrev.2018.09.013
45. Xiong TY, Wang X, Li YJ, Liao YB, Zhao ZG, Wei X, et al. Less pronounced reverse left ventricular remodeling in patients with bicuspid aortic stenosis treated with transcatheter aortic valve replacement compared to tricuspid aortic stenosis. *Int J Cardiovasc Imaging.* (2018) 34:1761–7. doi: 10.1007/s10554-018-1401-6
46. Zhou D, Pan W, Wang J, Wu Y, Chen M, Modine T, et al. VitaFlow^{TM} transcatheter valve system in the treatment of severe aortic stenosis: one-year results of a multicenter study. *Catheter Cardiovasc Interv.* (2020) 95:332–8. doi: 10.1002/ccd.28226
47. Elbadawi A, Saad M, Elgendy IY, Barssoum K, Omer MA, Soliman A, et al. Temporal trends and outcomes of transcatheter versus surgical aortic valve replacement for bicuspid aortic valve stenosis. *JACC Cardiovasc Interv.* (2019) 12:1811–22. doi: 10.1016/j.jcin.2019.06.037
48. Fu B, Chen Q, Zhao F, Guo Z, Jiang N, Wang X, et al. Efficacy and safety of transcatheter aortic valve implantation in patients with severe bicuspid aortic stenosis. *Ann Transl Med.* (2020) 8:873. doi: 10.21037/atm-20-4436
49. Halim SA, Edwards FH, Dai D, Li Z, Mack MJ, Holmes DR, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Circulation.* (2020) 141:1071–9. doi: 10.1161/CIRCULATIONAHA.119.040333
50. Ahuja KR, Nazir S, Saad AM, Isogai T, Alamir MA, Yun J, et al. Comparison of outcomes of urgent/emergent endovascular transcatheter aortic valve implantation in patients with tricuspid versus bicuspid stenotic aortic valve. *Am J Cardiol.* (2020) 132:165–6. doi: 10.1016/j.amjcard.2020.06.056
51. Du F, Zhu Q, Jiang J, Chen H, Liu X, Wang J. Incidence and predictors of permanent pacemaker implantation in patients who underwent transcatheter aortic valve replacement: observation of a Chinese population. *Cardiology.* (2020) 145:27–34. doi: 10.1159/000502792
52. Unbehaun A, Meyer A, Hamandi M, Buz S, Klein C, Sundermann S, et al. Transcatheter aortic valve implantation in bicuspid versus tricuspid valve pathologies-a propensity matched comparison. *Thorac Cardiovasc Surg.* (2017) 65:S1–110. doi: 10.1055/s-0037-1598799
53. Medranda GA, Rogers T, Forrestal BJ, Case BC, Yerasi C, Chezar-Azerrad C, et al. Balloon-expandable valve geometry after transcatheter aortic valve replacement in low-risk patients with bicuspid versus tricuspid aortic stenosis. *Cardiovasc Revasc Med.* (2021) 3:7–12. doi: 10.1016/j.carrev.2021.03.027
54. Makkar RR, Yoon SH, Chakravarty T, Kapadia SR, Krishnaswamy A, Shah PB, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke among patients at low surgical risk. *JAMA.* (2021) 326:1034–44. doi: 10.1001/jama.2021.13346
55. Kosek M, Witkowski A, Dabrowski M, Jastrzebski J, Michałowska I, Chmielak Z, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: a series of cases. *Kardiol Pol.* (2015) 73:627–36. doi: 10.5603/KP.a2015.0068
56. Saad M, Seoudy H, Frank D. Challenging anatomies for TAVR-bicuspid and beyond. *Front Cardiovasc Med.* (2021) 8:654554. doi: 10.3389/fcvm.2021.654554
57. Ielasi A, Moscarella E, Mangieri A, Giannini F, Tchetchè D, Kim WK, et al. Procedural and clinical outcomes of type 0 versus type 1 bicuspid aortic valve stenosis undergoing trans-catheter valve replacement with new generation devices: insight from the BEAT international collaborative registry. *Int J Cardiol.* (2021) 325:109–14. doi: 10.1016/j.ijcard.2020.10.050
58. Perlman GY, Blanke P, Dvir D, Pache G, Modine T, Barbanti M, et al. Bicuspid aortic valve stenosis: favorable early outcomes with a next-generation transcatheter heart valve in a multicenter study. *JACC Cardiovasc Interv.* (2016) 9:817–24. doi: 10.1016/j.jcin.2016.01.002
59. Jilaihawi H, Wu Y, Yang Y, Xu L, Chen M, Wang J, et al. Morphological characteristics of severe aortic stenosis in China: imaging corelab observations from the first Chinese transcatheter aortic valve trial. *Catheter Cardiovasc Interv.* (2015) 85:752–61. doi: 10.1002/ccd.25863
60. Frangieh AH, Michel J, Deutsch O, Joner M, Pellegrini C, Rheude T, et al. Aortic annulus sizing in stenotic bicommissural non-raphe-type bicuspid aortic valves: reconstructing a three-dimensional structure using only two hinge points. *Clin Res Cardiol.* (2019) 108:6–15. doi: 10.1007/s00392-018-1295-2
61. Xie X, Shi X, Xun X, Rao L. Efficacy and safety of transcatheter aortic valve implantation for bicuspid aortic valves: a systematic review and meta-analysis. *Ann Thorac Cardiovasc Surg.* (2016) 22:203–15. doi: 10.5761/atcs.ra.16-00032
62. Kumar A, Doshi R, Shariff M, Adalja D, Vallabhajosyula S. Supra annular sizing for TAVR in bicuspid aortic valve stenosis: a meta-analysis. *Indian Heart J.* (2020) 72:309–11. doi: 10.1016/j.ihj.2020.06.017

Conflict of Interest: MC and YF are consultants/proctors of Venus MedTech, MicroPort, and Peijia Medical.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 13 April 2022
doi: 10.3389/fcvm.2022.767906

The Presence of Calcified Raphe Is an Independent Predictor of Adverse Long-Term Clinical Outcomes in Patients With Bicuspid Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement

Yung-Tsai Lee[1,2], *Wei-Hsian Yin*[1,3]*, *Tien-Ping Tsao*[1,4], *Kuo-Chen Lee*[1,4], *Ming-Chon Hsiung*[1], *Yun-Hsuan Tzeng*[3,5] and *Jeng Wei*[1,4]

[1] Heart Center, Cheng Hsin General Hospital, Taipei, Taiwan, [2] Institute of Microbiology and Immunology, National Yang Ming Chiao Tung University, Taipei, Taiwan, [3] Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [4] Faculty of Medicine, National Defense Medical Center, Taipei, Taiwan, [5] Division of Medical Imaging, Health Management Center, Cheng Hsin General Hospital, Taipei, Taiwan

OPEN ACCESS

Edited by:
Mao Chen,
Sichuan University, China

Reviewed by:
Wolfgang Rottbauer,
Ulm University Medical Center, Germany
Ari Timerman,
Dante Pazzanese Institute of Cardiology (IDPC), Brazil

***Correspondence:**
Wei-Hsian Yin
yinwh88@gmail.com

Specialty section:
This article was submitted to Heart Valve Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: 31 August 2021
Accepted: 10 March 2022
Published: 13 April 2022

Citation:
Lee Y-T, Yin W-H, Tsao T-P, Lee K-C, Hsiung M-C, Tzeng Y-H and Wei J (2022) The Presence of Calcified Raphe Is an Independent Predictor of Adverse Long-Term Clinical Outcomes in Patients With Bicuspid Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. Front. Cardiovasc. Med. 9:767906. doi: 10.3389/fcvm.2022.767906

Objective: Current guidelines recommend that transcatheter aortic valve replacement (TAVR) for bicuspid aortic valve (BAV) with aortic stenosis (AS) should only be performed in selected patients. However, we consider it even more crucial to identify what the really important factors are while determining long-term outcomes in patients with BAV undergoing TAVR, which is precisely the aim of this study.

Methods: We retrospectively evaluated consecutive patients who underwent TAVR with balloon-expandable Sapien XT or Sapien 3 valves (Edwards Lifesciences, Irvine, CA) for the treatment of severe bicuspid AS. The primary end points were major adverse cardiac and cerebral events (MACCE), that is, mortality, non-fatal myocardial infarction (MI), disabling stroke, valve failure needing reintervention, or clinically relevant valve thrombosis during follow-up.

Results: A total of 56 patients who underwent TAVR with Sapien XT ($n = 20$) or Sapien 3 ($n = 36$) were included. The device and procedural success rates were similar between the two TAVR valves; however, the newer-generation Sapien 3 yielded a trend toward better long-term clinical outcomes than the early-generation Sapien XT did (MACCE rates 35 vs. 11%, $p = 0.071$). In the multivariate Cox proportional hazards analyses, the presence of calcified raphe > 4 mm was the only independent predictor of long-term MACCE (hazard ratio: 6.76; 95% confidence interval: 1.21–37.67, $p = 0.029$).

Conclusion: TAVR performed by a skilled heart team, while using newer-generation balloon-expandable Sapien 3 valve, may yield better long-term clinical outcomes compared to TAVR using early-generation Sapien XT valve. Moreover, the presence of calcified raphe >4 mm is an independent determinant of adverse clinical outcomes.

Keywords: transcatheter aortic valve replacement, bicuspid aortic valve, aortic stenosis, balloon-expandable valve, valve calcification, calcified raphe, clinical outcomes

INTRODUCTION

More often than not, bicuspid aortic valve (BAV) with aortic stenosis (AS) is congenital, whereas an acquired BAV occurs when there is a fibrous fusion between cusps of a preexisting tricuspid aortic valve (1, 2). Although there have existed sound enough data concerning the safety and efficacy of transcatheter aortic valve replacement (TAVR) in patients with tricuspid valve severe AS (3–5), patients with BAV have largely been excluded from randomized clinical trials involving TAVR (3–5). BAV consists of ∼10% of patients currently treated by TAVR; however, despite encouraging data from registries, including patients with BAV who showed similar or even better outcomes of TAVR in bicuspid vs. tricuspid AS, TAVR has yet to establish itself in this patient cohort (6–15).

Because of the improvements in the design of sealing skirts of newer-generation transcatheter heart valves (THVs), procedural success has increased, and the survival rates of patients with BAV have become similar to those of patients with tricuspid valve AS undergoing TAVR (9–15). However, complications, such as moderate or severe paravalvular leakage (PVL) and aortic root dissection are more commonly seen in patients with BAV compared with those in patients with tricuspid aortic valve (9–15). Hence, certain experts proposed new BAV imaging classification for the patients who underwent TAVR and, to reduce complications, various supra-annular sizing methods, algorithms, balloon sizing, or even computer simulation to improve valve sizing and device selection (12, 16–26). However, whether these approaches can truly provide additional benefits in terms of improving either device or procedural success, or even clinical outcomes, remain controversial (26–29).

In the future, specifically designed prospective studies are required to provide further evidence on THV durability, anatomical selection criteria, and long-term success before TAVR can be established as a preferred option for patients with BAV. At this stage, we consider it more pressing to identify what the truly important factors are that determine the device success and long-term outcomes in patients with BAV undergoing TAVR; hence, it was established as the aim of this study.

MATERIALS AND METHODS

Patient Population

From April 2016 to December 2020, a total of 56 consecutive patients with BAV disease and severe AS at intermediate or high risk for conventional cardiac surgery with sternotomy and cardiopulmonary bypass underwent TAVR with balloon-expandable valves in a high-volume center in Taiwan. They were referred to the TAVR multidisciplinary team composed of interventional cardiologists, imaging cardiologists, cardiothoracic surgeons, and anesthesiologists. This study was approved by the Institutional Review Board of Cheng Hsin General Hospital No. (769) 109A-09, and individual consent for this retrospective analysis was waived. In our institution, a shared decision-making approach is performed for all patients considering aortic valve replacement, with the implementation of best practices to ensure patient goals and preferences incorporated into final decision-making.

Choice of Device, Vascular Access, and TAVR Procedures

The heart team of Cheng Hsin General Hospital is one of the largest and most experienced in Taiwan and proficient in doing TAVR with all available devices. The decisions whether TAVR may be performed or which type and size of the prosthesis to be used were subject to the heart team's discretion.

The TAVR procedure was first performed in Taiwan in 2010. The early valve technologies available were, mainly, the Medtronic CoreValve, Lotus (Boston Scientific, Natick, MA), and Sapien XT (Edwards Lifesciences, Irvine, CA), launched respectively in 2012, 2015, and 2016. Although there are no data indicating any one TAVR device is superior to the other for patients with BAV and AS, we chose Sapien XT valve as the default TAVR device for all 20 patients with BAV and AS from April 2016 to October 2017, which consists of the Sapien XT group of the patients in this study, having considered that previous studies have already demonstrated how the balloon-expandable Sapien XT valve with a better radial strength may achieve symmetric expansion of the valve and effective sealing (6–8). Three newer-generation TAVR devices, Evolut R (Medtronic Inc., Minneapolis, MN), Sapien 3 (Edwards Lifesciences, Irvine, CA), and Portico (Abbott Vascular Inc., Santa Clara, CA), were introduced in 2017. Since the procedural outcomes of newer-generation Sapien 3 valves have been considered better than those of early-generation Sapien XT valves (9–11), we chose Sapien 3 valve as the default TAVR device and performed on 36 suchlike BAV cases from October 2017 to December 2020, also the Sapien 3 group in this study.

In our institution, the default strategy for all patients was the transfemoral (TF) approach. If a TF access was not feasible because of diseased peripheral vessels, a transapical implantation would then be considered for balloon-expandable valves. Decisions were made based on pre-procedural computed tomography (CT) scan performed on all patients. All implantations were performed in a hybrid theater, and almost all patients of the study population were treated under general anesthesia. TF TAVR was conducted using percutaneous closure devices or after surgical cutdown of the femoral artery in such cases with vessel calcifications or severe obesity. Regarding the transapical approach, anterolateral mini-thoracotomy is performed in the fifth or sixth intercostal space to obtain straight access to the left ventricular apex. This is best determined by the preoperative CT scan of the chest. In most cases, after balloon valvuloplasty had been done during rapid ventricular pacing, valve deployment was performed under fluoroscopy. After TAVR, all patients were referred to the intensive care unit and monitored for at least 1 day, whereas heart rate monitoring was continued until discharge. For the purpose of platelet inhibition, aspirin (100 mg per day) was dispensed to all patients. After TAVR, an additional dose of 75 mg of clopidogrel was administered postprocedurally for 3 months in most cases. Regarding the patients with an indication for anticoagulant

therapy, they received clopidogrel and warfarin or a direct oral anticoagulant without aspirin.

Wei's Method for Valve Sizing, Positioning, and Deployment

Currently, there is no consensus on BAV sizing, choice of THV, and/or THV implantation technique when performing TAVR in patients with BAV. This uncertainty may owe much to the different tricuspid morphological features of BAV. Nowadays, CT is the standard technique for THV sizing and procedural planning in TAVR. In addition to BAV morphological features, mentioned earlier, we have discovered from the very beginning in our series that, for BAV and AS, the THV anchoring plane is almost always supra-annular at the narrowest part of aortic valve leaflets instead of the annular level. Moreover, the presence of severe eccentric calcification can affect THV implantation and patency of the coronary ostia, so we have developed a comprehensive sizing method (the Wei's method) at our institution for patients with BAV (**Figure 1**).

The Wei's method is described in detail as follows:

- Identifying a supra-annular plane, which predicts THV prosthesis anchoring by scrolling the CT images in the axial view. Usually, this plane is at the narrowest part of aortic valve leaflets with the most severe and asymmetric calcifications, fibrosis, or raphes, whichever makes valve anchoring feasible.
- Measuring the longest inter-commissural distance (maximum diameter) and the shortest distance between the leading edge of the chunk of calcium/fibrosis/raphe and the opposite aortic wall at that level (minimum diameter), and then calculating the average diameter, that is, (maximum diameter + minimum diameter)/2.
- Deciding the size of prosthesis according to the calculated average diameter. A projected circle of the identical diameter to the measured average diameter is placed at that plane to simulate the apposition of the SAPIEN valve and skirt's height to the leaflets and commissures.
- Assessing the anchoring and sealing after valve expansion by taking into consideration the bulkiness of the calcium (thickness and length) and the interaction of deployed THV with calcification in the leaflets and/or raphe. Choose underfilling or overfilling of the THVs if the circle is deemed to be oversized or undersized.
- Following the supra-annular sizing, the THV is also sized in the same patient on the basis of annular area-derived diameter, which follows the conventional annular sizing method. If the proposed THV sizes from the two methods disagreed, the prosthesis is then sized according to the plane (annular or supra-annular) with the smaller derived diameter.
- Surveying the aortic root and valve anatomies to assess the risk of complications, including rupture, aortic root dissection, conduction disturbances, and coronary obstruction, and to determine the implantation depth.
- Pursuing a two-step safer implantation. That is, we deploy the THV-sized identical to the measured average diameter (anchoring), followed by post-dilatation with/without overfilling to improve conformity and reduce PVL (optimization) if needed.

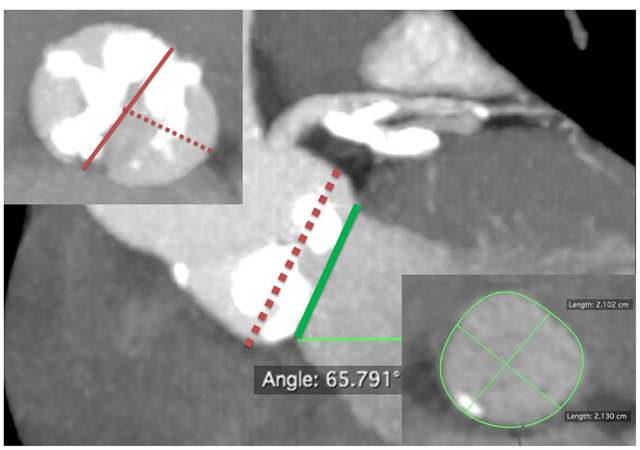


FIGURE 1 | Comprehensive sizing method or the Wei's method of transcatheter aortic valve replacement for bicuspid aortic valve. First, identify a supra-annular plane at end-systole with maximum aortic leaflet opening, which predicts transcatheter heart valve (THV) prosthesis anchoring. Usually, this is at the narrowest part in the aortic valve leaflets with the most severe and asymmetric calcifications, fibrosis, or raphes, whichever makes valve anchoring feasible (central panel, red dash line). Next, measure the maximum diameter (usually, the inter-commissural distance, left upper panel, red solid line) and the minimum diameter (the shortest distance between the leading edge of the chunk of calcium/fibrosis/raphe and the opposite aortic wall, left upper panel, red dash line) at that level. Then, calculate the average diameter: (maximum diameter + minimum diameter)/2. The prosthesis is sized according to the calculated average diameter. Then, the THV is also sized in the same patient on the basis at the level of aortic annulus (central panel, green solid line) of annular area-derived diameter (conventional annular sizing method, right lower panel). If the proposed THV sizes from the two methods disagree, the prosthesis is sized according to the plane (annular or supra-annular) with the smaller derived diameter.

Follow-Up and Data Collection

Echocardiography and clinical follow-up were performed before and after the operation. Echocardiographic studies performed at baseline and after TAVR were evaluated according to the criteria established by the American Society of Echocardiography (30). Prediction of patient operative mortality after TAVR was calculated using the Society of Thoracic Surgeons-predicted risk of mortality (STS-PROM). All patients were followed up by the heart valve team through telephone interviews and office visits. Data were prospectively collected and entered into our heart valve replacement database.

DEFINITIONS

Severe AS was defined as severe stenosis of the aortic valve with aortic valve area (AVA) <1.0 cm determined by transthoracic echocardiography, with or without aortic valve regurgitation. According to the Valve Academic Research Consortium-2 consensus document (31), device success was defined as (1) the absence of procedural mortality, (2) correct positioning of a single prosthetic heart valve into the proper

anatomical location, and (3) intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve pressure gradient [PG] <20 mmHg or peak velocity <3 m/s, and no moderate or severe prosthetic valve regurgitation). Procedural success was defined as the achievement of a successful deployment of the TAVR device and retrieval of the delivery system in the absence of mortality, conversion to surgical aortic valve replacement, or myocardial infarction (MI). The implantation depth in this study was measured in the perpendicular plane of the valve, the distance of the distal part of the transcatheter heart valve to the non-coronary cusp.

The main end points of this study were the major cardiac and cerebral adverse events (MACCE), i.e., all-cause mortality, major stroke, non-fatal MI, valve failure needing reintervention, and clinically relevant valve thrombosis during long-term follow-up. Clinically relevant valve thrombosis was defined as any thrombus attached to or near an implanted THV that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Other safety end points at 30 days included New York Heart Association (NYHA) functional class III/IV heart failure, life-threatening bleeding, acute kidney injury (AKI) stage 3, major vascular complications, paravalvular leaks, and the need for permanent pacer implantation for complete heart block. AKI stage 3 was defined as a change in serum creatinine (SCr) up to 72 h compared with baseline ≧3.0-fold increase in SCr or SCr ≧4.0 mg/dl (≧354 mmol/l) according to the VARC-2 criteria (30).

Statistical Analysis

Data were transferred from the database to the Statistical Program for Social Sciences program (version 18.0 for Windows, SPSS Inc., Chicago, IL, USA). Univariate comparisons of demographic, procedural, and outcome parameters between these two groups were made. Continuous variables are expressed as mean ± SD and were compared using the Student's *t*-test or the Wilcoxon rank-sum test. Categorical variables were presented as percent frequency and compared using the Pearson's chi-square test or the Fisher's exact test.

As for the survival analysis, the patients who underwent TAVR were divided into two groups, depending on whether or not MACCE occurred during follow-up. Univariate comparisons of clinical characteristics and laboratory measurements between the two groups were conducted using appropriate tests. The independent predictors of MACCE in the patients in this study were determined using multivariate Cox proportional hazards analyses. Variables with a p-value < 0.1 in the univariate analysis were included in the multivariate model, in addition to the use of early- vs. newer-generation valves, and important covariables associated with poor outcome, i.e., STS-PROM score, left ventricular ejection fraction, and chronic kidney disease ≧ stage 3.

A two-sided $p < 0.05$ was considered statistically significant for all analyses. Statistical analysis was performed using SPSS version 18.0 statistical software (IBM SPSS Inc.).

RESULTS

Baseline Characteristics of the Patients in This Study

Between 2016 and 2020, a total of 412 consecutive patients underwent TAVR at the Cheng Hsin General Hospital; BAV morphology was found in 56 of them (13.6%).

Baseline demographic and clinical characteristics between the Sapien XT ($n = 20$) and the Sapien 3 ($n = 36$) groups are summarized in **Table 1**. In general, the two groups were well matched. Although patients in the Sapien 3 group tended to have less frequently diabetes mellitus (Sapien XT vs. Sapien 3 = 45 vs. 19%, $p = 0.085$), coronary artery disease (Sapien XT vs. Sapien 3 = 70 vs. 39%, $p = 0.051$), and chronic kidney disease ≧ stage 3 (Sapien XT vs. Sapien 3 = 40 vs. 17%, $p = 0.107$), the statistical differences were non-significant. There was no significant difference in the incidence of patients in NYHA functional class III/IV at presentation; nevertheless, the STS-PROM score (Sapien XT vs. Sapien 3 = 9.01 ± 8.85 vs. 4.37 ± 3.97, $p = 0.009$) and frailty score (Sapien XT vs. Sapien 3 = 2.50 ± 1.28 vs. 1.58 ± 1.02, $p = 0.005$) were significantly lower in the Sapien 3 group. The baseline hemodynamics measured by echocardiography showed no significant differences between the two groups.

Baseline Echocardiographic and CT Measurements of the Patients in This Study

Bicuspid valve morphology can be readily identified by CT and is commonly described, following the classification proposed by Sievers and Schmidtke (1, 2), which categorizes three main types of BAV according to the number of seam-like raphes connecting the leaflets. In this study, the frequencies of types 0, 1, and 2 morphologies of bicuspid valve were, respectively, 23/56 (41%), 30/56 (54%), and 3/56 (5%), and were well-matched between the two groups. According to another TAVR directed and simplified non-numerical classifications based on heterogeneous leaflet morphologies and leaflet orientation proposed by (16), 23/56 (41%) were classified as bicommissural non-raphe type, 30/56 (54%) as bicommissural raphe type, and 3/56 (5%) as tricommissural, respectively, in the patients in this study (**Table 2**).

Moreover, CT assessment also showed that eccentric calcification was common in BAV and present in, respectively, 16/20 (80%) and 26/36 (72%) patients who underwent TAVR with Sapien XT and Sapien 3. There were 5/20 (25%) patients in the Sapien XT group and 14/36 (39%) in the Sapien 3 with a calcified raphe >4 mm present. The distribution of calcium was seen on two leaflets in 43/56 (77%), one commissure in 17/56 (30%), one leaflet in 11/56 (20%), and two commissures in 2/56 (4%) patients of the study population. Regarding the aortic root and ascending aorta anatomies, the coronary heights and aortic root angles were similar in both groups. But the patients in the Sapien 3 group had significantly larger sino-tubular junctions (Sapien XT vs. Sapien 3 = 28.95 ± 2.77 vs. 32.26 ± 4.81, $p = 0.002$), ascending aorta dimensions (Sapien XT vs. Sapien 3 = 39.03 ± 4.25 vs. 43.74 ± 6.71, $p = 0.002$), and more aortopathy

TABLE 1 | Baseline characteristics of the patients in this study.

	Sapien XT (*N* = 20)	Sapien 3 (*N* = 36)	*P*-value
Age, years	73 ± 8	70 ± 13	0.356
Male, *n* (%)	11 (55%)	21 (58%)	1
Body mass index, kg/m^2	23.25 ± 3.22	24.17 ± 4.08	0.389
Body surface area, m^2	1.61 ± 0.20	1.63 ± 0.15	0.676
Systemic hypertension, *n* (%)	14 (70%)	25 (69%)	1
Diabetes mellitus, *n* (%)	9 (45%)	7 (19%)	0.085
Dyslipidemia, *n* (%)	8 (40%)	15 (42%)	1
Current smoker, *n* (%)	2 (10%)	1 (3%)	0.596
Coronary artery disease, *n* (%)	14 (70%)	14 (39%)	0.051
Previous myocardial infarction, *n* (%)	4 (20%)	2 (6%)	0.221
Previous percutaneous coronary intervention, *n* (%)	8 (40%)	8 (22%)	0.270
Previous coronary artery bypass grafting, *n* (%)	0 (0%)	3 (8%)	0.479
Previous valve surgery, *n* (%)	0 (0%)	0 (0%)	-
Carotid artery disease, *n* (%)	1 (5%)	3 (8%)	1
Previous stroke, *n* (%)	4 (20%)	5 (14%)	0.828
Peripheral vascular disease, *n* (%)	3 (15%)	3 (8%)	0.747
Previous atrial fibrillation / atrial flutter, *n* (%)	4 (20%)	6 (17%)	1
Previous permanent pacemaker implantation, *n* (%)	1 (5%)	2 (6%)	1
Chronic obstructive pulmonary disease, *n* (%)	2 (10%)	2 (6%)	0.938
Chronic kidney disease ≧ stage 3, *n* (%)	8 (40%)	6 (17%)	0.107
Renal dialysis, *n* (%)	2 (10%)	1 (3%)	0.596
Heart failure, NYHA functional class III/IV, *n* (%)	17 (85%)	28 (78%)	0.764
Syncope, *n* (%)	2 (10%)	5 (14%)	1
STS-PROM score, %	9.01 ± 8.85	4.37 ± 3.97	0.009
Frailty score	2.50 ± 1.28	1.58 ± 1.02	0.005
Baseline echocardiographic findings			
Mean gradient, mmHg	50.15 ± 21.71	55.17 ± 24.34	0.446
Aortic valve area, cm^2	0.61 ± 0.19	0.64 ± 0.18	0.531
Aortic regurgitation ≧ moderate, n (%)	3 (15%)	9 (25%)	0.593
Mitral regurgitation ≧ moderate, *n* (%)	6 (30%)	11 (31%)	1
Left ventricular ejection fraction, %	48.40 ± 18.44	55.17 ± 13.79	0.162
Pulmonary hypertension (PASP ≧60 mmHg), *n* (%)	3 (15%)	3 (8%)	0.747

NYHA, New York Heart Association; STS-PROM, society for thoracic surgery-probability of mortality score; PASP, pulmonary artery systolic pressure.

(Sapien XT vs. Sapien 3 = 15% vs. 47%, $p = 0.034$), compared to those patients in the Sapien XT group.

Transcatheter Heart Valve Sizes Proposed by Annular vs. Supra-Annular Sizing Methods of the Study Populations

As shown in **Table 3**, the valve sizes ranged from 23 to 29 mm for the Sapien XT and Sapien 3 devices in both groups. The most commonly used valve sizes were 23 mm (45%) and 26 mm (45%) in the Sapien XT group, and 23 mm (39%), and 26 mm (33%) in the Sapien 3 group. The mean area-derived diameter and supra-annular sizing diameter were similar in both the Sapien XT and Sapien 3 groups. However, when the aforementioned valve sizing criteria were applied, there existed 11/56 (20%) discrepancies in the proposed THV size between the conventional valve sizing and supra-annular sizing methods. Compared with annular sizing, supra-annular sizing resulted in 45/56 (80%) similar sizes, 7/56 (13%) larger sizes, and 4/56 (7%) smaller sizes. Furthermore, a smaller valve was selected in the Sapien 3 cases compared to the Sapien XT cases, and the percentages of annular area oversizing were 2.89 ± 7.69 vs. 7.26 ± 4.44% ($p = 0.009$) as measured by the conventional annular sizing method, and 2.08 ± 5.56 vs. 5.77 ± 4.98% ($P = 0.017$) by supra-annular sizing method.

Procedural Characteristics and Immediate Complications

The technical aspects of the procedure and procedural outcomes are presented in **Table 4**. TAVR procedures were conducted *via* TF in 19 (95%) Sapien XT cases and 35 (97%) Sapien 3 cases. The Sapien XT and Sapien 3 valves were, respectively implanted *via* transapical access in one (5%) and one (3%) of the patients in this study. Besides, Sapien 3 was more frequently implanted with

TABLE 2 | Baseline computed tomographic measurements of the patients in this study.

	Sapien XT ($N = 20$)	Sapien 3 ($N = 36$)	*P*-value
Bicuspid morphology (Sievers classification)			
Type 0, *n* (%)	6 (30%)	17 (47%)	0.331
Type 1, *n* (%)	12 (60%)	18 (50%)	0.660
Type 2, *n* (%)	2 (10%)	1 (3%)	0.596
Bicuspid morphology (TAVR-Specific classification)			
Bicommissural non-Raphe-type, *n* (%)	6 (30%)	17 (47%)	0.331
Bicommissural Raphe-type, *n* (%)	12 (60%)	18 (50%)	0.660
Tricommissural type, *n* (%)	2 (10%)	1 (3%)	0.596
Distribution of calcium			
Calcified raphe > 4 mm, *n* (%)	5 (25%)	14 (39%)	0.449
One leaflet, *n* (%)	5 (25%)	6 (17%)	0.688
Two leaflets, *n* (%)	14 (70%)	29 (81%)	0.571
One commissure, *n* (%)	6 (30%)	11 (31%)	1
Two commissures, *n* (%)	1 (5%)	1 (3%)	1
Asymmetrical distribution of calcium, *n* (%)	16 (80%)	26 (72%)	0.747
Sino-tubular junction diameter, mm	28.95 ± 2.77	32.26 ± 4.81	0.002
Sinus of Valsalva diameter, mm	31.49 ± 3.12	32.85 ± 3.97	0.191
Left coronary height, mm	14.50 ± 3.33	15.53 ± 3.83	0.316
Right coronary height, mm	16.91 ± 3.12	18.10 ± 3.84	0.242
Porcelain aorta, *n* (%)	0 (0%)	0 (0%)	-
Aortic root angle, degree	52.65 ± 8.44	55.61 ± 10.42	0.282
Ascending aorta, 3 cm above the annulus, mm	39.03 ± 4.25	43.74 ± 6.71	0.002
Aortopathy (aortic diameter > 4.5 cm), *n* (%)	3 (15%)	17 (47%)	0.034

TAVR, transcatheter aortic valve replacement.

requirement for balloon valvuloplasty for post-dilatation (Sapien XT 35% vs. Sapien 3 89%, $p < 0.001$) rather than pre-dilatation (100% pre-dilatation before Sapien XT and 81% before Sapien 3, $p = 0.092$). The final implantation depth below the annulus was similar in both.

None of the 56 patients in this study required implantation of a second valve due to an initial implant embolization or malpositioning. Significant PVL (≧ moderate degree) after the TAVR procedure was found in two (10%) patients with Sapien XT and one (3%) with Sapien 3, respectively ($p = 0.596$). One (3%) patient in the Sapien 3 group had a post-procedural transvalvular gradient of >20 mmHg. To sum up, the device success rates were 85% for Sapien XT and 94% for Sapien 3 ($p = 0.485$).

Major intraoperative complications like emergency conversion to surgical aortic valve replacement, and annular or left ventricular rupture did not happen in either group. Two (10%) patients suffered from acute coronary occlusion and were successfully treated with percutaneous coronary intervention and stenting, although one of them needed emergent hemodynamic support. The procedural success rates were 95% for Sapien XT and 100% for Sapien 3 ($p = 0.764$). The mean procedure and fluoroscopic times of the two groups were similar; however, the Sapien 3 group received significantly less contrast volume (Sapien XT 148.55 ± 56.20 ml vs. Sapien 3 99.97 ± 28.27 ml; $p = 0.001$).

Thirty-Day Hemodynamic Performance of the THV and Clinical Outcomes

Transcatheter valve performance was determined by echocardiography at the 30-day follow-up (**Table 5**). A significant reduction in prosthetic valvular PG and an increase in prosthetic AVAs at 30 days were observed in all patients who underwent TAVR successfully. However, a trend toward higher mean trans-aortic valve PG (Sapien XT vs. Sapien 3 = 8.69 ± 3.05 mmHg vs. 11.03 ± 5.04 mmHg, $p = 0.066$) and smaller AVA (Sapien XT vs. Sapien 3 = 1.97 ± 0.35 cm^2 vs. 1.82 ± 0.25 cm^2, $p = 0.089$) was also observed in patients who underwent TAVR with Sapien 3, although these were not statistically significant. Echocardiography follow-up showed no significant difference in left ventricular ejection fraction and pulmonary artery systolic pressure of the two groups. Moderate/severe aortic regurgitation incidence was not statistically different between the two devices (Sapien XT vs. Sapien 3 = 10 vs. 6%, $p = 0.938$).

The intensive care unit stays were similar between the two groups. Significant improvement in NYHA functional class was observed in both groups. At 30 days, there were no all-cause mortality, cardiovascular mortality, non-fatal MI, major or life-threatening bleeding, AKI stage 3, or major vascular complications in either, though one patient in the Sapien XT group suffered from nonfatal stroke. The rates of needing a

TABLE 3 | Transcatheter heart valve size and valve sizes proposed by different sizing methods of the patients in this study.

	Sapien XT (*N* = 20)	Sapien 3 (*N* = 36)	*P*-value
Transcatheter heart valve size, mm			
20, *n* (%)	0 (0%)	0 (0%)	-
23, *n* (%)	9 (45%)	16 (44%)	1
26, *n* (%)	8 (40%)	16 (44%)	0.968
29, *n* (%)	3 (15%)	4 (12%)	1
Conventional annular sizing method			
Maximum diameter, mm	26.35 ± 2.85	27.36 ± 3.56	0.281
Minimum diameter, mm	20.67 ± 2.02	21.77 ± 2.59	0.106
Mean diameter, mm	23.52 ± 2.17	24.54 ± 2.84	0.167
Perimeter-derived diameter, mm	23.83 ± 2.21	24.89 ± 3.04	0.175
Area-derived diameter, mm	23.43 ± 2.15	24.45 ± 2.91	0.176
Proposed valve size, mm			
20, *n* (%)	0 (0%)	1 (3%)	1
23, *n* (%)	9 (45%)	14 (39%)	0.871
26, *n* (%)	9 (45%)	12 (33%)	0.565
29, *n* (%)	2 (10%)	9 (25%)	0.316
Oversizing, %	7.26 ± 4.44	2.89 ± 7.69	0.009
Supra-annular sizing (The Wei's method)			
Maximum diameter, mm	27.43 ± 2.59	28.10 ± 3.05	0.406
Minimum diameter, mm	20.08 ± 2.98	20.94 ± 2.88	0.296
Mean diameter, mm	23.75 ± 2.07	24.56 ± 2.40	0.206
Proposed valve size, mm			
20, *n* (%)	0 (0%)	0 (0%)	-
23, *n* (%)	9 (45%)	14 (39%)	0.871
26, *n* (%)	9 (45%)	18 (50%)	0.936
29, *n* (%)	2 (10%)	4 (11%)	1
Oversizing, %	5.77 ± 4.98	2.08 ± 5.56	0.017
Discordance of sizing (Annular vs. supra-annular), *n* (%)	4 (20%)	7 (19%)	1
Smaller, *n* (%)	2 (10%)	5 (14%)	1
Larger, *n* (%)	2 (10%)	2 (6%)	0.938

permanent pacemaker were similar in both groups (Sapien XT vs. Sapien 3 = 10 vs. 6%, $p = 0.938$).

During a median follow-up of 743 days (interquartile range: 393–1016 days), the long-term clinical outcomes of the newer-generation Sapien 3 group were better than those of the early-generation Sapien XT (MACCE rates 35 vs. 11%, $P = 0.071$). One patient in either group experienced clinically relevant valve thrombosis needing anticoagulant therapy. Valve failure needing reintervention was reported in one (5%) patient in the Sapien XT group and one (3%) in the Sapien 3 group.

The patients who underwent TAVR were further divided into two groups, depending on whether or not MACCE occurred during follow-up (**Table 6**). In the Cox proportional hazards analyses, the presence of a calcified raphe > 4 mm ($p = 0.032$), lower-left coronary height ($p = 0.045$), and the use of Sapien 3 device ($p = 0.041$) are significant predictors of MACCE according to the univariate analysis. The Kaplan-Meier analysis showed that the event-free survival rate was better in those patients who underwent TAVR with newer-generation Sapien 3 valves, but the statistical differences were non-significant (log-rank test, $p = 0.223$) (**Figure 2**). However, further multivariate analyses, using variables that included device types, important covariables associated with poor outcome, that is, STS-PROM score, left ventricular ejection fraction and chronic renal failure, and those variables associated with the MACCE in the univariate analysis, identified the presence of calcified raphe > 4 mm as the only independent predictor of long-term MACCE (hazard ratio: 6.76; 95% confidence interval: 1.21–37.67, $p = 0.029$). One such patient with Sapien 3 implantation needed percutaneous PVL repair following TAVR due to the development of refractory heart failure 3 months after TAVR procedure.

DISCUSSION

The main findings of our study are as follows: (1) to the best of our knowledge, this is the first report of the prevalence of BAV in patients with critical AS referred for TAVR in Taiwan; (2) the use of newer-generation balloon-expandable Sapien 3 valve may achieve better TAVR outcomes in patients with BAV

TABLE 4 | Procedural characteristics and immediate complications of the patients in this study.

	Sapien XT (*N* = 20)	Sapien 3 (*N* = 36)	*P*-value
Vascular access			
Trans-femoral, *n* (%)	19 (95%)	35 (97%)	1
Trans-apical, *n* (%)	1 (5%)	1 (3%)	1
Pre-dilatation, *n* (%)	20 (100%)	29 (81%)	0.092
Post-dilation, *n* (%)	7 (35%)	32 (89%)	<0.001
Implantation depth from annulus, mm	2.20 ± 1.60	2.36 ± 1.25	0.677
Device success, *n* (%)	17 (85%)	34 (94%)	0.485
Paravalvular leakage ≧ moderate, *n* (%)	2 (10%)	1 (3%)	0.596
2nd device needed, *n* (%)	0 (0%)	0 (0%)	-
Post-TAVR trans-valvular PG ≧ 20 mmHg, *n* (%)	0 (0%)	1 (3%)	1
Procedural success, *n* (%)	19 (95%)	36 (100%)	0.764
Conversion to SAVR, *n* (%)	0 (0%)	0 (0%)	-
Coronary obstruction, *n* (%)	2 (10%)	0 (0%)	0.238
Annulus rupture, *n* (%)	0 (0%)	0 (0%)	-
Left ventricular rupture, *n* (%)	0 (0%)	0 (0%)	-
Emergency CPB/ECMO, *n* (%)	1 (5%)	0 (0%)	0.764
Total procedure time, min	38.70 ± 25.54	31.11 ± 12.14	0.137
Total fluoroscopic time, min	22.93 ± 12.36	19.25 ± 7.15	0.163
Total contrast volume, mL	148.55 ± 56.20	99.97 ± 28.27	0.001

TAVR, transcatheter aortic valve replacement; PG, pressure gradient; SAVR, surgical aortic valve replacement; CPB/ECMO, cardiopulmonary bypass/extracorporeal membrane oxygenation.

compared to the early-generation Sapien XT valve; however, the benefit of reducing PVL due to the outer skirt of Sapien 3 may be accompanied by a tradeoff of reduced effective orifice area (EOA); (3) the complementary approach of supra-annular sizing to conventional annular sizing method (Wei's Method) developed by our team is useful in providing alternative guidance to perform safer THV implantation; and (4) the presence of calcified raphe > 4 mm was the only independent predictor of long-term outcomes in the present study so percutaneous PVL repair following TAVR in certain patients may be needed.

In our series, between 2016 and 2020, BAV morphology was found in 56/412 (13.6%) consecutive patients who underwent TAVR at the Cheng Hsin General Hospital, which was roughly 10% comparable to those reported from other Asian patient populations referred to TAVR (7, 32). Regarding the bicuspid valve morphology, according to the classification proposed by Sievers and Schmidtke, the frequencies of types 0, 1, and 2 morphologies of bicuspid valve were, respectively, 39, 55, and 5%. According to other simplified non-numerical classifications proposed by (16) 41, 54, and 5% of BAV in the patients in this study were classified, respectively, as bicommissural non-raphe type, bicommissural raphe type, and tricommissural. These were also roughly comparable to those reported by others (8–15).

Traditionally, surgical aortic valve replacement is performed to treat BAV with AS and/or aortic regurgitation (1, 5). The new American guidelines also recommend TAVR for BAV to be performed only in selected patients with BAV to address the concerns regarding the procedural and device success rates and long-term durability of THVs, particularly in the younger BAV population (5). However, since the indication of TAVR has been extended to younger low-risk patients with critical AS (5), the proportion of patients with BAV undergoing TAVR is likely to increase. TAVR originally developed for tricuspid AS has been applied to patients with BAV as an off-label indication, and there is a growing interest in the safety and efficiency of TAVR in these patients. The studies on TAVR with early-generation THVs have highlighted the complexity of performing the procedure in patients with BAV, with high rates of malposition, the need for multiple THVs, and relatively high rates of moderate-to-severe residual PVL (6–8). More recently, data from large registries demonstrated that the use of newer-generation devices featuring repositionability, sealing properties, and more accurate deployment yielded better outcomes than the early-generation devices had ever done in patients with BAV (9–15). However, complications such as moderate or severe PVL and aortic root dissection are more commonly seen in patients with BAV compared to those in patients with tricuspid aortic valve. Moreover, a clear-cut answer regarding whether newer-generation Sapien 3 valve is better than the early-generation Sapien XT valve for BAV or not has yet to be sought. In this study, we demonstrated that the use of newer-generation balloon-expandable Sapien 3 valve achieved better TAVR outcomes in patients with BAV compared to the early-generation Sapien XT valve, though it is considered statistically insignificant. The outer fabric seal of Sapien 3 did adapt better to the irregular annuli shapes and the asymmetrically calcified leaflets in patients with BAV; thus, compared with the Sapien XT group, the Sapien 3 group demonstrated numerical lower rates of ≧ moderate PVL (10 vs. 3%, $p = 0.596$), even though the CT oversizing percentage values were significantly lower in the Sapien 3 vs.

TABLE 5 | Thirty-day hemodynamic performance of the THV and 30-day and long-term clinical outcomes of the patients in this study.

	Sapien XT (*N* = 20)	Sapien 3 (*N* = 36)	*P*-value
Intensive care unit stay, days	2.85 ± 4.61	1.17 ± 0.45	0.120
30-day NYHA functional class			
III/IV, *n* (%)	4 (20%)	1 (3%)	0.094
30-day MACCE, *n* (%)	3 (15%)	3 (8%)	0.747
All-cause mortality, *n* (%)	0 (0%)	0 (0%)	-
Cardiac mortality, *n* (%)	0 (0%)	0 (0%)	-
Non-fatal myocardial infarction, *n* (%)	0 (0%)	0 (0%)	-
Non-fatal stroke, *n* (%)	1 (5%)	0 (0%)	0.764
Other 30-day VARC-2 complications			
Major vascular access complication, *n* (%)	0 (0%)	0 (0%)	-
Acute kidney injury, stage 3, *n* (%)	0 (0%)	0 (0%)	-
Permanent pacemaker implantation for CAVB, *n* (%)	2 (10%)	2 (6%)	0.938
Hemodynamics by echocardiography at 30-day			
Mean gradient, mmHg	8.69 ± 3.05	11.03 ± 5.04	0.066
Aortic valve area, cm^2	1.97 ± 0.35	1.82 ± 0.25	0.089
Aortic regurgitation ≧ moderate, *n* (%)	2 (10%)	2 (6%)	0.938
Left ventricular ejection fraction, %	55.70 ± 13.55	58.30 ± 11.13	0.451
Pulmonary hypertension (PASP ≧60 mmHg), *n* (%)	1 (5%)	2 (6%)	1
Long-term cumulative MACCE, *n* (%)	7 (35%)	4 (11%)	0.071
All-cause mortality, *n* (%)	3 (15%)	0 (0%)	0.077
Cardiac mortality, *n* (%)	0 (0%)	0 (0%)	-
Non-fatal myocardial infarction, *n* (%)	0 (0%)	1 (3%)	1
Non-fatal stroke, *n* (%)	2 (10%)	1 (3%)	0.596
Valve failure, *n* (%)	1 (5%)	1 (3%)	1
Clinically relevant Valve thrombus, *n* (%)	1 (5%)	1 (3%)	1

THV, transcatheter heart valve; NYHA, New York Heart Association; MACCE, major adverse cardiac cerebral events; VARC, valve academic research consortium; CAVB, complete atrioventricular block; PASP, pulmonary artery systolic pressure.

Sapien XT groups (percentages of annular area oversizing were 2.89 ± 7.69% vs. 7.26 ± 4.44%, $p = 0.009$ as measured by the conventional annular sizing method and 2.08 ± 5.56% vs. 5.77 ± 4.98%, $p = 0.017$ by the supra-annular sizing method, respectively). Nevertheless, it is worth noting that, at 30 days, follow-up echocardiography showed that the EOA was smaller (1.82 ± 0.25 vs. 1.97 ± 0.35 cm^2; $p = 0.089$) and the mean transvalvular PG higher (11.03 ± 5.04 vs. 8.69 ± 3.05 mmHg; $p = 0.066$) in Sapien 3 vs. Sapien XT, though again it is considered statistically insignificant. These findings are in line with those of previous reports, that is, the benefit of reducing PVL due to the outer skirt of Sapien 3 may be accompanied by a tradeoff of reduced EOA (33, 34). Although a smaller EOA is unlikely to affect short-term clinical outcomes, whether it may give rise to hemodynamic alterations and has a negative effect on valve durability still needs a longer-term follow-up investigation.

Some experts have proposed various supra-annular sizing methods, algorithms, balloon sizing, or even computer simulation to improve valve sizing and device selection, hoping to reduce complications (12, 16–26). Whether supra-annular sizing can truly provide additional benefits in terms of improving device and procedural success and/or clinical outcomes remains controversial (27–29) because the supra-annular sizing is less reproducible than annular sizing, and its techniques of measurements not yet standardized (17–26). However, as shown in this study, although there was no clinically significant difference between annular and supra-annular sizings, supra-annular sizing, which selects a smaller THV than suggested by annular sizing and thus avoids the oversizing-related risks for the minority of patients with tapered or funnel anatomy, appeared to be of incremental value. Suchlike cases as discussed here consisted of four out of the 56 (7%) of the patients in our series. Compared to the use of the circle method for supra-annular sizing, advocated in BAV cases by a Bicuspid Expert Panel of interventional cardiologists and cardiac surgeons (26), moreover, our method is much easier to apply and time-saving, and the diameter of THV derived is more precise and may guarantee safer implantation.

Regarding the procedural characteristics, pre-dilatation of the BAV is performed in TAVR more frequently with Sapien XT than with Sapien 3 valve (100 vs. 81%, $p = 0.092$) to facilitate the crossing of the delivery system and ensure appropriate expansion of the THVs. However, balloon pre-dilatation with contrast injection is also used often to observe the behavior of leaflets in relation to coronary ostia and aortic wall because of the presence of a heavy and asymmetrical distribution of calcium; and even with the use of Sapien 3, the risks of annular or aortic rupture and coronary obstruction are not entirely avoidable.

TABLE 6 | Independent prognostic determinants of long-term composite MACCE by univariate and multivariate analyses.

	MACCE (+) (*N* = 11)	MACCE (-) (*N* = 45)	Univariate *P*-value	Multivariate *P*-value
Baseline characteristics				
Age, years	71 ± 7	71 ± 13	0.912	
Male, *n* (%)	8 (73%)	24 (53%)	0.409	
Body mass index, kg/m^2	22.42 ± 2.91	24.19 ± 3.93	0.166	
Body surface area, m^2	1.66 ± 0.17	1.62 ± 0.17	0.481	
Systemic hypertension, *n* (%)	8 (73%)	31 (69%)	1	
Diabetes mellitus, *n* (%)	5 (46%)	11 (24%)	0.312	
Dyslipidemia, *n* (%)	7 (64%)	16 (36%)	0.175	
Current smoker, *n* (%)	1 (9%)	2 (4%)	1	
Coronary artery disease, *n* (%)	6 (55%)	22 (49%)	1	
Previous myocardial infarction, *n* (%)	2 (18%)	4 (9%)	0.727	
Previous percutaneous coronary intervention, *n* (%)	5 (46%)	11 (24%)	0.312	
Previous coronary artery bypass grafting, *n* (%)	1 (9%)	2 (4%)	1	
Previous valve surgery, *n* (%)	0 (0%)	0 (0%)	-	
Carotid artery disease, *n* (%)	0 (0%)	4 (9%)	0.709	
Previous stroke, *n* (%)	2 (18%)	7 (16%)	1	
Peripheral vascular disease, *n* (%)	1 (9%)	5 (11%)	1	
Previous atrial fibrillation / atrial flutter, *n* (%)	4 (36%)	6 (13%)	0.177	
Previous permanent pacemaker implantation, *n* (%)	0 (0%)	3 (7%)	0.894	
Chronic obstructive pulmonary disease, *n* (%)	2 (18%)	2 (4%)	0.351	
Chronic kidney disease ≧ stage 3, *n* (%)	5 (46%)	9 (20%)	0.174	0.159
Renal dialysis, *n* (%)	1 (9%)	2 (4%)	1	
Heart failure, NYHA functional class III/IV, *n* (%)	9 (82%)	36 (80%)	1	
Syncope, *n* (%)	1 (9%)	6 (13%)	1	
STS-PROM score, %	8.39 ± 10.07	5.45± 5.27	0.180	0.814
Frailty score	2.36 ± 1.36	1.80 ± 1.14	0.163	
Baseline echocardiographic findings				
Mean gradient, mmHg	45.18 ± 15.18	55.38 ± 24.67	0.197	
Aortic valve area, cm^2	0.64 ± 0.17	0.63 ± 0.18	0.932	
Aortic regurgitation ≧ moderate, *n* (%)	4 (36%)	8 (18%)	0.349	
Mitral regurgitation ≧ moderate, *n* (%)	3 (27%)	14 (31%)	1	
Left ventricular ejection fraction, %	45.36 ± 18.98	54.56 ± 14.58	0.083	0.713
Pulmonary hypertension (PASP ≧ 60 mmHg), *n* (%)	2 (18%)	4 (9%)	0.727	
Bicuspid morphology (Sievers classification)				
Type 0, *n* (%)	2 (18%)	21 (47%)	0.168	
Type 1, *n* (%)	8 (73%)	22 (49%)	0.278	
Type 2, *n* (%)	1 (9%)	2 (4%)	1	
Bicuspid morphology (TAVR-Specific classification)				
Bicommissural non-Raphe-type, *n* (%)	2 (18%)	21 (47%)	0.168	
Bicommissural Raphe-type, *n* (%)	8 (73%)	22 (49%)	0.278	
Tricommissural type, *n* (%)	1 (9%)	2 (4%)	1	
Distribution of calcium				
Calcified raphe >4 mm, *n* (%)	7 (64%)	12 (27%)	0.032	0.029
One leaflet, *n* (%)	1 (9%)	10 (22%)	0.576	
Two leaflets, *n* (%)	9 (82%)	34 (76%)	0.966	
One commissure, *n* (%)	4 (36%)	13 (29%)	0.906	
Two commissures, *n* (%)	1 (9%)	1 (2%)	0.846	
Asymmetrical distribution of calcium, *n* (%)	9 (82%)	33 (73%)	0.846	
Sino-tubular junction diameter, mm	29.55 ± 3.76	31.45 ± 4.59	0.208	
Sinus of Valsalva diameter, mm	31.31 ± 3.17	32.62 ± 3.83	0.299	
Left coronary height, mm	13.70 ± 2.15	15.52 ± 3.88	0.045	0.314
Right coronary height, mm	16.84 ± 2.59	17.88 ± 3.82	0.396	

(Continued)

TABLE 6 | Continued

	MACCE (+) (*N* = 11)	MACCE (-) (*N* = 45)	Univariate *P*-value	Multivariate *P*-value
Porcelain aorta, *n* (%)	0 (0%)	0 (0%)	-	
Aortic root angle, degree	51.27 ± 7.50	55.36 ± 10.18	0.218	
Ascending aorta, 3 cm above the annulus, mm	39.37 ± 6.20	42.72 ± 6.26	0.118	
Aortopathy (aortic diameter >4.5 cm), *n* (%)	2 (18%)	18 (40%)	0.316	
Transcatheter heart valve type				
≦23 mm, *n* (%)	6 (55%)	19 (42%)	0.690	
≧26 mm, *n* (%)	5 (45%)	26 (58%)	0.690	
Procedural characteristics				
Device type (Sapien 3), *n* (%)	4 (36%)	32 (71%)	0.041	0.176
Vascular access				
Trans-femoral access, *n* (%)	11 (100%)	43 (96%)	1	
Pre-dilatation, *n* (%)	11 (100%)	38 (84%)	0.374	
Post-dilatation, *n* (%)	7 (64%)	32 (71%)	0.906	
Implantation depth from annulus, mm	2.18 ± 0.85	2.33 ± 1.48	0.746	
Device success, *n* (%)	9 (82%)	42 (93%)	0.541	
Procedural success, *n* (%)	11 (100%)	44 (98%)	1	
30-day VARC complications				
Major vascular access complication, *n* (%)	0 (0%)	0 (0%)	-	
Acute kidney injury, stage 3, *n* (%)	0 (0%)	0 (0%)	-	
Permanent pacemaker implantation for CAVB, *n* (%)	1 (9%)	3 (7%)	1	
30-day NYHA functional class III/IV, *n* (%)	2 (18%)	3 (7%)	0.541	
Hemodynamics by echocardiography at 30-day				
Mean gradient, mmHg	8.91 ± 2.84	1.47 ± 4.83	0.312	
Aortic valve area, cm^2	1.89 ± 0.33	1.87 ± 0.29	0.801	
Aortic regurgitation ≧ moderate, *n* (%)	2 (18%)	2 (4%)	0.351	
Left ventricular ejection fraction, %	52.55 ± 13.85	58.57 ± 11.37	0.141	
Pulmonary hypertension (PASP ≧ 60 mmHg), *n* (%)	0 (0%)	3 (7%)	0.894	

MACCE, major adverse cardiac cerebral events; NYHA, New York Heart Association; STS-PROM, society for thoracic surgery-probability of mortality score; PASP, pulmonary artery systolic pressure; TAVR, transcatheter aortic valve replacement; VARC, valve academic research consortium; CAVB, complete atrioventricular block.

On the other hand, post-dilatation is performed in TAVR more frequently with Sapien 3 than with Sapien XT (89 vs. 35%, $p < 0.001$), a much higher frequency than reported in the published data on the Sapien 3 (9–15). This may be owing to the less aggressive oversizing of the Sapien 3 compared to that of the Sapien XT and more patients in the Sapien 3 group needed post-dilatation with/without overfilling to improve conformity and reduce PVL (optimization) in our series. During TAVR procedures, two (10%) patients suffered from acute coronary occlusion and were successfully treated with percutaneous coronary intervention and stenting, although one of them needed emergent hemodynamic support. Although we use coronary protection technique whenever coronary obstruction is anticipated on pre-procedural CT, these two events were not the case. Regarding the relatively high rates of moderate to severe PVL after TAVR procedure in two (10%) patients with Sapien XT and one (3%) with Sapien 3, they all resulted from the presence of severe calcification of the raphe or a bulky calcium on one cusp, instead of the undersizing THVs. One such patient with Sapien 3 implantation needed percutaneous PVL repair following TAVR due to the development of refractory heart failure 3 months after TAVR procedure.

At 30 days, there was no mortality, non-fatal MI, major bleeding, nor vascular complications or significant differences in the incidences of stroke and AKI stage 3, or rates of need for a permanent pacemaker in either group. During a median follow-up of 743 days, the long-term clinical outcomes of newer-generation Sapien 3 were better than those of early-generation Sapien XT, though it was statistically non-significant (MACCE rates 35 vs. 11%, $p = 0.071$). The presence of a calcified raphe >4 mm, lower-left coronary height, and the use of Sapien XT device are significant predictors of MACCE according to univariate analysis; nevertheless, multivariate analysis identified the presence of a calcified raphe >4 mm as the only independent predictor of long-term MACCE (hazard ratio: 6.76; 95% confidence interval: 1.21–37.67, $p = 0.029$) after adjustment of device types, important covariables associated with poor outcome, and those variables associated with MACCE in the univariate analysis. In other words, although the evolution in patient selection, valve sizing, choice of THV, and procedural

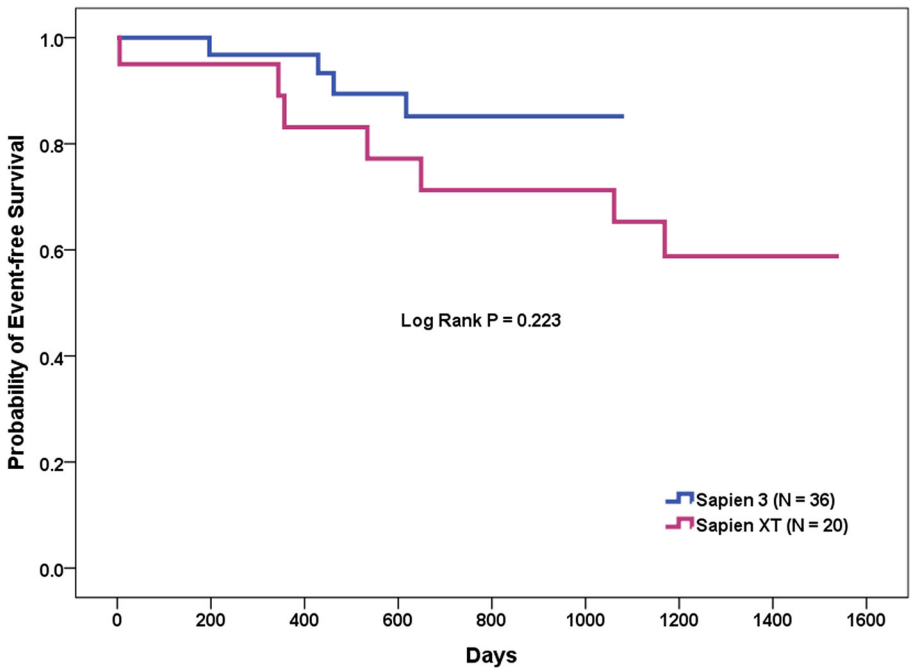


FIGURE 2 | Event-free survival curve of transcatheter aortic valve replacement for bicuspid aortic valve stenosis with the Sapien XT vs. Sapien 3 devices.

characteristics may affect clinical outcomes of patients with BAV undergoing TAVR over time, our results suggested that the most important factor in determining device success and long-term outcomes is the presence of unfavorable aortic and leaflets anatomies; in particular, a calcified raphe. As we already know, BAVs are more heavily calcified than tricuspid aortic valve and the calcification burden is more eccentric and asymmetrical as demonstrated in our study and others' (12–16). The presence of a calcified raphe and the heterogeneous distribution of the calcium of the BAV may prevent optimal expansion of the THV stent frame, resulting in elliptical implantation, malapposition, migration, and significant PVL. According to a recently published study by Yoon et al. (15) patients with combined calcified raphe and excessive leaflet calcium were of the highest risk phenotype associated with more frequent procedural complications like aortic root injury and PVL, and a 3-fold higher mortality, which is inconsistent with our findings. Therefore, in younger patients with unfavorable BAV anatomies and at low operative risk, the best strategy at this stage probably is a referral for surgical aortic valve replacement since the outcomes of surgery are excellent (1, 5). Moreover, the data concerning the outcomes of surgical aortic valve replacement in elderly patients with BAV at increased surgical risk are lacking. For these patients, less invasive approaches like intravascular lithotripsy are called for. The first-in-man report of intravascular lithotripsy is promising, but further studies are needed to confirm the safety and feasibility of its use in TAVR (34).

Finally, this study used only balloon-expandable valves; although previous studies of TAVR for BAV demonstrated that no difference existed in short- and mid-term TAVR outcomes with balloon-expandable valves and self-expanding valves, balloon-expandable valves still presented a higher risk of annular rupture in comparison with self-expanding valve, although it never happened to the patients in this study (9–15). Actually, the individual heart team's preferences decide what device types to choose, and the newer-generation devices may produce the same outcomes. In the future, specifically designed prospective studies are required to provide further evidence of anatomical selection criteria, durability, and long-term success rates of different devices before TAVR can really be deemed to be a viable option for all younger patients with BAV.

Study Limitations

Considering small number of patients in both groups and the fact that it was not a multicenter study, the results reported here, particularly concerning the comparisons between the two THVs, should be treated with caution. Secondly, although the two prosthesis groups were similar in terms of comorbidities and pre-procedural risk, our study was not a randomized trial and, hence, subjected to selection bias and unmeasured confounders; no definite conclusions can be drawn. Thirdly, two different TAVR devices were implanted across a long time frame of 4 years from 2016 to 2020. During that period, TAVR for the treatment of BAV with AS has evolved drastically. With the cumulating experiences of our heart team and the continuous technical refinements of the devices and delivery systems, a shift toward treating lower-risk patients who underwent TAVR has been taking place and is perhaps associated with a survival benefit in the patients in this study.

CONCLUSION

The results reported herein are of the largest series of TAVR for BAV with the use of balloon-expandable Sapien XT and Sapien 3 valves in Taiwan. We found that BAV anatomy, especially the presence of a calcified raphe and associated technical challenges for the TAVR procedure, is the most important determinant of procedural and clinical outcomes. Since patients with BAV are usually younger, with longer life expectancy, and perhaps need one or more interventions during the rest of their lives, we naturally expect the best possible results of the index procedure through optimal patient selection, anatomical consideration, and procedural planning in order to guarantee satisfactory long-term outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Cheng Hsin General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

W-HY, Y-TL, and JW conceived of the presented idea, developed the theory, performed the computations, analyzed and interpreted data, and verified the analytical methods. W-HY, Y-TL, T-PT, K-CL, M-CH, and JW provided the patients in this study and performed the TAVR procedures. W-HY, Y-TL, Y-HT, and JW collected and assembled data. W-HY and JW supervised the findings of this work. All authors discussed the results and contributed to the final manuscript and agree to be accountable for the content of the work.

FUNDING

The study was funded by the Cheng Hsin General Hospital grant number CHGH109-(IP)4.

ACKNOWLEDGMENTS

We thank Ms. Chin-Feng Cheng for her assistance in preparing this manuscript.

REFERENCES

1. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation.* (2005) 111:920–5. doi: 10.1161/01.CIR.0000155623.48408.C5
2. Kim WK, Liebetrau C, Fischer-Rasokat U, Renker M, Rolf A, Doss M, et al. Challenges of recognizing bicuspid aortic valve in elderly patients undergoing TAVR. *Int J Cardiovasc Imaging.* (2020) 36:251–6. doi: 10.1007/s10554-019-01704-8
3. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* (2019) 380:1695–705. doi: 10.1056/NEJMoa1814052
4. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* (2019) 380:1706–15. doi: 10.1056/NEJMoa1816885
5. Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *J Thorac Cardiovasc Surg.* (2021) 162:e183–353. doi: 10.1016/j.jtcvs.2021.04.002
6. Wijesinghe N, Ye J, Rodés-Cabau J, Cheung A, Velianou JL, Natarajan MK, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. *JACC Cardiovasc Interv.* (2010) 3:1122–5. doi: 10.1016/j.jcin.2010.08.016
7. Hayashida K, Bouvier E, Lefèvre T, Chevalier B, Hovasse T, Romano M, et al. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. *Circ Cardiovasc Interv.* (2013) 6:284–91. doi: 10.1161/CIRCINTERVENTIONS.112.000084
8. Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol.* (2014) 64:2330–9. doi: 10.1016/j.jacc.2014.09.039
9. Yoon SH, Lefèvre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. *J Am Coll Cardiol.* (2016) 68:1195–205. doi: 10.1016/j.jacc.2016.06.041
10. Perlman GY, Blanke P, Dvir D, Pache G, Modine T, Barbanti M, et al. Bicuspid aortic valve stenosis: favorable early outcomes with a next-generation transcatheter heart valve in a multicenter study. *JACC Cardiovasc Interv.* (2016) 9:817–24. doi: 10.1016/j.jcin.2016.01.002
11. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in transcatheter aortic valve replacement for bicuspid vs. tricuspid aortic valve stenosis. *J Am Coll Cardiol.* (2017) 69:2579–89. doi: 10.1016/j.jacc.2017.03.017
12. Tchetche D, de Biase C, van Gils L, Parma R, Ochala A, Lefevre T, et al. Bicuspid aortic valve anatomy and relationship with devices: the bavard multicenter registry. *Circ Cardiovasc Interv.* (2019) 12:e007107. doi: 10.1161/CIRCINTERVENTIONS.118.007107
13. Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, et al. Transcatheter aortic valve replacement in bicuspid vs. tricuspid aortic valves from the STS/ACC TVT registry. *JACC Cardiovasc Interv.* (2020) 13:1749–59. doi: 10.1016/j.jcin.2020.03.022
14. Halim SA, Edwards FH Dai D, Li Z, Mack MJ, Holmes DR, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the society of thoracic surgeons/American college of cardiology transcatheter valve therapy registry. *Circulation.* (2020) 141:1071–9. doi: 10.1161/CIRCULATIONAHA.119.040333
15. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, et al. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol.* (2020) 76:1018–30. doi: 10.1016/j.jacc.2020.07.005
16. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, et al. A bicuspid aortic valve imaging classification for the TAVR era. *JACC Cardiovasc Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
17. Liu X, He Y, Zhu Q, Gao F, He W, Yu L, et al. Supra-annular structure assessment for self-expanding transcatheter heart valve size selection in

patients with bicuspid aortic valve. *Catheter Cardiovasc Interv.* (2018) 91:986–94. doi: 10.1002/ccd.27467
18. Xiong TY, Feng Y, Li YJ, Zhao ZG, Liao YB, Ou Y, et al. Supra-annular sizing for transcatheter aortic valve replacement candidates with bicuspid aortic valve. *JACC Cardiovasc Interv.* (2018) 11:1789–90. doi: 10.1016/j.jcin.2018.06.002
19. Jeger R, Reuthebuch O, Fahrni G, Laborde JC, Vogel R, Kaiser C. Supra-annular sizing for transcatheter valve implantation in bicuspid aortic stenosis. *Postepy Kardiol Interwencyjnej.* (2018) 14:187–90. doi: 10.5114/aic.2018.76411
20. Frangieh AH, Michel J, Deutsch O, Joner M, Pellegrini C, Rheude T, et al. Aortic annulus sizing in stenotic bicommissural non-raphe-type bicuspid aortic valves: reconstructing a three-dimensional structure using only two hinge points. *Clin Res Cardiol.* (2019) 108:6–15. doi: 10.1007/s00392-018-1295-2
21. Xu YN, Xiong TY Li YJ, Liao YB, Zhao ZG, Wei X, et al. Balloon sizing during transcatheter aortic valve implantation: comparison of different valve morphologies. *Herz.* (2020) 45:192–8. doi: 10.1007/s00059-018-4714-2
22. Wang Y, Wang M, Song G, Wang W, Lv B, Wang H, et al. Optimal pre-TAVR annulus sizing in patients with bicuspid aortic valve: area-derived perimeter by CT is the best-correlated measure with intraoperative sizing. *Eur Radiol.* (2019) 29:259–69. doi: 10.1007/s00330-018-5592-y
23. Dowling C, Firoozi S, Brecker SJ. First-in-human experience with patient-specific computer simulation of tavr in bicuspid aortic valve morphology. *JACC Cardiovasc Interv.* (2020) 13:184–92. doi: 10.1016/j.jcin.2019.07.032
24. Iannopollo G, Romano V, Buzzatti N, Ancona M, Ferri L, Russo F, et al. Supra-annular sizing of transcatheter aortic valve prostheses in raphe-type bicuspid aortic valve disease: the LIRA method. *Int J Cardiol.* (2020) 317:144–51. doi: 10.1016/j.ijcard.2020.05.076
25. Petronio AS, Angelillis M, De Backer O, Giannini C, Costa G, Fiorina C, et al. Bicuspid aortic valve sizing for transcatheter aortic valve implantation: development and validation of an algorithm based on multi-slice computed tomography. *J Cardiovasc Comput Tomogr.* (2020) 14:452–61. doi: 10.1016/j.jcct.2020.01.007
26. Blackman D, Gabbieri D, Del Blanco BG, Kempfert J, Laine M, Mascherbauer J, et al. Expert consensus on sizing and positioning of SAPIEN 3/ultra in bicuspid aortic valves. *Cardiol Ther.* (2021) 10:277–88. doi: 10.1007/s40119-021-00223-9
27. Kim WK, Renker M, Rolf A, Fischer-Rasokat U, Wiedemeyer J, Doss M, et al. Annular versus supra-annular sizing for TAVI in bicuspid aortic valve stenosis. *EuroIntervention.* (2019) 15:e231–8. doi: 10.4244/EIJ-D-19-00236
28. Weir-McCall JR, Attinger-Toller A, Blanke P, Perlman GY, Sellers SL, Wood D, et al. Annular vs. supra-annular sizing for transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Cardiovasc Comput Tomogr.* (2020) 14:407–13. doi: 10.1016/j.jcct.2020.01.008
29. Kumar A, Doshi R, Shariff M, Adalja D, Vallabhajosyula S. Supra annular sizing for TAVR in bicuspid aortic valve stenosis: a meta-analysis. *Indian Heart J.* (2020) 72:309–11. doi: 10.1016/j.ihj.2020.06.017
30. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report from the American society of echocardiography's guidelines and standards committee and the task force on prosthetic valves, developed in conjunction with the American college of cardiology cardiovascular imaging committee, cardiac imaging committee of the American heart association, the European association of echocardiography, a registered branch of the European society of cardiology, the Japanese society of echocardiography and the Canadian society of echocardiography, endorsed by the American college of cardiology foundation, American heart association, European Association of Echocardiography, a registered branch of the European society of cardiology, the Japanese society of echocardiography, and Canadian society of echocardiography. *J Am Soc Echocardiogr.* (2009) 22:975–1014. doi: 10.1016/j.echo.2009.07.013
31. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. *Eur Heart J.* (2012) 33:2403–18. doi: 10.1093/eurheartj/ehs255
32. Yoon SH, Ahn JM, Hayashida K, Watanabe Y, Shirai S, Kao HL, et al. Clinical outcomes following transcatheter aortic valve replacement in Asian population. *JACC Cardiovasc Interv.* (2016) 9:926–33. doi: 10.1016/j.jcin.2016.01.047
33. Yang TH, Webb JG, Blanke P, Dvir D, Hansson NC, Nørgaard BL, et al. Incidence and severity of paravalvular aortic regurgitation with multidetector computed tomography nominal area oversizing or undersizing after transcatheter heart valve replacement with the Sapien 3: a comparison with the Sapien XT. *JACC Cardiovasc Interv.* (2015) 8:462–71. doi: 10.1016/j.jcin.2014.10.014
34. Kook H, Jang DH, Yang KS, Joo HJ, Park JH, Hong SJ, et al. Comparing the procedural and clinical outcomes of Sapien XT and Sapien 3 valves in transcatheter aortic valve replacement in Korean patients. *Korean Circ J.* (2020) 50:907–22. doi: 10.4070/kcj.2020.0061

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 26 May 2022
doi: 10.3389/fcvm.2022.884911

Pooled-Analysis of Association of Sievers Bicuspid Aortic Valve Morphology With New Permanent Pacemaker and Conduction Abnormalities After Transcatheter Aortic Valve Replacement

Jiajun Zhang[1,2,3†], *Xiaoxing Li*[4†], *Feng Xu*[1,2,3], *Yuguo Chen*[1,2,3*] *and Chuanbao Li*[1,2,3*]

[1] Department of Emergency Medicine and Chest Pain Center, Cheeloo College of Medicine, Qilu Hospital of Shandong University, Jinan, China, [2] Key Laboratory of Emergency and Critical Care Medicine of Shandong Province, Qilu Hospital of Shandong University, Jinan, China, [3] Key Laboratory of Cardiovascular Remodeling and Function Research, Qilu Hospital of Shandong University, Jinan, China, [4] Department of Geriatrics, Qilu Hospital of Shandong University, Jinan, China

OPEN ACCESS

Edited by:
Michel R. Labrosse,
University of Ottawa, Canada

Reviewed by:
Vladimir Uspenskiy,
Almazov National Medical Research Centre, Russia
Giuseppe Tarantini,
University of Padua, Italy

***Correspondence:**
Chuanbao Li
bao2460@126.com
Yuguo Chen
chen919085@sdu.edu.cn

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

Received: 27 February 2022
Accepted: 11 April 2022
Published: 26 May 2022

Citation:
Zhang J, Li X, Xu F, Chen Y and Li C (2022) Pooled-Analysis of Association of Sievers Bicuspid Aortic Valve Morphology With New Permanent Pacemaker and Conduction Abnormalities After Transcatheter Aortic Valve Replacement. Front. Cardiovasc. Med. 9:884911. doi: 10.3389/fcvm.2022.884911

Background: Studies on the association of Sievers bicuspid aortic valve (BAV) morphology with conduction disorders after transcatheter aortic valve replacement (TAVR) have not reached consensus.

Methods: We here performed a pooled-analysis to explore whether Sievers type 1 BAV morphology increased the risk of post-TAVR conduction abnormalities and permanent pacemaker implantation (PPI) compared to type 0. Systematic literature searches through EMBASE, Medline, and Cochrane databases were concluded on 1 December 2021. The primary endpoint was post-TAVR new PPI and pooled as risk ratios (RRs) and 95% confidence intervals (CIs). Conduction abnormalities as the secondary endpoint were the composites of post-TAVR PPI and/or new-onset high-degree of atrial-ventricle node block and left-bundle branch block. Studies that reported incidence of outcomes of interest in both type 1 and type 0 BAV morphology who underwent TAVR for aortic stenosis were included.

Results: Finally, nine studies were included. Baseline characteristics were generally comparable, but type 1 population was older with a higher surgical risk score compared to type 0 BAV morphology. In the pooled-analysis type 1 BAV had significantly higher risk of post-TAVR new-onset conduction abnormalities ($RR = 1.68$, 95%CI 1.09–2.60, $p = 0.0195$) and new PPI ($RR = 1.97$, 95%CI 1.29–2.99, $p = 0.0016$) compared to type 0. Random-effects univariate meta-regression indicated that no significant association between baseline characteristics and PPI.

Conclusion: Sievers type 1 BAV morphology was associated with increased risk of post-TAVR PPI and conduction abnormalities compared to type 0. Dedicated cohort is warranted to further validate our hypothesis.

Keywords: bicuspid aortic valve, transcatheter aortic valve replacement, conduction abnormalities, aortic stenosis (AS), Sievers classification, pacemaker

INTRODUCTION

Large randomized-controlled trials have proved the safety and efficacy of transcatheter aortic valve replacement (TAVR) for native tricuspid aortic valve stenosis (1, 2). Nevertheless, the bicuspid aortic valve (BAV) as the most common congenital cardiac anomaly was excluded from the pivotal trials (1–3). Clinical observations and meta-analyses have demonstrated that patients with BAV stenosis undergoing TAVR had comparable 30-day mortality to patients with tricuspid aortic valve stenosis (4). Observational registry studies evaluating the usefulness of TAVR for bicuspid aortic stenosis showed no statistical difference between surgical aortic valve replacement (SAVR) and TAVR in early mortality; however, the problem of post-procedural conduction abnormalities was tough and unsolved for TAVR (5–7).

Post-TAVR new-onset conduction disorders like high-degree atrial-ventricle node block (HAVB) and new permanent pacemaker implantation (PPI) were associated with increased adverse events (8). Procedure characteristics, such as lower implantation and oversizing of the implanted valve, are recognized risk factors for conduction abnormalities (9). Nevertheless, the association of Sievers BAV morphology with post-TAVR conduction disorders was controversial and poorly discovered. Ou et al. suggested type 1 BAV morphology as a strong predictor of HAVB (10). In contrast, one pooled-analysis demonstrated no significant difference in the incidence of post-TAVR new PPI between type 1 and type 0 BAV morphology but the primary endpoint of that study was 30-day mortality actually, which spoiled reliability of the conclusion (11). Accordingly, we performed a pooled-analysis focusing on post-TAVR conduction abnormalities and their association with Sievers BAV morphology.

METHOD

The systematic review and pooled-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12) and recommendations from Meta-Analyses of Observational Studies in Epidemiology (13).

Search Strategy and Eligibility Criteria

Systematic literature searches through EMBASE, Medline, and Cochrane databases were concluded on December 1, 2021. The search strategy included (1) "transcatheter aortic valve implantation" OR "transcatheter aortic valve replacement" OR "percutaneous aortic" OR "transcatheter aortic valve," (2) "conduction" OR "block" OR "pacemaker," (3) "bicuspid," then combined (1) AND (2) AND (3). A manual search was performed using references in published articles and conferences to identify potentially relevant research.

Abbreviations: TAVR, transcatheter aortic valve replacement; BAV, bicuspid aortic valve; PPI, permanent pacemaker implantation; HAVB, high-degree a trial-ventricle node block; LBBB, left-bundle branch block; SAVR, surgical aortic valve replacement; SEV, self-expanded valve; BEV, balloon-expanded valve; CI, confidence interval; RR, risk ratio.

The search results were screened and viewed in the title and abstract first to identify relevant studies. Case reports and case serials were not qualified for screening. All identified relevant studies were then placed under full-text review to further validate the eligibility.

Based on Population, Intervention, Control, Outcome, and Study Design (PICOS), studies were eligible if they met the following criteria: (1) enrolling BAV population; (2) undergoing TAVR for aortic stenosis; (3) available incidence of post-TAVR PPI or conduction abnormalities in Sievers type 1 and type 0 BAV morphology.

Outcomes of Interest

The primary outcome of interest was post-TAVR new PPI. The occurrence of high-degree atrial-ventricle node block (HAVB) or in some centers left-bundle branch block (LBBB) was an indication for PPI and might be associated with worse outcomes as well (8). We defined conduction abnormalities as the secondary endpoint composite of post-TAVR new PPI and/or new-onset HAVB and LBBB. To avoid repeat counting of HAVB and LBBB who subsequently received a permanent pacemaker, HAVB and LBBB were counted only in absence of reporting PPI or clearly stating the presented HAVB and LBBB were free from PPI. Definitions of outcomes were in line with the Valve Academic Research Consortium (VARC-2).

Specifically, type 1 BAV were further classified according to the location of fused raphe and cusp: L-R, raphe between left- and right-coronary cusp; R-N, raphe between right- and non-coronary cusp; L-N, raphe between left- and non-coronary cusp (14). The event rates across type 1 BAV subtypes were also collected and compared.

Evaluating the Risk of Bias

Considering all included studies were observational, we used Newcastle-Ottawa Scale to assess the quality of included studies. Two authors (JZ and XL) independently completed databases searching and study screening and evaluations. Discrepancies were settled by a third researcher (YC).

Duplicates and data overlap were confirmed by authors information and study start and end time, choices were made based on the evaluation of study quality, time period, and the number of subjects. The PRISMA flowchart is provided in **Figure 1**.

Statistical Analysis

Following statistical analyses were completed on R (version 4.1.3) with Meta package (15). The pooled estimates of outcomes were expressed as risk ratios (RRs) and 95% confidence intervals (*CIs*) using the Mantel-Haenszel method with random-effects models. A two-tailed $p < 0.05$ was considered statistically significant. Heterogeneity across studies was calculated by I^2 and $I^2 > 50\%$ was deemed unacceptable heterogeneity. Baujat plot and L'Abbé plot were drawn to visualize the origin of heterogeneity. Sensitivity analysis was conducted by removing one or more specific study/studies from the whole collection each time to evaluate the robustness of the pooled results and explore heterogeneity. As observational studies would introduce

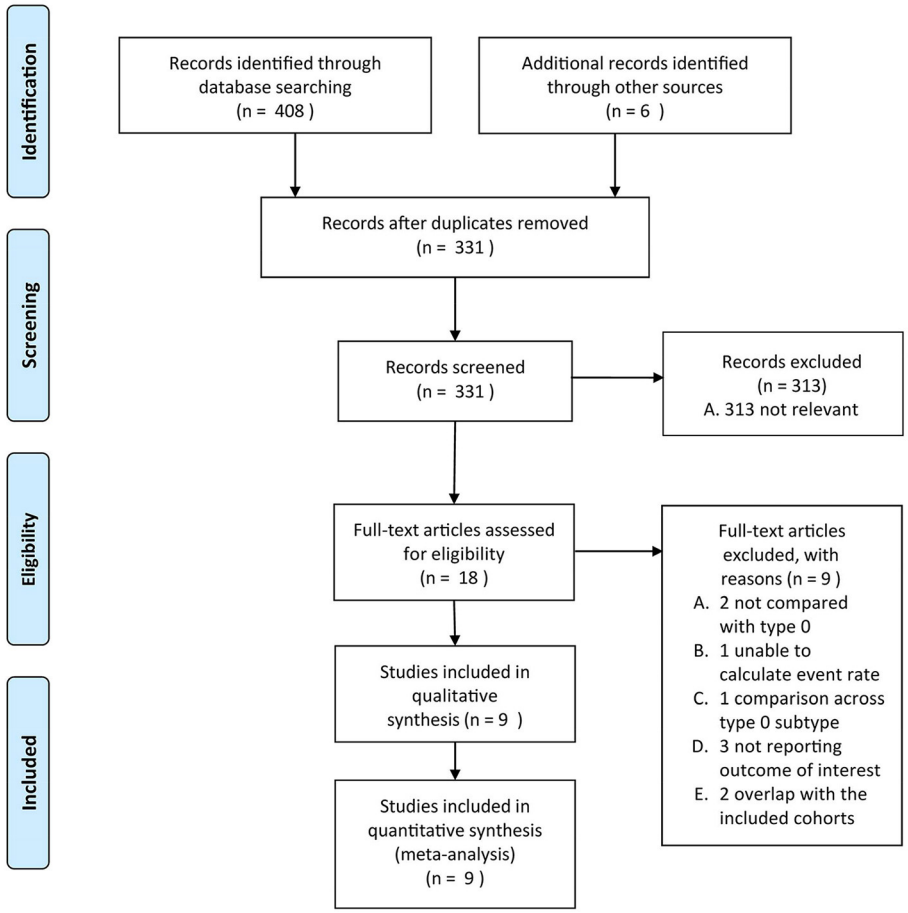


FIGURE 1 | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the present study.

huge confounding effects and may lead to a biased estimate, we performed a random-effects univariate meta-regression to adjust for the influence of potential effect modifiers. Demographic characteristics and clinical parameters were selected as covariates. Subgroup analyses were performed according to valve type (self-expanded valve, SEV vs. balloon-expanded valve, BEV). The publication bias of each item was examined by funnel plots visually based on the symmetry.

RESULTS

After dedicated literature search and selection, 9 studies were included in the final pooled-analysis (9, 10, 16–22). Study quality was evaluated by Newcastle-Ottawa Scale (**Table 1**) and there was generally a low risk of bias in the included studies. Features of included studies were presented in **Table 2**.

The Baseline and Procedural Characteristics Between Sievers Type 1 and Type 0

Generally, demographic characteristics were comparable between type 1 and type 0 BAV morphology; however, there was a relatively higher STS score in type 1 population. Patients across surgical risk profiles were included and most of them were in their 70's and had New York Heart Association functional class> 2. No patient included in the pooled-analysis had prior PPI. During the TAVR procedure pre-dilation was more frequently used in type 0 than type 1. No difference was found between type 1 and type 0 with regard to other procedural characteristics. In the 9 included studies, 4 were SEV-specific (9, 10, 16, 22) and in the other 5 studies both SEV and BEV were used. In the study of Yoon et al., statistically lower proportion of type 1 received SEV compared to type 0 (20), but in the other studies there was no such difference. The detailed characteristics could be found in **Tables 3**, **4**.

Post-TAVR PPI Between Sievers Type 1 and Type 0 Morphology

In the 9 included studies, the endpoint of the study of Ou et al. was solely post-TAVR HAVB rather than new PPI so included in the secondary analysis (10), Guo et al. and Hamdan et al. reported the incidence of composite conduction abnormalities besides new PPI (17, 22), and the other six only reported post-TAVR PPI rates. Therefore, the event rates of post-TAVR PPI between type 1 and type 0 BAV morphology were available in the 8 studies except for Ou et al. The pooled-analysis showed

TABLE 1 | Quality assessment of eligible studies by Newcastle–Ottawa scale.

	Jilaihawei et al.	Xiong et al.	Kumar et al.	Yoon et al.	Forrest et al.	Lelasi et al.	Hamdan et al.	Ou et al.	Guo et al.
Selection									
Exposed cohort	1	1	1	1	1	1	1	1	1
Non-exposed	1	1	1	1	1	1	1	1	1
Exposure	1	1	0	1	1	1	1	1	1
Outcome	1	1	1	1	1	1	1	1	1
Comparability									
Most important factor	0	0	0	0	0	0	0	0	0
Additional factor	0	0	0	0	0	0	0	0	0
Outcome									
Assessment	1	0	0	1	1	0	0	1	1
Follow-up	1	1	1	1	1	1	1	1	1
Adequacy	1	1	1	1	1	1	1	1	1
Sum	7	6	5	7	7	6	6	6	7

an increased risk of post-TAVR PPI for type 1 BAV morphology than type 0 ($RR = 1.97$, 95%CI 1.29–2.99, $p = 0.0016$) (**Figure 2**). After excluding the study of Yoon et al. as the only one with a significant difference between groups, the direction of pooled estimate was unchanged ($RR = 1.81$, 95%CI 1.12–2.91, $p = 0.0152$) which testified the stability of our pooled result (**Supplementary Figure 1**).

Conduction Abnormalities Between Sievers Type 1 and Type 0 BAV Morphology

Figure 3 demonstrated that the risk of post-procedural conduction abnormalities was significantly higher for type 1 BAV morphology compared to type 0 who underwent TAVR ($RR = 1.68$, 95%CI 1.09–2.60, $p = 0.0195$). The funnel plot was generally symmetric (**Supplementary Figure 2**). Notably, there was moderate heterogeneity in the pooled estimate ($I^2 = 42\%$, $\tau^2 = 0.1723$, $p = 0.09$). Drawing L'Abbé plot (**Figure 4A**) and Baujat plot (**Figure 4B**), we speculated the heterogeneity might be attributed most to the study of Guo et al., followed by Ou et al. **Table 5** summarized the pooled estimate and corresponding heterogeneity by excluding the specific study/studies from the whole collection. The study of Yoon et al., as a secondary contributor to heterogeneity, was chosen as a comparator (**Figure 4**). After excluding Guo et al. and Ou et al., the heterogeneity dropped markedly to zero with direction of the estimate unchanged but additionally excluding Yoon et al. would not further decrease the heterogeneity.

Meta-Regression and Subgroup Analysis

The included observational studies would introduce huge confounding bias due to non-randomization. To adjust for confounding factors and further explore the heterogeneity, we performed random-effects univariate meta-regression and included mean difference of STS score, logarithmic RR of hypertension and diabetes which were statistically different between type 1 and type 0 at baseline in the regression. Age, sex, and New York Heart Association class as general effect modifiers were also included. Nevertheless, the analysis indicated no correlation between effect modifiers and the primary endpoint (**Table 6**), which might strengthen the reliability of our pooled estimate.

In subgroup analysis limited to the SEV, the significance disappeared, and I^2surged. In contrast, there is no heterogeneity detected by I^2in the subgroup of SEV+BEV and the significance remained (**Supplementary Figure 3**). We failed to further stratify the analysis by valve generation due to most studies mixed with early- and newer- generations.

Comparison Between Type 1 L-R and Non-L-R

Type 1 L-R was reported to be related with more adverse events. To further explore the relationship between BAV morphology and conduction abnormalities, we compared the event rates between type 1 BAV subtypes. Of the included studies, 4 studies further reported incidence of post-TAVR conduction abnormalities in L-R, N-R, and N-L subtypes of type 1 BAV morphology (9, 10, 16, 17). However, the prevalence of L-N and R-N were relatively low in the included studies, so we combined L-N and R-N as a non-L-R group. Consequently, there were 233 patients with type 1 L-R subtype and 62 patients with non-L-R subtype. The pooled-analysis indicated that type 1 L-R was not associated with more post-TAVR conduction abnormalities at least compared to non-L-R ($RR = 1.38$, 95% CI 0.73–2.61, $p = 0.32$) (**Figure 5**).

DISCUSSION

This is the first pooled-analysis that focuses on the association of Sievers BAV morphology with post-TAVR conduction disorders. Our pooled-analysis demonstrated that there was a higher risk of post-TAVR PPI and conduction abnormalities for type 1 BAV morphology than for type 0.

The bicuspid aortic valve as the most common congenital heart disease affects 1∼2% of the world population and is the predominant etiology for aortic stenosis in the young population (3). TAVR for tricuspid aortic stenosis has revealed its at-least non-inferiority to SAVR (1, 2) and are approved for

TABLE 2 | Overview of the included studies.

	Jilaihawi et al.	Xiong et al.	Kumar et al.	Yoon et al.	Forrest et al.	Ielasi et al.	Hamdan et al.	Ou et al.	Guo et al.
No. of patients	130	80	67	1,034	150	243	67	181	209
Diagnosed by MDCT	70%	NA	NA	100%	100%	100%	100%	100%	100%
Type 0 morphology-no. (excluding prior PPI)*	21 (18)	46 (46)	11 (11)	107 (100)	14 (14)	25 (23)	17 (17)	102 (102)	99 (99)
Type 1 morphology-no. (excluding prior PPI)*	74 (60)	34 (34)	56 (56)	927 (866)	136 (132)	218 (198)	50 (50)	79 (79)	79 (79)
Type 1 morphology subtypes	NA	29 L-R; 3 N-R; 2N-L	NA	NA	107 L-R;27 N-R;2 N-L	NA	38 L-R; 12 N-R; 0 N-L	63 L-R; 16 Non-L-R	NA
Othermorphology-no†	25	0	0	NA	NA	0	0	0	31
Patients enrollment									
Time period	2005–2014	2012–2017	2017–2019	2016–2019	2018–2019	2013–2018	Since 2017	2015–2019	2016–2020
Data collection	Prospective	Retrospective	Retrospective	Prospective + retrospective	Prospective	Prospective	Prospective +retrospective	Prospective	Retrospective
Site	International; US, European, Asia, Canada	Single center in China	NA	International; European, Israel, US	Multicenter in US	Multicenter in European	Multi center in Israel	Single center in China	Multicenter in China
Exclusion criteria	NA	Prior PPI	NA	1) No pre-TAVR CT 2) Poor CT quality;	Predicted risk of 30-day mortality higher than 3.0	Type 2 and undetermined type	1) undetermined valve morphology; 2) priori PPI; 3) valve in valve; 4) no pre-TAVR CT	1) prior PPI 2) without pre- and post-TAVR CT	1) prior PPI; 2) transfer to open surgery; 3) poor quality of imaging; 4) valve other than SEV; 5) perioperative death

**Number in the bracket means counts after excluding patients with prior PPI.*

†Including type 2 and undetermined BAV morphology.

BAV, bicuspid aortic valve; L-R, left and right fusion; TAVR, transcatheter aortic valve replacement; MDCT, Multi-detector CT; PPI, permanent pacemaker implantation.

TABLE 3 | Baseline characteristics of patients with bicuspid aortic stenosis who underwent transcatheter aortic valve replace in the included studies.

	Jilaihawi		Xiong	Kumar	Yoon		Forrest		Ielasi		Hamdan	Ou	Guo		*MD* or RR[†]	95% *CI*	*p*
	Type 0	**Type 1**	**Overall***	**Overall***	**Type 0**	**Type 1**	**Type 0**	**Type 1**	**Type 0**	**Type 1**	**Overall***	**Overall***	**Type 0**	**Type 1**			
No.of pts	21	74	80	67	107	927	14	136	25	218	67	181	99	79	/	/	/
Age (yrs)	74.4 ± 7.3	76.1 ± 10.8	75 (70.0–77.0)	70.0 ± 9.9	69.5 ± 11.1	75.3 ± 8.9*	70.6 ± 4.1	70.3 ± 5.6	77.8 ± 9.3	79.1 ± 7.8	77.0 ± 8.8	73.1 ± 6.2	74.1 ± 7.0	76.3 ± 6.8	2.25	0.03–4.48	**0.0468**
Male *n*. (%)	11 ± 52.4	46 ± 62.2	47 ± 58.8	NA	63 ± 58.9	547 ± 59.0	5 ± 35.7	73 ± 53.7	19 ± 76.0	144 ± 66.1	42 ± 63	103 ± 56.9	54 ± 54.5	51 ± 64.6	1.03	0.91–1.18	0.611
STS PROMscore	4.2 (3.2–5.2)	5.1 (2.9–7.6)	7.7 ± 4.0	4.1 ± 3.7	3.0 ± 2.1	3.75 ± 3.4*	1.4 ± 0.5	1.4 ± 0.6	3.4 ± 1.8	4.5 ± 3.0	NA	6.3 ± 4.3	6.10 ± 3.8	7.77 ± 5.4	0.73	0.17–1.29	**0.0101**
NYHA III-IV no. (%)	18 (85.7)	60 (81.1)	NA	NA	72 (67.3)	667 (71.6)	2 (14.3)	39 (28.6)	17 (68.0)	146 (67.3)	NA	NA	NA	NA	1.03	0.92–1.14	0.614
Hypertension no. (%)	NA	NA	NA	NA	74 (69.2)	749 (80.8)	8 (57.1)	104 (76.5)	19 (76)	180 (72.6)	47 (70)	NA	49 (49.5)	36 (45.6)	1.13	1.02-1.25	**0.0221**
Diabetes no. (%)	8 (38.1)	15 (20.3)	NA	NA	32 (29.9)	232 (25.0)	5 (35.7)	32 (23.5)	6 (24)	45 (20.6)	20 (30)	NA	21 (21.2)	14 (17.7)	0.782	0.62–0.99	**0.0375**
Prior PCI no. (%)	4 (19)	8 (10.8)	NA	NA	88 (19.1)	113 (12.2)	1 (7.1)	10 (7.4)	6 (24.0)	54 (24.8)	16 (24)	NA	NA	NA	0.475	0.17–1.35	0.161
Prior CABG no. (%)	1 (4.8)	8 (10.8)	NA	NA	35 (7.6)	45 (4.9)	2 (14.3)	0	2 (8.0)	20 (9.2)	11 (16)	NA	NA	NA	0.351	0.06–2.04	0.244
Lung disease no. (%)	6 (28.6)	31(41.9)	NA	NA	14 (13.1)	79 (8.5)	2 (15.4)	24 (17.9)	7 (28)	52 (23.9)	NA	NA	21 (21.2)	14 (17.7)	0.87	0.64–1.18	0.369
Cerebrovascular disease no. (%)	3 (14.4)	9 (12.2)	NA	NA	13 (12.1)	108 (11.6)	0	10 (7.4)	4 (16)	27 (12.4)	NA	NA	NA	NA	0.923	0.60–1.42	0.718
Atrial fibrillation no. (%)	6(8.6)	24 (32.4)	NA	NA	16 (15.0)	171 (18.4)	0	11 (8.1)	6 (25.0)	54 (25.5)	9 (13.4)	NA	14 (14.1)	12 (15.2)	0.717	0.29–1.78	0.473
Echocardiographic findings																	
Aortic valve mean gradient (mmHg)	51.0 (41.0–59.0)	49.5 (41.0–62.0)	NA	NA	50.5 ± 17.5	47.1 ± 16.4	48.1 ± 9.7	50.0 ± 16.0	46.0 ± 10.4	49.2 ± 16.8	NA	NA	60.63 ± 23.6	60.77 ± 22.6	0.14	−2.85–3.14	0.9251
Aortic valve area ± SD (cm^2)	0.60 (0.50–0.80)	0.65 (0.55–0.80)	NA	NA	0.6 ± 0.2)	0.7 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	0.67 ± 0.22	0.69 ± 0.23	NA	NA	0.53 ± 0.26	0.47 ± 0.33	0.05	−0.01–0.11	0.1291

Values are mean ± SD, median (interquartile range), or n (%).

**Only rates of the whole population were available.*

[†]Comparing characteristics of type 1 to type 0.

[†]Bold values refer to $p < 0.05$ with significant difference between groups.

CI, Confidence Interval; CABG, coronary artery bypass graft; MD, Mean Difference; RR, risk ratio; NYHA, New York Heart Association; NA, not applicable; PCI, percutaneous coronary intervention; STS PROM, society of thoracic surgeons predicted risk of mortality.

TABLE 4 | Procedure characteristics of patients with bicuspid aortic stenosis who underwent transcatheter aortic valve replace in the included studies.

	Jilaihawi		Xiong	Kumar		Yoon		Forrest		Ielasi		Hamdan	Ou		Guo		*MD* or RR†	95% *CI*	*p*
	Type 0	Type 1	Overall*	Overall*	Type 0	Type 1	Type 0	Type 1	Type 0	Type 1	Overall*	Overall*	Type 0	Type 1				
Transfemoral access no. (%)	114 (87.7)	78 (97.5)	NA	NA	101 (94.4)	874 (94.3)	14 (100)	133 (98.5)	25 (100)	191 (88.5)	65 (97)	NA	NA	NA	0.952	(0.88–1.32)	0.30
Pre-dilation no. (%)	116/127 (91.3)	75 (93.7)	NA	NA	NA	NA	14 (100)	123 (90.4)	11 (44.0)	78 (35.8)	33 (49)	179 (98.9)	99 (100)	75 (94.9%)	**0927**	**0.0884–0.971**	**0.00147**
Post-dilation no. (%)	24/128 (18.8)	40 (50.0)	NA	NA	NA	NA	1 (7.1)	54 (40.0)	7 (28)	49 (22.5)	22 (33)	109 (60.2)	71 (71.7)	55 (69.6)	0.973	0.81–1.17	0.769
Implanted valve type																	
SEV no. (%)	60 (46.2)*		80 (100)	55 (82.1)	18 (16.8)	217 (23.4)	14 (100)	136 (100)	9 (36)	64 (29.4)	32 (48)	181 (100)	99 (100)	79 (100)	/	/	/
BEV no. (%)	70 (53.8)*		0	12 (17.9)	89 (83.2)	651 (70.2)	0	0	16 (64)	154 (70.6)	35 (52)	0	0	0	/	/	/

Values are mean ± SD, median (interquartile range), or n (%).

**Only rates of the whole population were available.*

†Comparing characteristics of type 1 to type 0.

†Bold values refer to p < 0.05 with significant difference between groups.

CI, Confidence Interval; MD, Mean Difference; RR, risk ratio; NA, not applicable; SEV, self-expanded valve; BEV, balloon-expanded valve.

BAV stenosis (7); however, previous studies demonstrated BAV stenosis who underwent TAVR suffered significantly higher risk of post procedural new PPI compared to SAVR (5–7). We failed to further reduce the incidence of post-TAVR PPI to the surgical benchmark for BAV stenosis even with the valve upgraded. Our analysis suggested Sievers BAV morphology might associate with post-TAVR PPI, which would facilitate accurately predicting conduction disorders.

Association of BAV morphology with conduction disorders was poorly discovered and such study was scarce. Current observations only indicated numerically but not a statistically higher incidence of post-TAVR PPI for type 1 BAV morphology than type 0. For example, in the Low Risk Bicuspid Study 22 in 132 type 1 needed PPI but none for type 0 (16). As for events other than PPI, Ou et al. proposed type 1 BAV morphology as an independent predictor of post-TAVR HAVB in the multivariable analysis, pitifully they failed to report the association with pacemakers (10). Kumar et al. reported 18 in 56 patients with type 1 developed new-onset LBBB after TAVR while the number of that for type 0 was 0 in 11 during 30-day follow-up (21). In the study of Shiyovich et al., BAV with raphe (type 1) compared to tricuspid counterparts had significantly increased risk of new-onset LBBB but BAV without raphe (type 0) did not, which supported the association of BAV morphology with conduction disorders in some degree (23).

Different from SAVR resecting the native valve, the valve in TAVR is reserved and has strong interaction with the implanted transcatheter heart valve (24). This could partially explain the association of BAV morphology with conduction abnormalities. Conduction abnormalities might result from injury of the conduction system, especially in the septum and the aortic root area during balloon expanding and valve implantation (8). In the view of mechanics, type 0 without fused raphe is in a relatively symmetric shape leading to less elliptical valve deployment and more symmetric distribution of contact pressure; however, raphe of type 1 might postpone symmetric expansion of implanted valve. Therefore, in the non-fused side of type 1 there was a smaller contact area with stent and resultant higher contact pressure than on the fused (25). Patient-specific simulation study indicated that there was higher contact pressure with the aortic root area in patients who experienced conduction disorders than in those who did not (26). Thus, type 1 BAV with raphe might enhance the contact pressure and increase the probability of conduction system injury.

In another view, there are several recognized risk factors for post-TAVR PPI in the BAV population. Deep implantation and oversizing of implanted valves would increase the chance to injure the conduction system (8–10, 17). Xiong et al. found that BAV patients complicated with post-TAVR PPI has significantly smaller sino-tubular junction diameter (9). Correspondingly Du et al. in their meta-analysis summarized type 1BAV morphology had smaller sino-tubular junction height and diameter than type 0. Therefore, we presumed valves implanted in type 1 might be relatively deeper and close to the membranous septum due to the smaller height and prone to be oversized due to the smaller diameter, which consequently damaged the conduction issue. For this reason, implantation depth and oversizing ratio as

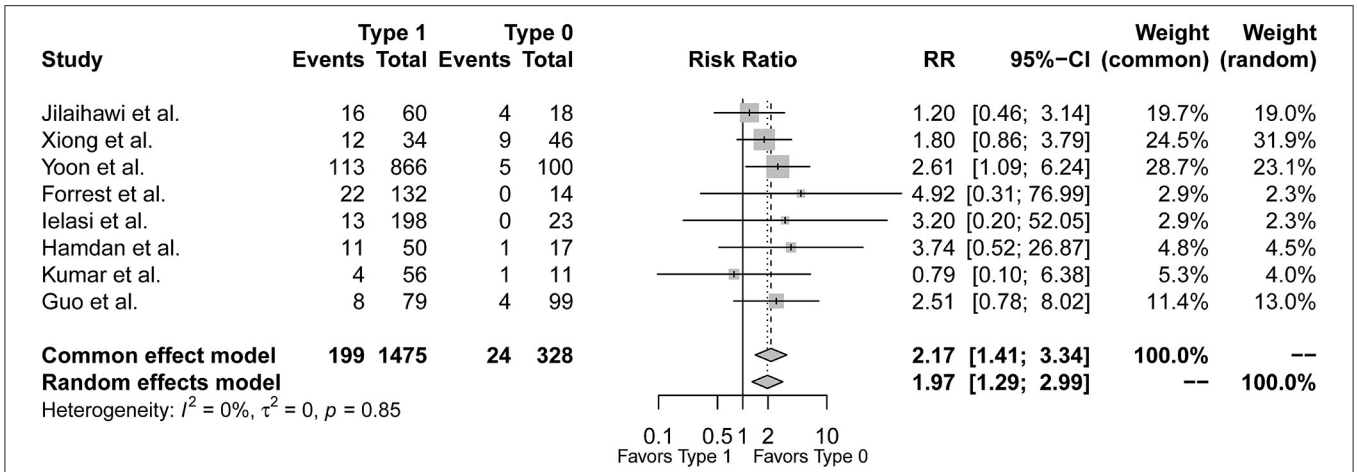


FIGURE 2 | The forest plot of the pooled-analysis comparing post-TAVR permanent pacemaker implantation between Sievers type 1 and type 0 BAV morphology. RR, risk ratio; CI, confidence interval.

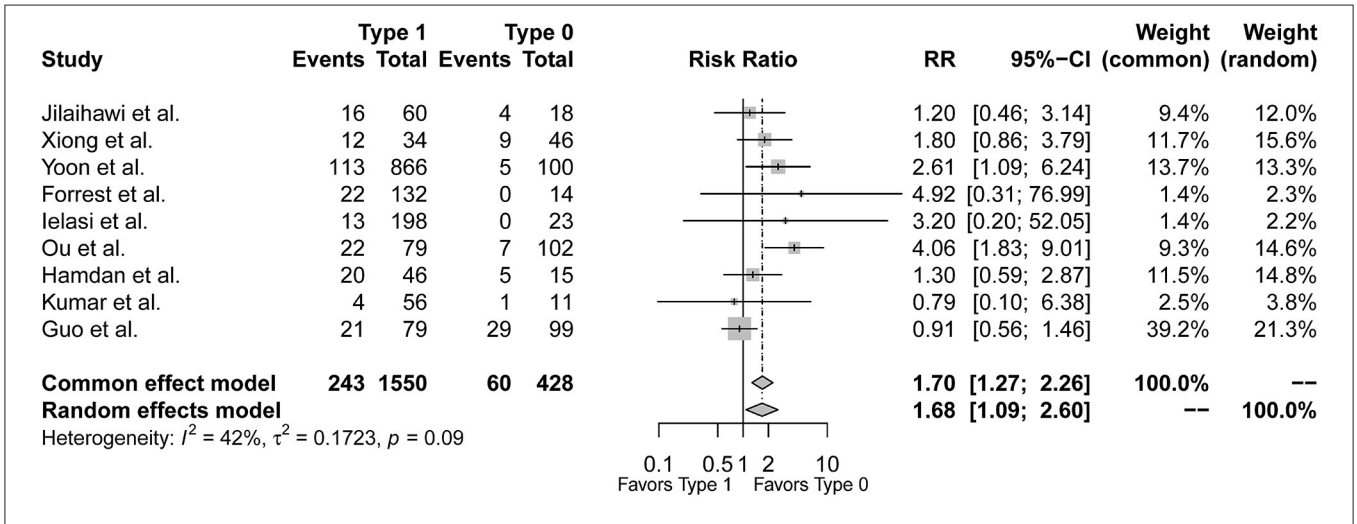


FIGURE 3 | The forest plot of the pooled-analysis comparing post-TAVR conduction abnormalities between Sievers type 1 and type 0 BAV morphology. RR, risk ratio; CI, confidence interval.

confounding factors should be adjusted but we failed to extract the data and include the factors in the meta-regression. Well-designed cohorts were warranted to further test our theory.

There was moderate heterogeneity in the pooled-analysis comparing the risk of post-TAVR conduction abnormalities between type 1 and 0. L'Abbé plot and Baujat plot indicated that the study of Ou et al. and Guo et al. contributed most to the heterogeneity, and the sensitivity analysis excluding the two showed I^2 dropped sharply to zero, which verified their contribution to the heterogeneity. Actually, in the present pooled-analysis, conduction abnormalities were composite of HAVB, LBBB, and/or PPI. Endpoints in studies of Guo et al. and Hamdan et al. were truly composite, but that in the Ou et al. and the other studies were solely new-onset HAVB and post-TAVR PPI, respectively. Differences among the definitions may lead to heterogeneity. Accordingly, we performed the pooled-analysis with a concentration on post-TAVR PPI then set the composite conduction abnormalities as the secondary endpoint, and the pooled estimates of both suggested a higher risk for type 1 BAV morphology with consistency.

According to Sievers classification, type 1 could be further divided into 3 subtypes depending on the fused cups and raphe location, namely L-R, R-N, and L-N (14). Type 1 L-R was reported to be associated with more adverse events than type 1 N-R or N-L (10, 27, 28). Different from the anatomy of R-N and L-N, the non-fused side of type 1 L-R opposite to the fused raphe was near to the septum. Consequently, based on the mechanic theory mentioned above (25, 26), conduction issue enriched in the septum was prone to be hurt by increased contact pressure around the L-R non-fused side. L-R fusion as

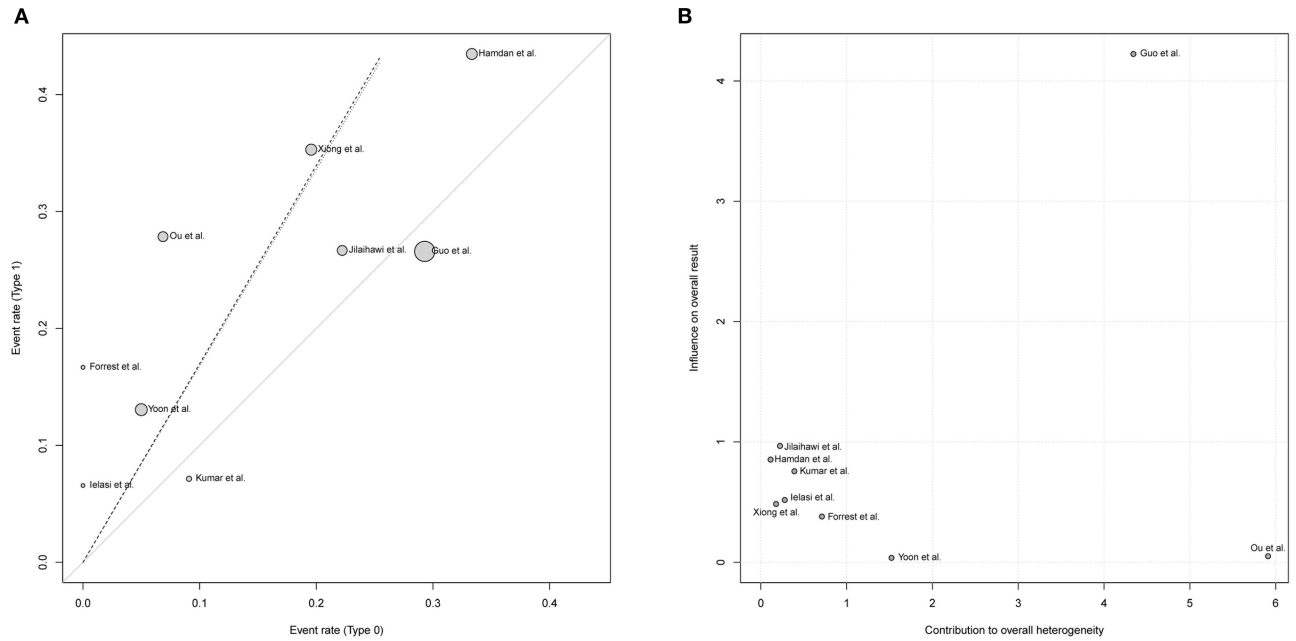


FIGURE 4 | Exploring the heterogeneity in the pooled estimate of post-TAVR conduction abnormalities, L'Abbé plot **(A)** and Baujat plot **(B)** indicated the greatest contributor to heterogeneity was the study of Guo et al. followed by Ou et al. RR, risk ratio; CI, confidence interval.

TABLE 5 | The pooled estimate and heterogeneity by excluding the specific study from the whole collection in the comparison of conduction abnormalities between type 1 and type 0 BAV morphology.

The excluded study/studies	*RR*	95%*CI*		*p* for RR	I^2(%)	τ^2	*p* for heterogeneity
		Lower	Upper				
Guo et al. and Ou et al.	1.68	1.13	2.50	0.0109	0	0	0.7857
Guo et al.	1.99	1.33	2.99	0.0009	0	0.0567	0.4338
Ou et al.	1.39	0.95	2.02	0.0906	0	0.0591	0.4360
Yoon et al.	1.57	0.98	2.53	0.0615	41.7	0.1830	0.1004

BAV, bicuspid aortic valve; RR, risk ratio; CI, confidence interval.

the most prevalent subtype in type 1 BAV morphology could be the driving factor that brought about the association of type 1 BAV morphology with conduction abnormalities and PPI. To test the hypothesis, we further compared the outcomes of L-R to non-L-R. Nevertheless, there was no difference between L-R and non-L-R in the risk of post-TAVR conduction abnormalities. Limited to a small subject number, we combined N-R and N-L up as non-L-R, which might decrease reliability of the evidence.

Limitations

The pooled results should be interpreted with caution because of the following reasons. First, besides type 0 and type 1 BAV morphology, the Sievers classification also included type 2 and undetermined BAV morphology, but they were not included in our analysis because of their extremely low prevalence and scarce data. Second, all included studies were observational so adjustment for confounding factors was necessary. Meta-regression, we preformed, demonstrated no correlation between the effect modifiers and the pooled estimate, which relieved the confounding bias; however, there was relatively small number of studies included in the regression. Moreover, baseline conduction disorders, such as LBBB and RBBB, could be predisposing factors to post-TAVR HAVB and PPI, but such prevalence was seldom reported. Only Guo et al. presented a similar prevalence between type 1 and type 0, so the effect of baseline conduction disorders on the association was unknown. Last but not least, we must recognize the purpose of the pooled analysis was hypothesis-generating rather than proving type 1 BAV morphology as a strong predictor. We uncovered a rarely noticed association that needs more research to further validate.

CONCLUSION

The current study found there was a higher risk of post-TAVR conduction abnormalities and PPI for Sievers type 1 BAV morphology than type 0, and the type 1 subtype L-R have no excess risk of post-TAVR conduction abnormalities compared

TABLE 6 | Meta-regression analysis using potential confounding factors for post-TAVR PPI in the comparison of type 1 BAV to type 0.

Covariates	Coefficient	95% *CI*		*p*-value
		Lower	Upper	
MD of STS	−0.18	−1.56	1.2	0.799
MD of age	0.0728	−0.193	0.339	0.592
MD of Aortic area	1.1	−8.42	10.6	0.821
logRR of DM	1.63	−0.947	4.21	0.215
logRR of Male	−0.973	−5.89	3.94	0.698
logRR of NYHAIII-IV	2.01	−1.81	5.84	0.303
logRR of hypertension	0.678	−4.83	6.18	0.809
logRR of pre-dilation	−2.21	−21.4	17	0.822
NOS	−0.31	−1.1	0.49	0.450

TAVR, Transcatheter aortic valve replacement; PPI, permanent pacemaker implantation; CI, Confidence interval; MD, Mean difference; logRR, logarithmic risk ratio; STS, Society of Thoracic Surgeons; DM, diabetes mellitus; NYHA, New York Heart Association; NOS, Newcastle-Ottawa Scale.

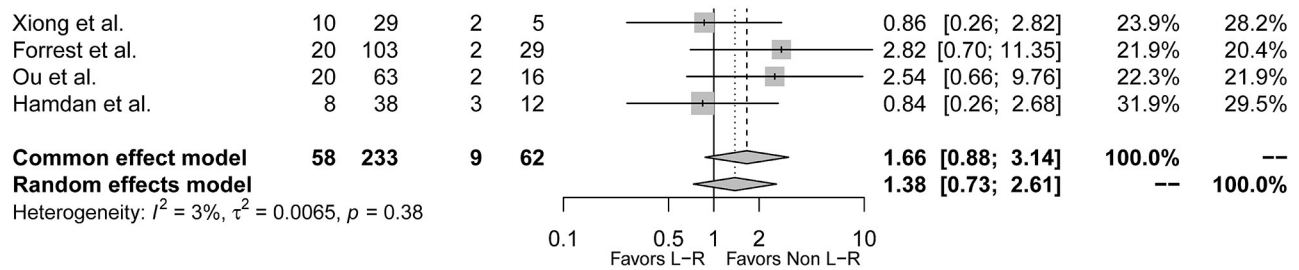


FIGURE 5 | The forest plot of the pooled-analysis comparing post-TAVR conduction abnormalities between type 1 BAV morphology L-R and non-L-R subtype. RR, risk ratio; CI, confidence interval.

to the non-L-R subtype. Our hypothesis that type 1 BAV morphology is a novel risk factor for conduction abnormalities warranted large cohorts to validate.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

JZ and XL independently completed the database searching, screening, and data extraction and wrote the manuscript. FX provided suggestions on statistical analysis and finished the pooled-analysis on R software. YC took responsibility for data checking and evaluated the eligibility of unsettled studies between JZ and XL. CL contributed to the discussion and revised the finished manuscript. All authors contributed toward data analysis, drafting and critically revising the paper, and agree to be accountable for all aspects of the work.

FUNDING

This study was supported by the National Natural Science Foundation of China (82070388), Taishan Pandeng Scholar Program of Shandong Province (tspd20181220), and the National Natural Science Foundation of Shandong Province (ZR2020MH035).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.884911/full#supplementary-material

REFERENCES

1. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* (2019) 380:1695–705. doi: 10.1056/NEJMoa1814052
2. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve

in low-risk patients. *N Engl J Med.* (2019) 380:1706–15. doi: 10.1056/NEJMoa1816885
3. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* (2010) 55:2789–800. doi: 10.1016/j.jacc.2009.12.068
4. Montalto C, Sticchi A, Crimi G, Laricchia A, Khokhar AA, Giannini F, et al. Outcomes after transcatheter aortic valve replacement in bicuspid versus tricuspid anatomy: a systematic review and meta-analysis. *JACC Cardiovasc Interv.* (2021) 14:2144–55. doi: 10.1016/j.jcin.2021.07.052
5. Elbadawi A, Saad M, Elgendy IY, Barssoum K, Omer MA, Soliman A, et al. Temporal trends and outcomes of transcatheter versus surgical aortic valve replacement for bicuspid aortic valve stenosis. *JACC Cardiovasc Interv.* (2019) 12:1811–22. doi: 10.1016/j.jcin.2019.06.037
6. Husso A, Airaksinen J, Juvonen T, Laine M, Dahlbacka S, Virtanen M, et al. Transcatheter and surgical aortic valve replacement in patients with bicuspid aortic valve. *Clin Res Cardiol.* (2021) 110:429–39. doi: 10.1007/s00392-020-01761-3
7. Waksman R, Craig PE, Torguson R, Asch FM, Weissman G, Ruiz D, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe bicuspid aortic valve stenosis. *JACC Cardiovasc Interv.* (2020) 13:1019–27. doi: 10.1016/j.jcin.2020.02.008
8. Sammour Y, Krishnaswamy A, Kumar A, Puri R, Tarakji KG, Bazarbashi N, et al. Incidence, predictors, and implications of permanent pacemaker requirement after transcatheter aortic valve replacement. *JACC Cardiovasc Interv.* (2021) 14:115–34. doi: 10.1016/j.jcin.2020.09.063
9. Xiong TY, Liao YB, Li YJ, Zhao ZG, Wei X, Tsauo JY, et al. Permanent pacemaker implantation after transcatheter aortic valve replacement in bicuspid aortic valve patients. *J Interv Cardiol.* (2018) 31:878–84. doi: 10.1111/joic.12546
10. Ou YW, He JJ, Zhou X, Li GY, Liao YB, Wei X, et al. The incidence and predictors of high-degree atrioventricular block in patients with bicuspid aortic valve receiving self-expandable transcatheter aortic valve implantation. *J Geriatr Cardiol.* (2021) 18:825–35. doi: 10.11909/j.issn.1671-5411.2021.10.004
11. Du Y, Wang Z, Liu W, Guo Y, Han W, Shen H, et al. Transcatheter aortic valve implantation in sievers type 0 vs. type 1 bicuspid aortic valve morphology: systematic review and meta-analysis. *Front Cardiovasc Med.* (2021) 8:771789. doi: 10.3389/fcvm.2021.771789
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (Prisma-P) 2015 statement. *Syst Rev.* (2015) 4:1. doi: 10.1186/2046-4053-4-1
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (Moose) group. *JAMA.* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
14. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg.* (2007) 133:1226–33. doi: 10.1016/j.jtcvs.2007.01.039
15. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health.* (2019) 22:153–60. doi: 10.1136/ebmental-2019-300117
16. Forrest JK, Ramlawi B, Deeb GM, Zahr F, Song HK, Kleiman NS, et al. Transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis. *JAMA Cardiol.* (2021) 6:50–7. doi: 10.1001/jamacardio.2020.4738
17. Hamdan A, Nassar M, Schwammenthal E, Perlman G, Arow Z, Lessick J, et al. Short membranous septum length in bicuspid aortic valve stenosis increases the risk of conduction disturbances. *J Cardiovasc Comput Tomogr.* (2020) 15:339–47. doi: 10.1016/j.jcct.2020.10.002
18. Ielasi A, Moscarella E, Mangieri A, Giannini F, Tchetchè D, Kim WK, et al. Procedural and clinical outcomes of type 0 versus type 1 bicuspid aortic valve stenosis undergoing trans-catheter valve replacement with new generation devices: insight from the beat international collaborative registry. *Int J Cardiol.* (2021) 325:109–14. doi: 10.1016/j.ijcard.2020.10.050
19. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodes-Cabau J, et al. A bicuspid aortic valve imaging classification for the tavr era. *JACC Cardiovasc. Imaging.* (2016) 9:1145–58. doi: 10.1016/j.jcmg.2015.12.022
20. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, et al. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol.* (2020) 76:1018–30. doi: 10.1016/j.jacc.2020.07.005
21. Kumar K, Simpson T, Rajotte K, Khouw S, Weller S, Fuss C, et al. New left bundle branch block and permanent pacemaker stratified by sievers type in severe bicuspid aortic stenosis after transcatheter aortic valve replacement. *Catheterization Cardiovas Interv.* (2020) 95:S151–2. doi: 10.1002/ccd 28864
22. Guo Y, Zhou D, Dang M, He Y, Zhang S, Fang J, et al. The predictors of conduction disturbances following transcatheter aortic valve replacement in patients with bicuspid aortic valve: a multicenter study. *Front Cardiovasc Med.* (2021) 8:757190. doi: 10.3389/fcvm.2021.757190
23. Shiyovich A, Kornowski R, Plakht Y, Aviv Y, Assa HV, Assali A, et al. Increased rate of new-onset left bundle branch block in patients with bicuspid aortic stenosis undergoing transcatheter aortic valve implantation (from a national registry). *Am J Cardiol.* (2021) 156:101–7. doi: 10.1016/j.amjcard.2021.06.046
24. Vincent F, Ternacle J, Denimal T, Shen M, Redfors B, Delhaye C, et al. Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. *Circulation.* (2021) 143:1043–61. doi: 10.1161/CIRCULATIONAHA.120.048048
25. Lavon K, Marom G, Bianchi M, Halevi R, Hamdan A, Morany A, et al. Biomechanical modeling of transcatheter aortic valve replacement in a stenotic bicuspid aortic valve: deployments and paravalvular leakage. *Med Biol Eng Comput.* (2019) 57:2129–43. doi: 10.1007/s11517-019-02012-y
26. Rocatello G, El Faquir N, De Santis G, Iannaccone F, Bosmans J, De Backer O, et al. Patient-specific computer simulation to elucidate the role of contact pressure in the development of new conduction abnormalities after catheter-based implantation of a self-expanding aortic valve. *Circ Cardiovasc Interv.* (2018) 11:e005344. doi: 10.1161/CIRCINTERVENTIONS.117.005344
27. Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol.* (2014) 64:2330–9. doi: 10.1016/j.jacc.2014.09.039
28. Yousef A, Simard T, Webb J, Rodés-Cabau J, Costopoulos C, Kochman J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: a patient level multi-center analysis. *Int J Cardiol.* (2015) 189:282–8. doi: 10.1016/j.ijcard.2015.04.066

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Genetics

ORIGINAL RESEARCH
published: 31 May 2022
doi: 10.3389/fgene.2022.872750

DNA Methylation Analysis of Turner Syndrome BAV

Jacob Gutierrez[1], *Brett A. Davis*[1], *Kimberly A. Nevonen*[1], *Samantha Ward*[1], *Lucia Carbone*[1,2,3,4] *and Cheryl L. Maslen*[5]*

[1]Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland, OR, United States, [2]Department of Medicine, Oregon Health and Science University, Portland, OR, United States, [3]Department of Molecular and Medical Genetics, Oregon Health and Science University, Portland, OR, United States, [4]Division of Genetics, Oregon National Primate Research Center, Beaverton, OR, United States, [5]Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR, United States

Turner Syndrome (TS) is a rare cytogenetic disorder caused by the complete loss or structural variation of the second sex chromosome. The most common cause of early mortality in TS results from a high incidence of left-sided congenital heart defects, including bicuspid aortic valve (BAV), which occurs in about 30% of individuals with TS. BAV is also the most common congenital heart defect in the general population with a prevalence of 0.5–2%, with males being three-times more likely to have a BAV than females. TS is associated with genome-wide hypomethylation when compared to karyotypically normal males and females. Alterations in DNA methylation in primary aortic tissue are associated with BAV in euploid individuals. Here we show significant differences in DNA methylation patterns associated with BAV in TS found in peripheral blood by comparing TS BAV (n = 12), TS TAV (n = 13), and non-syndromic BAV (n = 6). When comparing TS with BAV to TS with no heart defects we identified a differentially methylated region encompassing the BAV-associated gene *MYRF*, and enrichment for binding sites of two known transcription factor contributors to BAV. When comparing TS with BAV to euploid women with BAV, we found significant overlapping enrichment for ChIP-seq transcription factor targets including genes in the *NOTCH1* pathway, known for involvement in the etiology of non-syndromic BAV, and other genes that are essential regulators of heart valve development. Overall, these findings suggest that altered DNA methylation affecting key aortic valve development genes contributes to the greatly increased risk for BAV in TS.

Keywords: monosomy X, DNA methylation analysis, congenital heart defects, bisulfide sequencing, aortopathy

OPEN ACCESS

Edited by:
Andrew E. Teschendorff, Partner Institute for Computational Biology, China

Reviewed by:
Adam de Smith, University of Southern California, United States
Benedetta Izzi, Mediterranean Neurological Institute Neuromed (IRCCS), Italy

***Correspondence:**
Cheryl L. Maslen
maslenc@ohsu.edu

Specialty section:
This article was submitted to Epigenomics and Epigenetics, a section of the journal Frontiers in Genetics

Received: *09 February 2022*
Accepted: *13 April 2022*
Published: *31 May 2022*

Citation:
Gutierrez J, Davis BA, Nevonen KA, Ward S, Carbone L and Maslen CL (2022) DNA Methylation Analysis of Turner Syndrome BAV. Front. Genet. 13:872750. doi: 10.3389/fgene.2022.872750

INTRODUCTION

Turner syndrome (TS) is a rare cytogenetic disorder caused by the partial or complete loss of a second sex chromosome, which occurs in 1 in 2,000 female live births (Shankar and Backeljauw, 2018). Girls with TS show a variety of clinical manifestations including short stature, premature ovarian failure, webbed neck, specific cognitive/visual spatial disabilities, hearing loss, thyroid dysfunction, scoliosis, endocrine disorders, autoimmune disorders, and cardiovascular disease. The most common cause of early mortality in TS is due to congenital heart defects, where patients with the most common 45, X karyotype have the highest burden of congenital defects and negative outcomes (Barr and Oman-Ganes, 2002). In addition to the increased post-natal cardiovascular defect related mortality risk, it is thought that over 99% of 45, X embryos are lost *in*

utero with an increased prevalence for left-sided obstructive lesions otherwise known as Left Sided Heart Lesions (LSHL) (Barr and Oman-Ganes, 2002; Surerus et al., 2003; Urbach and Benvenisty, 2009).

Bicuspid Aortic Valve (BAV) is the most common congenital heart defect in the general population with a prevalence of 0.5%–2% (Giusti et al., 2017). BAV is defined as an aortic valve that consists of two leaflets as opposed to the normal three leaflet configuration of the Tricuspid Aortic Valve (TAV). BAV is considered to be a mild form of LSHL and is largely compatible with life, leading to the relatively high prevalence in the general population (Parker and Landstrom, 2021). The specific negative cardiovascular outcomes of BAV include valve calcification, stenosis, aortic endocarditis, aortic dilation, and aortic aneurysm; collectively known as aortopathy. Approximately 40% of patients with BAV go on to develop some form of aortopathy in their lifetime (Liu et al., 2019). TS patients with the 45, X karyotype have the highest burden of BAV with a prevalence around 30% with near complete penetrance of developing aortopathy (Miller et al., 1983). There is a significant sex bias within BAV, where males account for approximately 75% of all BAV cases (Liu et al., 2019). The high incidence of BAV in TS females and the bias towards karyotypically normal 46, XY males suggests that having one X chromosome predisposes individuals to the development of BAV and BAV associated aortopathy.

Despite the high prevalence in the general population, most of the etiology of BAV is not known. However, a genetic component of BAV has been identified as 10%–40% of BAV is familial (Silberbach, 2009). Mutations in *NOTCH1*, *GATA5*, *NKX2.5*, and *ROBO4* are known to cause BAV in some families, but the majority of BAV cases are simplex and of unknown etiology (McKellar et al., 2007; Qu et al., 2014; Shi et al., 2014; Gould et al., 2019). In the case of BAV in TS, a recent whole exome sequencing study has identified copy number variation of the X chromosome escape gene *TIMP1* coupled with functional linked SNPs in *TIMP3* to be associated with BAV and aortopathy in TS subjects with exome-wide significance (Corbitt et al., 2018). Although these genes show a very significant association with BAV, *TIMP1/3* deficiency only explains roughly 20% of the occurrence of BAV in TS. Taken together, these studies have shown that BAV is a complex and genetically heterogeneous condition.

DNA methylation (DNAm) alterations associated with BAV have been detected in primary aortic wall tissue and within the aortic valve itself in addition to non-coding RNA expression differences detectable in blood samples of BAV subjects (Pan et al., 2017; Björck et al., 2018; Pulignani et al., 2019). DNAm analysis of TS has identified genome-wide hypomethylation when compared to healthy 46, XX females and 46, XY males (Sharma et al., 2015; Trolle et al., 2016). Together, these findings suggest a role for epigenetic regulation both in TS and BAV that have not been explored. This study aims to address this gap by identifying DNAm alterations associated with TS BAV as well as between TS and euploid females with BAV to detect possible epigenetic modifications in BAV-associated genes and pathways that may further explain the high incidence of BAV and aortopathy in TS.

METHODS

Samples and Study Design

All blood samples were collected by the GenTAC consortium and supplied through the NIH-sponsored BioLINCC biorepository (Kroner et al., 2011). In order to control for known sources of variation that could confound DNAm studies, all samples included were of non-smoking individuals. Smoking status was determined by subject self-reporting at time of GenTAC enrollment. For TS subjects, karyotype and BAV status was primarily determined based on clinical information gathered at GenTAC enrollment. A subset of subjects had karyotype information confirmed *via* molecular karyotyping performed in a previous exome sequencing study (Corbitt et al., 2018). All subjects were over 13 years of age in order to minimize adolescent age effects and both biological groups displayed large overlap in age ranges (**Table 1**). Enrollment and studies have Internal Review Board approval and all study subjects had informed consent for participation. For subjects under the age of 18 years a child assent form was completed in addition to the informed consent signed by a legal guardian. A total of 36 whole blood DNA samples from three groups (TS with a confirmed BAV, TS BAV; TS with a confirmed tricuspid aortic valve, TS TAV; and euploid females with a simplex BAV, 46, XX BAV) were analyzed using targeted methylation sequencing. Three samples did not yield enough reads to be included in downstream analysis following read deduplication. Unexpectedly, two TS samples showed X chromosome methylation levels comparable with the 46, XX BAV samples indicating mosaicism of the X chromosome. The newly developed DAMEfindeR allelic methylation analysis method was used to confirm X inactivation within these samples leading to their exclusion (Orjuela et al., 2020). Following sample exclusion a total of 31 samples were used for differential methylation analysis.

Targeted Methylation Sequencing

Genomic DNA samples were submitted for targeted methylation sequencing library preparation at the OHSU Epigenetics Core. The Illumina TruSeq-Methyl Capture EPIC Library Prep Kit (TruSeq-Methyl Capture EPIC, cat # FC-151-1002, Illumina Inc., San Diego, CA, United States) was used to prepare libraries, which interrogates the same genomic loci as the Illumina MethylationEPIC microarray. Briefly, 500–1,000 ng of high-quality DNA was fragmented using the Bioruptor Pico sonicator (Diagenode). The captured fragments were then bisulfite converted and amplified by PCR. Fragment size was analyzed *via* TapeStation (Agilent), quantified by Qubit (Invitrogen), and qPCR (KAPA) prior to sequencing. All sequencing was done at the OHSU Massively Parallel Sequencing Shared Resource using the NovaSeq 6000.

TABLE 1 | Study subject characteristics.

Study Groups (karyotype and aortic valve status)	Sample Size (*n*)	Average Age and Range (years)
46,XX BAV	6	52 (28–67)
45,X TAV	13	35 (44–68)
45,X BAV	12	42 (16–65)

Data Processing and Quality Control

Bisulfite sequencing data was aligned using the ENCODE WGBS standard (ENCODE consortium, 2021). Raw sequencing reads were assessed for quality with FastQC v0.11.9, adapter trimmed with TrimGalore v0.6.6, aligned to the hg38 assembly using Bismark v0.23.0 and deduplicated (Andrews, 2010; Krueger and Andrews, 2011). Bismark coverage reports were generated using BismarkMethylationExtractor command and processed in R v3.6.2 using MethylKit v1.12.0 (Akalin et al., 2012). CpG data was filtered for 10X coverage for each sample, CpGs with majority coverage within each study group was used for differential methylation analysis.

Due to some TS samples showing X chromosome features similar to euploid samples, X inactivation status for all samples was validated using the newly developed allelic methylation analysis tool DAMEfinder v1.2.0 (Orjuela et al., 2020). Briefly, MethTuple v1.5.3 was applied to the same aligned data to detect di-CpG methylation status within the same molecule (read) (Hickey, 2020). These di-CpG loci are then filtered for 10X coverage and loci with complete coverage across all available samples were retained. Following the original publication, mean allelic methylation scores from X chromosome gene promoters were extracted to distinguish samples that have bi-allelic methylation as a proxy for X inactivation.

Principal components analysis (PCA) was done using the R stats prcomp function. Principal Components Partial R Squared (PCPR2) analysis is an extension of PCA which allows for the assessment of technical factors across all principal components and was performed using a custom R function following the original publication (Fages et al., 2014).

Differential Methylation Analysis

Surrogate Variable Analysis v3.34.0 from the sva R package was used to adjust the differential methylation model for batch effects and cell type heterogeneity, required for the analysis of DNAm in whole blood (Leek and Storey, 2007; Houseman et al., 2015). SVA models known batch effects such as the enrichment pool or sequencing run in addition to unknown sources of variation including cell type heterogeneity. SVA was selected to adjust for celltype composition due to stable performance across multiple studies, reference free nature, and application across multiple platforms (McGregor et al., 2016; Kaushal et al., 2017). DMRs were detected using a two-step approach with differentially methylated CpGs being detected using Limma v3.42.2 adjusted for Age and Surrogate Variables followed by DMR detection using Comb-P v33.1.1 using default parameters (Pedersen et al., 2012; Ritchie et al., 2015). The statistical significance threshold was set at <0.1 due to the hypothesis generating nature of this study. Significant DMRs were called with a sidak adjusted p value < 0.1 and no difference in methylation threshold was used due to the phenotype of interest, BAV, occurring early in development which may not lead to a large difference in methylation states between our groups of interest. Due to 46, XX karyotype samples being subject to X inactivation and being incomparable to a single activated X chromosome, the TS v. 46, XX comparison had CpGs on the sex chromosomes excluded from comb-p DMR detection.

Genes overlapping these DMRs were annotated using Genomation v1.18.0 with DMRs being annotated to genes overlapping exon, intron, or promoter regions being deemed genic and all other DMRs intergenic (Akalin et al., 2015). GeneHancer 2017 data was downloaded from GeneCards (Fishilevich et al., 2017). ENCODE cCRE regulatory regions were downloaded from the SCREEN ENCODE portal (The ENCODE Project Consortium Snyder et al., 2020). LOLA v1.16.0 was used to analyze enrichment for known genomic loci by comparing DMRs with their appropriate background regions to the available databases with cCRE and genehancer files processed into database collections for LOLA analysis using a custom script (Sheffield and Bock, 2016). TFBS motif enrichment was performed using HOMER v4.11.1 to analyze TF networks which could be altered by DNAm alterations. TFBS sequence logos were generated by using motifs files produced by HOMER and were visualized with ggseqlogo v0.1 (Wagih, 2017). DMRs were analyzed in bulk or subset by hypo/hyper methylation status, with background regions being defined as all tested regions extracted from Comb-P (Heinz et al., 2010). STRINGdb and ENRICHR were used to assess pathways contributing to the extracted gene lists (Chen et al., 2013; Szklarczyk et al., 2019). Reactome Pathway analysis was performed using web based Analysis Tools (Jassal et al., 2019). Plots were created using ggpubr v0.4.0 and ggplot2 v3.3.3 (Wickham, 2016; Kassambara, 2020).

RESULTS

Blood From Turner Syndrome Bicuspid Aortic Valve Patients Does Not Show Global DNAm Differences When Compared to Turner Syndrome Tricuspid Aortic Valve

All 31 samples analyzed in this study showed robust bisulfite conversion with <1% nonCpG methylation for all samples, with a mean alignment rate of 81%. After filtering for CpGs with at least 10X coverage, all samples yielded an average of 3.1M CpGs, with a mean read depth of 30X. Once CpGs were filtered for majority coverage across each study group, there were approximately 2.7M CpGs used for downstream analysis with a mean read coverage of 36X. PCA did not separate the samples by study group (**Figure 1A**), suggesting the absence of global DNAm differences and possibly the presence of high variability within each group. Such variability is expected due to the use of a cohort of human blood samples from a multi-site registry which could have differences in DNA extraction and storage. The contribution of both BAV and karyotype was inferred from Principal Component Partial R Squared (PC-PR2) analysis with the main variables of interest explaining roughly 11% of the variation (**Figure 1B**). PCA of the X chromosome CpGs shows clear separation based on karyotype (**Figure 1C**). Within the X chromosome, karyotype alone is the major contributor of the variation explaining roughly 80% of the variation (**Figure 1D**).

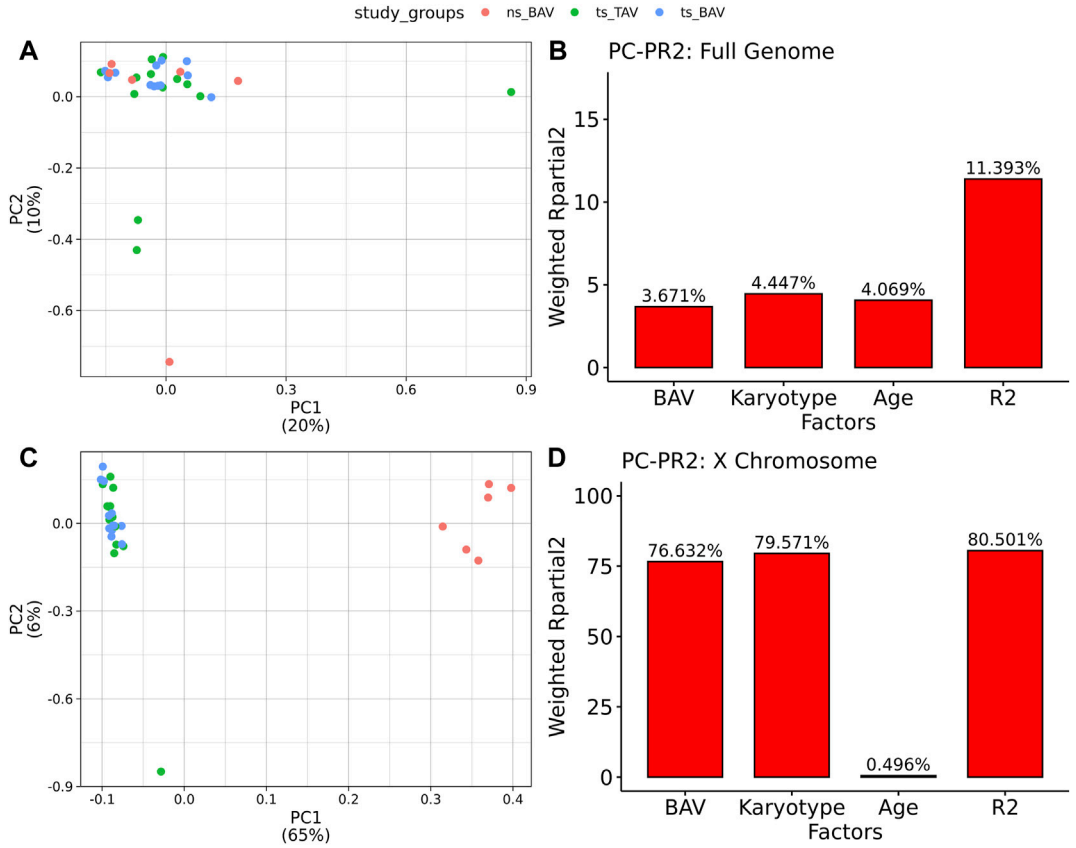


FIGURE 1 | Principal Components Analysis of Methylation data indicates TS samples are distinct from ns BAV on the X chromosome. **(A)** PCA biplot of first 2 principal components for all autosomes. **(B)** PCPR2 analysis of biological variables for autosomes. **(C)** PCA biplot of X chromosome. **(D)** PCPR2 analysis of biological variables for the X chromosome. Note, PCPR2 is sensitive to multicollinearity and overestimates BAV contribution due to unbalanced representation for each karyotype.

Detected DNAm Alterations Between Turner Syndrome Bicuspid Aortic Valve vs. Turner Syndrome Tricuspid Aortic Valve Suggests Functional Differences

When comparing TS BAV to TS TAV, a total of 76 significant DMRs (q-value < 0.1) were detected of which 44 showed a methylation difference >10% (**Figure 2A**). The detailed results for these DMR are shown in **Supplementary Table 1**. The majority of DMRs (n = 51; 71%) were found to be hypomethylated in TAV and largely overlapped with genes and lncRNAs (**Figures 2B,C**). However, gene set enrichment analysis and STRINGdb analysis did not detect any significant enrichment for biological function for genes overlapping DMRs (Chen et al., 2013; Szklarczyk et al., 2019).

To assess the possible function of the DMRs, we overlapped them with known regulatory enhancers from GeneHancer, ENCODE cCRE, and annotated CpG Islands (Fishilevich et al., 2017; The ENCODE Project Consortium Snyder et al., 2020; Karolchik et al., 2004). We found that the majority of DMRs overlap cCRE and CpG islands (72.4% and 71.1%, respectively) suggesting that these DMRs reside in functionally relevant regions of the genome (**Figure 3A**). To aid in the interpretation of these DMRs we sought to compare them to previously generated sequencing studies using locus overlap enrichment analysis (LOLA) which compares these DMRs to databases comprising of genomic regions to identify enrichment using Fisher's exact test for features such as transcription factor binding sites from ENCODE, Cistrome database features, DNase hypersensitive sites from Sheffield et al. (2013), CODEX database features, UCSC browser features, and a custom database reflecting ENCODE cCRE elements. We then tested for LOLA enrichment among hypermethylated and hypomethylated DMRs and found that only hypermethylated DMRs displayed significant enrichment for cCRE (**Figure 3B**) (Sheffield and Bock, 2016). To investigate the functional relevance of these significantly enriched cCRE elements the genes associated with these regions were explored. We identified various genes associated with congenital heart defects (*DUSP22* and *MYOM2*) and another gene (*UTS2*) which is known to protein expression changes affecting cardiovascular function in patients with congenital heart defects (Simpson et al., 2006; Grunert et al., 2014; Thorsson et al., 2015; Auxerre-Planti é et al., 2020). Together these results suggest that hypermethylated cCRE elements may play a functional role in the development or pathology of BAV in TS. Next we sought to determine if genes whose promoters

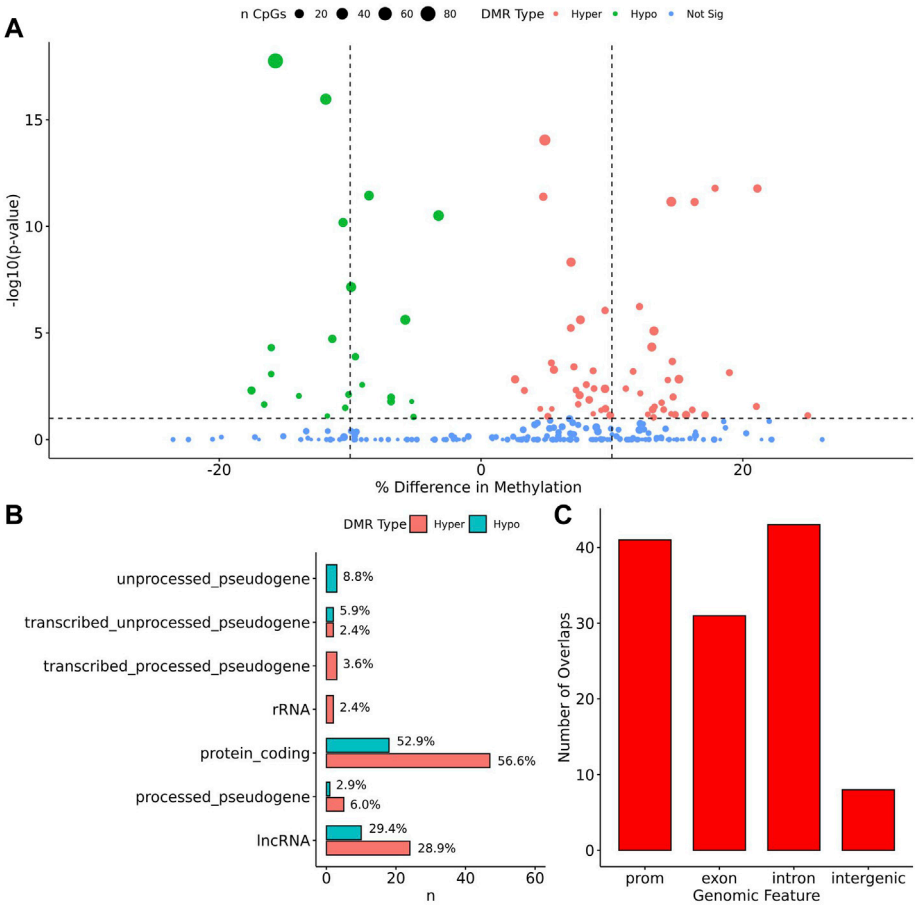


FIGURE 2 | 76 DMRs were detected in TS BAV mostly near protein coding regions. **(A)** Volcano plot of all regions detected colored by DMR type, hypermethylated, hypomethylated, or not significant with dashed lines at –log10 (0.1) and ±10% methylation difference. **(B)** Barplot of gene type annotations for all genes overlapping DMRs or the nearest gene when DMRs lack overlap. **(C)** Barplot of promoters, exon, intron, and intergenic regions overlapping DMRs.

overlap with DMRs belonged to biologically relevant pathways, we performed Reactome pathway enrichment analysis and observed significant enrichment for plasma lipoprotein clearance (*NR1H2, ACAT2*) (FDR = 0.04), glucagon signaling in metabolic regulation (*GNAS*) (FDR = 0.04), and NR1H2 & NR1H3 regulate gene expression to limit cholesterol uptake (*NR1H2*) (FDR = 0.07) (**Supplementary Table 2**). Metabolic regulation and cholesterol regulation do not have well understood connections to BAV and LSHL, however these results suggest a potential link that could be further explored.

Investigating genes directly overlapping DMRs, notable findings on autosomes include *DUSP22* on chromosome 6 which shows significant differences in methylation along most of the locus covering three separate DMRs with a 7.5% average difference in methylation (**Figure 3C**). Other noteworthy genes include *MYRF* and *ATP11A* which reside in the intronic regions of these genes and overlap cCRE elements which may regulate the expression of these genes (**Supplementary Figure 1**). There was special interest for DMRS present on the X chromosome could shed light on X chromosome dynamics predisposing TS individuals to develop BAV and BAV associated aortopathy. Two DMRs were detected on the X chromosome, both of which overlapped CpG islands within pseudogenes *ANKRD11P2* and *FTH1P27*. No known regulatory elements were overlapping these X chromosome DMRs nor protein coding genes were found nearby from these DMRs.

To analyze potential transcription factor networks that could be altered by changes to DNAm within their binding sites, we assessed if the DMRs were enriched for known transcription factor binding site (TFBS) motifs using HOMER. Although no TFBS reached significance, we found that known regulators of heart valve development *PBX3* and *PKNOX1* were 15 and 19-fold enriched, respectively, which approached significance (*q* values = 0.1041) (**Table 2**). Specifically, these binding sites were present in three DMRs and their binding co-occurred with one another, which potentially suggests that their functions may be altered together by changes in DNAm. Moreover, the same three DMRs also overlapped cCRE regulatory elements, suggesting that DNAm alterations could produce functional differences in genes regulated by these elements. To explore this observation further, the nearest genes were extracted in order to investigate which pathways may be altered by changes in TF binding through

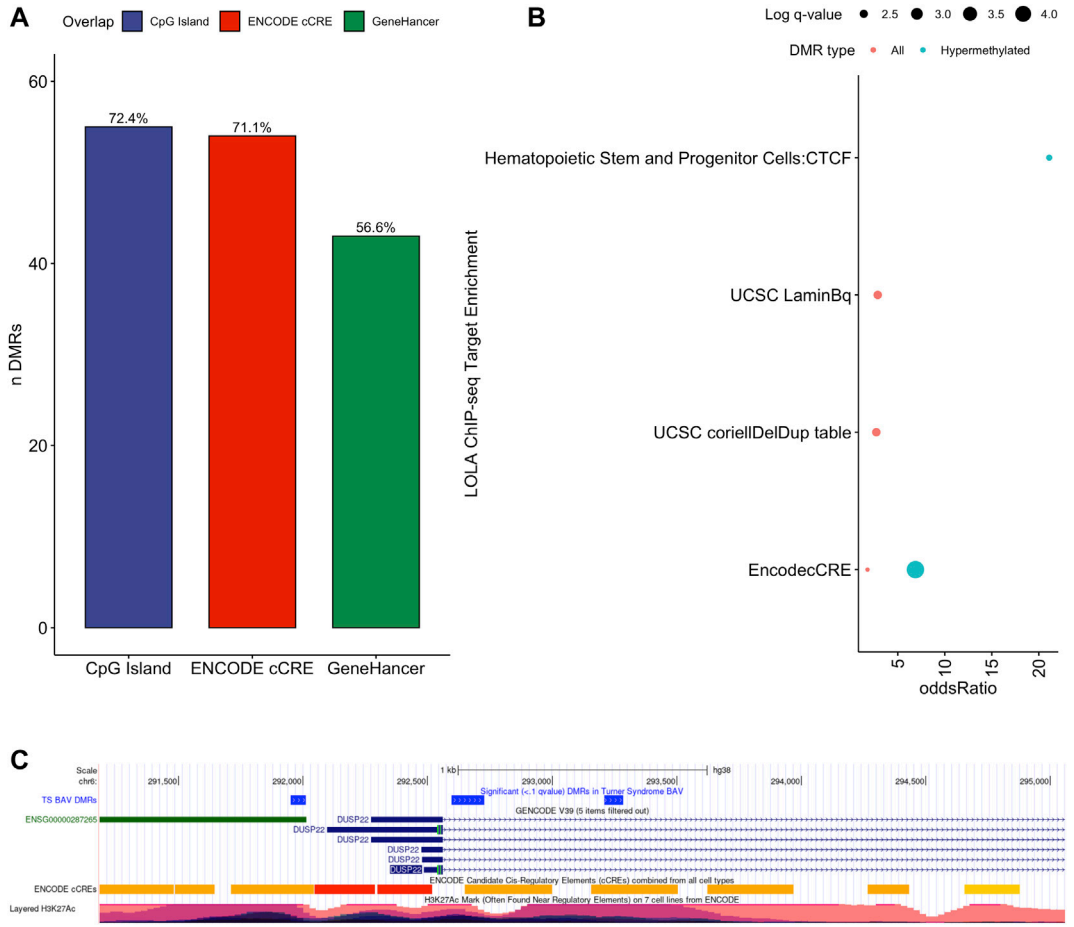


FIGURE 3 | Significant LOLA genome feature overlap enrichment for TS DMRs (<0.1 *q* value). **(A)** Dotplot of LOLA enrichment for UCSC features, Cistrome epigenomics database, Sheffield and Bock (2016) DNAse database, and Encode cCRE/GeneHancer overlap. **(B)** Dotplot of LOLA enrichment for CODEX database ChIP-seq peak overlap for NOTCH1, MYH11, KDM4A, and HDAC2. **(C)** Three significant TS BAV DMRs displayed in the UCSC Genome Browser (http://genome.ucsc.edu) with ENCODE cCREs and H3K27ac tracks over the *DUSP22* gene locus.

DNAm alterations. Reactome pathway enrichment analysis for genes associated with PBX3/PKNOX1 motif cCRE's revealed significant enrichment for signaling by hedgehog (*GNAS*) (FDR = 0.03), gene and protein expression by JAK-STAT signaling after interleukin-12 stimulation (*HNRNPF)* (FDR = 0.01), and metabolism of angiotensinogen to angiotensin (*CTSZ*) (FDR = 0.05) (**Supplementary Table 3**). These pathways are all critical for the development and maintenance of the cardiovascular system which suggests that DNAm alterations may produce functional changes relevant to BAV and aortopathy. Returning to the TFBS motif enrichment analysis results, many well characterized "late" HOX gene TFBS motifs, known to contribute to limb and heart development, were also enriched within these DMRs that approached statistical significance (**Table 2**). Specifically, *HOXA10* was found to be enriched and is known to regulate heart development through interactions with *NKX2-5* with mutations in this gene known to cause BAV (Behrens et al., 2013). Presently the connection between "late" HOX genes and BAV development is not well understood, however when taken together these results indicate that DNAm alterations in these DMRs may produce functional changes in both genes and pathways which could lead to increased susceptibility to aortopathy development.

Turner Syndrome Methylation Alterations Support Previous Findings

Within the TS vs. 46, XX comparison a total of 414 DMRs (**Supplemental Table 4**) were detected with an adjusted *p* value < 0.1, of which 329 had a methylation difference >10% the majority of which ($n = 281$, 68%) are hypomethylated (**Figure 4A**). Similar to what was noted above, these DMRs largely overlap with protein coding genes and lncRNA (**Figures 4B,C**). Genes overlapping DMRs were annotated as previously done to be used for Geneset, Reactome pathway, and STRING enrichment analysis. Reactome pathway analysis revealed significant enrichment (FDR = 0.003) for activation of anterior *HOX* genes in hindbrain development

TABLE 2 | Homer TFBS Motif enrichment results for all DMRs comparing TS BAV vs. TS TAV indicating *PBX3* and *PKNOX1* approach statistical significance (*q* value < 0.1).

All DMRs								
Motif	**Name**	***p*-value**	***q* value-FDR**	**n Targets**	**% Targets**	**n Background**	**% Background**	**Fold enrichment**
	Hoxd11(homeobox) ChickenMSG-Hoxd11.Flag-ChIP-Seq (GSE86088)	1.00E-05	0.004	12	16.67	5.9	4.20	3.97
	c-Myc (bHLH) mES-cMyc-ChIP-Seq (GSE11431)	1.00E-04	0.005	9	12.50	4	2.85	4.39
	bHLHE41 (bHLH) proB-Bhlhe41-ChIP-Seq (GSE93764)	1.00E-03	0.028	24	33.33	22.1	15.88	2.1
	Hoxa13(homeobox) ChickenMSG-Hoxa13.Flag-ChIP-Seq (GSE86088)	1.00E-03	0.028	10	13.89	5.1	3.68	3.77
	HINFP(Zf) K562-HINFP.eGFP-ChIP-Seq (Encode)	1.00E-03	0.039	15	20.83	12	8.60	2.42
	Max (bHLH) K562-Max-ChIP-Seq (GSE31477)	1.00E-03	0.068	11	15.28	7.8	5.57	2.74
	BMAL1 (bHLH) Liver-Bmal1-ChIP-Seq (GSE39860)	1.00E-02	0.104	19	26.39	18.7	13.42	1.97
	Hoxa10(homeobox) ChickenMSG-Hoxa10.Flag-ChIP-Seq (GSE86088)	1.00E-02	0.104	4	5.56	1.8	1.29	4.31
	HOXB13(homeobox) ProstateTumor-HOXB13-ChIP-Seq (GSE56288)	1.00E-02	0.104	4	5.56	1.6	1.18	4.71
	Hoxd13(homeobox) ChickenMSG-Hoxd13.Flag-ChIP-Seq (GSE86088)	1.00E-02	0.104	4	5.56	0.4	0.28	19.86
	Pbx3(homeobox) GM12878-PBX3-ChIP-Seq (GSE32465)	1.00E-02	0.104	4	5.56	0.5	0.35	15.89
	Pknox1(homeobox) ES-Prep1-ChIP-Seq (GSE63282)	1.00E-02	0.104	4	5.56	0	0.00	Inf

during early embryogenesis due to the presence of four *HOX* genes within DMRs *HOXB3*, *HOXB6*, *HOXA3*, *HOXA4*, and *HOXC4*. Notably, *HOXA3* and *HOXB3* are known to contribute to cardiac development (Roux and Zaffran, 2016).

Similar to the BAV comparison, cCRE and genehancer regulatory elements were overlapped to DMRs and LOLA analysis was used to augment interpretation of these gene regions by comparing them to previously generated datasets. DMRs were enriched for cCREs and only hypermethylated DMRs did not show enrichment for genehancer elements (**Figure 5A**). All DMRs subsets were enriched for cCREs and only hypermethylated DMRs did not show enrichment for genehancer elements (**Figure 5A**). The enrichment for these functional elements suggests that these DMRs may have functional roles at some stages of development. It was found TS DMRs show enrichment for CpG islands and evolutionarily conserved CpG islands identified by Cohen et al. (2011) (**Figure 5A**). These DMRs show enrichment for hematopoietic cells and weak stem-epithelial cell DNAse hypersensitivity sites derived from Sheffield et al., 2013 reflecting the use of blood DNA samples.

DMRs were significantly enriched for *ZNF143*, *GABPA*, *EZH2*, *RBBP5*, *HDAC2*, and *KDM4A* ChIP-seq binding sites (*q* values < 0.05) identified from the CODEX and ENCODE databases. All of

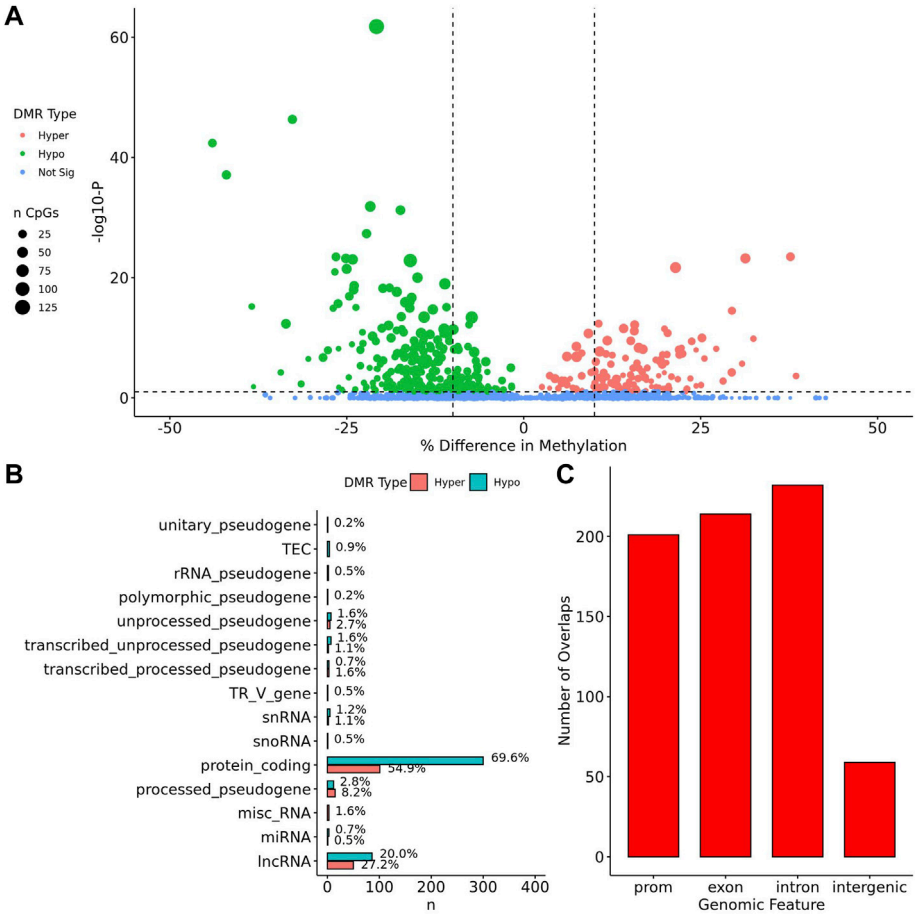


FIGURE 4 | Feature enrichment for genes overlapping TS BAV DMRs. **(A)** Barplot of DMR overlap with CpG islands, ENCODE cCRE, and GeneHancer elements. **(B)** Dotplot of LOLA feature overlap with enrichment for cCREs, CTCF ChIP-seq peaks, Lamin B1 nuclear lamina interactions, and Coriell Cell Line Copy Number Variants (coriellDelDup table). **(C)** Three significant TS BAV DMRs displayed in the UCSC Genome Browser with ENCODE cCREs and H3K27Ac tracks over the DUSP22 gene locus.

these transcription factors are known epigenetic regulators of gene expression and development. In addition, there was significant enrichment for many known chromatin states such as heterochromatin (H3K9me3; assayed in prostate, breast, and hematopoietic stem cells) and promoters and primed enhancers (H3K4me3 and H3K4me1; assayed in prostate and breast) (q values < 0.05). In addition, there was significant enrichment for TFBS overlap for gene expression regulators including *SIN3A*, *CTCF*, *YY1*, and *POL2* (q values < 0.05) derived from ENCODE database (**Supplementary Figure 2**). DMRs show TFBS enrichment for *NOTCH1* (q value = 0.038) and the downstream *NOTCH* pathway gene *MYH11* (q values < 0.002) (**Figure 5B**). Mutations in *NOTCH1* are known to cause familial BAV disease, whereas mutations in *MYH11* cause hereditary thoracic aortic aneurysms (McKellar et al., 2007; Takeda et al., 2015; Kerstjens-Frederikse et al., 2016).

Homer TFBS motif enrichment was performed and it was found that all DMRs display enrichment for *PIT1* (q value = 0.00, a regulator of hormone expression), and *TBX20* approaching significance (q value = 0.15), a known regulator of heart development (**Table 3**) (Pfaffle et al., 1999; Kirk et al., 2007). Hypomethylated DMRs show enrichment for *TBX20* and *ZFX*. Interestingly, *ZFX* is an X escape gene that could contribute to the phenotypes seen in TS due to these individuals only having one X chromosome which has been previously detected to be differentially methylated in TS subjects (Trolle et al., 2016).

DISCUSSION

TS individuals are at a 60-fold increased risk of BAV compared to the general population. Although BAV is the most common congenital heart defect, there is little understanding of the epigenetic alterations associated with this condition in the general population let alone in TS individuals. Considering BAV is a developmental disorder, DNAm alterations might provide an insight into the genes or pathways that contribute to this condition. In this study we compared DNAm in blood obtained from 45, X TS individuals with BAV against TS individuals who have the normal tricuspid aortic valve to

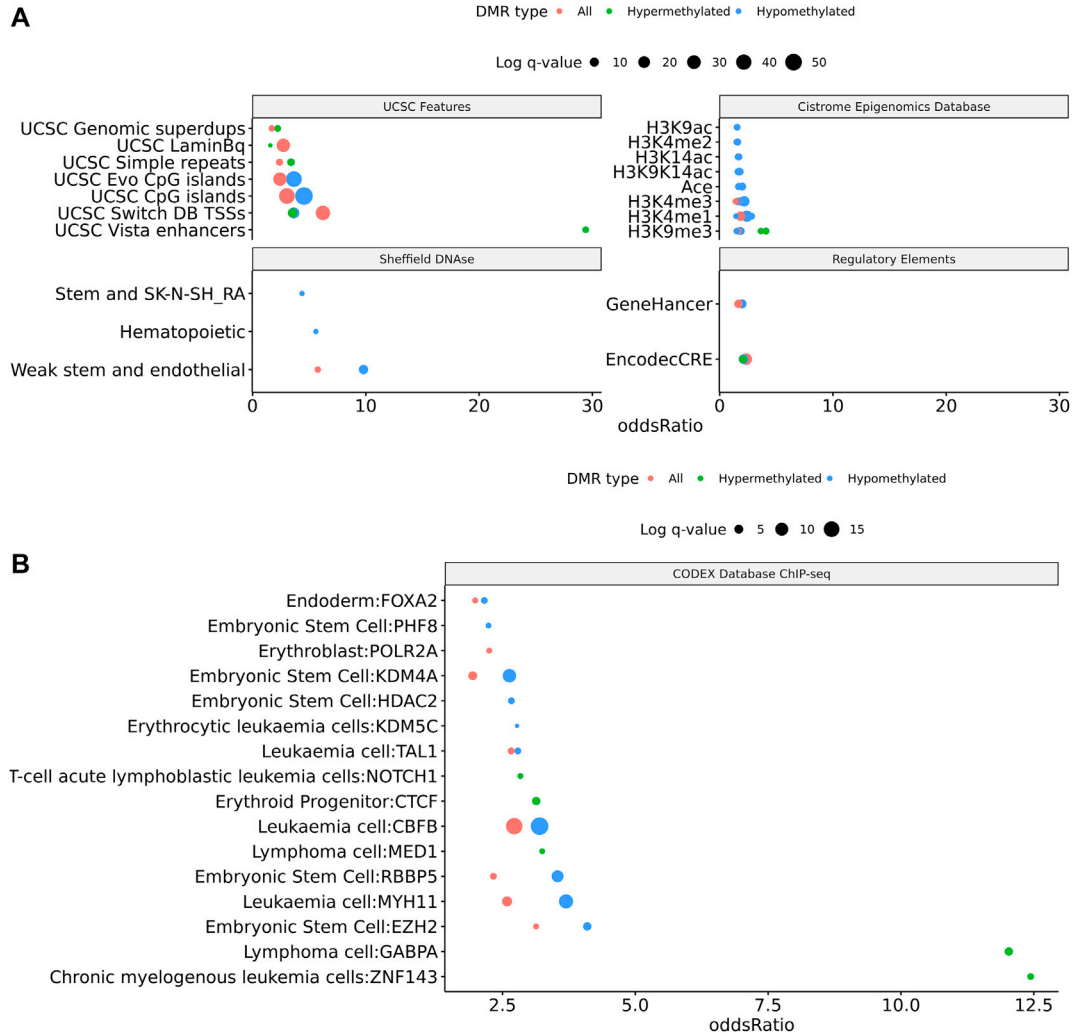


FIGURE 5 | 414 DMRs were detected in TS v. 46, XX which are largely hypomethylated and near protein coding regions. **(A)** Volcano plot of all regions detected colored by DMR type, hypermethylated, hypomethylated, or not significant with dashed lines at –log10 (0.1) and ±10% methylation difference. **(B)** Barplot of gene type annotations for all genes overlapping DMRs or the nearest gene when DMRs lack overlap.

determine if differential DNA methylation could contribute to BAV etiology in TS. In addition, we compared individuals with TS and BAV to euploid women with BAV to see if DNA methylation alterations due to monosomy X correlates with the significantly increased risk for BAV in TS compared to having two X chromosomes.

We found significant DNAm differences between BAV and TAV in TS and observed that most of these DMRs overlap regulatory elements. Interestingly, when looking for TFBS motif enrichment we observed that *PBX3*, known to contribute to BAV in mice models through interactions with the chromatin remodeling complex MEIS1, approached significance (Stankunas et al., 2008). The regulator of *PBX-MEIS* interactions, *PKNOX1,* was also found to have motifs the same DMRs suggesting possible co-regulation of nearby genes during development (Schulte and Geerts, 2019).

Notable genes of relevance on autosomes include *DUSP22* on chromosome 6, which is known to activate JNK signaling in T cells and aged knockout mice show increased autoimmunity implicating immune system response. Additionally, a CNV in this gene has been linked to cardiac atrial septal defects suggesting this gene is important to the development and maintenance of the cardiovascular system (Li et al., 2014; Thorsson et al., 2015). We identified DMRs overlapping *MYRF* and *ATP11A* which are both genes directly associated with congenital heart disease including BAV (Rossetti et al., 2019; Szumska et al., 2019). In humans, *MYRF* is a key regulator of myelin development and is required for biosynthesis of oligodendrocytes; mutations in this gene are associated with a newly identified disorder, cardiac-urogenital syndrome, which is characterized by congenital heart defects including BAV (Bujalka et al., 2013; Rossetti et al., 2019). Mutations in this gene are also associated with non-myelin

TABLE 3 | HOMER TFBS motif enrichment results for all DMRs and hypomethylated DMRs for TS v. 46, XX indicating significant enrichment for *PIT1* and *ZFX* (*q* value < 0.1).

Motif	Name	*p*-value	*q* value-FDR	*n* Targets	% Targets	*n* Background	% Background	Fold enrichment
All DMRs								
	Pit1+1bp (homeobox) GCrat-Pit1-ChIP-Seq (GSE58009)	1.00E-04	0.026	7	1.79%	2.5	0.30%	5.97
	OCT:OCT-short (POU,Homeobox) NPC-OCT6-ChIP-Seq (GSE43916)	1.00E-03	0.139	11	2.82%	7.8	0.95%	2.97
	Znf263(Zf) K562-Znf263-ChIP-Seq (GSE31477)	1.00E-03	0.139	106	27.18%	167.2	20.34%	1.34
	NF-E2 (bZIP) K562-NFE2-ChIP-Seq (GSE31477)	1.00E-02	0.158	4	1.03%	1.8	0.22%	4.68
	Tbx20 (T-box) Heart-Tbx20-ChIP-Seq (GSE29636)	1.00E-02	0.158	12	3.08%	10	1.21%	2.55
	Pknox1(homeobox) ES-Prep1-ChIP-Seq (GSE63282)	1.00E-02	0.158	11	2.82%	8.9	1.09%	2.59
	Isl1(homeobox) Neuron-Isl1-ChIP-Seq (GSE31456)	1.00E-02	0.158	49	12.56%	67.2	8.17%	1.54
Hypomethylated DMRs								
	Pit1+1bp (homeobox) GCrat-Pit1-ChIP-Seq (GSE58009)	1.00E-06	0.001	6	2.76%	1.7	0.17%	16.24
	ZFX (Zf) mES-Zfx-ChIP-Seq (GSE11431)	1.00E-04	0.007	68	31.34%	189	19.77%	1.59
	PRDM15 (Zf) ESC-Prdm15-ChIP-Seq (GSE73694)	1.00E-02	0.154	29	13.36%	69.5	7.27%	1.84

disease and orthologs play important roles in organisms without myelin such as *C. elegans*. Overall, these observations support an important role for *MYRF* during development which have not yet been fully explored (An et al., 2020). ATP11A is a ubiquitously expressed phospholipid flippase which could be important for cell-cell signaling through the cell membrane (Takatsu et al., 2014; Miyano et al., 2016; Segawa et al., 2016; Hawkey-Noble et al., 2020). The Deciphering Mechanisms of Developmental Disorders (DMDD) project conducted a mouse knockout screen to identify genes which confer embryonic lethality and found that *ATP11A* knockout mice had aortic defects indicating this gene is critical for normal heart development (Szumska et al., 2019). These two genes are interesting candidates for further analysis because they both have been independently associated with non-syndromic BAV and likely act outside of known pathogenic mechanisms of BAV development such as through *NOTCH* signaling (Szumska et al., 2019). Taken together, these findings support the hypothesis that in TS DNAm alterations might occur in genes and pathways relevant to BAV etiology.

An unexpected finding was enrichment for cholesterol biosynthesis and regulation within BAV DMRs. Studies of BAV in the euploid population have linked increased cholesterol levels in BAV patients with aortic stenosis and linear correlation of low-density lipoprotein levels and ascending aorta diameter (Alegret et al., 2015; Endo et al., 2015). BAV patients undergoing statin treatment were observed to have reduced progression of aortopathy following heart surgery, which was not found in the TAV counterparts

(Taylor et al., 2016; Sequeira Gross et al., 2018). An interesting connection can be found when we consider that TS individuals are at an increased risk for dyslipidemia which presents at an early age, although cholesterol levels improve following hormone replacement therapy (Ross et al., 1995; Mavinkurve and O'Gorman, 2015). These findings suggest that there might be an unexplored connection between BAV, cholesterol regulation, and aortopathy which may contribute to TS BAV.

There were significantly more DMRs found when comparing TS BAV to 46, XX BAV subjects than the TS BAV to TS TAV comparison which is consistent with a larger impact of X chromosome monosomy on the epigenetic landscape. Over 99% of embryos with 45, X karyotype are not viable during development with most of these fetuses failing *in utero* due to LSHL. Therefore it would not be expected that DNAm alterations on the same scale as monosomy X, genome-wide hypomethylation, to be found in the TS BAV subjects who are compatible with life (Urbach and Benvenisty, 2009; Mortensen et al., 2012). Similar to previous findings, TS DMRs are hypomethylated across the full genome indicating that loss of a second sex chromosome leads to global changes to DNAm and potentially other epigenetic regulators which may predispose TS individuals to CHD during development.

An interesting result from this analysis has detected multiple HOX genes, critical for embryogenesis and hindbrain development, were found to be differentially methylated in TS compared to euploid women. This result is consistent with previous analyses of TS methylation patterns which found *HOXA4* and *HOXB6* to be hypermethylated compared to female controls (Sharma et al., 2015). Additionally, a rare copy number variant within the *HOXA* cassette has been identified to contribute to cases of LSHL in TS (Prakash et al., 2016). Together, these results suggests that dysregulation of *HOX* gene function may contribute to the greatly increased incidence of LSHL in TS. However, we cannot rule out the possibility that this methylation difference is broadly related to TS as opposed to being TS BAV-specific. Considering that *HOX* gene function is critical for the normal development of various body and organ systems, the dysfunction of this key developmental regulatory system may also contribute to the other phenotypes seen in TS which have yet to be fully explored.

We have found that TS DMRs show significant overlap with genomic targets for *NOTCH1*, and the downstream *NOTCH* pathway gene *MYH11*. *NOTCH1* mutations are known to cause familial BAV (McKellar et al., 2007). However, *MYH11* mutations are known to cause familial thoracic aortic aneurysms (Takeda et al., 2015). Vascular smooth muscle cells (VSMC) derived from induced pluripotent stem cells from BAV subjects implicate *NOTCH1* and *MYH11* expression in VSMC differentiation in aortopathy (Harrison et al., 2019). Together, *NOTCH1* and *MYH11* appear to contribute to both BAV development and BAV associated aortopathy. TS DMRs also show TFBS motif enrichment for *TBX20*; copy number variations involving this gene have been identified in BAV subjects with a prevalence ~1% (MIBAVA Leducq Consortium et al., 2019). *TBX20* is an ancient member of the *TBX* family which has been characterized to be essential for heart development and valvulogenesis in multiple animal models and mutations have been found in congenital heart disease probands (Kirk et al., 2007). Alterations in the function of this transcription factor could lead to heart defects especially in concert with dysregulation of other heart development pathways such as *NOTCH1*. In addition to these findings, the epigenetic regulators *KDM4A* and *HDAC2* were significantly enriched within TS DMRs and these genes have been linked to increased risk of congenital heart disease (Zaidi et al., 2013). Overall, the presence of DMRs within these genes suggest dysregulation of known epigenetic pathways, *TBX20* mediated heart development regulation, and *NOTCH* signaling present in TS which could predispose these individuals to a higher risk of BAV.

Strengths of this study include utilizing a high throughput sequencing approach to analyze DNAm changes and leveraging newly developed allelic methylation analysis techniques to validate biallelic DNAm expression to only analyze TS individuals with a lack of X inactivation within our comparison of interest. Limitations of this study include using whole blood DNA to probe DNAm alterations relevant to the heart in addition to limited study size for each group of interest. The diabetic and lipid status of study participants was not captured at time of enrollment which means we cannot exclude potential confounding due to participants with metabolic disease or dyslipidemia within our study. Diabetes and dyslipidemia could confound this analysis due to potential methylation alterations associated with these diseases being detected by contributing as another unknown source of variation reducing statistical power.

Alternate interpretations of the data include the possibility that having a BAV somehow alters DNA methylation of the blood over time as our study cohort does not include infants. However, the likelihood of BAV having a substantial effect on DNA methylation in remote tissues such of that of the bone marrow (hematopoietic stem progenitors) seems unlikely. We propose that it is more likely that monosomy X leads to genetic and epigenetic dysregulation which causes changes in the canonical cell regulation cascades leading to increased risk of BAV. It is also possible that altered DNA methylation could be a compensatory effect of BAV rather than a risk factor. This study does not have the ability to rule out this possible alternate mechanism. However, the fact that deficiency of a second sex chromosome is a powerful modulator of DNA methylation in general, it is a reasonable premise that specific differences in DNA methylation between individuals with Turner syndrome is a driving force underlying differences in comorbidities such as BAV. Alternate interpretations of the data include the possibility that having a BAV somehow alters DNA methylation of the blood over time as our study cohort does not include infants. However, the likelihood of BAV having a substantial effect on DNA methylation in remote tissues such as bone marrow (hematopoietic stem progenitors) seems unlikely. We propose that it is more likely that monosomy X leads to genetic and epigenetic dysregulation which causes changes in the canonical cell regulation cascades leading to increased risk for BAV. It is also possible that altered

DNA methylation could be a compensatory effect of BAV rather than a risk factor. This study does not have the ability to rule out this possible alternate mechanism. However, the fact that deficiency of a second sex chromosome is a powerful modulator of DNA methylation in general, it is a reasonable premise that specific differences in DNA methylation between individuals with Turner syndrome is a driving force underlying differences in comorbidities such as BAV.

Together, these findings suggest that alterations in pathways directed by *TBX20* and *NOTCH1* pathways are altered in TS generally, with BAV individuals also showing DNAm alterations at *PBX3* and *PKNOX1* TFBS. These findings are not powered to distinguish whether these alterations are causal to BAV formation or a downstream effect of the X chromosome monosomy, which leads to BAV. Further studies to validate these findings, as well as functional studies in the appropriate model systems, are needed to elucidate the mechanisms behind the epigenetic basis of BAV formation in TS. Overall, these DNAm changes are most likely due to haploinsufficiency of X escape genes that lead to alterations in epigenetic programming causing the phenotypes associated with TS. This hypothesis is supported by previous epigenetic studies of other sex chromosome abnormalities (47, XXY or 47, XXX) where TS individuals have the largest change in DNAm compared to euploid controls (Trolle et al., 2016; Skakkeb æ k et al., 2018; Zhang et al., 2020). It is important to note that, although X escape genes have been studied for many years, we still lack a complete map of all X escape genes and functional studies of their activity in normal development (Di Palo et al., 2020). Considering the X chromosome has more non-coding RNA than expected and that known genes on the X chromosome have regulatory roles critical to development, there is still much to learn about the function of genes on the X chromosome (Guo et al., 2009; Di Palo et al., 2020).

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Gene Expression Omnibus, GSE198262.

ETHICS STATEMENT

Enrollment and studies have Internal Review Board approval and all study subjects had informed consent for participation.

AUTHOR CONTRIBUTIONS

Study design: JG, BD, LC, and CM. Clinical data collection: JG and CM. Bioinformatic analysis: JG and BD. Genetic analysis: KN and SW. Data interpretation: JG and LC. Figures, Tables, Graphics: JG and CM. Manuscript writing: JG and CM. Manuscript critical review: BD, KN, SW, LC, and CM. Manuscript supervision: LC and CM.

FUNDING

National Heart, Lung and Blood Institute, R21HL148093.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.872750/full#supplementary-material

REFERENCES

Akalin, A., Franke, V., Vlahovi ek, K., Mason, C. E., and Schubeler, D. (2015). Genomation: a Toolkit to Summarize, Annotate and Visualize Genomic Intervals. *Bioinformatics* 31, 1127–1129. doi:10.1093/bioinformatics/btu775

Akalin, A., Kormaksson, M., Li, S., Garrett-Bakelman, F. E., Figueroa, M. E., Melnick, A., et al. (2012). methylKit: a Comprehensive R Package for the Analysis of Genome-wide DNA Methylation Profiles. *Genome Biol.* 13, R87. doi:10.1186/gb-2012-13-10-r87

Alegret, J. M., Masana, L., Martinez-Micaelo, N., Heras, M., and Beltrán-Debón, R. (2015). LDL Cholesterol and Apolipoprotein B Are Associated with Ascending Aorta Dilatation in Bicuspid Aortic Valve Patients. *QJM* 108, 795–801. doi:10.1093/qjmed/hcv032

An, H., Fan, C., Sharif, M., Kim, D., Poitelon, Y., and Park, Y. (2020). Functional Mechanism and Pathogenic Potential of MYRF ICA Domain Mutations Implicated in Birth Defects. *Sci. Rep.* 10, 814. doi:10.1038/s41598-020-57593-8

Andrews, S. (2010). *FASTQC. A Quality Control Tool for High Throughput Sequence Data*. www.bioinformatics.babrham.ac.uk

Auxerre-Plantié, E., Nielsen, T., Grunert, M., Olejniczak, O., Perrot, A., Özcelik, C., et al. (2020). Identification of MYOM2 as a Candidate Gene in Hypertrophic Cardiomyopathy and Tetralogy of Fallot and its Functional Evaluation in the Drosophila Heart. *Dis. Model. Mech.* 13. doi:10.1242/dmm.045377

Barr, M., and Oman-Ganes, L. (2002). Turner Syndrome Morphology and Morphometrics: Cardiac Hypoplasia as a Cause of Midgestation Death. *Teratology* 66, 65–72. doi:10.1002/tera.10064

Behrens, A. N., Iacovino, M., Lohr, J. L., Ren, Y., Zierold, C., Harvey, R. P., et al. (2013). Nkx2-5 Mediates Differential Cardiac Differentiation through Interaction with Hoxa10. *Stem Cell Dev.* 22, 2211–2220. doi:10.1089/scd.2012.0611

Björck, H. M., Du, L., Pulignani, S., Paloschi, V., Lundströmer, K., Kostina, A. S., et al. (2018). Altered DNA Methylation Indicates an Oscillatory Flow Mediated Epithelial-To-Mesenchymal Transition Signature in Ascending Aorta of Patients with Bicuspid Aortic Valve. *Sci. Rep.* 8, 2777. doi:10.1038/s41598-018-20642-4

Bujalka, H., Koenning, M., Jackson, S., Perreau, V. M., Pope, B., Hay, C. M., et al. (2013). MYRF Is a Membrane-Associated Transcription Factor that Autoproteolytically Cleaves to Directly Activate Myelin Genes. *PLOS Biol.* 11, e1001625. doi:10.1371/journal.pbio.1001625

Chen, E. Y., Tan, C. M., Kou, Y., Duan, Q., Wang, Z., Meirelles, G. V., et al. (2013). Enrichr: Interactive and Collaborative HTML5 Gene List Enrichment Analysis Tool. *BMC Bioinformatics* 14, 128. doi:10.1186/1471-2105-14-128

Cohen, N. M., Kenigsberg, E., and Tanay, A. (2011). Primate CpG Islands Are Maintained by Heterogeneous Evolutionary Regimes Involving Minimal Selection. *Cell* 145, 773–786. doi:10.1016/j.cell.2011.04.024

Corbitt, H., Morris, S. A., Gravholt, C. H., Mortensen, K. H., Tippner-Hedges, R., Silberbach, M., et al. (2018). TIMP3 and TIMP1 Are Risk Genes for Bicuspid

Aortic Valve and Aortopathy in Turner Syndrome. *PLOS Genet.* 14, e1007692. doi:10.1371/journal.pgen.1007692

Di Palo, A., Siniscalchi, C., Salerno, M., Russo, A., Gravholt, C. H., and Potenza, N. (2020). What microRNAs Could Tell Us about the Human X Chromosome. *Cell. Mol. Life Sci.* 77, 4069–4080. doi:10.1007/s00018-020-03526-7

ENCODE consortiumCherry, J., and Michael (2021). *ENCODE Standards and Guidelines for Whole Genome Shotun Bisulfite Sequencing (WGBS)*. WGBS paired-end pipeline. Available at: https://urldefense.com/v3/__https://www.encodeproject.org/about/experiment-guidelines/ https://www.encodeproject.org/about/experiment-guidelines/. Accessed October 1, 2021

Endo, M., Nabuchi, A., Okuyama, H., Muto, Y., Hiranuma, S., Miyazaki, T., et al. (2015). Differing Relationship between Hypercholesterolemia and a Bicuspid Aortic Valve According to the Presence of Aortic Valve Stenosis or Aortic Valve Regurgitation. *Gen. Thorac. Cardiovasc. Surg.* 63, 502–506. doi:10.1007/s11748-015-0561-8

Fages, A., Ferrari, P., Monni, S., Dossus, L., Floegel, A., Mode, N., et al. (2014). Investigating Sources of Variability in Metabolomic Data in the EPIC Study: the Principal Component Partial R-Square (PC-PR2) Method. *Metabolomics* 10, 1074–1083. doi:10.1007/s11306-014-0647-9

Fishilevich, S., Nudel, R., Rappaport, N., Hadar, R., Plaschkes, I., Iny Stein, T., et al. (2017). GeneHancer: Genome-wide Integration of Enhancers and Target Genes in GeneCards. *Database J. Biol. Databases Curation* 2017. doi:10.1093/database/bax028

Giusti, B., Sticchi, E., De Cario, R., Magi, A., Nistri, S., and Pepe, G. (2017). Genetic Bases of Bicuspid Aortic Valve: The Contribution of Traditional and High-Throughput Sequencing Approaches on Research and Diagnosis. *Front. Physiol.* 8, 612. doi:10.3389/fphys.2017.00612

Gould, R. A., Aziz, H., Aziz, H., Woods, C. E., Seman-Senderos, M. A., Sparks, E., et al. (2019). ROBO4 Variants Predispose Individuals to Bicuspid Aortic Valve and Thoracic Aortic Aneurysm. *Nat. Genet.* 51, 42–50. doi:10.1038/s41588-018-0265-y

Grunert, M., Dorn, C., Schueler, M., Dunkel, I., Schlesinger, J., Mebus, S., et al. (2014). Rare and Private Variations in Neural Crest, Apoptosis and Sarcomere Genes Define the Polygenic Background of Isolated Tetralogy of Fallot. *Hum. Mol. Genet.* 23, 3115–3128. doi:10.1093/hmg/ddu021

Guo, X., Su, B., Zhou, Z., and Sha, J. (2009). Rapid Evolution of Mammalian X-Linked Testis microRNAs. *BMC Genomics* 10, 97–98. doi:10.1186/1471-2164-10-97

Harrison, O. J., Torrens, C., Salhiyyah, K., Modi, A., Moorjani, N., Townsend, P. A., et al. (2019). Defective NOTCH Signalling Drives Smooth Muscle Cell Death and Differentiation in Bicuspid Aortic Valve Aortopathy. *Eur. J. Cardiothorac. Surg.* 56, 117–125. doi:10.1093/ejcts/ezy464

Hawkey-Noble, A., Umali, J., Fowler, G., and French, C. R. (2020). Expression of Three P4-Phospholipid Flippases-Atp11a, Atp11b, and Atp11c in Zebrafish (Danio rerio). *Gene Expr. Patterns* 36, 119115. doi:10.1016/j.gep.2020.119115

Heinz, S., Benner, C., Spann, N., Bertolino, E., Lin, Y. C., Laslo, P., et al. (2010). Simple Combinations of Lineage-Determining Transcription Factors Prime Cis-Regulatory Elements Required for Macrophage and B Cell Identities. *Mol. Cel* 38, 576–589. doi:10.1016/j.molcel.2010.05.004

Hickey, P. (2020). *PeteHaitch/methtuple*.

Houseman, E. A., Kim, S., Kelsey, K. T., and Wiencke, J. K. (2015). DNA Methylation in Whole Blood: Uses and Challenges. *Curr. Envir Health Rpt* 2, 145–154. doi:10.1007/s40572-015-0050-3

Jassal, B., Matthews, L., Viteri, G., Gong, C., Lorente, P., Fabregat, A., et al. (2019). The Reactome Pathway Knowledgebase. *Nucleic Acids Res.* 46 (D1), gkz1031. doi:10.1093/nar/gkz1031

Karolchik, D., Hinrichs, A. S., Furey, T. S., Roskin, K. M., Sugnet, C. W., Haussler, D., et al. (2004). The UCSC Table Browser Data Retrieval Tool. *Nucleic Acids Res.* 32, D493–D496. doi:10.1093/nar/gkh103

Kassambara, A. (2020). *Ggpubr: "Ggplot2" Based Publication Ready Plots*. https://github.com/kassambara/ggpubr

Kaushal, A., Zhang, H., Karmaus, W. J. J., Ray, M., Torres, M. A., Smith, A. K., et al. (2017). Comparison of Different Cell Type Correction Methods for Genome-Scale Epigenetics Studies. *BMC Bioinformatics* 18, 216. doi:10.1186/s12859-017-1611-2

Kerstjens-Frederikse, W. S., van de Laar, I. M. B. H., Vos, Y. J., Verhagen, J. M. A., Berger, R. M. F., Lichtenbelt, K. D., et al. (2016). Cardiovascular Malformations Caused by NOTCH1 Mutations Do Not Keep Left: Data on 428 Probands with Left-Sided CHD and Their Families. *Genet. Med.* 18, 914–923. doi:10.1038/gim.2015.193

Kirk, E. P., Sunde, M., Costa, M. W., Rankin, S. A., Wolstein, O., Castro, M. L., et al. (2007). Mutations in Cardiac T-Box Factor Gene TBX20 Are Associated with Diverse Cardiac Pathologies, Including Defects of Septation and Valvulogenesis and Cardiomyopathy. *Am. J. Hum. Genet.* 81, 280–291. doi:10.1086/519530

Kroner, B. L., Tolunay, H. E., Basson, C. T., Pyeritz, R. E., Holmes, K. W., Maslen, C. L., et al. (2011). The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC): Results from Phase I and Scientific Opportunities in Phase II. *Am. Heart J.* 162, 627–632. doi:10.1016/j.ahj.2011.07.002

Krueger, F., and Andrews, S. R. (2011). Bismark: a Flexible Aligner and Methylation Caller for Bisulfite-Seq Applications. *Bioinformatics* 27, 1571–1572. doi:10.1093/bioinformatics/btr167

Leek, J. T., and Storey, J. D. (2007). Capturing Heterogeneity in Gene Expression Studies by Surrogate Variable Analysis. *PLOS Genet.* 3, e161. doi:10.1371/journal.pgen.0030161

Li, J.-P., Yang, C.-Y., Chuang, H.-C., Lan, J.-L., Chen, D.-Y., Chen, Y.-M., et al. (2014). The Phosphatase JKAP/DUSP22 Inhibits T-Cell Receptor Signalling and Autoimmunity by Inactivating Lck. *Nat. Commun.* 5, 3618. doi:10.1038/ncomms4618

Liu, T., Xie, M., Lv, Q., Li, Y., Fang, L., Zhang, L., et al. (2019). Bicuspid Aortic Valve: An Update in Morphology, Genetics, Biomarker, Complications, Imaging Diagnosis and Treatment. *Front. Physiol.* 9, 1921. doi:10.3389/fphys.2018.01921

MIBAVA Leducq ConsortiumLuyckx, I., Kumar, A. A., Kumar, A. A., Reyniers, E., Dekeyser, E., Vanderstraeten, K., et al. (2019). Copy Number Variation Analysis in Bicuspid Aortic Valve-Related Aortopathy Identifies TBX20 as a Contributing Gene. *Eur. J. Hum. Genet.* 27, 1033–1043. doi:10.1038/s41431-019-0364-y

Mavinkurve, M., and O'Gorman, C. S. (2015). Cardiometabolic and Vascular Risks in Young and Adolescent Girls with Turner Syndrome. *BBA Clin.* 3, 304–309. doi:10.1016/j.bbacli.2015.04.005

McGregor, K., Bernatsky, S., Colmegna, I., Hudson, M., Pastinen, T., Labbe, A., et al. (2016). An Evaluation of Methods Correcting for Cell-type Heterogeneity in DNA Methylation Studies. *Genome Biol.* 17, 84. doi:10.1186/s13059-016-0935-y

McKellar, S. H., Tester, D. J., Yagubyan, M., Majumdar, R., Ackerman, M. J., and Sundt, T. M. (2007). Novel NOTCH1 Mutations in Patients with Bicuspid Aortic Valve Disease and Thoracic Aortic Aneurysms. *J. Thorac. Cardiovasc. Surg.* 134, 290–296. doi:10.1016/j.jtcvs.2007.02.041

Miller, M. J., Geffner, M. E., Lippe, B. M., Itami, R. M., Kaplan, S. A., DiSessa, T. G., et al. (1983). Echocardiography Reveals a High Incidence of Bicuspid Aortic Valve in Turner Syndrome. *J. Pediatr.* 102, 47–50. doi:10.1016/s0022-3476(83)80284-4

Miyano, R., Matsumoto, T., Takatsu, H., Nakayama, K., and Shin, H.-W. (2016). Alteration of Transbilayer Phospholipid Compositions Is Involved in Cell Adhesion, Cell Spreading, and Focal Adhesion Formation. *FEBS Lett.* 590, 2138–2145. doi:10.1002/1873-3468.12247

Mortensen, K. H., Andersen, N. H., and Gravholt, C. H. (2012). Cardiovascular Phenotype in Turner Syndrome-Integrating Cardiology, Genetics, and Endocrinology. *Endocr. Rev.* 33, 677–714. doi:10.1210/er.2011-1059

Orjuela, S., Machlab, D., Menigatti, M., Marra, G., and Robinson, M. D. (2020). DAMEfinder: a Method to Detect Differential Allele-specific Methylation. *Epigenetics & Chromatin* 13, 25. doi:10.1186/s13072-020-00346-8

Pan, S., Lai, H., Shen, Y., Breeze, C., Beck, S., Hong, T., et al. (2017). DNA Methylome Analysis Reveals Distinct Epigenetic Patterns of Ascending Aortic Dissection and Bicuspid Aortic Valve. *Cardiovasc. Res.* 113, 692–704. doi:10.1093/cvr/cvx050

Parker, L. E., and Landstrom, A. P. (2021). Genetic Etiology of Left-Sided Obstructive Heart Lesions: A Story in Development. *J. Am. Heart Assoc.* 10, e019006. doi:10.1161/JAHA.120.019006

Pedersen, B. S., Schwartz, D. A., Yang, I. V., and Kechris, K. J. (2012). Comb-p: Software for Combining, Analyzing, Grouping and Correcting Spatially Correlated P-Values. *Bioinformatics* 28, 2986–2988. doi:10.1093/bioinformatics/bts545

Pfaffle, R., Blankenstin, O., Wüller, S., and Kentrup, H. (1999). Combined Pituirary Hormone Deficency: Role of Pit-1 and Prop-1. *Acta Paediatr.* 88, 33–41. doi:10.1111/j.1651-2227.1999.tb14401.x

Prakash, S. K., Bondy, C. A., Maslen, C. L., Silberbach, M., Lin, A. E., Perrone, L., et al. (2016). Autosomal and X Chromosome Structural Variants Are Associated with Congenital Heart Defects in Turner Syndrome: The NHLBI GenTAC Registry. *Am. J. Med. Genet.* 170, 3157–3164. doi:10.1002/ajmg.a.37953

Pulignani, S., Borghini, A., and Andreassi, M. G. (2019). microRNAs in Bicuspid Aortic Valve Associated Aortopathy: Recent Advances and Future Perspectives. *J. Cardiol.* 74, 297–303. doi:10.1016/j.jjcc.2019.03.005

Qu, X.-K., Qiu, X.-B., Yuan, F., Wang, J., Zhao, C.-M., Liu, X.-Y., et al. (2014). A Novel NKX2.5 Loss-Of-Function Mutation Associated with Congenital Bicuspid Aortic Valve. *Am. J. Cardiol.* 114, 1891–1895. doi:10.1016/j.amjcard.2014.09.028

Ritchie, M. E., Phipson, B., Wu, D., Hu, Y., Law, C. W., Shi, W., et al. (2015). Limma powers Differential Expression Analyses for RNA-Sequencing and Microarray Studies. *Nucleic Acids Res.* 43, e47. doi:10.1093/nar/gkv007

Ross, J. L., Feuillan, P., Long, L. M., Kowal, K., Kushner, H., and Cutler, G. B. (1995). Lipid Abnormalities in Turner Syndrome. *J. Pediatr.* 126, 242–245. doi:10.1016/s0022-3476(95)70551-1

Rossetti, L. Z., Glinton, K., Yuan, B., Liu, P., Pillai, N., Mizerik, E., et al. (2019). Review of the Phenotypic Spectrum Associated with Haploinsufficiency of *MYRF*. *Am. J. Med. Genet. A. ajmg.a.* 6118.

Roux, M., and Zaffran, S. (2016). Hox Genes in Cardiovascular Development and Diseases. *J. Dev. Biol.* 4. doi:10.3390/jdb4020014

Schulte, D., and Geerts, D. (2019). MEIS Transcription Factors in Development and Disease. *Development* 146, dev174706. doi:10.1242/dev.174706

Segawa, K., Kurata, S., and Nagata, S. (2016). Human Type IV P-type ATPases that Work as Plasma Membrane Phospholipid Flippases and Their Regulation by Caspase and Calcium. *J. Biol. Chem.* 291, 762–772. doi:10.1074/jbc.m115.690727

Sequeira Gross, T., Naito, S., Neumann, N., Petersen, J., Kuntze, T., Reichenspurner, H., et al. (2018). Does Statin Therapy Impact the Proximal Aortopathy in Aortic Valve Disease? *QJM Int. J. Med.* 111, 623–628. doi:10.1093/qjmed/hcy129

Shankar, R. K., and Backeljauw, P. F. (2018). Current Best Practice in the Management of Turner Syndrome. *Ther. Adv. Endocrinol.* 9, 33–40. doi:10.1177/2042018817746291

Sharma, A., Jamil, M. A., Nuesgen, N., Schreiner, F., Priebe, L., Hoffmann, P., et al. (2015). DNA Methylation Signature in Peripheral Blood Reveals Distinct Characteristics of Human X Chromosome Numerical Aberrations. *Clin. Epigenet* 7, 76. doi:10.1186/s13148-015-0112-2

Sheffield, N. C., and Bock, C. (2016). LOLA: Enrichment Analysis for Genomic Region Sets and Regulatory Elements in R and Bioconductor. *Bioinformatics* 32 (4). doi:10.1093/bioinformatics/btv612

Sheffield, N. C., Thurman, R. E., Song, L., Safi, A., Stamatoyannopoulos, J. A., Lenhard, B., et al. (2013). Patterns of Regulatory Activity Across Diverse Human Cell Types Predict Tissue Identity, Transcription Factor Binding, and Long-Range Interactions. *Genome Res.* 23, 777–788.

Shi, L.-M., Tao, J.-W., Qiu, X.-B., Wang, J., Yuan, F., Xu, L., et al. (2014). GATA5 Loss-Of-Function Mutations Associated with Congenital Bicuspid Aortic Valve. *Int. J. Mol. Med.* 33, 1219–1226. doi:10.3892/ijmm.2014.1700

Silberbach, M. (2009). Bicuspid Aortic Valve and Thoracic Aortic Aneurysm: Toward a Unified Theory**Editorials Published in the Journal of the American College of Cardiology reflect the Views of the Authors and Do Not Necessarily Represent the Views of JACCor the American College of Cardiology. *J. Am. Coll. Cardiol.* 53, 2296–2297. doi:10.1016/j.jacc.2009.03.028

Simpson, C. M., Penny, D. J., and Stocker, C. F. (2006). Urotensin II Is Raised in Children with Congenital Heart Disease. *Heart* 92, 983–984. doi:10.1136/hrt.2005.074039

Skakkebæk, A., Nielsen, M. M., Trolle, C., Vang, S., Hornshøj, H., Hedegaard, J., et al. (2018). DNA Hypermethylation and Differential Gene Expression Associated with Klinefelter Syndrome. *Sci. Rep.* 8, 13740. doi:10.1038/s41598-018-31780-0

Stankunas, K., Shang, C., Twu, K. Y., Kao, S.-C., Jenkins, N. A., Copeland, N. G., et al. (2008). Pbx/Meis Deficiencies Demonstrate Multigenetic Origins of Congenital Heart Disease. *Circ. Res.* 103, 702–709. doi:10.1161/circresaha.108.175489

Surerus, E., Huggon, I. C., and Allan, L. D. (2003). Turner's Syndrome in Fetal Life. *Ultrasound Obstet. Gynecol.* 22, 264–267. doi:10.1002/uog.151

Szklarczyk, D., Gable, A. L., Lyon, D., Junge, A., Wyder, S., Huerta-Cepas, J., et al. (2019). STRING V11: Protein-Protein Association Networks with Increased Coverage, Supporting Functional Discovery in Genome-wide Experimental Datasets. *Nucleic Acids Res.* 47, D607–D613. doi:10.1093/nar/gky1131

Szumska, D., Wilson, R., Weninger, W., and Mohun, T. (2019). "Deciphering the Mechanisms of Developmental Heart Disease: Research from Embryonic Knockout Mice," in *Fetal Therapy*. Editors M. D. Kilby, A. Johnson, and D. Oepkes (Cambridge, England: Cambridge University Press), 133–145. doi:10.1017/9781108564434.015

Takatsu, H., Tanaka, G., Segawa, K., Suzuki, J., Nagata, S., Nakayama, K., et al. (2014). Phospholipid Flippase Activities and Substrate Specificities of Human Type IV P-type ATPases Localized to the Plasma Membrane. *J. Biol. Chem.* 289, 33543–33556. doi:10.1074/jbc.m114.593012

Takeda, N., Morita, H., Fujita, D., Inuzuka, R., Taniguchi, Y., Nawata, K., et al. (2015). A Deleterious MYH11 Mutation Causing Familial Thoracic Aortic Dissection. *Hum. Genome*2, 15028. doi:10.1038/hgv.2015.28

Taylor, A. P., Yadlapati, A., Andrei, A.-C., Li, Z., Clennon, C., McCarthy, P. M., et al. (2016). Statin Use and Aneurysm Risk in Patients with Bicuspid Aortic Valve Disease. *Clin. Cardiol.* 39, 41–47. doi:10.1002/clc.22492

The ENCODE Project ConsortiumSnyder, M. P., Snyder, M. P., Gingeras, T. R., Moore, J. E., Weng, Z., et al. (2020). Perspectives on ENCODE. *Nature* 583, 693–698. doi:10.1038/s41586-020-2449-8

Thorsson, T., Russell, W. W., El-Kashlan, N., Soemedi, R., Levine, J., Geisler, S. B., et al. (2015). Chromosomal Imbalances in Patients with Congenital Cardiac Defects: A Meta-Analysis Reveals Novel Potential Critical Regions Involved in Heart Development. *Congenit. Heart Dis.* 10, 193–208. doi:10.1111/chd.12179

Trolle, C., Nielsen, M. M., Skakkebæk, A., Lamy, P., Vang, S., Hedegaard, J., et al. (2016). Widespread DNA Hypomethylation and Differential Gene Expression in Turner Syndrome. *Sci. Rep.* 6, 34220. doi:10.1038/srep34220

Urbach, A., and Benvenisty, N. (2009). Studying Early Lethality of 45,XO (Turner's Syndrome) Embryos Using Human Embryonic Stem Cells. *PLoS ONE* 4, e4175. doi:10.1371/journal.pone.0004175

Wagih, O. (2017). Ggseqlogo: A "Ggplot2" Extension for Drawing Publication-Ready Sequence Logos. *Bioinformatics* 33, 3645–3647.

Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag.

Zaidi, S., Choi, M., Wakimoto, H., Ma, L., Jiang, J., Overton, J. D., et al. (2013). De Novo mutations in Histone-Modifying Genes in Congenital Heart Disease. *Nature* 498, 220–223. doi:10.1038/nature12141

Zhang, X., Hong, D., Ma, S., Ward, T., Ho, M., Pattni, R., et al. (2020). Integrated Functional Genomic Analyses of Klinefelter and Turner Syndromes Reveal Global Network Effects of Altered X Chromosome Dosage. *Proc. Natl. Acad. Sci. U.S.A.* 117, 4864–4873. doi:10.1073/pnas.1910003117

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

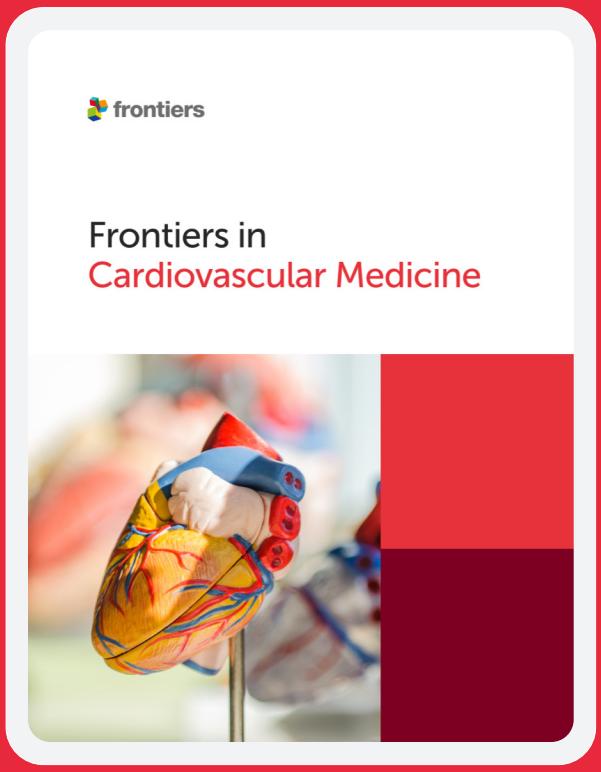
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact