Current Cardiology Reports (2022) 24:1021–1030
https://doi.org/10.1007/s11886-022-01716-2

CONGENITAL HEART DISEASE(RA KRASUSKI AND G FLEMING, SECTION EDITORS)

Bicuspid Aortic Valves: an Up-to-Date Review on Genetics, Natural History, and Management

Eman R. Rashed[1] · Alexandra Dembar[2] · Maria Riasat[3] · Ali N. Zaidi[4]

Accepted: 10 May 2022 / Published online: 22 July 2022

Abstract

Purpose of Review Bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality. It has a wide spectrum of clinical manifestations including aortic regurgitation (AR), aortic stenosis, and an associated aortopathy with a small but increased risk of aortic dissection. This review describes current knowledge of BAV, from anatomy and genetics to a discussion of multifaceted strategies utilized in the management of this unique patient population. This review will also highlight critical knowledge gaps in areas of basic and clinical research to enhance further understanding of this clinical entity.

Recent Findings The current knowledge regarding pathophysiologic mechanisms, screening, and surveillance guidelines for BAV and the associated aortopathy is discussed. We also discuss current management techniques for aortic valve repair versus replacement, indications for aortic surgery (root or ascending aorta), and the emergence of the Ross procedure as a viable management option not only in children, but also in adolescents and adults.

Summary The varied clinical phenotype of the BAV, resulting in its specific complex hemodynamic interactions, renders it an entity which is separate and distinct from the tricuspid aortic valve pathologies. While various aortic histopathologic and protein alterations in BAV patients have been described, it remains unclear if these changes are causal or the result of hemodynamic alterations imposed by sheer stress on the intrinsically dysfunctional BAV. Medical management for patients with BAV with AS, AI, or dilated aortic roots/ascending aortas remains challenging and needs further investigation. More than 50% of patients with BAV will undergo AVR during their lifetime, and more than 25% of patients with BAV undergo aortic surgery performed for dilation of the aortic root or ascending aorta, often concurrently with AVR. The search for the ultimate genetic or epigenetic cause of the different bicuspid phenotypes will ultimately be facilitated by the next-generation sequencing tools that allow for study of large populations at low cost. Improvements in diagnostic and stratification criteria to accurately risk assess BAV patients are critical to this process.

Keywords Bicuspid aortic valve · Ross procedure · Aortopathy · Aneurysm · Genetics

Introduction

Bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality, with an estimated prevalence of 1–2% [1, 2•]. It is almost three times more common in men than women [3]. Its high burden of morbidity and mortality is derived not only from valve dysfunction (stenosis due to early calcification or aortic regurgitation) but also due to complications from an associated aortopathy. Though its clinical implications are profound, often the diagnosis of BAV is an incidental finding discovered during routine echocardiography. BAV may manifest with aortic regurgitation (AR) (13–30%), aortic stenosis (AS) (12–37%), and mixed valvular disease (both AS and AR), predisposing the patient to various clinical sequelae, such as dilatation of the aorta

This article is part of the Topical Collection on *Congenital Heart Disease*

✉ Ali N. Zaidi
ali.zaidi@mountsinai.org

[1] Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2] Division of Medicine and Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[3] Division of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY, USA

[4] Mount Sinai Adult Congenital Heart Center, Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1030, New York, NY 10029, USA

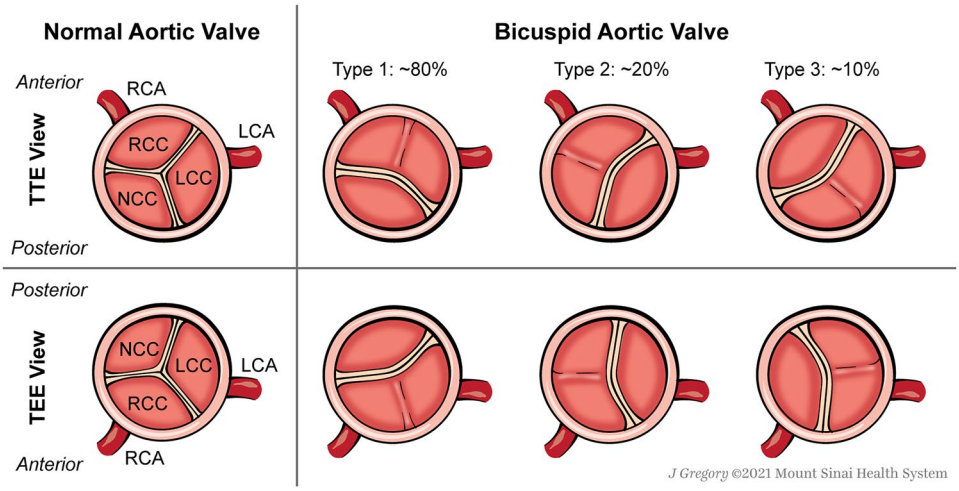

Fig. 1 Anatomical classification for bicuspid aortic valves. Abbreviations: RCC, right coronary cusp; LCC, left coronary cusp; NCC, noncoronary cusp; LCA, left coronary artery; RCA, right coronary artery

(20–50%) or infective endocarditis (2–5%) [4–6]. There also remains a small but significantly increased risk of aortic dissection [7]. Though most often occurring in isolation, BAV may occur in conjunction with other cardiovascular malformations (CVM), including coarctation of the aorta (50–80%), interruption of the aorta (36%), and atrial or ventricular septal defects (20%) [8]. The 25-year risk for BAV patients requiring aortic interventions is 25% and aortic valve replacement (AVR) is 53% [9]. The underlying mechanism as to why some BAV becomes stenotic or regurgitant, while others have mixed valvular disease, or aortic dilatation, while still others function normally throughout a lifetime, remains fundamentally uncertain and requires further investigation. Failure to recognize this clinical heterogeneity leads to an oversimplified approach to management. This review describes our current knowledge of BAV, the emerging multifaceted approach to the optimal management strategy, and more importantly, highlights areas where basic and clinical research is needed to better understand and care for this unique patient population.

Anatomy and Classification of BAV

The genetic basis of a BAV is poorly understood. Inadequate fibrillin-1 production during valvulogenesis [10•] is hypothesized to be the culprit for matrix alterations, which contributes to BAV-associated aortopathy, similar to that in Marfan syndrome (MFS) [11]. While the typical structure of a normal aortic valve encompasses three semilunar leaflets, the BAV is composed of two unequal cusps, and a central raphe [12]. The classification of Sievers and Schmidtke, based on autopsy reports of patients with diseased BAV, is commonly used (Fig. 1). The BAV is categorized as type 0 (without raphe), type 1 (1 raphe) which accounts for about 90% of the patients, and type 2 (2 raphes). There are subdivisions within each category of the spatial orientation of the cusps and commissures (anteroposterior versus lateral) and valvular function (graded as primarily regurgitation, stenosis, or a mixed presentation of regurgitation and stenosis, or a lack of stenosis or regurgitation) [13]. Type 1, which is right-left coronary cusp fusion, has 70–80% prevalence (Fig. 2), type 2 (right-noncoronary cusp fusion) has 20–30% prevalence, and type 3 (left-noncoronary cusp fusion) has 1% prevalence. On the basis of the raphe position with coronary sinuses, types 1 and 2 were classified as left (L), right (R), and none (N) types [12, 14]. The larger leaflet is referred to as the conjoined leaflet. Two commissures (or hinge points) are present; usually, neither is partially fused. It has been postulated that the anatomic morphology is a critical determinant of the pathology of the valve. Kang et al. showed that AS predominated in patients with type I BAV, while AR was more prevalent in type 2 or type 3 BAV [15]. Redundancy of a conjoined leaflet may lead to prolapse and insufficiency [16], while a partially fused commissure likely results in eventual valvular stenosis.

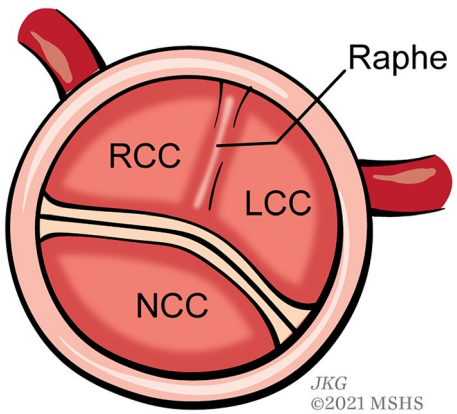

Fig. 2 Type 1 BAV with right-left coronary cusp fusion. Abbreviations: R, right coronary cusp; L, left coronary cusp; N, noncoronary cusp

Genetics

BAV exhibits autosomal dominant (AD) inheritance, with reduced penetrance and various levels of expressivity in syndromic and non-syndromic forms. Recent studies have identified several genetic mutations leading to the different valvular manifestations in BAV patients, though 5–10% of cases remain unexplained [17•]. Complex inheritance has been described in large families with non-syndromic BAV. The prevalence of BAV in first-degree family members is tenfold higher than the general population [18, 19]. Inheritance is observed in more than half of the families if associated nonvalvular complications such as coarctation of the aorta (CoA), thoracic aortic aneurysms (TAA), mitral valve, or ventricular septal defects (VSDs) are included [1]. The heritability of BAV has been cited as high as 90%, with multiple alleles interacting to cause BAV [20]. It is on this basis that echocardiographic screening of first-degree family members is recommended in current guidelines [21••]. NOTCH signaling pathways have been implicated in BAV formation and the presence of accelerated calcific valve disease, as well as the vascular complications. The NOTCH protein is expressed highly in the left ventricular outflow tract mesenchyme and the endocardium of the nascent aortic valve cusps, and is responsible for the development and acceleration of valvular calcium deposition. BAV and TAA are highly correlated with impairment of endothelial to mesenchymal transition during embryonic development in *NOTCH1*-deficient vascular cells. A homozygous *NOTCH1* mutation causes premature cellular death due to vascular endothelial defects [19], while a deregulation of the NOTCH signaling pathway [22] is involved in the development of vascular complications associated with BAV. *GATA5* is another protein involved in signaling which affects valve remodeling and extracellular matrix composition through dysregulation of molecules such as matrix metalloproteinases, and thus may also play a role in BAV-related aortopathy [12, 23].

The variability observed in BAV aortopathy, in terms of phenotype and natural history, is a combination of primary genetic defects, interactions of other modifier genes, epigenetic factors (DNA methylation or histone modifications, microRNA), and hemodynamic factors. Although BAV are mostly an isolated finding in adults, they can be found in conjunction with other congenital heart defects and genetic disorders with cardiovascular manifestations. It is most often associated with congenital left-sided obstructive lesions [24] (i.e., CoA or interruption of the aorta (IAA), Shone's complex), or atrial and ventricular septal defects. Turner's syndrome is a genetic syndrome with the highest prevalence of BAV, thought to be secondary to genetic alternation on the X chromosome, such as *KDM6A* and *TIMP1* (proteins which play a role in aortic integrity and in aortic valve development) [25]. Another clinical syndrome is Loeys-Dietz, of which 10% of patients will have BAV, which is found to be due to pathogenic mutations in *TGFBR1* or *TGFBR2*, which are also implicated in heritable non-syndromic TAA and aortic dissections [26]. Although there are several genes linked to BAV and BAV aortopathy, knowledge of this complex and heterogeneous disease continues to develop with ongoing investigation.

BAV Aortopathy: Anatomy and Pathogenesis

BAV-related aortopathy also has a varied and heterogeneous presentation. The dilatation may involve the ascending aorta (most commonly), but may also involve the aortic root or transverse aortic arch. There have been various classification systems proposed, but the simplest classification divides the spectrum into two classes [27•]: aortic root phenotype (area of dilation is located below the sinotubular junction [STJ]) and tubular aortopathy (area of dilation is located above the STJ). The tubular ascending aorta dilatation is the most common phenotype (60–70% of dilated aortas) and has the fastest growing rate in adults (≈ 0.4–0.6 mm/y) [28] (Fig. 3). The etiology and pathogenesis that lead to dilation of the ascending aorta in patients with a BAV remain a debatable topic. BAV-related aortopathy can be attributed to various factors such as intrinsic wall properties, hemodynamics, genetics, and established cardiovascular risk factors such as smoking and hypertension. Keane et al. demonstrated that younger BAV patients had larger aortic diameters when compared with sex-matched control patients with normal tricuspid aortic valves (TAV) with comparable degrees of regurgitation and stenosis. More severe aortic valvular regurgitation is associated with aortic dilatation in BAV patients, but intrinsic pathology appears to be a significant component contributing to aortic enlargement beyond isolated hemodynamic factors [29]. It has been shown that 50% of patients with BAV have aortas which exhibit premature cystic medial necrosis and decreased fibrillin content [30], with increased activity of matrix metalloproteinases, which leads to increased apoptosis and degradation of the aortic wall at a cellular level [31].

BAV patients with AS showed an increase in the prevalence of dilatation in the tubular ascending aorta, which may in part be related to dysfunctional flow secondary to the BAV structure [5, 32]. It has been shown that the distinctive morphology of the BAV results in excessive strain on the valvular leaflets during ventricular ejection, as well as an increased shear stress secondary to abnormal flow patterns, which may explain the rapid progression of valvular disease and aortopathy when compared to TAV [33,

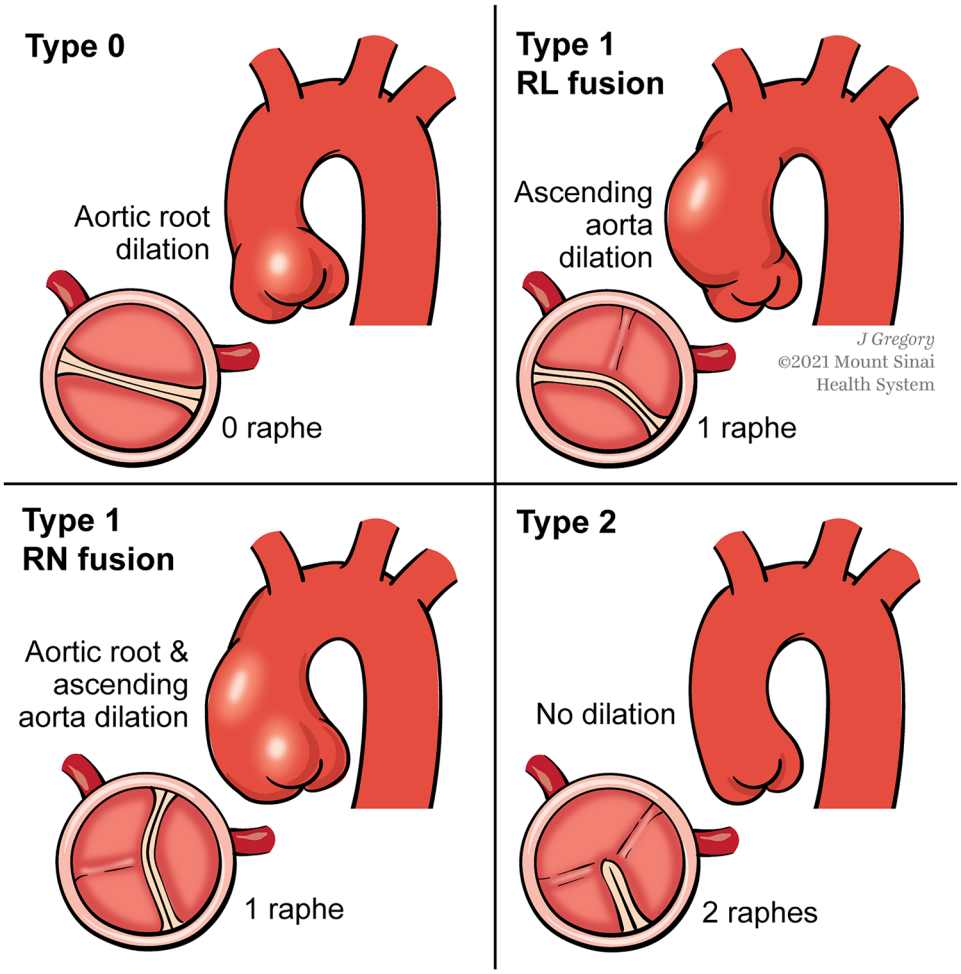

Fig. 3 Aortic root and ascending aorta dilation with bicuspid aortic valve. Abbreviations: RL, right coronary cusp-left coronary cusp; RN, right coronary cusp-noncoronary cusp

34]. BAV with right and noncoronary cusp fusion have been more commonly associated with dilation of the tubular ascending aorta. Specific risk factors including family history of aortic dissection, aortic growth rate > 0.5 cm per year, and CoA are associated with a greater risk of aortic dissection [6].

About 15% of patients with ascending aortic dilatation have a dilated aortic root characterized by dilated sinuses and annulus, often including the STJ, seen more commonly with BAV patients with aortic regurgitation. These patients present at a younger age with severe AR in the absence of calcific aortic valve disease. This phenotype has been more frequently associated in males with right-left cusp fusion [5, 35, 36]. It is postulated to result from a primary structural lesion of the aortic root and annulus, rather than the hemodynamic effects of altered flow patterns of the tubular ascending aorta. Retrospective studies of patients with a BAV have shown that the incidence of aortic dissection is very low and is estimated to be approximately 0.4% with routine surveillance of the aorta [37•].

Surveillance and Timing of Interventions for BAV and BAV-Related Aortopathy

Patients with BAV may develop isolated aortic valve disease, such as AR, AS, or a combination of AR and AS, while aortic aneurysms have been reported in 20 to 40% of patients with BAV. BAV aortopathy can occur independently of valve dysfunction and may consist of dilation of the aortic sinuses, the ascending aorta, or the aortic arch. Thus, patients with BAV require careful evaluation and follow-up of both the aortic valve and the aorta throughout their lifetimes [38]. Given the AD inheritance pattern, first-degree family members of patients with BAV are at a tenfold increased risk of having a BAV [39]; therefore, current guidelines provide a IIB recommendation to screen first-degree relatives of patients with BAV with an echocardiogram for the presence of BAV and for asymptomatic dilation of the aortic sinuses and ascending aorta [40••, 41••]. Once diagnosed, it is important to evaluate for the presence of coexistent findings such ASDs, VSDs,

or CoA. Once identified, echocardiographic monitoring of BAV function should adhere to current valvular and echocardiography appropriateness guidelines [42].

Once aortic root or ascending aorta dilatation is detected by echocardiography (i.e., ≥ 40 mm in diameter), lifelong serial evaluation of the aortic root and ascending aorta by echocardiography, CMR, or CTA is recommended. Aortic imaging is advised at least annually in patients with BAV with significant aortic dilation (> 4.5 cm) to determine the timing of surgical intervention. Patients with risk factors which increase the risk of aortic dissection, such as aortic growth rate > 0.5 cm per year, the presence of CoA, or a family history of dissection, should be imaged at shorter intervals. Those patients with BAV with stability of aortic size on sequential imaging studies and with a negative family history may undergo imagining follow-up at longer periods.

The most recent ACC/AHA guidelines [38] recommend an individualized approach to the timing of surgery for a dilated aorta in patients with BAV. Surgery is recommended in patients with a BAV regardless of symptoms with a diameter of the aortic sinuses or the ascending aorta of ≥ 5.5 cm. In patients with specific risk factors thought to confer an increased risk of aortic dissection, operative intervention to replace the aortic sinuses and/or the ascending aorta is reasonable when the aortic dimension is 5.0 to 5.5 cm, as long as the surgery is performed at a comprehensive valve center. In patients undergoing AVR because of severe AS or AR, replacement of the ascending aorta is reasonable when the aortic diameter is > 4.5 cm [38, 43]. Interventions on patients with BAV with AS or AI follow currently accepted valvular guidelines as outlined in the "Management of BAV" section [38].

Management of BAV

Medical management of BAV-related aortopathy remains limited. The use of β-blockers in slowing the progression of aortic dilatation by decreasing the load on the aortic wall through their negative inotropic and chronotropic effects has been studied in the Marfan population [44]; however, their use in BAV-associated aortopathy remains limited. Angiotensin II receptor blockers (ARB) are thought to be beneficial therapeutic agents by mitigating the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle. ARBs also cause inhibition of the TGF-β signaling pathway, which is responsible for increasing MMPs leading to apoptosis and consequently fibrosis [45••]. Thus, the development and progression of aortic dilatation can potentially be slowed by utilizing AT1 blocking agents such as losartan [46], though this requires further investigation. Given the likelihood of a coexisting aortopathy, patients with BAV must be counseled on tobacco cessation and aggressive treatment of hypertension [7]. Though the actual risk of dissection in BAV is not well documented, the 2021 ESC Guidelines suggest counseling against pregnancy in the setting of aortic diameters > 50 mm (> 27 mm^2 BSA) [47].

Infective endocarditis is the most common complication in this population, with incidence ranging from 10 to 30% [48]. BAV endocarditis patients have also shown to have a higher rate of peri-annular complications. The short-term mortality rate in patients with IE in BAV is lower than that in patients with IE in native TAV, likely due to the fact that they are younger at diagnosis than their TAV counterparts with less medical comorbidities [49]. Thus, it is imperative given this elevated risk they be counselled on meticulous dental hygiene.

More than 50% of patients with BAV undergo AVR during their lifetime, and more than 25% of patients with BAV undergo aortic surgery performed for dilation of the aortic root or ascending aorta, often concurrently with AVR [17]. Surgically excised aortic valves of 932 patients aged 26 to 91 years were examined post-operatively and 458 of them were found to be bicuspid [50]. Overall, it is shown that the BAV stenosis patient population undergoes surgery approximately 5–10 years earlier compared to TAV, despite fewer comorbidities due to their younger age. Traditionally, SAVR has been considered the first-line treatment for symptomatic patients with BAV and AS. Surgical repair of the aortic valve may also be feasible in selected patients, depending on valve and aortic root anatomy and tissue characteristics. Over the years, the Ross procedure has also emerged as a viable surgical alternative in patients with BAV in need of surgical aortic valve intervention.

Several studies have suggested that valve repair is a feasible option when performed by surgeons with training and experience in these techniques, and when performed at centers of excellence in aortic valve surgery [38]. Schneider et al. presented a large series of BAV repair with root remodeling over a 20-year period, where he showed that in 357 BAV patients, reoperation became necessary for recurrent AR in 24 patients and for recurrent AS in 6 patients, showing that cumulative incidence of reoperation at 15 years was 21.7%. In AVIATOR (Aortic Valve Repair International Registry), 177 patients underwent valve repair with remodeling and external aortic annuloplasty, of which 33.6% patients had a BAV. Freedom from reintervention in the BAV cohort was 100% at 10 years with the use of external annuloplasty. The only predictor of recurrent AR in this series was preoperative AR [51]. De Kerchove et al. reported that the valve-sparing root replacement with the reimplantation technique (as described in Harky et al. [52•]) has led to longevity of the BAV repair and freedom from > 2 + AR at 6-year postoperative [53]. A follow-up study showed that patients with

residual AR were more likely to have an asymmetric valve phenotype [54••]. Most recently, it was shown that in 1200 patients with BAV without severe aortic stenosis, valve preservation was successful in approximately 90% of patients, with valve calcification and endocarditis identified as the most frequent causes for repair failure [55, 56]. Overall, anatomic risk factors for surgical repair failure were the presence of symmetric prolapse (both cusps), annular dilatation, the use of pericardium as partial cusp replacement or augmentation, and the application of standard repair techniques in BAVs with a commissural angle of < 160° (this results in higher systolic gradients and impaired durability; optimum durability is seen with a commissural angle between 160° and 180°) [57]. Excellent repair durability and freedom from valve-related complications has been shown to be feasible if a tailored approach to the BAV repair is utilized, and all pathologic aspects of the BAV and the dilated root are addressed.

With a large body of literature demonstrating excellent short- and long-term outcome, the Ross procedure, which initially was considered only as an alternative option in patients for whom anticoagulation is not acceptable, is emerging as an excellent option in a wider array of patients. The Ross procedure may be a potential option for selected patients with BAV without annuloaortic ectasia requiring valve replacement. Guidelines have described the role of the Ross procedure as an option for younger patients with appropriate anatomy and tissue characteristics in whom anticoagulation is not tolerated or undesirable [58]. This surgical technique was originally described in 1967, and consists of replacing the aortic valve with the patient's own pulmonary root (autograft) and replacing the pulmonary root with a pulmonary homograft. It is a technically more complex operation requiring specific surgical expertise and understanding of the aortic root dynamic and functional anatomy. It does guarantee long-term viability of the aortic valve substitute with improved clinical outcomes; however, the Ross procedure should only be considered at centers of expertise and performed by experienced surgeons proficient in the procedure [59]. One of the frequently cited trepidations of the Ross procedure is the long-term function of the pulmonary homograft as well as premature autograft failure or dysfunction and the presence of AR. In a study conducted in Germany by Hanke et al., 1277 patients (mean age 42.2), of which 71% had BAV (with 188 with stenosis, 207 with regurgitation, and the remainder a mixed picture), underwent a Ross procedure (divided between sub-coronary technique and a root replacement technique). Patients with BAV, irrespective of the surgical technique, did not show any clinically relevant difference regarding early post-operative AR, nor its increase over time; but they did however demonstrate a higher degree of annulus and sinus dilation over time [60]. Starnes et al. conducted a retrospective cohort study between 1992 and 2019, where 129 adult patients with BAV underwent the Ross procedure with either a standard root inclusion technique or a modified technique where the pulmonary autograft was wrapped in a vascular conduit, and showed that the wrapped cohort had a lower need for autograft reintervention at 1-, 5-, and 10-year post-operation. A study by Poh et al., where 129 BAV patients with AR and a mean age of 34 years underwent the Ross procedure, demonstrated that freedom from reoperation for AVR and more-than-mild AR at 10- and 20-year post-surgery was 89% and 85% [61••]. Late survival at 10- and 20-year post-surgery was 99% and 95% (95% CI 85–99), respectively. Longer aortic cross-clamp and cardiopulmonary bypass times and a larger preoperative STJ diameter were significant predictors of redo AVR or for having significant AR at follow-up. Thus when performed by surgeons experienced in the Ross procedure and at centers of excellence in aortic valve surgery [38], the Ross procedure should be strongly considered in BAV patients with AR.

BAV has previously been considered an exclusion criterion for TAVR due to technical concerns about under deployment. The heavy calcification as well as the asymmetry of BAV leaflets may lead to inadequate expansion of the valve frame, which may negatively affect valve hemodynamics and long-term durability, leading to higher transvalvular gradients and paravalvular leak. Furthermore, the risk of aortic dissection or rupture during TAVR is increased in the presence of aortic disease. An analysis of over 40,000 TAVR procedures showed that TAVR was rarely performed in BAV patients with severe AS (they represented only 1% of all TAVR procedures undertaken in the USA as captured by the National Inpatient Sample from 2011 to 2014) [62]. But more and more, TAVR for BAV patients is considered a feasible alternative, with TAVR being successfully performed in many patients with BAV. Patients with BAV undergoing TAVR were younger with less comorbidities and fewer adverse clinical characteristics compared with older adults with TAV. Yoon et al. showed that BAV patients who underwent TAVR with newer generation devices compared with their tricuspid AS counterparts had comparable procedural results and similar cumulative all-cause mortality rates at 2 years. There were no cases of moderate-to-severe paravalvular regurgitation with newer generation devices, compared with 8.5% incidence of paravalvular regurgitation with the early-generation devices [63, 64]. Makkar et al. demonstrated that propensity matching between patients with BAV and those with TAV showed similar mortalities at 30 days and 1 year, similar valve gradients/areas, and incidences of paravalvular leak that were not significantly different. Stroke risk, however, was significantly higher for patients with BAV at 30 days (2.5% vs 1.6%) [65]. Fan et al. has also shown that BAV patients undergoing TAVR compared to their TAV counterparts were more likely to sustain embolic

phenomena, with risk factors being frequent deployment of self-expandable devices, longer procedure duration, and more frequent need for post-dilatation [65, 66]. Future trials are needed to help better understand optimal selection of BAV patients for TAVR, minimizing procedural risks and improving long-term outcomes.

Conclusion: Future Directions

The varied clinical phenotype coupled with complex hemodynamic interactions and underlying genetic make-up renders the patient with a BAV an entity completely separate than the TAV patient with valvular disease. The clinical significance of BAV phenotypes remains unknown between adults and children, with RCC-NCC phenotype being more prevalent in children (30–40%) [24] than in adults (≈20%) [67]. Patients with BAV may have a genetic predisposition for aortopathy but aneurysmal disease may also be seen in unaffected first-degree relatives [68]. It also remains unclear why a small number of BAV patients will suffer aortic dissection in their lifetime, while the majority of patients with BAV will not. Aortic dilation is not halted after AVR and thus the need for long-term surveillance continues [69]. The management of BAV in adults includes long-term surveillance, intervention for aortic valve disease, and aortopathy based on consensus guidelines. Counseling and management prior to and during pregnancy is also often needed. For patients with BAV and dilated aortic root or ascending aorta (without hypertension), there are no directed evidence-based pharmacologic therapies targeted to lessen aortic dilation or reduce the risk of aortic dissection or rupture. Finally, since the BAV patient is younger and with less comorbidities than an adult patient with TAV-related AR or AS [70], the approach to treatment should be expected to vary. The ideal aortic valve substitute for young adults with BAV requiring AVR remains elusive. Considerations for the safety, feasibility, and long-term outcomes utilizing techniques such as TAVR in patients with BAV await larger scale randomized controlled trials. When performed at valvular centers of excellence by experienced surgeons, the Ross procedure may constitute a viable available treatment option in young and middle-aged adults requiring AVR, especially those with BAV and AS or AR.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Paige SL, Lechich KM, Tierney ESS, Collins RT. Cardiac involvement in classical or hypermobile Ehlers–Danlos syndrome is uncommon. Genet Med. 2020.
2.• Ward C. Clinical significance of the bicuspid aortic valve. Heart. 2000;83. **Succinct review of the clinical significance of the bicuspid aortic valve - clinical presentation and associated complications.**
3. Kong WKF, Bax JJ, Michelena HI, Delgado V. Sex differences in bicuspid aortic valve disease. Prog Cardiovasc Dis. 2020;63.
4. Cecconi M, Nistri S, Quarti A, Manfrin M, Colonna PL, Molini E, Perna GP. Aortic dilatation in patients with bicuspid aortic valve. J Cardiovasc Med. 2006;7.
5. Della Corte A, Bancone C, Buonocore M, Dialetto G, Covino FE, Manduca S, Scognamiglio G, D'Oria V, De Feo M. Pattern of ascending aortic dimensions predicts the growth rate of the aorta in patients with bicuspid aortic valve. JACC Cardiovasc Imaging. 2013;6.
6. Masri A, Svensson LG, Griffin BP, Desai MY. Contemporary natural history of bicuspid aortic valve disease: a systematic review. Heart. 2017;103.
7. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. N Engl J Med. 2014;370.
8. Bayerová K, Dostálová G, Hlubocká Z, Paleček T, Hlubocký J, Kuchynka P, Karetová D, Linhart A. An unrecognized combined congenital heart defect – bicuspid aortic valve and ventricular septal defect as a cause of acute heart failure in adulthood. Cor Vasa. 2018;60.
9. Thanassoulis G, Yip JWL, Filion K, Jamorski M, Webb G, Siu SC, Therrien J. Retrospective study to identify predictors of the presence and rapid progression of aortic dilatation in patients with bicuspid aortic valves. Nat Clin Pract Cardiovasc Med. 2008;5.
10.• Fedak PWM, de Sa MPL, Verma S, Nili N, Kazemian P, Butany J, Strauss BH, Weisel RD, David TE, Yacoub MH, Sundt TM, Sellke FW, Pizarro C. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. J Thorac Cardiovasc Surg. 2003;126. **This paper outlines the molecular mechanisms behind vascular matrix remodelling which may contribute to aortic dilation in patients with a BAV**.
11. Sticchi E, de Cario R, Magi A, Giglio S, Provenzano A, Nistri S, Pepe G, Giusti B. Bicuspid Aortic Valve: role of multiple gene variants in influencing the clinical phenotype. Biomed Res Int. 2018.
12. Liu T, Xie M, Lv Q, Li Y, Fang L, Zhang L, Deng W, Wang J. Bicuspid aortic valve: an update in morphology, genetics, biomarker, complications, imaging diagnosis and treatment. Front Physiol. 2019;10.
13. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg. 2007;133.
14. Sievers HH, Stierle U, Mohamed SA, Hanke T, Richardt D, Schmidtke C, Charitos EI. Toward individualized management of the ascending aorta in bicuspid aortic valve surgery: the role of valve phenotype in 1362 patients. J Thorac Cardiovasc Surg. 2014;148.

15. Kang JW, Song HG, Yang DH, Baek S, Kim DH, Song JM, Kang DH, Lim TH, Song JK. Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction and bicuspid aortopathy: comprehensive evaluation using MDCT and echocardiography. JACC Cardiovasc Imaging. 2013;6.
16.•• Kim JS, Ko SM, Chee HK, Shin JK, Song MG, Shin HJ. Relationship between bicuspid aortic valve phenotype, valvular function, and ascending aortic dimensions. J Heart Valve Dis. 2014;23. **This paper highlights that BAV morphology is helpful for predicting the type of aortic valve dysfunction and the location of aortic dilatation**.
17.• Junco-Vicente A, del Río-García Á, Martín M, Rodríguez I. Update in biomolecular and genetic bases of bicuspid aortopathy. Int J Mol Sci. 2021;22. **This review is important because it focuses on the latest and outstanding developments on the molecular and genetic investigations of the bicuspid aortopathy.**
18. Tessler I, Albuisson J, Goudot G, Carmi S, Shpitzen S, Messas E, Gilon D, Durst R. Bicuspid aortic valve: genetic and clinical insights. AORTA. 2021;9.
19. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. J Am Coll Cardiol. 2004;44.
20. Bravo-Jaimes K, Prakash SK. Genetics in bicuspid aortic valve disease: where are we? Prog Cardiovasc Dis. 2020;63.
21.•• Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, Thompson A, Toly C. 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. Circulation. 2021. **Guidelines from the ACC/AHA: this is a landmark manuscript for valvular heart disease with a dedicated section on aortic valvular conditions including a bicuspid aortic valve**.
22. Balistreri CR, Crapanzano F, Schirone L, Allegra A, Pisano C, Ruvolo G, Forte M, Greco E, Cavarretta E, Marullo AGM, Sciarretta S, Frati G. Deregulation of Notch1 pathway and circulating endothelial progenitor cell (EPC) number in patients with bicuspid aortic valve with and without ascending aorta aneurysm. Sci Rep. 2018;8.
23. Padang R, Bagnall RD, Richmond DR, Bannon PG, Semsarian C. Rare non-synonymous variations in the transcriptional activation domains of GATA5 in bicuspid aortic valve disease. J Mol Cell Cardiol. 2012;53.
24. Fernandes SM, Sanders SP, Khairy P, Jenkins KJ, Gauvreau K, Lang P, Simonds H, Colan SD. Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol. 2004;44.
25. Corbitt H, Morris SA, Gravholt CH, Mortensen KH, Tippner-Hedges R, Silberbach M, Maslen CL. TIMP3 and TIMP1 are risk genes for bicuspid aortic valve and aortopathy in Turner syndrome. PLoS Genet. 2018;14.
26. Cedars A, Braverman AC. The many faces of bicuspid aortic valve disease. Prog Pediatr Cardiol. 2012;34.
27.• Della Corte A, Bancone C, Dialetto G, Covino FE, Manduca S, Montibello MV, De Feo M, Buonocore M, Nappi G. The ascending aorta with bicuspid aortic valve: a phenotypic classification with potential prognostic significance. Eur J Cardio-thoracic Surg. 2014;46. **Important paper which highlights that the phenotypic class of the aorta could be a factor to integrate in future risk stratification models for BAV aortopathy**.
28. 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.
29. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, John Sutton MG St. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. Circulation. 2000;102.
30. Niwa K, Perloff JK, Bhuta SM, Laks H, Drinkwater DC, Child JS, Miner PD. Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. Circulation. 2001;103.
31. Wilton E, Bland M, Thompson M, Jahangiri M. Work in progress report - valves: matrix metalloproteinase expression in the ascending aorta and aortic valve. Interact Cardiovasc Thorac Surg. 2008;7.
32. AC P. The bicuspid aortic valve syndrome: a multifaceted challenge: do we know enough? Open Access J Cardiol. 2018;2.
33. Katayama S, Umetani N, Hisada T, Sugiura S. Bicuspid aortic valves undergo excessive strain during opening: a simulation study. J Thorac Cardiovasc Surg. 2013;145.
34. Entezari P, Schnell S, Mahadevia R, Malaisrie C, McCarthy P, Mendelson M, Collins J, Carr JC, Markl M, Barker AJ. From unicuspid to quadricuspid: influence of aortic valve morphology on aortic three-dimensional hemodynamics. J Magn Reson Imaging. 2014;40.
35. Jassal DS, Bhagirath KM, Tam JW, Sochowski RA, Dumesnil JG, Giannoccaro PJ, Jue J, Pandey AS, Joyner CD, Teo KK, Chan KL. Association of bicuspid aortic valve morphology and aortic root dimensions: a substudy of the aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study. Echocardiography. 2010;27.
36. Girdauskas E, Rouman M, Disha K, Dubslaff G, Fey B, Theis B, Petersen I, Borger MA, Kodolitsch Y von, Kuntze T, Reichenspurner H. Aortopathy in bicuspid aortic valve stenosis with fusion of right-left versus right-non-coronary cusps: are these different diseases? J Heart Valve Dis. 2016;25.
37.• Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, Eidem B, Edwards WD, Sundt TM, Enriquez-Sarano M. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA - J Am Med Assoc. 2011;306. **This paper highlights the the incidence of aortic complications in patients with BAV in a community cohort and in the general population**.
38. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger E V., Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, Thompson A, Toly C. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2021.
39. Huntington K, Hunter AGW, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. J Am Coll Cardiol. 1997;30.
40.•• Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. J Am Coll Cardiol. 2010;2010:55. **Guideline document establishing clinical practice guidelines for patients with valvular heart disease including those with a bicuspid aortic valve**.
41.•• Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines. J Am Coll Cardiol. 2014;2014:63. **Guideline document from the AHA/ACC to establish clinical practice guidelines for patients with valvular heart disease, including those with a BAV**.

42.• Michelena HI, Prakash SK, Corte A Della, Bissell MM, Anavekar N, Mathieu P, Bosse Y, Limongelli G, Bossone E, Benson DW, Lancellotti P, Isselbacher EM, Enriquez-Sarano M, Sundt TM, Pibarot P, Evangelista A, Milewicz DM, Body SC. Bicuspid aortic valve identifying knowledge gaps and rising to the challenge from the international bicuspid aortic valve consortium (BAVCON). Circulation. 2014;129. **This review describes the current knowledge of BAV, but, more importantly, it highlights knowledge gaps and areas where basic and clinical research is still warranted**.

43. Serbia C, Germany SB, Germany JB, Germany LC, Freemantle N, Kingdom U, France MG, Ju P, France CT, Poland WW, Eacts ESC. OUP accepted manuscript. Eur Heart J. 2021:1–72.

44. Vaidyanathan B. Role of beta-blockers in Marfan's syndrome and bicuspid aortic valve: a time for re-appraisal. Ann Pediatr Cardiol. 2008;1.

45.•• Abdulkareem N, Smelt J, Jahangiri M. Bicuspid aortic valve aortopathy: genetics, pathophysiology and medical therapy. Interact Cardiovasc Thorac Surg. 2013;17. **This review highlights the mechanisms, pathophysiology, genetics and modern drug therapy in the context of BAV-associated aortopathy**.

46. Yang HHC, Kim JM, Chum E, Breemen C Van, Chung AWY. Effectiveness of combination of losartan potassium and doxycycline versus single-drug treatments in the secondary prevention of thoracic aortic aneurysm in Marfan syndrome. J Thorac Cardiovasc Surg. 2010;140.

47. Vahanian A, Beyersdorf F. ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardio-thoracic Surg. 2021;2021:60.

48. Kahveci G, Bayrak F, Pala S, Mutlu B. Impact of bicuspid aortic valve on complications and death in infective endocarditis of native aortic valves. Texas Hear Inst J. 2009;36.

49. Kiyota Y, Corte A Della, Vieira VM, Habchi K, Huang CC, Ratta EE Della, Sundt TM, Shekar P, Muehlschlegel JD, Body SC. Risk and outcomes of aortic valve endocarditis among patients with bicuspid and tricuspid aortic valves. Open Heart. 2017;4.

50. 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.

51. Lansac E, Centa I Di, Sleilaty G, Lejeune S, Berrebi A, Zacek P, Debauchez M. Remodeling root repair with an external aortic ring annuloplasty. J Thorac Cardiovasc Surg. 2017;153.

52.• Harky A, Antoniou A, Howard C, Rimmer L, Ahmad MU, Bashir M. Valve sparing aortic root surgery: from revolution to evolution? J Vis Surg. 2019;5. **A comprehensive systematic review outlining that Valve-sparing and composite root replacement remain feasible options for replacement of the aortic root**.

53. de Kerchove L, Boodhwani M, Glineur D, Vandyck M, Vanoverschelde JL, Noirhomme P, El Khoury G. Valve sparing-root replacement with the reimplantation technique to increase the durability of bicuspid aortic valve repair. J Thorac Cardiovasc Surg. 2011;142.

54.• de Kerchove L, Mastrobuoni S, Froede L, Tamer S, Boodhwani M, Van Dyck M, El Khoury G, Schäfers HJ. Variability of repairable bicuspid aortic valve phenotypes: towards an anatomical and repair-oriented classification. Eur J Cardio-thoracic Surg. 2019;56. **Findings from this study describe the main anatomical parameters of a bicuspid aortic valve (including commissure orientation, length of fusion and non-functional commissure height) and propose a new repair-oriented classification system based on those parameters that can be used to predict valve repair techniques.**

55. Svensson LG. The art of aortic valve repair. JTCVS Tech. 2021;7.

56. Schneider U, Schöpe J, Schäfers H-J. Advances in aortic valve repair, particularly bicuspid valves—reply. JAMA Cardiol. 2021;6.

57. Ehrlich T, de Kerchove L, Vojacek J, Boodhwani M, El-Hamamsy I, De Paulis R, Lansac E, Bavaria JE, El Khoury G, Schäfers HJ. State-of-the art bicuspid aortic valve repair in 2020. Prog Cardiovasc Dis. 2020;63.

58.• Svensson LG, Adams DH, Bonow RO, Kouchoukos NT, Miller DC, O'Gara PT, Shahian DM, Schaff HV, Akins CW, Bavaria JE, Blackstone EH, David TE, Desai ND, Dewey TM, D'Agostino RS, Gleason TG, Harrington KB, Kodali S, Kapadia S, Leon MB, Lima B, Lytle BW, MacK MJ, Reardon M, Reece TB, Reiss GR, Roselli EE, Smith CR, Thourani VH, Tuzcu EM, Webb J, Williams MR. Aortic valve and ascending aorta guidelines for management and quality measures. Ann Thorac Surg. 2013;95. **Important document outlining management of aortic valve and ascending aorta from the Society of Thoracic Surgeons (STS)**.

59. El-Hamamsy I, Bouhout I. The ross procedure: time for a hard look at current practices and a reexamination of the guidelines. Ann Transl Med. 2017;5.

60. Hanke T, Charitos EI, Stierle U, Robinson DR, Hemmer W, Moritz A, Lange R, Sievers HH. The Ross operation - a feasible and safe option in the setting of a bicuspid aortic valve? Eur J Cardio-thoracic Surg. 2010;38.

61.• Starnes VA, Elsayed RS, Cohen RG, Olds AP, Bojko MM, Mack WJ, Cutri RM, Baertsch HC, Baker CJ, Kumar SR, Bowdish ME. Long-term outcomes with the pulmonary autograft inclusion technique in adults with bicuspid aortic valves undergoing the Ross procedure. J Thorac Cardiovasc Surg. 2021. **Findings from this study suggest that in adults with bicuspid aortic valves, the Ross procedure with pulmonary autograft inclusion stabilizes the aortic root preventing dilatation and reduces the need for reoperation. The autograft inclusion technique allows the Ross procedure to be performed in this population with excellent long-term outcomes.**

62. Nagaraja V, Suh W, Fischman DL, Banning A, Martinez SC, Potts J, Kwok CS, Ratib K, Nolan J, Bagur R, Mamas MA. Transcatheter aortic valve replacement outcomes in bicuspid compared to trileaflet aortic valves. Cardiovasc Revascularization Med. 2019;20.

63. Yoon SH, Bleiziffer S, de Backer O, Delgado V, Arai T, Ziegelmueller J, Barbanti M, Sharma R, Perlman GY, Khalique OK, Holy EW, Saraf S, Deuschl F, Fujita B, Ruile P, Neumann FJ, Pache G, Takahashi M, Kaneko H, Schmidt T, Ohno Y, Schofer N, Kong WKF, Tay E, Sugiyama D, Kawamori H, Maeno Y, Abramowitz Y, Chakravarty T, Nakamura M, Kuwata S, Yong G, Kao HL, Lee M, Kim HS, Modine T, Wong SC, Bedgoni F, Testa L, Teiger E, Butter C, Ensminger SM, Schaefer U, Dvir D, Blanke P, Leipsic J, Nietlispach F, Abdel-Wahab M, Chevalier B, Tamburino C, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. J Am Coll Cardiol. 2017;69.

64. Barker CM, Reardon MJ. Bicuspid aortic valve stenosis: is there a role for tavr? JAMA - J Am Med Assoc. 2019;321.

65. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, Skipper ER, Thourani VH, Babaliaros V, Cheng W, Trento A, Vemulapalli S, Kapadia SR, Kodali S, MacK MJ, Tang GHL, Kaneko T. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. JAMA - J Am Med Assoc. 2019;321.

66. Fan J, Fang X, Liu C, Zhu G, Hou CR, Jiang J, Lin X, Wang L, He Y, Zhu Q, Ng S, Chen Z, Hu H, Liu X, Wang J, Leon MB. Brain injury after transcatheter replacement of bicuspid versus tricuspid aortic valves. J Am Coll Cardiol. 2020;76.

67. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, Pellikka PA, Tajik AJ, Enriquez-Sarano M. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation. 2008;117.
68. Loscalzo ML, Goh DLM, Loeys B, Kent KC, Spevak PJ, Dietz HC. Familial thoracic aortic dilation and bicommissural aortic valve: a prospective analysis of natural history and inheritance. Am J Med Genet Part A. 2007;143.
69. Yasuda H, Nakatani S, Stugaard M, Tsujita-Kuroda Y, Bando K, Kobayashi J, Yamagishi M, Kitakaze M, Kitamura S, Miyatake K. 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.
70. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol. 2012;60.