

## AHA SCIENTIFIC STATEMENT

# Cardiovascular Risk Reduction in High-Risk Pediatric Patients

## A Scientific Statement From the American Heart Association

**ABSTRACT:** This scientific statement presents considerations for clinical management regarding the assessment and risk reduction of select pediatric populations at high risk for premature cardiovascular disease, including acquired arteriosclerosis or atherosclerosis. For each topic, the evidence for accelerated acquired coronary artery disease and stroke in childhood and adolescence and the evidence for benefit of interventions in youth will be reviewed. Children and adolescents may be at higher risk for cardiovascular disease because of significant atherosclerotic or arteriosclerotic risk factors, high-risk conditions that promote atherosclerosis, or coronary artery or other cardiac or vascular abnormalities that make the individual more vulnerable to the adverse effects of traditional cardiovascular risk factors. Existing scientific statements and guidelines will be referenced when applicable, and suggestions for risk identification and reduction specific to each setting will be described. This statement is directed toward pediatric cardiologists, primary care providers, and subspecialists who provide clinical care for these young patients. The focus will be on management and justification for management, minimizing information on pathophysiology and epidemiology.

This document is an update of the 2006 American Heart Association (AHA) scientific statement on “Cardiovascular Risk Reduction in High-Risk Pediatric Patients.”<sup>1</sup> Since the writing of that statement, new information has emerged about cardiovascular risk factors in childhood and their relationship to premature atherosclerosis and cardiovascular disease (CVD).

The purpose of this scientific statement is to present considerations for clinical management regarding the assessment and risk reduction of select pediatric populations at high risk for premature CVD. For each topic, the evidence for accelerated acquired coronary artery disease (CAD) and stroke in childhood and adolescence and the evidence for benefit of interventions in youth will be reviewed. Existing scientific statements and guidelines will be referenced when applicable, and suggestions for risk identification and reduction specific to each setting will be described.

In this statement, we will describe significant presentations during childhood of traditional CVD risk factors, important high-risk medical conditions, and cardiac and vascular abnormalities that make the young heart more vulnerable to accelerated arteriosclerosis, including coronary artery abnormalities. The statement is directed toward pediatric cardiologists, primary care providers, and subspecialists who manage the primary processes in these young patients. The focus will be on management and justification for management, eschewing or minimizing information

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on pathophysiology and epidemiology. The overall approach of risk stratification and preferential use of pharmacotherapy to reduce CVD risk in the highest-risk individuals, with a foundation in heart-healthy therapeutic lifestyle change behaviors for all, is consistent with the guidelines for treatment of CVD risk in adults.<sup>2,3</sup>

## BACKGROUND

CVD remains the leading cause of death in the United States.<sup>4</sup> Atherosclerosis and other coronary artery pathology, termed for the purposes of this statement as *arteriosclerosis*, can begin in youth, generally exacerbated by exposure to factors associated with increased cardiovascular risk.<sup>5</sup> Interventions are available to prevent risk factors (primordial prevention), as well as to identify and then to treat risk factors in childhood (primary prevention) and to address the risk of additional events in those who already have coronary artery pathology (secondary prevention) in childhood. Early identification and treatment are important for all youth but particularly for the high-risk patient, who, because of underlying conditions, is more prone to premature CVD. Since the publication of the 2006 AHA scientific statement on “Cardiovascular Risk Reduction in High-Risk Pediatric Patients,”<sup>1</sup> the evidence base has grown sufficiently to justify the need for an updated scientific statement to guide the provider, researcher, and policy maker concerned with youth at increased risk for premature CVD.

CVD risk in youth can be attributed to several different types of exposures. For example, there are youth with traditional CVD risk factors presenting in childhood (eg, homozygous or heterozygous familial hypercholesterolemia [FH],<sup>6</sup> hypertension, severe obesity, and type 2 diabetes mellitus [T2DM]). Additionally, some medical conditions increase the risk for future CVD, (eg, type 1 diabetes mellitus [T1DM], chronic renal disease, childhood cancer treatment,<sup>7</sup> and chronic inflammatory conditions such as juvenile inflammatory arthritis) and may warrant aggressive therapy for relatively mild elevations in traditional cardiovascular risk factors. Children and adolescents with underlying heart disease (HD), either structural or functional, also deserve special consideration with regard to future CVD. Those with underlying coronary artery abnormalities, either congenital or acquired, should be carefully surveyed for other risk factors and managed to minimize other additional injury to the coronary arteries. This statement discusses these exposures on the basis of those general paradigms. CVD risk in children and adolescents can also be described on the basis of the magnitude of the risk for arteriosclerotic coronary artery pathology compared with the general population, that is, high, moderate, and increased (Table 1), as presented by Kavey et al<sup>1</sup> in the previous statement. Considerations for management of CVD risk factors presented in this statement

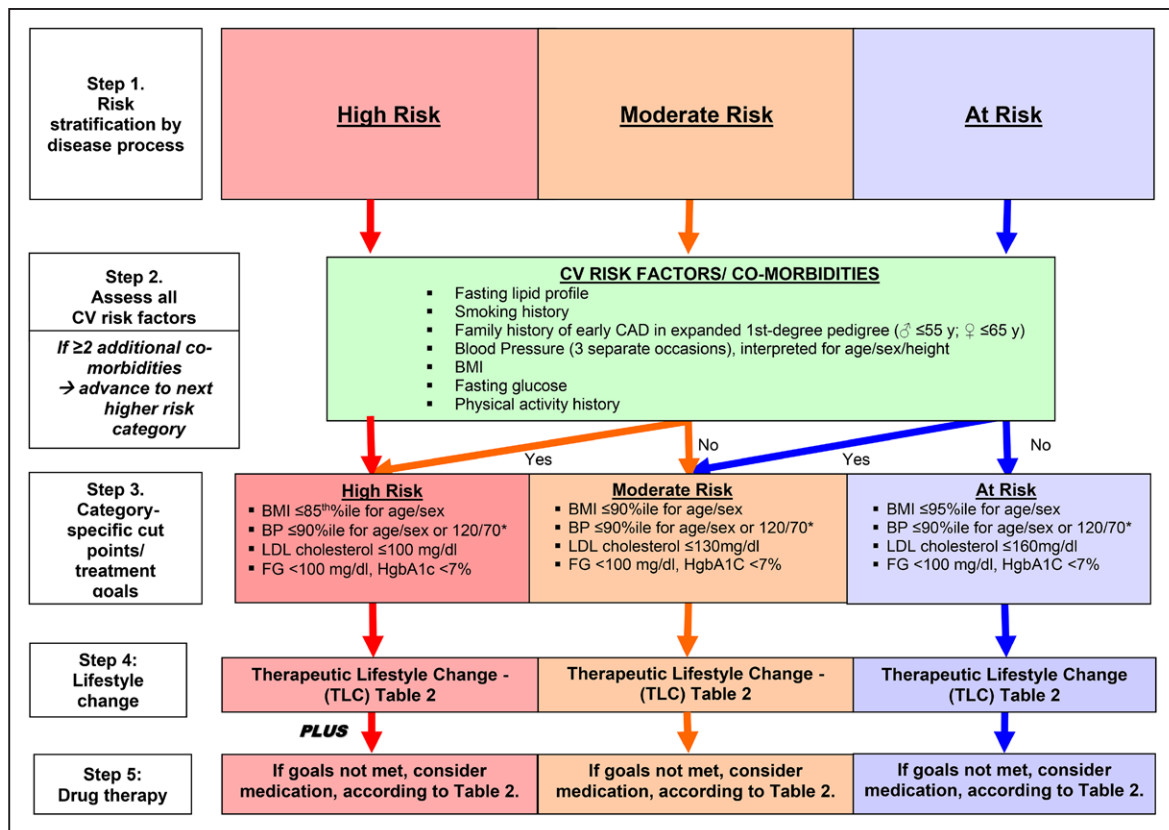
**Table 1. Disease Stratification by Risk**

Category	Condition
High risk	Homozygous FH, T2DM, end-stage renal disease, T1DM, Kawasaki disease with persistent aneurysms, solid-organ transplant vasculopathy, childhood cancer survivor (stem cell recipient)
Moderate risk	Severe obesity, heterozygous FH, confirmed hypertension, coarctation, Lp(a), predialysis CKD, AS, childhood cancer survivor (chest radiation)
At risk	Obesity, insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS), white-coat hypertension, HCM and other cardiomyopathies, pulmonary hypertension, chronic inflammatory conditions (JIA, SLE, IBD, HIV), s/p coronary artery translocation for anomalous coronary arteries or transposition of the great arteries, childhood cancer (cardiotoxic chemotherapy only), Kawasaki disease with regressed aneurysms (zMax $\geq 5$ )

AS indicates aortic stenosis; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; IBD, inflammatory bowel disease; JIA, juvenile rheumatoid arthritis; Lp(a), lipoprotein (a); NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovarian syndrome; SLE, systemic lupus erythematosus; s/p, status post; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; and zMax, maximum z score at any time during the course of illness.

are driven by the risk category (Figure, Table 2), using updated risk categories.

Although the precise physiological mechanisms by which these diverse exposures promote adverse cardiovascular outcomes likely vary and remain to be elucidated, several unifying themes can be described. At least some of this CVD risk is likely mediated through insulin resistance and oxidative stress, because even the risk of developing T2DM is greater in chronic inflammatory conditions.<sup>10,11</sup> Insulin resistance, oxidative stress, and inflammation are linked multidirectionally, but emerging evidence supports a mechanism by which inflammation comes first.<sup>12,13</sup> Inflammation likely acts to increase CVD risk through the dyslipidemic atherogenic triad of elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and an increase in small, cholesterol-poor low-density lipoprotein (LDL) particles.<sup>14</sup> This profile is characterized by excessive apolipoprotein B binding and accelerated atherosclerotic risk,<sup>15</sup> related in part to small LDL particles in circulation.<sup>16</sup> The inflammatory process triggers insulin resistance as a mechanism to keep glucose availability high to meet the metabolic needs of an activated immune system, as might be seen in an important infection.<sup>17</sup> This process leads to impaired lipoprotein lipase activity, blocking normal adipogenesis and contributing to increased triglycerides (to help sequester infectious toxins) and hepatic overproduction of triglyceride-rich lipoprotein particles (smaller LDL and HDL particles). The formation of small LDL particles might be functional in acute inflammation



**Figure.** Risk-stratification and treatment algorithm for high-risk pediatric populations.

**Directions:** Step 1: Risk stratification by disease process (Table 1). Step 2: Assess all cardiovascular risk factors. If there are ≥2 comorbidities, assign patient to the next-higher-risk category for subsequent management. Step 3: Category-specific treatment goals/intervention cut points are defined. Step 4: Initial therapy: For the “High Risk” category, initial management is therapeutic lifestyle change PLUS disease-specific management (Table 2). For the “Moderate Risk” and the “At Risk” category, initial management is therapeutic lifestyle change (Table 2). Step 5: For “Moderate” and “At Risk” categories, if goals are not met, consider medication as outlined in Table 2. \*BP ≤90<sup>th</sup>ile for age/sex or 120/70, whichever is lower. CV indicates cardiovascular; BP, blood pressure; %ile, percentile; FG, fasting glucose; HgbA1c, hemoglobin A1c; ht%ile, height percentile; pt, patient; and TLC, therapeutic lifestyle change.

because small particles are poorly cleared by the LDL receptor and more easily penetrate the subendothelial space. By binding to the subendothelial matrix, they can efficiently deliver cholesterol to damaged tissue.<sup>18</sup> Moreover, the oxidation of small LDL particles further enhances their atherogenic potential. The decrease in HDL cholesterol seen on a standard lipid profile in the context of inflammation is associated with a decrease in reverse cholesterol transport and promotes the accumulation of cholesterol in the tissues, where it is needed for the synthesis of steroid hormones (particularly cortisol in the adrenal glands) and cellular membranes that become damaged by presumed infection.<sup>19</sup>

Patients with chronic kidney disease (CKD) have decreased HDL compared with individuals with preserved kidney function. Several mechanisms have been implicated in this process: (1) patients with CKD often have decreased levels of apolipoproteins AI and AII, the main components of HDL<sup>20</sup>; (2) the activity of lecithin-cholesterol acyltransferase, the enzyme important for the esterification of free cholesterol in HDL, is impaired; and (3) the activity of cholesterol ester transfer protein, which

supports the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, is increased. Furthermore, patients with CKD have reduced activity of the HDL-associated enzymes, such as paraoxonase, which might be responsible for impaired antioxidative and anti-inflammatory function of HDL. All these factors can contribute to accelerated atherosclerosis in this specific population.<sup>21–23</sup> For childhood cancer survivors, the mechanism for accelerated atherosclerosis is not clear and likely multifactorial. Insulin resistance and the dyslipidemic atherogenic triad clearly play a role, with the process likely exacerbated by mechanisms such as growth hormone deficiency. Engagement of the sympathetic nervous system in this stress response contributes to hypertension.<sup>24</sup>

## TRADITIONAL CARDIOVASCULAR RISK FACTORS PRESENTING IN CHILDHOOD FH, Lipoprotein(a)

FH is an autosomal dominant genetic disorder of cholesterol metabolism that affects 1 of every 250 indi-

**Table 2. Management Considerations for Patients in High-Risk, Moderate-Risk, and At-Risk Categories**

Risk Factor	Measurement and Operationalization	General Treatment Strategies		Treatment Targets Based on CVD Risk Categories			
		Lifestyle	Pharmacotherapy	High Risk	Moderate Risk	At Risk	
BP	<p>Measure and interpret BP based on age, sex, and height percentile per AAP 2017 guidelines.<sup>8</sup> If initial SBP or DBP is ≥90th percentile, perform 2 additional oscillometric or auscultatory measurements at the same visit, average and determine BP stage (see below). If abnormal, provide therapeutic lifestyle change counseling and repeat within 1–2 wk.</p> <p>If still abnormal, obtain diagnostic evaluation, including right arm and leg BP, ABPM, and echo, and treat based on risk category, level of BP elevation, and informed by diagnostic evaluation.</p> <p>Elevated BP (SBP or DBP 90–95th percentile, or 120/70 to 130/80 mmHg, whichever is lower): Continue therapeutic lifestyle change counseling and reassess in 3 mo and every 3–6 mo thereafter.</p> <p>Stage 1 (SBP or DBP ≥95th percentile or &gt;130/80 mmHg, whichever is lower, but &lt;95th percentile + 12 mmHg and &lt;140/90 mmHg) and stage 2 hypertension (SBP or DBP &gt;95th percentile + 12 mmHg or 140/90 mmHg, whichever is lower): treat based on risk category.</p>	<p>Diet low in sodium (target &lt;2300 mg/d), high in fruits and vegetables and other sources of dietary fiber, and incorporating lean protein. Avoid sugar-sweetened beverages.</p> <p>Obtain ≥5 h/wk of moderate to vigorous physical activity.</p>	<p>Choose antihypertensive medication based on clinical circumstances, according to AAP 2017 clinical practice guideline.</p>	<p>Therapeutic lifestyle change threshold: Confirmed SBP or DBP ≥90th percentile. Pharmacotherapy threshold: SBP or DBP ≥95th percentile, or ≥130/80 mmHg (whichever is lower)</p>	<p>Treatment stage 1 and stage 2: Initiate pharmacotherapy and therapeutic lifestyle change simultaneously within 1 wk.</p>	<p>Treatment stage 1: Therapeutic lifestyle change for 1 mo; if BP remains above goal, initiate pharmacotherapy.</p> <p>Treatment stage 2: Initiate pharmacotherapy and therapeutic lifestyle change simultaneously within 1 wk.</p>	<p>Treatment stage 1: Therapeutic lifestyle change for 3 mo; if BP remains above goal, initiate pharmacotherapy.</p> <p>Treatment stage 2: Initiate pharmacotherapy and therapeutic lifestyle change simultaneously within 1 wk.</p>
Lipids: LDL-C	<p>Screen yearly for lipid disorders with nonfasting non-HDL, followed by fasting lipid profile if initial TC &gt;200, HDL &lt;45, or non-HDL &gt;145 mg/dL.</p> <p>If LDL-C is abnormal, consider diagnostic evaluation and initiate therapeutic lifestyle change and statin therapy based on risk category.</p>	<p>Diet high in fiber from fruits and vegetables, whole grains, high in polyunsaturated and monounsaturated fats, low in saturated fat, and devoid of <i>trans</i> fats.</p> <p>Consider phytosterol supplements.</p> <p>Obtain ≥5 h/wk of moderate to vigorous physical activity.</p>	<p>Statins, adding additional agents (cholesterol absorption inhibitors) if goals are not met. Individuals with homozygous FH will also require nonstatin treatments such as LDL apheresis, PCSK9 agents.</p>	<p>Threshold: LDL-C ≥130 mg/dL</p>	<p>Threshold: LDL-C ≥160 mg/dL</p>	<p>Threshold: LDL-C ≥160 mg/dL</p>	
				<p>Treatment: Initiate statin and therapeutic lifestyle change simultaneously.</p>	<p>Treatment: Therapeutic lifestyle change for 3 mo; if LDL remains above goal, add statin.</p>	<p>Treatment: Therapeutic lifestyle change for 6 mo; if LDL remains above goal, add statin.</p>	
				<p>Treatment goal: LDL-C &lt;100 mg/dL</p>	<p>Treatment goal: LDL-C &lt;130 mg/dL</p>	<p>Treatment goal: LDL-C &lt;130 mg/dL</p>	
Lipids: TG	<p>Screen yearly for lipid disorders with nonfasting non-HDL, followed by fasting lipid profile if initial TC &gt;200, HDL &lt;45, or non-HDL &gt;145 mg/dL.</p> <p>If TG is abnormal, provide therapeutic lifestyle change counseling and repeat within 1–2 wk.</p> <p>If still abnormal, obtain diagnostic evaluation and treat based on TG level.</p> <p>Moderate: TG 130–400 mg/dL and non-HDL &lt;145 mg/dL—treat with therapeutic lifestyle change modification; reassess in 3 mo and then periodically.</p> <p>Significant: TG &gt;400–999 mg/dL or TG 130–400 mg/dL and non-HDL ≥145 mg/dL—treat based on risk category.</p> <p>Severe: TG &gt;1000 mg/dL, confirmed on repeat testing—initiate therapeutic lifestyle change and omega 3 fatty acids or pharmacotherapy simultaneously.</p>	<p>Diet low in simple carbohydrates, added sugars, high in dietary fiber from fruits and vegetables, moderate amounts of complex carbohydrates, high in polyunsaturated and monounsaturated fats, without specific restriction of saturated fats.</p> <p>Obtain ≥5 h/wk of moderate to vigorous physical activity.</p> <p>Weight loss as necessary.</p>	<p>Fenofibrate, taking into consideration hepatic and muscle effects and drug interactions.</p> <p>Omega-3 fatty acid supplements high dose (≈4 g/d EPA + DHA).</p> <p>Statin, if non-HDL (or apoB) is elevated.</p>	<p>Threshold: TG &gt;400 mg/dL, or TG 150–400 mg/dL and non-HDL ≥145 mg/dL</p>	<p>Treatment: Initiate therapeutic lifestyle change and pharmacotherapy simultaneously.</p>	<p>Treatment: Initiate therapeutic lifestyle change followed at 3 mo by pharmacotherapy.</p>	<p>Treatment: Initiate therapeutic lifestyle change followed at 6 mo by pharmacotherapy.</p>
				<p>Treatment goal: TG &lt;150 mg/dL and non-HDL &lt;145 mg/dL</p>	<p>Treatment goal: TG &lt;150 mg/dL and non-HDL &lt;145 mg/dL</p>	<p>Treatment goal: TG &lt;150 mg/dL and non-HDL &lt;145 mg/dL</p>	
				<p>Treatment goal: TG &lt;150 mg/dL and non-HDL &lt;145 mg/dL</p>	<p>Treatment goal: TG &lt;150 mg/dL and non-HDL &lt;145 mg/dL</p>	<p>Treatment goal: TG &lt;150 mg/dL and non-HDL &lt;145 mg/dL</p>	

(Continued)

**Table 2. Continued**

Risk Factor	Measurement and Operationalization	General Treatment Strategies		Treatment Targets Based on CVD Risk Categories		
		Lifestyle	Pharmacotherapy	High Risk	Moderate Risk	At Risk
Blood glucose (without diagnosis of diabetes mellitus)	Screen yearly with fasting glucose or A <sub>1c</sub> . If FBG ≥126 mg/dL or A <sub>1c</sub> ≥6.5%, refer to endocrinology for evaluation of new-onset diabetes mellitus.	Low glycemic diet limiting intake of added sugar to ≤5% of total calories, high in fruits and vegetables, encouraging intake of polyunsaturated and monounsaturated fats, and without specific limitation to dietary saturated fats.  Obtain ≥5 h/wk of moderate to vigorous physical activity.  Weight loss as necessary.	Consider metformin.	Threshold: FBG ≥100 mg/dL or A <sub>1c</sub> ≥5.7%		
				Treatment: Initiate therapeutic lifestyle change counseling; if response is insufficient in 1 mo, refer to endocrinology.	Treatment: Initiate therapeutic lifestyle change counseling; if response is insufficient in 3 mo, refer to endocrinology.	Treatment: Initiate therapeutic lifestyle change counseling; if response is insufficient in 6 mo, refer to endocrinology.
Activity	Obtain physical activity and inactivity history at least yearly, including organized sports, activity for transportation, and recreational screen time.	Advise ≥5 h of moderate to vigorous physical activity per week* and ≤2 h/d non-school-related screen time, per individualized AAP activity plan.	NA	Provide counseling and reassess at each encounter.	Provide counseling and reassess at least every 6 mo.	Provide counseling and reassess at least every 12 mo.
Diet	Obtain dietary history	Healthy diet consists of the following, scaled to reflect age- and activity-appropriate caloric needs: fruits and vegetables ≥4- to 5-cup servings/d, fish ≥2- to 3.5-oz servings/wk, sodium ≤1500 mg/d, zero sugar-sweetened beverages, whole grains ≥3 servings/d.	NA	Provide dietary counseling and reassess at each encounter.	Provide dietary counseling and reassess at least every 6 mo.	Provide dietary counseling and reassess at least every 12 mo.
Weight	Calculate BMI percentile for age and sex according to CDC, or percent above the 95th percentile if necessary (consider measuring waist circumference).  Provide age-appropriate reduced-calorie training for child and family.  Follow-up for weight-related counseling every 2–4 wk for 6 mo.	Healthy diet and physical activity (as above).  If follow-up BMI percentile remains above cut point, refer to subspecialty weight loss program.	Pharmacological management within the context of subspecialty weight management program	Threshold: BMI ≥95th percentile		
				Treatment: Therapeutic lifestyle change modification, including referral to subspecialty program; consider weight loss medications.	Treatment: Therapeutic lifestyle change modification; refer to subspecialty program in 3 mo if response insufficient.	Treatment: Therapeutic lifestyle change modification; refer to subspecialty program in 6 mo if response insufficient.
Smoking	Screen for smoke exposure (personal use, secondhand smoke exposure, e-cigs).	Provide counseling on lowering exposure and quitting.	Nicotine patch or gum can be considered if counseling is ineffective.	No exposure or other treatments		

A<sub>1c</sub> indicates hemoglobin A<sub>1c</sub>; AAP, American Academy of Pediatrics; ABPM, ambulatory blood pressure monitoring; apoB, apolipoprotein B; BMI, body mass index; BP, blood pressure; CDC, Centers for Disease Control and Prevention; CVD, cardiovascular disease; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; echo, echocardiography; e-cigs, e-cigarettes; EPA, eicosapentaenoic acid; FBG, fasting blood glucose; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; PCSK9, proprotein convertase subtilisin/kexin type 9; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

\*Physical activity should be discussed with the patient's clinician before starting any new regimen for safety's sake.



**Table 3. Risks of CVD by Type of Congenital HD**

	Coronary Artery Disease	Cerebrovascular Disease	Peripheral Vascular Disease
Repaired ASD/VSD	Not known to have increased risk	Increased risk if residual shunt	Not known to have increased risk
Bicuspid aortic valve	Potential risk after Ross procedure with reimplantation of coronary arteries	Not known to have increased risk	Increased risk related to aortic aneurysm
Coarctation of aorta	Increased risk could be related to accelerated atherosclerosis vs late hypertension	Increased risk related to residual hypertension or intracranial aneurysms	Increased risk related to residual coarctation or aortic aneurysm
Ebstein anomaly	Not known to have increased risk	Increased risk if interatrial shunt	Not known to have increased risk
Tetralogy of Fallot	Increased risk could be related to coronary anomalies	Increased risk if residual intracardiac shunt	Increased risk related to aortic dilation
TGA atrial switch	Increased risk could be related to coronary anomalies	Increased risk if residual baffle leak	Increased risk could be related to prior catheterizations
TGA arterial switch	Increased risk related to reduced coronary flow reserve, proximal intimal thickening, and coronary anomalies	Not known to have increased risk	Increased risk related to neo-aortic dilation
Fontan	Increased risk could be related to coronary anomalies	Increased risk if Fontan fenestration	Increased risk related to Fontan venous pressures and prior catheterizations
Cyanotic congenital HD	Potential decreased risk	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome
Eisenmenger syndrome	Potential decreased risk	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome

ASD indicates atrial septal defect; CVD, cardiovascular disease; HD, heart disease; TGA, transposition of the great arteries; and VSD, ventricular septal defect.

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viduals in its heterozygous form,<sup>25,26</sup> is characterized by very high levels of LDL cholesterol (LDL-C), which causes premature atherosclerosis, and leads to early cardiovascular mortality and morbidity.<sup>27–29</sup> The pathophysiology of FH relates to the excessive circulating LDL-C because of defective sensing of circulating LDL-C levels by the liver at the level of the LDL receptor, in binding to the receptor, or in receptor metabolism. The severity of atherosclerosis, and thus the risk of coronary HD, is directly related to lifetime exposure to LDL-C, with higher levels and longer exposure leading to more disease. Natural history studies of FH are sparse, but available data suggest FH is associated with accelerated vascular aging; a 30-year-old man with FH can be projected to have a risk for cardiovascular events similar to that of a 40- or 50-year-old.<sup>27</sup> Even in its heterozygous form, FH is associated with premature CAD in young adults.<sup>30–32</sup>

Although the optimal way to identify FH at the population level is still a topic of debate,<sup>6</sup> the identification of heterozygous FH in clinical practice requires a high degree of clinical suspicion because it is asymptomatic in childhood. At the very least, children with a family history of premature CVD or significant hypercholesterolemia should be screened for FH using a fasting lipid profile beginning at 2 years of age, and then every 3 to 5 years through adulthood, even if previous profiles are within normal ranges.<sup>6,34</sup> The pediatric clinical diagnosis

of a heterozygous FH patient can be suspected in the presence of an LDL-C level  $\geq 160$  mg/dL (4.0 mmol/L) associated with a family history of elevated LDL-C or premature CVD in first- or second-degree relatives. It can be considered confirmed if there is a positive genetic testing for an LDL-C-raising gene defect (LDL receptor, apolipoprotein B, or proprotein convertase subtilisin/kexin type 9 [PCSK9]) in a first-degree relative.<sup>6</sup> Secondary causes of hypercholesterolemia should be excluded, including hypothyroidism, nephrotic syndrome, or liver diseases. If a child is found to be carrying a causative mutation associated with the disease, then family members should be tested and referred to an adult lipid specialist.<sup>6</sup> The presence of a known genetic defect in the presence of elevated LDL is correlated with an increased cardiovascular event rate, which suggests that although genetic testing is not currently part of usual care of heterozygous FH in the United States, there could be a role for genetic testing in the future.<sup>35</sup>

Treatment for heterozygous FH should include statins, a low-saturated-fat diet high in fiber, adequate physical activity, and a smoke-free environment.<sup>6,36</sup> Phytosterol supplements have also been shown to reduce LDL in children and adolescents.<sup>37</sup> Previously, concerns were raised about the effect of statins on pubertal progression and somatic growth; however, randomized trials have demonstrated the safety of statins in children and adolescents with FH, with no

demonstrated abnormalities in growth or puberty and low rates of adverse effects (liver and muscle).<sup>38–40</sup> In a recent Cochrane review, Vuorio et al<sup>41</sup> examined 9 randomized, placebo-controlled studies (1177 pediatric participants) and reported no significant difference between statin and placebo in terms of adverse effects, including delayed sexual maturation (Tanner staging), liver enzymes, or creatine kinase elevation, and no rhabdomyolysis. Low-dose statin therapy initiated in children 8 to 10 years old with heterozygous FH has demonstrated a long-term benefit, with a lower incidence of atherosclerotic CVD (close to that of the normal population) over 40 years of follow-up.<sup>26</sup> The CHARON study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label) recently demonstrated that rosuvastatin initiated in children as young as 6 years of age led to regression of the carotid intima-media thickness (cIMT), to a thickness that was identical to their unaffected siblings.<sup>42</sup> In light of these studies, statins can be initiated in heterozygous FH patients at age 10 years (and as early as 8 years of age in very high risk circumstances) and titrated to achieve a 50% reduction in LDL-C or an LDL-C <130 mg/dL.<sup>5</sup>

If a 50% reduction of LDL-C is not achieved or if there are adverse effects to multiple statins (rare), then ezetimibe or a bile acid binding resin can be added as a second-line agent. Currently there is no pediatric indication for PCSK9 inhibitors in heterozygous FH patients; a clinical trial is ongoing. With early identification and treatment, life expectancy in FH patients now has the potential to be normal.<sup>2</sup>

Homozygous FH is characterized by an untreated LDL-C >400 mg/dL (10.0 mmol/L) and 1 or both parents having clinically diagnosed FH, xanthomata in childhood, supraaortic stenosis, positive genetic testing for an LDL-C-raising genetic mutation, or autosomal-recessive FH.<sup>6,43</sup> The treatment of pediatric homozygous FH patients begins with the treatment regimen for heterozygous FH at the time of diagnosis (often in infancy) and includes additional therapies to achieve sufficient reduction in LDL-C levels, including LDL apheresis, PCSK9 inhibitors (except in individuals with double-null LDL receptor defects), and, more recently, lomitapide and mipomersen.<sup>44</sup> Expert opinion of an international panel recommends treatment goals for homozygous FH patients of a reduction of 50% in LDL-C or <100 mg/dL (<2.5 mmol/L), with ideal LDL-C levels of <70 mg/dL (<1.8 mmol/L) in those with a history of ASCVD events.<sup>45</sup> Liver transplantation has been used in patients with homozygous FH, particularly individuals with intractable vasculopathy.<sup>6</sup>

Lipoprotein (a) [Lp(a)] is a large particle with 2 linked components. One is LDL-C, identified by its apolipoprotein B, and the second is apolipoprotein(a), which is structurally like plasminogen and can interfere with fibrinolysis and thus promote thrombosis. Genome-wide as-

sociation and mendelian randomization studies indicate that Lp(a) is a causal and independent risk factor for CVD in adults<sup>46,47</sup> and is associated with increased cardiovascular risk in adults with FH in cross-sectional and prospective data.<sup>48</sup> Lp(a) is highly heritable and atherogenic and becomes stable within the first 2 years of life.<sup>49</sup> This could represent a useful marker to identify young FH patients at very high risk of premature CVD. Elevated Lp(a) has also been associated with thromboembolic events in youth.<sup>50</sup> The recent development of selective and potent Lp(a)-lowering agents, currently in phase III trials in adults, has restimulated interest in Lp(a).<sup>51</sup> The role of Lp(a) in pediatric FH patients has yet to be evaluated prospectively in long-term studies, and the current approach is to focus on minimizing the impact of other cardiovascular risk factors, including LDL-C.

## Obesity

Childhood obesity and overweight, defined as a body mass index (BMI) greater than or equal to the 95th percentile and the 85th to 94th percentile for age and sex, respectively, are risk factors for future CVD. A recent study of almost 2.3 million individuals followed up for over 40 years found the risks of CVD mortality were 2- to 3-fold higher if their BMI as adolescents had been in the overweight (hazard ratio, 2.25; 95% confidence interval, 1.96–2.58) or obese (hazard ratio, 3.46; 95% confidence interval, 2.93–4.10) category compared with youth with normal weight.<sup>52</sup> Obesity has been shown to be a prominent correlate of aortic and coronary fatty streaks or other atherosclerotic lesions.<sup>53,54</sup> Obesity, or more precisely aberrant or ectopic adiposity that accompanies obesity,<sup>55</sup> is widely considered an independent risk factor yet is also associated with other resultant CVD risk factors, including dyslipidemia (most often manifested as high levels of triglycerides and low levels of HDL cholesterol), elevated blood pressure, hyperglycemia and insulin resistance, and inflammation and oxidative stress.<sup>56,57</sup> Youth with severe obesity (BMI ≥120% of the 95th percentile or absolute BMI ≥35 kg/m<sup>2</sup>) are generally viewed as being at the highest level of risk because of the high number and magnitude of CVD risk factors, the presence of endothelial activation and subclinical atherosclerosis,<sup>58–60</sup> and the strong tracking of adiposity from childhood into adulthood.<sup>61</sup>

## Epidemiology

Using the 2013 AHA definition,<sup>57</sup> BMI ≥120% of the 95th percentile or absolute BMI ≥35 kg/m<sup>2</sup>, it is estimated that ≈6% of all youth 2 to 19 years old (equating to >4000000 children and adolescents) are afflicted with severe obesity in the United States.<sup>62</sup> Unlike moderate (class I) obesity or overweight, rates of severe obesity have increased over the past decade.<sup>62</sup>

## Screening

Annual assessment for obesity is recommended by the American Academy of Pediatrics<sup>63</sup> and others via measurement of height and weight to calculate BMI and plotting the results on growth charts from the Centers for Disease Control and Prevention. Severe obesity should be identified and tracked.<sup>64</sup> Once obesity is identified, consideration should be given to screening for associated cardiovascular risk factors.<sup>65</sup> Insulin resistance, dyslipidemia, and hypertension can be seen as part of the polycystic ovarian syndrome,<sup>66</sup> which should be considered in girls with irregular menses, particularly in the setting of excess adiposity. The inclusion of a waist measurement can improve sensitivity for the detection of adiposity-related CVD risk, even before BMI criteria are met.<sup>67</sup>

## Treatment

Effective, easily adoptable, and durable treatments for obesity have proven elusive. A multimodal and graduated approach to treatment is generally required, incorporating improvements in dietary quality, reduction in caloric intake, optimization of moderate to vigorous physical activity, meal replacements, pharmacotherapy, and bariatric surgery, depending on the severity of the excess adiposity. Reduction of excess adiposity is recommended as the primary treatment goal, and obesity-related risk factors or comorbidities not sufficiently reduced with weight loss should be treated independently, as described elsewhere in this document and in other statements. Obesity-related dyslipidemia is generally treated with therapeutic lifestyle change modification, with a focus on lowering of the dietary glycemic index,<sup>68</sup> including limiting the intake of added sugar to 5% of total calories, as recommended by the AHA and the World Health Organization, and increasing moderate to vigorous physical activity.<sup>69</sup> Programs that combine nutrition, behavioral change, and physical activity have been shown to be effective,<sup>70</sup> perhaps more effective in improving low HDL.<sup>71</sup> The magnitude of weight loss necessary to elicit meaningful improvements in CVD risk factors among youth with obesity has not been fully determined; a BMI reduction of 5% to 10% or 0.25 to 0.5 in BMI standard deviation score could be required.<sup>72-74</sup>

Therapeutic lifestyle change modification therapy, including counseling on diet and physical activity, is the cornerstone of pediatric obesity treatment; however, its effectiveness is limited in severe obesity because of small effect size and difficulty with sustainability.<sup>75,76</sup> Promising intensive multidisciplinary options that combine parental coaching and motivational interviewing have shown interesting results with respect to lowering pediatric obesity; however, long-term studies are still needed, especially those that are more inclusive of ethnic minorities. A strong governmental investment

is required to sustain such intensive preventive approaches. Outcomes appear to be better, but far from ideal, in severely obese children <10 years of age versus adolescents<sup>77</sup> and when treatment is initiated at earlier stages of obesity.<sup>75</sup> Meal replacements (shakes and pre-prepared entrees) have been shown to modestly reduce BMI ( $\approx 5\%$ ) among adolescents with severe obesity, but the effect waned over 1 year of treatment, primarily because of poor long-term adherence.<sup>78</sup> Home-delivery of food and beverages has been trialed as a way to more directly modify intake, with some effect<sup>73,79,80</sup>; questions remain about how to scale up this type of intervention for broader application. Residential obesity treatment, (eg, immersion therapy in a hospital, camp, or boarding school setting with a carefully controlled calorically restricted diet, daily structured physical activity, and comprehensive behavioral counseling) reduces BMI in the short- to medium-term.<sup>81</sup> However, weight regain is common once participants are reintegrated into their obesogenic environment.<sup>82</sup> Social networks can be useful as a tool to affect weight, but they raise concerns about supervision and internet safety in young teens.

Pharmacotherapy for pediatric obesity is relatively understudied. Only 1 medication, orlistat (a lipase inhibitor), is approved by the US Food and Drug Administration for the treatment of obesity in adolescents  $\geq 12$  years old. Unfortunately, orlistat is associated with only modest weight loss efficacy ( $<3\%$  placebo-subtracted BMI reduction), no improvements in cardiovascular risk factors, and undesirable side effects of fecal urgency and oily stools.<sup>83</sup> Metformin (biguanide), although not approved by the Food and Drug Administration as an obesity treatment, has been studied in a number of pediatric trials; it modestly reduces BMI ( $\approx 3\%$ ), with small improvements in cardiovascular risk factors.<sup>84-88</sup> A few small trials examining the weight loss efficacy of exenatide (a glucagon-like peptide-1 agonist)<sup>89</sup> and topiramate (a  $\gamma$ -amino butyrate modulator)<sup>90</sup> among adolescents with severe obesity have shown modest BMI reductions of 2% to 5%.<sup>89,91</sup> Four new medications have been approved recently by the Food and Drug Administration for the treatment of adult obesity and will soon be evaluated in pediatric trials.<sup>57,92</sup> The topic of pediatric obesity pharmacotherapy is comprehensively reviewed by Sherafat-Kazemzadeh et al<sup>93</sup> and Kelly et al.<sup>92</sup>

Bariatric surgery is the only treatment for severe pediatric obesity consistently associated with clinically meaningful and durable weight loss for most patients.<sup>57,94</sup> Typically reserved for adolescents with severe obesity and serious comorbidities, it is rarely offered to children <12 years old. A large, multicenter, prospective study of 242 adolescents undergoing bariatric surgery in the United States (Teen-LABS [Teen-Longitudinal Assessment of Bariatric Surgery]) reported a 3-year BMI reduction of  $\approx 30\%$  and remission of hypertension, dyslipidemia, and T2DM in the majority of participants.<sup>95</sup>



Bariatric surgery has been shown to reduce markers of inflammatory and oxidative stress, including the highly atherogenic oxidized LDL-C.<sup>96</sup> Moreover, bariatric surgery appears to improve functional mobility and cardiorespiratory fitness and reduces musculoskeletal pain among adolescents with severe obesity.<sup>97</sup> Risks include procedure-related complications such as thromboembolic events, micronutrient deficiencies (particularly hypoferritinemia), and the need for additional abdominal surgical procedures.<sup>98</sup> Long-term pediatric ( $\geq 5$  years) safety and effectiveness data are scant, but 2 recently published studies suggest sustained BMI reduction and cardiometabolic improvements.<sup>99,100</sup> When potential risks of bariatric surgery are measured against the known perils of persistent severe obesity and its associated comorbidities, the balance of evidence indicates bariatric surgery is a reasonable treatment option in some individuals as an effective treatment for this serious and intractable disease.

## T1DM and T2DM

Diabetes mellitus, either caused by a lack of insulin (T1DM) or a lack of response to insulin (T2DM), is characterized by hyperglycemia and the development of CVD. At least 68% of people  $>65$  years of age with diabetes mellitus (likely primarily T2DM) die of some form of HD, with mortality among adults with diabetes mellitus being 2 to 4 times higher than for adults without diabetes mellitus.<sup>4</sup> Adults with diabetes mellitus live on average 8 years less than people without diabetes mellitus<sup>4</sup> because of the increased prevalence of both microvascular disease (eye, kidney, neurological) and macrovascular disease (myocardial infarction [MI], stroke, peripheral vascular disease). Additional accompanying CVD risk factors accelerate atherosclerosis, including hyperlipidemia,<sup>102,103</sup> hypertension, and kidney disease.

Macrovascular complications are unlikely to occur during childhood; however, subclinical vascular abnormalities associated with clinical cardiovascular events in the general adult population<sup>104–106</sup> have been demonstrated in youth with both T1DM and T2DM, including increased cIMT<sup>107</sup> and worsened arterial stiffness by pulse-wave velocity.<sup>108</sup> Compared with nonaffected youth, youth with T1DM and T2DM have increased left ventricular mass,<sup>109</sup> abnormal cardiac geometry,<sup>110</sup> and diastolic dysfunction.<sup>111,112</sup> These findings are particularly worrisome given that these types of cardiac target-organ damage are independent predictors of CVD events in adults with T2DM.<sup>108,113</sup>

The differences in pathophysiology between T1DM and T2DM suggest CVD risk should differ, and indeed, the risk was previously thought to be higher for children with T1DM. However, emerging evidence suggests risks are also high for youth diagnosed with T2DM. When subjects with onset of T2DM between age 15 and 30

years were matched to those with T1DM with a similar age of onset, cardiovascular mortality was significantly higher in the subjects with T2DM even if there was shorter duration of disease.<sup>114</sup> This is likely related to early development of diabetic nephropathy,<sup>115</sup> which generally takes more than a decade to develop in youth with T1DM but is often manifest at the time of diagnosis in adolescents with T2DM.<sup>108</sup> Subclinical vascular abnormalities are also more prevalent in T2DM. Adolescents and young adults with T2DM are more likely to have increased cIMT (3.93 versus 2.38)<sup>116</sup> and stiffer central and peripheral arteries than those with T1DM.<sup>117</sup> In the previous AHA scientific statement on “Cardiovascular Risk Reduction in High-Risk Pediatric Patients,”<sup>1</sup> only T1DM was considered a high-risk disease; T2DM was placed in the moderate-risk category. However, newer research supports the notion that youth with T2DM are also at high risk of CVD, and both types of diabetes mellitus are now categorized as high risk.

## Epidemiology

In the Search for Diabetes in Youth study, a national surveillance effort to identify diabetes mellitus in youth,  $\approx 18\,000$  children and adolescents were diagnosed with T1DM and  $>5000$  were diagnosed with T2DM from 2008 to 2009. Incidence has increased over the past 26 years.<sup>4</sup> The prevalence of T2DM in youth is increasing at a rate more rapid than T1DM, likely because of high rates of obesity, with a 30.5% increase in incidence rate between 2001 and 2009; T2DM now constitutes almost half of all childhood diabetes mellitus.<sup>4</sup>

## Screening

Although T1DM is generally recognized clinically, presenting as fatigue, polyuria, and polydipsia, and often in diabetes ketoacidosis, T2DM is often detected by screening of youth with obesity and a family history of T2DM.<sup>118</sup> Once diagnosed, youth with diabetes mellitus should be screened yearly for additional CVD risk factors<sup>108</sup> because of their high prevalence in both types of diabetes mellitus, especially in the presence of obesity<sup>119</sup> or insulin resistance.<sup>120</sup> The SEARCH study showed that the prevalence of dyslipidemia in T1DM and T2DM was 15% and 24%, respectively.<sup>121</sup> Hypertension was also common, affecting 5.9% of youth with T1DM and 23.7% of youth with T2DM.<sup>122</sup> Microalbuminuria was found in 9.2% of youth with T1DM and 22.2% of youth with T2DM.<sup>123</sup> Obesity was also more common, affecting 79.4% of youth with T2DM.<sup>124</sup>

## Treatment

Cardiovascular risk factors are more common in youth with T1DM and T2DM than in the general population; they are also undertreated. The SEARCH CVD substudy found that none of the 190 youth with T1DM met all 7 metrics for ideal cardiovascular health defined by the AHA, with the fewest achieving an adequate healthy

diet score.<sup>125</sup> Only 1% of diabetic youth in SEARCH were receiving therapy for either high blood pressure or abnormal lipids.<sup>126</sup> The TODAY 2 study (Treatment Options for Type 2 Diabetes in Adolescents and Youth Phase II Study) found only 55.9% of youth with T2DM were treated to an ideal LDL level.<sup>127</sup> Similarly, the T1D Exchange study found that only 36% of patients with microalbuminuria were appropriately prescribed an angiotensin-converting enzyme or receptor blocker.<sup>128</sup> Fortunately, evidence suggests that addressing cardiovascular risk factors will lead to a lowering of risk, because youth with both T1DM and T2DM in the SEARCH CVD study who maintained a healthy diet had lower LDL-C levels,<sup>129</sup> and those who met more of the 7 ideal cardiovascular health metrics had lower arterial stiffness.<sup>125</sup> Reducing cardiovascular risk in youth with diabetes mellitus should take a 2-pronged approach, both optimizing glycemic control and reducing additional CVD risk. Tools for treatment include therapeutic lifestyle change modification (diet and physical activity) and pharmacotherapy.

Hyperglycemia is the primary mediator of atherosclerosis in T1DM<sup>130</sup> and has been implicated in the development of abnormal cardiac structure<sup>110,131</sup> and function.<sup>112</sup> For this reason, reducing the risk of future atherosclerosis should focus in large part on promoting optimal glycemic control. In both T1DM and T2DM, poor glycemic control<sup>132–134</sup> and insulin resistance<sup>135</sup> appear to accelerate atherosclerosis. Intensive control of diabetes mellitus has been shown to improve preclinical abnormalities in endothelial function in adolescents with T1DM,<sup>136</sup> and in adults with both types of diabetes mellitus, reduction of hemoglobin A<sub>1c</sub> to  $\approx 7\%$  reduces microvascular complications.<sup>108</sup> Unfortunately, as many as half of all children with T2DM are not adequately treated with a single agent, a rate higher than that observed in adults, as shown in the TODAY study.<sup>137</sup> The reader is referred to other comprehensive references for guidance on the use of insulin and insulin-sensitizing agents.<sup>118</sup>

Unfortunately, because many drugs used to treat hyperglycemia are associated with weight gain (insulin, thiazolidinediones, and sulfonylureas),<sup>108</sup> it is not surprising that achieving lasting weight loss in diabetes mellitus is difficult.<sup>137</sup> Metformin is associated with modest weight loss, but other diabetes mellitus treatments known to have beneficial effects on weight, such as glucagon-like peptide-1 receptor agonists (associated with weight loss) and dipeptidyl peptidase-4 inhibitors (weight neutral), do not have specific Food and Drug Administration labeling for use in pediatric patients.<sup>108</sup> Insulin resistance, a process previously thought to be predominately that of T2DM, is now becoming recognized as an important modifier of cardiovascular risk in T1DM because of the increasing prevalence of obesity among youth with T1DM.<sup>138</sup> Insulin resistance compounds CVD risk by contributing to hypertension through urinary sodium

retention, increased sympathetic drive, and stimulation of smooth muscle growth, which leads to vascular hypertrophy and increased arterial stiffness.<sup>139</sup>

Therapeutic lifestyle change modification is not only an important management tool for hyperglycemia and insulin resistance but also improves other CVD risk factors in youth with diabetes mellitus. Adolescents with a diagnosis of diabetes mellitus (type not specified) are more sedentary by 1 hour per day, measured by accelerometry, than youth with obesity but without diabetes mellitus.<sup>4</sup> This is worrisome because exercise is known to improve glycemic control,<sup>140</sup> cardiovascular risk factors,<sup>141</sup> and endothelial function in youth with T1DM.<sup>142</sup> Poor diet also likely plays a role in cardiovascular complications; in the SEARCH study, an unhealthy diet pattern in adolescents with T1DM was associated with poor glycemic control, higher lipid levels,<sup>143</sup> and greater arterial stiffness.<sup>144</sup> Optimization of therapeutic lifestyle change habits requires comprehensive family-based interventions with sufficient contact hours to promote behavior change.<sup>125,145</sup> Best practices for supporting therapeutic lifestyle change in patients with diabetes mellitus are analogous to those in the general pediatric population and have been described elsewhere in this statement and in other comprehensive guidelines.

Optimal therapeutic lifestyle change behavior is difficult to maintain and might not be sufficient to achieve ideal cardiovascular health,<sup>145,146</sup> and pharmacotherapy or other treatments might be needed to reduce lipids and lower blood pressure. Studies in adults with diabetes mellitus demonstrate reduction in cardiovascular events with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Because they also are effective in lowering albuminuria in adults, these drugs are recommended as first-line agents for treatment in youth with diabetes mellitus.<sup>118</sup> A small study suggests that lowering LDL with statins will lead to improvement in arterial properties in youth with T1DM,<sup>147</sup> but more data are needed, and studies in T2DM are lacking. Some providers have suggested bariatric surgery for adolescents with T2DM, severe obesity, and related comorbidities because it provides superior weight reduction<sup>148</sup> and has been associated with reversal of diabetes mellitus<sup>149</sup> and improvement in left ventricular mass<sup>150</sup> and cIMT.<sup>151</sup>

## Hypertension

Hypertension, whether primary or secondary, is a major contributor to adult CVD and a known risk factor for developing atherosclerosis in youth and CVD events in adulthood.<sup>152,153</sup> Data from individual and combined population cohorts have been used to follow cardiovascular risk factors in children for the prediction of atherosclerotic precursors in young adulthood and beyond. Two longitudinal cohort studies demonstrated that elevated blood pressure in childhood predicts increased central

large artery stiffness in adulthood, denoting a worsening of arterial function.<sup>154,155</sup> Another demonstrated that elevated blood pressure predicts worse cIMT, itself a summary structural marker of accumulated arterial insults.<sup>156</sup> Coronary artery calcium in adulthood, a specific marker of coronary atherosclerosis, is also predicted by childhood arterial blood pressure elevation.<sup>155,157</sup> Recent data also link youth blood pressure levels to CVD mortality. A study from Pima and Tohono O'odham children of the American Southwest demonstrated that the presence of physician-diagnosed hypertension in childhood significantly increased the risk of mortality before age 55 years.<sup>158</sup> Data from >1 million people (mostly males) entering mandatory military service at a mean age of 18 years in Sweden demonstrated a similar continuous relationship between young adult blood pressure and CVD mortality over the rest of the life course.<sup>159</sup> A recent study from the Harvard Alumni cohort of mostly males who had blood pressure measured on matriculation around age 19 years found a graded relation between worsening blood pressure category and risk of CVD events decades later.<sup>160</sup> This relationship was still significant after adjustment for middle-aged blood pressure, demonstrating specific utility for the determination of hypertension in youth. The National Heart, Lung, and Blood Institute guidelines include hypertension as a risk condition, with the severity of the risk category determining the use of pharmacotherapy.<sup>5</sup> In addition to being a known cardiovascular risk condition itself, hypertension is a feature of other high-risk disease states such as chronic renal disease, inflammatory conditions like systemic lupus erythematosus (SLE), T2DM, obesity, and polycystic ovarian syndrome.<sup>5</sup>

### Epidemiology

The prevalence in 2011 to 2012 of a high blood pressure measurement was 4%<sup>160a</sup>; however, the prevalence of confirmed hypertension (ie, repeated high readings over multiple occasions) was likely lower. Multiple national studies have shown a declining mean blood pressure and proportion of youth with elevated blood pressure despite increasing rates of obesity.<sup>161–163</sup>

### Screening

The American Academy of Pediatrics "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents," endorsed by the AHA and others, recommends measuring blood pressure at all routine healthcare visits beginning at age 3 years, and earlier in higher-risk individuals.<sup>8</sup> The guidelines also affirm population distribution-based thresholds for defining hypertension and detail new cross-cultural, international reference norms that could be of additional value in the future.<sup>164</sup> These new international reference norms attempt to solve cross-national normative comparison and remedy the inclusion of excess-weight children in constructing the norma-

tive data in the National High Blood Pressure Education Program Working Group on Children and Adolescents' Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. The US Preventive Services Task Force reviewed the evidence in support of and against childhood screening for blood pressure as "insufficient."<sup>165–166</sup> In contrast to this determination by the US Preventive Services Task Force, recent data support the association between hypertension in childhood and atherosclerosis, as described under Hypertension.<sup>160a</sup>

### Treatment

Pediatric hypertension treatment includes therapeutic lifestyle change modification and pharmacotherapy to reduce short- and long-term complications.<sup>8</sup> Both therapeutic lifestyle change modification and pharmacotherapy aim to lower blood pressure to below 90% of the age-sex-height-referenced norm or <130/80 mm Hg, whichever is lower. Therapeutic lifestyle change recommendations focus on the Dietary Approaches to Stop Hypertension (DASH), which is a diet rich in fruits and vegetables, incorporating low- and no-fat dairy, whole grains, and lean proteins. Low dietary sodium is advised.<sup>168</sup> Moderate to vigorous physical activity is recommended, 60 minutes on most days, as is weight loss as necessary to reach a normal BMI. Pharmacotherapy choices should be tailored to characteristics of the individual and have been described elsewhere.<sup>8</sup> Therapeutic lifestyle change modification counseling to improve both diet and physical activity should always be offered and likely provides other preventive benefits in addition to blood pressure lowering.<sup>8,170</sup> Cohort studies show that youth who were able to lower their elevated childhood blood pressure to normal adult levels had cIMT measurements in adulthood similar to individuals with persistently normal blood pressure.<sup>171,172</sup> These youth also tended toward healthier body weight and fewer CVD risk factors over time, which supports the idea that interventions that modify multiple CVD outcomes offer the promise of arresting atherosclerosis. However, data regarding the role of pediatric hypertension in atherosclerotic progression are sparse, especially when children are examined by sex, race, or ethnicity group.

## HIGH-RISK MEDICAL CONDITIONS (DIAGNOSES)

### Chronic Kidney Disease

End-stage renal disease is the last stage of CKD, which requires treatment with dialysis or kidney transplantation. There are ≈10 000 children in the United States treated with maintenance dialysis, with ≈1 000 children receiving a kidney transplant annually.<sup>173</sup> Despite significant improvement in survival over the past 2 decades for individuals with childhood onset of end-stage renal

disease,<sup>174,175</sup> children treated with long-term dialysis have mortality rates  $\approx$ 30 times that of the general pediatric population,<sup>175</sup> and kidney transplant recipients have an overall mortality rate 10 times that of the general population.<sup>174</sup> CVD is the most common cause of death, accounting for 25% to 35% of all deaths, and is the biggest obstacle to long-term survival of children and adolescents with CKD.

CKD is a vasculopathic state<sup>176</sup> characterized by the accumulation of numerous traditional risk factors (hypertension, dyslipidemia, and obesity) and nontraditional, CKD-related risk factors (abnormal mineral metabolism, anemia, chronic inflammation) acting synergistically to result in early abnormalities of vascular (increased cIMT and stiffness, coronary artery calcification) and cardiac (left ventricular hypertrophy [LVH] and left ventricular dysfunction) structure and function.<sup>177</sup> Different factors play greater or lesser roles, depending on the stage of CKD. For example, hypertension is the leading contributor to cardiac LVH during early CKD; however, during dialysis, fluid overload, mineral bone disease, and anemia are more important. These cardiovascular risk factors and subclinical cardiovascular abnormalities are already evident in the early, predialysis stages of pediatric CKD, become increasingly common during maintenance dialysis, and persist after kidney transplantation.<sup>177</sup>

### Screening

Because of this extremely accelerated cardiovascular risk, children with end-stage renal disease should be screened at least yearly for traditional risk factors, including hypertension, dyslipidemia, and obesity. Kidney Disease Improving Global Outcomes (KDIGO) has developed recommendations for the management of most common CVD risk factors based on the available pediatric evidence.<sup>178–181</sup> Mineral metabolism abnormalities (ie, high phosphorus level, secondary hyperparathyroidism) should also be screened for and treated to prevent coronary artery calcification, and children with end-stage renal disease should undergo regular echocardiographic monitoring for LVH.

### Treatment

As is true for screening, management of CVD risk factors in youth with CKD should be tailored to the specific stage (predialysis, dialysis, or transplantation), because each has a unique subset of risk factors. Because the culmination of cardiovascular risk occurs during dialysis, the primary strategy to minimize the development of CVD in children with CKD is preemptive transplantation, avoiding long-term dialysis if feasible. For those children who must have long-term dialysis, the management strategy is directly linked to achieving adequate dialysis outcomes, including aggressive monitoring and management of hypertension, dyslipidemia, abnormal

mineral metabolism, anemia, malnutrition, inflammation, and other dialysis complications.

## Chronic Inflammatory Diseases

Several chronic inflammatory diseases, including but not limited to rheumatoid arthritis, psoriasis, inflammatory bowel diseases (IBD), and systemic lupus erythematosus (SLE), confer an increased risk for CVD in adults. Relative risk of CVD is 2-fold higher in rheumatoid arthritis,<sup>182</sup> 1.5-fold in psoriasis, and 1.2-fold in IBD and SLE.<sup>183</sup> This association approaches the risk conferred by metabolic syndrome<sup>184</sup> and T2DM, both of which are also associated with inflammation.<sup>185–189</sup> In addition, it has been shown that coronary HD patients with underlying inflammatory conditions have more severe atherosclerotic involvement.<sup>186</sup> Up to 50 000 children in America are affected with juvenile idiopathic arthritis<sup>190</sup> and another 100 000 with IBD.<sup>191</sup> Pediatric prevalence data are more limited for SLE and psoriasis, but 20% to 30% of adult cases are thought to have onset before 20 years of age, which suggests that as many as 32 000 and 2.5 million cases of these conditions, respectively, afflict children.<sup>192,193</sup> A fully 10-fold lower prevalence of pediatric psoriasis was documented in a southern California cohort, attributed to the preventive effect of more sunlight exposure,<sup>194</sup> but the number of affected children and adolescents remains considerable. This group of patients collectively represents an important portion of the pediatric population, and the prevalence of all autoimmune conditions is increasing for complex reasons that might relate to dysregulation of immunity at the level of the intestinal interface. A common inflammatory nexus has been linked in juvenile idiopathic arthritis and IBD to circulating concentrations of gut-derived lipopolysaccharide binding protein.<sup>195,196</sup> There is also evidence that low levels of lipopolysaccharide can boost de novo fatty acid synthesis, lipolysis, and lipoprotein production in the liver, leading to hypertriglyceridemia; this might help to explain the tight linkage between inflammation, dyslipidemia, and CVD risk.<sup>197</sup>

The APPLE study (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) explored predictors of atherosclerotic progression in SLE, as measured by cIMT. Roughly 50% to 85% of pediatric lupus patients have dyslipidemia,<sup>198–200</sup> 50% to 67% have nephritis, and 40% of those with nephritis have hypertension.<sup>201–203</sup> The usual risk factors, such as age, sex, race, BMI, lipids, Lp(a), proteinuria, and creatinine clearance, along with more disease-specific factors, such as duration of lupus exposure, azathioprine use, and prednisone dosing, were evaluated in the APPLE study.<sup>204,205</sup> Despite the high prevalence of dyslipidemia in the study group and the decrease in C-reactive protein and cholesterol concentrations seen in the atorvastatin arm, the APPLE randomized controlled trial did not show a benefit to



cIMT progression with atorvastatin. Secondary analyses did, however, suggest reduction in cIMT by atorvastatin in pubertal participants with increased inflammation, as indicated by an elevated baseline C-reactive protein level.<sup>206</sup> Finally, it is important to mention the provocative results from an adult trial of the anti-inflammatory biologic canakinumab, a selective inhibitor of interleukin-1 $\beta$ , in adult patients with high risk of CVD who had an elevated C-reactive protein level after an MI.<sup>207</sup> In the absence of lipid lowering, there was a 15% reduction in the composite end point of nonfatal MI or stroke and cardiovascular death with 150 mg of canakinumab compared with placebo. The full implications of this approach to therapy on lipid metabolism and CVD risk remain to be established in adults before its use in pediatrics, but it serves to accentuate the importance of therapeutic attenuation of inflammation for CVD prevention.

### Screening

There is an uneven association between various inflammatory conditions and CVD risk factors, both typical and nonclassic, and pediatric data that demonstrate that CVD risk factor modification can arrest atherosclerotic progression are needed. Although these data are accruing, it is prudent to screen these children for CVD risk factors on a periodic basis, to tailor the screening to the disease activity and medication regimen, and to assertively treat the disease and CVD risk factors to enhance overall health. Children with inflammatory disorders, including but not limited to juvenile idiopathic arthritis, IBD, SLE, and psoriasis, should be screened periodically, in accordance with current pediatric cardiovascular risk guidelines,<sup>5</sup> for diabetes mellitus, obesity, hypertension, lipid disorders, and other CVD risk behaviors or conditions at health maintenance encounters.<sup>5,8</sup> Given the proven capacity of inflammatory conditions to accelerate vascular aging, augmenting CVD risk factors, treatment should be initiated with vigor.

### Treatment

Regular exercise has been shown to have anti-inflammatory benefits<sup>208</sup> as has better dietary quality.<sup>208</sup> The therapeutic focus must be to counter the standard American diet. Strong evidence supports the use of a plant-centered diet high in fiber, including whole grains, vegetables, fruits, and nuts, to alleviate chronic pediatric inflammation. Fiber protects the intestinal lining and strengthens immunoregulation.<sup>209</sup> Fiber is also metabolized by intestinal bacteria into short-chain fatty acids that have important immunoregulatory functions. Short-chain fatty acids can also be formed from the metabolism of proteins and glycoproteins found in food, but carbohydrates are the predominant source.<sup>210</sup> These metabolites can activate metabolite-sensing G-protein-coupled receptors and can affect

epigenetic and gene transcription programs, with favorable immunologic outcomes.<sup>211</sup> It is also increasingly evident that polyphenolic compounds present in fruits and vegetables and many herbs and spices, as well as essential omega-3 fatty acids from fish and select plant foods, have important effects on both innate and adaptive immunity that are hypothesized to attenuate the immune hyperactivity that characterizes chronic inflammatory conditions.<sup>212</sup> This nutritional approach replicates the Mediterranean diet that has proven benefits for immunomodulation and CVD risk reduction.<sup>213-215</sup> Furthermore, when inflammatory conditions necessitate anti-tumor necrosis factor biologic agents, a Western-style diet (also considered an inflammatory diet, rich in meats, simple sugars, and other refined carbohydrates and deficient in fiber, plant foods, and essential fatty acids) can compromise the impact of pharmacological therapy.<sup>216</sup> Pediatric inflammatory conditions, and their secondary dyslipidemia, are factored into lipid-lowering pharmacological guidelines for statin therapy.<sup>5</sup>

### Childhood Cancer

Approximately 1 in 408 children between birth and 14 years of age and 1 in 285 adolescents between 15 and 19 years old will develop cancer in the United States.<sup>219</sup> Surgical interventions, radiotherapy, and chemotherapeutic approaches continue to improve childhood cancer survival rates, and now the 5-year survival rate for all childhood cancers combined is estimated to be 81%.<sup>220</sup> As a consequence, there is a growing group of adult childhood cancer survivors (CCS); in 2010, an estimated 400 000 US adults (1 in 530 adults between 20 and 39 years old) had survived cancer.<sup>219</sup> With improved rates of survival, the focus has turned toward understanding and treating their late morbidity and mortality, which are  $\approx$ 8 times that of the general population.<sup>221</sup> Recurrence of the original cancer is the leading cause of death among CCS ( $\approx$ 70% of late deaths).<sup>221</sup> That being said, CCS are 8 to 10 times more likely to die of CVD than age-matched control subjects.<sup>222</sup> The Childhood Cancer Survivor Study compared 10 397 CCS with 3034 siblings without cancer and found the CCS had a 10-fold increased risk of coronary artery disease (CAD), a 9-fold increased risk of cerebrovascular accident, and a 15-fold increased risk of congestive heart failure compared with their siblings.<sup>7</sup> CCS have been shown to have higher fat mass, lower lean body mass, greater insulin resistance, lower carotid distensibility and compliance, and increased arterial stiffness compared with sibling control subjects in childhood<sup>222</sup> and adulthood.<sup>223</sup> The pathogenesis of this increased cardiovascular risk is multifactorial and related to higher rates of traditional risk factors in a more vulnerable host. Precision about the pathophysiology is challenging because of the di-

versity of both diagnosis and treatments within the CCS population. However, some overall comments can be made about the primary cancer treatment modalities and their association with key risk factors.

### **Radiation**

Radiation exposure has been linked to CVD in a dose-dependent fashion<sup>221,224</sup>; receiving >1500 centigray of radiation is associated with a 2- to 6-fold increased risk of congestive heart failure, MI, pericardial disease, and valvular abnormalities compared with rates in CCS not exposed to radiation.<sup>224</sup> Cranial radiation therapy has also been linked to increased cIMT measurements,<sup>225,226</sup> and chest wall radiation has been linked to development of CAD.<sup>227–229</sup> Radiation exposure is also associated with traditional cardiovascular risk factors such as hypertension, dyslipidemia, and T2DM.<sup>230–237</sup> This is true for both total body irradiation<sup>235,238,239</sup> and chest or abdominal radiation.<sup>235,238,240</sup>

### **Anthracycline Exposure**

Anthracycline treatment leads to dilated cardiomyopathy in a dose-dependent fashion, as comprehensively reviewed in a previous AHA statement.<sup>241</sup>

### **Hematopoietic Stem Cell Transplantation**

Compared to the general population hematopoietic stem cell transplantation is associated with a 2 to 3 times greater risk of CVD mortality<sup>242</sup> and increased CVD morbidity attributable to cardiomyopathy, congestive heart failure, cerebrovascular accident, CAD, and rhythm disorders.<sup>243</sup> Graft versus host disease places a hematopoietic stem cell transplantation survivor at higher risk for cardiovascular risk factors, with an up to 9-fold increase in relative risk for hypertension, a 5-fold increased risk of T2DM, and a 3-fold increased risk for dyslipidemia.<sup>240</sup>

### **Traditional CVD Risk Factors in Survivors of Childhood Cancer**

In addition to the specific treatment-related risks of radiation, anthracycline, and stem cell transplantation, CVD risk factors are more common in CCS and represent important opportunities for intervention in these high-risk youth. Some studies show CCS have higher rates of obesity,<sup>244,245</sup> particularly in certain subpopulations,<sup>236,246–251</sup> but not greater than their siblings without cancer. Steinberger et al<sup>252</sup> compared 319 CCS to 208 siblings and found that CCS overall had a lower lean body mass and greater fat mass than their siblings but had no difference in weight or BMI percentile. These results have been confirmed by others<sup>233,253,254</sup> and appear to be associated particularly with cranial radiation therapy,<sup>230–232,236,237</sup> which suggests that BMI does not capture the excess adiposity of CCS. Exposure to corticosteroids has been linked to increased rates of obesity in CCS as well.<sup>247</sup> Growth hormone deficiency is a

possible mechanism for increased body fat percentage and abdominal adiposity in CCS and has been linked to increased visceral adiposity, development of the metabolic syndrome, increased cardiovascular risk,<sup>234,239,255,256</sup> and increased cIMT.<sup>257,258</sup> One study of 75 survivors of childhood acute lymphoblastic leukemia found that 64% had untreated abnormal growth hormone levels. This increased to 85% among those who had received cranial radiation therapy.<sup>234</sup> Treatment with total body irradiation has also been linked to growth hormone deficiency.<sup>239</sup> CCS also have higher rates of impaired glucose tolerance, T2DM,<sup>253</sup> and insulin resistance<sup>232</sup> than both their siblings<sup>235,252</sup> and population control subjects,<sup>253</sup> at rates out of proportion to the degree of overall obesity.<sup>252,253</sup> Perhaps not surprisingly, CCS have higher rates of dyslipidemia<sup>232</sup> than their siblings<sup>238,252,255</sup> and population-based control subjects.<sup>239,253</sup> CCS are at increased risk for renal insufficiency and hypertension because of exposure to nephrotoxic medications such as ifosfamide and methotrexate, as well as radiation to the abdomen and graft versus host disease. The prevalence of hypertension in survivors is not well characterized,<sup>250</sup> but one study showed 15% of children had at least stage 1 hypertension at the conclusion of therapy, with greater risk related to younger age at diagnosis, female sex, and exposure to corticosteroids.<sup>247</sup>

### **Screening**

Because of the known increased CVD risk, screening of CCS for risk factors is recommended by the Children's Oncology Group's "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer."<sup>259,260</sup> All CCS should have a fasting lipid profile and fasting glucose or hemoglobin A<sub>1c</sub> every 2 years. If a CCS develops any criteria for metabolic syndrome, providers should screen for associated findings. Waist/height ratio, skinfold thickness, or dual-energy x-ray absorptiometry can allow for more accurate evaluation of adiposity.

Treatment should include therapeutic lifestyle change counseling regarding maintenance of appropriate weight, consumption of a heart-healthy diet, participation in adequate physical activity, and avoidance of smoke exposure (see Table 1 and the Figure for risk categories and treatment considerations). Just as in the general population, the traditional CVD risk factors can be related to common lifestyle causes. Studies report suboptimal adherence to standardized dietary recommendations,<sup>261–266</sup> but this is not necessarily different from their siblings<sup>267</sup> or the general population. However, CCS are known to be less active than their siblings or sex-matched population samples. CCS not only have a lower self-reported duration of exercise,<sup>268,269</sup> they generally have an inferior performance on standardized tests of strength and endurance.<sup>270</sup> A low threshold should be used when considering the initiation of phar-

macological agents because of the high risk of these youth. Treatment of cardiovascular risk factors should consider the cancer therapies the patient has received previously. Standard pharmacological agents can be used.

## THE VULNERABLE HEART

### Congenital HD

The prevalence of congenital HD is estimated at 9 per 1000 live births,<sup>4</sup> with 3 per 1000 requiring catheter-based or surgical intervention early in life.<sup>271</sup> Because surgical and medical management of congenital HD have become more successful over recent decades, the contribution of acquired morbidities, especially acquired heart conditions, to patient outcome has become increasingly important. Advances in surgical, percutaneous, and medical management mean that  $\geq 90\%$  of children with congenital HD survive into adulthood, yielding an estimated 1.0 to 2.9 million adults living with congenital HD in the United States.<sup>272,273</sup> Individuals with congenital HD have structural and functional abnormalities that can make their hearts more vulnerable to both the development of atherosclerosis and the adverse sequelae of a CVD event; thus, the contribution of premature CVD to long-term patient outcomes in this growing population is increasingly important.<sup>9,274–276</sup> Some data suggest that individuals with congenital HD are at risk for developing atherosclerotic CVD, with a median estimated lifetime risk of  $\approx 36\%$ . Adults with congenital HD have been reported to have all types of CVD, including MI, stroke, transient ischemic attacks, aortic aneurysms, and peripheral vascular disease.<sup>275,277,278</sup> Emerging data suggest that some types of congenital HD (or the process of their repair) are associated with an increased risk for premature CVD compared with the general population.<sup>275</sup> A systematic review of specific congenital HD lesions suggests that patients with different complexities of congenital HD remain at risk for the development of CVD, as shown in Table 3.<sup>9</sup>

Although the diagnosis of congenital HD includes rare and diverse disorders, as shown in Table 1, some specific diagnoses appear to be associated with increased risk for premature atherosclerotic CAD in children. This risk of premature atherosclerotic CVD in patients with congenital heart defects is based on the following 3 conditions: (1) obstructive lesions of the left ventricle and aorta, (2) cyanotic congenital heart defects leading to Eisenmenger syndrome, and (3) lesions with coronary artery abnormalities (see Congenital Coronary Anomalies).<sup>275</sup>

Obstructive lesions of the left ventricle and aorta have been associated with increased risk of CVD in adulthood. Coarctation of the aorta is the best described lesion associated with early cardiovascular

events, presumed atherosclerotic in nature. It is likely that the pathophysiology for acquired CVD associated with coarctation of the aorta (CoA) is primarily related to systemic hypertension. Arterial abnormalities can persist after correction of the coarctation and result in long-term systemic hypertension, with a reported prevalence of 10% to 50%.<sup>279–281</sup> Beyond hypertension, CoA is associated with other important sequelae that lead to morbidity and mortality, which suggests a more widespread vascular abnormality. Multiple studies have shown that the main cause of late death in patients with corrected CoA is CAD.<sup>282</sup> Cerebrovascular accidents have also been described in association with systemic hypertension in patients with repaired CoA.<sup>283</sup> Intracerebral berry aneurysms and visceral hemangiomas are associated with coarctation, with a frequency of as high as 5-fold that of the general population.<sup>284</sup> Persistent hypertension, older age at repair, association with bicuspid aortic valve, aortic atherosclerosis, and dilation of the aorta proximal to the repair site all predispose coarctation patients to this serious risk.<sup>285</sup> Furthermore, the life expectancy of patients with CoA, even after repair, is significantly reduced compared with the general population, with premature cardiovascular death as the primary contributing factor to this outcome.<sup>286</sup>

Congenital aortic stenosis is also associated with CVD and occurs most often at the level of the aortic valve but can also be subvalvular or supra-valvular and can result in myocardial changes that predispose to CVD. Significant aortic stenosis is associated with LVH, which is known to be an independent risk factor for CVD morbidity and mortality in adults.<sup>287,288</sup> Myocardial blood flow can be compromised in patients with aortic stenosis with severe LVH, despite normal coronary artery patency. Increased myocardial work results in increased demand for oxygen, exceeding the capacity of the coronary supply.<sup>289</sup> Even mild aortic stenosis during childhood can progress and can therefore be associated with increased left ventricular mass and increased risk for CVD over time. Supra-valvular aortic stenosis (most commonly associated with Williams syndrome) can confer an additional increased cardiovascular risk because of its association with arterial stenosis. Coronary artery ostial stenosis can result directly in myocardial ischemia and exercise-induced syncope, and renal artery stenosis can lead to hypertension.<sup>290</sup>

Some data suggest that adults with cyanotic congenital HD might be protected from atherosclerosis because of upregulation of antiatherosclerotic factors, including nitric oxide, hyperbilirubinemia, and others that are frequently encountered with cyanosis.<sup>291</sup> Results have shown that patients with cyanotic congenital HD have coronary arteries free from plaque and cIMT measurements that are lower than expected, which indicates a reduced risk of later development of atherosclerosis.<sup>292</sup> However, evidence is sparse, and a

conclusive explanation for the decreased risk of atherosclerosis in patients with cyanotic congenital HD is still missing. A small case series by Yalonetsky et al<sup>293</sup> reported the presence of CAD in 7 patients with Eisenmenger syndrome. There are no established current guidelines that recommend routine screening for CAD in such patients.

## Congenital Coronary Anomalies

Congenital coronary anomalies, in isolation or in association with other congenital defects, can predispose individuals to developing premature CVD.<sup>277,294</sup> Atherosclerosis in a segment of the abnormal artery has been demonstrated even in young people.<sup>295,296</sup> Other congenital anomalies of coronary origin and course (origin of the left circumflex from the right main coronary artery being the most common) are thought to have little clinical importance; however, these coronary arteries have also been reported to have a high incidence of coronary atheroma.<sup>295,296</sup> Surgical repair of congenital heart defects can also result in abnormalities of the coronary arteries, as occurs in the arterial switch operation for d-transposition of the great arteries and in repair of anomalous origin of left coronary artery from the pulmonary artery. In these settings, coronary ostial stenosis can develop over time, and there can be increased risk of associated atherosclerosis.<sup>295,296</sup>

### Screening

To further improve the outcome of these patients, attention must be given to the prevention, detection, and adequate therapy of acquired heart conditions. Therefore, it seems prudent to be aggressive about the evaluation of CVD risk status. Screening for cardiovascular risk factors and attempts to modify these risks earlier in life could improve their long-term outcomes, and this strategy has been recommended.<sup>297</sup> Modifiable CVD risk factors, including smoking, diabetes mellitus, systemic hypertension, and obesity, have been described in older patients (up to 70% of individuals with congenital HD),<sup>297</sup> but data on the true prevalence of premature CVD and CVD risk factors in congenital HD are relatively sparse.<sup>277,298</sup> Some postulate that traditional atherosclerotic risk factors, such as physical inactivity, smoking, obesity, diabetes mellitus, hypertension, and lipid abnormalities, might be as prevalent in patients with congenital HD as in the general population.<sup>275,277</sup> More than 80% of adults with congenital HD have been identified to have  $\geq 1$  such cardiovascular risk factor.<sup>4</sup> It is also suggested that preventive measures, such as smoking cessation, diet and exercise, and screening and treatment for hypertension, diabetes mellitus, and hyperlipidemia, could lower cardiovascular risk over the long term.<sup>9,275,277,278,298</sup>

## Kawasaki Disease

Kawasaki disease (KD) affects 30 per 100 000 children in the United States and is a leading cause of acquired HD, resulting in coronary artery aneurysms (CAAs) in 20% to 25% of untreated children.<sup>299,300</sup> The incidence of CAAs is significantly lower,  $<4\%$ , in children who have been treated with intravenous immunoglobulin early in the illness.<sup>301</sup> Fortunately, those who never experience coronary artery complications have an excellent clinical prognosis and should be considered at usual risk for atherosclerosis.<sup>302</sup> Studies examining vascular function and structure suggest children who had KD without coronary aneurysm are likely similar to those who never had KD.<sup>303–305</sup> Early in the illness, the lipid profile shows high triglycerides in the acute illness and low HDL in the years after, but without evidence to suggest an increase in early HD in patients without CAA.<sup>304</sup> Patients with CAA are certainly at increased CVD risk, but it is unclear whether accelerated atherosclerosis plays a role in later coronary complications.<sup>303</sup> Rather, it is more likely that damage to the vessel sustained during acute KD accounts for increased risk in these patients.<sup>306</sup>

Thus, children whose coronary arteries always had normal dimensions should have cardiovascular assessment and lipid screening as per the recommendations for healthy children.<sup>5</sup> Risk factor assessment and counseling should be provided for a heart-healthy diet, regular aerobic exercise, and avoidance of smoking.

In contrast, optimizing coronary health is particularly important for children with known aneurysms. Patients with regressed or persistent aneurysms are vulnerable to future events.<sup>307</sup> A child's individual prognosis is related to the extent of coronary damage. Patients who developed giant coronary aneurysms have the highest morbidity and mortality from this illness. These patients are at risk for thrombus formation where flow is disrupted. As damaged vessels heal, these same patients are at risk for coronary stenosis. Vascular testing reveals increased arterial stiffness and cIMT measurements in patients with aneurysms.<sup>305</sup> All children with coronary artery dilation/aneurysm formation that is persistent and greater than mild (coronary artery z score  $>2.5$ – $5$ ) should receive aspirin as antithrombotic therapy. Patients with moderate-sized aneurysms should receive dual-agent antiplatelet therapy. Anticoagulation is warranted for infants and children with persistent large or giant aneurysms.<sup>308</sup> All children who have had KD with CAA should be screened for lipid disorders beginning at 2 years of age and for hypertension subsequent to diagnosis. Attempts to decrease additional risk factors should be optimized.

Statins are being trialed in acute KD as primary therapy, as well as in children with CAA in the convalescent stage. Data are still limited regarding the role of statin therapy in patients with CAAs. The use of statin



therapy in children or adults with CAA is based on the generalized anti-inflammatory effect of statins on the arterial wall. The evidence for statin therapy in KD with aneurysms comes from a positron emission tomography study that suggested diminished inflammation in the arterial wall,<sup>309,310</sup> as well as animal and cell culture models demonstrating diminished myointimal proliferation in response to statins.<sup>311</sup>

## Heart Transplantation

Approximately 550 children undergo heart transplantation each year, with one-third of those being adolescent recipients; there are an estimated 4000 youth currently living with a heart transplant (HTx). HTx recipients are at risk for developing cardiac allograft vasculopathy (CAV), an unusual version of CAD that portends high rates of graft loss.<sup>312</sup> CAV is the leading cause of late cardiac allograft failure; children with moderate to severe CAV have a 50% to 75% chance of cardiac allograft loss within 3 years of diagnosis.<sup>313</sup> The incidence in pediatric HTx recipients is 5%, 15%, and 28% at 2, 5, and 10 years, respectively, after orthotopic HTx.<sup>313</sup> Even in those with mild CAV by angiography, the presence of cardiac allograft dysfunction, either by echocardiogram or invasive hemodynamic measurements at catheterization, is a predictor of graft loss.<sup>313</sup>

The mechanism for development of CAV is poorly understood but is thought to be multifactorial, related to lipid abnormalities associated with immunosuppres-

sive agents,<sup>314</sup> chronic inflammation, endothelial dysfunction, infection, and other cardiac risk factors such as hypertension, diabetes mellitus, and obesity that are common in post-HTx patients.<sup>315</sup> Some of the known risk factors in adult HTx recipients, such as donor age, donor atherosclerotic disease, and hypertension, could be important for adolescent recipients.<sup>316</sup> Rejection within the first year after HTx is one of the known risk factors for development of CAV in the pediatric HTx recipient.<sup>312</sup> However, despite decreases in rejection in the current era, the incidence of CAV has not changed,<sup>312</sup> which suggests that the mechanism is multifactorial and still not well understood.

### Screening

A review of the modalities used to detect CAV is beyond the scope of this article, but most commonly the diagnosis is made by cardiac catheterization with coronary angiography, including intravascular ultrasound.<sup>317</sup> Identification and treatment of traditional risk factors such as hyperlipidemia, obesity, hypertension, and diabetes mellitus early after HTx may reduce risk.

### Treatment

Because the mechanism is poorly understood, identifying specific treatment strategies in this population is a challenge. Treating the underlying condition (ie, minimizing risks for graft rejection) is therefore of primary importance. Thus, it is imperative to optimize immunosuppression to decrease the risk of rejection and

**Table 4. Relevant Guidelines and Statements**

Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report. <sup>63</sup>
Cardiovascular Disease Risk Factors in Youth With Diabetes Mellitus: A Scientific Statement From the American Heart Association <sup>108</sup>
Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association <sup>331</sup>
Update: Ambulatory Blood Pressure Monitoring in Children and Adolescents: A Scientific Statement From the American Heart Association <sup>332</sup>
Severe Obesity in Children and Adolescents: Identification, Associated Health Risks, and Treatment Approaches: A Scientific Statement From the American Heart Association <sup>57</sup>
Promotion of Physical Activity for Children and Adults With Congenital Heart Disease: A Scientific Statement From the American Heart Association <sup>333</sup>
Long-Term Cardiovascular Toxicity in Children, Adolescents, and Young Adults Who Receive Cancer Therapy: Pathophysiology, Course, Monitoring, Management, Prevention, and Research Directions: A Scientific Statement From the American Heart Association <sup>241</sup>
NHLBI Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report <sup>5</sup>
Nontraditional Risk Factors and Biomarkers for Cardiovascular Disease: Mechanistic, Research, and Clinical Considerations for Youth: A Scientific Statement From the American Heart Association <sup>334</sup>
Noninvasive Assessment of Subclinical Atherosclerosis in Children and Adolescents: Recommendations for Standard Assessment for Clinical Research: A Scientific Statement From the American Heart Association <sup>335</sup>
Progress and Challenges in Metabolic Syndrome in Children and Adolescents: A Scientific Statement From the American Heart Association <sup>336</sup>
Primary Prevention of Cardiovascular Disease in Nursing Practice: Focus on Children and Youth: A Scientific Statement From the American Heart Association Committee on Atherosclerosis, Hypertension, and Obesity in Youth of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity, and Metabolism <sup>337</sup>
Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association <sup>338</sup>
Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism; High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research <sup>1</sup>
Dietary Recommendations for Children and Adolescents: A Guide for Practitioners: Consensus Statement From the American Heart Association <sup>339</sup>

**Table 5. Resources for Practitioners and Patients**

Disease or Condition	Guidelines and Statements	Patient Resources
FH and lipoprotein(a)	The agenda for familial hypercholesterolemia (AHA, Gidding et al) <sup>6</sup> ; National Lipid Association; International Atherosclerosis Society	FH Foundation; Lipoprotein(a) Foundation
Obesity	Endocrine Society 2017 pediatric obesity guideline <sup>340</sup> USPSTF 2017 pediatric obesity guideline <sup>341</sup> Kelly et al, AHA scientific statement on severe obesity <sup>57</sup> Barlow et al, <sup>63</sup> 2007 Expert Committee recommendations Improving Access and Systems of Care for Evidence-Based Childhood Obesity Treatment: Conference Key Findings and Next Steps <sup>343</sup>	The Obesity Society Patient Pages: Obesity in Young Children <sup>342</sup>
Diabetes mellitus, type 1 and type 2	American Diabetes Association standards of care <sup>344</sup>	American Diabetes Association: For Parents & Kids <sup>345</sup>
Hypertension	AAP 2017 clinical practice guideline <sup>8</sup>	UpToDate blood pressure percentiles for boys (by subscription only) <a href="https://www.uptodate.com/contents/calculator-blood-pressure-percentiles-for-boys-0-17-years-old-revised-2017">https://www.uptodate.com/contents/calculator-blood-pressure-percentiles-for-boys-0-17-years-old-revised-2017</a> UpToDate blood pressure percentiles for girls (by subscription only) <a href="https://www.uptodate.com/contents/calculator-blood-pressure-percentiles-for-girls-0-17-years-old-revised-2017">https://www.uptodate.com/contents/calculator-blood-pressure-percentiles-for-girls-0-17-years-old-revised-2017</a>
Chronic kidney disease	KDIGO: <a href="https://kdigo.org/">https://kdigo.org/</a> National Kidney Foundation, <a href="https://www.kidney.org">https://www.kidney.org</a>	
Childhood cancer survivors	Childhood Cancer Survivor Study <sup>346</sup> Children's Oncology Group long-term follow-up guidelines <sup>259</sup>	Children's Oncology Group: long-term follow-up care <sup>347</sup>
Congenital heart disease	American Heart Association <a href="http://www.heart.org">http://www.heart.org</a> American College of Cardiology <a href="http://www.acc.org">http://www.acc.org</a> Adult Congenital Heart Association <a href="https://www.achaheart.org/">https://www.achaheart.org/</a>	American Heart Association <a href="http://www.heart.org">http://www.heart.org</a> American College of Cardiology <a href="http://www.acc.org">http://www.acc.org</a> Adult Congenital Heart Association <a href="https://www.achaheart.org/">https://www.achaheart.org/</a> The Children's Heart Foundation (pediatric congenital heart disease) <a href="http://www.childrensheartfoundation.org/">http://www.childrensheartfoundation.org/</a> Pediatric Congenital Heart Association <a href="http://conqueringchd.org/">http://conqueringchd.org/</a>
Heart transplantation	Organ Procurement and Transplantation Network: pediatric heart allocation <a href="https://optn.transplant.hrsa.gov/learn/professional-education/pediatric-heart-allocation">https://optn.transplant.hrsa.gov/learn/professional-education/pediatric-heart-allocation</a>	Patient education: heart transplantation (beyond the basics) <sup>348</sup> UNOS <a href="https://transplantliving.org/children/">https://transplantliving.org/children/</a>
Kawasaki disease	Diagnosis, treatment, and long-term management of Kawasaki disease (AHA) <sup>308</sup>	<a href="http://www.kdfoundation.org/">http://www.kdfoundation.org/</a>

AAP indicates American Academy of Pediatrics; AHA, American Heart Association; FH, familial hypercholesterolemia; KDIGO, Kidney Disease: Improving Global Outcomes; UNOS, United Network for Organ Sharing; and USPSTF, US Preventive Services Task Force.

reduce the chance of CAV. This includes screening for presence of CAV every 6 to 12 months, or at any time of development of graft dysfunction, with angiography by catheterization, as well as screening and early treatment for infection, particularly cytomegalovirus, which can induce microvascular inflammation and increase development of CAV.<sup>318</sup> In addition, treatment should be initiated to modify any other CVD risk factors.

Multiple studies have shown that HTx recipients have deranged lipid metabolism,<sup>319,320</sup> and statin use is recommended. However, a recent publication by Greenway et al<sup>321</sup> showed that only 50% of pediatric HTx recipients over age 10 years were taking a statin by 2 years after HTx. In addition to their lipid-lowering properties, statins have anti-inflammatory effects that

can be particularly helpful in HTx recipients, given the chronic microvascular inflammation that can occur. Despite these properties of statins, data regarding the efficacy of statins in the pediatric HTx population are conflicting, with earlier reports suggesting a survival benefit and decreased rates of CAV and graft loss,<sup>322,323</sup> and a more recent report suggesting no change in CAV or overall survival and higher rates of early rejection in patients receiving statins.<sup>321</sup> Because the number of events in this recent report was small, current recommendations still include standard use of statin therapy in the pediatric HTx recipient, particularly if the patient has lipid abnormalities. Newer immunosuppressive agents known as mTOR (mammalian target of rapamycin) inhibitors (sirolimus and everolimus)

**Table 6. Future Research**

Disease or Condition	Basic	Clinical	Population
General	Comparing pathophysiology of atherosclerosis and arteriosclerosis across risk conditions	Best therapeutic lifestyle change and pharmacotherapeutic choices for reducing CV risk in the presence of multiple risk factors Accurate risk prediction calculators for children	Cost-effectiveness of selective screening based on risk conditions
FH, Lp(a)	Reversibility of atherosclerosis during childhood vs adulthood	Role for nonstatin therapy in childhood heterozygous FH	Best screening strategies to identify FH
Obesity	Developmental origins and determinants of obesity Neurohormonal mediators of metabolic rate and appetite in children; age at which BMI “set point” is fixed	Best therapeutic lifestyle change implementation practices Development and evaluation of pharmacotherapy agents, devices, and surgery in childhood	Effective societal, community, and school-based interventions, policy efforts that reduce childhood obesity
Diabetes mellitus, type 1 and type 2	Differences in histology, distribution of atherosclerosis in type 1 vs type 2	CV benefits of various diabetes mellitus therapies in childhood	Best screening strategies (including which test) to identify T2DM
Hypertension	Mechanisms of early-life elevated BP, especially in obese children	Comparative effectiveness of pharmacological agents for BP in children	Impact of lower thresholds on appropriate vs inappropriate management and cost Impact of the “Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents” <sup>8</sup> recommendation for ABPM on rates of hypertension and hypertension treatment
CKD	Mechanisms of early atherosclerosis and cardiac dysfunction	Effect of CV risk reduction on CKD progression	Defining optimal BP targets in children with CKD
Childhood cancer survivors	Pathophysiology of visceral adiposity and insulin resistance out of proportion to BMI Role of GH in CVD risk	Safety, timing, and long-term impact of medical therapy for CV risk reduction (insulin-sensitizing drugs, statins) Safety and efficacy of therapeutic lifestyle change modification in long-term CV risk reduction	Timing and strategies for screening childhood cancer survivors, tailored to risk exposures
Congenital HD	Mechanisms by which cyanotic HD is protective for atherosclerosis	Larger-scale studies to confirm preliminary findings on ASCVD risk among patients with congenital HD Treatment cut points and goals	Safe strategies to promote physical activity among congenital HD
Congenital coronary artery abnormalities	Flow mechanics that promote arteriosclerosis in congenital coronary abnormalities	Best modality and optimal use of imaging (eg, intravascular ultrasound, coronary CT angiography) for atherosclerosis	
Heart transplantation	Pathophysiology of CAV development	mTOR studies on reduction of CAV risk Role of usual preventive strategies in heart transplantation patients	
KD	Pathophysiology of additional CV risk factors in patients with KD and CAA	Role of statin therapy in children with CAAs and KD	Variation in long-term CV outcomes across geography and race/ethnicities

ABPM indicates ambulatory blood pressure monitoring; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAA, coronary artery aneurysm; CAV, cardiac allograft vasculopathy; CKD, chronic kidney disease; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolemia; GH, growth hormones; HD, heart disease; KD, Kawasaki disease; Lp(a), lipoprotein(a); mTOR, mammalian target of rapamycin; and T2DM, type 2 diabetes mellitus.

can also function as proliferation signal inhibitors and hence decrease the incidence or progression of CAV. Small adult studies have shown some promising results of mTOR inhibitors in decreasing CAV,<sup>324–328</sup> and small pediatric studies have shown a relatively good safety profile,<sup>329</sup> but mTOR inhibitors are yet to be studied in larger populations to prove efficacy and safety. A large, multicentered randomized controlled trial for use of everolimus in the pediatric HTx population could provide further details on the risk reduction of CAV. Prevention of CAV is important because coronary re-

vascularization in pediatric HTx patients is technically successful but does not seem to prevent cardiac graft loss.<sup>330</sup> Thus, coronary revascularization could provide short-term benefit, but patients with moderate to severe CAV should be considered for retransplantation.

## OTHER HIGH-RISK EXPOSURES

Other conditions are likely to be associated with more than average cardiovascular risk but are beyond the scope of this statement. These include secondhand

smoke exposure, e-cigarettes, drug addiction, psychiatric disorders (as primary drivers of risk and as related to their pharmacotherapies), social determinants of health, perinatal exposures, polycystic ovary syndrome, obstructive sleep apnea, and childhood stroke. Many are the subject of dedicated scientific statements from the AHA and other organizations. A prudent approach to children with these exposures and conditions is to try to maximize overall cardiovascular health via therapeutic lifestyle change approaches to minimize the burden of acquired atherosclerosis while treating the primary condition as much as possible. Thus, all children and adolescents should be encouraged to maintain good cardiovascular health lifelong.

## LITERATURE GAPS AND CHALLENGES FOR PRACTITIONERS

### Summary

In contrast to the healthy pediatric population, children with specific underlying conditions (either severe expressions of usual CVD risk factors or underlying cardiovascular abnormalities that make a child more vulnerable to adverse effects of CVD risk factors) are at risk for accelerated atherosclerosis that leads to early CVD. In this statement, we have reviewed what is known about CVD and the atherosclerotic process for specific diagnoses associated with CVD and described current approaches to cardiovascular risk identification and treatment. We also provide considerations for management in the Figure (overall approach) and in Table 2 (evaluation and treatment by risk factor) based on the risk categories described in Table 1, incorporating previously published guidance and data (Table 4) as presented in this statement. In general, we have strived to keep treatment cut points aligned with published guidelines, updating them based on what is known about cardiovascular risk. We have suggested an accelerated pace for initiating a diagnostic workup and pharmacotherapy for the higher-risk categories. Our intent was not to present formal guidelines; this statement is provided as a resource for clinicians to consider as they care for their patients. A modified nominal group process was used to risk-stratify the diagnoses and to develop considerations to assist clinicians in risk identification and intervention. Further research is needed to explore the pathophysiology of atherosclerosis unique to each specific diagnosis, to develop improved methods for assessment of preclinical disease, and to critically

evaluate therapeutic interventions. Because the time course to clinical disease with some of these diagnoses is short, they offer a unique opportunity in pediatric cardiovascular research to perform randomized trials of the safety and efficacy of interventions. The considerations presented here are directed toward the primary care providers and pediatric subspecialists who care for these patients in childhood, as well as to internists, family practitioners, and adult subspecialists who will assume their care as they reach adult life (additional resources for practitioners can be found in Table 5). When published data did not permit evidence-based practice, we suggested practical interim guidance (Figure, Table 2). We provide considerations for management; decisions on the management of individual patients must be tailored to their unique circumstances. As new information develops, this statement will necessarily be modified to effectively provide guidance on CVD risk reduction in these high-risk pediatric settings; we have provided topics for future research to address gaps in the literature in Table 6.

### ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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**Disclosures****Writing Group Disclosures**

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\*Modest.

†Significant.

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