Circulation

AHA SCIENTIFIC STATEMENT

Cardiovascular Management of Aortopathy in Children: A Scientific Statement From the American Heart Association

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ABSTRACT: Aortopathy encompasses a spectrum of conditions predisposing to dilation, aneurysm, dissection, or rupture of the aorta and other blood vessels. Aortopathy is diagnosed commonly in children, from infancy through adolescence, primarily affecting the thoracic aorta, with variable involvement of the peripheral vasculature. Pathogeneses include connective tissue disorders, smooth muscle contraction disorders, and congenital heart disease, including bicuspid aortic valve, among others. The American Heart Association has published guidelines for diagnosis and management of thoracic aortic disease. However, these guidelines are predominantly focused on adults and cannot be applied adeptly to growing children with emerging features, growth and developmental changes, including puberty, and different risk profiles compared with adults. Management to reduce risk of progressive aortic dilation and dissection or rupture in children is complex and involves genetic testing, cardiovascular imaging, medical therapy, lifestyle modifications, and surgical guidance that differ in many ways from adult management. Pediatric practice varies widely, likely because aortopathy is pathogenically heterogeneous, including genetic and nongenetic conditions, and there is limited published evidence to guide care in children. To optimize care and reduce variation in management, experts in pediatric aortopathy convened to generate this scientific statement regarding the cardiovascular care of children with aortopathy. Available evidence and expert consensus were combined to create this scientific statement. The most common causes of pediatric aortopathy are reviewed. This document provides a general framework for cardiovascular management of aortopathy in children, while allowing for modification based on the personal and familial characteristics of each child and family.

Key Words: AHA Scientific Statements ■ aneurysm ■ aorta ■ aortic diseases ■ bicuspid aortic valve disease ■ Ehlers-Danlos syndrome, Type IV ■ Loeys-Dietz syndrome ■ Marfan syndrome

Aortopathy encompasses a spectrum of conditions predisposing to dilation, aneurysm, dissection, or rupture of the aorta and other blood vessels. Although most literature focuses on adults, aortopathy is diagnosed commonly in children, from infancy through adolescence. Pediatric aortopathy primarily affects the thoracic aorta, with the most common pathologies being bicuspid aortic valve (BAV) and connective tissue disorders. Involvement of other segments of the aorta and the peripheral vasculature varies by specific condition.

Genetic testing, noninvasive imaging, medical therapy, and surgery are commonly used in the care of these children. However, published evidence to guide care is limited, and pediatric practice varies widely, likely because aortopathy is etiologically heterogeneous, with genetic and nongenetic conditions.[1]

The American College of Cardiology and American Heart Association published guidelines for the diagnosis and management of thoracic aortic disease in 2010 and 2022.[2,3] These guidelines are predominantly focused on

adults and cannot be applied adeptly to growing children, who have emerging features, growth and developmental changes, including puberty, and different risk profiles compared with adults. Although sufficient level I evidence is not yet available to produce guidelines for children, observational and epidemiologic studies have been published. To optimize care and reduce variation in management, experts in pediatric aortopathy convened to generate this scientific statement regarding the cardiovascular care of children with aortopathy.

This document provides a general framework for management of aortopathy in children, allowing for modification on the basis of personal and familial characteristics of each child. Consultation with a pediatric aortopathy specialist should be pursued in complex or severe cases, such as when the genetic diagnosis is unclear, or when escalation in medical therapy or surgical intervention is being considered. This scientific statement does not include Turner syndrome; the 2018 American Heart Association scientific statement on Turner syndrome covered its associated aortopathy.[4]

Along with cardiovascular evaluation, many children need other specialists, ideally as part of a multidisciplinary team that provides services in genetics, ophthalmology, pulmonary, orthopedics, podiatry, rehabilitation medicine, physical and occupational therapy, neurology, neurosurgery, gastroenterology, allergy, developmental pediatrics, psychology, and psychiatry. Detailed discussion of noncardiovascular management is beyond the scope of this article. Smooth transition of care to a multidisciplinary adult aortopathy service is essential.

EVALUATION OF THE CHILD WITH SUSPECTED AORTOPATHY

Heritable thoracic aortic diseases (HTADs) are a defined group of conditions under the aortopathy umbrella that are genetically mediated and predominantly involve the thoracic aorta. Timely diagnosis of HTADs can be lifesaving and allows for an accurate understanding of natural history, associated risks, and personalized management for the child and family. HTADs can be syndromic, such as in Marfan syndrome (MFS), with evolving multisystem features over the pediatric age range,[5–14] or nonsyndromic, without obvious external features, as seen in *ACTA2*-related HTAD. A list of HTADs with affected gene, inheritance, molecular pathway, and distinguishing characteristics is listed in Supplemental Table 1. Each genetic disorder has its own natural history (Supplemental Tables 1–3). There is wide variability in childhood presentations, ranging from little or no aortic enlargement to severe pathology of the aorta and other vessels, with unique factors associated with higher risk in each condition (Table 1).[15] Genetic testing can often confirm a diagnosis, ensuring disease-specific medical and surgical management of cardiovascular and noncardiovascular manifestations.

History and Physical Examination

The history and physical examination of a child with suspected aortopathy should be comprehensive, with specific focus on craniofacial features and the cardiovascular, ocular, skeletal, integumentary, and neurologic systems (Figure 1 and Supplemental Tables 1–3).[11] Many children with aortopathy present with syndromic features, but others, particularly young children, may have subtle or emerging features or normal physical examination results.[16–18] Ectopia lentis is highly specific for MFS, whereas children with other forms of HTAD may have other distinctive features that can be helpful in diagnosis, such as iris flocculi, mydriasis, or Moyamoya-like cerebrovascular disease (*ACTA2*), or craniosynostosis or cleft palate/bifid uvula (Loeys-Dietz syndrome [LDS]). Serial evaluations including history and physical examination are essential because many associated features are dependent on age.

Family History

Detailed family history with a pedigree of ≥3 generations is an important tool, given the wide variability in age at presentation and penetrance for HTAD.[19] Emphasis should be placed on any cardiovascular issues in the family, such as congenital heart disease, aortic valve disease, aneurysms or stenoses of the aorta and arteries, age and size of the aorta at the time of cardiovascular events, unexplained sudden death, premature stroke or myocardial infarction, and systemic findings that could be related to HTAD (Figure 1).

Highlights: Evaluation of the Child With Suspected Aortopathy

- Evaluation for suspected aortopathy in a child should include a detailed history, physical examination, and family history of ≥3 generations, focusing on cardiovascular and extracardiac findings.
- Normal physical examination results or negative family history does not rule out a genetic aortopathy.

IMAGING CONSIDERATIONS

Transthoracic echocardiography (TTE) is the primary imaging modality used for diagnosis and surveillance in children with aortopathy. A framework to determine frequency of routine clinical follow-up with imaging is presented in Table 2. More frequent imaging may be indicated on the basis of individual findings and the presence of high-risk features (Table 1). For children, the American Society of Echocardiography Guidelines and Standards for Performance of a Pediatric Echocardiogram should be applied, including measuring maximal diameters of semilunar valves and vessels from inner edge to inner

Table 1. High-Risk Presentations in Pediatric Aortopathy

Diagnostic group	High-risk features*
All	Family history of aortic dissection, especially in aorta with diameter <5 cm
	Family history of aortic surgery or dissection or rupture in childhood
	Aortic valvar dysfunction, moderate or greater
	Rapid aortic growth (≥0.8 cm/y before 2 y of age, ≥0.5 cm/y after 2 y of age, >0.3 cm/y for 2 consecutive y once adult height is reached)
	Pregnancy
Marfan syndrome	Early-onset Marfan syndrome, often but not always associated with variants in *FBN1* exons 23–32
	Marked arterial tortuosity (vertebral artery tortuosity index >50)†
Loeys-Dietz syndrome	*TGFBR1* or *TGFBR2* variants generally involve earlier age at onset and more severe presentation compared with other genes associated with Loeys-Dietz syndrome; *TGFBR2* R528 is associated with the worst prognosis[5]
	Among people with *TGFBR1* or *TGFBR2* variants, higher risk when any of these are present: craniosynostosis, cleft palate/bifid uvula, marked arterial tortuosity, widened scars, translucent skin
	Marked arterial tortuosity (vertebral artery tortuosity index >50)†
	Female patients with *TGFBR2* variants and small body size
Vascular Ehlers-Danlos syndrome	Glycine substitutions or splice site variants‡
	Vertebral artery tortuosity index adjusted for height ≥15.5†
	Frequent hematomas, frequent need for stitches or staples
	History of preterm delivery
	History of major arterial or organ event (eg, aortic or arterial dissection or rupture; intervention for aneurysm; intestinal, splenic, hepatic, bladder, or uterine perforation; pneumothorax) in patient or family member
ACTA2 variant	Smooth muscle dysfunction syndrome attributable to *ACTA2* R179 but also with other missense pathogenic variants
	Patent ductus arteriosus, Moyamoya-like cerebrovascular disease
PRKG1 variant	All affected patients have a risk for dissection as early as adolescence with minimal or no dilation
EFEMP2 variant	Cutis laxa, type IB is a rare, autosomal recessive condition presenting in early infancy with severe dilation, elongation, tortuosity, and narrowing of the aorta and systemic and pulmonary arteries and airway obstruction

*In the presence of high-risk features, more aggressive management should be considered, including more frequent monitoring, additional use of cross-sectional imaging, escalation of medical therapy, exercise modification, and earlier surgical intervention.

†A vertebral tortuosity index calculator is available at https://clarityregistry.com/calculators/risk-calculators/vti-calculator.[7,8]

‡A glycine substitution with valine does not appear to be as high risk as other glycine substitution variants. Some splice site sequence variations are predicted to cause decreased collagen and therefore would be classified as low risk. For a list of specific sequence variations, see Pepin et al.[15]

edge in systole (Supplemental Figure 1).[20,21] Recommended TTE reporting in pediatric aortopathy is listed in Supplemental Table 4.

In pediatrics, echocardiographic and cross-sectional measurements are normalized by body size, most commonly body surface area.[21,22] A Z score indicates the number of standard deviation units above (positive Z score) or below (negative Z score) the expected mean value for that structure and body surface area. By convention, aortic root and ascending aortic dilation are defined by a Z score >2 SD. Severity classifications of dilation by Z score are listed in Table 2. Previous publications have used different measures to define severity of aortic dilation. The grading scale presented in this scientific statement is new, based on expert consensus of the writing committee, and devised in an effort to align clinicians. Different Z score calculations are available for pediatric populations (Supplemental Table 5).[22] The same nomogram should be used for serial measurements. The most commonly used nomograms in the United States are from Boston Children's Hospital and the Pediatric Heart Network.[23,24]

When presented with an aortic root or ascending aortic Z score >2 SD, one must ascertain whether the aorta is truly dilated. Potential sources of error when calculating Z scores include inaccurate height or weight, population-inappropriate Z score calculator, and measurement technique. At extremes of height and weight, the Z score may be erroneous, because the existing calculators are derived from children with normal distributions of weight and height[25] (eg, with severe growth restriction, there may be a high Z score in the absence of true aortic dilation).

Transesophageal Echocardiography

Transesophageal echocardiography is essential for intraoperative assessment and comprehensive evaluation of true versus false lumen within dissected aortas before and after repair. Transesophageal echocardiography is an alternative imaging modality for suspected dissection when computed tomography angiography (CTA) is not definitive.[20]

Cross-Sectional Imaging

When TTE does not allow for satisfactory images of the heart and aorta, when considering surgical intervention, or in conditions at high risk for extravascular disease, cross-sectional techniques (ie, magnetic resonance imaging [MRI] or magnetic resonance angiography [MRA], CTA) provide excellent assessment of the aorta and peripheral vasculature and additional information about arterial and aortic tortuosity and dissection (Supplemental Table 6 and Supplemental Figure 2). Indications for cross-sectional imaging in pediatric aortopathy are listed in Supplemental Table 7.

Aortic measurements have been shown to be larger and more reproducible by MRI compared with TTE.[26] Multiple measurement techniques of the aortic root have been reported (Supplemental Figure 2A).[27] For
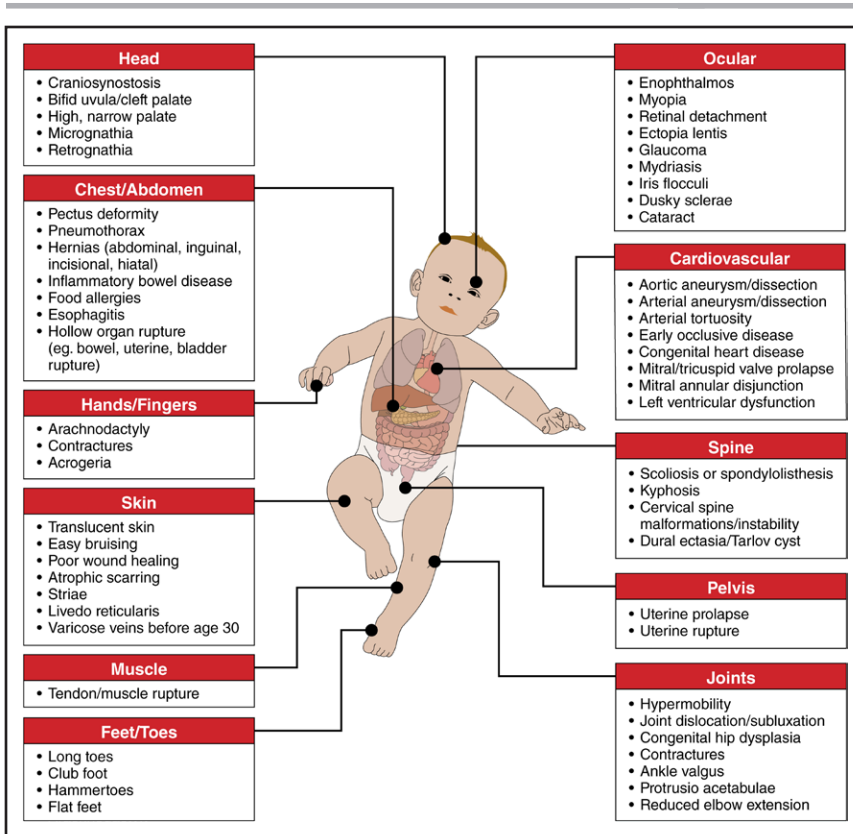
Figure 1. Findings that may be present in children with aortopathy by organ system.

standardization and easy comparison across institutions, primary assessment of the aortic root ideally uses cineographic imaging in a short axis en face plane using double-oblique techniques. The 3 maximum sinus-to-sinus distances from inner edge to inner edge in systole should be measured, and the maximum of these considered the reportable aortic root dimension. MRI also allows for detailed assessment of atrioventricular valve function and ventricular size and function.[29] Given the lack of ionizing radiation, MRI should be prioritized over CTA when possible. Sedation is typically necessary for MRI in patients <9 years of age; for lower-risk HTAD, in which cross-sectional imaging is indicated, clinicians may wait until 3 years of age or use CTA to avoid the risks of sedation reported in infants and young children.[28]

CTA is highly sensitive for monitoring the progression of aortic disease, with indications and measurements similar to MRI. CTA should be ECG-gated, and aortic measurements should be performed using double-oblique techniques. CTA is the optimal imaging modality for emergent evaluation of aortic dissection. When spinal hardware, pacemakers, or other implanted devices interfere with MRI, CTA may be indicated, although MRI may be reasonable when the interference is minimal or distant from the region being studied.

Although arterial tortuosity can be assessed qualitatively, quantitation can be performed from MRA or CTA (Supplemental Figure 2E and 2F), including the vertebral artery tortuosity index (VTI) and the aortic tortuosity index.[29,30] Both VTI and aortic tortuosity index have prognostic value, with higher values being associated with increased severity of aortic disease and risk for complications. A VTI >50 has been associated with earlier aortic surgery, aortic dissection, and death in MFS and LDS with *TGFBR1* or *TGFBR2* variants.[29] Height-adjusted VTI ≥15.5 has been associated with earlier arterial events in vascular Ehlers-Danlos syndrome (VEDS).[31] Aortic tortuosity index ≥1.95 has been associated with earlier aortic dissection and aortic surgery in MFS.[30]

Some genetic conditions carry a high risk for peripheral arterial abnormalities, and cross-sectional imaging is indicated at regular intervals depending on the underlying genetic diagnosis and the presence and severity of vascular abnormalities on initial imaging.

Fetal Echocardiography

Some features of HTAD can be identified in the fetus, including aortic root dilation and atrioventricular valve disease.[32,33] However, measurement of the fetal aortic root is not standard and should be specifically performed with appropriate *Z* scores (Supplemental Table 5). Extracardiac anomalies may also be noted, including diaphragmatic hernia (in MFS and LDS),

Table 2. Cardiovascular Imaging Intervals

Characteristics	Degree of aortic root or ascending dilation			
	None	Mild	Moderate	Severe
Age <16 y (Z score)	<2	≥2 and <3.5	≥3.5 and <5	≥5
Age ≥16 y (maximum dimension), cm	<3.5	≥3.5 and <4	≥4 and <4.5	≥4.5
Classic Marfan syndrome				
Early-onset Marfan syndrome	Imaging is driven by assessment of the atrioventricular valves, ventricular size, and function as much as by aortic dimensions; therefore, imaging frequency typically is every 1–3 mo, but may extend to every 6 mo with stable disease			
TGFBR1, TGFBR2			*	*
TGFB2, TGFB3, SMAD2				*†
SMAD3	‡			*
Vascular EDS				*
Classic EDS	§			
ACTA2 (not R179)				*
ACTA2 (R179)			*	*
MYH11, LOX				*
MYLK	‡			
PRKG1	‖	‖	*‖	*‖
FLNA				
EFEMP2, arterial tortuosity syndrome	Rare; imaging is driven by specific cardiovascular lesions. More severe stenoses or dilation should be followed closely			
Bicuspid aortic valve (more frequent with AS or AR)	‡			
Dilated aorta or suspected HTAD with negative genetic testing and no other diagnosis	‡			
TGA, TAC, TOF, PA-VSD, Fontan	Based on underlying congenital heart disease			

Color code	
	Every 12–24 mo
	Every 12–18 mo
	Every 6–12 mo
	Every 3–6 mo

In the presence of high-risk features (see Table 1) or rapid aortic growth (≥0.5 and <0.8 cm/y before 2 years of age; >0.3 and <0.5 cm/y after 2 years of age), more frequent monitoring may be considered. Increased aortic growth rate may occur during puberty with somatic growth, so increased surveillance during this time may be considered. The first follow-up visit after diagnosis or transfer for imaging may be within a shorter time frame than described previously to assess the rate of growth. In addition, patients with congenital heart disease or young age may undergo more frequent assessment driven by lesion and age.

*Surgery is recommended at aortic diameter of 4 to 4.5 cm based on gene and high-risk features (see Table 5).

†Surgery is recommended in TGFB3 if aortic diameter ≥5 cm (see Table 5).

‡Imaging interval can be extended up to 36 months as these cases are generally milder.

§If initial imaging has normal results, no follow-up is recommended.

‖At high risk for dissection beginning around age 17 years, even with minimal or no dilation.

AR indicates aortic insufficiency; AS, aortic stenosis; EDS, Ehlers-Danlos syndrome; HTAD, heritable thoracic aortic disease; PA-VSD, pulmonary atresia with ventricular septal defect; TAC, truncus arteriosus communis; TGA, transposition of the great arteries; and TOF, tetralogy of Fallot.

contractures (in MFS), hypertelorism (in LDS), clubfoot (in VEDS), limb deficiency (in VEDS), and amniotic bands (in VEDS).[32–34]

Highlights: Imaging Considerations

- Z scores adjusted for body-surface-area allow for appropriate interpretation of aortic size in growing children. A Z score >2 SD defines dilation of both the aortic root and ascending aorta.

- TTE is the primary imaging modality used for diagnosis and surveillance.
- Baseline TTE should be performed to assess aortic dimensions, intracardiac anatomy, and ventricular function. Semilunar valves and vessels should be measured in systole from inner edge-to-inner edge.
- Indications for cross-sectional imaging (MRI or computed tomography) include need for better visualization of the aorta or other arteries, history of

or being at risk for extracardiac vascular disease, approaching surgical threshold, or ventricular dilation or dysfunction.

- MRI or CTA should use double-oblique techniques, measuring maximum sinus-to-sinus dimensions in systole, inner edge-to-inner edge.
- CTA is optimal to evaluate for aortic dissection.

GENETIC TESTING, DIAGNOSIS, AND FAMILIAL EVALUATION

The role of genetic testing for aortopathy has expanded with greater recognition of the importance of a specific genetic diagnosis in risk assessment as well as medical and surgical management. Genetic testing should be targeted to those with the highest likelihood of confirming a diagnosis and those for whom a genetic diagnosis would affect clinical management. Figure 2 summarizes the indications for genetic testing in children with suspected HTAD.[35,36]

Multigene panels that include genes associated with HTAD are most commonly used; however, the genes included vary widely by laboratory. When there is a known familial pathogenic variant or when the clinical presentation strongly suggests a specific diagnosis, single gene testing can be used; for example, in the presence of ectopia lentis (lens dislocation), MFS associated with a variant in *FBN1* is most likely.[3] An HTAD panel may be considered for nonsyndromic presentations or in those with predominant systemic connective tissue findings. Broader testing (eg, whole exome sequencing) may be considered for early-onset and severe clinical presentations with features that are atypical for defined HTADs. Genetic testing should be initiated in the family member with the most severe and typical presentation. Overall, disease-causing variants are identified by genetic testing in 8% to 36% of individuals evaluated for thoracic aortic disease, with a higher yield in young children with syndromic manifestations.[37–40] Once a pathogenic or likely pathogenic variant is identified in one affected family member, cascade genetic testing of at-risk family members should follow. Family members without the familial variant do not need ongoing cardiac evaluation, and their offspring are not at increased risk for aortopathy.

Whenever genetic testing is offered, genetic counseling should be provided by a trained health care professional, ideally as part of a specialized aortopathy center.[41–44] Genetic counseling allows for the education of families regarding the benefits and limitations of genetic testing, as well as psychological, social, and ethical considerations. Genetic counseling also involves interpreting genetic testing results, identifying at-risk family members, and communicating with other family members. The genetic test result can lead to changes in management for the child and other family members, including the need for additional imaging to screen for

peripheral aneurysms, altered surgical thresholds, or the need for consultation with other specialists.

The American College of Medical Genetics and the Association of Molecular Pathologists have established guidelines for the interpretation of rare variants, with variants grouped into 5 categories: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign.[43,50] Pathogenic and likely pathogenic variants have sufficient evidence to support their role in triggering aortopathy and can therefore be used to identify other family members at risk. Variants of uncertain significance have limited or conflicting evidence that they are disease-causing, and should not be used to confirm or exclude a diagnosis in the person carrying the variant of uncertain significance or their family members. A wide range of variants are in this category and should be reassessed as data emerge over time.[42,44,45] Benign and likely benign variants are unlikely to cause disease. Consultation with a medical geneticist or aortopathy specialist is necessary for the proper interpretation of genetic testing results, particularly when a variant of uncertain significance is found. These variants require reevaluation over time as some will eventually be confirmed to be either pathogenic or benign.

If genetic testing fails to identify a cause, genetic testing is not pursued but aortic dilation is present, or BAV is present, noninvasive cardiovascular imaging screening of first-degree relatives should be performed. If the first imaging screening for family history of aortopathy is performed at a young age, a follow-up examination later in childhood may be considered. Additional information about aortic size in family members, particularly if aortic dilation is present or aortic dissection has occurred, provides information about the natural history of the familial aortopathy. Subsequent patient management in the absence of a genetic cause will depend on the cardiovascular presentation (see Aortic Dilation Attributable to Other Causes or Without Clear Genetic Cause).

Highlights: Genetic Testing, Diagnosis, and Familial Evaluation

- Genetic diagnosis affects all aspects of clinical management. Genetic testing should be considered when there is reasonable likelihood of HTAD or when a specific genetic diagnosis might affect management (Figure 2).
- Whenever genetic testing is offered, formal genetic counseling should be provided by a trained health care professional.
- Once a likely pathogenic or pathogenic variant is identified, cascade genetic testing should be offered to at-risk family members.
- If genetic testing is negative, first-degree relatives should undergo imaging screening for aortic disease, and cascade imaging should be pursued if other family members are found to be affected.
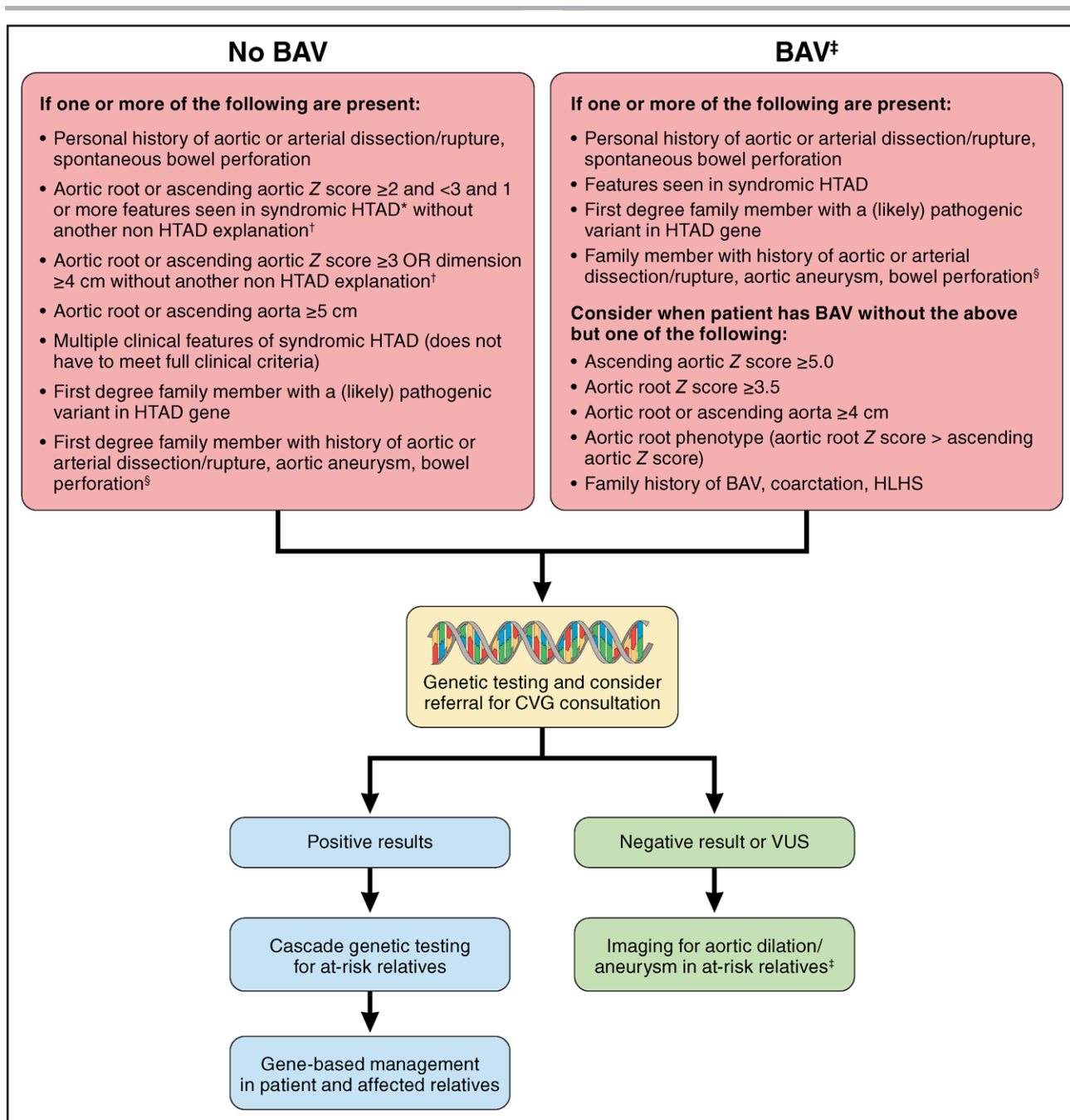
Figure 2. Evaluation and genetic testing algorithm for patients with suspected heritable thoracic aortic disease.
*Heritable thoracic aortic disease (HTAD) features can be seen in Supplemental Table 1. †Common non-HTAD associations with aortic root or ascending aortic Z score ≥2 include congenital heart block; chronic renal disease and hypertension; certain congenital heart defects (ie, truncus arteriosus, dextro-transposition of the great arteries, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, single ventricle status post Fontan); very low weight for height or age; or single or erroneous measurement. ‡For patients with bicuspid aortic valve (BAV), aortic imaging in all first-degree family members should be performed regardless of genetic testing plan. §Especially when testing cannot be performed on the affected family member. CVG indicates cardiovascular genetics; HLHS, hypoplastic left heart syndrome; and VUS, variants of uncertain significance.

MEDICAL THERAPY

The evidence supporting the use of pharmacologic therapy for aortopathy derive from randomized clinical trials (RCTs) of angiotensin receptor blocker (ARB) and β-blocker (BB) therapy in MFS.[46–54] Data on pharmacologic therapy for other causes of aortopathy are limited; therefore, clinical experience from MFS is largely extrapolated to other aortopathies.[55,56]

The Pediatric Heart Network trial, the largest MFS clinical trial, compared losartan and atenolol in 608 children and young adults (age, 6 months to 25 years) with MFS and aortic root Z score >3 SD, and showed that atenolol (BB) and losartan (ARB) each reduced the rate

of aortic dilation, without significant difference between the 2 arms.[48] For each medication, the magnitude of benefit, as measured by reduction in Z score over a 3-year period, was greater in younger versus older patients, suggesting that medical therapy should be instituted even in the youngest children with aortic dilation. Both drugs were generally well tolerated and safe.

In a collaborative individual patient data meta-analysis including 7 RCTs in patients with MFS and no previous aortic surgery, ARB use reduced the rate of growth of the aortic root, including among those also taking a BB.[54] When using dual therapy, the dose of the first drug should be optimized to a therapeutic level before the addition and careful uptitration of the second drug, also to a therapeutic level, while monitoring for intolerance.

Pharmacologic therapy for patients with aortopathy and titration (Table 3 and Supplemental Table 8) should be tailored to the individual's characteristics, diagnosis, and risk profile. The goal of initiating therapy early in life is to slow aortic growth to delay surgery as long as possible; risk of aortic dissection may also be decreased or deferred to later in life. Hypertension should be treated aggressively.

Pharmacologic agents to avoid unless there are no acceptable alternatives include the following:

1) Agents that cause vasoconstriction, hypertension, or tachycardia, including excessive caffeine use and long-term use of decongestants, should be avoided. Triptan use has not been studied in HTAD, but given that triptans are vasoconstrictors, alternate treatment strategies should be exhausted before considering their use in patients with HTAD.
2) Fluoroquinolone antibiotics may exacerbate risk for aneurysm and dissection, and the US Food and Drug Administration advises avoiding these drugs for those with or at risk of aortic aneurysm.[57–60]
3) ARBs are teratogenic and should be avoided in pregnancy.[61]

Given the importance of functioning in school and other settings for children, and the success of both nonstimulant and stimulant medication in treating symptoms of attention-deficit/hyperactivity disorder, these medications should not be restricted for most children with aortopathy. Heart rate and blood pressure should be monitored closely.[62–64] There are animal data to suggest that calcium channel blockers may predispose to aneurysm and dissecton[65]; however, there are not adequate human data to limit their use. Calcium channel blockers are often the mainstay of therapy for patients with renal disorders and hypertension. Further research is warranted among patients with HTAD.[72]

Highlights: Medical Therapy

- Medical therapy for pediatric aortopathy is primarily derived from RCTs in MFS.

- Both ARBs and BBs have been shown to be safe and effective in slowing the rate of aortic growth.
- Medical therapy may be of greatest benefit if initiated at younger ages.
- Single and dual therapies may be considered; pharmacologic management should be individualized on the basis of personal and familial characteristics (Table 3).
- Fluoroquinolone antibiotics and agents that cause vasoconstriction, hypertension, or tachycardia should be avoided when possible.

EXERCISE AND ACTIVITY

Exercise and activity considerations for children with aortopathy should promote safe and healthy cardiovascular lifestyle practices starting at a young age, emphasizing the positive contributions to physical well-being, emotional growth, and community building. Routine aortopathy evaluation should encourage discussion of safe exercise and activity practices, be reevaluated frequently in the context of age-appropriate risks and benefits, and be balanced continuously by shared decision-making between the physician and family.[3,66–70] Safe exercise and activity should also consider noncardiovascular issues, such as ectopia lentis (in MFS), risk for retinal detachment (in MFS and LDS), joint hypermobility (in MFS and LDS), cervical spine instability (in LDS), and increased susceptibility to internal organ and arterial perforation with minimal trauma (in VEDS).

Intense exertion raises concern for exacerbating aortopathy pathophysiology, because acute elevation in blood pressure induces aortic wall stress, further increasing risk for aortic dilation, aortic aneurysm, dissection, or rupture.[3,71–73] Adult aortopathy expert consensus guidelines primarily risk stratify activities by individual sport and physical component (eg, static versus dynamic), restricting most competitive athletics.[2,3,66,67,71,74] However, adult-based recommendations are challenging to apply to younger ages, and will likely over-restrict youth participation in sports.[68] Pediatric activity considerations should differ and extend beyond static versus dynamic profiles.[3,71,72] Table 4 provides age-appropriate guidance to help practitioners identify and address exercise practices by developmental stage (eg, mental and physical growth), scholastic and community or family expectations, personal risk-taking behaviors, and team and social pressures, and offer an earlier opportunity to learn healthy cardiovascular lifestyle practices.

A comprehensive pediatric aortopathy evaluation should be completed before sports or activity participation, including cardiovascular and noncardiovascular screening, with genetic and subspecialty consultations when appropriate. Underlying diagnosis and aortic size should be considered in counseling. Mild to moderate

Table 3.   Medical Therapy for Aortopathy

Characteristics	Degree of aortic root or ascending dilation			
	None	**Mild**	**Moderate**	**Severe**
Age <16 y (Z score)	<2	≥2 to <3.5	≥3.5 to <5	≥5
Age ≥16 y (maximum dimension), cm	<3.5	≥3.5 to <4	≥4 to <4.5	≥4.5
Marfan syndrome	*			
TGFBR1 or *TGFBR2*	*			
TGFB2, TGFB3, SMAD3, or *SMAD2*	*			
Vascular EDS	See section on Vascular Ehlers-Danlos Syndrome			
Classic EDS				
ACTA2 (not R179)				
ACTA2 R179	†‡	‡	‡	‡
MYH11, LOX, MYLK				
PRKG1	†			
FLNA				
EFEMP2				
Arterial tortuosity syndrome		§	§	§
Bicuspid aortic valve‖			¶	¶
Dilated aorta or suspected HTAD with negative genetic testing and no other diagnosis		*		
TGA, TAC, TOF, PA-VSD, Fontan				#

Color code	
	No medication
	Single therapy
	At least single therapy, consider dual therapy (if tolerated)
	Dual therapy (if tolerated)**

In the presence of high-risk features (see Table 1) or moderately rapid aortic growth (≥0.5 and <0.8 cm/y before 2 y of age; >0.3 and <0.5 cm/y after 2 y of age), more aggressive medical therapy may be considered. Increased aortic growth rate may occur during puberty with rapid somatic growth; increased surveillance during this time may be considered for appropriate weight-based medical therapy. In presence of valvar disease or ventricular dysfunction, additional medications may be indicated.

*Consider starting single therapy.

†Medical therapy, preferably β-blockers, should be considered in individuals in their early teenage years even in the absence of enlargement of the thoracic aorta to minimize the risk for both Type A and Type B dissection.

‡In *ACTA2* R179, given hypotension and steno-occlusive disease, lower doses should be used initially, with close monitoring of blood pressure and symptoms.

§Patients are at risk of renal artery stenosis and stenoses in other arterial beds. Be aware of hypotension and hypoperfusion. Use caution with angiotensin receptor blocker therapy if renal artery stenosis is present.

‖Includes bicuspid aortic valve caused by *NOTCH1* and *SMAD6* variants; does not include bicuspid aortic valve associated with other heritable thoracic aortic diseases (HTADs) listed in the table. When substantial aortic valve stenosis or regurgitation is present, the medication strategy may need to be altered to minimize risk to the coronary circulation.

¶Data are limited for use of medical therapy in bicuspid aortic valve with aortic dilation and include only a retrospective study of pediatric patients[65] with aortic Z score ≥4 and a survey of pediatric aortopathy programs.[66] The authors suggest that medical treatment for aortic Z score ≥4 is reasonable.

#May follow without medication depending on growth trajectory.

**Dual therapy has only been systematically studied in Marfan syndrome.

EDS indicates Ehlers-Danlos syndrome; PA-VSD, pulmonary atresia with ventricular septal defect; TAC, truncus arteriosus communis; TGA, transposition of the great arteries; and TOF, tetralogy of Fallot.

cardiovascular effort, including in age-appropriate recreational sports, group activities, childhood play, and physical education, should be routinely encouraged, and may be cardioprotective.[75] Shared decision-making should begin in early childhood to help evaluate and mitigate potential risks of physical activity (eg, considering intensity, duration, location, and supervision). In general, lower-impact sports avoiding intense isometric exertion, and exercise that does not involve frequent or forceful Valsalva maneu-ver (eg, heavy weightlifting), are considered safer.[3,67,71,74,76] Elite competition, training that requires sustained, intense exertion to the point of exhaustion, or activities that elevate the risk for bodily collision (eg, heavy contact sports, such as tackle football, hockey, or wrestling), trauma, or syncope are generally considered above the acceptable risk. Additional studies investigating safe exercise in pediatric aortopathy are warranted and would encourage physical activity among these patients.[75]

Table 4. Exercise and Activity Considerations by Age, Diagnosis, and Intensity

Consideration	Age 0–5 y (preschool)	Age 5–10 y (elementary school)	Age 10–14 y (middle school)	Age 14–18 y (high school)
Counseling				
	Introduce main concept of shared decision-making Provide guidance and reassurance for exercise safety and organized athletics (moderate intensity); with routine supervision, general play is safe and strongly encouraged		Revisit shared decision-making process: discuss lifelong cardiovascular health habits Help identify and encourage specific activities and team positions that decrease risk of exertion, collision, and repeated intense training Explore safe outdoor recreational habits (eg, buddy systems) Counsel regarding pediatric hypertension and obesity	Solidify shared decision-making process: identify and support lifelong cardiovascular health, help balance risks and benefits of desired activities, advise against high-risk adolescent behaviors (eg, substance abuse, smoking, vaping) and sedentary habits
Exercise and activity prescription				
Routine physical activity	Encourage regular childhood play (minimum 1–3 h/d)	Encourage regular moderate cardiovascular physical activity (30–60 min/d, 5 d/wk) as a healthy lifestyle choice		
Physical education	Encourage complete participation		Encourage routine participation; peak exertion activities discouraged (eg, rope climbing, timed sprints, push-up/pull-up competitions)	
Recreational sports	Encourage complete participation		Encourage routine participation with avoidance of contact sports (eg, tackle football, hockey, wrestling)	
Competitive sports			Competitive sports may be considered with regular risk/benefit discussions; avoid contact sports (eg, tackle football, hockey, wrestling) and high-intensity training, leagues, and competitions	
Amusement parks	Encourage full participation per size limitations	Caution may be warranted for high-intensity rides, including those with abrupt stops and starts in high-risk groups; use all proper safety equipment		
Intensity				
	Encourage developmentally appropriate childhood play	Encourage all age-appropriate recreational sports and group activities, including physical education class; frequent mild to moderate cardiovascular activity is safe and healthy		
			Guidance toward organized sports, certain team positions, and recreational activities with lower risk for bodily collision, physical trauma, strenuous training, or frequent unsupervised exertion	
			Avoid strenuous training and prolonged physical exertion, heavy weightlifting (requiring forceful Valsalva), and sustained exertion to exhaustion	
				Encourage lower-intensity varsity and junior varsity athletics, club sports participation
				Refrain from more intense training or competition for highly select state or regional travel teams, Olympic development programs, collegiate varsity recruitment
Higher-risk criteria: diagnosis-specific considerations				

Marfan syndrome
 	
  Lens subluxation
 	
  Retinal detachment
 	
  Joint hypermobility
	Loeys-Dietz syndrome
	
	  Joint hypermobility
	
	  Atlantoaxial instability
		Vascular Ehlers-Danlos syndrome
		
		  Internal organ and arterial perforation with minimal trauma
		
		  Prone to dislocations
		
		  Avoid trampolines in addition to guidelines
			FLNA deficiency
			
			  Extreme joint hypermobility
				Bicuspid aortic valve
				
				  Moderate to severe valvular disease

▢	Low risk
▢	Low risk with modification as indicated
▢	Higher risk

All participants should be permitted normal restroom breaks, water, and rest upon request. In the presence of high-risk features (see Table 1), more aggressive management should be considered, including more aggressive exercise modification. In a group setting, appropriate replacement activities should be recommended to remain inclusive, especially in physical education and recreational settings. Standard protective equipment (eg, helmets, eye and mouth guards) should be encouraged and used when appropriate. Condition-specific considerations should be reevaluated frequently throughout all ages. Tailoring exercise counseling to the patient is encouraged in a shared decision-making model with additional guidance from aortopathy experts.

Table 5. Surgical Thresholds for Children with Aortopathy

Disorder or gene	Standard surgical threshold, maximum of aortic root or ascending aorta, cm	If high-risk features* are present, maximum of aortic root or ascending aorta, cm
Marfan syndrome	5.0 or maximum cross-sectional aortic area/height (cm²/m) ≥10, age ≥16 y†	≥4.5 cm For early-onset Marfan syndrome with severe dilation (when aortic valve annulus ≥2): <2 y: 3.3–3.4 ≥2 and <5 y: 3.7–3.8 ≥5 y: 4
TGFBR1 or *TGFBR2*	≥4.5	When aortic valve annulus ≥2: <2 y: 3.3–3.4 ≥2 and <5 y: 3.7–3.8 ≥5 y: 4.0
TGFB2	≥4.5	≥4.5
TGFB3	≥5.0	≥5.0
SMAD3 or *SMAD2*	≥4.5	≥4.5
ACTA2	≥4.5‡	≥4.2‡ Insufficient data in young patients with severe dilation, as often seen in smooth muscle dysfunction syndrome (R179 variants); consider using early Marfan syndrome numbers
PKRG1	§	§
MYH11	≥4.5	≥4.5
MYLK	Although events occur without dilation, no events have been reported in childhood; if considering surgery, discuss with aortopathy expert	Although events occur without dilation, no events have been reported in childhood; if considering surgery, discuss with aortopathy expert
LOX	≥5.0	Consider earlier intervention
FLNA	≥5.0	Consider earlier intervention
Vascular EDS	≥4.5	≥4.5
EFEMP2	None established; aggressive; consider using criteria for *TGFBR1/2* with high-risk features	None established; aggressive; consider using criteria for *TGFBR1/2* with high-risk features
Arterial tortuosity syndrome	≥5.0	NA (no dissections reported)
Dilated aorta without other diagnosis	≥5.0	≥4.5
Bicuspid aortic valve	≥5.5†‖	≥5.0
TGA, TAC, TOF, PA-VSD, Fontan	≥5.5–6.0	≥5.5–6.0
Previous Ross procedure	≥5.0–6.0¶	≥5.0–6.0

	Standard risk
	High risk

These thresholds are based on consensus agreement and published reports. Each case must be considered individually, and other factors (eg, need for surgery for other cardiovascular disease, aggressive family history, extremely rapid aortic growth) may necessitate modification of timing of surgery.

*See Table 1.

†In patients who are substantially smaller or taller than average, surgical thresholds may incorporate indexing of the aortic root or ascending aortic diameter to patient body surface area or height or aortic cross-sectional area to patient height.

‡If cerebral blood flow is compromised, the higher perioperative stroke risk may warrant larger diameter aortic thresholds.

§Surgery recommended at age ≥17 years if there is any degree of dilation (Z score ≥ 2).

‖In patients with bicuspid aortic valve undergoing surgical aortic valve repair or replacement, and who have a diameter of the aortic root or ascending aorta ≥4.5 cm, concomitant replacement of the aortic root, ascending aorta, or both is reasonable.

¶Institutional practice varies greatly. Given that Ross procedure is often performed in children with bicuspid aortic valve who may be susceptible to aortic dissection, threshold for surgery may be lower than in those with other congenital heart disease.

EDS indicates Ehlers-Danlos syndrome; PA-VSD, pulmonary atresia with ventricular septal defect; TAC, truncus arteriosus communis; TGA, transposition of the great arteries; and TOF, tetralogy of Fallot.

Highlights: Exercise and Activity

- Age-appropriate, safe, and healthy exercise practices should be encouraged for all children with aortopathy, starting in early childhood.
- Pediatric exercise participation offers important opportunities for community building, teamwork, and a healthy cardiovascular lifestyle.
- Application of adult aortopathy guidelines will overrestrict youth exercise participation.
- Routine, ongoing counseling should involve shared decision-making; consider underlying diagnosis and cardiovascular findings, including aortic size; and evaluate type of activity and level of effort.
- Noncardiovascular HTAD manifestations, such as ectopia lentis, retinal detachment, joint hypermobility, cervical spine instability, and susceptibility to minimal trauma, need to be considered when defining safe exercise and activity.

AORTIC DISSECTION AND PROPHYLACTIC AORTIC SURGERY

Aortic dissection in children is rare, but catastrophic. Type A dissection, involving the proximal aorta, is most often but not always preceded by aortic root or ascending aortic dilation, and elective repair of the aneurysmal aorta is lifesaving. In contrast, acute Type B dissection often occurs in the absence of substantial dilation of the descending thoracic aorta. Management of aortic dissection is described in detail in the 2022 American College of Cardiology and American Heart Association guideline for the diagnosis and management of aortic disease.[3] Given the rarity of acute dissection or rupture in children, clinicians are referred to that document for comprehensive management.

As in adults, aortic size is the best predictor of Type A aortic dissection in children. Risk for dissection varies by genetic diagnosis, specific gene and pathogenic variant, severity of craniofacial features in patients with *TGFBR1* or *TGFBR2* variants, family history, degree of arterial tortuosity, aortic growth rate, and moderate or greater aortic insufficiency (Table 1).[29,31,77,78]

Surgical Intervention in Children

Whereas *Z* scores are useful to guide imaging surveillance and medical therapy in children, absolute dimensions are primarily used to guide timing of surgical intervention for aortic root and ascending aortic dilation (Table 5). Commercially available aortic grafts cannot be used until the aortic annulus is ≈20 mm; both annular size and maximum aortic dimension should guide surgical timing.

Specific consideration should be given to whether the altered gene is known to cause Type A aortic dissection with minimal or no enlargement of the aorta or at a young age. For example, patients with pathogenic *PRKG1* variants may be offered elective surgical repair with little to no aortic enlargement because aortic dissection can occur at normal aortic diameters. Patients with HTAD without identifiable genetic cause should be treated on the basis of the presentation and natural history in family members; if this information is not available, the patient should be managed as in classic MFS unless there are high-risk features (Table 1).

Care for aggressive aortic disease in children should be delivered at a specialized aortic center, incorporating shared decision-making and a personalized approach balancing aortic and surgical risk for each patient.

Elective replacement of the root and ascending aorta prevents Type A dissection and improves survival for patients with HTAD.[79,80] The entire ascending aorta should be replaced along with the root at the time of elective surgery for root aneurysms in all patients with HTAD. Selective replacement of the proximal arch (hemiarch) may be both protective and safely performed by expert centers,[81,82] particularly for those with *TGFBR1* or *TGFBR2* variants or smooth muscle dysfunction syndrome attributable to *ACTA2* R179 variants,[83] although data to support this approach in all patients with aortopathy are lacking. Total arch replacement is not indicated for patients undergoing elective surgery for isolated root aneurysms, but could be considered for individuals with aggressive family history or high-risk genetic variants (eg, *ACTA2* R179 or *TGFBR2* R528).[83]

Surgical options to replace the aortic root include valve-sparing and valve-replacing approaches (Supplemental Figure 3). There are 2 techniques for valve-sparing root replacement: reimplantation of the valve, which has become the accepted standard, and aortic root remodeling, which preserves the physiologic flow in the sinuses. Reimplantation of the valve addresses all components of the pathologic root, including correcting and stabilizing annuloaortic ectasia, excising all pathologic root tissue, and correcting any associated aortic cusp abnormality, such as prolapse. Aortic root remodeling carries a higher risk for late annular dilation and aortic insufficiency if not supported by external annuloplasty. The dominant technique for preservation of the aortic valve in the pediatric population and patients with HTAD has been reimplantation of the aortic valve.

Benefits of valve-sparing root replacement include avoidance of valve-related adverse events (eg, anticoagulant-related hemorrhage, thromboembolic complications, endocarditis, reoperation). If the aortic valve is not salvageable, root replacement with a composite valved conduit should be considered. Indications for a bioprosthetic or homograft repair are limited given the predisposition for aggressive calcification in young children, limited durability, and challenges inherent to revision in the pediatric population. Valve-sparing options are limited if the aortic annulus is <≈19 mm. Both mechanical and bioprosthetic

valved conduits are possible. Root replacement with a pulmonary autograft is contraindicated in patients with aortopathy, except for those with BAV (in whom it is typically performed to address aortic valve dysfunction).

Several centers have reported excellent early and mid-term results of aortic root replacement in children.[84–86] The relative rarity of these interventions in children suggests that referral to a center with dedicated expertise may be advisable to optimize outcomes.[87]

Novel external aortic root support techniques (eg, Florida sleeve, personalized external aortic root support) have been reported as alternatives to replacement of the aortic root, but data in children are limited.[84,85,88]

Highlights: Aortic Dissection and Prophylactic Aortic Surgery

- Aortic dissection in children is rare but catastrophic.
- Elective replacement of the aortic root and ascending aorta aneurysms is lifesaving.
- Elective root replacement includes valve-sparing and valve-replacing approaches.
- Timing of elective surgery is based on aortic dimension, genetic diagnosis, and presence of high-risk factors (Table 5).
- Surgical management should be directed by a specialized multidisciplinary aortic center.

MARFAN SYNDROME

MFS is a multisystem connective tissue disorder caused by pathogenic *FBN1* variants with cardinal manifestations involving the ocular, musculoskeletal, and cardiovascular systems.[89] The estimated prevalence is 1:5000 to 10 000, and there is wide clinical variability in the number of systems involved and the severity of involvement of each manifestation, even within the same family. MFS is an autosomal dominant condition affecting female and male individuals with equal frequency, although male patients on average have a younger and more severe presentation.[16] All ethnic and racial groups are affected, but skeletal and systemic manifestations may be less common in Asian and Hispanic populations compared with White populations.[17,18] With prospective management, the life expectancy for affected individuals is similar to that of the general population.[90] Individuals with MFS should be managed by multidisciplinary care teams when possible.

Cardiovascular findings that lead to major morbidity and early death in MFS include dilation of the aortic root predisposing to aortic dissection and rupture, mitral and tricuspid valve prolapse and regurgitation, mitral annular disjunction, and left ventricular dysfunction. Dilation typically is predominantly at the aortic root (ie, sinuses of Valsalva). The age at onset and rate of progression of root dilation is highly variable. In MFS, one of the strongest predictors of aortic dissection is aortic root dimension.

Aortic dissection is extremely rare in childhood and rare in adolescence. Peripheral aneurysms are uncommon.

Mitral and tricuspid valve prolapse, with or without regurgitation, are common. Mitral annular disjunction is a distinct separation of the mitral annulus from the contiguous myocardium, can be diagnosed by echocardiography or MRI, and is associated with an increased risk of ventricular arrhythmias, but the implications of mitral annular disjunction warrant further research (Supplemental Figure 1G and 1H and Supplemental Tables 4 and 6).[91] Cardiomyopathy manifesting as ventricular dilation and dysfunction is seen in a subset of individuals and can occur independent of volume overload. Enlargement of the proximal pulmonary artery is common, but need for intervention is rare.[97]

Early-onset (previously called neonatal or infantile) MFS refers to a subset of cases in individuals who typically present as neonates with the most severe, progressive presentation, including cardiovascular, pulmonary, ocular, musculoskeletal, and diaphragmatic abnormalities. Cardiovascular manifestations include severe mitral and tricuspid valve prolapse and regurgitation, congestive heart failure, and progressive aortic root dilation. A scoring system based on history, physical, and genetic testing has been proposed to aid in diagnosis of early-onset MFS.[92]

History and Physical Examination

Diagnostic criteria for classic MFS were defined in 2010.[93] Common findings in MFS that contribute to the systemic score are listed in Supplemental Table 9. Musculoskeletal findings include bone overgrowth and disproportionately long extremities and digits, scoliosis, and rib overgrowth leading to pectus excavatum and pectus carinatum. Ocular findings include ectopia lentis, myopia, and increased risk for retinal detachment, glaucoma, and early cataracts.

The systemic score can be useful in considering a clinical diagnosis of MFS, but has limitations when applied in children. Many children with MFS do not have sufficient features in early childhood to meet criteria using the systemic score because features accrue and worsen with age (Supplemental Figure 4).[16,32]

Genetic testing should be performed in children in whom MFS is suspected. A small percentage (<3%–5%) of individuals who meet clinical criteria for MFS will have negative genetic testing results. On the contrary, some children who meet clinical criteria for MFS will have another HTAD, particularly LDS, which has a distinct risk profile requiring different management.

Imaging

Genetic Testing, Diagnosis, and Familial Evaluation and Table 2 provide a framework for baseline and surveillance imaging. A TTE should be performed at the time of

diagnosis to assess the aortic root, ascending aorta, and mitral valve; serial imaging is primarily based on aortic size. Annual TTEs are adequate for most children with MFS. Because peripheral aneurysms are uncommon, routine cross-sectional imaging is usually not necessary, except for indications listed in Imaging Considerations. MRA of the neck can provide a VTI, which can be helpful in risk assessment.

Medical Therapy, Exercise, and Surgical Intervention

See Medical Therapy, Exercise and Activity, Aortic Dissection and Prophylactic Aortic Surgery, and Tables 3 through 5.

Highlights: Marfan Syndrome

- Clinical diagnostic criteria for classic MFS have limitations in children. The MFS systemic score (Supplemental Table 9) is a useful screening tool for historical and physical findings suggestive of MFS, but should not be relied upon in isolation.
- Genetic testing should be performed in children suspected to have MFS; variants in FBN1 are found in >95% of children with MFS.
- A TTE should be performed at the time of diagnosis and during surveillance. TTE provides adequate assessment of the aortic dimensions for most children. Frequency of serial imaging is driven by aortic dimensions and associated high-risk factors (Table 1).
- Cross-sectional imaging is indicated selectively in MFS (see Imaging Considerations).
- In RCTs, BBs and ARBs have been shown to reduce the rate of growth of the aortic root. Monotherapy or dual therapy should be considered depending on aortic root size.
- Aortic dissection is rare in children.

LOEYS-DIETZ SYNDROME

LDS is a spectrum of conditions with involvement of the cardiovascular, craniofacial, skeletal, cutaneous, and immunologic systems.[94] The LDS spectrum is caused by heterozygous pathogenic loss-of-function variants in 6 genes encoding direct effectors of the transforming growth factor–β cellular-signaling cascade: TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, and SMAD2 cause LDS1 through LDS6, respectively. As with all HTADs, clinical presentation and natural history vary dramatically between the genes as well as within variants in 1 gene.

Cardiovascular features that overlap with MFS include high risk for progressive aortic root dilation, type A dissection, and myxomatous degeneration of the mitral valve with prolapse and regurgitation. Both LDS and MFS increase risk for Type B dissection, which may be preceded by only minor changes in aortic dimension, necessitating close surveillance particularly after surgical repair of the proximal aorta.

Features specific to LDS include a predisposition for aneurysms and dissections throughout the arterial tree, with frequent involvement of head and neck vessels, descending aorta, and superior mesenteric, celiac, and iliac arteries. Penetrance of other aneurysms is much lower than aortic events for all the LDS genes.[77] Arterial tortuosity is particularly frequent and severe in many forms of LDS, particularly in the head and neck. Unlike MFS and HTAD attributable to other genes, vascular events can occur in childhood, especially with TGFBR1 and TGFBR2 variants, but rarely, if ever, with TGFB2, TGFB3, or SMAD3 variants, and can occur at relatively small vascular dimensions when compared with most other conditions.[77,95] Select forms of congenital heart disease (eg, BAV, patent ductus arteriosus [PDA], atrial septal defect) show increased frequency in LDS. Mitral annular disjunction may also occur in children with LDS.[13]

History and Physical Examination

In LDS, there is considerable overlap in phenotype with other vascular HTADs, particularly MFS and VEDS (Supplemental Tables 1 and 2). Craniofacial features more commonly seen in LDS than others include craniosynostosis, hypertelorism, cleft palate/bifid uvula (but not cleft lip), exotropia, dusky sclerae, and extensive tooth discoloration and decay.

Cutaneous features seen in LDS include easy bruising, skin translucency with easily visible veins, dystrophic scar formation, persistence of facial milia past infancy and often into adulthood, eczema, and subcutaneous cysts. Skeletal features apart from those seen in MFS include club foot and cervical spine instability, which may progress to spinal cord injury without intervention. Allergic and autoinflammatory features in LDS include environmental and food allergies, anaphylaxis, asthma, eczema, and autoinflammatory gastrointestinal disease, including eosinophilic esophagitis, gastritis, colitis, and Crohn disease, although many patients have few or none of these complications.

Imaging

Genetic Testing, Diagnosis, and Familial Evaluation and Table 2 provide a framework for baseline and surveillance imaging. A TTE should be performed at the time of diagnosis to assess for congenital heart disease, the aorta and valve, and ventricular structure and function (Supplemental Table 4); serial imaging is based on aortic size. The high predisposition for aneurysms beyond the aortic root in all forms of LDS mandates the use cross-sectional imaging (eg, MRA, CTA) from head to pelvis at the time

of diagnosis, although this may be delayed until later in childhood in milder presentations of LDS (eg, *TGFB3*, *SMAD2*, *SMAD3*) unless the family history or specific variant warrants earlier surveillance. In young children, CTA is often used because of the speed of image acquisition to minimize or avoid sedation. The frequency of subsequent imaging will vary depending on the specific diagnosis and genotype, age, family and surgical history, symptoms or signs, and previous imaging findings.

Medical Therapy

See Medical Therapy and Table 3.

There have been no RCTs of medical therapy in LDS. Current practice is based on mouse models of LDS and extrapolation from RCTs in humans with MFS. More aggressive medical and surgical therapy should be considered when there are high-risk features in an individual or family (Table 1). Among the 6 subtypes of LDS, the risk for aortic dissection varies by gene and specific variant, although there is considerable variability and overlap. Individuals with variants in *TGFBR1* or *TGFBR2* generally have earlier age at onset and more severe presentation compared with the other LDS genes. Among those with variants in *TGFBR1* or *TGFBR2*, risk is highest when high-risk features are present (Table 1).[78] *TGFBR2* variants that substitute histidine or cysteine for arginine at codon 528 (R528H/C) are associated with the worst prognosis, with most patients undergoing surgical intervention or presenting with dissection ≥20 years of age.[77]

There is no consensus regarding the optimal age for beginning medical therapy, but in the presence of moderate to severe aortic dilation, high-risk features (even with little or no aortic dilation), or a family history of severe aortic disease, initiation of medical treatment at the time of diagnosis should be considered, even in infancy.

Exercise

In addition to general concerns about exercise and activity (see Exercise and Activity and Table 4), risk assessment in children with LDS should include risk of retinal detachment and spinal cord injury attributable to cervical spine instability. Regular physical activity contributes positively to emotional and physical health. Decisions regarding physical activity should be made using shared decision-making among the child, family, and health care professional, considering the child's personal risk profile.

Surgical Intervention

See Aortic Dissection and Prophylactic Aortic Surgery and Table 5.

There is consensus that aortic root size thresholds for surgical repair should be somewhat smaller in LDS than those typically used in MFS and some other HTADs (Table 5). Other factors that should be integrated into surgical decision-making include comorbid events that could influence outcome and the assessment of risk versus benefit for the individual and family. Within the LDS spectrum, the thresholds for surgical repair vary depending on the natural history of each condition and presence of high-risk features (Table 1), generally >4.0–4.5 cm for all subtypes except *TGFB3* (>5.0 cm).[3]

Surgical outcomes are similar to those observed in MFS, without evidence for excessive tissue fragility, although emerging reports suggest the potential for increased risk of anastomotic dehiscence, pseudoaneurysm, or formation of vascular fistulae at the site of repair in a subset of severely affected children with variants in *TGFBR1* or *TGFBR2*.[96] Dissection or aneurysm may occur distal to the repair site, and sequential replacement or repair of involved segments may be needed.[97,98] As in other HTADs, coronary button aneurysms can be seen, with rare progression to a size warranting reintervention.[85]

The thresholds and approaches for repair of aneurysms or dissections in vascular segments distant from the aortic root are largely based on expert opinion rather than rigorous studies, although the practice of avoiding intravascular stents in native tissue unless needed as a temporizing measure appears both broadly accepted and defendable through experience.

Highlights: Loeys-Dietz Syndrome

- Clinical presentation is highly variable in children. A pathogenic or likely pathogenic variant in one of the LDS genes is usually present.
- TTE and cross-sectional imaging from head to pelvis should be performed at baseline and during surveillance.
- Serial imaging is driven by gene, variant, associated risk factors (Table 1), and findings at baseline.
- It is reasonable to treat children with LDS with an ARB or BB, or both.
- Compared with MFS, congenital heart disease is more common, risk for aortic dissection is higher, and involvement of the distal aorta and peripheral arteries is more common.
- Surgical thresholds for aortic dimensions in LDS tend to be smaller than for MFS.

VASCULAR EHLERS-DANLOS SYNDROME

VEDS, previously Ehlers-Danlos syndrome (EDS) type IV, is a rare autosomal dominant HTAD caused by variants in *COL3A1* that encode part of type III collagen.[34] The prevalence of VEDS has been estimated at 1:50 000 to 150 000, which may underestimate the true prevalence.[34] The variant is inherited in ≈50% of cases; 50% of cases are de novo.

Bruising and skin lacerations are the most common adverse events in children. Dissection and rupture of the aorta and other arteries, pneumothorax, and hollow organ perforation are the highest-risk events.[15] Approximately 20% of affected individuals experience an aortic or arterial event ≥20 years of age.[99] Death >20 years of age is more common in male patients (male:female ratio 3:1).[34] Stratifying risk factors are presented in Table 1. Dissection and rupture can occur in almost any medium or large artery, but most commonly occur in the carotid or vertebral arteries. VEDS is the most common known genetic cause of spontaneous coronary artery dissection.[100]

History and Physical Examination

Affected individuals most frequently present with a history of abnormal bruising or other VEDS-related events, or with a family history of VEDS or VEDS-related events. VEDS may be diagnosed incidentally on genetic testing for other indications, but this is rare.[44]

Children often have subtle or no dysmorphic features, and the diagnosis is often delayed or missed. Common features include translucent skin with easily visible veins, which is more difficult to appreciate in those with dark skin, deep-set eyes with dark circles under the eyes, a small, narrow nose, and thin lips. Skin may be soft and may easily bleed or bruise. Needing stitches or staples for minor injuries is common but not universal. Affected children commonly sleep with their eyes open. Other common findings include club or flat feet, small-joint hypermobility, and acrogeria. Other features are listed in Supplemental Table 2. A pathogenic or likely pathogenic variant in *COL3A1* is necessary for diagnosis.

Imaging

Approximately 15% of individuals with VEDS have dilation of the aortic root or ascending aorta[31]; however, aneurysm can occur anywhere in the arterial tree. Unlike in MFS and LDS, aortic or arterial dissection or rupture in VEDS often occur in the absence of aneurysm.[100] Normal results on TTE or MRA or CTA do not rule out risk of an arterial event. However, presence of an aneurysm likely increases the risk of dissection or rupture.

Whether to conduct systematic imaging has been controversial because interventions have involved extremely high risk, although this observation was likely biased because intervention was used as a last resort.[99] In recent years, safer endovascular and surgical approaches for aneurysms and dissections have been developed.[101] Surveillance imaging to detect abnormalities now has the potential to improve survival. A French cohort instituting systematic arterial imaging showed improved survival compared with previous eras, although further studies are warranted to confirm this finding.[102] A European survey of experts also reached a consensus favoring serial imaging in VEDS.[103] A suggested schedule for serial follow-up is given in Table 2, with guidance for cross-sectional imaging in Supplemental Table 7. More frequent imaging can be considered in the presence of high-risk features (Table 1).

Medical Therapy

The results of a single RCT suggested that the 3rd-generation BB celiprolol reduced adverse cardiovascular outcomes.[55] However, the study had several major limitations, and celiprolol is not available in the United States. No other agents have been studied systematically in humans.[62] Based on overlapping properties between celiprolol and other 3rd-generation BBs (eg, carvedilol, labetalol, nebivolol), some physicians have used one of these agents, regardless of the presence of aortic or arterial dilation or hypertension (Supplemental Table 8).[104] Extrapolating from RCTs in MFS, some clinicians have used ARBs in children with VEDS.[104] A retrospective cohort study of children and adults from the United Kingdom demonstrated that individuals receiving a long-term BB or ARB had fewer vascular events than those not on cardiac medication who received the same lifestyle and emergency care advice.[104] Given trial and observational data, treatment with a BB is reasonable, even in the absence of aortic dilation, or if not tolerated, an ARB may be considered, although further investigations are warranted. For patients with high-risk features (Table 1), therapy with BBs or ARBs may be more strongly considered. For medications to avoid, see Medical Therapy.

The use of vitamin C in doses ranging from 1 to 4 grams daily in adults has been advocated by some in an effort to decrease bruising and improve wound healing.[105]

Exercise

Data on VEDS and exercise are primarily limited to case reports and surveys.[106–108] In addition to general concerns about exercise and activity (see Exercise and Activity and Table 4), risk assessment in children with VEDS focuses on hematoma, muscle rupture, aortic and arterial dissection, and organ injury. Some children can develop major hematomas with minimal trauma, whereas others go through childhood without a major bruise or injury. Regular physical activity contributes positively to emotional and physical health. Decisions regarding physical activity should be made using shared decision-making among the child, family, and health care professional, taking into account the child's personal risk profile.

Surgical and Transcatheter Interventions

Surgical and catheter-based interventions carry high risk because of tissue fragility and poor healing. However, multiple cohort studies have demonstrated successful surgical intervention when specific precautions are taken, such as minimizing tissue and vascular trauma, avoiding manual angiography when possible, ensuring strict blood pressure control and tolerance of hypotension, and using soft, maneuverable guidewires and catheters.[109] Common complications include access site issues, iatrogenic arterial dissection, and pseudoaneurysm. See Aortic Dissection and Prophylactic Aortic Surgery and Table 5.

Highlights: Vascular Ehlers-Danlos Syndrome

- Clinical presentation is highly variable in children. A pathogenic or likely pathogenic variant in *COL3A1* is necessary for diagnosis.
- TTE should be performed at the time of diagnosis to evaluate for congenital heart disease and assess the aortic dimensions.
- Cross-sectional imaging from head to pelvis should be performed but may be delayed until after age 3 years to avoid risks of sedation.
- Normal TTE or MRA or CTA results do not rule out the risk of an arterial event.
- Serial imaging is driven by associated risk factors (Table 1) and baseline findings.
- It is reasonable to treat children with VEDS with a 3rd-generation BB or ARB, but further study is warranted.
- Risks and benefits of any surgical or catheter-based intervention must be weighed carefully; when undertaken, precautions to minimize tissue and arterial damage should be taken, and complications should be anticipated.

CLASSIC EHLERS-DANLOS SYNDROME

Classic EDS, formerly type I or gravis type, is one of 13 subtypes of EDS with shared features of skin hyperextensibility, generalized joint hypermobility, and tissue fragility.[110] Classic EDS is autosomal dominant and caused by variants in *COL5A1* or *COL5A2*, leading to abnormalities in type V collagen. Genetic testing confirms the diagnosis and rules out other conditions.

Cardiovascular findings are uncommon. The incidence of aortic dilation and valvar abnormalities (eg, BAV) is similar to that of the general population.[111] Mitral and tricuspid valve prolapse and regurgitation, when present, are typically mild.[112] Aortic dissection is exceedingly rare and not reported in children.[113] Intracranial aneurysms, arteriovenous fistulae, and spontaneous rupture of large arteries are rare.[112]

Skin findings include soft and doughy texture, easy bruising, hyperextensibility and fragility (traumatic splitting), atrophic scarring, molluscoid pseudotumors, subcutaneous spheroids, and hernias.

A baseline TTE should be performed as part of the initial diagnostic evaluation. Long-term serial aortic imaging is not necessary if initial TTE results are normal.

ACTA2 VARIANTS

Heterozygous pathogenic variants in *ACTA2* are responsible for 10% to 14% of nonsyndromic HTAD cases.[114,115] In addition to thoracic aortic disease, specific *ACTA2* variants predispose individuals to PDA, occlusive vascular diseases in muscular arteries, including early-onset coronary artery disease, strokes attributable to occlusive vascular lesions resembling Moyamoya disease (MMD), and pulmonary hypertension.[114,116,117] Other systemic features include iris flocculi and livedo reticularis. Recurrent *ACTA2* variants disrupting arginine 149 and arginine 118 are associated with an increased risk of early-onset coronary artery disease in patients with minimal or no cardiovascular risk factors. In contrast, variations disrupting arginine 258 (R258) or arginine 179 (R179) are associated with early-onset strokes attributable to MMD-like cerebrovascular disease, PDA, or pulmonary hypertension. MMD-like cerebrovascular disease is characterized by bilateral stenosis or occlusion of the supraglenoid internal carotid arteries without collateral artery formation, straightening of the cerebrovascular arteries, fusiform aneurysms of the carotid artery proximal to the occlusive lesion, and periventricular hyperintensities suggestive of small vessel disease.

The most robust genotype–phenotype correlation involves the most severe *ACTA2* variant—a recurrent, de novo variant involving arginine 179 (R179) causing smooth muscle dysfunction syndrome.[117] This variant is fully penetrant <20 years of age for PDA and thoracic aortic disease, and is often associated with MMD-like cerebrovascular changes and pulmonary hypertension. Additional phenotypic features include abnormal lung development, fixed, dilated pupils (congenital mydriasis), malrotation or hypoperistalsis of the gut, and hypotonic bladder. Specific management recommendations have been published.[83,118]

History and Physical Examination

Most individuals with *ACTA2* pathogenic variants who have an aortic event present with acute aortic dissections (88%); of those with type available, 63% present with Type A and 25% present with Type B dissection.[119] Type A dissection is usually preceded by dilation of the aortic root or ascending aorta, but not

always.[120] Type B dissections occur at a much younger age than Type A dissections with *ACTA2* variants (27 years versus 36 years), and aortic events are more common in men than women.[119] Aortic aneurysm and dissection risk has the earliest onset for *ACTA2* variants disrupting R258 and R179, with the majority of patients with smooth muscle dysfunction syndrome undergoing surgical intervention or presenting with dissection <20 years of age.[83] Pregnancy introduces high risk for aortic dissection.[121]

Imaging

TTE should be performed at the time of diagnosis to assess the aortic root and ascending aortic dimensions; serial imaging is based on aortic size (Table 2). Patients with *ACTA2* pathogenic R179 or R258 variants and patients with PDA or MMD should be informed of the risk and symptoms of ischemic strokes or transient ischemic attacks, and should seek medical attention and undergo head imaging if symptoms occur.

Medical Therapy

There are no data on the efficacy of prophylactic therapy for *ACTA2* or other nonsyndromic forms of HTAD. Initiation of BBs or ARBs to reduce hemodynamic stress should be considered in patients with aortic dilation or hypertension (Table 3). Medical therapy should be considered in the absence of dilation of the thoracic aorta starting in the early teen years to minimize the risk of Type B dissection. Patients with *ACTA2* R179 often have hypotension and steno-occlusive cerebrovascular disease; lower doses should be used initially, with close monitoring of blood pressure and symptoms. Although there are no data to support the routine use of antiplatelet agents and statins, antiplatelet agents could be considered in patients with MMD-like cerebrovascular occlusions, and statins could be considered late in childhood for children with *ACTA2* pathogenic variants that also predispose to atherosclerosis.

Exercise

See Exercise and Activity and Table 4.

Surgical Intervention

Surgical repair of a thoracic aortic aneurysm is recommended when the diameter of any segment of the aortic root or ascending aorta is ≥4.5 cm[3] (Table 5).[3] Surgical repair at a diameter ≥4.2 cm is reasonable in patients with high-risk features (Table 1).[3] Concurrent arch repair at the time of root or ascending aortic repair should be considered in smooth muscle dysfunction syndrome.

OTHER HTAD GENES, INCLUDING *MYH11, MYLK, LOX,* AND *PRKG1*

History and Physical Examination

Heterozygous pathogenic *MYH11* variants cause thoracic aneurysms involving the aortic root and ascending aorta.[122] Although *MYH11* variants are identified throughout the gene, only a subset of these variants in a limited region of the gene are pathogenic or likely pathogenic. Although aortic events have only been described in adults, pediatric PDA and cerebrovascular disease have been described.[123,124] *MYH11* carriers have fusiform dilation of the root and ascending aorta, and repair is recommended at 4.5 cm.

Heterozygous pathogenic *MYLK* variants cause thoracic aortic aneurysm and dissection in adults, with aortic dissection occurring at a relatively small dimension.[77,125,126] Although familial pathogenic variants have been detected in children, aortic dilation and dissection are rare in childhood.

Heterozygous pathogenic *LOX* variants also cause HTAD.[10,127] Individuals with *LOX* variants may have systemic manifestations similar to MFS (eg, skeletal features, joint hypermobility, dural ectasia, striae), but these features are typically insufficient to reach a clinical diagnosis of MFS. Individuals with *LOX* variants can present with aortic root dilation in childhood or later, fusiform dilation of the root and ascending aorta that can extend into the aortic arch, and Type A dissection. Aortic dimension at the time of aneurysm repair ranged from 4.2 to 10.5 cm, but data on aortic size at the time of Type A dissection are limited. Infrarenal aortic, hepatic, and brain aneurysms have been reported in members of one family, and an unrelated individual was reported with multiple aneurysms (in the infrarenal aorta, iliac, and femoral arteries).[128]

A single, recurrent heterozygous pathogenic *PRKG1* variant (c.530G>A, p.R177Q) is a rare cause of HTAD presenting with early-onset aortic aneurysm and dissection, as early as adolescence, with minimal or no dilation.[5,77] BBs should be initiated in the early teenage years, and aggressive surgical repair of the aorta should be considered regardless of the presence or absence of enlargement of the aorta.

Imaging

A TTE should be performed at the time of diagnosis to assess the diameter of the aortic root and ascending aorta; serial imaging is based on aortic dimensions (Table 2).

Medical Therapy

There are no data on the efficacy of prophylactic therapy for HTAD associated with *MYH11, MYLK, LOX,* or

PRKG1 variants. Initiation of BBs or ARBs to reduce hemodynamic stress could be considered in patients with aortic dilation or hypertension, particularly if there is a family history of dissection (Table 3).

Exercise and Surgical Intervention

See Exercise and Activity, Aortic Dissection and Prophylactic Aortic Surgery, and Tables 4 and 5.

FLNA-RELATED CARDIOVASCULAR DISEASE

History and Physical Examination

Heterozygous, loss-of-function sequence variations in *FLNA* are associated with X-linked periventricular nodular heterotopias and seizures[129] and various cardiovascular abnormalities, including dilation of the ascending aorta and aortic root (with the ascending almost always larger than the root), BAV, aortic regurgitation, PDA, valvular dysplasia, and pulmonary hypertension.[6,130,131] The majority of affected patients are female; hemizygosity for null variants typically leads to fetal death in male embryos.[132] Noncardiovascular manifestations, including obstructive lung disease, joint hypermobility, and thin, soft skin, are common.[132]

Thoracic aortic aneurysms associated with *FLNA* variants tend to progress. Aortic dissection and rupture are rare, but have been reported at aortic dimensions as small as 4 to 4.5 cm.[131] Other vascular events include myocardial ischemia, stroke, transient ischemic attack, or subarachnoid hemorrhage, at ages as young as 19 years.[131] The most common cause of death in infancy is lung disease with pulmonary hypertension.[130]

Imaging

TTE should be performed at the time of diagnosis to identify any congenital heart disease and to assess the diameter of the aortic root and ascending aorta (Table 2). Serial imaging should be performed in all patients with *FLNA* variants, including ones with normal thoracic aortic dimensions; frequency of serial imaging depends on aortic size and rate of growth.

Medical Therapy

There are no data on the efficacy of prophylactic therapy for *FLNA* variants. Use of BBs or ARBs to reduce hemodynamic stress have been described and should be considered in patients with aortic dilation or hypertension (see Medical Therapy and Table 3).[130,131] Standard medical management for pulmonary hypertension including sildenafil is reasonable.

Exercise and Surgical Intervention

See Exercise and Activity, Aortic Dissection and Prophylactic Aortic Surgery, and Tables 4 and 5.

ARTERIAL TORTUOSITY SYNDROME

History and Physical Examination

Arterial tortuosity syndrome is a rare autosomal recessive condition caused by biallelic variants in *SLC2A10*. Arterial tortuosity syndrome is characterized by generalized tortuosity of large and medium-sized arteries, focal stenoses of the pulmonary arteries and aorta, aortic root and ascending aortic dilation, arterial stenoses including coarctation of the aorta, and ischemic stroke.[133,134] Stenoses and dilation can progress. Large aneurysms can develop, but dissection and rupture have not been reported. Dilation and tortuosity of veins are common.[135]

Manifestations of a generalized connective tissue disorder are common, including soft, doughy, hyperextensible skin, inguinal and diaphragmatic hernias, joint hypermobility, contractures, arachnodactyly, pectus excavatum or carinatum, and scoliosis. The face can be long, with a long philtrum and a high-arched palate. Keratoconus has been reported.[133]

Cardiac care is driven by lesions present in the individual.[133,134] Multidisciplinary care should include ophthalmology, orthopedics, and orthodontics, and monitoring for keratoconus, refractive errors, scoliosis, and dental crowding.

Imaging

TTE should be performed at the time of diagnosis (Table 2). Comprehensive MRA or CTA (head to pelvis) is helpful to delineate the extent of tortuosity, dilation, and stenosis. Serial imaging will depend on individual findings and rate of progression.

Medical Therapy and Surgical Intervention

There are no data on the efficacy of prophylactic therapy for arterial tortuosity syndrome. Aortic dissection and rupture have not been reported (see Medical Therapy and Table 3). ARBs should be used with caution in the presence of aortic or renal artery stenosis compromising renal blood flow.

Surgical intervention for aortic aneurysm is uncommon, although it has been performed.[134,136]

Pulmonary artery stenoses tend to be bilateral and multifocal in nature. Complications include right ventricular hypertension, right heart failure, exercise intolerance, and respiratory insufficiency. Other arterial stenoses are also common in arterial tortuosity

syndrome. Complications can include refractory systemic hypertension, heart failure, progressive prestenotic or poststenotic dilation, tissue ischemia, transient ischemic attack, or stroke. Intervention is individualized on the basis of vascular anatomy; both catheter-based and surgical approaches for arterial stenoses have been described.[137–139]

Exercise

See Exercise and Activity and Table 4.

AUTOSOMAL RECESSIVE CUTIS LAXA TYPE 1B (*EFEMP2*)

Autosomal recessive cutis laxa type 1B is an ultrarare condition caused by variants in *EFEMP2* (previously *FBLN4*) and characterized by cutis laxa, diffuse arterial disease (eg, extensive arterial tortuosity, aneurysms, stenoses), retrognathia, joint laxity, hernias, and arachnodactyly.[7] Perinatal lethality is common, often secondary to respiratory failure because of tracheobronchial compression by aneurysms.[140] Manifestations are highly variable. Imaging recommendations are listed in Table 2 and Supplemental Table 7. Medical therapy, interventions, and exercise guidance should be tailored to specific lesions. Arterial and aortic dissection in humans have not been described, although the mouse model is susceptible to dissection and rupture, and humans are thought to be susceptible as well.

BICUSPID AORTIC VALVE

Bicuspid aortopathy encompasses abnormal aortic valve morphologies in association with proximal aortic dilation. BAV is the most common congenital heart disease, occurring in 0.5% to 2% of the general population, with a near 3:1 male predominance.[3,71,141–143] Dilation of the aortic root (20%; *Z* score >2) and ascending aorta (50%; *Z* score >2 SD) is frequent. Dilation is more commonly present with partial or total fusion of the right–left commissures, with persistent progression through childhood and adolescence.[144–147] Aortic dissection in children with isolated BAV without a known specific HTAD sequence variation has not been reported; however, adults with BAV and aortic aneurysm are at risk for aortic dissection.[148]

History and Physical Examination

A focused aortopathy family history screens for familial aortic dilation, congenital heart disease, surgical intervention, dissection, and sudden death.[148,149] Physical examination includes evaluation for valvar stenosis and regurgitation, and an aortic ejection click. Genetics

evaluation is often considered in the presence of syndromic features or prominent family history of aortopathy (Figure 2).[3]

Imaging

TTE offers appropriate evaluation of aortic valve morphology and function, identifies accompanying congenital heart disease, and provides accurate assessment of aortic size in most patients (Table 3).[3] Computed tomography or MRI may be used if TTE does not offer accurate acoustic windows.[3,71] Lifelong imaging surveillance is routine.[3] Serial TTE frequency is based on aortopathy degree, dilation rate, and valve function. First-degree relatives of individuals with BAV can have BAV, aortic dilation with trileaflet aortic valve, or both BAV and aortic dilation.[150,151] TTE screening for first-degree relatives is suggested and cost effective.[3,71,148,152]

Medical Therapy

Medical therapy aims to decrease the rate of aortic dilation throughout childhood, but has not been studied prospectively in children with BAV. Some guidance for medical therapy has been extrapolated from more common aortopathy syndromes, and includes BBs.[71] A large degree of regional practice variation exists.[1,69,153] One retrospective study demonstrated a slower rate of aortic growth after treatment with either losartan or atenolol compared with baseline with no treatment.[56] A regional bicuspid aortopathy registry has agreed upon irbesartan as first-line treatment.[69] Table 3 summarizes a potential medication strategy, with consideration of treatment for aortic *Z* score >4.

Exercise

See Exercise and Activity and Table 4.

Surgical Intervention

Isolated bicuspid aortopathy remains an uncommon surgical indication during childhood or adolescence. Multidisciplinary surgical review is encouraged to evaluate absolute aortic dimensions and rate of dilation, accompanying aortic valve disease, and family history.[3] Surgical intervention is recommended for aortic dimension ≥5.5 cm, and considered between 5.0 and 5.5 cm in the presence of additional risk factors (eg, rapid growth >3 mm/year, predominant aortic root dilation, known as root phenotype, coarctation, family history of dissection) or when performed by experienced surgeons at multidisciplinary aortic centers. Surgery at aortic dimension as low as 4.5 cm can be considered for aortic valve repair or replacement at multidisciplinary aortic centers.[3,71]

AORTIC DILATION ATTRIBUTABLE TO OTHER CAUSES OR WITHOUT CLEAR GENETIC CAUSE

The differential diagnosis of aortopathy in a child with a structurally normal heart and negative aortopathy testing results (Supplemental Table 10) includes presumed HTAD with negative testing; acquired pathogeneses, such as chronic hypertension or stimulant abuse; congenital complete heart block; PHACE syndrome; autoimmune or infectious aortitis; renal disease; and genetic conditions, including 22q11.2 deletion, Alagille, Noonan, or Turner syndromes and neurofibromatosis.

Suspected HTAD With Negative Genetic Testing

Many children and adults undergoing genetic testing will not have a pathogenic variant identified on initial analysis despite clinical evidence of a genetic condition (eg, a positive family history).[3] Absence of a positive genetic test result should not be assumed to rule out HTAD if clinical suspicion is otherwise high. Reclassification of uncertain variants, discovery of new genes, and addition of these genes to aortopathy panels occur on an ongoing basis. Thus, continued follow-up with genetics should be considered.

Imaging in Suspected HTAD With Negative Genetic Testing

TTE should be performed at the time of diagnosis to assess the size of the aortic root and ascending aorta; the need for serial imaging is based on aortic dimensions, age, and family history (Table 2). For patients with suspected HTAD, multiple studies have confirmed the use of screening first-degree relatives with TTE, even in the absence of positive genetic test results.[3] In the case of a child with aortic dilation, TTE of the parents is important, because the risk of aortic complications is greater with older age. If a parent is found to have aortic dilation, all their first-degree family members should undergo imaging. On the contrary, if a child is being evaluated because of having a gene-negative parent with aortic aneurysm, and imaging results are normal, repeat imaging should be performed in 5 to 10 years. If there is a family history of vascular disease involving the distal aorta or peripheral vasculature, cross-sectional imaging may be considered.

Medical Therapy

There are no data on the efficacy of prophylactic therapy for the child with suspected HTAD and negative genetic testing results (see Medical Therapy and Table 3). Clinicians should work closely with families in a shared decision-making process to weigh potential risks and benefits of medical therapy. Initiation of BBs, ARBs, or angiotensin-converting enzyme inhibitors should be considered in patients with hypertension or aggressive family history.[32] Calcium channel blockers are often the mainstay of therapy for patients with renal disorders.[154]

Exercise and Surgical Intervention

See Exercise and Activity, Aortic Dissection and Prophylactic Aortic Surgery, and Tables 4 and 5.

SUMMARY

Care of children with aortopathy is driven by genetic diagnosis, cardiac phenotype, family history, and age. Many advancements have been made in terms of risk stratification by condition, and stratification tools should be used to individualize and optimize care. Consultation with a pediatric aortopathy specialist should be considered, especially in complex or severe cases, or when escalation in medical therapy or surgical intervention is being considered. Smooth transition of care to a multidisciplinary adult aortopathy service is essential.

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Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

†Significant.

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*Modest.

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