International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes

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REPORT

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International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes

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Abstract

This International Consensus Classification and Nomenclature for the congenital bicuspid aortic valve condition recognizes 3 types of bicuspid valves: 1. The fused type (right-left cusp fusion, right-non-coronary cusp fusion and left-non-coronary cusp fusion phenotypes); 2. The 2-sinus type (latero-lateral and antero-posterior phenotypes); and 3. The partial-fusion (forme fruste) type. The presence of raphe and the symmetry of the fused type phenotypes are critical aspects to describe. The International Consensus also recognizes 3 types of bicuspid valve-associated aortopathy: 1. The ascending phenotype; 2. The root phenotype; and 3. Extended phenotypes.

Keywords: Bicuspid aortic valve • Aortopathy • Nomenclature • Classification

INTENDED AUDIENCE AND PURPOSE

This international evidence-based nomenclature and classification consensus on the congenital bicuspid aortic valve (BAV) is intended to be universally used by clinicians (both paediatric and adult), echocardiography sonographers and physicians, cardiovascular advanced-imaging specialists, interventional cardiologists, cardiovascular surgeons, pathologists, geneticists and researchers encompassing these clinical and basic research areas. In addition, if and when new landmark research is available, this international consensus may be subject to change in accordance with evidence-based data.

GENERAL NOSOLOGY OF THE CONGENITAL BICUSPID AORTIC VALVE CONDITION

The congenital BAV condition is fundamentally a valvulo-aortopathy characterized by significant heterogeneity of its valvular and aortic phenotypic expressions, of its associated disorders, of its complications and its prognosis [1–5]. From the nosology perspective, and in order to reconcile this clinical and prognostic heterogeneity, the BAV condition is broadly categorized into 3 clinical-prognostic (Fig. 1) subgroups: (i) complex valvulo-aortopathy [5, 6], where concomitant or associated disorders may be clinically and prognostically worse than the BAV condition *per se* (i.e. Turner syndrome, Loeys-Dietz syndrome, Shone complex, severe aortic coarctation) and/or there is early/accelerated valve dysfunction and/or aortopathy, more commonly diagnosed earlier in the paediatric, adolescent and young adult population [7, 8]. This presentation frequently requires early surgical/invasive treatment and close surveillance. (ii) Typical valvulo-aortopathy [2, 6], the most common group, with progressive BAV dysfunction and/or aorta dilatation without major associated or concomitant disorders, more commonly diagnosed in the young adult and adult, requires long-term surveillance and usually necessitates subsequent surgical/invasive treatment. Patients with complex-presentation and those with typical-presentation valvulo-aortopathies are at risk of developing infective endocarditis and aortic dissection (Fig. 1), although aortic dissection is extremely rare in young children with BAV and rare in adults without aortic dilatation [2, 9]. Importantly, complex-presentation valvulo-aortopathies may also occur in adults and typical-presentation valvulo-aortopathies may occur in children. (iii) Undiagnosed or uncomplicated BAV, a subgroup [2], is a lifelong silent condition with mild or non-progressing valvulo-aortopathy that does not manifest clinically but may come to light at autopsy or incidentally by imaging (Fig. 1); therefore, it represents a retrospective definition, yet it requires surveillance if incidentally diagnosed. Some of these cases will never be diagnosed which hampers the assessment of the true incidence and prevalence of BAV complications due to a smaller denominator of diagnosed cases.

A critical difference between the typical and complex valvulo-aortopathies is the preserved long-term overall life expectancy, which is similar to that of the age- and sex-matched general population with typical valvulo-aortopathy [11], whereas life expectancy may be reduced in those with the complex

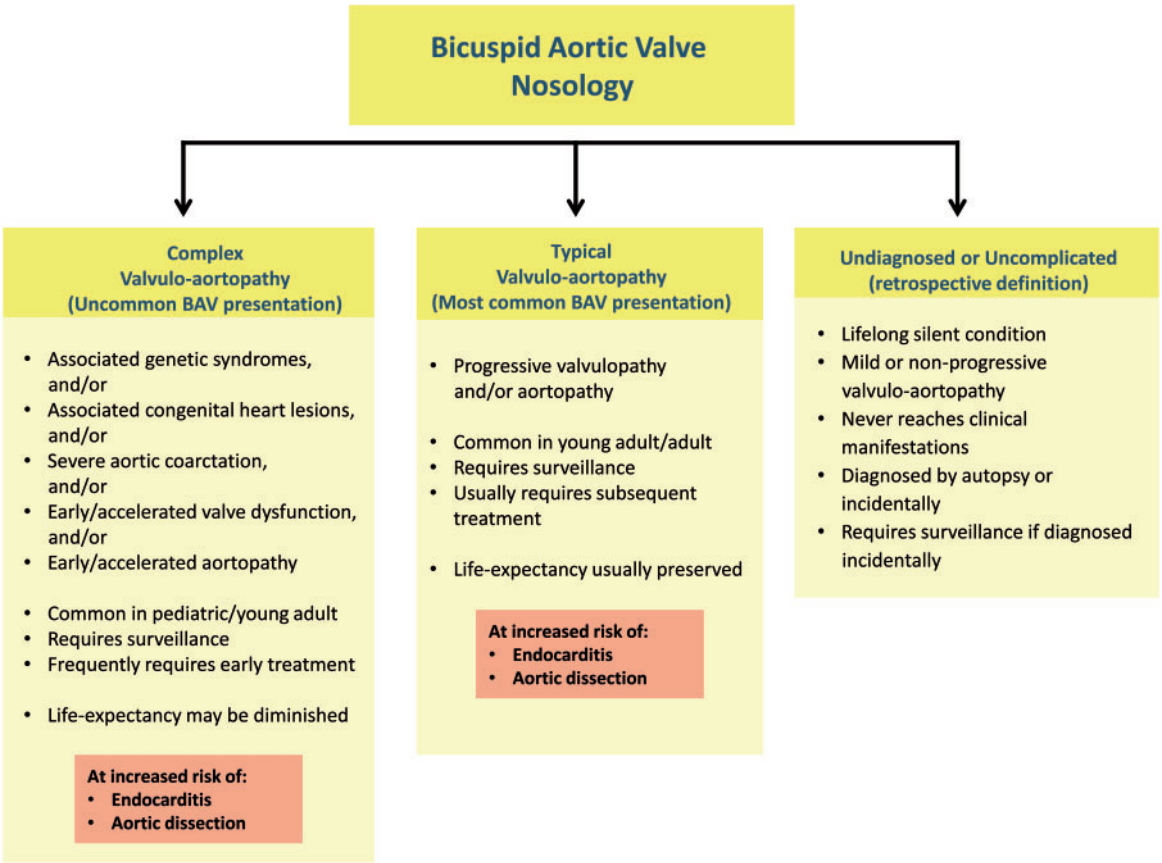


Figure 1: Nosology of the congenital BAV condition. (**Left**) Anatomically and prognostically complex presentations of the BAV valvulo-aortopathy are those associated with syndromes, left-sided obstructions, significant aortic coarctation, early/accelerated valve dysfunction (stenosis or regurgitation) and/or early aortopathy, manifested as thoracic aorta dilatation. These conditions are more commonly diagnosed in childhood, adolescence and young adulthood. (**Middle**) The anatomically and prognostically typical valvulo-aortopathy is usually diagnosed in young and middle-aged adults, although it may be diagnosed in children as well and comprises various degrees of progressive valvular dysfunction with a high cumulative incidence of aortopathy over the long run, manifested as thoracic aortic dilatation, without major associated conditions. Complex- and typical-presentation forms are susceptible to development of infective endocarditis and aortic dissection, although dissection is rare in the paediatric population and adults without aortic dilatation. (**Right**) The undiagnosed or uncomplicated form is rarely diagnosed in the patient's lifetime (without any BAV-related complications, some are diagnosed post-mortem) or is diagnosed during the patient's lifetime but does not cause complications requiring treatment. Therefore, it is a retrospective definition. Modified from Michelena *et al.* [10] with permission from Elsevier. BAV: bicuspid aortic valve.

valvulo-aortopathy. For example, long-term survival in patients with severe aortic coarctation requiring surgery is significantly inferior to that in the general population [12]. Similarly, long-term survival in patients with Turner syndrome is also significantly compromised compared to the general population [13].

FUNDAMENTALS OF IMAGING ASSESSMENT OF THE CONGENITAL BICUSPID AORTIC VALVE CONDITION

At the centre of the BAV condition is echocardiography, which serves as the first-line imaging modality in 6 major capacities [6]: (i) BAV diagnosis, (ii) valvular phenotyping, (iii) assessment of valvular function [6], (iv) measurement of the thoracic aorta (the expression of BAV aortopathy is dilatation of the thoracic aorta), (v) exclusion of aortic coarctation and other associated congenital lesions [2, 7] and (vi) assessment of uncommon but serious complications such as infective endocarditis [14] and aortic dissection [9]. Transthoracic echocardiography (TTE) is the first-line BAV diagnostic and phenotyping modality, the best modality for haemodynamic assessment of valvular dysfunction, and the initial modality for assessment of thoracic aorta size, presence of aortic coarctation and other congenital lesions. Transoesophageal echocardiography may aid in the diagnosis and phenotyping of BAV that is not well visualized by TTE, has excellent accuracy for the diagnosis of aortic dissection [15] and is mandatory in the assessment of infective endocarditis [16], whether it is native or prosthetic.

Also at the centre of the BAV condition are advanced imaging modalities: electrocardiographic (ECG)-gated cardiac computed tomography (CCT) and ECG-gated cardiac magnetic resonance (CMR). These imaging techniques improve diagnostic accuracy and phenotyping of BAV [17, 18] and represent the gold standard for measuring the thoracic aorta because they accurately assess aortic diameters that are truly perpendicular to the longitudinal axis of the aorta by use of the double-oblique technique. In addition, interval measurements can be performed at the same exact anatomical locations for comparison. After initial TTE imaging, if any aortic segment cannot be visualized or coarctation cannot be ruled out or any thoracic segment measures ≥45 mm by TTE, then ECG-gated computed tomography (CT) angiography or

magnetic resonance angiography is recommended [19], with magnetic resonance angiography preferred for younger patients (i.e. <50 years old) to avoid repeated radiation exposure at follow-up examinations. Further recommendations on echocardiographic and CCT/CMR assessment of congenital BAV and aortopathy have been recently published [6, 19], including echocardiographic assessment of BAV function [6].

SYNOPSIS OF THE CLINICAL HISTORY OF THE CONGENITAL BICUSPID AORTIC VALVE CONDITION

The most common complication of the BAV condition in adults is valve dysfunction that necessitates surgical aortic valve replacement (AVR) or repair, and it is strongly determined by the development of aortic stenosis (AS) [2, 20]. The community risk of AVR 25 years after BAV diagnosis is greater than 50% [2]. Surgical AVR is the gold standard for treating BAV-related AS. Nonetheless, with the latest generation of transcatheter aortic valve replacement (TAVR) devices, guided by careful preprocedural ECG-gated CCT analysis [21, 22], the technical success of TAVR has improved significantly, and TAVR may be an alternative to AVR for patients with BAV with AS and a high surgical risk (see Section Interventional cardiology considerations); indeed, up to 20% of patients ≥80 years old undergoing AVR have a congenital BAV [23]. Significant aortic regurgitation (AR) in BAV is considerably less common than AS (30% vs 70%) and is more frequent in men [3]. Surgical AVR remains the gold standard for treatment of BAV-related AR; nonetheless, surgical repair is an option, and echocardiography plays a critical role in determining reparability of the regurgitant BAV [6, 24], which is successful more frequently in BAV than in tricuspid aortic valves, with a low cumulative reoperation incidence of 20% at 15 years when combined with root remodelling [25].

The next most common complication of the BAV condition is aortopathy [19], which manifests clinically as dilatation of the thoracic aorta. The prevalence of any aortic dilatation in patients with BAV is reported to be from 40% to 70% depending on the population studied and the definition of dilatation [2]. The population incidence of aortic dilatation ≥45 mm is greater than 25% at 25 years of follow-up, with more than 20% undergoing surgery for aorta repair [9]. Coarctation of the aorta is present in 7–10% of adults with BAV [26], whereas BAV is present in 50–60% of patients with coarctation [27]. Concomitant coarctation is associated with a higher risk of aortic complications [27]. Mitral valve prolapse affects 2–3% of patients with BAV; this value is not different from that of the general population, but isolated anterior prolapse including 'giant' anterior leaflet prolapse is 2 times more frequent in patients with BAV and may hamper successful mitral repair [28]. The least frequent yet most deadly complications are infective endocarditis and aortic dissection. The incidence of BAV endocarditis [native and prosthetic (aortic position)] has been reported at 2% in most contemporary cohorts with BAV [2, 29]; the population incidence of approximately 14 cases per 10 000 patient-years is 11 times that of the general population [14]. Among patients with BAV, the overall community incidence of aortic dissection is approximately 3 cases per 10 000 patient-years, which is 8 times that of the general population, increasing to 0.5% in patients with aortic diameters ≥45 mm [9] but generally <1% [29].

WHY A STANDARD NOMENCLATURE AND CLASSIFICATION CONSENSUS FOR THE CONGENITAL BICUSPID AORTIC VALVE CONDITION?

Nomenclature refers to the choice of 'name' that is given to a particular structure, abnormality or phenotype, whereas classification refers to the process of 'arranging or categorizing' something according to shared features. The clinician evaluating the patient with BAV must be able to communicate in a common language all specific morphological, functional and prognostic aspects of the BAV condition to patients, other clinicians, surgeons, interventionalists and researchers [6, 10]. In addition, there are multiple gaps in the knowledge and understanding of the BAV condition [2]. In order to advance the clinical, biological and genetic understanding of the BAV condition, a common language must be articulated among researchers in all clinical and laboratory research disciplines. There are multiple nomenclatures and classifications for the BAV condition, and they are as heterogeneous or more so than the BAV condition itself (Table 1) [4, 30–38]. For example, the Sievers and Schmidtke [34] and Schaefer *et al.* [33] classifications use multiple numbers and letters for the BAV and aorta phenotypes, with Sievers including an incomplete definition of unicuspid aortic valves within the BAV classification (Table 2). Although the morphological spectrum of human congenital aortic valve abnormalities includes unicuspid, bicuspid and quadricuspid aortic valves, their genetic and embryological origin may not necessarily be closely linked [39, 40], and their prevalence, age at presentation, prognosis and associated conditions are not equivalent [6, 41, 42], with BAV being much more prevalent and heterogeneous. In addition, the surgical Sievers classification does not incorporate the evaluation of the symmetry of the BAV, a critical surgical-repair feature in current times [25, 43] (Table 2). Other BAV classifications are extremely succinct-dichotomous, as proposed by Sun *et al.* [36], or extremely complex as proposed by Kang *et al.* [30], with 5 numerical types of BAV phenotypes and 4 numerical types of aortic phenotypes (Table 1). Others have used a combination of previous classifications and added new observations: For example, Murphy *et al.* [38] proposed the clock-face orientation combined with the Sievers classification, adding partial cusp fusion and leaflet asymmetry by CMR (Table 1). Additionally, the use of one or another classification system for research varies by author and institution. A consistent description of the subtle variations in valve morphology, as well as newly developed *in vivo* metrics of haemodynamic changes associated with differing aortic valve morphologies, highlights the need for a universal, uniform classification scheme [44]. Finally, there are specific nomenclatures that lead to confusion such as the 'true' BAV: Does it mean that the others are not really BAV? And, as mentioned, Sievers' type 2 BAV is actually not bicuspid; it is unicuspid (Table 2). These numerous and heterogeneous classifications cause confusion in clinical practice, failure to identify phenotypes that may predict outcomes, inability to analyse clinical outcomes data in registries, systematic review and meta-analysis formats, failure to capture anatomical information critical for surgical aortic valve repair and TAVR and hamper identification of phenotypic-genetic associations. Herein, we present an imaging-based, descriptive, simple-but-comprehensive nomenclature and classification system that is based on the English language and not on numbers or letters and is based on important and available anatomical, clinical,

Table 1: Heterogeneous bicuspid aortic valve nomenclature

Author and year	Type of study	Number of patients	Nomenclature	Additional comments
Roberts [4] 1970	Pathology	85	Anterior–posterior cusps Right–left cusps Presence of raphe	Discussed differentiating congenital BAV versus acquired
Brandenburg *et al.* [37] 1983	Echocardiography	115	Clock-face nomenclature: Commissures at 4–10 o'clock with raphe at 2 o'clock (R-L) Commissures at 1–6 o'clock with raphe at 10 o'clock (RN) Commissures at 3–9 o'clock without raphe (L-N)	Noted different sizes of the resulting 2 functional cusps
Angelini *et al.* [31] 1989	Pathology	64	Anterior–posterior cusps Right–left cusps Presence of raphe	Noted presence of 2 (true BAV) versus 3 sinuses
Sabet *et al.* [32] 1999	Pathology	534	RL RN LN Presence of raphe	Noted symmetry of cusps: equal, unequal, thirds
Sievers and Schmidtke [34] 2007	Pathology	304	Type 0 (no raphe): anteroposterior or lateral cusps (true BAV) Type 1 (1 raphe): R-L, RN, L-N Type 2 (2 raphes): L-R, RN	Noted type 2 morphology associated with more aortic aneurysms
Schaefer *et al.* [33] 2008	Echocardiography	186	Type 1: RL Type 2: RN Type 3: LN Presence of raphe Aorta: Type N: normal shape Type E: sinus effacement Type A: ascending aorta dilatation	Noted type 1 BAV was associated with type N aorta with dilated root Noted type 2 BAV associated with type A aorta
Kang *et al.* [30] 2013	Computed tomography	167	Anteroposterior orientation: type 1: R-L with raphe type; 2: R-L without raphe Right–left orientation: Type 3: RN with raphe Type 4: L-N with raphe Type 5: symmetrical cusps with 1 coronary artery originating from each cusp Aorta: Type 0: normal Type 1: dilated root Type 2: dilated ascending aorta Type 3: diffuse involvement of the ascending aorta and arch	Noted AS and type 3 aorta more commonly in right–left orientation and AR and type N aorta more commonly in anteroposterior orientation
Michelena *et al.* [2] 2014	Echocardiography	Multiple studies	BAVCon nomenclature: Type 1: R-L Type 2: RN Type 3: L-N Presence of raphe	Noted symmetry of cusps and presence of 2 (true BAV) or 3 sinuses Noted predominant ascending aorta dilatation in all BAV and the existence of 'root phenotype'
Jilaihawi *et al.* [35] 2016	Computed tomography	130	Tricommissural: functional or acquired bicuspidity of a trileaflet valve Bicommissural with raphe Bicommissural without raphe	Noted no association between nomenclature and TAVR complications
Sun *et al.* [36] 2017	Echocardiography	681	Dichotomous nomenclature: R-L Mixed: (RN or L-N)	Noted mixed phenotype was associated with AS and surgery of the aorta Good interobserver variability of phenotypes
Murphy *et al.* [38] 2017	Cardiac magnetic resonance	386	Clock-face nomenclature: Type 0: partial fusion/eccentric leaflet? Type 1: RN, RL, LN partial fusion/eccentric leaflet? Type 2: RL and RN, RL and LN, RN and LN partial fusion/eccentric leaflet?	Noted partial fusion and/or eccentric leaflet

AR: aortic regurgitation; AS: aortic stenosis; BAV: bicuspid aortic valve; BAVCon: bicuspid aortic valve consortium; LN: left non-coronary fusion; RL: right–left fusion; RN: right non-coronary fusion; TAVR: transcatheter aortic valve replacement.

Table 2: Critical limitations of the Sievers classification compared to the new international consensus

Sievers and Schmidtke [34] type of limitation	Specific Sievers limitation	International consensus
Comprehension and retention	Not language-intuitive: Types: 0, 1 and 2	Language-intuitive: Types: fused, 2-sinus and partial fusion
Unable to define all BAV phenotypes	Type 0 does not differentiate between a fused BAV with no raphe and a 2-sinus BAV	Fused types may have raphe or not, 2-sinus types do not have raphe
Lack of prerepair symmetry assessment	Non-existent	Fused types require assessment of symmetry for surgical repair planning
Lack of recognition of BAV phenotypes	Does not recognize partial fusion (forme fruste), does not recognize fused BAV with no raphe	Recognizes partial fusion (forme fruste) Recognizes fused BAV with no raphe, which is different than 2-sinus BAV
Lack of recognition of aortopathy phenotypes	Non-existent	Aortic phenotypes: root, ascending and extended
Includes a non-BAV congenital aortic valve abnormality	Type 2 is not BAV, is unicuspid aortic valve, incompletely defined	Does not include unicuspid aortic valves
Evidence-based	Anatomical pathology only	Imaging, anatomical pathology, surgical-functional pathology, clinical-associations

BAV: bicuspid aortic valve.

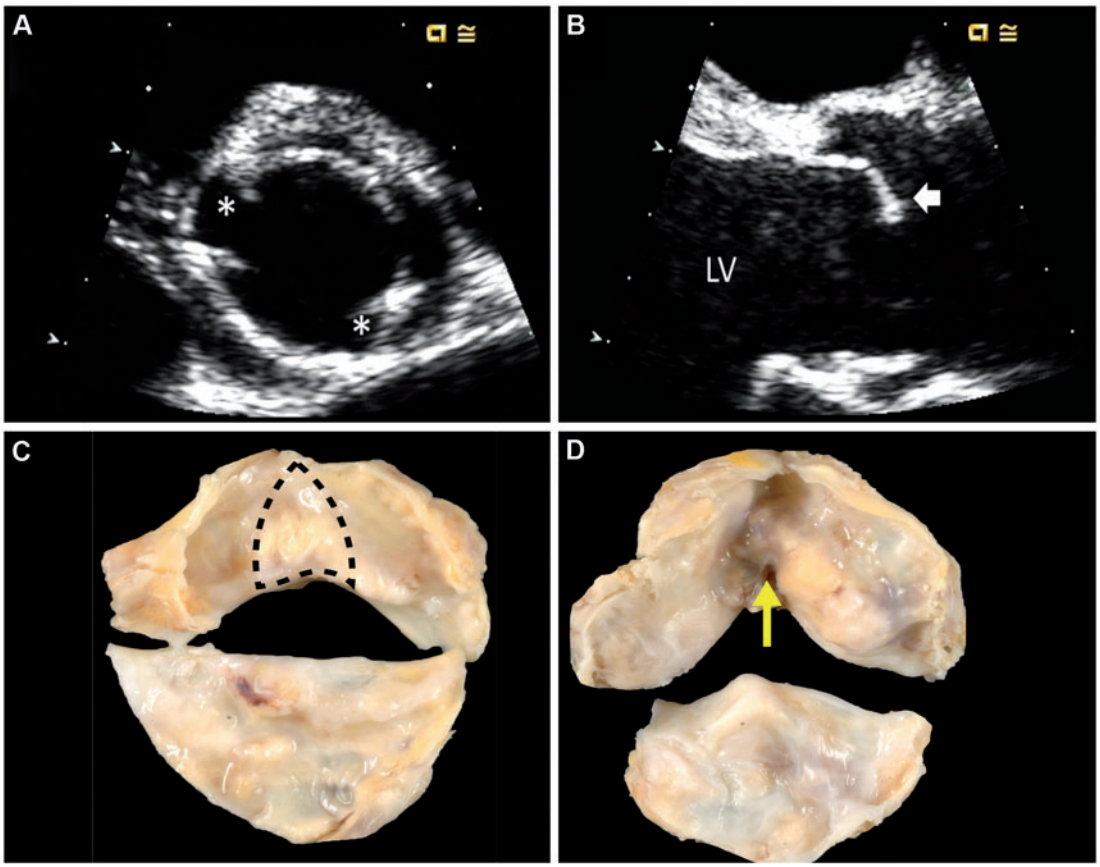
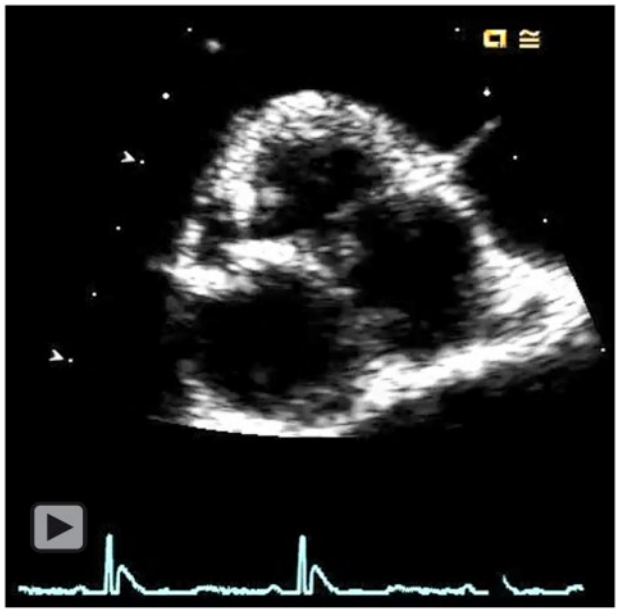


Figure 2: Diagnosis of congenital bicuspid aortic valve by transthoracic echocardiography and pathological manifestations. (**A**) Parasternal short-axis aortic valve systolic still image demonstrating the existence of only 2 commissures (asterisks) delimiting only 2 cusps (see Video 1). (**B**) Parasternal long-axis systolic still shows systolic doming of the fused (conjoined) cusp (arrow), common for right–left coronary cusp fusion (see Video 2). (**C**) Pathological congenital bicuspid aortic valve specimen shows the area of the raphe (dashed line) from the left ventricular perspective, forming an obtuse angle between the fused cusps. (**D**) Ventricular side of a tricuspid aortic valve with acquired rheumatic fusion shows the cleavage plane with acute angle (yellow arrow). LV: left ventricle.



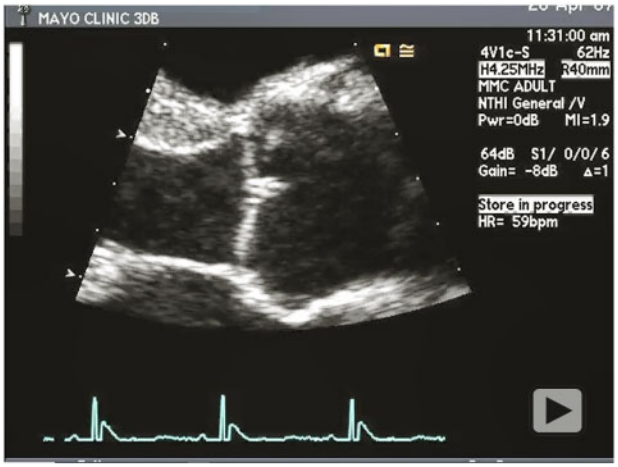
Video 1: Transthoracic echocardiography parasternal short axis of right–left cusp fusion with raphe.

surgical and pathological scientific data [10]. This new nomenclature/classification system represents the combined efforts of international BAV experts including clinicians (both adult and paediatric), surgeons, interventionalists, pathologists, geneticists and imagers (echocardiography, CT and magnetic resonance experts).

DEFINITION of CONGENITAL BICUSPID AORTIC VALVE AND AORTIC ROOT COMPLEX

Congenital bicuspid aortic valve

The aortic valve includes the cusps and the annulus. The congenital BAV is most commonly diagnosed by base-of-the-heart short-axis aortic valve imaging with TTE, ECG-gated CCT or CMR, demonstrating the existence of only 2 commissures delimiting only 2 valve cusps [2, 45] (Fig. 2; Video 1). On echocardiographic long-axis imaging, systolic doming of the conjoined cusp may be appreciated particularly for right–left coronary cusp fusion (Fig. 2; Video 2), but it is less reliable for other BAV phenotypes. The diagnosis can also be made by direct surgical observation [31, 43] and pathological examination [32]. It is important to recognize that a tricuspid aortic valve that is fibrotic and calcified or rheumatic may present a pattern of acquired (non-congenital) fusion of 2 cusps that may be difficult to differentiate from congenital BAV. In these cases, surgical inspection and/or pathological examination may identify whether the fusion is congenital or not. In the operating theatre, although it is not always possible, the surgeon can define the congenital bicuspid nature by observing the height of the 'pseudocommissure' (the attachment of the raphe at the aortic wall), which is lower within the root compared to the height of the true commissures, whose attachment is higher (Fig. 3). Additional gross features can be used on surgical or pathological inspection, such as the angle formed between the fused cusps (obtuse: congenital fusion; acute: acquired fusion) and the cleavage plane on the



Video 2: Transthoracic echocardiography parasternal long axis of right–left cusp fusion; note systolic conjoined cusp doming.

ventricular aspect of the fused cusps (absent: congenital; present: acquired) (Fig. 2). It is critical to utilize the information provided by the surgeon and especially by the pathologist [46] to determine the presence of a congenital BAV in cases of severely calcified AS.

Aortic root and root complex

Understanding the topographical anatomy of the proximal aorta is critical because it is an integral part of the aortic valve function, akin to the annulus and subvalvular apparatus for the mitral valve. Although 'ascending aorta' and 'aortic root' are sometimes used interchangeably to indicate the entire vascular segment from the aortic valve to the brachiocephalic artery take-off (beginning of the arch), the term aortic root refers only to the most proximal part of the ascending thoracic aorta, from the distal end of the left ventricular outflow tract to the sinotubular junction (STJ), formed by the sinuses of Valsalva and containing the aortic valve [47] (Fig. 3). The anatomy and physiology of the aortic root complex and its interaction with the valve have been thoroughly investigated as contemporary techniques for aortic valve repair have been introduced and more widely adopted [48, 49]. Functionally, and particularly in relation to the competency of the BAV and surgical repair of the regurgitant BAV, 3 elements form the aortic root complex and cooperate in determining physiological valve dynamics [50]: (i) the STJ, (ii) the aortic sinuses with the crown-like attachment line of the aortic valve cusps to the aortic wall at the aortic sinuses which, as mentioned, assumes a peculiar form in the fused BAV, with 1 of the 3 'crown tips' corresponding to the under-the-raphe pseudocommissure, reaching a lower height than the other 2, i.e. not reaching the STJ (Fig. 3) and (iii) the aortic annulus, which is a virtual circular line inside the left ventricular outflow tract, running through the nadir of the aortic cusps and the respective bases of the inter-cusp triangles (Fig. 3). The aortic annulus is a virtual surrogate for the ventriculo-aortic junction, which is the real boundary of the aortic root complex identified anatomically as the transition from the ventricular muscle to the aortic media. It is located circumferentially slightly above the nadir of the aortic cusps, crossing the semilunar lines of each cusp's attachment (Fig. 3). In both surgery and imaging, however, the surrogate of the ventriculo-aortic junction (aortic annulus) is the practical and clinically used

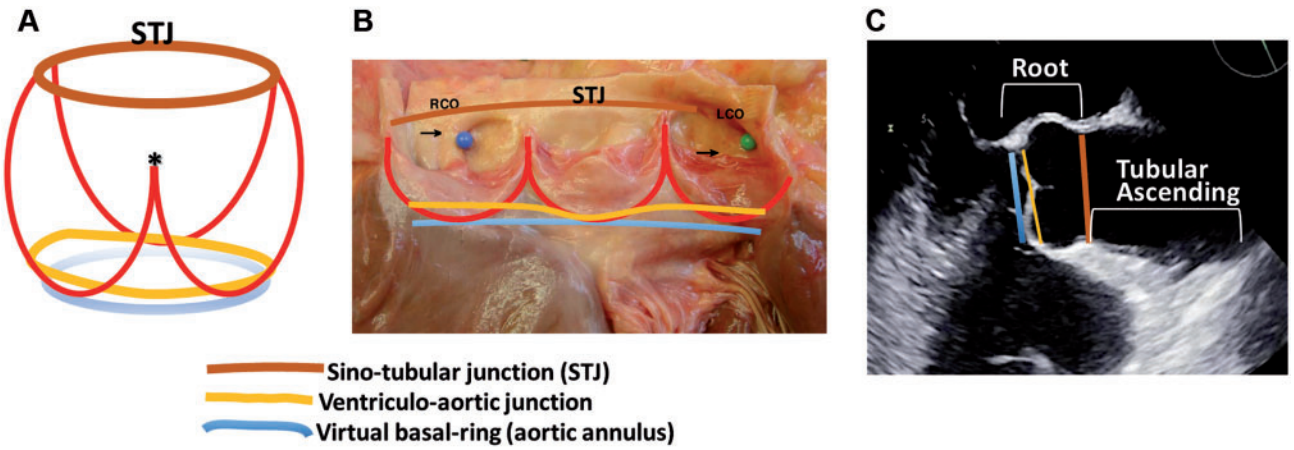


Figure 3: The aortic root complex. (**A**) Schematic drawing of the aortic root: The blue line indicates the virtual basal ring (aortic annulus); the yellow line depicts the ventriculo-aortic junction (whose non-planar nature is emphasized schematically) [48]; the red lines show the crown-shaped attachments of the cusps to the wall of the aortic sinuses [note the different height of the underdeveloped commissure (asterisk) under the raphe compared to the other 2 true commissures]; and the brown line depicts the STJ. (**B**) All the above boundaries and structures are shown (same colours as above) in an anatomical specimen of a normal aortic root and tricuspid aortic valve. (**C**) Echocardiographic view of the aortic root: the levels of the aortic annulus, ventriculo-aortic junction and STJ are shown (same colours as above). It is important to recognize that it is the measurement of the virtual annulus, sinuses and STJ that have clinical and practical implications for the patient with BAV. LCO: left coronary orifice (green pin and arrow); RCO: right coronary orifice (blue pin and arrow); STJ: sinotubular junction.

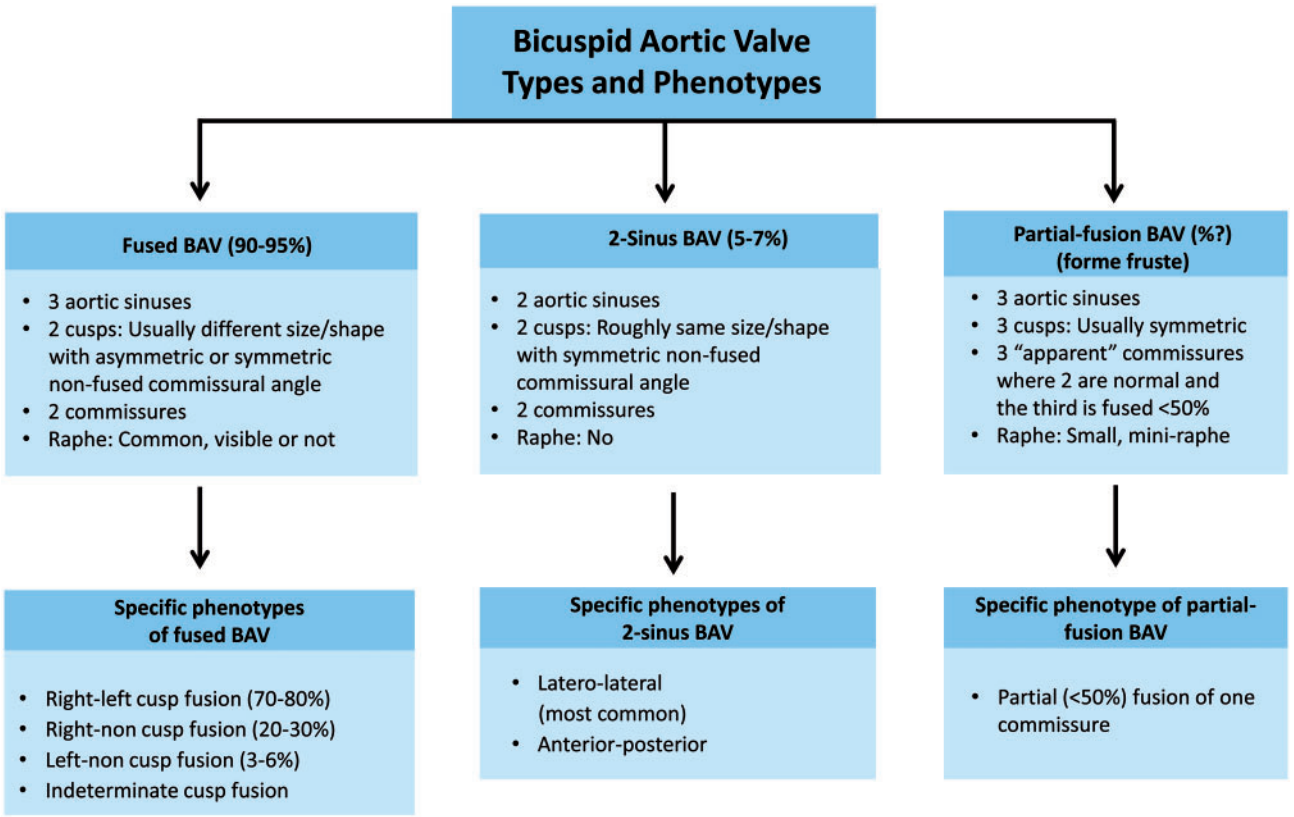


Figure 4: Types and specific phenotypes of the congenital BAV. There are 3 major types of BAVs and each type has specific phenotypes: fused BAV (right–left cusp fusion, right non-cusp fusion, left non-cusp fusion and indeterminate phenotypes); 2-sinus BAV (laterolateral and anteroposterior phenotypes) and partial-fusion BAV or forme fruste BAV (small raphe, single phenotype). Symmetrical or asymmetrical refers to the angle of the commissures of the non-fused cusp (see Fig. 9). BAV: bicuspid aortic valve.

anatomical landmark that constitutes the third component of the root complex, as described above. It has been reported that the distance between the ventriculo-aortic junction and the virtual annulus levels is variable and usually greater in BAV than in the normal aortic valve, particularly in the right coronary sinus [48]. The aortic root complex, particularly the size of the aortic annulus and the STJ, is indispensable in the maintenance of sufficient diastolic cusp coaptation area to prevent the progression of AR [51] and its recurrence after surgery [52]. Therefore, the aortic root complex is the anatomical scaffold that maintains BAV competency, with the BAV cusps acting as a stentless valve and the root complex as its native stent [50].

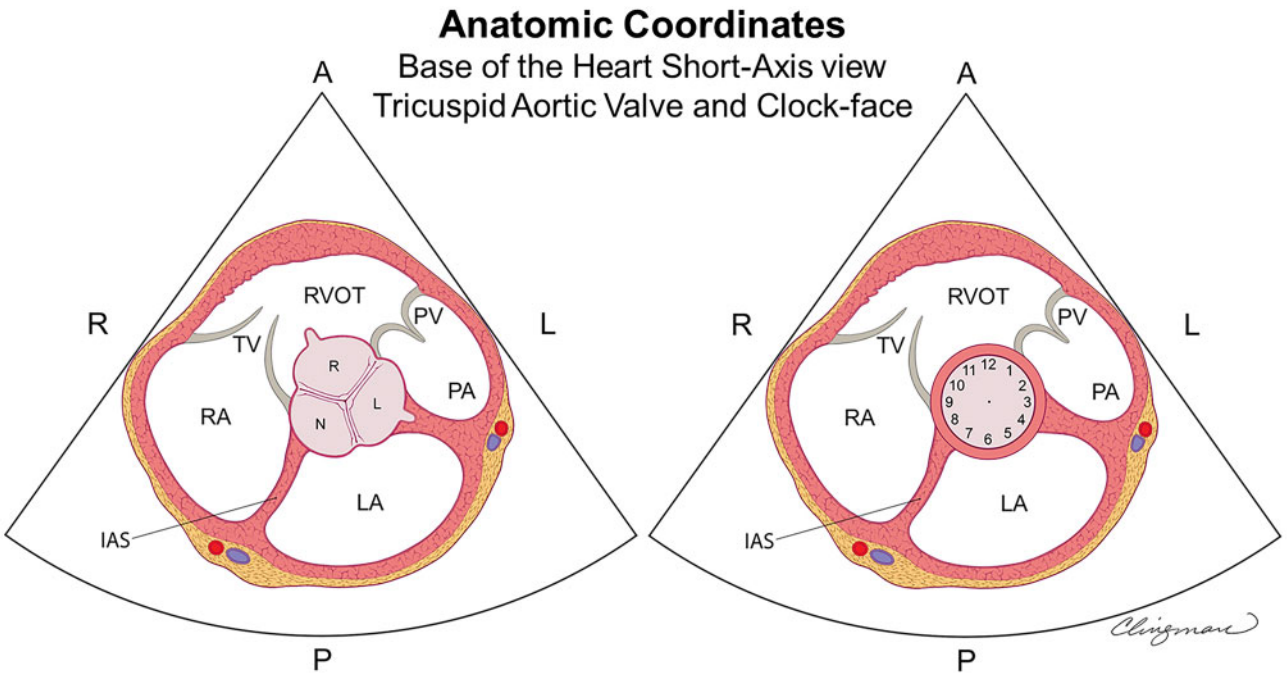


Figure 5: Schematic transthoracic echocardiography-based short-axis, base-of-the-heart anatomical landmarks and clock face for bicuspid aortic valve diagnosis and phenotyping. (**Left panel**) Schematic of the normal tricuspid aortic valve in the echocardiographic parasternal short-axis view, applicable to similar views obtained with cardiac computed tomography and cardiac magnetic resonance. The right coronary cusp (small R) is anterior and positioned between the TV and PV insertions. The left coronary cusp (small L) is posterior-lateral and related to the LA, whereas the non-coronary cusp (small N) is the most posterior and related to the IAS. Note the origin of the coronary arteries at the right and left cusps. These landmark anatomical relations of each cusp relative to adjacent structures are critical in determining which 2 cusps are fused. Modified from Michelena *et al.* [10] with permission from Elsevier. (**Right panel**) The annular circumference of the aortic valve can be visualized like the face of a clock. Fused bicuspid valves with right–left cusp fusion usually have commissures at 4 and 10 or 5 and 11 o'clock (see Figs 6 and 7), and the anatomy relative to adjacent structures suggests right–left cusp fusion. In right non-coronary cusp fusion, the commissures are usually at 1 and 7 or 12 and 6 o'clock (see Figs 6 and 7); the anatomy relative to adjacent structures suggests right non-cusp fusion. In left non-coronary cusp fusion, usually 2 and 8 or 9 and 3 o'clock (see Figs 6 and 7) and the anatomy relative to adjacent structures suggest left non-fusion. It is important to note that there can be overlap between the clock positions; thus, it is critical to know the landmark anatomical relations of each cusp. Identification of the raphe can be invaluable in determining the conjoined cusp. Identification of the origin of the left and right coronary arteries (left panel) may also be invaluable. IAS: interatrial septum; LA: left atrium; large L: left side of the patient; large R: right side of the patient; P: posterior aspect of the heart; PA: pulmonary artery; PV: pulmonary valve; RA: right atrium; RVOT: right ventricular outflow tract; TV: tricuspid valve. Modified from Michelena *et al.* [10] with permission from Elsevier.

The tract of the proximal aorta spanning from the STJ to the brachiocephalic artery take-off should be referred to as the 'tubular ascending aorta' or the ascending aorta. The subsequent tract, from the brachiocephalic artery to the isthmus (the physiological narrowing just distal to the left subclavian artery origin), is called the aortic arch.

CONSENSUS ON BICUSPID AORTIC VALVE NOMENCLATURE AND CLASSIFICATION FOR CLINICAL, SURGICAL, INTERVENTIONAL AND RESEARCH PURPOSES

Bicuspid types and specific phenotypes

There are 3 BAV types: the fused BAV, the 2-sinus BAV and the partial-fusion BAV, each with specific phenotypes [10] (Fig. 4).

The fused bicuspid aortic valve type. The fused BAV is the most common type (Figs 5 and 6), accounting for approximately 90–95% of cases [2, 32]. The fused BAV is characterized by 2 of the 3 cusps appearing fused or joined within 3 distinguishable aortic sinuses, resulting in 2 functional cusps (1 fused or conjoined and the other non-fused) that are usually different in size and shape, with non-fused cusp commissural angles of varying degrees (Figs 6–8). Commonly, both adult and paediatric patients with BAV demonstrate eccentric dominance of the non-fused aortic sinus and its cusp (compared to the other 2 sinuses and 2 fused cusps), irrespective of age [53] (Figs 6 and 7). Frequently (approximately 70%), but not always, there is a congenital fibrous ridge between the fused cusps, termed raphe [32, 54]. The presence of a raphe has been associated with the progression of valvular dysfunction (particularly AS) and future valvular surgery [45, 54, 55]. A raphe may be present but not initially visible by echocardiography and may become visible years later [56]. Significant calcification of a raphe can be identified by echocardiography (highly echogenic, casting a shadow) but less-severe calcification versus raphe-fibrosis cannot be easily discerned. Conversely, raphe calcification can be readily identified by the specific attenuation pattern on CCT (highly dense, usually more than 130 HU).

There are 3 specific BAV phenotypes within the fused type: right–left cusp fusion, right non-(non-coronary) cusp fusion and left non (non-coronary) cusp fusion (Figs 6 and 7; Videos 1–4). The right–left cusp fusion phenotype is the most common (70–80%) across American, European and Asian populations [2, 32,

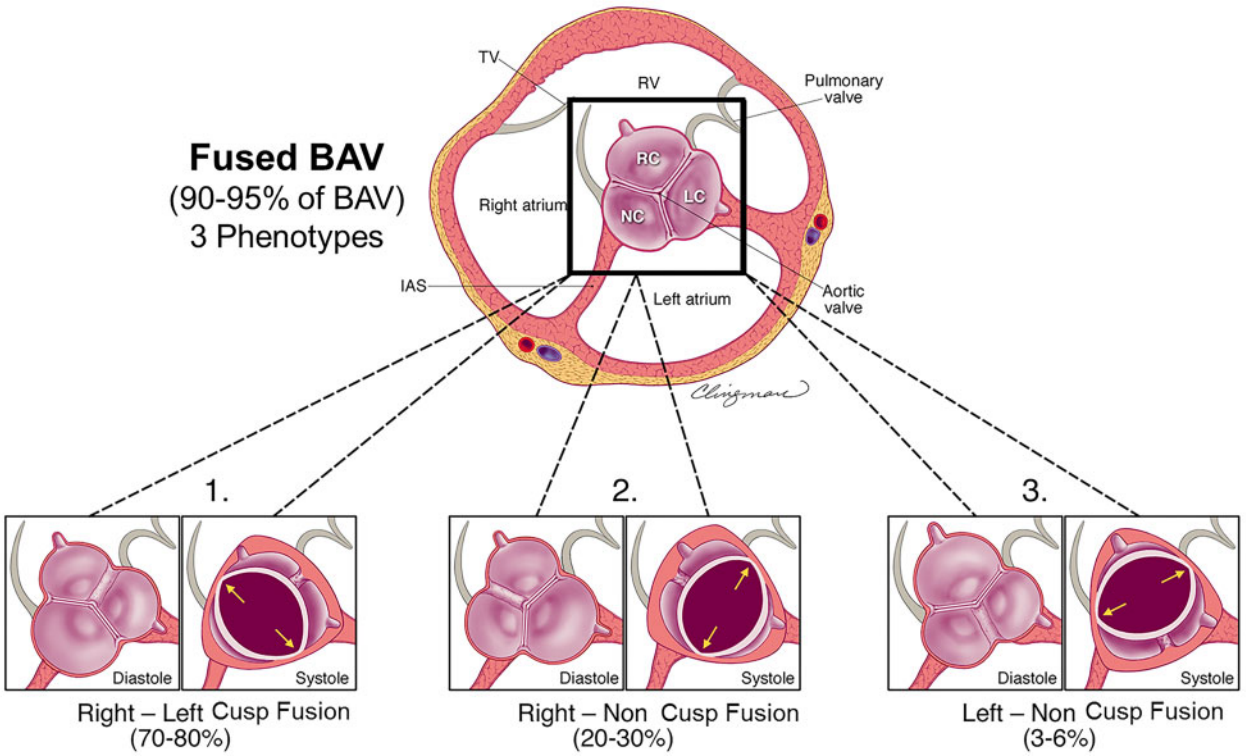


Figure 6: Schematic of fused BAV phenotypes as seen by parasternal short-axis transthoracic echocardiography. Applicable to similar tomographic views by cardiac computed tomography and cardiac magnetic resonance, the figure demonstrates the 3 fused BAV phenotypes as zoomed views of the base of the heart (black square) for anatomical landmark correlation. Note that all fused BAVs have 3 distinguishable aortic sinuses. Note the oval (American football shape) systolic opening of these 3 valves as opposed to the triangular opening of a tricuspid aortic valve. (**1**) Right–left cusp fusion (most common) with visible raphe, 2 different size/shape functional cusps [the non-fused cusp (non-coronary) is commonly of larger 'compensatory' size than the others]. (**2**) Right non-cusp fusion with visible raphe, 2 different size/shape functional cusps [the non-fused cusp (left) is larger than the others]. (**3**) Left non-cusp fusion with a visible raphe (least common), 2 different size/shape functional cusps [the non-fused cusp (right) is larger than the others]. It is important to note that these short-axis imaging views do not correspond to the surgeon's intraoperative view. Note how, in diastole, the commissural angle of the non-fused cusp of these 3 asymmetrical BAVs is <170–180° (see Fig. 9); in systole, the right–left commissures are at 10 and 4 o'clock (1: yellow arrows), right non-commissures at 1 and 7 o'clock (2: yellow arrows) and left-non-commissures at 2 and 8 o'clock (3: yellow arrows) (see Fig. 7). These 3 fused phenotypes may not have a visible raphe and may also have symmetrical non-fused cusp angle (see Fig. 8). BAV: bicuspid aortic valve; IAS: interatrial septum; LC: left cusp; NC: non-coronary cusp; RC: right cusp; RV: right ventricle; TV: tricuspid valve. Modified from Michelena *et al.* [10] with permission from Elsevier.

57]. The right–left cusp fusion phenotype is also the most common across all phenotypic variations of the aorta (normal aorta, dilated ascending aorta, dilated arch or dilated root) and across valve dysfunction (regurgitation or stenosis). Although this right–left fusion phenotype statistically develops more AS [2], it has been associated in some patients, both children/adolescents [58] and adults [59, 60], with aortic root dilatation, AR and male preponderance (these associations have been termed the 'root phenotype'). The right–left cusp fusion is also strongly associated with aortic coarctation in children [61].

The right non-cusp fusion phenotype is the next most common (20–30%); it is associated with a higher prevalence of AS in adults [55] and independently predicts AR progression in adults [51]. Similarly, the right non-cusp fusion phenotype is associated with a more rapid progression of AS and regurgitation in children and adolescents [61, 62]. The right non-cusp fusion phenotype is also more prevalent in Asian populations, as is the left non-cusp fusion phenotype [57, 63], which is the least common phenotype (3–6%) across studies. Interestingly, African American patients are reported to have a lower prevalence of BAV and aortopathy altogether [64].

In complex-presentation forms like BAV associated with genetic syndromes, right non-cusp fusion is more common in patients with Down syndrome, and right–left cusp fusion is more common in patients with Turner's syndrome and Shone complex, suggesting different abnormalities in developmental pathways [8]. Based on the results from animal experiments, it can be assumed that the embryological background of the fused types is that of abnormal remodelling/maturation (excavation) of the valve cushions (the 3 fused types may be explained by defective excavation) or a mild defect during outflow tract septation for fused right–left phenotypes and during endocardial cushion formation/positioning for the fused right non- and left non-phenotypes [65–69].

Referring to the fused phenotypes as BAV with right–left cusp fusion, right non-cusp fusion or left non-cusp fusion is appropriate. Occasionally, it is possible to recognize a BAV with 3 aortic sinuses but not be able to discern the fusion phenotype, in which case BAV with indeterminate cusp fusion is appropriate (Fig. 4). It is important to recognize that some fused BAVs may not have a congenital raphe [32] or have a raphe that is not visible by imaging [56], yet they have 3 distinguishable aortic sinuses and the 2 fused cusps can be identified (Fig. 8; Video 5).

Symmetry of the fused bicuspid aortic valve types. Evaluation of BAV symmetry for the fused BAV type is defined by the angle

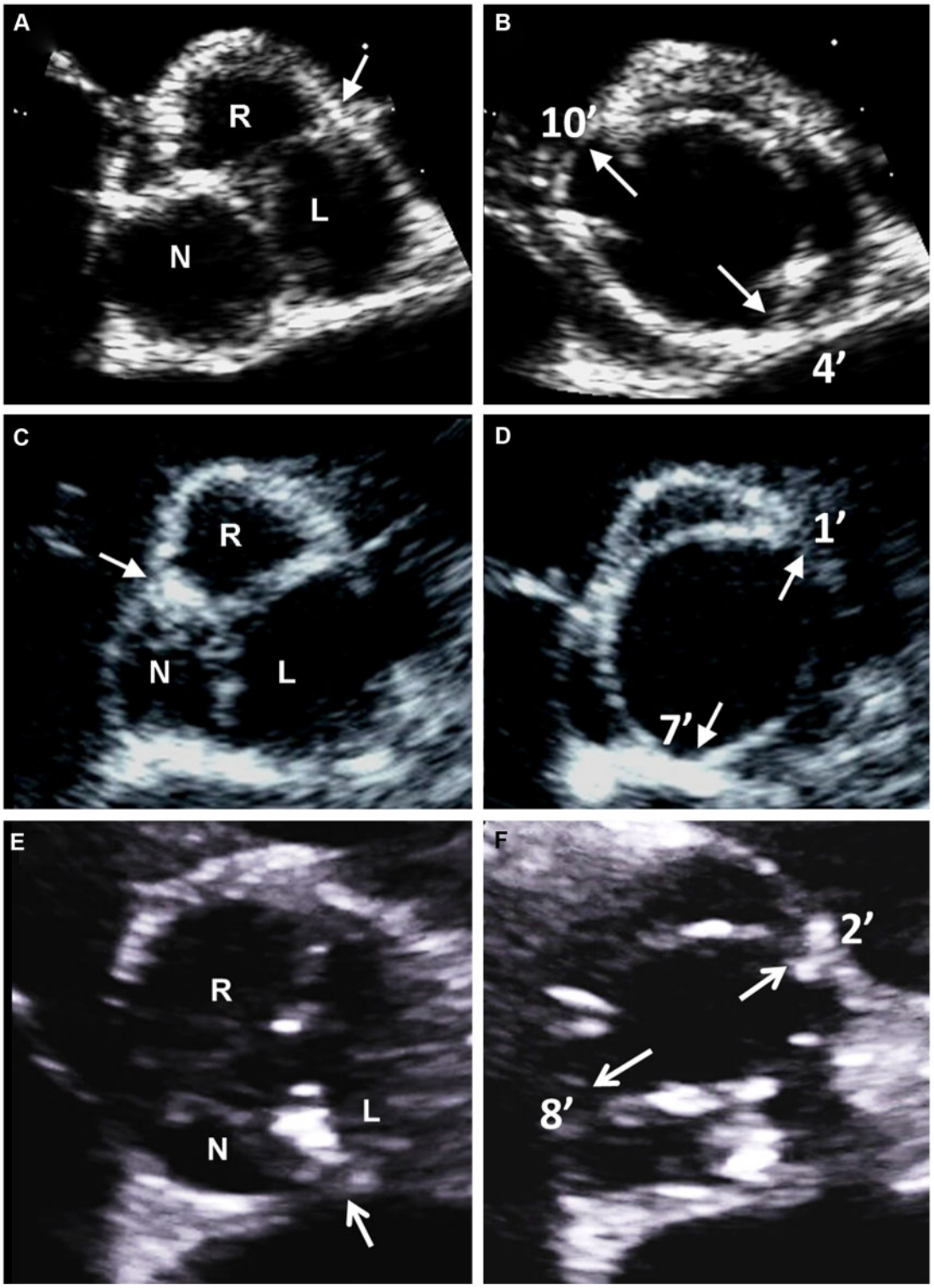


Figure 7: Diastolic and systolic transthoracic echocardiography parasternal short-axis still images of the 3 phenotypes of fused bicuspid aortic valve (BAV). Applicable to similar tomographic views obtained with cardiac computed tomography and cardiac magnetic resonance. (**A**) Right–left cusp fusion BAV within 3 distinguishable aortic sinuses, with raphe (arrow) in diastole and (**B**) typical systolic opening with commissures marked as the clock face (arrows) (see Video 1). (**C**) Right non-cusp fusion BAV within 3 distinguishable aortic sinuses, with raphe (arrow) in diastole and (**D**) typical systolic opening with commissures marked as the clock face (arrows) (see Video 3). (**E**) Left non-cusp fusion BAV within 3 distinguishable aortic sinuses, with raphe (arrow) in diastole and (**F**) typical systolic opening with commissures marked as the clock face (arrows) (see Video 4). Modified from Michelena *et al.* [6] with permission from Elsevier. L: left coronary cusp; N: non-coronary cusp; R: right coronary cusp.

between the commissures of the non-fused cusp and has recently become a critical aspect in the planning and performance of BAV repair for pure AR [10, 43, 70]. From a regurgitation-treatment perspective, the BAV concept offers a simple, single-line coaptation surface [a tricuspid aortic valve has 3 coaptation lines (Fig. 5, left)]; as long as that single coaptation line is straight or almost

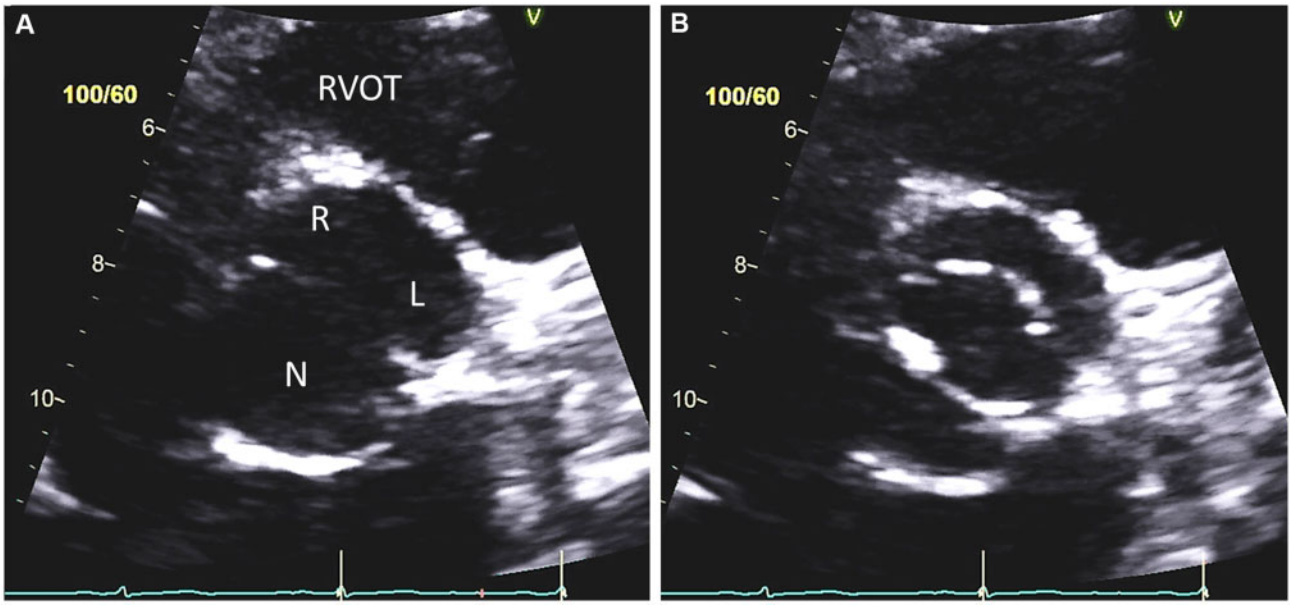
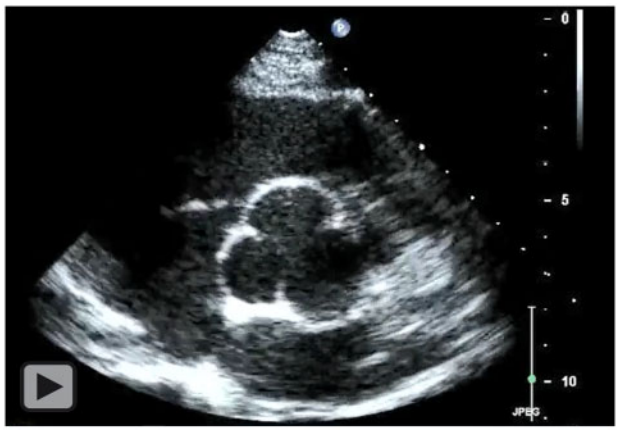
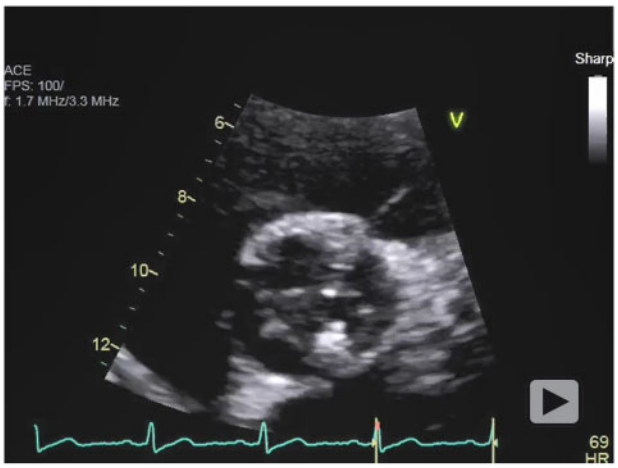


Figure 8: Fused-type right–left cusp fusion without visible raphe and symmetrical non-fused cusp commissural angle. (**A**) Diastolic transthoracic echocardiography short-axis still frame shows right-left cusp fusion without visible raphe (uncommon) and 180° angle of the non-fused cusp commissures, yet the sizes and shapes of the 2 functional cusps are different, the conjoined cusp is smaller than the predominant non-fused non-coronary cusp (N) and there are 3 aortic sinuses. (**B**) Systolic transthoracic echocardiography short-axis still frame confirms the absence of a visible raphe and the 180° commissural angle (Video 5). L: left coronary cusp; N: non-coronary cusp; R: right coronary cusp; RVOT: right ventricular outflow tract.



Video 3: Transthoracic echocardiography parasternal short axis of right non-cusp fusion with raphe.

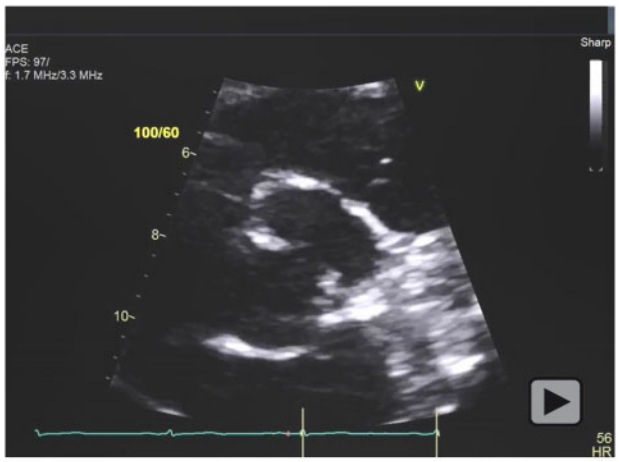


Video 4: Transthoracic echocardiography parasternal short axis of left non-cusp fusion with raphe.

straight (Figs 8 and 9, symmetrical), the repair of the regurgitant BAV is reproducible (see Section Surgical considerations). As the angle between the commissures of the non-fused cusp decreases to <160° [70], the BAV becomes less symmetrical, more closely resembling a tricuspid (especially <140°) valve (Fig. 9, very asymmetrical), which becomes technically more challenging for the surgeon to 'bicuspidize' during the repair yet remains repairable in experienced hands. Asymmetrical valves may exhibit retraction of the free edge of the fused cusp at the raphe level, which is best appreciated by direct surgical visualization (Figs 2 and 9) or gross pathological inspection, and not reliably by imaging. This retraction may contribute to valve regurgitation. Figure 8 shows a fused BAV with right–left cusp fusion with a 180° non-fused cusp commissural angle (symmetrical), although the 2 cusps are not the same size/shape. Measuring the non-fused cusp commissural angle on precardiopulmonary bypass transoesophageal echocardiography aids the surgeon in planning the repair (Fig. 10; Video 6). Therefore, the symmetry of a fused-type BAV is defined by the angle between the commissures of the non-fused cusp.

The 2-sinus bicuspid aortic valve type. The 2-sinus BAV is uncommon, accounting for approximately 5–7% of cases [2, 10, 32]. In contrast to that of the fused type, the appearance of the 2-sinus BAV does not suggest that 2 of the 3 cusps have fused; instead, it suggests that 2 cusps, roughly equal in size and shape, each cusp occupying 180° of the annular circumference, were 'formed' within only 2 aortic sinuses, resulting in a 2-sinus/2-cusp valve (Figs 11–13; Videos 7–10) without raphe and with 180° commissural angles. It is often difficult to determine which 2 cusps could have coalesced to form a 2-sinus BAV, but it is usually evident whether the cusps are laterolateral (side-to-side) or

anteroposterior (front-and-back) within the short-axis base of the heart plane (Figs 11–13; Videos 7–10**)**; thus, these are the 2 specific phenotypes of the 2-sinus BAV category. The 2-sinus laterolateral BAV has 1 coronary artery arising from each cusp, whereas the anteroposterior BAV may have 1 coronary artery arising from each cusp or both coronary arteries arising from the anterior cusp (Figs 11 and 13). Based on results from animal experiments, it can be assumed that the embryological background of the 2-sinus BAV is that of abnormal endocardial cushion formation/positioning for the laterolateral and abnormal outflow tract septation for the anteroposterior. The 2-sinus BAV likely represents a more severe expression of the embryological mechanisms leading to the fused BAV. Referring to these phenotypes as 2-sinus laterolateral BAV and 2-sinus anteroposterior BAV is appropriate. Occasionally, despite suspicion, it may be difficult to be certain whether there are only 2 sinuses, in which case, terms such as possible or probable 2-sinus BAV may be used. There is a lack of scientific data on the clinical/prognostic associations of the 2-sinus BAV, which represents a 'morphologically severe' form of BAV. Therefore, we hope that through this nomenclature/classification, the research community directs more attention towards this type of BAV.



Video 5: Transthoracic echocardiography parasternal short axis of right–left cusp fusion without raphe and 180° symmetrical non-fused cusp commissural angle.

The partial-fusion bicuspid aortic valve (or forme fruste bicuspid aortic valve) type. The partial-fusion BAV (or forme fruste BAV) type has recently been recognized; its prevalence is unknown [71] (Fig. 14). The appearance of the partial-fusion BAV [72] is that of a typical tricuspid aortic valve with 3 symmetrical cusps with a systolic triangular opening and commissural angles of 120°, yet on surgical inspection or high-resolution imaging, cusp fusion of less than 50% is noted at the base of a commissure, forming a small 'mini-raphe' [10, 71, 73, 74]. It is important to recognize and further study the partial-fusion BAV, which has been described mostly in the operating room in patients undergoing surgery for aorta dilatation [71] (Fig. 15; Videos 11 and 12) [74]. This forme fruste BAV results in alteration of the aortic flow patterns, consisting of increased flow eccentricity and increased vortexes [73], perhaps partially explaining the apparent high prevalence of aorta dilatation in these patients. Referring to this phenotype as partial-fusion BAV or forme fruste BAV is appropriate. Based on results from animal experiments, it can be assumed that the embryological background of the partial-fusion BAV is that of a mild defect during outflow tract septation or during

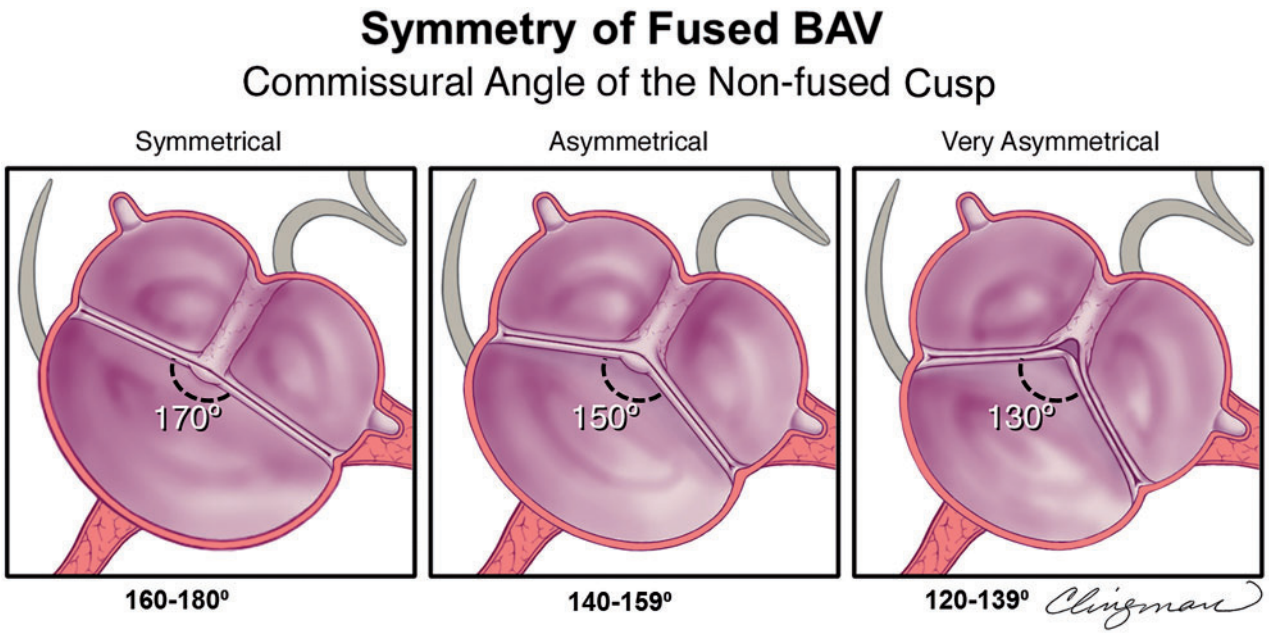


Figure 9: Schematic of the transthoracic echocardiographic evaluation of fused BAV symmetry in the parasternal short axis. Applicable to similar tomographic views obtained from cardiac computed tomography and cardiac magnetic resonance, the figure demonstrates different commissural angles of the non-fused cusps (applicable to the 3 fused BAV phenotypes, although only right–left cusp fusion is shown) that define symmetry. (**Left panel**) Symmetrical (angle 160–180°) right–left cusp fusion BAV with raphe, where the 2 functional cusps are almost the same size/shape (the non-fused cusp is a little larger) and the commissural angle of the non-fused cusp is about 170°. (**Middle panel**) Asymmetrical (angle 140–159°) right–left fusion BAV with a raphe, and the commissural angle of the non-fused cusp is about 150°. (**Right panel**) Very asymmetrical (angle 120–139°) right–left fusion BAV shows retraction of the conjoined cusp at the raphe area and the commissural angle of the non-fused cusp is about 130°. Note that retraction is more prominent as the angle decreases and that this may cause aortic regurgitation. Modified from Michelena *et al.* [10] with permission from Elsevier. BAV: bicuspid aortic valve.

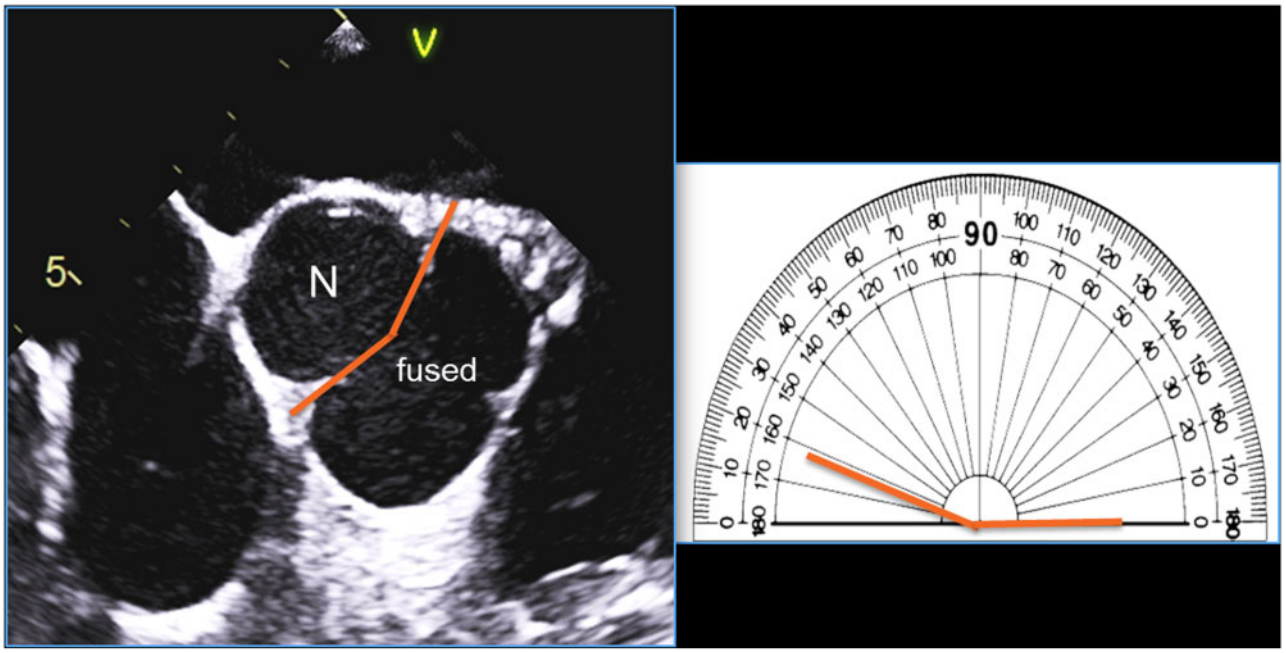
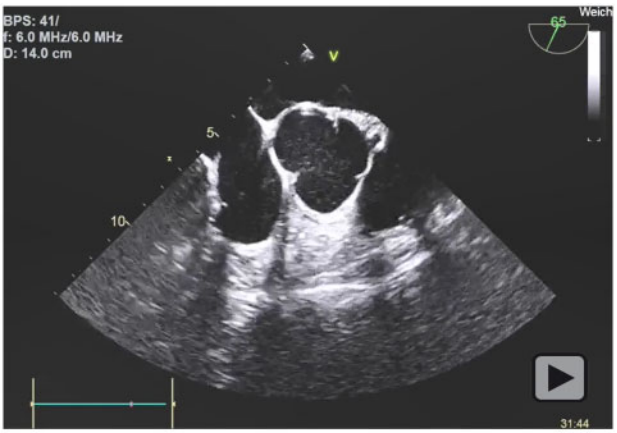


Figure 10: Transoesophageal echocardiographic measurement of the commissural angle of the non-fused cusp prior to valve repair. Applicable to similar tomographic views obtained using cardiac computed tomography and cardiac magnetic resonance, after careful visualization of the systolic and diastolic motion (Video 6) of this regurgitant fused-type right–left cusp fusion bicuspid aortic valve, the non-fused commissures are identified, and a line is drawn from the position of the commissures to the centre of the valve in diastole (left). The angle of the non-fused cusp (N) is then carefully measured at approximately 162° on the protractor to the right, suggesting a good chance for repair. Modified from Michelena *et al.* [6] with permission from Elsevier.



Video 6: Prebypass transoesophageal echocardiography mid-oesophageal short axis of right–left cusp fusion for measurement of non-fused cusp commissural angle.

remodelling/maturation (excavation) of the valve cushions [65, 66, 69, 75, 76].

The bicuspid aortic valve anatomical spectrum.

The BAV phenotypic expression represents an anatomical continuum that is likely related to the severity of its embryological mechanisms [10]. Therefore, we propose a general BAV anatomical spectrum (Fig. 16) of BAV phenotypes in order of 'bicuspidity', defined as the resemblance to a 2-sinus BAV. This spectrum represents a continuum of increasing non-fused cusp commissural angles and increasing similarity of cusp size and shape. The spectrum begins with the partial-fusion BAV, which most closely resembles a tricuspid aortic valve and represents the mildest embryological defects, on to asymmetrical fused phenotypes, to symmetrical fused phenotypes with and without a raphe, ending with the 2-sinus BAV, which represents the most severe embryological defects and is anatomically close to perfect 'bicuspidity'. This BAV anatomical spectrum can be demonstrated surgically and pathologically (Fig. 17). Virtually the same spectrum has been described in animal models, in which the anatomical variation depends on the severity of the embryonic defect [66, 67, 69, 76].

Definition of aorta dilatation and bicuspid aortic valve aortopathy

Definition of aorta dilatation. The clinical expression of the BAV-related aortopathy is dilatation of the thoracic aorta. The definition of aortic aneurysm [77] is rarely applied in clinical practice, and the term aneurysm carries a somber or dismal connotation for patients. Therefore, we propose a simple and universal term: aortic dilatation. Qualitative-descriptive terms such as saccular or fusiform dilatation or STJ effacement may be important for aorta specialists and surgeons. Echocardiographic studies in populations of apparently normal individuals have shown that the diameters of the root and ascending aorta are proportionally related to body size (most commonly expressed as body surface area), age (increasing by 0.1 mm/year in 'healthy' adults) and male sex in adults [78–80]. These studies and normative data in children [78, 81] allow identification of aortic root and/or ascending aorta dilatation by echocardiography when the aortic diameter is above the upper 95% confidence limit of 'normal' values (Fig. 18) or the calculated *z*-score exceeds +2.0. However, data on 'normal' aortic diameters are limited, with continued publications reporting varying 'normal' values depending on different demographics and anthropometrics of the populations observed

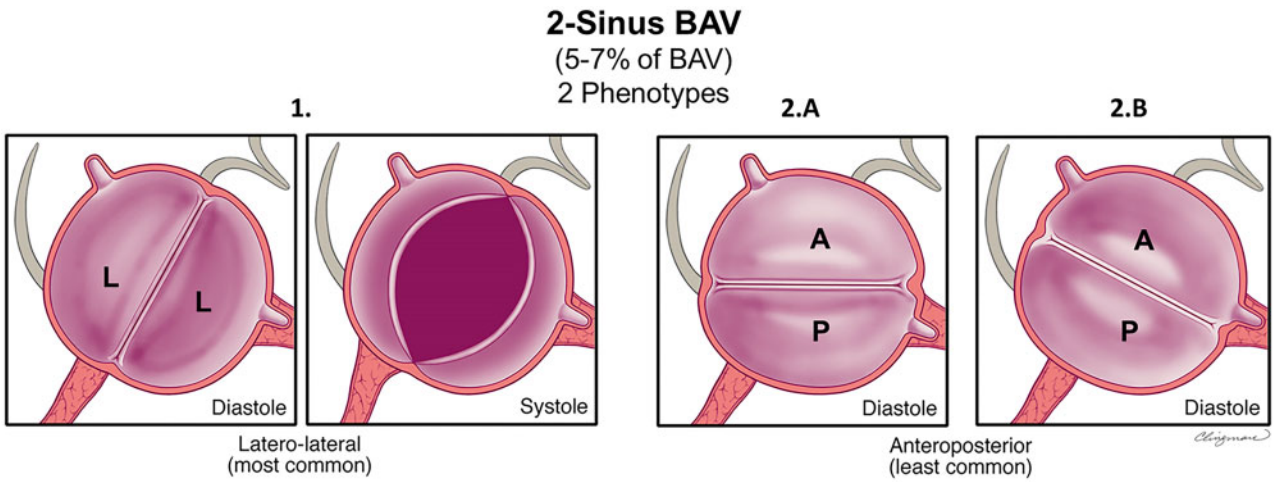
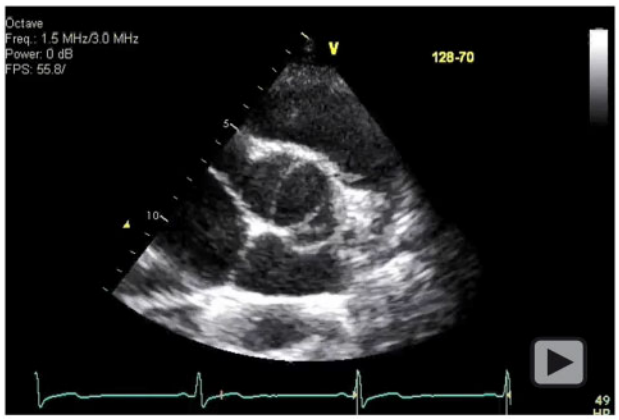
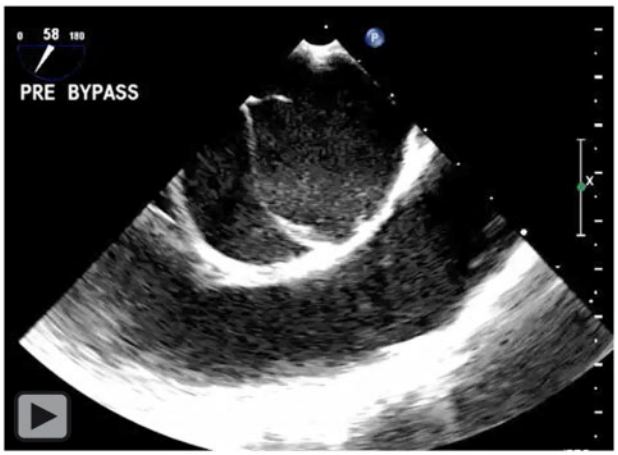


Figure 11: Schematic of the 2-sinus BAV phenotypes as seen by the transthoracic echocardiogram parasternal short axis. Applicable to similar tomographic views obtained from cardiac computed tomography and cardiac magnetic resonance, the figure demonstrates 2-sinus BAV phenotypes as zoomed views of the base of the heart for anatomical landmark correlation. (**Left panels**) (**1**) 2-sinus laterolateral BAV with only 2 distinguishable aortic sinuses in diastole and 2 cusps of roughly same size and shape, each occupying 180° of the circumference, with a 180° angle of the commissures. Note that although it is possible to suspect right non-fusion, the landmark anatomical relations are not clear because both the normal geographic 'left' and 'non-coronary' cusps occupy portions of the normal geographic location of the 'non-coronary' cusp, and the posterior commissural line is almost aligned with the interatrial septum, bisecting the geographical location of the normal non-coronary cusp (Figs 5 and 12). The 2-sinus BAV laterolateral phenotype has 1 coronary artery arising from each sinus. (**Right panel**) (**2.A**) A 2-sinus anteroposterior BAV with only 2 distinguishable aortic sinuses in diastole and 2 cusps of roughly same size and shape each occupying 180° of the circumference, with a 180° angle of the commissures. Note that although it is possible to suspect right–left fusion, the landmark anatomical relations are not clear because the commissural line actually bisects the normal geographical location of the left cusp, such that both anterior and posterior functional cusps appear to have a 'piece' of the left cusp (see Figs 5 and 12). (**2.B**) A 2-sinus anteroposterior BAV that resembles a fused right–left fusion but without a raphe, with only 2 distinguishable aortic sinuses in diastole and 2 same size/shape cusps each occupying 180° of the circumference. The 2-sinus anteroposterior BAV may have coronary arteries arising from each cusp (**2.A**) or from the anterior cusp (**2.B**). Modified from Michelena *et al.* [10] with permission from Elsevier. A: anterior cusp; BAV: bicuspid aortic valve; L: lateral cusp; P: posterior cusp.



Video 7: Transthoracic echocardiography parasternal short axis of 2-sinus laterolateral bicuspid aortic valve.

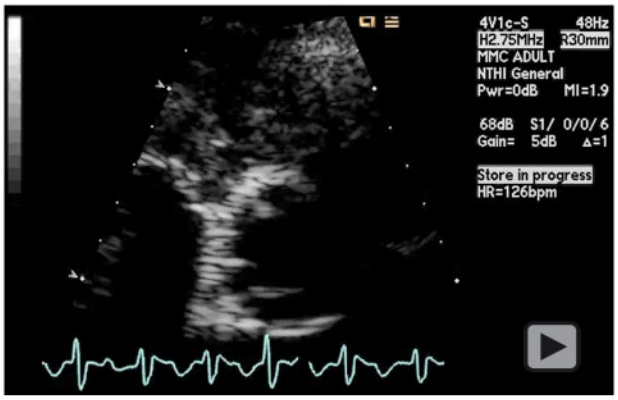


Video 8: Transoesophageal echocardiography mid-oesophageal short axis of 2-sinus laterolateral bicuspid aortic valve.

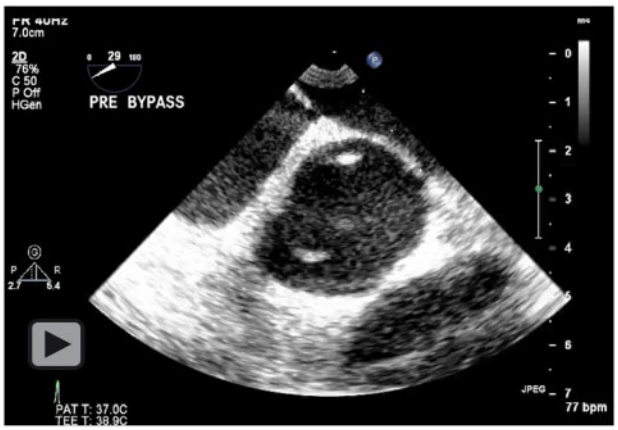
and on methodological aspects: i.e. diastolic leading-edge to leading-edge (adult echo) versus systolic inner-edge to inner-edge (paediatric echo) measurements, echocardiography(Fig. 18) versus CCT/CMR (inner wall-to-inner wall versus outer wall-to-outer wall). These factors should be also considered when comparing serial imaging results in an individual patient during follow-up: The difference between current and previously reported aortic diameters (at the same level) can be considered a reliable quantifier of the progression of the dilatation only when measured by the same modality and exact anatomical location and method [82–84]. In adults with BAV, TTE systematically underestimates the aortic root measurement (asymmetrical aortic sinuses) compared to CCT, whereas the measurements are generally unbiased between TTE and maximum diastolic inner wall-to-inner wall CCT for the ascending aorta [85]. Therefore, in adults, diastolic leading-edge to leading-edge echocardiography is generally equivalent to diastolic inner wall-to-inner wall CCT/CMR except for the root, where CCT/CMR should be used for accurate measurement when it is enlarged (i.e. >45 mm) or asymmetrical [15, 19].

Due to the tremendous change in body size and cardiac structures that occurs from infancy to adolescence, utilization of *z*-scores to compare obtained aortic measurements to normative data is essential. This approach allows for easy identification of infants, children and adolescents who have echocardiographic aortic dimensions that fall outside the normal range for their age and body size, typically identified as a *z*-score that is 2 standard

deviations above the mean (97.7th percentile); +2.0 [86]. Alternatively, CMR-derived percentile curves for normal cross-sectional areas of the ascending aorta, arch and descending thoracic aorta in children, adolescents and young adults have been published [87]. However, for clinical care in most settings, categorization of aortic dilatation as mild, moderate or severe for adults with BAV is more practical than referring to z-scores. Because most available data in adults relate the risks of aortic complications to the measured absolute aortic diameter without further indexing for body size, age or sex, it is reasonable at present to 'initially' separate these categories by simple aortic diameter partitions. Thus, in general, dilatation of the root or ascending aorta in patients with typical valvulo-aortopathy BAV (Fig. 1) is considered mild if the diameter is between the age-, body size- and sex-specific upper limit of normal (Fig. 18) [78] and 45 mm; moderate for diameters between 46 mm and 50–54 mm; severe for diameters ≥55 mm (elective surgical cut-off) if no associated risk factors are present, and also severe for ≥50 mm (elective surgical cut-off) if there are associated risk factors (any risk factor) [1, 19]. These risk factors that increase the likelihood of aortic complications (i.e. dissection) in patients with BAV with typical-presentation valvulo-aortopathy are the 'root-phenotype', severe BAV regurgitation, uncontrolled hypertension, personal



Video 9: Transthoracic echocardiography parasternal short axis of 2-sinus anteroposterior bicuspid aortic valve.



Video 10: Transoesophageal echocardiography mid-oesophageal short axis of 2-sinus anteroposterior bicuspid aortic valve.

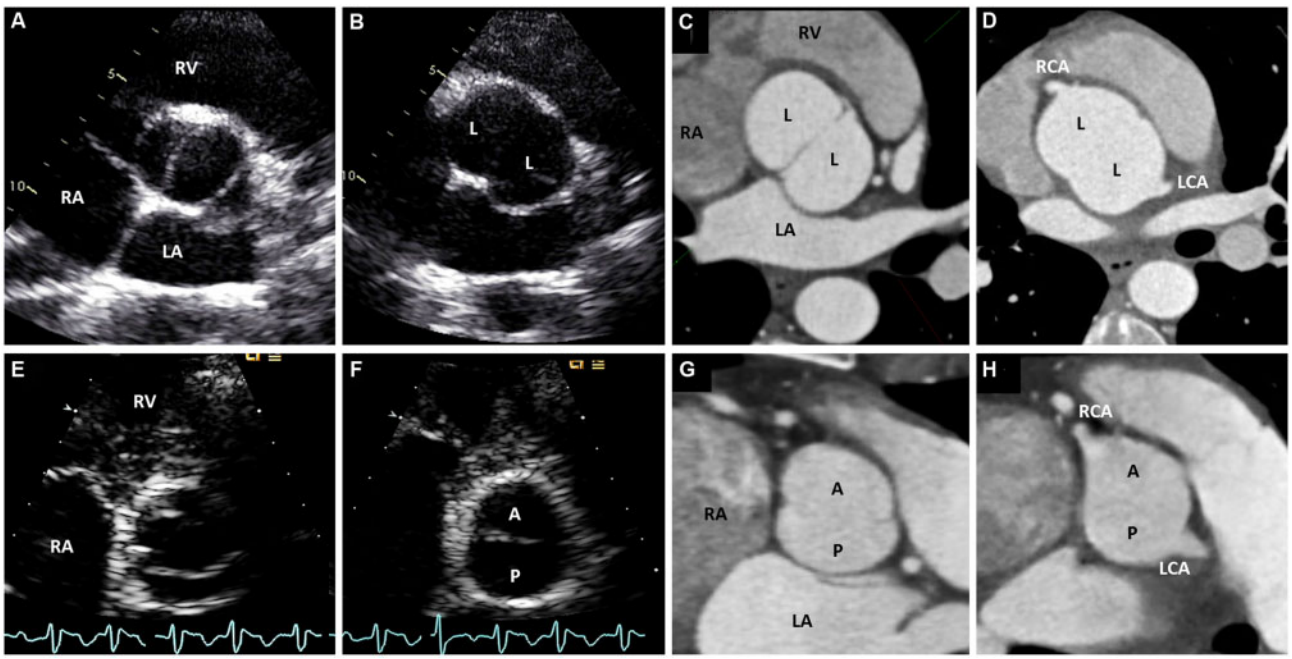


Figure 12: Diastolic and systolic short-axis still images of the 2-sinus bicuspid aortic valve phenotypes obtained from transthoracic echocardiographic and diastolic still images from electrocardiographic-gated cardiac computed tomography. (**A**) A 2-sinus laterolateral bicuspid aortic valve in systole, with the commissural line bisecting the normal geographic position of the non-coronary cusp (**B** and **C**), with only 2 distinguishable aortic sinuses in diastole (**B**), and roughly equal size/shape cusps occupying 180° of the circumference, reproducible on an equivalent tomography cut as seen with cardiac computed tomography (**C**). Note the coronary arteries arising, 1 from each cusp (**D**). See Videos 7 and 8 for the transthoracic and transoesophageal short axes of this valve. (**E**) A 2-sinus anteroposterior bicuspid aortic valve in systole, with the commissural line bisecting the left-coronary cusp geographic position (**F**) (diastolic still frame), with only 2 distinguishable aortic sinuses and roughly equal size/shape cusps occupying 180° of the circumference, reproducible on an equivalent tomographic cut as seen with cardiac computed tomography (**G**). Note the coronary arteries arising, 1 from each cusp in this particular example (**H**). See Videos 9 and 10 for the transthoracic and transoesophageal short axes of this valve, respectively. A: anterior cusp; L: lateral cusp; LA: left atrium; LCA: left coronary artery; P: posterior cusp; RA: right atrium; RCA: right coronary artery; RV: right ventricle.

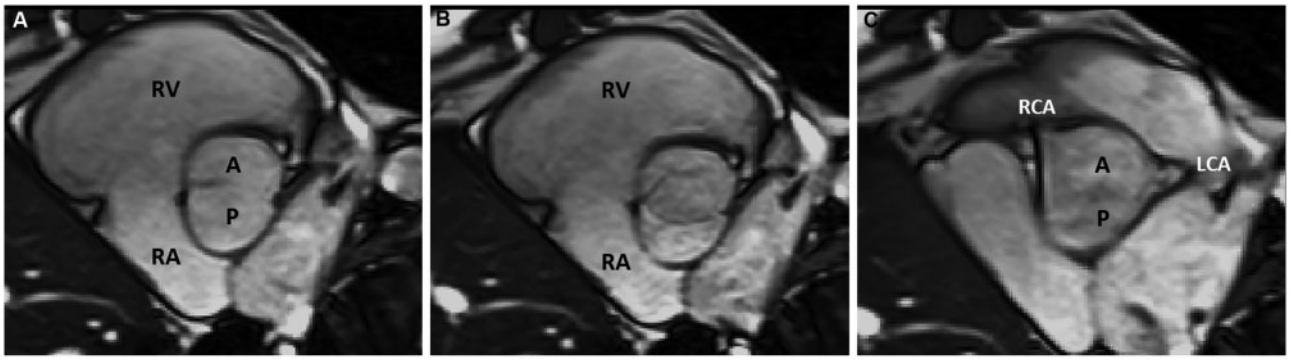


Figure 13: A 2-sinus anteroposterior bicuspid aortic valve evaluated by electrocardiographic-gated cardiac magnetic resonance. (**A**) A diastolic still frame depicts a 2-sinus bicuspid aortic valve with roughly similar size/shape cusps and sinuses, clearly suggestive of a 2-sinus bicuspid aortic valve in the systolic frame. (**B**). In this case, both coronary arteries arise from the anterior cusp (**C**), see fig. 11. A: anterior cusp; LCA: left coronary artery; P: posterior cusp; RA: right atrium; RCA: right coronary artery; RV: right ventricle.

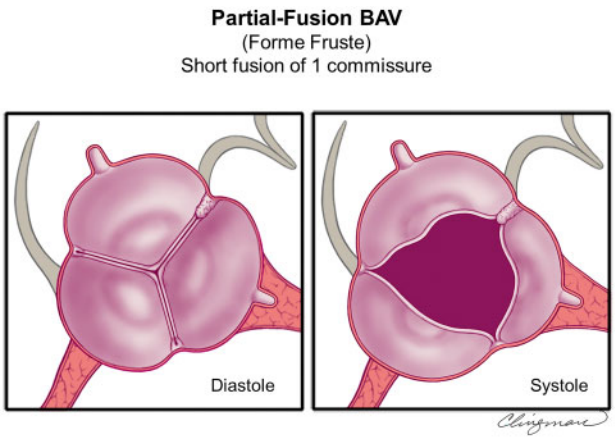


Figure 14: Schematic of the partial-fusion BAV phenotype as seen from the transthoracic echocardiogram parasternal short-axis view. (**Left panel**) The imaging appearance in diastole of the partial-fusion or forme fruste BAV is that of a tricuspid aortic valve. (**Right panel**) The imaging diagnosis is usually made in systole. Although the opening appears triangular, there is a small fusion of the right and left cusps with a 'mini-raphe'. These can be suspected by transthoracic or transoesophageal echocardiogram, and confirmed by a 3-dimensional transoesophageal echocardiogram, cardiac magnetic resonance or cardiac computed tomography. Definitive confirmation is usually made by surgical inspection or pathological analysis. Modified from Michelena *et al.* [10] with permission from Elsevier. BAV: bicuspid aortic valve.

history of coarctation, family history of aortic dissection or early unexplained sudden cardiac death or aortic diameter increase >3 mm/year [1, 19]. For patients with complex valvulo-aortopathy (Fig. 1), for example associated with genetic syndromes [5], the severity of aortic dilatation varies according to the specific underlying disease: In Loeys-Dietz syndrome, severe dilatation may be within 40–45 mm [88] depending on sex, and for women >15 years of age with Turner syndrome(short stature and small body size), severe dilatation is considered at 2.5 cm/m^2 of aortic diameter corrected for body surface area [89]. Indeed, because patients may vary significantly in body size, for patients with typical valvulo-aortopathy, it is important also to report the aortic diameters adjusted for the patient's size; for example, utilizing the aortic root cross-sectional area-to-height ratio [r^2 Π (cm^2)/height (m)] where values >10 cm^2/m are associated with worse aortic outcomes [90, 91]. Alternatively, imagers may choose not to report 'severity' but just the measurements in millimetres, and let the clinician/surgeon define the severity according to each patient's clinical circumstance [5].

Bicuspid aortic valve aortopathy phenotypes. The importance of recognizing BAV aortopathy phenotypes is that their presence and association with specific valvular phenotypes and patterns of valvular dysfunction may imply different clinical histories for the BAV patient [92]. There are 2 major forms of aortic dilatation BAV phenotypes: the ascending phenotype (dilatation preferentially located at the tubular ascending tract beyond the STJ) (Fig. 19), which accounts for approximately 70% of BAV aortopathy cases; and the root phenotype [dilatation preferentially located at the root (sinuses of Valsalva), possibly involving also the ventriculo-aortic junction/annulus], which accounts for approximately 20% of BAV aortopathy cases (Fig. 19) [10, 59, 60, 93]. Importantly, the root phenotype may have mild ascending dilation but significantly prevails at the root, and the ascending phenotype may have mild root dilatation but significantly prevails at the ascending portion. In addition, these 2 categories often correspond to 2 clearly distinct overall patient phenotypes: roughly, the older patient with BAV, either male or female, presenting more often with aortic valve sclerosis/stenosis (ascending phenotype); and the younger BAV patient, usually male, presenting with mild to severe AR (root phenotype) [59, 94, 95]. The greater prevalence of the ascending phenotype in BAV is consistent with the tubular ascending tract being the site of maximal growth rate of the BAV aorta in multiple studies [60, 93, 96–98], the growth rate ranging from 0.2 to 2.3 mm per year, usually 0.4 to 0.6 mm per year. A small percentage of patients demonstrate more rapid growth rates [93, 97]. Besides age, baseline aortic diameter and family history of aorta disease, the associated valve dysfunction (regurgitation vs stenosis) and the location of the dilatation (ascending versus root) impact the rate of growth [93, 96–98].

It is possible that the 2 aortic phenotypes may have different genetic bases [99, 100] explaining their occurrence, but the influence of different 4-dimensional (4D) CMR aortic flow patterns has also been suggested (see Section Cardiac magnetic resonance considera**tions**), mostly based on the fact that BAV stenosis and the right non-cusp fusion valvular phenotype are infrequently associated with the root phenotype and frequently associated with dilatation at the level of the ascending aorta and arch [101]. Conversely, the right–left cusp fusion exerts greater wall shear stress (WSS) on the root/proximal aorta and is frequently

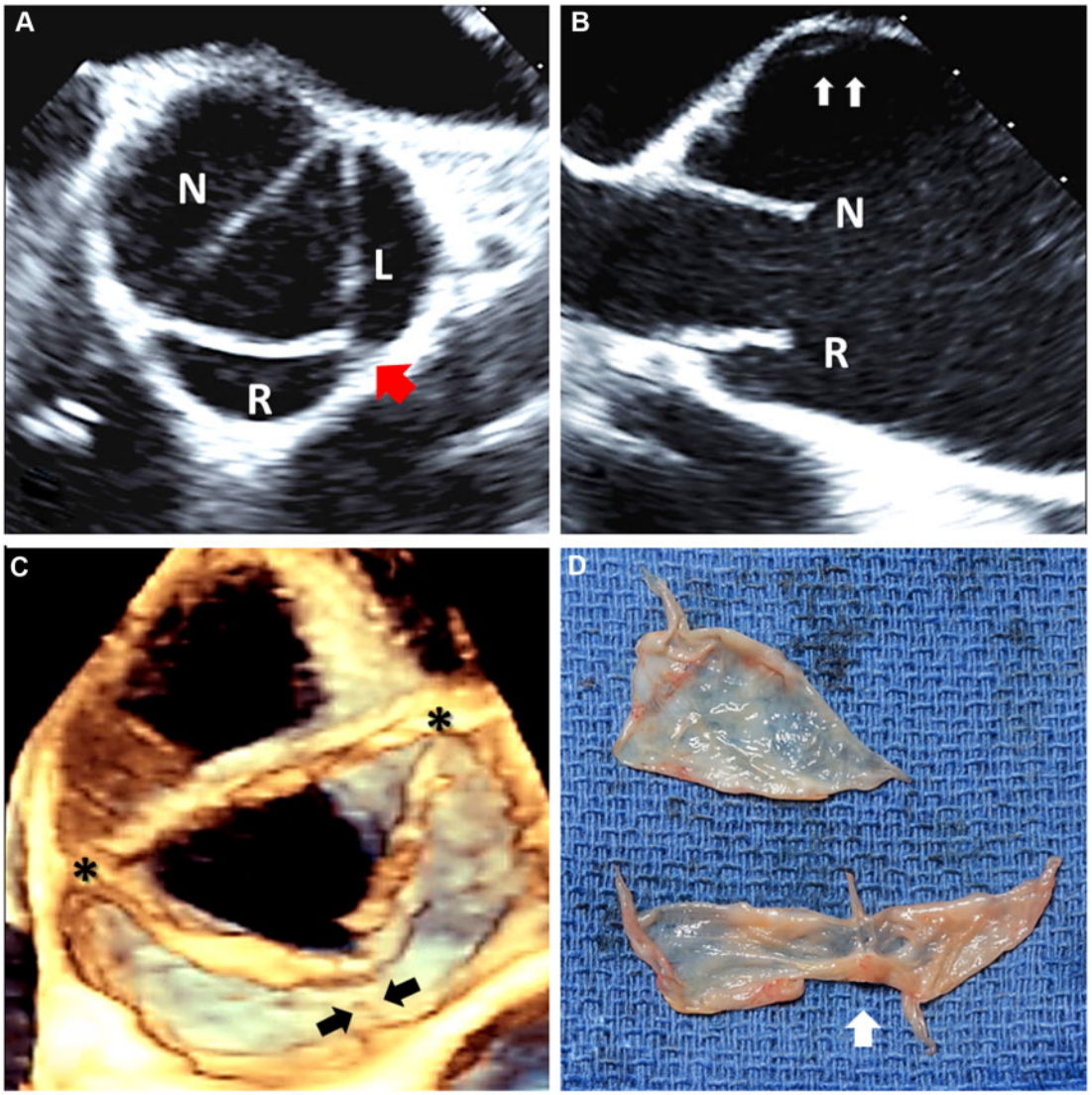


Figure 15: Systolic transoesophageal echocardiogram still images and intraoperative photograph of a partial-fusion bicuspid aortic valve. (**A**) Intraoperative 2-dimensional transoesophageal echocardiogram shows a triangular systolic opening with a suspected small fusion between the right (R) and left (L) cusps (red arrow) (Video 11). (**B**) The 2-dimensional transoesophageal long axis demonstrates no evidence of systolic doming with asymmetrical dilatation of the non-coronary sinus (arrows), which was accompanied by significant dilatation of the ascending aorta in this patient. (**C**) 3-Dimensional transoesophageal systolic short axis demonstrates a small raphe (arrows) between the right and left coronary cusps with 2 other normal commissures (asterisks) (Video 12). (**D**) Explanted valve shows the small raphe between the right and left cusps (arrow). N: non-coronary cusp.

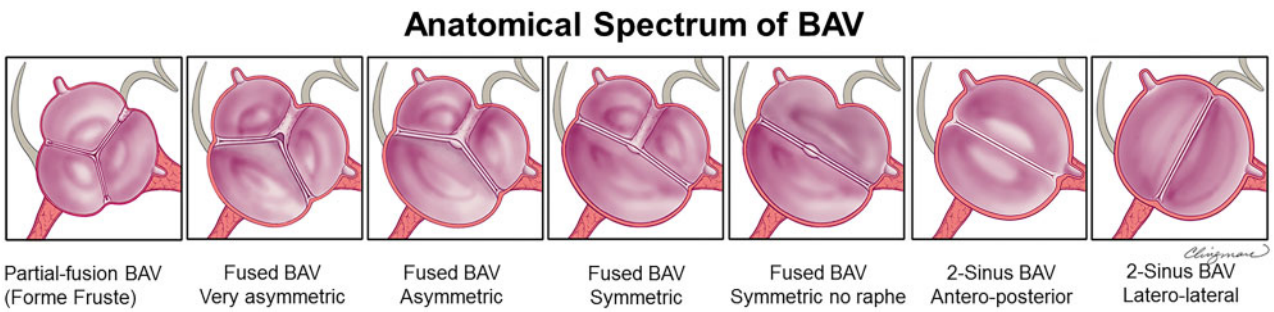


Figure 16: Schematic of the BAV anatomical spectrum using the most common right–left cusp fusion as the example. From left to right, note the partial-fusion BAV resembling a tricuspid aortic valve, likely associated with a mild embryological defect, then spanning a continuum of increasing non-fused cusp commissural angles and increasing cusp size/shape similarity, ending with the 2-sinus BAV phenotypes that represent almost perfect 'bicuspidity' and are likely associated with the most severe embryological defects. Modified from Michelena *et al.* [10] with permission from Elsevier. BAV: bicuspid aortic valve.

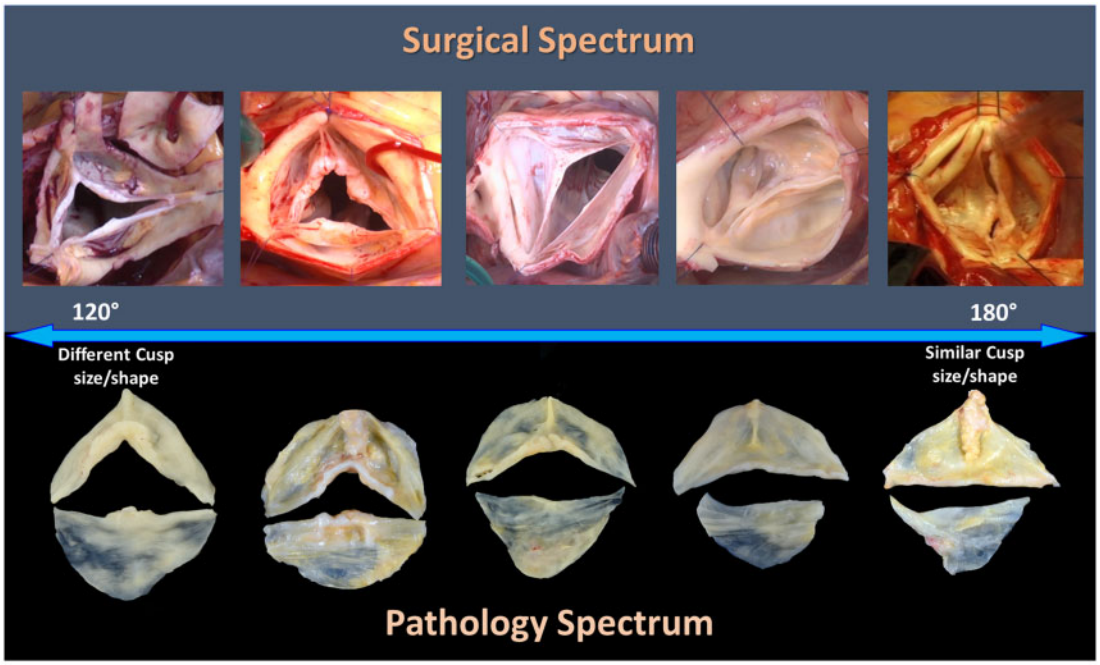


Figure 17: Surgical and pathological demonstration of the bicuspid aortic valve anatomical spectrum according to non-fused cusp commissural angles and cusp size/shape. (**Top**) Intraoperative photographs demonstrate the bicuspid aortic valve phenotypic spectrum. (**Bottom**) Photographs of the pathological specimens demonstrate the bicuspid aortic valve phenotypic spectrum.

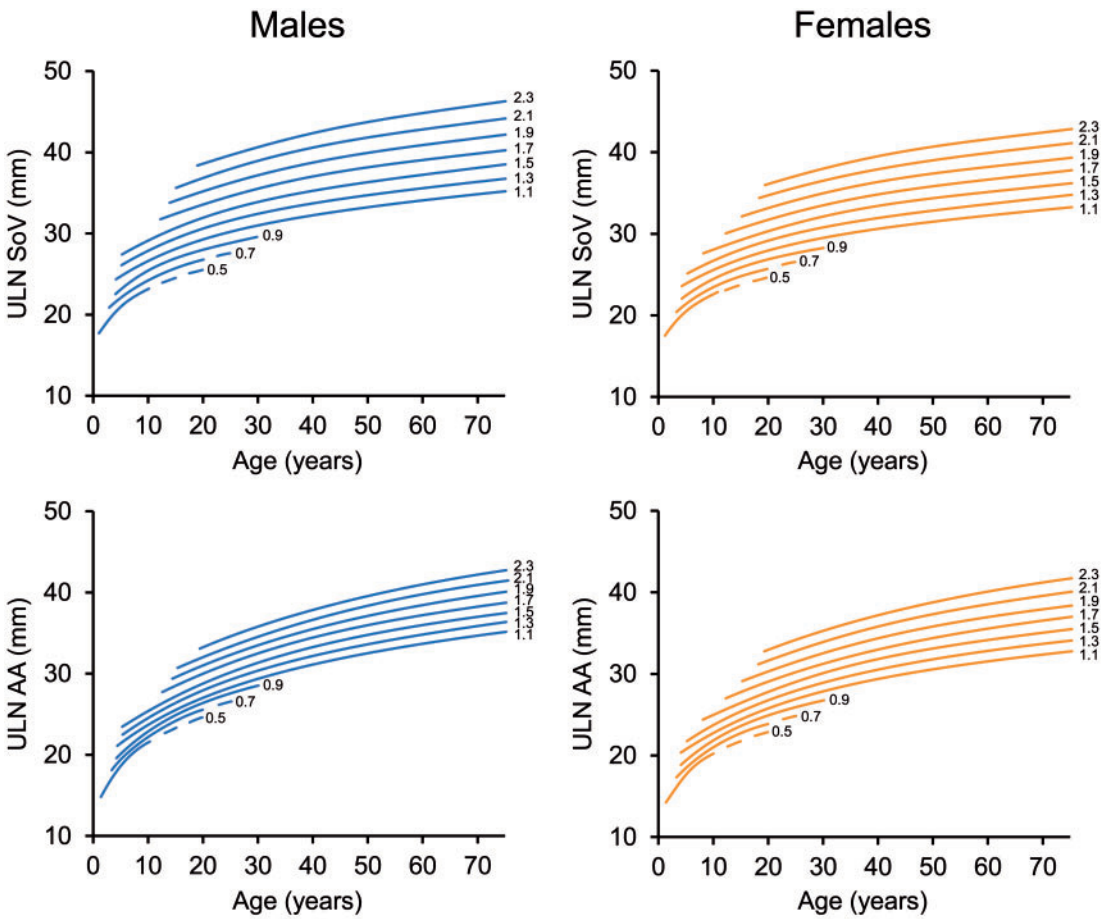


Figure 18: Nomograms based on transthoracic echocardiographic long-axis end-diastolic leading-edge-to-leading-edge measurements. Graphs display the ULN in millimetres (mm) for the root (SoV) and AA diameters as a function of body surface area (Dubois and Dubois formula) and age for both sexes. Modified from Campens *et al.* [78] with permission from Elsevier. AA: ascending aorta; ULN: upper limit of normal.

associated with the root phenotype [55, 102, 103]. However, those associations are not unequivocal, and the right–left cusp fusion BAV can be associated with either aortic phenotype [95].

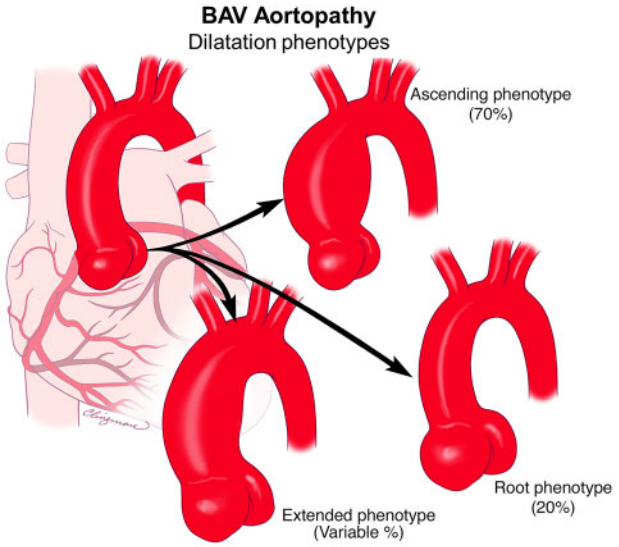


Figure 19: BAV aortopathy phenotypes. On the left is a normal aorta. (**Top**) The most common phenotype (approximately 70%), the ascending phenotype, is preferential dilatation of the tubular ascending aorta. (**Middle**) The root phenotype involves preferential dilatation of the root, seen in approximately 20% of patients with bicuspid aortic valve with aortopathy. (**Bottom**) The extended phenotype shows dilatation of the root, the ascending aorta and the arch. The most common extended phenotypes are root plus ascending aorta and ascending aorta plus arch. BAV: bicuspid aortic valve.

In addition, the presence of concomitant BAV stenosis can complicate the pattern of WSS expression independently of the cusp fusion phenotype [104]; therefore, the severity of the AS must be considered in the investigation of the valve-mediated aortopathy.

Notably, in some cases, the dilation of the aorta does not significantly prevail at 1 segment. In a proportion of patients, a localized dilatation at first observation can evolve during the follow-up period, with possible dilatation of previously normal adjacent segments of the aorta. In this scenario, the ascending phenotype can present, especially if a right non-cusp fusion valve is present [30, 33, 94, 105], with associated dilatation of the aortic arch; it is appropriate to refer to this condition as ascending phenotype extended. Similarly, the root phenotype has been demonstrated to be independently associated with faster growth of the ascending tubular tract, so that cases of 'cross-over' from an initial root phenotype configuration to significant dilatation of both tracts (and even extension into the proximal arch) have been observed [93, 105] (Fig. 19): Root phenotype extended would be an appropriate definition of this form. In the context of a root phenotype, the presence and progression of effacement of the STJ may be an initial sign of this kind of evolution.

The root phenotype has been associated with greater rates of acute aortic dissection in the postoperative follow-up of patients with BAV who had undergone simple AVR compared to the ascending phenotype [106]. The root phenotype may represent the expression of a bicuspid form of aortopathy fundamentally driven by some still unknown genetically determined connective tissue disorder, and it represents a risk factor for aortic complications within BAV aortopathy [1, 19], as previously mentioned.

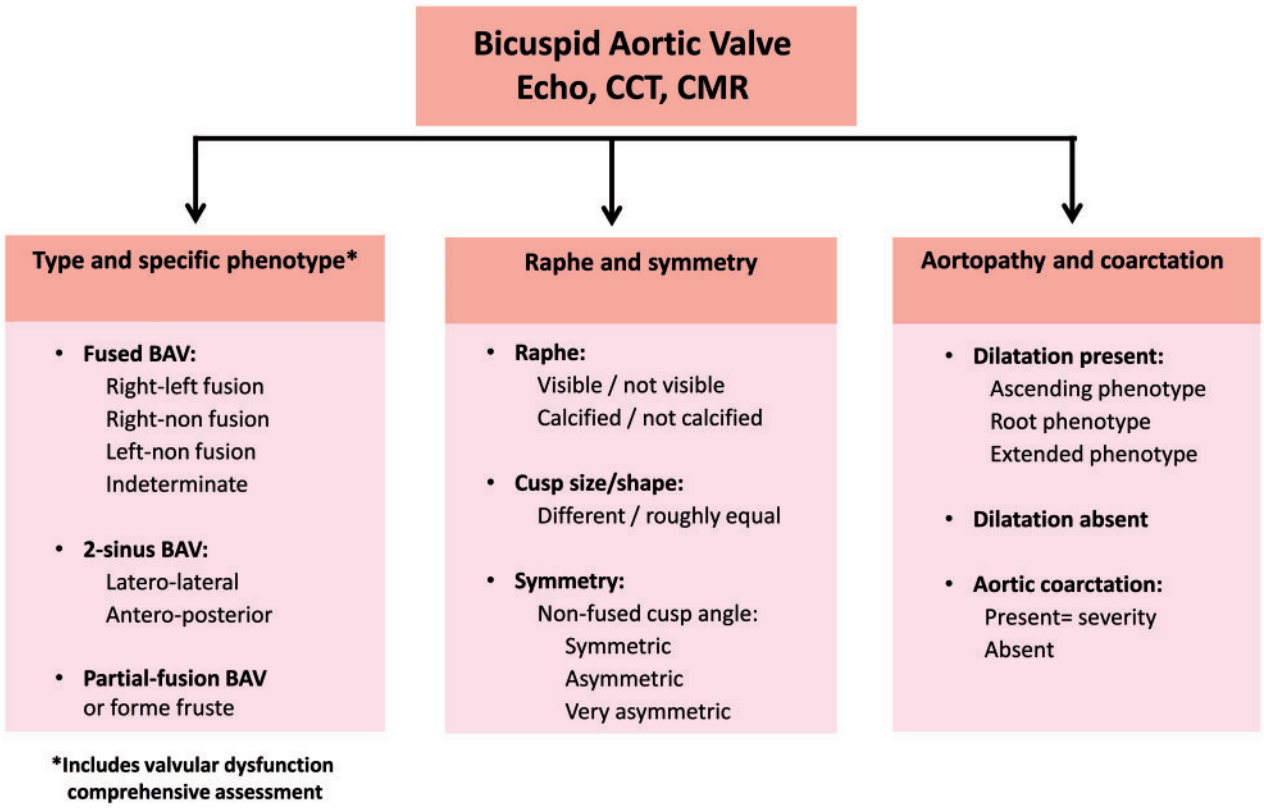
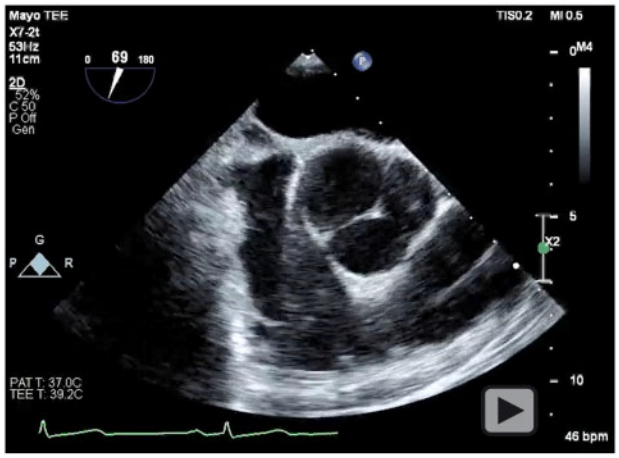


Figure 20: Critical imaging evaluation of the congenital BAV condition. BAV: bicuspid aortic valve; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance.



Video 11: Transoesophageal echocardiography mid-oesophageal short axis of partial-fusion bicuspid aortic valve (right–left).

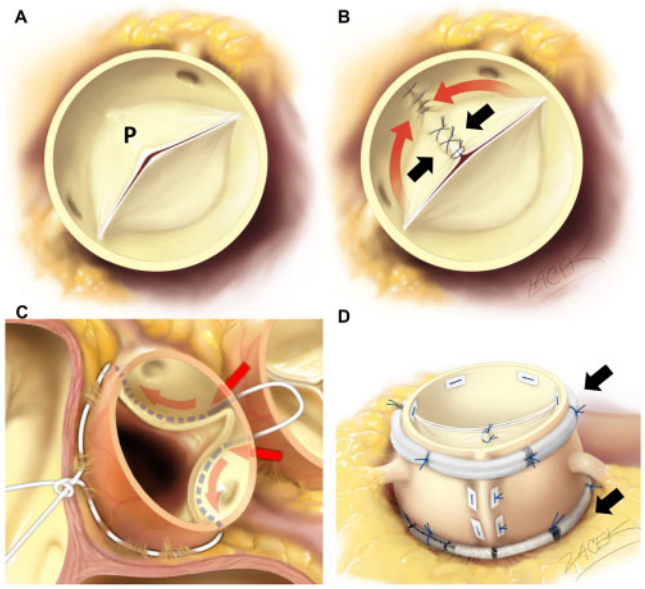


Figure 21: Schematic of surgical bicuspid aortic valve repair for aortic regurgitation. (**A**) Fused bicuspid aortic valve with the fused or conjoined cusp having prolapse (P). (**B**) Central plication sutures are applied to correct the prolapse of the fused cusp (black arrows). The sutures are best placed in the central portion of the cusp. The circumference of the fused sinus has been reduced through plication of the aortic wall, thus bringing the commissures into a more symmetrical configuration ('bicuspidization') (red arrows). (**C**) Suture annuloplasty placed at the basal level of the root, i.e. the functional (virtual) aortic annulus. (**D**) Alternatively, an external band annuloplasty may be used to stabilize the annulus (bottom arrow). A second band or ring has been placed at the sinotubular junction (top arrow), which would not be needed if the tubular ascending aorta needed replacement, because the proximal anastomosis of the ascending graft would stabilize the sinotubular junction. Modified from Pavel Zacek, MD, PhD, with permission.

Conversely, for the ascending phenotype, the inherently altered flow patterns of the bicuspid valve may mainly drive the disease, which is suggested not only by the previously mentioned associations between WSS patterns and the location of the dilatation (more proximal with the right–left cusp fusion, more distal with right non-cusp fusion) but also by the typical asymmetrical dilatation of the ascending tract, i.e. with dominant involvement of the greater curvature, that is, where the greatest WSS nearly

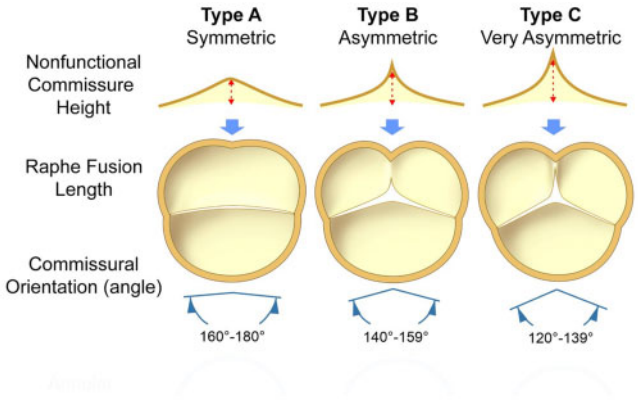


Figure 22: Repair-oriented bicuspid aortic valve classification according to commissural orientation. Commissural orientation optimal for repair is shown in the symmetrical type; the asymmetrical bicuspid aortic valve benefits from increasing its commissural angle; the very asymmetrical type should likely be best treated as a tricuspid aortic valve (see also Fig. 9). Note how the height of the fused commissure increases as the asymmetry increases and looks more like a tricuspid aortic valve. Note that the annulus tends to be more circular in symmetrical bicuspid aortic valve and becomes more elliptic with increasing bicuspid aortic valve asymmetry. From Pavel Zacek, MD, PhD, with permission.

invariably occurs [107, 108] (see Section Cardiac magnetic resonance considerations).

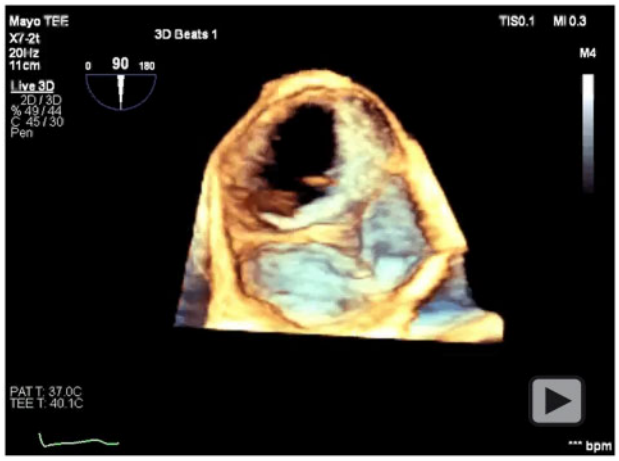
Summary

Based on the new nomenclature and classification consensus, Fig. 20 presents a simple algorithm of the critical imaging evaluation for the BAV valvulo-aortopathy. Three critical anatomical aspects must be described in all patients with BAV.

(i) The type and specific phenotype of the BAV and the valve function; (ii) the presence and characteristics of the raphe and the cusp size/shape and symmetry of the BAV; and (iii) the presence and phenotype of aortopathy (aortic dilatation) and whether or not coarctation is present.

SURGICAL CONSIDERATIONS

The current consensus nomenclature/classification proves critical for surgical practice and surgical research. The recent American Association for Thoracic Surgery consensus document [19] recommended surgery for aortic dilatation (root or ascending) exceeding 55 mm in the general population of patients with BAV and 50 mm in patients with BAV with further risk factors for dissection, including significant AR and/or root phenotype (Fig. 19) (see Section Definition of aorta dilatation). The knowledge about the segmental nature of the majority of aortopathy cases with non-syndromic BAV indicates that liberal extension of resection to adjacent non-dilated segments (i.e. extending ascending aorta repair to the root, especially with stenotic and/or right non-fused BAV, or to the arch) is not justified at the time of tubular ascending replacement [19]. Therefore, if the patient with BAV exhibits the most common aortopathy phenotype (ascending dilatation) with a normal or only mildly dilated root/arch, replacement of the tubular portion alone will suffice. Earlier diameter indication (i.e. 50 mm) for root replacement in the root phenotype with severe AR, especially in younger patients, emphasizes the need for valve repair rather than replacement, in centres with extensive



Video 12: 3-Dimensional transoesophageal echocardiography mid-oesophageal short axis of partial-fusion bicuspid aortic valve (right–left).

experience. Repair of the BAV has become an accepted alternative to replacement in patients with BAV regurgitation [25, 109]. Typically, the main mechanism leading to BAV regurgitation is the prolapse of the fused cusp (for fused BAV types) (Figs 6 and 7) and prolapse of 1 of the symmetrical cusps in the 2-sinus type (Figs 11–13). Other concomitant mechanisms include prolapse of the non-fused cusp and cusp retraction (Fig. 9). In addition, the aortic annulus is often dilated (i.e. >25 mm) [51], the sinuses may be enlarged and there may be STJ dilatation, all of which contribute to AR (root complex) (see Section Aortic root and root complex) (Fig. 3). Therefore, in general, the BAV repair comprises the plication of the free margins of the prolapsing cusps to correct the prolapse (Fig. 21) plus an annuloplasty suture or ring [110] to correct annular dilatation and stabilize the repair (Fig. 21). Additionally, stabilization of the STJ may require placement of a ring or ascending aorta replacement [110]. Alternatively, root replacement via a reimplantation technique will also stabilize the root at multiple levels. A critical discovery has been the importance of valve symmetry (see Section Symmetry of the fused bicuspid aortic valve types) (Figs 8 and 9), which can be measured preoperatively (Fig. 10). The closer the BAV phenotype is to a 2-sinus type with a symmetrical non-fused cusp commissural angle, the more feasible the repair will be [70] (Fig. 22). Otherwise, the surgeon uses techniques directed at 'bicuspidizing' the valve more (Section The bicuspid aortic valve anatomical spectrum) (Fig. 21). If the BAV is very asymmetrical, the surgeon will treat it as a tricuspid valve instead [43, 110].

GENETIC CONSIDERATIONS

Patients with a transforming growth factor beta (TGF-ß) ligand and receptor mutations that cause Loeys-Dietz syndrome (*TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*) and *ACTA2* mutations that cause heritable thoracic aortic aneurysms and dissections (HTAD) have a higher prevalence of BAV (4–15%) than the general population (1%), along with rapidly progressive aortic root dilation [5], a highly penetrant risk for aortic dissection, a variety of other congenital heart defects and, in some cases, a recognizable appearance with Marfanoid body features [88, 111]. Mutations of other HTAD genes that are not known to cause BAV, including *FBN1*, were identified in some patients with BAV with aortic root dilation who lack syndromic features, leading to speculation that 2 different genetic mutations may cause BAV and root phenotype aortopathy in rare individuals [99, 100, 112, 113]. In these cases, recommendations about medical therapies or the timing of interventions may be based on the specific HTAD gene [114]. However, more than 95% of BAV cases are sporadic, lack recognizable syndromic features and are not caused by mutations in known HTAD genes. Instead, rare or unique sequence or copy number variants in dozens of cardiac developmental genes have been identified in BAV [115]. Because any single gene may contribute to fewer than 1% of BAV cases, it is not possible to correlate mutated genes with specific valvular or aortic structural features before the results of large-scale sequencing studies involving thousands of patients with BAV with a common nomenclature and classification are available. Until then, clinical genetic testing should be reserved for the minority of patients with BAV with suspected HTAD gene mutations due to syndromic features, early onset or severe vascular disease or a family history of aortic dissection. This group includes a substantial proportion of individuals with *TGFBR1* pathogenic variants and BAV, who do not have recognizable features of Loeys-Dietz syndrome but who may present with rapidly progressive aortic root dilation [5].

CARDIAC MAGNETIC RESONANCE CONSIDERATIONS

Compared to echocardiography, CMR offers additional functional, anatomical, perfusion and myocardial viability information. It also allows for tissue characterization and myocardial fibrosis imaging and quantification (delayed gadolinium enhancement, T1-mapping). In addition, CMR has greater spatial resolution than echocardiography and is an ionizing radiation-free technique that is preferred over CT angiography (CTA) imaging when possible in younger patients and those who will likely have multiple interval imaging studies over their lifetime. Contrast-enhanced (gadolinium-based) CMR or cine CMR (without contrast media) is indicated in patients with BAV in the following situations: (i) when morphology and/or diameter of the aortic sinuses, STJ, ascending aorta or arch cannot be assessed accurately or fully by echocardiography; (ii) in the serial evaluation of size and morphology of the aorta; at least yearly in patients with BAV with >45-mm diameters or with a family history of aortic dissection; (iii) when echocardiography-derived aortic diameters are discrepant with those obtained using CMR, CMR should be the modality of choice for interval aortic imaging.

In patients with aortic valve stenosis, cellular hypertrophy and diffuse fibrosis progress in a rapid and balanced manner but are reversible after AVR. Mid-wall late gadolinium enhancement may allow for improved clinical outcomes by prompting timely AVR in patients with BAV and AS with fibrosis [116].

Scientific evidence for new CMR applications in BAV research and its associated complications is emerging at a fast pace. For example, 4D-flow CMR has shown potential value in the clinical setting when examining traditional risk factors for maximal aortic diameter (age, gender, body surface area, peak valve velocity and valve morphology), and concepts related to flow displacement or eccentric blood flow have shown encouraging correlations with aortic dilatation [117]. 4D flow is an ECG-gated 3-dimensional (3D) phase contrast-CMR velocity encoding technique that

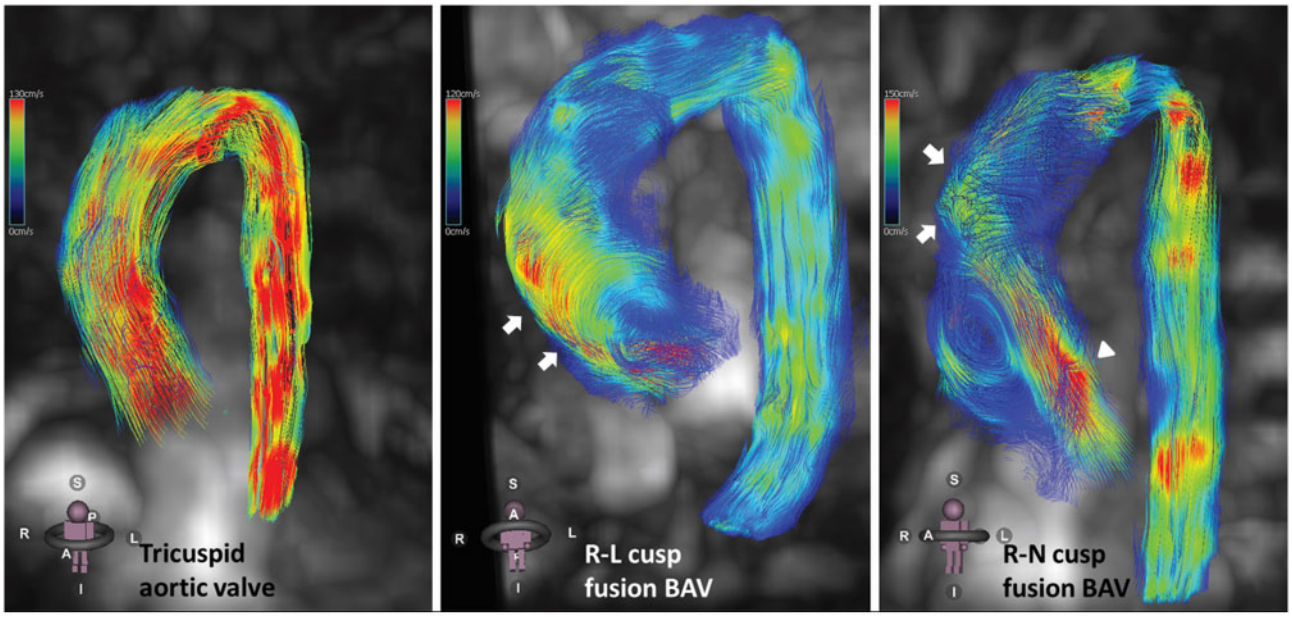
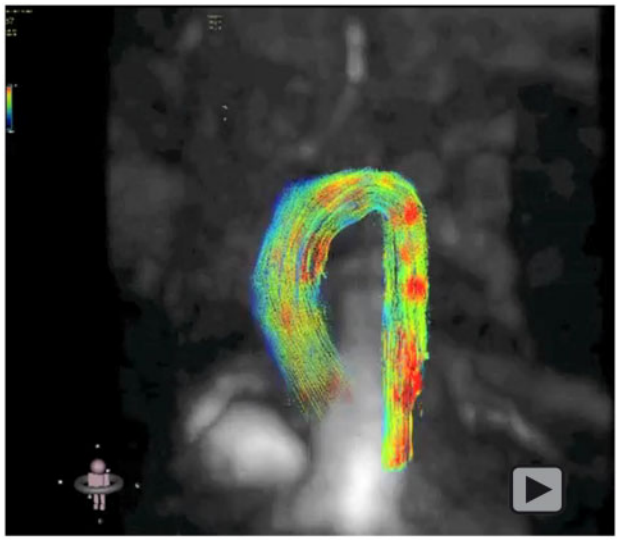
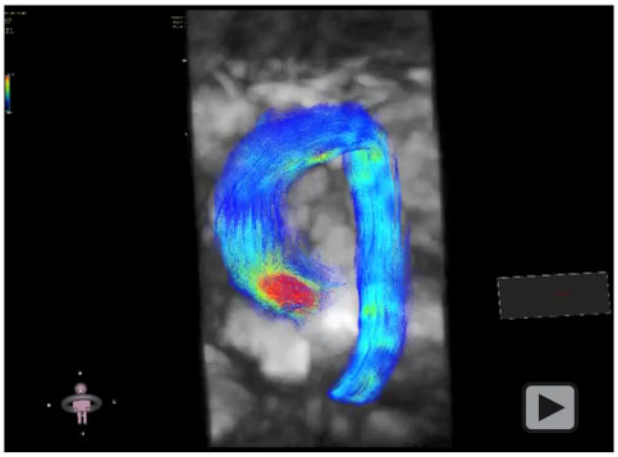


Figure 23: Cardiac magnetic resonance 4-dimensional flow. Systolic streamlines in a healthy volunteer (left), in a right–left cusp fusion (RL) patient with BAV (middle) and in a right non-cusp fusion (RN) patient (right). Neither the patients nor the volunteer had aortic valve stenosis, and neither had aortic surgery. Notice the difference in the flow direction: In right–left cusp fusion, flow impinges on the outer curvature of the proximal ascending aorta (arrows), including the root. In right non-cusp fusion, flow is posteriorly directed in the proximal aorta (arrowhead) and impinges on the outer wall in the distal ascending aorta (arrows) [Videos 13 (normal), 14 (right–left fusion) and 15 (right non-fusion)]. Visualization of the streamlines was obtained with CVI42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada by Andrea Guala, PhD, Vall d'Hebron Hospital. BAV: bicuspid aortic valve; L: left cusp; N: non-cusp; R: right cusp.



Video 13: Aorta 4-dimensional flow cardiac magnetic resonance of normal tricuspid aortic valve.



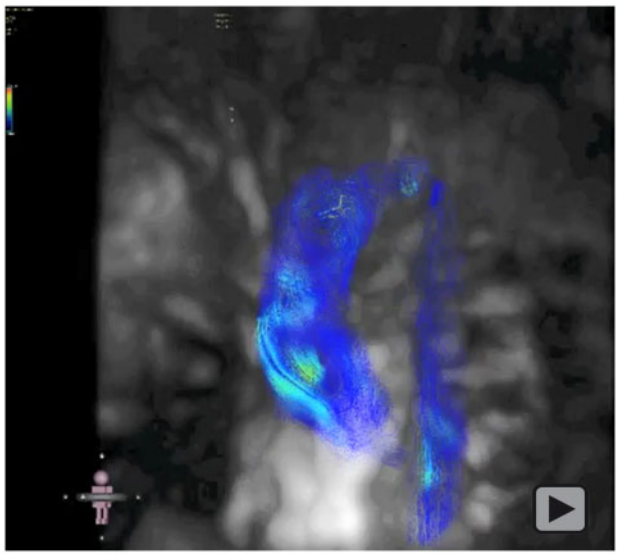
Video 14: Aorta 4-dimensional flow cardiac magnetic resonance of right–left fusion bicuspid aortic valve.

allows the visualization of global and local 3D blood flow characteristics in the heart and large vessels. It also allows for the measurement of different components of vascular mechanics, such as the WSS, which is the viscous shear force that blood flow exerts tangentially to the vessel wall, a known haemodynamic measure implicated in vascular remodelling. As mentioned previously (see Section Bicuspid aortic valve aortopathy phenotypes), 4D flow has allowed the study of 3D aortic blood-flow dynamics and its dependence on BAV phenotypes. In right–left cusp fusion BAV, the flow impinges on the outer curvature of the proximal ascending aorta, whereas right non-cusp fusion displays a posteriorly directed flow jet directed towards the proximal ascending aorta and the outer wall of the distal ascending aorta (Fig. 23; Videos 13–15). Therefore, BAV phenotype-dependent flow abnormalities can cause increased aortic wall segmental stress, which partially explains BAV aortopathy phenotypic associations (i.e. right–left cusp fusion associated with root dilatation, right non-cusp fusion with ascending/arch dilatation). 4D flow CMR has the potential of becoming an imaging biomarker for risk stratification of BAV aortopathy.

CARDIAC COMPUTED TOMOGRAPHY CONSIDERATIONS

Cardiac CT, in particular CTA, owing to its superior spatial resolution and 4D display, provides unparalleled visualization of the

aortic valve, the aortic root complex and the ascending aorta and serves as an important complement to echocardiography and other techniques in the evaluation of the BAV. Unlike echocardiography and CMR, CTA permits 4D isovolumetric imaging, which allows precise post hoc selection of imaging planes. A proper protocol is critical to an optimal quality CCT study, as has been described [118].



Video 15: Aorta 4-dimensional flow cardiac magnetic resonance of right non-fusion bicuspid aortic valve.

Appropriate evaluation of the aortic valve requires systolic phase imaging that is best achieved using retrospective ECG synchronized imaging. Whereas a full multiphase CCT data set allows for comprehensive imaging of the aortic valve (systole and diastole), coronary CTA is often performed during diastole. Given the high resolution of CCT, it is useful always to evaluate the aortic valve on all studies to determine, if possible, whether it is bicuspid or tricuspid. If imaging is done only during diastole, as is usually the case for routine coronary CTA, it may lead to overlooking the partial or complete fusion of the cusps and to mistaking the valve as tricuspid. One is unlikely to make this mistake if the tricuspid valve is symmetrical and has no leaflet/cusp thickening or asymmetrical calcifications. Although reconstructions to assess BAV can be obtained using preselected R-R intervals, it is advisable to identify the absolute delay after the R peak, usually specified in milliseconds, for best results. Tube modulation should be turned off during systole to reduce image noise during the critical phase of imaging. Intravenous contrast of 50–100 ml is administered with flow rates of 4–6 ml/s. Multiphasic data sets should be acquired and reconstructed with thin slices (<1 mm). Reformatting can be performed manually or with semiautomated software [118]. The annulus, sinuses and STJ levels can be defined using double-oblique views that permit measurement of the in-plane and through-plane aorta. For these reasons, CCT has been critical in surgical planning for conventional surgical AVR and has become the gold standard for pre-TAVR BAV evaluation [119]. In addition, because of high spatial resolution, ease of reformatting, significantly reduced radiation doses with newer scanners and the ability to simultaneously 'clear' the coronary arteries and avoid the need for coronary angiography in these younger

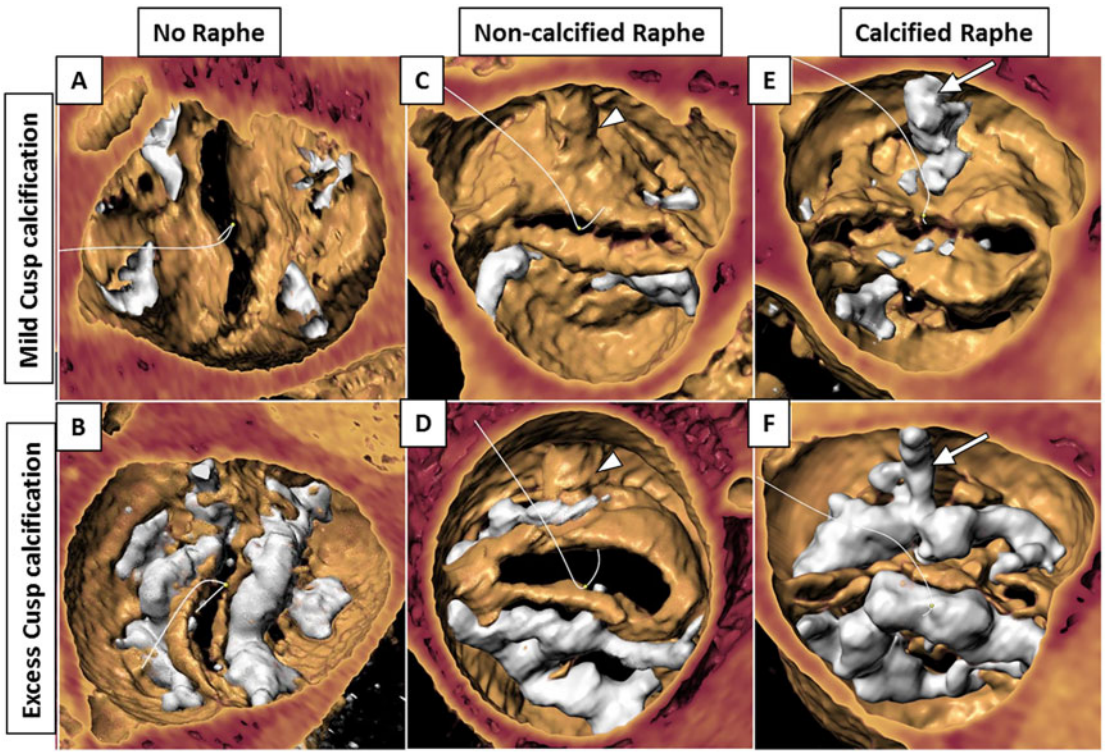


Figure 24: Cardiac computed tomography pre-transcatheter aortic valve replacement bicuspid aortic valve morphologies. Various aortic valve morphologies on volume-rendered computed tomography for bicuspid aortic valve stenosis (**A** through **F**) are shown. The bicuspid aortic valve is categorized as no raphe type (**A** and **B**) and raphe type (**C** through **F**). Raphe type is further categorized as non-calcified raphe type (**C** and **D**) and calcified raphe type (**E** and **F**). Arrowheads indicate non-calcified raphe and arrows indicate calcified raphe. Upper panels represent aortic valve with mild leaflet calcification and lower panels represent aortic valves with excess leaflet calcification. Modified from Yoon *et al.* [128] with permission from Elsevier.

patients with BAV, CCT/CTA is also the gold standard for preoperative surgical evaluation of BAV valvulo-aortopathy. A technique based on 3D multiplanar images has recently been described that optimizes visualization of the hinge points of the valve leaflets, allowing a distinction between commissures and raphes and thus may prove valuable in accurate characterization of the anatomy of the BAV [120]. More specifically, CTA can evaluate the specific BAV phenotypes including the presence of fusion and the orientation of the cusps in the 2-sinus BAV type, the extent of cusp symmetry, the degree of raphe calcification and the size of the cusps. The dimensions and morphology of the root, ascending aorta and arch can be optimally assessed on CTA to determine the presence of dilatation, its phenotype with respect to the aortic root or more distal aorta and the presence of aortic coarctation.

Akin to CMR, when the morphology and/or diameter of the aortic sinuses, the STJ or the ascending aorta cannot be assessed accurately or fully by echocardiography, CCT should be used; when echocardiography-derived aortic diameters are discrepant with those obtained with CTA, CTA should be the modality of choice for interval aortic imaging.

INTERVENTIONAL CARDIOLOGY CONSIDERATIONS

Based on numerous large randomized clinical trials, TAVR has emerged as an alternative to surgery for patients with severe aortic valve stenosis [121–123]. Within these studies, however, patients with BAV anatomy were excluded, due in part to concerns that TAVR in bicuspid valves may have suboptimal outcomes and/or increased complications. Indeed, with early generation transcatheter valves and limited use of CCT, TAVR in bicuspid anatomy was associated with lower device success rates and an increased incidence of significant paravalvular leak (PVL) [20, 124]. However, more recently, with careful CCT analysis as the standard for procedural planning and using current generation transcatheter valves designed to minimize PVL, non-randomized registry reports have suggested that TAVR in patients with BAV stenosis shows improving results [125, 126]. Yet, the impact of different bicuspid anatomies on TAVR outcomes remains an area of ongoing research and controversy. Although the classification system outlined here will help interventional cardiologists to categorize patients with bicuspid valves, to date there have been limited studies that have looked at TAVR outcomes stratified by bicuspid anatomy subtype (phenotype). This situation has been compounded by the fact that the Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapy Registry, which serves as an archive for all patients undergoing TAVR in the USA, does not collect information on the type of BAV. In contrast, the STS Surgical Database Form began collecting information on the Sievers classification in 2017 for patients with bicuspid valve disease undergoing surgical AVR. Much of the limited data on TAVR outcomes based on different bicuspid anatomical forms comes from Jilaihawi *et al.* [35], who in 2016 proposed a TAVR BAV classification whereby they characterized patients with a bicuspid anatomy into 3 categories: 'tricommissural', 'bicommissural raphe-type' and 'bicommissural non-raphe-type' (Table 1). Using primarily early generation TAVR devices, they found that for patients with a 2-sinus BAV (Figs 11–13), increased intracommissural distance was associated with increased PVL. There was also a trend towards an increased incidence of new pacemakers in patients with fused BAV with left–right cusp fusion (Figs 6 and 7). Results from the STS/ACC/TVTRegistry compared the outcomes of new-generation, balloon-expandable TAVR devices for bicuspid versus tricuspid AS in 2,691 propensity score matched pairs of bicuspid and tricuspid patients [126]. There were no differences in mortality, symptom improvement, PVL and valve haemodynamics, but there was an increase in 30-day strokes and periprocedural complications requiring surgery in the BAV cohort. A recent study reported on 929 propensity matched pairs (bicuspid versus tricuspid) with self-expandable TAVR devices; the researchers found no difference in 30-day or 1-year all-cause death or stroke; however, patients with a bicuspid valve undergoing TAVR were more likely to require aortic valve reintervention at both 30 days and 1 year compared to patients with tricuspid valve undergoing TAVR [127]. Finally, the Bicuspid AS TAVR Registry, which included 1,034 patients with analyses of CCT images [128] showed that patients with a calcified raphe or excess leaflet calcification had increased early mortality and higher rates of periprocedural complications including aortic root injury and moderate or severe PVL (Fig. 24). Therefore, universal equipoise between TAVR and surgical AVR for BAV AS has not been attained, and it will be critical to better understand the relationship between bicuspid anatomy, calcification patterns and TAVR outcomes, in particular, whether there are specific bicuspid phenotypes that are less conducive to TAVR.

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REFERENCES

[1] 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.
[2] 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.
[3] Michelena HI, Suri RM, Katan O, Eleid MF, Clavel MA, Maurer MJ *et al.* Sex differences and survival in adults with bicuspid aortic valves: verification in 3 contemporary echocardiographic cohorts. J Am Heart Assoc 2016;5:e004211.
[4] Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. Am J Cardiol 1970;26:72–83.
[5] Michelena HI, Vallabhajosyula S, Prakash SK. Nosology spectrum of the bicuspid aortic valve condition: complex-presentation valvulo-aortopathy. Circulation 2020;142:294–9.
[6] 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.
[7] Niaz T, Poterucha JT, Johnson JN, Craviari C, Nienaber T, Palfreeman J *et al.* Incidence, morphology, and progression of bicuspid aortic valve in pediatric and young adult subjects with coexisting congenital heart defects. Congenit Heart Dis 2017;12:261–9.
[8] Niaz T, Poterucha JT, Olson TM, Johnson JN, Craviari C, Nienaber T *et al.* Characteristic morphologies of the bicuspid aortic valve in patients with genetic syndromes. J Am Soc Echocardiogr 2018;31:194–200.
[9] 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.
[10] Michelena HI, Della Corte A, Evangelista A, Maleszewski JJ, Enriquez-Sarano M, Bax JJ *et al.* Speaking a common language: introduction to a standard terminology for the bicuspid aortic valve and its aortopathy. Prog Cardiovasc Dis 2020;63:419–24.
[11] Masri A, Svensson LG, Griffin BP, Desai MY. Contemporary natural history of bicuspid aortic valve disease: a systematic review. Heart 2017;103:1323–30.
[12] Brown ML, Burkhart HM, Connolly HM, Dearani JA, Cetta F, Li Z *et al.* Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol 2013;62:1020–5.
[13] Fuchs MM, Attenhofer JC, Babovic-Vuksanovic D, Connolly HM, Egbe A. Long-term outcomes in patients with turner syndrome: a 68-year follow-up. J Am Heart Assoc 2019;8:e011501.
[14] Michelena HI, Katan O, Suri RM, Baddour LM, Enriquez-Sarano M. Incidence of infective endocarditis in patients with bicuspid aortic valves in the community. Mayo Clin Proc 2016;91:122–3.
[15] Goldstein SA, Evangelista A, Abbara S, Arai A, Asch FM, Badano LP *et al.* Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging: endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2015;28:119–82.
[16] Saric M, Armour AC, Arnaout MS, Chaudhry FA, Grimm RA, Kronzon I *et al.* Guidelines for the use of echocardiography in the evaluation of a cardiac source of embolism. J Am Soc Echocardiogr 2016;29:1–42.
[17] 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.
[18] Gleeson TG, Mwangi I, Horgan SJ, Cradock A, Fitzpatrick P, Murray JG. Steady-state free-precession (SSFP) cine MRI in distinguishing normal and bicuspid aortic valves. J Magn Reson Imaging 2008;28:873–8.
[19] 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: executive summary. J Thorac Cardiovasc Surg 2018;156:473–80.
[20] 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.
[21] 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.
[22] 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.
[23] 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.
[24] Hagendorff A, Evangelista A, Fehske W, Schafers HJ. Improvement in the assessment of aortic valve and aortic aneurysm repair by 3-dimensional echocardiography. JACC Cardiovasc Imaging 2019;12:2225–44.
[25] Schneider U, Feldner SK, Hofmann C, Schope J, Wagenpfeil S, Giebels C *et al.* Two decades of experience with root remodeling and valve repair for bicuspid aortic valves. J Thorac Cardiovasc Surg 2017;153:S65–S71.
[26] Eleid MF, Forde I, Edwards WD, Maleszewski JJ, Suri RM, Schaff HV *et al.* Type A aortic dissection in patients with bicuspid aortic valves: clinical and pathological comparison with tricuspid aortic valves. Heart 2013;99:1668–74.
[27] Oliver JM, Alonso-Gonzalez R, Gonzalez AE, Gallego P, Sanchez-Recalde A, Cuesta E *et al.* Risk of aortic root or ascending aorta complications in patients with bicuspid aortic valve with and without coarctation of the aorta. Am J Cardiol 2009;104:1001–6.
[28] Padang R, Enriquez-Sarano M, Pislaru SV, Maalouf JF, Nkomo VT, Mankad SV *et al.* Coexistent bicuspid aortic valve and mitral valve prolapse: epidemiology, phenotypic spectrum, and clinical implications. Eur Heart J Cardiovasc Imaging 2019;20:677–86.
[29] 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.
[30] Kang JW, Song HG, Yang DH, Baek S, Kim DH, Song JM *et al.* Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction and bicuspid aortopathy: comprehensive evaluation using MDCT and echocardiography. JACC Cardiovasc Imaging 2013;6:150–61.
[31] Angelini A, Ho SY, Anderson RH, Devine WA, Zuberbuhler JR, Becker AE *et al.* The morphology of the normal aortic valve as compared with the aortic valve having two leaflets. J Thorac Cardiovasc Surg 1989;98:362–7.
[32] 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.
[33] 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.
[34] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226–33.
[35] 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.
[36] Sun BJ, Lee S, Jang JY, Kwon O, Bae JS, Lee JH *et al.* Performance of a simplified dichotomous phenotypic classification of bicuspid aortic valve to predict type of valvulopathy and combined aortopathy. J Am Soc Echocardiogr 2017;30:1152–61.
[37] Brandenburg RO Jr, Tajik AJ, Edwards WD, Reeder GS, Shub C, Seward JB. Accuracy of 2-dimensional echocardiographic diagnosis of congenitally bicuspid aortic valve: echocardiographic-anatomic correlation in 115 patients. Am J Cardiol 1983;51:1469–73.

[38] Murphy IG, Collins J, Powell A, Markl M, McCarthy P, Malaisrie SC *et al.* Comprehensive 4-stage categorization of bicuspid aortic valve leaflet morphology by cardiac MRI in 386 patients. Int J Cardiovasc Imaging 2017;33:1213–21.
[39] Fernández B, Durán AC, Martire A, López D, Sans-Coma V. New embryological evidence for the formation of quadricuspid aortic valves in the Syrian hamster (*Mesocricetus auratus*). J Comp Pathol 1999;121: 89–94.
[40] Lopez-Garcia A, Carmen Fernandez M, Duran AC, Sans-Coma V, Fernandez B. Quadricuspid aortic valves in Syrian hamsters and their formation according to current knowledge on valvulogenesis. Jpn J Vet Res 2015;63:37–43.
[41] Slostad BD, Witt CM, O'Leary PW, Maleszewski JJ, Scott CG, Dearani JA *et al.* Unicuspid aortic valve: demographics, comorbidities, echocardiographic features, and long-term outcomes. Circulation 2019;140:1853–5.
[42] Tsang MY, Abudiab MM, Ammash NM, Naqvi TZ, Edwards WD, Nkomo VT *et al.* Quadricuspid aortic valve: characteristics, associated structural cardiovascular abnormalities, and clinical outcomes. Circulation 2016; 133:312–9.
[43] 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.
[44] Barker AJ, Robinson JD, Markl M. Bicuspid aortic valve phenotype and aortopathy: nomenclature and role of aortic hemodynamics. JACC Cardiovasc Imaging 2013;6:921.
[45] 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.
[46] Roberts WC, Vowels TJ, Ko JM. Comparison of interpretations of valve structure between cardiac surgeon and cardiac pathologist among adults having isolated aortic valve replacement for aortic valve stenosis (+/- aortic regurgitation). Am J Cardiol 2009;103:1139–45.
[47] Sievers HH, Hemmer W, Beyersdorf F, Moritz A, Moosdorf R, Lichtenberg A *et al.*; on behalf of the Working Group for Aortic Valve Surgery of the German Society of Thoracic and Cardiovascular Surgery. The everyday used nomenclature of the aortic root components: the tower of Babel? Eur J Cardiothorac Surg 2012;41:478–82.
[48] de Kerchove L, Jashari R, Boodhwani M, Duy KT, Lengele B, Gianello P *et al.* Surgical anatomy of the aortic root: implication for valve-sparing reimplantation and aortic valve annuloplasty. J Thorac Cardiovasc Surg 2015;149:425–33.
[49] Khelil N, Sleilaty G, Palladino M, Fouda M, Escande R, Debauchez M *et al.* Surgical anatomy of the aortic annulus: landmarks for external annuloplasty in aortic valve repair. Ann Thorac Surg 2015;99:1220–6.
[50] El KG, Glineur D, Rubay J, Verhelst R, d'Acoz Y, Poncelet A *et al.* Functional classification of aortic root/valve abnormalities and their correlation with etiologies and surgical procedures. Curr Opin Cardiol 2005; 20:115–21.
[51] Yang LT, Pellikka PA, Enriquez-Sarano M, Maalouf JF, Scott CG, Michelena HI. Stage B aortic regurgitation in bicuspid aortic valve: new observations on progression rate and predictors. JACC Cardiovasc Imaging 2020;13:1442–5.
[52] Schneider U, Hofmann C, Aicher D, Takahashi H, Miura Y, Schafers HJ. Suture annuloplasty significantly improves the durability of bicuspid aortic valve repair. Ann Thorac Surg 2017;103:504–10.
[53] Stefek HA, Lin KH, Rigsby CK, Michelena HI, Aouad P, Barker AJ *et al.* Eccentric enlargement of the aortic sinuses in pediatric and adult patients with bicuspid aortic valves: a cardiac MRI study. Pediatr Cardiol 2020;41:350–60.
[54] 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.
[55] Evangelista A, Gallego P, Calvo-Iglesias F, Bermejo J, Robledo-Carmona J, Sanchez V *et al.* Anatomical and clinical predictors of valve dysfunction and aortic dilation in bicuspid aortic valve disease. Heart 2018;104: 566–73.
[56] Yang LT, Enriquez-Sarano M, Michelena HI. The bicuspid aortic valve raphe: an evolving structure. Eur Heart J Cardiovasc Imaging 2020;21: 590.
[57] Kong WKF, Regeer MV, Poh KK, Yip JW, van Rosendael PJ, Yeo TC *et al.* Inter-ethnic differences in valve morphology, valvular dysfunction, and aortopathy between Asian and European patients with bicuspid aortic valve. Eur Heart J 2018;39:1308–13.
[58] Fernandes S, Khairy P, Graham DA, Colan SD, Galvin TC, Sanders SP *et al.* Bicuspid aortic valve and associated aortic dilation in the young. Heart 2012;98:1014–9.
[59] 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.
[60] 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.
[61] Fernandes SM, Sanders SP, Khairy P, Jenkins KJ, Gauvreau K, Lang P *et al.* Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol 2004;44:1648–51.
[62] Fernandes SM, Khairy P, Sanders SP, Colan SD. Bicuspid aortic valve morphology and interventions in the young. J Am Coll Cardiol 2007;49: 2211–4.
[63] Sun BJ, Jin X, Song JK, Lee S, Lee JH, Park JB *et al.* Clinical characteristics of Korean patients with bicuspid aortic valve who underwent aortic valve surgery. Korean Circ J 2018;48:48–58.
[64] Chandra S, Lang RM, Nicolarsen J, Gayat E, Spencer KT, Mor-Avi V *et al.* Bicuspid aortic valve: inter-racial difference in frequency and aortic dimensions. JACC Cardiovasc Imaging 2012;5:981–9.
[65] Fernandez B, Duran AC, Fernandez-Gallego T, Fernandez MC, Such M, Arque JM *et al.* Bicuspid aortic valves with different spatial orientations of the leaflets are distinct etiological entities. J Am Coll Cardiol 2009;54: 2312–8.
[66] Sans-Coma V, Fernandez B, Duran AC, Thiene G, Arque JM, Munoz-Chapuli R *et al.* Fusion of valve cushions as a key factor in the formation of congenital bicuspid aortic valves in Syrian hamsters. Anat Rec 1996; 244:490–8.
[67] Fernández B, Soto-Navarrete MT, López-García A, López-Unzu MÁ, Durán AC, Fernández MC. Bicuspid aortic valve in 2 model species and review of the literature. Vet Pathol 2020;57:321–31.
[68] Phillips HM, Mahendran P, Singh E, Anderson RH, Chaudhry B, Henderson DJ. Neural crest cells are required for correct positioning of the developing outflow cushions and pattern the arterial valve leaflets. Cardiovasc Res 2013;99:452–60.
[69] Soto-Navarrete MT, Lopez-Unzu MA, Duran AC, Fernandez B. Embryonic development of bicuspid aortic valves. Prog Cardiovasc Dis 2020;63:407–418.
[70] Aicher D, Kunihara T, Abou Issa O, Brittner B, Gräber S, Schäfers H-J. Valve configuration determines long-term results after repair of the bicuspid aortic valve. Circulation 2011;123:178–85.
[71] Sperling JS, Lubat E. Forme fruste or 'Incomplete' bicuspid aortic valves with very small raphes: the prevalence of bicuspid valve and its significance may be underestimated. Int J Cardiol 2015;184:1–5.
[72] Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. J Am Soc Echocardiogr 2011;24:229–67.
[73] Guala A, Rodriguez-Palomares J, Galian-Gay L, Teixido-Tura G, Johnson KM, Wieben O *et al.* Partial aortic valve leaflet fusion is related to deleterious alteration of proximal aorta hemodynamics. Circulation 2019; 139:2707–9.
[74] Michelena HI, Yang LT, Enriquez-Sarano M, Pochettino A. The elusive 'forme fruste' bicuspid aortic valve: 3D transoesophageal echocardiography to the rescue. Eur Heart J Cardiovasc Imaging 2020;21:1169–1169.
[75] Wang Y, Wu B, Farrar E, Lui W, Lu P, Zhang D *et al.* Notch-Tnf signalling is required for development and homeostasis of arterial valves. Eur Heart J 2017;38:675–86.
[76] Odelin G, Faure E, Coulpier F, Di Bonito M, Bajolle F, Studer M *et al.* Krox20 defines a subpopulation of cardiac neural crest cells contributing to arterial valves and bicuspid aortic valve. Development 2018;145: dev151944.
[77] Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr *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.

[78] Campens L, Demulier L, De Groote K, Vandekerckhove K, De Wolf D, Roman MJ *et al.* Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. Am J Cardiol 2014;114:914–20.

[79] Devereux RB, de Simone G, Arnett DK, Best LG, Boerwinkle E, Howard BV *et al.* Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons ≥15 years of age. Am J Cardiol 2012;110:1189–94.

[80] Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;64:507–12.

[81] Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. J Appl Physiol (1985) 2005;99:445–57.

[82] Garcier JM, Petitcolin V, Filaire M, Mofid R, Azarnouch K, Ravel A *et al.* Normal diameter of the thoracic aorta in adults: a magnetic resonance imaging study. Surg Radiol Anat 2003;25:322–9.

[83] Vriz O, Aboyans V, D'Andrea A, Ferrara F, Acri E, Limongelli G *et al.* Normal values of aortic root dimensions in healthy adults. Am J Cardiol 2014;114:921–7.

[84] Wolak A, Gransar H, Thomson LE, Friedman JD, Hachamovitch R, Gutstein A *et al.* Aortic size assessment by noncontrast cardiac computed tomography: normal limits by age, gender, and body surface area. JACC Cardiovasc Imaging 2008;1:200–9.

[85] Park JY, Foley TA, Bonnichsen CR, Maurer MJ, Goergen KM, Nkomo VT *et al.* Transthoracic echocardiography versus computed tomography for ascending aortic measurements in patients with bicuspid aortic valve. J Am Soc Echocardiogr 2017;30:625–35.

[86] Colan SD. The why and how of Z scores. J Am Soc Echocardiogr 2013;26:38–40.

[87] Voges I, Jerosch-Herold M, Hedderich J, Pardun E, Hart C, Gabbert DD *et al.* Normal values of aortic dimensions, distensibility, and pulse wave velocity in children and young adults: a cross-sectional study. J Cardiovasc Magn Reson 2012;14:77.

[88] Jondeau G, Ropers J, Regalado E, Braverman A, Evangelista A, Teixedo G *et al.* International registry of patients carrying TGFBR1 or TGFBR2 mutations: results of the MAC (Montalcino Aortic Consortium). Circ Cardiovasc Genet 2016;9:548–58.

[89] Silberbach M, Roos-Hesselink JW, Andersen NH, Braverman AC, Brown N, Collins RT *et al.*; On behalf of the American Heart Association Council on Cardiovascular Disease in the Young; Council on Genomic and Precision Medicine; and Council on Peripheral Vascular Disease. Cardiovascular Health in Turner Syndrome: a scientific statement from the American Heart Association. Circ Genom Precis Med 2018;11:e000048.

[90] Wojnarski CM, Svensson LG, Roselli EE, Idrees JJ, Lowry AM, Ehrlinger J *et al.* Aortic dissection in patients with bicuspid aortic valve-associated aneurysms. Ann Thorac Surg 2015;100:1666–73; discussion 1673–4.

[91] Masri A, Kalahasti V, Svensson LG, Alashi A, Schoenhagen P, Roselli EE *et al.* Aortic cross-sectional area/height ratio and outcomes in patients with bicuspid aortic valve and a dilated ascending aorta. Circ Cardiovasc Imaging 2017;10:e006249.

[92] Della Corte A, Michelena HI, Citarella A, Votta E, Piatti F, Lo Presti F *et al.* Risk stratification in bicuspid aortic valve aortopathy: emerging evidence and future perspectives. Curr Probl Cardiol 2021;46:100428.

[93] Della Corte A, Bancone C, Buonocore M, Dialetto G, Covino FE, Manduca S *et al.* Pattern of ascending aortic dimensions predicts the growth rate of the aorta in patients with bicuspid aortic valve. JACC Cardiovasc Imaging 2013;6:1301–10.

[94] Della Corte A, Bancone C, Dialetto G, Covino FE, Manduca S, Montibello MV *et al.* The ascending aorta with bicuspid aortic valve: a phenotypic classification with potential prognostic significance. Eur J Cardiothorac Surg 2014;46:240–7; discussion 247.

[95] Wojnarski CM, Roselli EE, Idrees JJ, Zhu Y, Carnes TA, Lowry AM *et al.* Machine-learning phenotypic classification of bicuspid aortopathy. J Thorac Cardiovasc Surg 2018;155:461–9.e4.

[96] Adamo L, Braverman AC. Surgical threshold for bicuspid aortic valve aneurysm: a case for individual decision-making. Heart 2015;101:1361–7.

[97] Avadhani SA, Martin-Doyle W, Shaikh AY, Pape LA. Predictors of ascending aortic dilation in bicuspid aortic valve disease: a five-year prospective study. Am J Med 2015;128:647–52.

[98] Thanassoulis G, Yip JW, Filion K, Jamorski M, Webb G, Siu SC *et al.* Retrospective study to identify predictors of the presence and rapid progression of aortic dilatation in patients with bicuspid aortic valves. Nat Rev Cardiol 2008;5:821–8.

[99] Girdauskas E, Geist L, Disha K, Kazakbaev I, Groß T, Schulz S *et al.* Genetic abnormalities in bicuspid aortic valve root phenotype: preliminary results. Eur J Cardiothorac Surg 2017;52:156–62.

[100] Pepe G, Nistri S, Giusti B, Sticchi E, Attanasio M, Porciani C *et al.* Identification of fibrillin 1 gene mutations in patients with bicuspid aortic valve (BAV) without Marfan syndrome. BMC Med Genet 2014;15:23.

[101] Barker AJ, Markl M, Burk J, Lorenz R, Bock J, Bauer S *et al.* Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. Circ Cardiovasc Imaging 2012;5:457–66.

[102] Mahadevia R, Barker AJ, Schnell S, Entezari P, Kansal P, Fedak PW *et al.* Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. Circulation 2014;129:673–82.

[103] Rodriguez-Palomares JF, Dux-Santoy L, Guala A, Kale R, Maldonado G, Teixido-Tura G *et al.* Aortic flow patterns and wall shear stress maps by 4D-flow cardiovascular magnetic resonance in the assessment of aortic dilatation in bicuspid aortic valve disease. J Cardiovasc Magn Reson 2018;20:28.

[104] van Ooij P, Markl M, Collins JD, Carr JC, Rigsby C, Bonow RO *et al.* Aortic valve stenosis alters expression of regional aortic wall shear stress: new insights from a 4-dimensional flow magnetic resonance imaging study of 571 subjects. J Am Heart Assoc 2017;6:e005959.

[105] 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.

[106] Girdauskas E, Disha K, Rouman M, Espinoza A, Borger MA, Kuntze T. Aortic events after isolated aortic valve replacement for bicuspid aortic valve root phenotype: echocardiographic follow-up study. Eur J Cardiothorac Surg 2015;48:e71–6.

[107] Forte A, Yin X, Fava M, Bancone C, Cipollaro M, De Feo M *et al.* Locally different proteome in aortas from patients with stenotic tricuspid and bicuspid aortic valvesdagger. Eur J Cardiothorac Surg 2019;56:458–69.

[108] Guzzardi DG, Barker AJ, van Ooij P, Malaisrie SC, Puthumana JJ, Belke DD *et al.* Valve-related hemodynamics mediate human bicuspid aortopathy: insights from wall shear stress mapping. J Am Coll Cardiol 2015;66:892–900.

[109] Zeeshan A, Idrees JJ, Johnston DR, Rajeswaran J, Roselli EE, Soltesz EG *et al.* Durability of aortic valve cusp repair with and without annular support. Ann Thorac Surg 2018;105:739–48.

[110] Lansac E, de Kerchove L. Aortic valve repair techniques: state of the art. Eur J Cardiothorac Surg 2018;53:1101–7.

[111] Lindsay ME, Schepers D, Bolar NA, Doyle JJ, Gallo E, Fert-Bober J *et al.* Loss-of-function mutations in TGFB2 cause a syndromic presentation of thoracic aortic aneurysm. Nat Genet 2012;44:922–7.

[112] Braverman AC, Roman MJ. Bicuspid aortic valve in Marfan syndrome. Circ Cardiovasc Imaging 2019;12:e008860.

[113] Yassine NM, Shahram JT, Body SC. Pathogenic mechanisms of bicuspid aortic valve aortopathy. Front Physiol 2017;8:687.

[114] Milewicz DM, Regalado ES. Use of genetics for personalized management of heritable thoracic aortic disease: how do we get there? J Thorac Cardiovasc Surg 2015;149:S3–5.

[115] Gillis E, Kumar AA, Luyckx I, Preuss C, Cannaerts E, van de Beek G *et al.* Candidate gene resequencing in a large bicuspid aortic valve-associated thoracic aortic aneurysm cohort: SMAD6 as an important contributor. Front Physiol 2017;8:400.

[116] Everett RJ, Tastet L, Clavel MA, Chin CWL, Capoulade R, Vassiliou VS *et al.* Progression of hypertrophy and myocardial fibrosis in aortic stenosis:

a multicenter cardiac magnetic resonance study. Circ Cardiovasc Imaging 2018;11:e007451.
[117] Garcia J, Barker AJ, Murphy I, Jarvis K, Schnell S, Collins JD *et al.* Four-dimensional flow magnetic resonance imaging-based characterization of aortic morphometry and haemodynamics: impact of age, aortic diameter, and valve morphology. Eur Heart J Cardiovasc Imaging 2016;17: 877–84.
[118] 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. J Cardiovasc Comput Tomogr 2019;13:1–20.
[119] Francone M, Budde RPJ, Bremerich J, Dacher JN, Loewe C, Wolf F *et al.* CT and MR imaging prior to transcatheter aortic valve implantation: standardisation of scanning protocols, measurements and reporting-a consensus document by the European Society of Cardiovascular Radiology (ESCR). Eur Radiol 2020;30:2627–50.
[120] Amoretti F, Cerillo AG, Mariani M, Stefano P. A simple method to visualize the bicuspid aortic valve pathology by cardiac computed tomography. J Cardiovasc Comput Tomogr 2020;14:195–8.
[121] 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.
[122] 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.
[123] 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.
[124] Mylotte D, Lefevre T, Sondergaard 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.
[125] 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.
[126] 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.
[127] 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;13:1749–1759.
[128] 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.