Bicuspid Aortic Valve is the most common congenital heart defect in adults, affecting 1.3% of the population worldwide, and is responsible for more deaths and complications than the combined effects of all the other congenital heart defects.\textsuperscript{1,2} Although aortic stenosis and regurgitation are the most common complications of a bicuspid aortic valve, dilatation of any or all segments of the proximal aorta from the aortic root to the aortic arch, called bicuspid aortopathy, is also present in approximately 50% of affected persons.\textsuperscript{4-7} Accumulating evidence suggests that the pattern of aortic dilatation in persons with a bicuspid aortic valve is diverse, possibly reflecting heterogeneity in molecular, rheologic, and clinical features.\textsuperscript{4-9} This article provides a brief overview of the basic principles, recent advances, and recommendations for the treatment of adults with bicuspid aortopathy.

**TERMINOLOGY AND DEFINITIONS**

A normal aortic valve is composed of three aortic-valve cusps, each semilunar in appearance. The leaflets are housed within a small dilatation of the proximal aorta associated with each cusp, called the sinuses of Valsalva or aortic sinuses, and their association with the respective coronary ostia identifies them: left, right, and noncoronary sinuses. Each cusp is attached to the wall of the aorta by the outward edges of its semicircular border, and the attachment point between each leaflet is called a commissure.

A bicuspid aortic valve typically comprises two leaflets of unequal size.\textsuperscript{2} The most common fusion pattern involves the right and left cusps (RL fusion pattern, resulting in an anterior–posterior leaflet orientation; also called the typical pattern), followed by fusion of the right and noncoronary cusps (RN fusion pattern, resulting in a right–left leaflet orientation; also called the atypical pattern). The least common pattern involves fusion of the left and noncoronary cusps. In rare cases, the leaflets are symmetrical or there is no raphe.

The aorta is anatomically divided into the ascending aorta (approximately 5 cm in length and 20 to 37 mm in diameter),\textsuperscript{10} aortic arch, thoracic aorta, and abdominal aorta. The aortic root comprises the aortic sinuses, aortic valve, and coronary ostia; the tubular portion of the ascending aorta begins at a point distal to the aortic root (sinotubular junction) and ends at the origin of the innominate artery. The aortic arch is composed of the origins of the innominate artery, the left common carotid artery, and the left subclavian artery (Fig. 1).

**PREVALENCE OF BICUSPID AORTIC DILATATION**

The reported prevalence of dilatation of the ascending aorta among persons with a bicuspid aortic valve ranges from 20 to 84%.\textsuperscript{1,2,7,14-15} This variation is related to differences in study populations, assessment techniques, and aortic-size thresholds,
Aortic Dilatation

Figure 1. Patterns of Bicuspid Aortopathy, with Representative Findings on Echocardiography and Computed Tomography (CT).

Panel A shows the biologic features of the aorta and the three types of bicuspid aortopathy. The transthoracic echocardiogram at the left in Panel B shows normal dimensions of the sinuses of Valsalva (arrow) and a dilated ascending aorta. AscAO denotes proximal ascending aorta, and LV left ventricle. The CT images in the middle and at the right show dilatation of the aortic root and dilatation of the ascending aorta and proximal arch, respectively.
as well as the heterogeneous nature of the disease. All the segments of the ascending aorta are larger in adults with a bicuspid valve than in those with a tricuspid aortic valve.

Aortic dilatation begins in childhood and is progressive. Children born with a bicuspid aortic valve have a larger ascending aorta that increases in size at a higher rate than that of matched controls with a tricuspid aortic valve. The prevalence of dilatation at the level of the tubular ascending aorta increases with age and has been reported to be 56%, 74%, 85%, 91%, and 88% at the respective age quintiles of younger than 30 years, 30 to 39 years, 40 to 49 years, 50 to 60 years, and older than 60 years of age. The prevalence also varies widely according to the site of dilatation (annulus, aortic root, or tubular ascending aorta).

**PATHOLOGICAL FEATURES**

Classification schemes that are based on histologic features, morphologic valve-fusion patterns, and hierarchical cluster analyses have been proposed for describing bicuspid aortopathy, but none have been widely adopted. The patterns of aortic involvement can be classified into three types to guide future management. Type 1, the most common type, involves dilatation of the tubular ascending aorta (particularly along its convexity), accompanied by varying degrees of aortic-root dilatation (Fig. 1). This type has been associated with an older age at diagnosis (>50 years), valvular stenosis, and the RL fusion pattern. Type 2 involves isolated involvement of the tubular ascending aorta (with relative sparing of the aortic root), frequently extending into the transverse aortic arch (Fig. 1), and has been associated with the presence of the RN fusion pattern. Type 3, also called the root phenotype, involves isolated dilatation of the aortic root (Fig. 1). This rare type has been associated with a younger age at diagnosis (<40 years), male sex, and aortic regurgitation and has been proposed to be the form of bicuspid aortopathy that is most likely to be associated with a genetic cause.

The development of bicuspid aortopathy has been attributed to genetic and hemodynamic bases. Although the relative contribution of genetics and hemodynamics remains debated, both factors are probably operative.

The evidence supporting a genetic basis includes the following observations: aortopathy is prevalent in first-degree relatives of patients with a bicuspid aortic valve; differences in aortic dimensions in persons with a bicuspid aortic valve persist even after adjustment for blood pressure, peak aortic-jet velocity, and left ventricular ejection time and are also observed in persons with apparently normal-functioning bicuspid valves; and the prevalence of aortic dilatation among persons with a bicuspid aortic valve is greater than that predicted according to the severity of aortic stenosis or aortic regurgitation.

Abnormal migration of neural-crest cells has been postulated as a common pathway that results in a bicuspid aortic valve and aortopathy. Abnormal dilatation of the aorta increases with age and has been reported to persist even after adjustment for blood pressure, peak aortic-jet velocity, and left ventricular ejection time and are also observed in persons with apparently normal-functioning bicuspid valves.

The histologic changes observed in bicuspid aortopathy, previously called cystic medial necrosis, are the end result of abnormal regulatory pathways of vascular smooth-muscle cells within the aortic media. Abnormal processing of the extracellular matrix protein fibrillin 1 by vascular smooth-muscle cells initiates detachment of vascular smooth-muscle cells from the extracellular matrix, leading to the release of matrix metalloproteinases (MMPs) together with their tissue inhibitors. The resulting matrix disruption and elastin and lamellar fragmentation lead to increased apoptosis of vascular smooth-muscle cells and disruption of the media layer, adversely affecting the structural integrity and flexibility of the aorta.

The concept that abnormal valve dynamics lead to bicuspid aortopathy is supported by the observation that even normally functioning bicuspid aortic valves can have abnormal transvalvular-flow patterns, resulting in regional increases in wall shear stress that are predicted largely by the morphologic features of the bicuspid valve. Magnetic resonance imaging (MRI) studies have shown that an RL fusion pattern results in a flow jet directed toward the right anterior aortic wall, which is then propagated in a right-handed helical direction (Fig. 3, and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The increase in regional wall shear stress might be the basis of the
Aortic Dilatation

The association of the RL fusion pattern with dilatation of the aortic root and asymmetric dilatation of the tubular ascending aorta. Conversely, an RN fusion pattern results in a flow toward the posterior aorta, with increased wall shear stress at the right posterior aspect of the aorta (Fig. 3), leading to dilatation of the aortic arch. These preliminary observations in small samples of patients are intriguing but require further clarification in unselected populations and linkage to outcomes. Indeed, valve orientation did not predict events in the three largest outcome studies. 29-31

NATURAL HISTORY

Aortic aneurysm formation and aortic dissection are the two major complications of bicuspid aortopathy. The rate of growth of the ascending aorta

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**Figure 2. Pathophysiological Features of Bicuspid Aortopathy.**

Structural support and elasticity are afforded to the aorta by means of alternating layers of elastic lamellae and smooth-muscle cells. At the histologic level, the smooth-muscle cells in the aorta in persons with tricuspid valves are secured to the adjacent elastin and collagen matrix by fibrillin 1 microfibrils (Panel A). The aorta in persons with bicuspid valves may be deficient in fibrillin 1. This deficiency culminates in a disrupted architecture whereby smooth-muscle cells detach, accompanied by a surge in local levels of matrix metalloproteinases (MMPs), leading to loss of integrity in the extracellular matrix and the accumulation of apoptotic cells. These events may lead to an aorta with weakened structural integrity and reduced elasticity (Panel B).
in persons with a bicuspid aortic valve (range, 0.2 to 1.9 mm per year) is considerably higher than the rate in persons with a tricuspid aortic valve.

7,14,32-38 The aortic diameter at baseline is an important predictor of aortic expansion. A study involving 88 patients showed expansion rates of approximately 2.1 mm per year among patients with a bicuspid aortic valve that had an initial aortic diameter of 35 to 40 mm, as compared with a rate of 5.6 mm per year among patients with an aortic diameter of more than 60 mm.

39 A recent study involving 416 consecutive patients with a bicuspid aortic valve showed that an aortic diameter of 40 mm or more at baseline independently predicted the subsequent development of an aneurysm, as compared with a baseline diameter of less than 40 mm (hazard ratio, 3.3; 95% confidence interval, 1.5 to 7.2).29 Other predictors of progression of bicuspid aortopathy include older age, male sex, elevated systolic blood pressure, coexisting aortic-valve stenosis or regurgitation, and morphologic features of the valve (RL fusion pattern).2 Prior coarctation repair may provide protection against rapid aortic dilatation.15

The incidence of aortic dissection, the most-feared complication of bicuspid aortopathy, was once estimated to be as high as 5% but has been much lower in contemporary studies. The incidence of aortic dissection was 0.1% per patient-year of follow-up in a Toronto study involving 642 patients with a bicuspid aortic valve.30 Likewise, in an Olmsted County, Minnesota, study involving 416 patients with a bicuspid aortic valve, there were two aortic dissections during a mean (±SD) follow-up of 16±7 years, with an incidence of 3.1 cases per 10,000 person-years and an age-adjusted relative risk of 8.4.29 The incidence of aortic dissection was 17.4 cases per 10,000 person-years among patients 50 years of age or older and 44.9 cases per 10,000 person-years among patients with a baseline echocardiogram showing an aneurysm. There were no dissections in patients with an aortic diameter of less than 45 mm at baseline or in those with a normally functioning aortic valve. Thus, despite a high rela-

Figure 3. Morphologic Features of the Bicuspid Aortic Valve That Influence the Pattern of Aortopathy.

The fusion configuration of the aortic-valve cusps lays the foundation for changes in aortic wall shear stress and the resultant flow pattern. In the right–left fusion pattern (Panel A), the jet is directed toward the right anterior wall of the ascending aorta, where it travels in a right-handed helical direction to promote dilatation predominantly of the ascending aorta. In the pattern with fusion of the right and noncoronary cusps (Panel B), the jet is directed toward the posterior wall of the aorta, whereby the pattern of wall shear stress it causes may promote aortic dilatation within the proximal arch. Further details regarding the influence of morphologic features of bicuspid aortic valve on patterns of aortopathy are provided in Figure S1 in the Supplementary Appendix.
tive risk that increased with age, the absolute risk of aortic dissection was quite low. Furthermore, the 25-year survival rate in the entire cohort was 80% — identical to the survival rate in the general population of Olmsted County.

The low rates of aortic dissection in contemporary series reflect the practice of serial surveillance and surgical intervention once aortic size exceeds a threshold.\textsuperscript{29,30} The actual risk in the absence of surgery is probably higher, since patients with a large aorta will have undergone surgery. For example, among the 32 patients in the Olmsted County study who had an aortic diameter of 45 mm or more at baseline, the long-term rate of aortic dissection was 7%, but 46% of the patients underwent aortic surgery.\textsuperscript{29} In the entire study group, the rates of aneurysm formation and aortic surgery at 25 years were 26% and 25%, respectively, reflecting the effect of aortopathy on morbidity (Fig. S2 in the Supplementary Appendix).

Patients with a bicuspid aortic valve and an aortic diameter of less than 50 mm at baseline who underwent isolated aortic-valve replacement continued to be at risk for future aortic complications. In a mixed group of patients with aortic stenosis and those with aortic regurgitation, the rate of freedom from aortic complications (need for surgery, aortic dissection, or death) at 15 years was 43% among patients with an aortic diameter of 45 to 49 mm, as compared with 86% among those with an aortic diameter of less than 40 mm, suggesting that moderate aortic dilatation is an important risk factor for aortic complications, even after valve replacement.\textsuperscript{40} No aortic dissection was observed during follow-up in a more recent series of patients with aortic stenosis and concomitant mild-to-moderate dilatation of the ascending aorta at the time of aortic-valve replacement.\textsuperscript{23} However, patients with aortic regurgitation and mild-to-moderate dilatation of the aortic root (root phenotype) were at risk for aortic complications after aortic-valve replacement.

**ASSESSMENT AND TREATMENT**

**DIAGNOSIS**

The initial diagnosis of bicuspid aortopathy is likely to be made with the use of transthoracic echocardiography (TTE). Although TTE is usually adequate in assessing the aortic root and proximal ascending aorta, visualization of the mid-distal ascending aorta and the arch may be difficult in adults, in which case either a computed tomographic (CT) or MRI study should be considered for comprehensive assessment of the ascending aorta. If there are contraindications to CT or MRI, then a transesophageal echocardiogram can be obtained.\textsuperscript{41} MRI is preferable to CT for serial surveillance since it is not associated with radiation exposure.

**DECISION-MAKING ALGORITHM**

Figure 4 outlines a proposed approach to the management of bicuspid aortopathy in asymptomatic adults. This algorithm integrates U.S., European, and Canadian recommendations, which are based largely on expert opinion and observational studies.\textsuperscript{41-45} Risk factors, particularly smoking and hypertension, should be aggressively addressed in all patients with bicuspid aortopathy. Beta-adrenergic blockers, angiotensin-converting–enzyme inhibitors, and angiotensin-receptor blockers are the antihypertensive agents of choice. Beta-adrenergic blockers have the theoretical advantage of reducing aortic wall shear stress, whereas angiotensin-receptor blockers have been shown to reduce the rate of aortic growth in patients with Marfan’s syndrome.\textsuperscript{46}

Yearly echocardiographic surveillance is recommended in patients who have an aortic root or an ascending aorta with a diameter of more than 40 mm, as assessed by means of TTE, and no concomitant indication for valvular replacement or repair. In patients who have an aortic root or ascending aorta with a diameter of 40 to 44 mm and no concomitant valvular indication for intervention, a baseline CT or MRI scan may be obtained. If ongoing imaging surveillance, by means of echocardiography, CT, or MRI, reveals a growth rate exceeding 5 mm per year, surgical management may be considered.

In patients who have an aortic root or ascending aorta with a diameter of 45 to 49 mm, a CT or MRI scan should be obtained. If there are concomitant indications for either valvular or coronary surgery, then a tailored surgical approach will be required, dictated largely by the aortopathy pattern, perioperative risk, and surgeon and center experience. In patients with dilatation of the tubular ascending aorta, surgical options include supracoronary replacement of the ascending aorta, or if substantial aortic-valve dysfunction and aortic-root dilatation are also present, then replacement of the aortic valve, aortic root, and ascending aorta is indicated. In
Figure 4. Decision-Making Algorithm for the Management of Bicuspid Aortopathy.
Management includes risk-factor modification in all persons and includes the treatment of hypertension, treatment of dyslipidemia, and smoking cessation. If the entire ascending aorta (from aortic root to arch) is not completely visualized by means of transthoracic echocardiography, supplemental MRI or CT is recommended. CT or MRI is also recommended in planning the surgical approach.
patients with a dilated ascending aorta and aortic arch, surgical options may include aortic-valve replacement with supracoronary replacement of the ascending aorta and hemiarch. In most instances, this intervention will require deep hypothermic circulatory arrest and the potential use of antegrade cerebral perfusion.

In patients with isolated involvement of the aortic root, surgical options may include aortic-valve and aortic-root replacement with the use of a composite valved conduit (Bentall procedure). In most cases, surgical repair for bicuspid aortopathy can be achieved with excellent results at an experienced center. If aortic-valve surgery will be performed concurrently with ascending-aorta replacement, it is important to incorporate non-surgical factors into the decision-making process, such as the lifestyle of the patient, need for long-term anticoagulation, and in the case of female patients, future reproductive plans. A summary of surgical results from various publications are provided in Table S1 in the Supplementary Appendix.

In the absence of a valvular indication, patients who have an aortic root or ascending aorta with a diameter of 45 to 50 mm may be considered for surgery only if they have high-risk features such as a family history of aortic dissection, rupture, or sudden death and an aortic growth rate of more than 5 mm per year. A ratio of aortic area to body height of more than 10 cm^2 per meter has also been recommended for patients of short stature. In the absence of these factors, yearly reassessment of the risk stratification with the use of CT or MRI is suggested.

Surgery has previously been recommended for patients with an aortic root or ascending aorta that has a diameter of 5.0 cm or more, with guidelines recommending a threshold of 5.5 cm and a more individualized approach. European guidelines recommend that the aorta be replaced when the diameter of the aortic root or ascending aorta is 5.0 cm or more and in the presence of risk factors including coarctation of the aorta, systemic hypertension, family history of dissection, or an increase in the aortic diameter of more than 2 mm per year. European guidelines are in agreement with U.S. guidelines that recommend a lower threshold for ascending-aorta replacement in patients who are undergoing aortic-valve surgery (aortic diameter, 45 mm) and when valve repair will be performed at an experienced center with high rates of success.

The 2014 Canadian guidelines recommended a threshold range (aortic diameter, 50 to 55 mm), recognizing the importance of also incorporating patient size and patient-specific factors when deciding on the timing and nature of elective aorta replacement. Prophylactic surgery at the lower threshold limit of 50 mm would be appropriate in patients with risk factors for aortic complications (e.g., rapid aortic growth or concomitant aortic-valve disease, connective-tissue disorders, or genetic syndromes) but may not be prudent in those at increased risk for complications during surgery. These recommendations are based on the premise that aortic complications, representing a long-term risk that increases with time, will be avoided if elective aortic-valve replacement is performed at experienced centers with low mortality (≤1%).

**SPECIAL POPULATIONS**

During pregnancy, there are changes in hemodynamic variables as well as changes in the aortic media, and pregnant women who have a bicuspid aortic valve and concomitant aortic dilatation are therefore at increased risk for complications. In general, women with a bicuspid aortic valve and an aortic diameter of more than 45 mm should be advised against pregnancy. Summary recommendations regarding treatment during pregnancy are provided in Table S2 in the Supplementary Appendix.

Athletes with or without valvular disease who have a dilated aortic root or ascending aorta (diameter ≥45 mm) should be advised to participate only in low-intensity competitive sports (Table S3 in the Supplementary Appendix). First-degree relatives of patients with a bicuspid aortic valve should be screened for the presence of a bicuspid aortic valve and asymptomatic aortic disease.

**UNANSWERED QUESTIONS AND FUTURE DIRECTIONS**

Advances in imaging, biomarker-based risk assessments, and genetics should be used to gain a better understanding of the mechanisms underlying the development and progression of bicuspid aortopathy. The Beta Blockers and Angiotensin Receptor Blockers in Bicuspid Aortic Valve Disease Aortopathy (BAV) study (ClinicalTrials.gov number, NCT01202721) is an ongoing trial.
that is being conducted by the Canadian Network and Centre for Trials Internationally. The purpose of this study is to evaluate the efficacy of atenolol and telmisartan in slowing the progression of bicuspid aorticopathy. A trial of medical versus surgical management in patients with a moderately dilated ascending aorta (45 to 50 mm) would be highly informative. Future studies should focus on improving the selection of subgroups of patients who are most likely to benefit from earlier intervention, as well as those for whom watchful waiting is appropriate.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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