# Bicuspid aortic valve disease

*James C. Lee and Catherine M. Otto*

Division of Cardiology, University of Washington, Seattle, United State of America

Address for correspondence:
James C. Lee and Catherine M. Otto
Division of Cardiology
University of Washington
Seattle
WA 98195
United State of America

Email:
jamchlee@cardiology.washington.edu, cmotto@uw.edu

## ABSTRACT

**The prevalence of bicuspid aortic valve (BAV) disease is 0.5 - 2% of the population with a 3:1 male predominance. The genetic basis remains unknown although 9% of families have more than one affected individual. Life expectancy in patients with BAV is similar to the general population with a 10-year survival of over 95%. Adverse outcomes are most often due to aortic stenosis late in life, aortic regurgitation in young adulthood or endocarditis in a small number of patients. The BAV syndrome is also associated with an aortopathy characterised by aortic dilation and an increased risk of aortic dissection. Clinical management of patients with a BAV focuses on periodic evaluation of valve function and aortic size, patient education about the expected disease course, prevention of endocarditis and optimal timing of aortic valve replacement for stenosis and/or regurgitation; with concurrent root replacement if aortic dilation (>4.5cm diameter) is present. In addition, aortic root replacement is recommended if aortic diameter exceeds 5.5cm, even if aortic valve function remains normal.** SAHeart 2017;14:76-85

## INTRODUCTION

Aortic valve abnormalities have been recognised from the earliest days of medicine. Leonardo da Vinci's notes include comments on the efficiency of trileaflet valve morphology and contain a sketch of what appears to be a bicuspid aortic valve (BAV).[1,2] In the 19th century, case reports and series highlighting BAV pathology began appearing along with suggestions of the now well known relationship between aortic valve dysfunction, endocarditis, and aortopathy.[3-5] Currently, the prevalence of BAV is estimated to be 0.5 - 2%[6] with a male: female ratio of approximately 3:1. Consistent with a congenital anomaly, these frequencies remain essentially unchanged whether evaluated in neonates,[7] children,[6] adults[8] or at necropsy.[9]

## ETIOLOGY

Development of the heart is a complex process that begins with the formation of the heart tube at approximately 21 days post fertilisation, with completion of the mature heart at approximately day 50.[10-12] The cardiac outflow tract is initially formed by migration of cardiac neural crest cells with the development of a common semilunar valve. The conotruncal cushions form the right and left coronary leaflets of the aortic valve and the non-coronary leaflet forms separately from the right posterior intercalated cushion.[11] As the heart develops, the common semilunar valve is septated into the adult aortic and pulmonary valves with the leaflets developing via a process of cavitation into three distinct layers (fibrosa, spongiosa, and ventricularis).[11]

The development of the aorta is also a complex process in which the common truncus arteriosus is septated into the aorta and pulmonary arteries. Abnormalities in septation are the cause of common congenital heart defects such as tetraology of Fallot. This process is also likely related to the migration of cardiac neural crest cells from the pharyngeal arches and heart;[10] and these neuronal crest cells may be similar in origin to the cells involved in the development of the aortic outflow tract and aortic valve.[13] This common pathway may explain the dual involvement of abnormalities in the elastic matrix, seen in both the tissue of the BAV as well as the proximal ascending aorta.[14]

Despite a growing knowledge of the tightly regulated process of valve formation, the cause of the BAV syndrome remains unclear. A genetic basis is suggested by observations in first-degree relatives, where the incidence of BAV is approximately

9.1 - 14.6%.[15,16] Additional familial clustering is seen with approximately 36.7% of families having more than one relative with a BAV.[16] The most notable gene mutation associated with BAV is in NOTCH1, an autosomal dominant signaling and transcriptional regulator involved in valve development.[17] Several other genes have been associated with BAV, including mutations in GATA5, TGFBR1 and TGFBR2.[18,19] Likely related to the complexities of BAV inheritance patterns and variable classification schemes, a clear single gene basis for the BAV phenotype has not been clearly established; it is plausible that the BAV syndrome is actually a complex multifactorial manifestation of both environmental and genetic issues.

Wide availability of rapid gene sequencing has increased interest in using Genome Wide Association Studies (GWAS) to evaluate valve disease; however the heterogeneity of the BAV syndrome has made primary analysis of the genetics challenging. Instead, early research has centered on the idea of secondary calcification of the BAV developing as a similar but accelerated process compared to the tricuspid aortic valve; and in this realm, progress has been made in the identification of novel loci for aortic valve and mitral annular calcification.[20,21] As imaging technology continues to develop, improved phenotyping of the BAV may improve the utility of GWAS in understanding its underlying genetics and pathophysiology. Regardless, it has become clear that further advancement will depend on efforts to create a targeted and planned approach for future studies.[22, 23]

## PHENOTYPE

One of the main challenges in identifying BAV-associated genes is the large number of differing phenotypic classification schemes.[24-28] Despite this challenge, the many prognostic implications of diagnosis of a BAV demand caution and meticulous care in establishing a diagnosis, as even a phenotype with partial valve fusion may express features of the early valve degeneration and aortopathy (Figure 1). Although classifications often differ in the names given for each phenotype, most systems focus on leaflet morphology and include (1) orientation of the open leaflets or position of the commissures and (2) the presence or absence of a raphe. Some classifications include the presence and orientation of coronary arteries, although this information is implicit in most current classifications.[27] In addition to valve morphology, more complete phenotypic classifications also include typing of aortic dilation.[25]

In most patients, a BAV is an isolated anomaly, but can be more prevalent in certain conditions (Table 1). For example, in patients with an aortic coarctation about 50% have a BAV. Correspondingly, only about 5 - 10% of BAV patients have an aortic coarctation, but this diagnosis should still be excluded in this population. It is hoped that further study into these special populations may provide further information regarding the etiology and development of the BAV syndrome.

## LEAFLET MORPHOLOGY

Transthoracic echocardiography (TTE) is the standard approach for evaluation of leaflet morphology due to widespread avail-

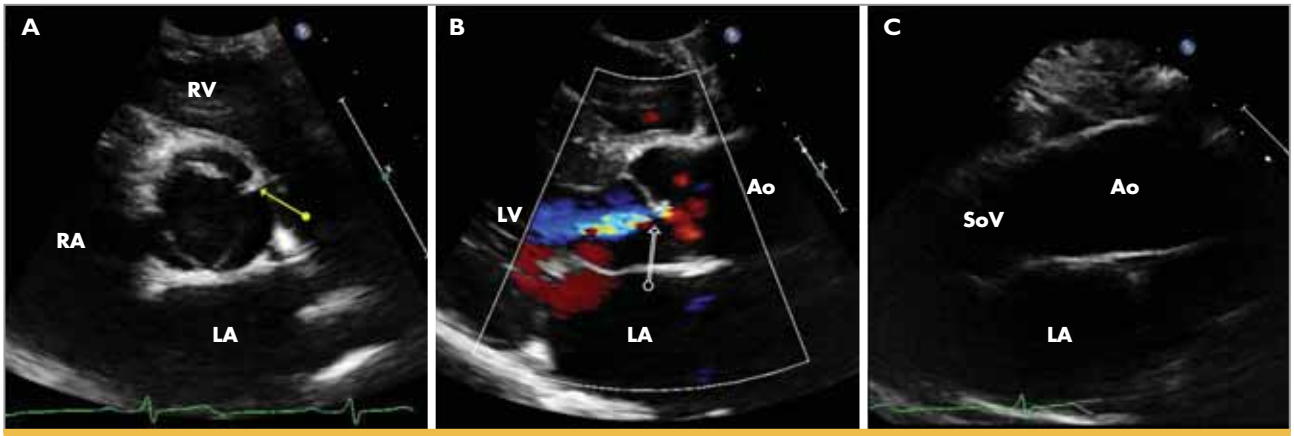


**FIGURE 1: Transthoracic echocardiographic findings in a 19-year-old patient on the spectrum of the bicuspid aortic valve syndrome.** A. Short axis of the aortic valve demonstrating partial fusion of the base of the right and left coronary cusps (yellow arrow). B. Colour Doppler in the parasternal long axis showing mild aortic regurgitation. C. Parasternal view of the proximal ascending aorta with a mild dilation of the ascending aorta but normal aortic sinuses and sinotubular junction.

*Ao = Aorta, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, SoV = Sinus of Valsalva.*

**TABLE 1: BAV commonly associated conditions and syndromes.**

| Condition | Frequency of BAV Involvement | Notes |
|---|---|---|
| Coarctation of the aorta | 36 - 70%[47-49] | Large variability due in part due to heterogeneous reporting and nomenclature |
| Subvalvular aortic stenosis | 23%[50] | Subaortic stenosis predisposes to valve damage leading to aortic regurgitation<br>Recurrence of subaortic stenosis after resection is common (20%) |
| Shone complex | 84 - 89%[51, 52] | BAV was not initially described as part of the Shone complex |
| Supravalvular aortic stenosis | 39 - 47%[53,54] | Frequent structural abnormalities of aortic valve are present[55] |
| Turner syndrome | 14 - 30%[56-58] | 95% show R-L cusp fusion<br>High prevalence of both ascending aortic dilation and aortic coarctation |
| Williams syndrome | 5 - 11%[55, 59] | Other common valvular pathology in Williams syndrome include supravalvar aortic stenosis, peripheral pulmonary stenosis, mitral valve prolapse, mitral regurgitation and supravalvar pulmonary stenosis[55] |

ability, low cost and lack of ionising radiation. The imaging diagnosis of a BAV can be challenging as off axis acquisitions of a normal trileaflet aortic valve may be easily mistaken for a bicuspid valve. Conversely, a bicuspid valve may be mistaken for a trileaflet valve in diastole, especially if a raphe is present. A correct diagnosis relies on visualisation of the open leaflets in systole, with 2 distinct commissures. We recommend describing (1) leaflet orientation, (2) the presence or absence of a raphe, (3) coronary artery ostia locations and (4) a qualitative assessment of valve calcification or thickening (Figure 2). The phenotypic description we recommend is:

- Type 1 with congenital "fusion" of the right and left cusps resulting in a larger anterior/rightward leaflet with both coronaries arising from this sinus.
- Type 2 with congenital "fusion" of the right and non-coronary cusps, with the coronary ostia arising from separate sinuses.
- Type 3 with congenital "fusion" of the left and non-coronary cusps, with the coronary ostia arising from separate sinuses.

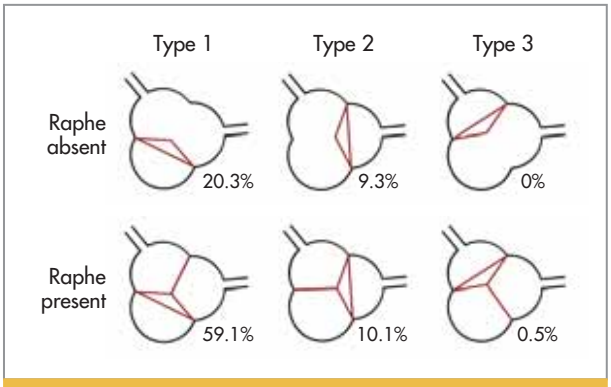


**FIGURE 2: Bicuspid aortic valve (BAV) classification and prevalence of each morphology.** Each schematic diagram shows the 3 aortic sinuses with the left and right coronary ostia. Leaflet opening and the presence of a raphe between "fused" leaflets is shown by the red lines. The percent of BAV patients with each valve type from the study by Schafer, et al.[25] is shown. Type 1 BAV, with congenital fusion of the right and left coronary cusps (both coronaries originate from the same anterior/rightward larger cusp) occurs in about 80% of BAV patients. Type 2 BAV, with fusion of the right and non-coronary cusps is present in about 20% of patients with the coronaries arising from separate cusps. Type 3 BAV is rare.

Although rarely needed, better visualisation of valve anatomy can be obtained with transesophageal echocardiography, cardiac magnetic resonance imaging (MRI) or gated computed tomography (CT).

Other variants of congenitally abnormal aortic valves may be mistaken for a BAV (Figure 3). This occurs most often with a unicuspid valve which has a single commissure, a single leaflet and a characteristic teardrop-shaped or round opening. Patients with unicuspid aortic valves typically present with aortic stenosis (AS) at a much earlier age than patients with a BAV.

## VALVE HEMODYNAMICS

Evaluation of AS and aortic regurgitation (AR) is essential in evaluation of the BAV patient. Standard measures of AS severity include an echocardiographic assessment of maximum aortic jet velocity, mean transaortic pressure gradient and continuity equation valve area (Figure 4). AR is evaluated per guidelines based on colour Doppler vena contracta width, the continuous wave Doppler velocity curve, and evidence for holodiastolic flow reversal in the thoracic and abdominal aorta. Quantitative measures of left ventricle (LV) size and systolic function are also essential when regurgitation is present. MRI can provide more quantitative measures of AR severity as well as accurate assessments of LV size and function if needed (Figure 5).

## ASSOCIATED AORTOPATHY

Dilation of the aortia is common in BAV patients, even with normal valve function.[29] Evidence that intrinsic structural abnormalities underlie the valvular pathology of BAV is seen in pathologic specimens that show increased extracellular matrix production, tissue disorganisation and valvular interstitial cell disruption.[12] By the time patients reach the age of 50 - 60, 91% are found to have some degree of aortic dilation.[30] Variation exists in the aortic shape and regions of dilation, which may involve the sinuses of Valsalva, ascending aorta, or both (Figure 6). The rate of progression of aortic dilation does not appear to be related to the severity of associated AS or AR.[29,31,32] In a study of 353 BAV patients followed for an average of 3.5 years, 43% had no evidence of progressive aortic dilation; and in those with progressive dilation, the rate of change averaged 0.42mm/year with a wide variation in the yearly rate of change among patients.[33]

The underlying cause of the association between the BAV and aortic dilation is unclear. While the theories of common structural abnormalities are popular, the cystic medial degen-

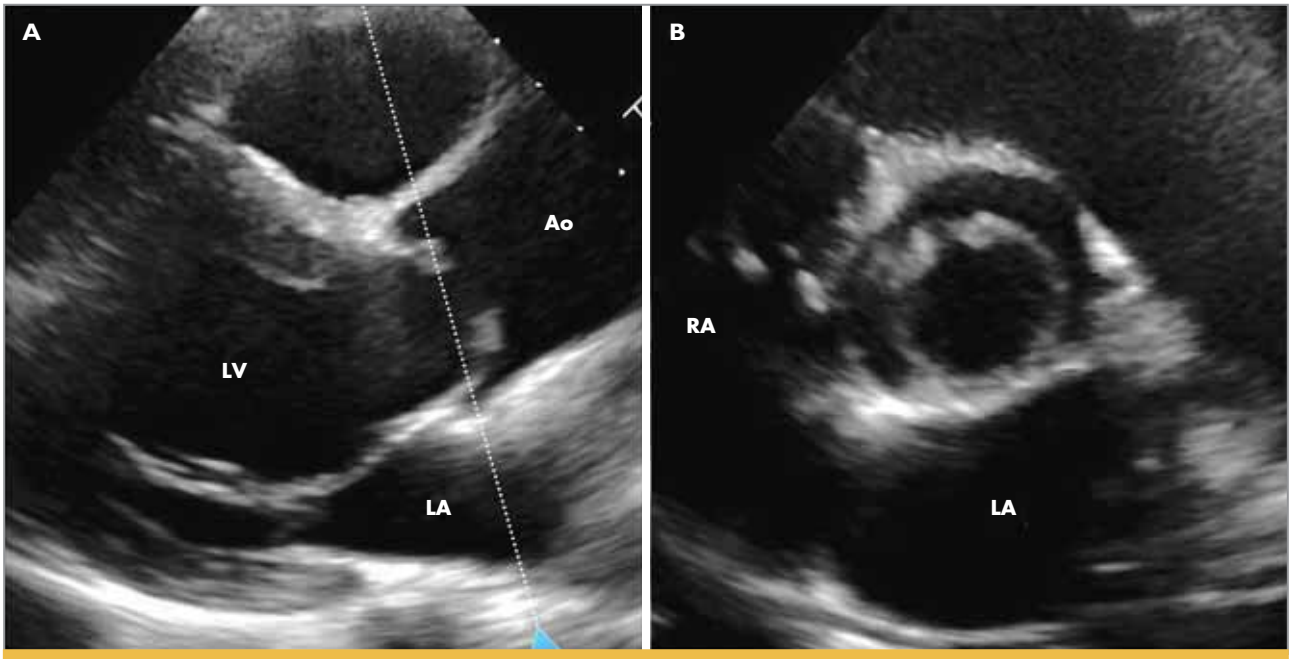


**FIGURE 3: Unicupsid aortic valve.** A. Parasternal long axis showing the domed shape of a unicuspid aortic valve in systole. B. Corresponding short axis view demonstrating the round shape of a unicuspid aortic valve in short axis. Imaging illustrates the challenge of visualising most stenotic portion of leaflet tips.

*Ao = Aorta, LA = left atrium, LV = left ventricle, RA = right atrium.*

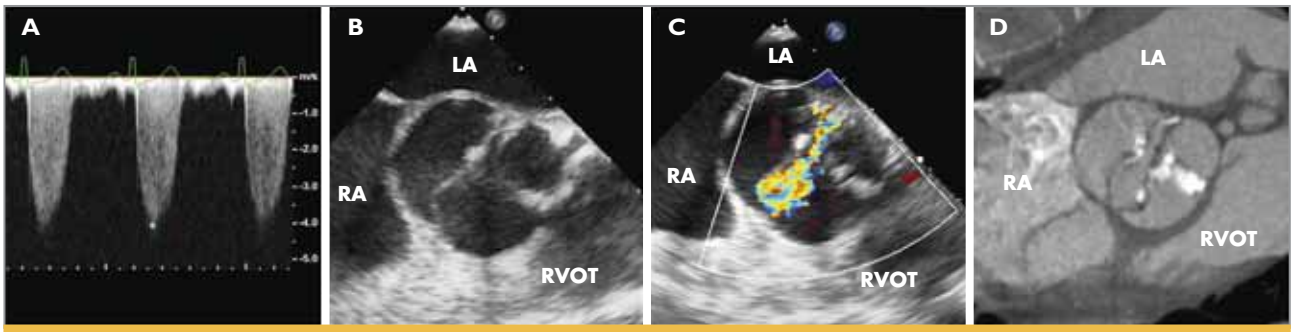


**FIGURE 4: Bicuspid aortic valve stenosis.** A. Continuous wave Doppler indicates a peak velocity of 4.1m/s consistent with severe aortic stenosis. B. Transesophageal echocardiogram (TEE) image of a bicuspid aortic valve (BAV) in short axis. C. Colour Doppler with aliasing through BAV leaflet tips. D. ECG-gated computed tomography (CT) scan shows aortic valve in short axis and illustrates the benefit of CT for evaluation of valve morphology if not well seen on an echocardiogram.

*LA = left atrium, RA = right atrium, RVOT = right ventricular outflow tract.*

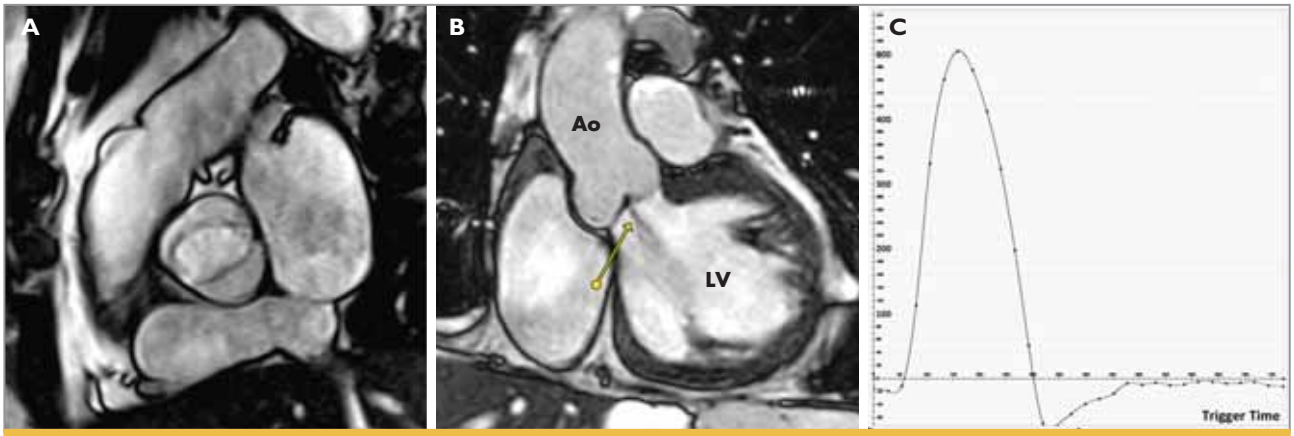


**FIGURE 5: Bicuspid aortic valve regurgitation.** Magnetic resonance imaging (MRI) shows (A) a short axis view of the bicuspid valve in systole (B) a long axis view in diastole showing the regurgitant jet (arrow). As with colour Doppler, the jet itself is not accurate for determining severity of regurgitation. (C) A MRI derived flow curve in the ascending aorta demonstrates forward flow in systole and reverse flow in diastole due to AR. This approach allows accurate quantitation of regurgitant volume and fraction.

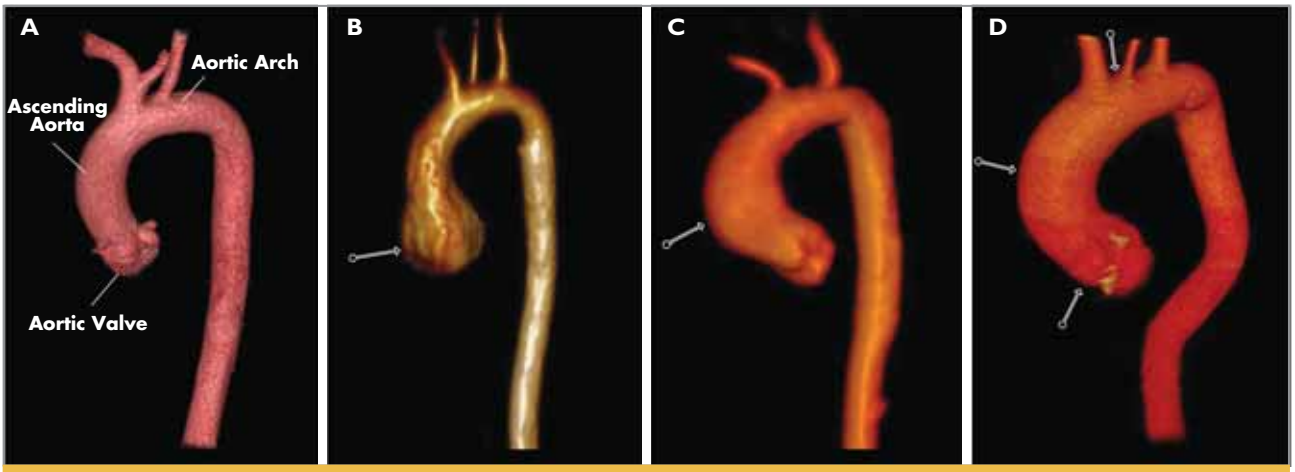


**FIGURE 6: Aortic dilation associated with bicuspid aortic valve disease.** A. Computed tomography angiography (CTA) of normal aorta. B. Magnetic resonance angiography (MRA) of isolated dilation of aortic sinuses. C. MRA showing aorta with dilation limited to the proximal ascending portion. D. CTA of an aorta that is dilated through the aortic arch.

eration is not universally seen in all patients with BAV and aortopathy. Abnormal flow patterns from the BAV have also been suspected as the underlying mechanism of aortopathy. Flow patterns as visualised with 4D flow MRI may give new insights into this theory, but a definite cause-effect relationship has not been established. Most likely, the etiology of the aortopathy with BAV is more complex and multifactorial in nature.[34-36]

## CLINICAL OUTCOMES

In patients with the BAV syndrome, age, severity of AS and AR are independently associated with primary cardiac events. Despite this, asymptomatic patients with BAV with minimal or no hemodynamic abnormalities enjoy excellent long-term survival[37] (Figure 7). In a series of 642 BAV patients, 25% had a cardiac event within 10 years of follow-up; and most of

**TABLE 11: Long term clinical outcomes in patients >50 years of age.**

| Outcome | Frequency |
|---|---|
| Overall survival (at 15 years) | 40 - 78% |
| Aortic valve surgery | ~100% |
| Endocarditis | 1 - 4% |
| Ascending aortic aneurysm (>5.0cm) | 3 - 10% |
| Aortic dissection | 0 - 10% |

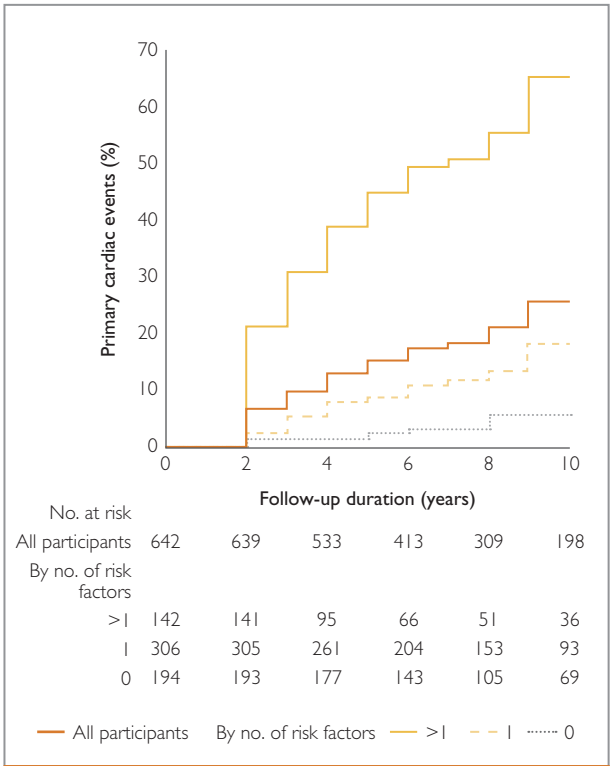


**FIGURE 7: Long term outcomes with bicuspid aortic valve disease.** The frequency of primary cardiac events in patients with more than 1 risk factor at baseline (n=142) was 65% (SD, 5%); in all participants (n=642), 25% (SD, 2%); in patients with 1 risk factor at baseline (n=306), 18% (SD, 3%); and in patients with no risk factors at baseline (n=194), 6% (SD, 2%). The risk factors for primary cardiac events were age older than 30 years, moderate or severe aortic regurgitation, and moderate or severe aortic stenosis.[37] Reprinted with permission.

these events were aortic valve replacement for AS or AR (22%), with aortic complications in only 2%, cardiac death in 3% and heart failure in 2%. Predictors of adverse outcomes over this time period included older age, more severe AS or AR, and more severe valve thickening and calcification.[37,38] Over the lifetime of BAV patients, nearly all eventually will require AVR for stenosis and/or regurgitation (Table II).

## AORTIC STENOSIS

The most common outcome in adults with a BAV is severe AS due to progressive leaflet thickening and calcification.[26] In patients undergoing aortic valve replacement (AVR) for AS, over 50% have a BAV. A BAV is the cause of AS requiring AVR in 60% of patients under age 70 years but also accounts for 40% of cases in those over age of 70.[39] The average age at symptom onset in patients with severe AS due to a BAV is younger (about age 60 - 70 years) than in patients with a trileaflet aortic valve (typically age 70 - 90 years). At the tissue level, both age groups do appear to share the same pathophysiology.[40]

## AORTIC REGURGITATION

Although most patients with a BAV have some degree of AR,[41] severe AR leading to progressive LV dilation, symptoms and the need for AVR is less common, probably occurring in 10 - 20% of BAV patients. Clinical outcomes with AR due to a BAV are reflected in data on the natural history of chronic AR.[42] AVR for significant AR due to a BAV typically occurs in young adulthood (age <40 years) and is unlikely in older BAV patients, although is still periodically required in the cases of infective endocarditis.

## AORTIC DISSECTION

Aortic dilation is common in BAV patients, with a risk of aortic dissection that is 5 - 10 times higher than in the general population. However, a recent study showed an overall low rate of aortic dissection over 16 years of follow-up, with an incidence of aortic dissection of only of 3.1 (95% CI, 0.5 - 9.5) cases per 10 000 patient-years.[43] Less than 10% of all aortic dissections occur in patients younger than 40 years of age; and in this younger age group, common causes of dissection are Marfan syndrome, hypertension and familial aneurysm; with less than 10% having a BAV. In patients over age 40 years with aortic dissection, BAV is rare.[44] In patients who have undergone AVR, however, the presence of a BAV is a risk factor for subsequent dissection, particularly in those with an aortic diameter greater than 4.5cm.

## ENDOCARDITIS

The endocarditis risk of BAV is elevated compared to the general population with a long-term risk of approximately 2 - 3%. Antibiotics at the time of dental procedures are not currently recommended, and the prevention of endocarditis relies on optimal dental care and oral health, along with patient education about signs and symptoms of endocarditis to ensure prompt diagnosis.

## PATIENT MANAGEMENT

### Medical Therapy

There is no medical therapy known to change the clinical course of BAV disease. Instead, management is centered on early diagnosis, monitoring of disease progression to determine optimal timing of intervention, treatment of concurrent con-

ditions (such as hypertension), and primary prevention of atherosclerotic coronary disease (Figure 8). Although the process of valve calcification at the tissue level is similar to atherosclerosis, there is no convincing evidence that lipid-lowering treatment alters the disease course. However, patients should have standard risk factor evaluation and treatment based on current guidelines for primary prevention of cardiovascular disease. Treatment of hypertension follows standard guidelines with no evidence to support use of beta-blockers or other therapies in normotensive patients with a BAV.

## Periodic Imaging

After the initial diagnosis of BAV, the timing of periodic imaging is based on the degree of valve dysfunction and the presence of aortic dilation. In younger patients with a normally functioning BAV and normal aortic dimensions, intermittent re-evaluation in 3 - 5 years intervals is appropriate. When AS or AR is present, timing of follow-up is based on the severity and rate of progression of the valve dysfunction (Figure 8).

If well visualised, evaluation and follow up of the proximal aorta should be performed with TTE. In patients with no family history of aortic dissection; and if the aortic sinuses, sinotubular junction and ascending aorta are well visualised and normal in size; further imaging is not needed. If the aorta is not well visualised, is significantly dilated, or there is a family history of aortic dilation or dissection, additional imaging of the aorta with CT or MRI is recommended. The interval of repeat aortic imaging should be determined by the degree and rate of aortic dilation.

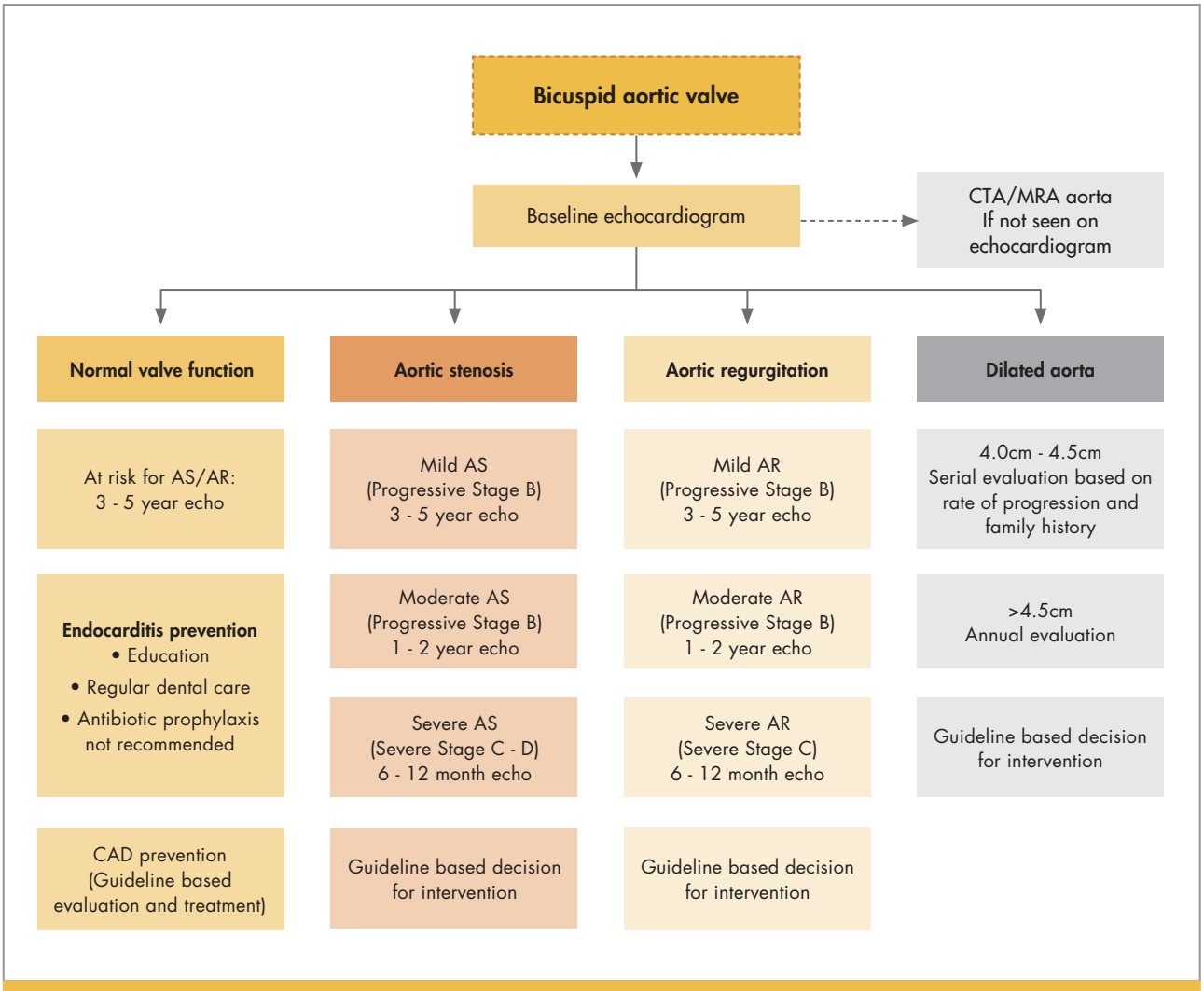


**FIGURE 8: Overview of the basic management of a bicuspid aortic valve disease.** The primary outcomes of stenosis, regurgitation and aortic dilation determine the timing of periodic imaging and clinical evaluation as well as timing of optimal intervention. However, even patients with normal valve function benefit from preventative care. Patients in all groups should receive education about the expected disease course, expected symptoms and a healthy life style.

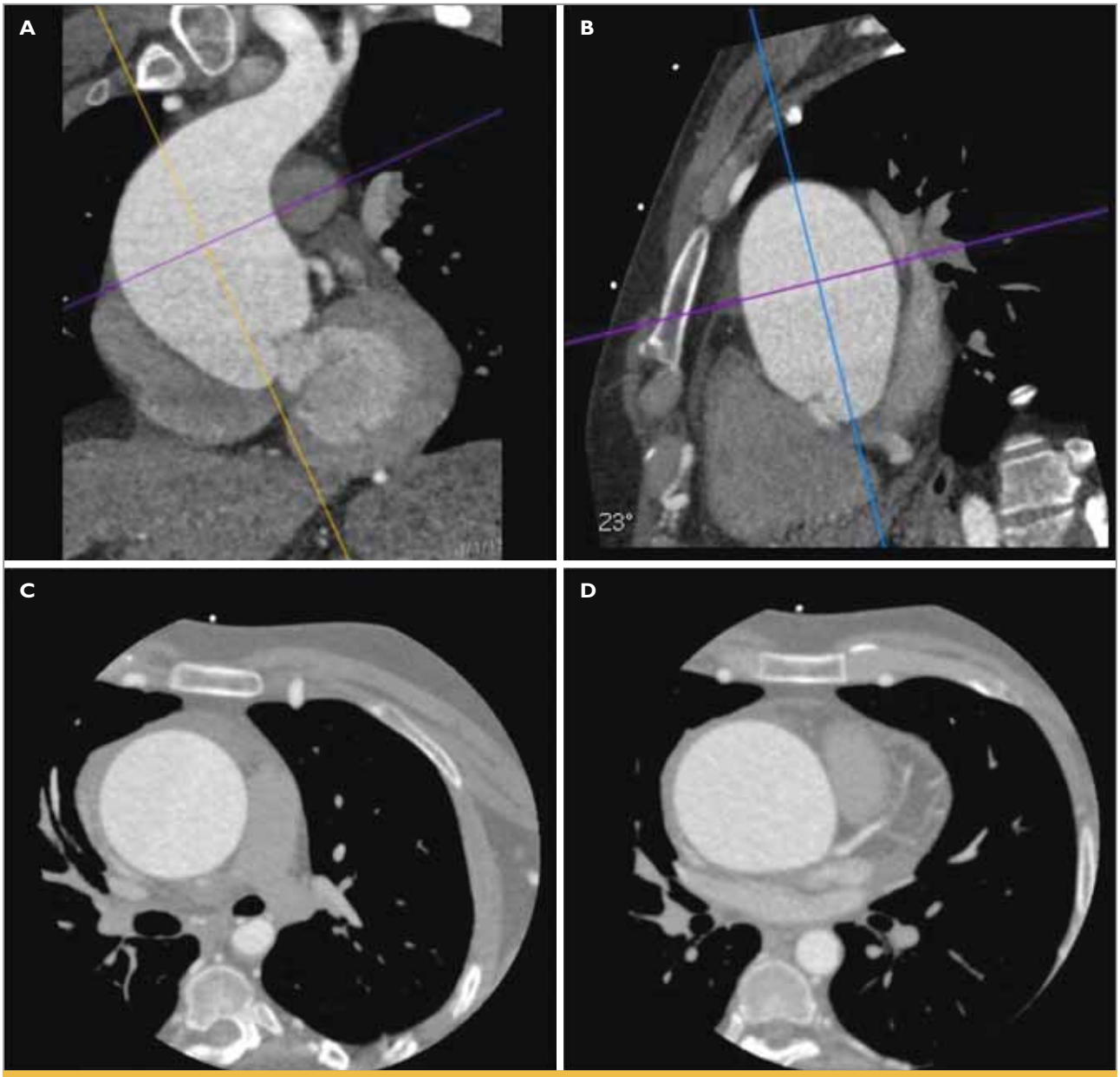


**FIGURE 9: Measurement of aortic size.** A-B. Dilated proximal ascending aorta being measured in 2 double oblique planes through the proximal ascending aorta. The two purple lines create a double oblique plane through the true cross section of the aorta seen in panel C. This contrasts with panel D where the aorta in same region is seen in the true radiologic axial plane, which obliquely cuts the aorta leading to a falsely elongated appearance. An understanding of the underlying measurement methodology is important to avoid making clinical decisions based solely on differing measurement techniques.

With all aortic imaging modalities, it is important to understand the sources of potential measurement variability between studies and within different modalities. On echocardiography, aortic diameter is measured at end-diastole from the black-white interface of the inner edges of the aortic lumen. However, CT and MRI measurements typically include the thickness of the aortic walls, usually adding about 2mm compared to the echocardiographic measurements. CT and MRI measurements are ideally made on dedicated 3D workstations where the aorta can be measured in double oblique views at the widest region of dilation (Figure 9). Major management decisions should take these differences into account.

## TIMING AND METHOD OF INTERVENTION

The timing of intervention for BAV disease follows standard guidelines for management of AS, AR and aortic dilation. The major indications for AVR in BAV patients are severe

symptomatic AS or AR, severe AR or AS with LV systolic dysfunction and progressive LV dilation with severe AR.

Surgical aortic valve replacement (SAVR) has long been the standard of care for BAV patients with excellent and durable results. As patients with BAV often are younger and may require aortic root replacement at the time of valve surgery, SAVR remains the preferred strategy. Although a BAV initially was considered a contraindication in the early clinical trials for transcatheter aortic valve implantation (TAVI), recent data suggests that TAVI is effective for treatment of severe AS due to a BAV. Thus, in older adults with normal aortic dimensions, current guidelines for TAVI are appropriate whether AS is due to a trileaflet or bicuspid valve.

Aortic root replacement is indicated for an aortic diameter over 5.5cm but may be considered with a diameter of 5.0cm if there is evidence for rapid progression, a strong family history or other considerations. The optimal timing of aortic root replacement is when the annual risk of aortic dissection is greater than the risk of the surgical procedure; thus the timing for surgery vs periodic monitoring can be dependent on individual patient risk factors. In patients undergoing AVR, concurrent replacement of the aortic root is recommended if aortic diameter is over 4.5cm to prevent subsequent dissection. The specific surgical approach depends on the pattern of aortic dilation. If the sinuses are normal and dilation is isolated to the ascending aorta, an interposition graft replacement of the ascending aorta is the simplest approach. If dilation involves the aortic sinuses, a Bentall procedure with coronary reimplantation and a prosthetic aortic valve may be necessary. Some centres perform reimplanatation of the native BAV (the David procedure) although only limited long-term outcome data for this procedure in BAV patients is available.[45]

## FUTURE DIRECTIONS

Despite advances in the understanding and management of patients with a BAV, many unknowns remain. We continue to lack a robust understanding of the embryologic and genetic underpinnings of the BAV syndrome and its variants. As no effective disease modifying medical therapies have been identified for the BAV syndrome, management relies on monitoring and appropriately timed surgical intervention. However, better risk prediction models are needed to guide intervention as only a subset of BAV patients has progressive aortic dilation or aortic dissection. BAV patients offer an ideal opportunity for prevention of disease progression as imaging allows for diagnosis early in life. If basic research can identify therapeutic targets, perhaps in the future, prevention of leaflet calcification or aortic dilation will be possible. Finally, as TAVI continues to be refined, it may offer improved options for mechanical intervention in BAV patients with valve dysfunction.[46]

**Conflict of interest: none declared.**

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