

## 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**

*Endorsed by the American Academy of Pediatrics*

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**Abstract**—Although for most children the process of atherosclerosis is subclinical, dramatically accelerated atherosclerosis occurs in some pediatric disease states, with clinical coronary events occurring in childhood and very early adult life. As with most scientific statements about children and the future risk for cardiovascular disease, there are no randomized trials documenting the effects of risk reduction on hard clinical outcomes. A growing body of literature, however, identifies the importance of premature cardiovascular disease in the course of certain pediatric diagnoses and addresses the response to risk factor reduction. For this scientific statement, a panel of experts reviewed what is known about very premature cardiovascular disease in 8 high-risk pediatric diagnoses and, from the science base, developed practical recommendations for management of cardiovascular risk. (*Circulation*. 2006;114:2710-2738.)

**Key Words:** AHA Scientific Statements ■ atherosclerosis ■ cardiovascular diseases ■ risk factors  
■ prevention ■ pediatrics

The atherosclerotic process begins in childhood, with progression clearly shown to be mediated by the presence of identified risk factors. Pathological studies in children and young adults demonstrate that the extent of atherosclerotic vascular change is associated with both the number of premortem risk factors and their intensity.<sup>1-6</sup> In vivo noninvasive studies relate each of the known risk factors measured in childhood to abnormalities of vascular structure and function.<sup>7-19</sup> Finally, a decrease in number or intensity of risk factors is associated with improvement in the vascular abnormalities.<sup>20-24</sup>

For most children, the degree of vascular involvement is minor, the rate of progression is slow, and the appropriate therapeutic approach is preventive, with an emphasis on healthy lifestyles and behavior modification.<sup>25,26</sup> By contrast, certain pediatric disease states are associated with dramatically accelerated atherosclerosis, with clinical coronary events occurring in childhood or very early in adult life. A classic example is homozygous hypercholesterolemia, in which markedly elevated low-density lipoprotein (LDL) cholesterol levels are associated with coronary disease in the first decade of life.<sup>27</sup> Another is Kawasaki disease, in which

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coronary pathology developed as part of the acute disease process predisposes patients to very early coronary events.<sup>28</sup> For children with diagnoses like these, intensive cardiovascular risk reduction is of critical importance. However, awareness of the risk for premature atherosclerosis is often limited when the main focus of medical care is the complex primary diagnosis. The goal of this statement is to summarize the evidence for accelerated atherosclerosis in high-risk pediatric settings and to present guidelines for cardiovascular risk management. The recommendations are directed toward both the pediatric care providers and the subspecialists who manage the primary disease process in these complex young patients.

The statement was developed by a writing group convened under the joint direction of the American Heart Association’s Expert Panel on Population and Prevention Science and the Council for Cardiovascular Disease in the Young, cosponsored by the Councils on Epidemiology and Prevention, Nutrition, Physical Activity, and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Cardiovascular Disease and by the Quality of Care and Outcomes Research Working Group. Members were nominated by ≥1 of these scientific councils and are each recognized experts in premature atherosclerosis beginning in childhood. The group selected 8 pediatric disease settings for inclusion: (1) familial hypercholesterolemia; (2) diabetes mellitus, type 1 and type 2; (3) chronic kidney disease; (4) heart transplantation; (5) Kawasaki disease; (6) congenital heart disease; (7) chronic inflammatory disease; and (8) childhood cancer. For each, the evidence for early coronary disease was reviewed by an expert in the area. On the basis of the risk of manifest coronary disease in childhood and very early adult life, a stratification protocol was established, and each disease was classified as follows (Table 1):

- Tier I: Pathological and/or clinical evidence for manifest coronary disease before 30 years of age
- Tier II: Pathophysiological evidence for arterial dysfunction indicative of accelerated atherosclerosis before 30 years of age
- Tier III: Increased cardiovascular risk factors with epidemiological evidence for manifest coronary disease with or without arterial dysfunction early in adult life but after 30 years of age

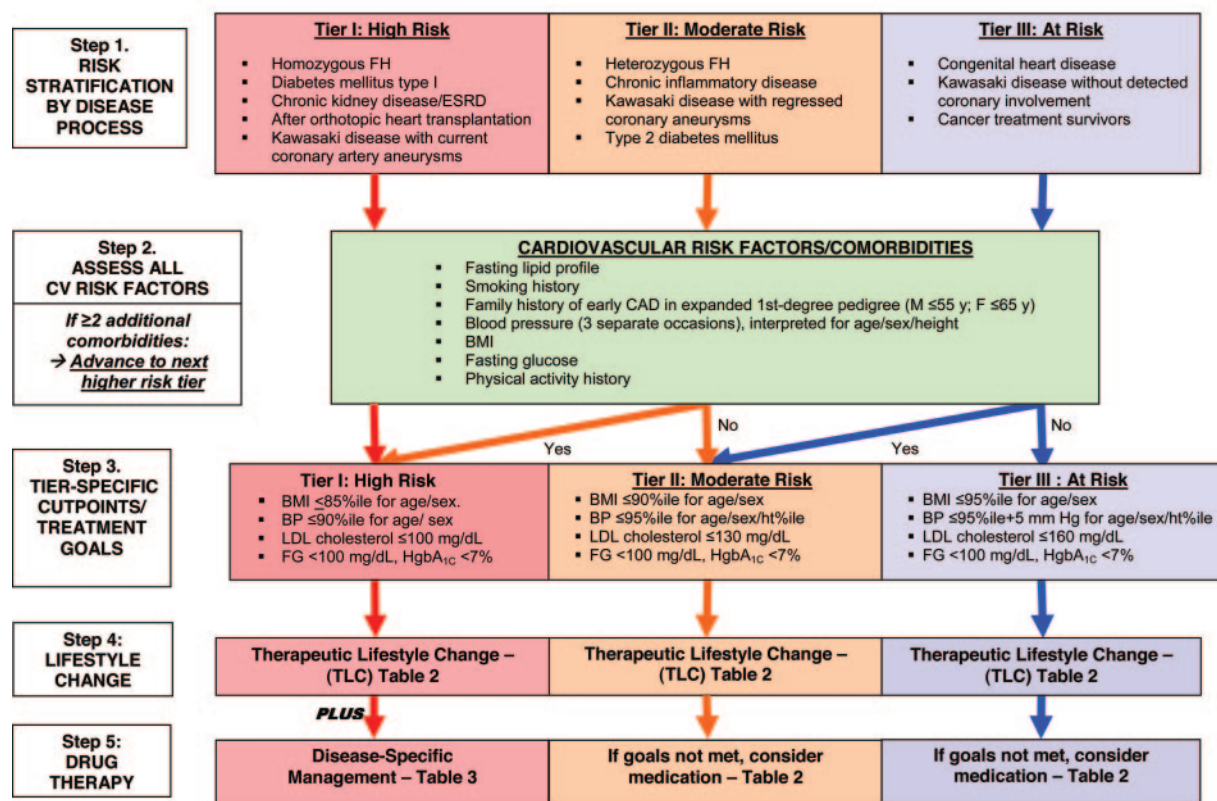
Recommendations for cardiovascular risk identification and reduction specific to each disease setting were developed as a consensus of the group, and an algorithm was developed outlining the risk factor evaluation and management strategy by disease tier (Figure). As in current risk-reduction recommendations for adults and for children with type 1 diabetes, critical levels for intervention and goals for risk reduction have been tailored to the risk intensity (Table 2).<sup>29,30</sup> For children with diagnoses in tier I, complete risk factor assessment is recommended, and therapy is instituted essentially at the time of diagnosis, aimed at maximally decreasing risk factor levels; the intervention strategy for tier I patients regards the diagnosis as a “coronary heart disease equivalent,” with recommendations similar to the secondary prevention guidelines for adults with established coronary disease (Table 3). For children in tier II, complete assessment of all risk factors is recommended, with defined therapeutic goals. For children in tier III, complete risk factor assessment is recommended, with therapeutic goals as recommended for children in general.

In this era of evidence-based medicine, most scientific statements require positive results from multiple randomized trials to recommend any intervention. To date, no randomized trials beginning in childhood have demonstrated an improvement in hard clinical cardiac end points in response to risk factor reduction; given the major cost and time limitations, the potential for such trials in the near future seems low. There is, however, a large and growing knowledge base in pediatric populations with regard to the presence of accelerated atherosclerosis, the relationship of the atherosclerotic process to the presence and intensity of risk factors, and the response to risk factor change at the vascular level. The present scientific statement is not intended to preclude or inhibit the design and execution of future randomized treatment trials. Rather, we hope to assist physicians in learning what is already known about increased risk for premature atherosclerosis in children with these diagnoses, as well as the range of approaches to risk assessment and treatment. Until evidence-based data are available, the present statement provides practical interim recommendations based on a consensus of the group after a careful review of the available science for each diagnosis, including all published guidelines. Typical statements about level of evidence and the strength of

**TABLE 1. Disease Stratification by Risk**

	Risk Category	Rationale	Disease Process/Condition
Tier I	High risk	Manifest CAD <30 years of age: Clinical evidence	Homozygous familial hypercholesterolemia (FH) Diabetes mellitus, type 1 Chronic kidney disease (CKD)/end-stage renal disease (ESRD) Post-orthostatic heart transplantation (OHT) Kawasaki disease with current coronary aneurysms
Tier II	Moderate risk	Accelerated atherosclerosis: Pathophysiological evidence	Heterozygous FH Kawasaki disease with regressed coronary aneurysms Diabetes mellitus, type 2 Chronic inflammatory disease
Tier III	At risk	High-risk setting for accelerated atherosclerosis: Epidemiological evidence	Post-cancer-treatment survivors Congenital heart disease Kawasaki disease without detected coronary involvement

## HIGH-RISK PEDIATRIC POPULATIONS: RISK STRATIFICATION AND TREATMENT



**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  $\geq 2$  comorbidities, assign patient to the next higher risk tier for subsequent management. *Step 3:* Tier-specific treatment goals/intervention cut points defined. *Step 4:* Initial therapy: For tier I, initial management is therapeutic lifestyle change (Table 2) PLUS disease-specific management (Table 3). For tiers II and III, initial management is therapeutic lifestyle change (Table 2). *Step 5:* For tiers II and III, if goals are not met, consider medication as outlined in Table 2.

CV indicates cardiovascular; BP, blood pressure; %ile, percentile; FG, fasting glucose; HgbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; ht%ile, height percentile; pt, patient; and TLC, therapeutic lifestyle change.

each recommendation are not included. For easy access, references for each section of the report are grouped together.

## Familial Hypercholesterolemia

### Introduction

Aggressive management of hyperlipidemia in adults, particularly directed toward lowering LDL cholesterol levels, has led to major reductions in cardiovascular morbidity and mortality. In children and adolescents, hyperlipidemia may be secondary to associated conditions such as medications or obesity, but extreme LDL elevations are more commonly associated with primary or genetic hyperlipidemias.<sup>47</sup> Both types of lipid abnormalities have been shown to be associated with vascular pathology in youth: a greater extent of vascular involvement, with fatty streaks and fibrous plaques at autopsy; higher presence of coronary artery calcium by electron-beam computed tomography; and increased carotid intima-media thickness, reduced arterial distensibility and compliance, and endothelial dysfunction by ultrasound.<sup>7,48,49</sup> Increasing evidence indicates that appropriate therapy can reverse these changes.<sup>20,21</sup> Of the primary hyperlipidemias, familial hypercholesterolemia (FH) is the most common and

the most clearly documented to have important cardiovascular consequences beginning in childhood.<sup>49–52</sup> Therefore, the identification and management of FH in children is of great consequence.<sup>53</sup>

### Pathophysiology

FH is an autosomal dominant monogenetic condition. Homozygous hypercholesterolemia is rare, with an occurrence of 1:1 000 000 individuals, but the heterozygous state exists in the general population with an incidence of 1:500. It is the most common monogenetic disorder in North America and Europe. Certain populations have a higher frequency and greater concentrations of specific mutations.

The genetic defect is characterized by various mutations that affect the production and processing of cell-surface LDL receptors.<sup>54–56</sup> Defectiveness or deficiency of these receptors results in impaired hepatic clearance of circulating LDL particles, which leads to their accumulation in the bloodstream. A similar phenotype can be produced by mutations in the receptor that recognizes apolipoprotein B100 protein on the surface of LDL particles, known as familial defective apolipoprotein B100.<sup>57,58</sup>

The elevated levels of LDL contribute to accelerated atherosclerosis, with manifest cardiovascular disease within the first 2 decades of life for homozygotes<sup>59</sup> and beginning in early to mid-adulthood for heterozygotes.<sup>60</sup> Elevated LDL levels are evident before birth<sup>61</sup> and persist throughout the lifespan.

Homozygous FH can be distinguished from heterozygous FH clinically by the much more extreme elevations in LDL and can be confirmed by either genetic characterization of the LDL receptor mutations (from leukocytes) or by quantification of LDL receptor activity (from skin fibroblasts). Children with homozygous FH have more severe and earlier functional and structural vascular abnormalities, including clinical coronary artery disease (CAD), aortic valve disease, and aortic disease, beginning in the first decade of life.<sup>59</sup>

Children with heterozygous FH have been shown to have abnormalities on noninvasive vascular assessments, including greater carotid-intima media thickness and abnormal arterial endothelial function.<sup>11,13,49,62–64</sup> Effective lipid-lowering therapy has been shown to improve these abnormalities.<sup>20,21</sup>

### Identification

Children with homozygous FH usually present within the first decade of life, most commonly after investigation of physical findings related to cholesterol deposition, such as tendon xanthomata, cutaneous xanthelasma, or corneal arcus, or with clinical manifestations of atherosclerotic cardiovascular disease.<sup>59</sup> Children and adolescents with heterozygous FH are asymptomatic, with no findings on physical examination related to their hypercholesterolemia.<sup>65</sup> Often, they present with either elevated LDL levels noted on blood screening or after investigation prompted by a family history of premature cardiovascular disease or hyperlipidemia.

The lipid profile abnormalities are strikingly abnormal in homozygous patients. Although LDL levels vary between individuals, they are often in the 15- to 25-mmol/L (500- to 1000-mg/dL) range, with high-density lipoprotein (HDL) levels reduced between 0.5 and 1.0 mmol/L (20 to 40 mg/dL). Both parents will have lipoprotein profiles consistent with heterozygous FH. Although not necessary for clinical management, determination of an LDL receptor mutation on skin biopsy or leukocyte culture confirms the diagnosis.

In heterozygous FH, fasting lipoprotein profile characteristics include LDL levels well above the 95th percentile for age and gender, often associated with low HDL and normal triglyceride levels. Additional criteria include the presence of a parent with a similar profile in a family with a history of premature cardiovascular disease in conjunction with tendon xanthomata.<sup>66</sup> Determination of an LDL receptor mutation is not routinely performed.

A Dutch study of 1034 children with heterozygous FH showed that an LDL level >3.5 mmol/L (135 mg/dL) had a 98% posttest probability of the presence of an LDL receptor mutation.<sup>65</sup> Mean LDL levels were 5.8 mmol/L (225 mg/dL) for girls and 5.42 mmol/L (210 mg/dL) for boys. A positive family history of premature cardiovascular disease in a first-degree relative was present for 31% of children. Children of a parent with FH and premature cardiovascular disease had higher LDL, lower HDL, and higher lipopro-

tein(a) levels. Children with lower HDL levels were heavier and had higher triglyceride levels. LDL levels appeared to be independent of lifestyle or anthropometric characteristics.

### Risk Factors/Comorbidities

A study of 2400 heterozygous FH Dutch adults showed that during 112 943 person-years of follow-up, 33% had at least 1 atherosclerotic cardiovascular event, predominantly clinical CAD.<sup>66</sup> Male gender, smoking, hypertension, diabetes mellitus, low HDL, and elevated lipoprotein(a) levels were shown to independently contribute to the development of cardiovascular disease.

### Treatment Recommendations for Children With FH

#### *Children With Homozygous FH Who Are at High Risk for Very Early Cardiovascular Disease (Tier I)*

- Complete cardiovascular assessment is necessary at diagnosis, because important subclinical cardiovascular disease requiring intervention may already be present.<sup>59</sup>
- Treatment should be instituted as soon as possible.<sup>41,67,68</sup> The cornerstone of therapy in the majority of patients is weekly or biweekly plasmapheresis, preferably LDL apheresis.<sup>67,69</sup> Although the majority of lipid-lowering drugs lower LDL primarily by feedback mechanisms that upregulate LDL receptor activity, patients with homozygous FH may still benefit.<sup>68,70</sup> Use of high-dose statins is therefore recommended, in combination with a cholesterol absorption inhibitor.
- Low-dose anticoagulation may also be indicated. Ongoing surveillance for cardiovascular disease is essential.
- The presence of homozygous FH mandates intensive therapy aimed at reducing LDL levels. Interventions to prevent or reduce associated risk factors are important, but the critical therapy is lipid lowering.

#### *Children With Heterozygous FH Who Are at Moderate Risk for Premature Cardiovascular Disease (Tier II)*

- Routine cardiovascular assessment is not generally indicated, although referral to a lipid specialist is recommended.
- The presence of heterozygous FH merits therapy focused primarily at reducing LDL levels.<sup>71,72</sup> Lifestyle interventions are important to prevent or reduce associated risk factors but are insufficient for lipid lowering.<sup>73–76</sup>
- There is uniform consensus that lipid-lowering drug therapy is the cornerstone of management in adults, but considerable controversy exists over when to initiate pharmacological treatment in children.<sup>77</sup> Randomized clinical trial results indicating a decline in future atherosclerotic disease in response to lipid-lowering therapy begun in childhood are not available. However, extrapolation from adult studies suggests that lipid-lowering therapy should be considered when LDL cholesterol levels are severely elevated. The only existing guideline, from 1991, recommends consideration of drug therapy after 10 years of age in children with specific LDL cutpoints.<sup>36</sup> We are in general agreement with this recommendation, but we also recommend tailoring therapy to each child, considering actual LDL levels, sex, presence of other risk

factors, and important family history of premature disease. The wishes of the family with regard to drug therapy also need to be taken into account. Thus, there is room for discretion and clinical judgment.

- When the decision is made to begin drug treatment, initial therapy with a statin is recommended, because bile-acid binding resins<sup>78–81</sup> and cholesterol absorption inhibitors (not yet studied in children) are usually inadequate alone to achieve sufficient LDL reduction.<sup>52,82</sup> Several recent studies of statins in children have shown similar safety and efficacy as in adults.<sup>21,83–87</sup>
- Statin therapy is recommended at age  $\geq 10$  years in males and after the onset of menses in females.<sup>77</sup> In selected patients with extremely high LDL levels, associated lipid abnormalities or other risk factors, or the presence of a particularly worrisome family history, statin therapy may be initiated at a younger age. Appropriate safety monitoring and surveillance of growth and development is recommended.<sup>77</sup> The use of bile-acid binding resins and the cholesterol absorption inhibitors should be considered important adjunctive therapy in combination with a statin.
- Some evidence suggests that consumption of plant sterol esters may be a useful adjunct to therapy.<sup>88–91</sup> Other therapies, such as antioxidant vitamins<sup>92,93</sup> and docosahexanoic acid,<sup>94</sup> are more controversial, and some other complementary therapies have been shown to have no therapeutic effect.<sup>95</sup>
- Identification and treatment of comorbidities have been shown to be effective. Specific management is outlined in the algorithm shown in the Figure and in Tables 2 and 3.

## Diabetes Mellitus

### Introduction

Diabetes mellitus, a metabolic disease characterized by hyperglycemia that results from defects in insulin secretion (type 1) and insulin action (type 2), is associated with accelerated development of vascular disease. Diabetic vascular disease in children and adolescents with type 1 diabetes mellitus is represented mainly by microangiopathy that involves the eye and kidney. In adults with diabetes, microangiopathy persists and is responsible for the high incidence of renal failure; however, a major cause of morbidity and early mortality is macroangiopathy, characterized by clinical cardiovascular, cerebrovascular, and peripheral vascular disease.<sup>96–98</sup>

Because insulin is the only significant hypoglycemic hormone, hyperglycemia is the result of impaired secretion of insulin; resistance to the effect of insulin in liver, muscle, and fat cells; or a combination of these pathophysiological situations. Insulin resistance is very frequently seen in association with obesity, particularly abdominal obesity.

The most recent criteria for diagnosis of diabetes recommended by the American Diabetes Association are as follows<sup>99</sup>:

1. Symptoms of diabetes (polyuria, polydipsia, or unexplained weight loss) plus casual plasma glucose concentration  $\geq 200$  mg/dL (11.1 mmol/L). (“Casual” means any time of day, without regard to time since last meal.) *OR*

2. Fasting plasma glucose concentration  $\geq 126$  mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. *OR*
3. Two-hour plasma glucose concentration  $\geq 200$  mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization with a glucose load that contains the equivalent of 75 g of anhydrous glucose dissolved in water.
4. Current American Diabetes Association guidelines recommend 100 mg/dL as the upper limit of normal for fasting glucose in adults.
5. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. An oral glucose tolerance test is not recommended for routine clinical testing.

The progression from insulin resistance and impaired carbohydrate metabolism to type 2 diabetes mellitus has been documented in adults<sup>100,101</sup> and children.<sup>102,103</sup> In adults, weight loss has been shown to reverse this, with frank diabetes regressing to insulin resistance.<sup>104</sup> Patients with impaired fasting glucose and/or impaired glucose tolerance are referred to as “prediabetic,” which acknowledges the relatively high risk for development of frank diabetes.<sup>105</sup> With the current obesity epidemic and its metabolic consequences, the identification of children with early prediabetes is very important, because appropriate management may decrease the progression to overt diabetes. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defines impaired fasting glucose as  $>100$  mg/dL (5.6 mmol/L) but  $<126$  mg/dL (7.0 mmol/L) and impaired glucose tolerance as 2-hour oral glucose tolerance test values  $>140$  mg/dL (7.8 mmol/L).<sup>99,106</sup> Specific guidelines have been defined for screening for type 2 diabetes mellitus in obese children, particularly those from high-risk racial/ethnic groups (Native American, Hispanic-American, black, Asian, and Pacific Islander), those with a positive family history of type 2 diabetes mellitus, and those with physical signs of insulin resistance.<sup>37</sup>

### Epidemiology: Type 1 Diabetes Mellitus

Epidemiological data from the Third National Health and Nutrition Examination Survey (NHANES III) reveal that the prevalence of type 1 diabetes mellitus in adolescents is 1.7/1000. Although limited, data show a significant increase in atherosclerosis in adolescents and young adults with diabetes relative to nondiabetics.<sup>107–109</sup>

Adolescents with type 1 diabetes mellitus have increased levels of subclinical atherosclerosis as measured by carotid intima-media thickness and by radial tonometry.<sup>110–112</sup> In children, type 1 diabetes mellitus is independently associated with oxidative modification of LDL cholesterol.<sup>113</sup>

### Pathogenesis of Premature Atherosclerosis: Type 1 Diabetes Mellitus

Hyperglycemia is the primary mediator of atherosclerosis in type 1 diabetes mellitus; insulin therapy to control this should be under the direction of endocrinology specialists. Hyperglycemia causes raised levels of atherogenic, cholesterol-

enriched, apolipoprotein B-containing remnant particles by reducing the expression of heparin sulfate.<sup>114</sup>

Autopsy studies in young adults with fatal myocardial infarction and type 1 diabetes mellitus showed that the atherosclerotic plaque in these patients was more dense in fibrous tissue than the more calcific plaques of nondiabetic individuals; this may influence the timing and severity of clinical disease in these patients.<sup>115</sup> In addition, microalbuminuria is a predictor of increased risk for vascular complications.<sup>116</sup>

In defining risk for adults, the presence of type 1 diabetes mellitus is considered the equivalent of a history of coronary disease.<sup>98</sup> The intensity of lipid-lowering therapy is correspondingly increased in this setting.

### Epidemiology: Type 2 Diabetes Mellitus

In 2003, the US Centers for Disease Control and Prevention reported that 40% (5.2 million) of all diabetic individuals >35 years of age had been diagnosed with cardiovascular disease. Although it was previously considered a disease of adults, in the past decade, type 2 diabetes mellitus has become a far more common occurrence in the pediatric population. Depending on the ethnic composition of the population, between 8% and 50% of newly diagnosed adolescent diabetic patients have type 2 diabetes mellitus.<sup>117,118</sup> Data from NHANES III reveal that the prevalence of type 2 diabetes mellitus in adolescents is 4.1/1000. These increases coincide with increasing rates of overweight and physical inactivity in children.<sup>119</sup>

Because type 2 diabetes mellitus is a relatively recent problem in adolescents, few long-term follow-up data exist. One study of Pima Indians followed a cohort of 36 individuals for a mean of 10 years to a median age of 26 years. At baseline (age 5 to 19 years), 85% were obese, and 14% had hypertension, whereas 30% had total cholesterol >200 mg/dL, and 55% had triglyceride concentrations >200 mg/dL. Fifty-eight percent of the patients had microalbuminuria, and 16% had a urinary albumin/creatinine ratio >300 mg/g, which indicates that the renal effects of diabetes were already present at diagnosis. After 10 years of follow-up, the number of patients with increased urinary albumin excretion was increased significantly, as was the magnitude of albuminuria, which is evidence of increased cardiovascular risk over that relatively short period of time.<sup>120</sup>

In adults, the metabolic syndrome is now an extremely common diagnosis. This cluster of findings (abdominal obesity, insulin resistance, dyslipidemia, and hypertension) frequently appears together and has been shown to predict future overt diabetes and early cardiovascular disease.<sup>121</sup> There is no current definition for metabolic syndrome in children, but the components of this diagnosis are known to cluster together as they do in adults.<sup>122</sup> Presence of the components of the metabolic syndrome in adolescence has been shown to predict early cardiovascular disease.<sup>123</sup> Although no current guidelines address management of the metabolic syndrome in children, it is important to identify and address the individual elements of the syndrome whenever a child presents with obesity.

### Pathogenesis of Premature Atherosclerosis: Type 2 Diabetes Mellitus

Both hyperglycemia and insulin resistance are implicated in endothelial dysfunction, to a greater degree in type 2 diabetes mellitus than in type 1.<sup>124</sup> Microalbuminuria is a predictor of increased risk for vascular complications.<sup>116</sup>

Insulin resistance has been implicated in the development of dyslipidemia by enhancing hepatic synthesis of very-low-density lipoprotein (VLDL), which results in increased plasma triglyceride and LDL cholesterol levels.<sup>125</sup> Resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated triglyceride and LDL cholesterol levels.<sup>126,127</sup> Insulin resistance may also be responsible for the reduced levels of HDL cholesterol observed in type 2 diabetes mellitus, and this is accounted for by an increase in the rate of apolipoprotein A1/HDL cholesterol degradation, which exceeds the rate of its synthesis.<sup>128</sup> The increase of triglyceride-rich lipoproteins due to both exaggerated postprandial lipemia and VLDL overproduction in the face of low lipoprotein lipase activity results in long residence time of these particles in circulation and the formation of small, dense LDL.

Insulin resistance is also associated with hypertension through urinary sodium retention, increased sympathetic nervous system activity,<sup>129</sup> and stimulation of vascular smooth muscle growth.<sup>130</sup> Insulin levels have been found to be significantly higher in adult patients with essential hypertension<sup>131–133</sup> and borderline hypertension<sup>134</sup> than in normotensive control patients. In addition hyperinsulinemia is known to directly stimulate the formation of the atherogenic plaque by promoting smooth muscle proliferation, connective tissue formation, and LDL deposition in the plaque.

Other intrinsic metabolic factors such as apolipoproteins, lipoprotein(a), and homocysteine are known to influence the development of cardiovascular disease; their potential relationship to insulin resistance remains to be clarified. Free fatty acids may also stimulate, either independently or in concert with hyperglycemia, the production of reactive oxygen species (oxidative stress),<sup>135</sup> which has been associated with target-organ damage such as that related to diabetes and atherosclerotic cardiovascular disease.<sup>136</sup> Finally, oxidative stress is associated with an increase in insulin resistance.<sup>137</sup>

### Risk Factors/Comorbidities

Patients with type 2 diabetes mellitus often have other risk factors for cardiovascular disease. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time. At some point, a loss of control of blood glucose begins to emerge, resulting in dietary glucose intolerance and ultimately in type 2 diabetes mellitus. Obese individuals develop different degrees of insulin resistance, and not all those with obesity develop glucose intolerance. Obesity-associated insulin resistance varies significantly with genetic background. Black children are more insulin resistant than age-, sex-, and body mass index (BMI)-matched white children.<sup>138</sup> The factors that make some individuals more likely to progress to type 2 diabetes mellitus are not well understood at the present time.<sup>139</sup> A strong family predisposition is known to exist, and parental history is therefore

important in risk assessment. In the future, genetic markers may help identify those offspring of diabetic parents who are at greatest risk of developing diabetes. Children with type 2 diabetes mellitus are usually diagnosed after 10 years of age and are almost always obese. The mean BMI in clinical series has ranged from 26 to 38 kg/m<sup>2</sup>.<sup>117,118</sup> Current American Diabetes Association guidelines recommend routine glucose testing in obese children >10 years of age with 2 additional risk factors for type 2 diabetes mellitus.<sup>37</sup>

The prevalence of hypertriglyceridemia has ranged from 4% to 32%.<sup>113,114</sup> Weight control improves glucose tolerance, with a recommended weight loss in adults of 10% to 15%.

The prevalence of hypertension has ranged from 17% to 32%. Essential hypertension is known to be associated with diabetes in adults,<sup>139</sup> and it is estimated that the cardiovascular risk doubles when hypertension and diabetes coexist. Prevalence data are not available for hypertension in children with diabetes.

Exercise training improves insulin sensitivity and endothelial vascular function beyond the benefits of glycemic control and blood pressure reduction in children and adults.<sup>140,141</sup> Agents such as metformin and thiazolidinediones have been used effectively in adolescents with type 2 diabetes mellitus and have been shown to decrease BMI and improve glucose tolerance.<sup>142,143</sup>

### Recommendations in Children With Diabetes Mellitus

#### *Children With Type 1 Diabetes Mellitus Who Are at High Risk for Early Cardiovascular Disease (Tier I)*

Optimal management of hyperglycemia will modify this risk, but aggressive management of related risk factors has been shown to improve outcome and is recommended. Specific management recommendations are presented in the algorithm (Figure) and accompanying tables.

#### *Children With Type 2 Diabetes Mellitus Who Are at Moderate Risk for Cardiovascular Disease (Tier II)*

The differences between type 1 and type 2 diabetes mellitus are significant: Age at presentation for type 1 diabetes mellitus is younger, with 25% of patients diagnosed between 5 and 10 years of age and another 40% between 10 and 15 years of age; typically, the degree of hyperglycemia in type 1 diabetes mellitus is severe, and patients are very symptomatic. By contrast, type 2 diabetes mellitus diagnosed in childhood usually presents asymptotically, with mild to moderate hyperglycemia in adolescence in combination with obesity, signs of insulin resistance, and other components of the metabolic syndrome. When type 2 diabetes mellitus begins in childhood, the risk for accelerated atherosclerosis is increased beyond that seen in those who develop this diagnosis as adults, but less than when type 1 diabetes mellitus is diagnosed in a child. Specific recommendations for management are contained in the algorithm (Figure) and accompanying tables; using the treatment algorithm, patients with type 2 diabetes mellitus are defined as being at moderate risk but will almost always be managed as "high risk" because of associated comorbidities.

## Pediatric Chronic Kidney Disease

### Introduction

Success with renal replacement therapy has lengthened the life expectancy of children with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Now, morbidity and mortality in children with CKD/ESRD are not only related to chronic renal failure and renal replacement therapy but also to cardiovascular disease as a result of prolonged exposure to cardiovascular risk factors.

### Epidemiology

Cardiovascular disease now accounts for the majority of deaths in adults with ESRD and approximately one fourth of pediatric ESRD deaths.<sup>144–146</sup> The cardiac abnormalities associated with ESRD include pericardial disease, arrhythmias, abnormalities of left ventricular function, and CAD.<sup>144,145</sup> Twenty percent of hospitalizations in pediatric ESRD patients enrolled in Medicare are reported to be due to arrhythmias, 10% to cardiomyopathy, and 3% to a cardiac arrest.<sup>147</sup> The incidence of cardiomyopathy reported among pediatric ESRD patients doubled over the 6-year period from 1991 to 1996.<sup>147</sup>

### Pathogenesis

The mechanisms that lead to cardiovascular disease in CKD primarily originate with vascular or myocardial injury from a multitude of highly prevalent cardiovascular risk factors in renal failure, and perhaps uremia itself. Damage to the vascular endothelium and left ventricle manifests as accelerated CAD and cardiomyopathy and has been described extensively in adults undergoing dialysis or after kidney transplantation. In children with CKD, subclinical manifestations of vascular disease have been reported.

Subclinical evidence of atherosclerosis with intimal plaque has been reported in pediatric ESRD. In a series of children with iliac artery biopsy at the time of transplantation, atherosclerosis in the uropathy group was also associated with increased serum calcium and longer duration of dialysis.<sup>148</sup>

Medial vessel calcification and arteriosclerosis or Mönckeborg's arteriosclerosis has also been reported in the pediatric ESRD population, with vascular calcification in the coronary arteries, aorta, peripheral vessels, and aortic valve. An autopsy series of subjects with CKD revealed soft tissue calcification in 60% of the pediatric patients, half of whom were undergoing dialysis at the time of death.<sup>149</sup> In a small autopsy series, 4 of 8 had evidence of arteriosclerosis, diffuse vascular calcification, and calcified valves.<sup>150</sup>

There is evidence of significant left ventricular hypertrophy in children with CKD and ESRD.<sup>151</sup> Depending on the setting and the classification system used, hypertrophy is reported in 40% to 75% of the pediatric ESRD population.<sup>152–156</sup> At initiation of dialysis, 69% of subjects 4 to 18 years of age had evidence of left ventricular hypertrophy.<sup>152</sup> Postmortem studies have shown >50% of children with ESRD have evidence of left ventricular hypertrophy.<sup>150</sup>

Decreased arterial wall compliance is also common among dialysis patients, coincident with worsening left ventricular hypertrophy.<sup>157</sup> Stiffness of the aorta has been shown to be higher in children undergoing dialysis than in healthy control subjects.<sup>157</sup> Carotid artery compliance has been shown to be

significantly lower in children undergoing dialysis, with the decrease correlating significantly with age and blood pressure.<sup>157</sup>

### Risk Factors/Comorbidities

Most risk factors for the development of cardiovascular disease are highly prevalent in CKD. Hypertension is seen in 49% of children with CKD<sup>158</sup> and 50% to 60% of patients undergoing dialysis.<sup>159</sup> Hypertension is even more common in the transplant population, with 65% to 80% of patients being treated.<sup>159</sup> In the young adult population, 18 to 35 years of age, systolic hypertension occurs in 51% and diastolic hypertension in 35% of the dialysis population.<sup>160</sup>

Approximately 29% to 87% of pediatric peritoneal dialysis patients have elevated cholesterol levels, with LDL >100 mg/dL (>2.29 mmol/L).<sup>44</sup> Similarly, 72% to 84% of pediatric kidney transplant recipients had LDL >100 mg/dL (>2.29 mmol/L).<sup>44</sup> In ESRD, triglycerides are consistently elevated, with average triglyceride levels >150 mg/dL and HDL cholesterol levels reduced. Lipoprotein(a), a lipoprotein associated with a mild increase in cardiovascular risk in the general population, is significantly elevated in ESRD, although the contribution to increased risk is unclear. Lipoprotein(a) is primarily genetically regulated, but increasing levels are also related to worsening renal function.<sup>162,163</sup>

Homocysteine levels also increase with worsening renal function, because metabolism of homocysteine may require intrarenal metabolism.<sup>164</sup> Homocysteine has been shown to be elevated in 65% of children with CKD.<sup>165</sup> Interestingly, the level only increases after 7 years of age and appears to be independent of renal function.<sup>165,166</sup> The higher the homocysteine levels in children with CKD, the lower the vitamin B<sub>12</sub> and folate levels.<sup>165,166</sup>

C-reactive protein levels are elevated 3-fold in pediatric ESRD patients undergoing dialysis and 2-fold in renal transplant recipients compared with healthy control subjects.<sup>167</sup> C-reactive protein is highly correlated with coronary calcium, especially in patients who also have an elevated parathyroid hormone level. An elevated C-reactive protein level may reflect chronic inflammation from many sources, including overt or occult infectious processes, comorbid conditions such as access complications, and factors associated with the dialysis procedure per se, including bioincompatible membrane and possibly dialysate leak in the membrane.<sup>168</sup>

Coronary calcium burden is increased, as measured by coronary computed tomography with either helical or electron-beam computed tomography. In young adults with a history of pediatric ESRD, higher calcium scores are associated with longer dialysis duration and elevated C-reactive protein levels.<sup>167,169</sup> It is not known to what extent this represents a dramatic acceleration of atherosclerosis in ESRD or an increased propensity for calcium to accumulate in the medial wall of the coronary vessel owing to altered calcium phosphorus metabolism in ESRD.

Endothelial dysfunction assessed by brachial artery reactivity in CKD is independent of lipid levels and hypertension but is correlated with left ventricular hypertrophy expressed as left ventricular mass index.<sup>166,170</sup> In 25 children with CKD, a double-blind, placebo-controlled, randomized crossover

trial of folic acid for 8 weeks showed statistically significant improvement in endothelium-dependent dilatation with lowering of homocysteine levels.<sup>171</sup>

### Treatment Recommendations for Children With CKD

#### *Children With CKD Who Are at High Risk for Cardiovascular Disease (Tier I)*

- The origins of cardiovascular morbidity and mortality are in childhood, when the cardiovascular risk milieu is established. Recommendations are directed toward children with CKD stage 5 (estimated glomerular filtration rate <15 mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup>), children undergoing dialysis, and renal transplant recipients.
- The risk of cardiovascular disease can be reduced by modifying traditional cardiovascular risk factors and monitoring for end-organ injury through the use of echocardiography to estimate left ventricular mass<sup>172</sup> and, in young adults, computed tomography studies for coronary calcium. Chronic cardiovascular risk factor reduction, begun early in the course of CKD, should be an essential part of clinical management.
- Specific guidelines for cardiovascular risk factor management in children with advanced CKD or ESRD are available from the National Kidney Foundation–Kidney Dialysis Outcomes and Quality Initiative. The guidelines include recommendations for management of cardiovascular disease in dialysis patients and for treatment of hypertension and dyslipidemias in CKD.<sup>44,172,173</sup>

These recommendations were considered in development of the algorithm shown in the Figure and the treatment guidelines described in Tables 2 and 3.

## Pediatric Heart Transplantation

### Introduction/Epidemiology

Orthotopic heart transplantation (OHT) in children continues to increase in frequency, with ≈400 transplantations performed annually in children in the United States.<sup>174</sup> After heart transplantation, transplant CAD is the most important cause of mortality beyond the first year after surgery in adults.<sup>175</sup> In pediatric survivors of OHT, transplant CAD has been found to be the primary cause of late mortality in 20% to 30% of cases.<sup>176,177</sup> On the basis of combined angiographic and intracoronary ultrasound imaging, 74% of pediatric heart transplant patients have evidence of transplant CAD.<sup>178</sup> In a recent pathology series, 94% of pediatric OHT specimens showed evidence of cardiac allograft vasculopathy.<sup>179</sup>

### Pathology/Natural History

The histopathology of transplant CAD is the same in children as it is in adults and differs markedly from the typical atherosclerotic process. Histologically, monocyte and T-cell accumulation plus concurrent smooth muscle proliferation comprise the intimal hyperplasia of the coronary arteries.<sup>180</sup> Some degree of coronary intimal thickening is seen in virtually every heart transplant recipient beginning in the first year after transplantation.<sup>181</sup>



Angiographically, affected coronary vessels demonstrate diffuse concentric narrowing along their entire length. With intravascular ultrasound, the pathological process is characterized by concentric intimal thickening.<sup>182</sup>

When stenosis is diagnosed in the context of transplant CAD, both surgical and catheter revascularization techniques have been used with initial procedural success rate. However, over a very short period of time, the restenosis rate is high, and the long-term outcome is poor.<sup>183</sup> The only other option is retransplantation, with known limitations on organ procurement and potential development of coronary vasculopathy in the retransplanted heart.<sup>184</sup>

### Pathogenesis

The pathogenesis of transplant CAD is complex and is still not completely understood. The underlying mechanism has been shown to involve multiple factors including those mechanisms discussed below.

### Rejection

Development and progression of transplant CAD have been shown to correlate with evidence of increased rejection.<sup>185</sup> Noncompliance with immune-suppressive regimens correlates significantly with increased transplant CAD in children<sup>186</sup> and adults.<sup>187</sup> Conversely, regression of transplant CAD has been demonstrated with improved immunosuppression in adults.<sup>188</sup>

In children, late rejection is an independent predictor of transplant CAD, and increased immune suppression has been shown to correlate with a decreased incidence of transplant CAD.<sup>189,190</sup> Introduction of novel proliferation signal inhibitors such as sirolimus as part of immunosuppressive therapy has been associated with a decrease in transplant CAD in adults; this type of drug is now being used in children.<sup>191</sup>

### Donor Status

In adults, older donor age, donor atherosclerotic disease, donor hypertension, and male sex of either donor or recipient have been shown to correlate with transplant CAD.<sup>192</sup> Donor hearts from patients who suffered explosive brain death have also been shown to have earlier onset of transplant CAD.<sup>193</sup>

### Cytomegalovirus Infection

In adults and in children, cytomegalovirus infection has been associated with accelerated coronary vasculopathy after OHT.<sup>194,195</sup> Preemptive treatment with ganciclovir and cytomegalovirus hyperimmune globulin has reduced the incidence and delayed the progression of transplant CAD.<sup>196</sup>

### Risk Factors/Comorbidities

#### Hyperlipidemia

After transplantation, the combination of immunosuppressive therapy, obesity, and an underlying genetic predisposition to hyperlipidemia promotes combined hyperlipidemia, with elevated total and LDL cholesterol, high triglycerides, and reduced HDL cholesterol.<sup>197,198</sup> Hyperlipidemia is present in  $\approx 60\%$  of adults and at least 40% of children in the first year after transplantation.<sup>198,199</sup>

Elevated levels of triglycerides have been shown to correlate directly with increased prevalence of transplant CAD in

adults.<sup>200</sup> In adults, a greater increase in LDL cholesterol in the first year after transplantation has been associated with increased severity of transplant vasculopathy.<sup>201</sup> Lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has led to lower total and LDL cholesterol levels and a significantly lower incidence of transplant vasculopathy in both adults and children.<sup>201,202</sup> Benefits have been maximized when lipid therapy has been initiated immediately after transplantation.

#### Obesity

After transplantation, progressive obesity is common in both children and adults, correlating with the intensity and duration of steroid treatment.<sup>203,204</sup> In adults and children, pretransplantation and posttransplantation BMI have been shown to be strong predictors of transplant CAD.<sup>204</sup> The association of obesity and the metabolic syndrome confers additional risk for transplant CAD and for progression of donor atherosclerosis.<sup>205</sup>

#### Hypertension

Cyclosporine therapy, a mainstay of immune suppression after heart transplantation, is associated with hypertension and with renal dysfunction. By 3 years after transplantation, 35% of pediatric heart transplant patients are undergoing chronic antihypertensive therapy; however, in cyclosporine-treated children, 83% of long-term survivors required antihypertensive therapy.<sup>174,176</sup>

Both hypertension and renal failure are predictors of progressive atherosclerotic disease and of transplant CAD.<sup>185</sup> Treatment with angiotensin-converting enzyme inhibitors and calcium channel blockers is associated with a reduction in transplant CAD in adults.<sup>206,207</sup>

Use of the antioxidant L-arginine has been shown to reverse endothelial dysfunction and attenuate hypertension after transplantation.<sup>208</sup> Use of omega-3 fatty acids has also been shown to reduce the rise in blood pressure after heart transplantation.<sup>209</sup> Immune suppression with proliferation signal inhibitors, such as everolimus, has resulted in a decrease in cyclosporine dose and in renal dysfunction in adults.<sup>210</sup>

#### Insulin Resistance/Diabetes Mellitus

Both chronic hyperglycemia as evidenced by elevated hemoglobin A<sub>1c</sub> and overt diabetes are prevalent in adult patients after heart transplantation.<sup>205,211</sup> Approximately 2% of pediatric heart transplant recipients develop diabetes.<sup>212</sup> In adults, higher glucose and insulin levels and elevated levels of hemoglobin A<sub>1c</sub> are associated with increased evidence of transplant CAD.<sup>205,211</sup>

#### Deconditioning

In both children and adults, exercise performance, expressed as measured maximum oxygen uptake, improves from pretransplantation levels but remains significantly reduced compared with normal subjects. This has been attributed in part to chronotropic incompetence caused by cardiac denervation, but deconditioning is also common.<sup>213,214</sup>

In children and adults, exercise training programs result in increased exercise capacity and in decreased resting heart rate and blood pressure, improved endothelial function, and in-

creased lean body mass, all known factors in the pathogenesis of allograft vasculopathy.<sup>215,216</sup> With serial exercise testing, exercise performance deteriorates as transplant CAD develops.

### **Hyperhomocysteinemia**

In adults and children, elevated homocysteine levels are common after OHT.<sup>217,218</sup> In adult subjects with evidence of transplant CAD, homocysteine levels have been shown to be significantly higher than in those without evidence of vasculopathy.<sup>217</sup> Folate supplementation in adults and children after OHT normalized homocysteine levels, with no evidence to date of any impact on development of transplant CAD.<sup>219</sup>

## **Treatment Recommendations After Pediatric Heart Transplantation**

### **After Pediatric Heart Transplantation, Children Are at High Risk for Very Early Cardiovascular Disease (Tier I)**

- Please see the algorithm in the Figure and Tables 2 and 3 for specific treatment guidelines.
- Although the process appears to be primarily mediated by chronic rejection, modification of traditional risk factors, particularly reduction in LDL cholesterol, has significantly affected the disease process in children and adults.
- Risk factor identification and intensive modification are indicated beginning in the early posttransplantation period.<sup>184</sup> Although there are no guidelines for lipid management after heart transplantation in children, usual care in the United States includes initiation of lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A enzyme inhibitors in the early posttransplantation period.<sup>220</sup>
- Optimization of immunosuppression, improved compliance, and preemptive treatment of cytomegalovirus are all critical factors in the pathogenesis of transplant CAD that are being addressed by transplantation cardiologists.
- Specific screening for evidence of transplant CAD is recommended every 6 to 12 months with angiography, with optional intravascular coronary ultrasound.<sup>221</sup> Dobutamine stress echocardiography or stress perfusion imaging may be helpful in risk stratification.<sup>222</sup>
- Patients who develop any evidence of graft dysfunction should be screened specifically for transplant CAD.

### **Kawasaki Disease**

Kawasaki disease is an acute, self-limited vasculitis of unknown origin that occurs predominantly in infants and young children. First described in 1967 in Japan, the disease is now known to occur throughout the world in children of all races.<sup>223</sup> Kawasaki disease is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. The cause of Kawasaki disease remains unknown, and no specific diagnostic test or pathognomonic clinical feature can confirm the diagnosis early in the illness. Kawasaki disease is likely to be caused by an infectious agent(s) that produces clinically apparent disease in genetically predisposed individuals.<sup>224</sup> Coronary artery aneurysms or ectasia develops in approximately 15% to 25% of untreated children with the disease and may lead to myocardial

infarction, sudden death, or ischemic heart disease.<sup>225,226</sup> Kawasaki disease has now surpassed acute rheumatic fever as the leading cause of acquired heart disease in children<sup>227</sup>; >4000 hospitalizations associated with Kawasaki disease occurred in the United States in 2000.<sup>228</sup> Therapy of Kawasaki disease in the acute phase is aimed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis. Long-term management is guided by stratification of patients according to the severity of their CAD and consequent risk of myocardial ischemia. Although coronary artery aneurysms produce the most serious sequelae of Kawasaki disease, vascular inflammation during the acute stage of the illness is diffuse. Children with coronary aneurysms, and even those in whom coronary dilatation was never detected, appear to be at increased risk for future atherosclerotic CAD on the basis of abnormalities in arterial stiffness and endothelial function.

### **Pathology**

Kawasaki disease is a generalized systemic vasculitis that involves blood vessels throughout the body. Aneurysms affect medium-sized extraparenchymal arteries and result from segmental destruction of the vessel wall in sites strikingly similar to those affected by atherosclerosis.<sup>229</sup> Although aneurysms in the coronary arteries are the main cause of morbidity and mortality, they can also occur in other vessels, such as the celiac, mesenteric, femoral, iliac, renal, axillary, and brachial arteries.<sup>229</sup>

Early in the illness, coronary arteries demonstrate marked edema and infiltration of the arterial wall, initially by neutrophils,<sup>230</sup> with a rapid transition to mononuclear cells, primarily CD8+ T cells, monocytes, macrophages, and IgA plasma cells.<sup>231–234</sup> This cellular infiltration is accompanied by destruction of the internal elastic lamina and media, which results in aneurysm formation. Matrix metalloproteinases (MMPs) are likely to effect destruction and remodeling in the arterial wall.<sup>235,236</sup> MMP-2 expression is prominent in the thickened neointima and in endothelial cells of new capillaries in areas of angiogenesis, and MMP-9 is expressed in coronary artery aneurysms, nonaneurysmal coronary arteries, and noncoronary arteries.

Coronary arterial remodeling occurs over months to years, sometimes with progressive stenosis due to intimal proliferation and neoangiogenesis; it differs from that seen in adult atherosclerosis by extensive expression of vascular growth factors, such as tumor necrosis factor- $\beta$ , platelet-derived growth factor- $\alpha$ , basic fibroblast growth factor, and vascular endothelial growth factor, in the microvessels of the intima.<sup>237</sup> These growth factors are prominently expressed at the inlet and outlet of aneurysms, where they are activated by high shear stress.<sup>237</sup>

Few postmortem studies are available in children in whom coronary abnormalities were not detected in the acute phase. Recently, Suzuki and colleagues<sup>238</sup> performed the first immunohistochemical study of the coronary arteries of a child without coronary dilation by echocardiography at any stage of illness and who died of unrelated causes. The coronary artery intima was mildly thickened, and platelet-derived growth factor- $\alpha$ , transforming growth factor- $\beta$ 1, and induc-

ible nitric oxide synthase were expressed in the intimal smooth muscle cells in the child with normal coronary dimensions after Kawasaki disease but not in control subjects.

### Natural History

Cardiovascular complications and long-term sequelae of Kawasaki disease depend on the severity of coronary artery lesions. The risk of coronary aneurysms is highest among children who do not receive timely treatment with high-dose intravenous immunoglobulin ( $\leq 10$  days and ideally 7 days from the onset of fever), who have persistent fever despite treatment with intravenous immunoglobulin, or who have laboratory test results that reflect severe, persistent inflammation. Young ( $< 6$  months) or old ( $> 8$  years) age and male sex are also risk factors.

### Patients With Aneurysms (High Risk)

Among patients with aneurysms, the incidence of coronary stenosis secondary to myointimal proliferation increases linearly with time since illness onset.<sup>225,239,240</sup> The likelihood of progression to coronary artery stenosis is directly related to aneurysm size and is especially high among arterial segments with giant aneurysms ( $\geq 8$  mm in diameter).<sup>240,241</sup> Patients with persistent aneurysms have systemic inflammation years after disease onset, as evidenced by C-reactive protein levels that are significantly higher than those seen in normal age-matched children or among those who had Kawasaki disease without aneurysms or with regressed aneurysms.<sup>242</sup>

### Patients With Regressed Aneurysms (Moderate Risk)

Angiographic regression of aneurysms to normal lumen diameter occurs in  $\approx 50\%$  of vessels by 2 years after illness onset.<sup>225,243</sup> The likelihood of resolution of an aneurysm is inversely related to its size.<sup>243–245</sup> Pathological studies have shown that regression occurs primarily through fibrous intimal thickening.<sup>246–248</sup> Intravascular ultrasound of regressed coronary aneurysms demonstrates either marked symmetrical or asymmetrical myointimal thickening.<sup>249–251</sup> Regressed coronary artery aneurysms are not only histopathologically abnormal but also have reduced vascular reactivity to isosorbide dinitrate and constriction with acetylcholine, which indicates endothelial dysfunction.<sup>252–254</sup>

Intravascular ultrasound has revealed a significant direct correlation between the initial diameters of the coronary arteries and the degree of intimal-medial thickness  $> 10$  years later.<sup>250</sup> Individuals with persistent or regressed aneurysms have greater stiffness of the proximal and peripheral arterial beds, as well as higher arterial wave reflection, than normal control patients.<sup>255</sup> Indeed, aortic pressure waveforms of Kawasaki disease patients with persistent or regressed aneurysms late after illness onset resemble those generally observed in the elderly.<sup>255</sup>

The carotid artery wall in patients with coronary artery lesions 6 to 20 years after illness onset has been found to be less distensible and thicker than that in control patients.<sup>256</sup> These changes of arterial properties in patients with Kawasaki disease are not associated with major alterations of the lipid profile and are postulated to be secondary to the changes in arterial walls that occur after the diffuse vasculitis. Extrapolation from these findings in carotid arteries suggests that

the coronary arteries may be predisposed to accelerated atherosclerosis in patients with Kawasaki disease and coronary artery lesions.

### Patients Without Detectable Coronary Aneurysms (At Risk)

With careful clinical follow-up 10 to 20 years after Kawasaki disease onset, such patients appear to have morbidity and mortality that are similar to those in the normal population.<sup>257</sup> Increased risk for premature atherosclerosis in these children is suggested by research studies that have demonstrated subclinical abnormalities of arterial function and myocardial flow reserve.<sup>258–261</sup>

Kawasaki disease patients with normal coronary arteries have been reported to have higher brachial-radial artery mean pulse-wave velocity than normal children, which suggests increased arterial stiffness.<sup>262,263</sup> Lower myocardial flow reserve and higher total coronary resistance have been found in children without coronary dilation after Kawasaki disease compared with normal controls.<sup>264</sup> Children without detectable coronary abnormalities have been reported to have abnormal endothelium-dependent brachial artery reactivity.<sup>261</sup> Data conflict with regard to impairment of endothelium-dependent relaxation of the epicardial coronary arteries among children in whom coronary artery dilation was never detected.<sup>265,266</sup>

### Presence of Comorbidities

With or without overt coronary artery sequelae, Kawasaki disease produces altered lipid metabolism (in particular, lower HDL cholesterol) that persists beyond clinical resolution of disease.<sup>262,267,268</sup> North American children with Kawasaki disease have been reported to have a more adverse cardiovascular risk profile, with higher blood pressure and greater adiposity, than control children.<sup>269</sup>

### Recommendations for Children After Kawasaki Disease

Kawasaki disease is associated with significant coronary artery pathology and comorbidities that predispose patients to atherosclerosis. Cardiovascular risk assessment and treatment in children with Kawasaki disease are based on the status of the coronary arteries: patients with persistent aneurysms, high risk (tier I); patients with regressed aneurysms, moderate risk (tier II); and patients without detected abnormalities, at risk (tier III). The algorithm and tables contain tier-specific management. In addition, patients should be encouraged to exercise to the greatest extent possible given coronary artery status, in accordance with the 36th Bethesda Conference recommendations.<sup>41</sup> Prospective counseling and annual assessment of risk factors for atherosclerotic CAD are recommended.

## Chronic Inflammatory Disease

### Introduction

In adults with chronic inflammatory disease, increased prevalence of cardiovascular disease is well documented. Specifically, patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis experience cardiovascular events at a

significantly greater incidence than age-matched normal controls.<sup>270,271</sup> In women with SLE 35 to 44 years of age, the incidence of myocardial infarction is 50 times greater than for women without the disease. In adults with rheumatoid arthritis, cardiovascular disease is the leading cause of death, with rates that average 2 to 4 times those of age-matched controls. For both SLE and rheumatoid arthritis, the increased incidence of cardiovascular disease is not explained by traditional risk factors alone.<sup>272,273</sup>

For a substantial number of children with chronic inflammatory disease, the process will persist into adult life. Children constitute 15% to 20% of patients with SLE, and survival into adult life is now the norm.<sup>274</sup> In at least 50% of children with rheumatoid arthritis, active disease persists into adult life.<sup>275</sup> To date, no studies have tracked the development of atherosclerotic disease as children with chronic inflammatory disease age. In a small series, 16% of 31 children with SLE were shown to have abnormalities of coronary perfusion with thallium perfusion scanning.<sup>276</sup> Several studies document evidence of increased markers for subclinical atherosclerosis in young adults with both rheumatoid arthritis and SLE.<sup>277,278</sup> Extrapolating from these, the atherosclerotic process appears to begin at an earlier age and progress at an accelerated pace for those with chronic inflammatory disease that begins in childhood.

### Pathophysiology of Accelerated Atherosclerosis in Adults With Chronic Inflammatory Disease (Rheumatoid Arthritis and SLE)

Major similarities exist between the inflammatory and immune responses in atherosclerosis and in chronic inflammatory disease.<sup>279</sup> Inflammation is part of the pathology of atherosclerotic plaque, and serum markers of inflammation, including C-reactive protein, cytokines, serum amyloid- $\alpha$ , and tumor necrosis factor- $\alpha$ , have been shown to mediate the development of atherosclerosis.<sup>280–283</sup>

At autopsy, coronary stenotic lesions are typical of traditional atherosclerotic plaque, with the addition of a higher population of cellular components. In a very small number of cases, an acute vasculitic process alone has been associated with a coronary thrombotic event.<sup>284</sup>

The degree of inflammation in adult SLE and rheumatoid arthritis patients as measured by laboratory testing correlates with markers of subclinical atherosclerosis, including increased carotid intima-media thickness and impaired arterial dilation assessed by ultrasound, as well as increased coronary calcification by electron-beam computed tomography.<sup>278,285–288</sup> In adults, increased severity of disease and greater cumulative damage assessed by standard scoring systems have been shown to correlate with evidence for atherosclerosis, which suggests that systemic inflammation itself is a major mediator of the development of atherosclerosis in these disease settings.<sup>278,287–289</sup>

Conflicting reports exist with regard to a potential role for antiinflammatory and immunosuppressive treatment. Several studies have shown a negative correlation between the extent of atherosclerosis and the cumulative dose and duration of immunotherapy. This suggests that optimization of immune therapy is a potential approach to reducing

the development of atherosclerosis.<sup>285,290</sup> Conversely, others have reported increased coronary disease in adult patients with more long-term antiinflammatory and immunosuppressive therapy, which implicates either increased severity of the disease process itself or an atherosclerotic response to treatment in the development of CAD.<sup>278,291</sup>

Glucocorticoid, cyclophosphamide, and methotrexate therapy are all associated with metabolic changes that have been shown to increase atherosclerotic risk by augmenting standard risk factors such as obesity, dyslipidemia, insulin resistance, and hypertension, independent of underlying diagnosis.<sup>292</sup> By contrast, methotrexate therapy has been shown to decrease cardiovascular mortality in patients with rheumatoid arthritis.<sup>293</sup>

A prothrombotic state associated with the presence of antiphospholipid antibodies develops in a significant proportion of adult patients with SLE (34% to 44%) compared with only 1% to 5% of the general population. The presence of these antibodies increases the risk of a vascular thrombotic event by a factor of at least 10 times when patients with lupus are compared with those without.<sup>294</sup>

In adult patients with rheumatoid arthritis, several thrombotic markers have also been shown to be elevated.<sup>295</sup> In addition, elevated levels of lipoprotein(a), considered to be a prothrombotic agent, have been demonstrated in patients with both rheumatoid arthritis and SLE.<sup>296,297</sup>

Renal disease is a common complication of SLE, and severe renal involvement with nephrotic-range proteinuria has been suggested to be a major risk factor for early atherosclerosis on the basis of a small series of young adults with juvenile-onset SLE studied by carotid ultrasound. Nephritis is associated with hypertension, and this may be the major mediator of increased carotid intima-media thickness, a subclinical marker of atherosclerosis noted to be abnormal in these patients. Nephritis may simply indicate overall increased severity of disease. Its presence needs to be expressly considered in the evaluation of cardiovascular risk in patients with SLE.<sup>298,299</sup>

### Traditional Risk Factors/Comorbidities

#### Dyslipidemia

Abnormalities of the lipid profile have been identified in children and adults with both SLE and rheumatoid arthritis.<sup>300,301</sup> Typical findings vary with the disease state. During clinical flare-ups, the lipid profile pattern is typical of that seen in diverse inflammatory states, with elevated triglyceride and VLDL levels and reduced HDL cholesterol. After steroid therapy, elevated total and LDL cholesterol levels, with persistent but less impressive elevation in VLDL and triglycerides, have been described.<sup>301,302</sup> In addition, increased LDL susceptibility to oxidation has been reported in patients with chronic inflammatory disease in general and in pediatric patients with SLE in particular.<sup>302,303</sup>

Increased lipoprotein(a) levels are reported in patients with SLE and rheumatoid arthritis.<sup>296,297</sup> Clinical coronary disease and measures of subclinical disease correlate with dyslipidemia in adult patients with SLE and rheumatoid arthritis.<sup>286,304–306</sup> A single study of children with SLE demon-

strated normal endothelial function despite recorded lipid profile abnormalities.<sup>307</sup>

Statin therapy has been shown to have both lipid-lowering and antiinflammatory effects. A randomized, placebo-controlled trial of atorvastatin in adult patients with rheumatoid arthritis showed a reduced disease activity score, decreased levels of inflammation, and decreased levels of total/LDL cholesterol and triglycerides in the statin-treated group after 6 months.<sup>308</sup> A similar trial is ongoing for adult patients with SLE. No trial of lipid-lowering therapy and CAD incidence has been reported.

### **Hypertension**

Hypertension occurs in a significant proportion of patients with SLE. At diagnosis in adults, 18% of patients with SLE have hypertension; by 10 years from diagnosis, this has increased to 59%.<sup>309</sup> In adults with rheumatoid arthritis and SLE, hypertension has been shown to be associated with an increased risk for manifest cardiovascular disease on long-term follow-up.<sup>310,311</sup>

Hypertension is much more prevalent in SLE patients with renal involvement and in children; nephritis is present in as many as 80% of patients. The combination of renal involvement and hypertension predicts an adverse outcome in juvenile onset SLE.<sup>298,312</sup> In addition to hypertension-related renal disease, both steroid and immunosuppressive therapies can be associated with hypertension and on this basis, hypertension occurs with increased incidence in patients with rheumatoid arthritis and is a factor for all children with chronic inflammatory disease. In both SLE and rheumatoid arthritis, hypertension is strongly associated with increased BMI.<sup>313,314</sup>

### **Obesity**

Obesity is a frequent complication of chronic inflammatory disease in adults and children, reflecting the inactivity imposed by the disease process and the effects of steroid treatment. BMI has been shown to be higher in patients with SLE and rheumatoid arthritis who develop coronary disease than in age-matched patients with these diagnoses who do not develop cardiovascular disease.<sup>313,314</sup> The role of obesity is exaggerated by its association with the metabolic syndrome.<sup>305</sup>

### **Homocysteine**

In adults in general, elevated levels of plasma homocysteine have been identified as a potential risk factor for atherosclerosis.<sup>315</sup> In patients with both rheumatoid arthritis and SLE, homocysteine levels have been shown to be increased, particularly in association with methotrexate therapy.<sup>316,317</sup> Oral administration of folic acid reduces homocysteine levels in both groups, but no reduction in atherosclerotic disease has been shown.<sup>316,318</sup>

## **Recommendations for Children With Chronic Inflammatory Disease**

Children with chronic inflammatory disease are at moderate risk for premature cardiovascular disease (tier II) based on the combination of a chronic inflammatory state and the documented presence of multiple traditional risk factors.

- The atherosclerotic process is primarily mediated by chronic inflammation and immune dysregulation, but traditional risk factors are prevalent. Extrapolating from studies of adults with SLE and rheumatoid arthritis and of children in other high-risk settings, reduction in traditional risk factors should ameliorate the atherosclerotic process. A routine rigorous process of risk factor identification and treatment is indicated. Please see the algorithm (Figure) and Table 2 for specific diagnosis and treatment guidelines.
- Per immunology and rheumatology, treatment of the primary disease process with optimization of therapy to suppress the inflammatory response and its contribution to accelerated atherosclerosis is an important focus for disease management.

## **Congenital Heart Disease**

### **Introduction/Epidemiology**

Although the diagnosis of congenital heart disease includes rare and diverse disorders, some specific diagnoses appear to be associated with increased risk for premature atherosclerotic CAD. Children with congenital heart disease represent a growing population: The incidence of congenital heart defects is almost 1 in 100 live births, and of these, ≈23 of 1000 newborns will require invasive treatment or will die as a consequence of their diagnosis by 1 year of age.<sup>319,320</sup> Because of improved interventions, >1 million adults are now living with congenital heart disease.<sup>321</sup> Selected congenital heart defects (or the process of their repair) lead to an increased risk for adult cardiovascular disease compared with the general population. To date, relatively few data exist to provide an understanding of the presence of cardiovascular disease risk factors and the development of atherosclerosis in these patients.

### **Pathophysiology**

Risk of premature atherosclerotic cardiovascular disease in patients with congenital heart defects is based on 2 principal mechanisms: lesions with coronary artery abnormalities and obstructive lesions of the left ventricle and aorta.

### **Lesions With Coronary Artery Abnormalities**

Congenital coronary anomalies (in isolation or in association with other congenital defects) may predispose individuals to coronary events relatively early in life. In addition, surgical repair of congenital heart defects may result in abnormalities of the coronary arteries. The clinical outcome of coronary artery defects depends on the anatomy of the lesion.

Origin of the left main coronary artery from the right sinus of Valsalva, passing between the aorta and pulmonary artery, has been associated with sudden death, particularly during or just after physical activity.<sup>322</sup> In these patients, autopsies may reveal subendocardial scars and occasionally, large myocardial infarction. Importantly, atherosclerosis in a segment of the abnormal artery has been demonstrated even in young individuals.<sup>322</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 anomalous coronary

arteries have been reported to have a high incidence of coronary atheroma.<sup>322</sup> This high incidence may be due to abnormal blood flow patterns.

Some surgeries for congenital heart disease involve manipulation of the coronary arteries. These surgeries include the arterial switch operation for d-transposition of the great arteries and repair of anomalous origin of left coronary artery from the pulmonary artery. In these settings, coronary ostial stenosis may develop over time, and there may be increased risk of associated atherosclerosis.<sup>323</sup> A recent intravascular ultrasound study demonstrated proximal eccentric intimal thickening, a finding compatible with early atherosclerosis, in all the translocated coronary arteries in a small series of survivors of the arterial switch procedure studied at a median age of 9.5 years.<sup>324</sup> Abnormal epicardial coronary artery dilation in response to pharmacological stimulation has also been demonstrated in a small group of d-transposition subjects evaluated at a mean of 5 years after arterial switch.<sup>325</sup>

### Obstructive Lesions of the Left Ventricle and Aorta

One group of congenital cardiac lesions that has been shown to be associated with increased risk of cardiovascular disease in adulthood is obstructive lesions of the left side of the heart.

#### *Coarctation of the Aorta*

The pathophysiology for acquired cardiovascular disease associated with coarctation of the aorta is primarily related to systemic hypertension.<sup>326</sup> Arterial abnormalities may persist after correction of the coarctation and result in long-term systemic hypertension and, therefore, increased risk of cardiovascular disease.

A 20-year postoperative follow-up study of patients who underwent repair in an era when coarctation repair was delayed (mean age at repair 20 years) reported a mortality rate of 12% at a mean age of 32.5 years. Deaths were secondary to myocardial infarction, stroke, congestive heart failure, and aortic rupture, which indicates the potential negative impact of the combination of this congenital diagnosis and chronic hypertension.<sup>327</sup>

Upper-body hypertension is related to constriction of the aorta at the site of repair, but coarctation may also be associated with abnormalities of vascular reactivity, arterial wall compliance, or abnormal baroreceptor function.<sup>328–330</sup> The prevalence of hypertension at rest after repair of coarctation is at least 10%.<sup>331</sup> Exercise-induced systolic hypertension may also occur in patients after repair of coarctation of the aorta, even when the blood pressure is normal at rest.<sup>332</sup> To evaluate for this, patients with coarctation should have routine exercise/blood pressure evaluation.

Beyond hypertension, coarctation of aorta is associated with other important sequelae that lead to morbidity and mortality, which suggests a more widespread vascular abnormality. Cerebrovascular accidents occur in association with systemic hypertension<sup>326</sup> and even in its absence, in the setting of berry aneurysms in the circle of Willis. Aortic dissection in the ascending aorta or near the repair site may occur whether or not an aneurysm forms in the aorta at the site of the repair. 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>327,332</sup>

#### *Aortic Stenosis*

Aortic stenosis 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 cardiovascular disease. Valvular aortic stenosis occurs in 3% to 6% of patients with congenital cardiovascular defects.<sup>333</sup>

Significant aortic stenosis is associated with left ventricular hypertrophy (due to increased left ventricular pressure and peak systolic wall stress, a powerful stimulus for hypertrophy). Left ventricular hypertrophy is known to be an independent risk factor for cardiovascular disease morbidity and mortality in adults.<sup>334</sup>

Myocardial blood flow may be compromised in patients with aortic stenosis, despite normal coronary artery patency. Increased myocardial work results in increased demand for oxygen, exceeding the capacity of the coronary supply (abnormal coronary flow reserve). Furthermore, redistribution of blood away from the subendocardium can result in ischemia in the subendocardium.<sup>335</sup>

Even mild aortic stenosis during childhood can progress and may therefore be associated with increased left ventricular mass and increased risk for cardiovascular disease over time. Increase in the left ventricular outflow tract gradient is caused by progressive calcification of the aortic valve.<sup>333</sup>

Supra-valvular aortic stenosis (most commonly associated with Williams syndrome<sup>336</sup>) may confer an additional increased cardiovascular risk because of its association with arterial stenoses. Coronary artery ostial stenoses can result directly in myocardial ischemia and exercise-induced syncope, and renal artery stenosis can lead to hypertension.<sup>337</sup>

#### *Hypertrophic Cardiomyopathy*

Hypertrophic cardiomyopathy may occur in as many as 1 in 500 people. It is the most common genetically transmitted form of cardiovascular disease.<sup>338,339</sup> Hypertrophic cardiomyopathy is associated with an increased risk for sudden death in children and in adults.<sup>340</sup> The overall cardiovascular mortality rate is  $\approx 2\%$  per year for those diagnosed in childhood and  $\approx 1\%$  per year for those diagnosed as adults.<sup>341</sup> A number of pathophysiological sequelae may contribute to sudden death and potentially to increased cardiovascular disease risk in general.

Sudden death in patients with hypertrophic cardiomyopathy is usually due to a ventricular arrhythmia.<sup>342</sup> It is the most common cause of sudden death in the young. Vigorous physical activity may contribute to increased risk of sudden death in these patients.

Left ventricular hypertrophy is the major manifestation of hypertrophic cardiomyopathy, with a pathognomonic finding of cellular myocardial disarray. In addition, left ventricular outflow tract obstruction may exacerbate the development of hypertrophy.

Hypertrophic cardiomyopathy may be associated with myocardial bridging, in which epicardial coronary arteries can be compressed by muscle overgrowth. The presence of these vessels may result in increased risk of sudden death,

abnormal myocardial perfusion, and localized atherosclerosis in adjacent coronary segments.

The long-term role of hypertrophic cardiomyopathy in the development of atherosclerotic cardiovascular disease is not known. Similarly, the effect of modification of risk factors for atherosclerosis on the long-term prognosis of hypertrophic cardiomyopathy has not been established. Further study is needed to evaluate these issues.

### Traditional Risk Factors/Comorbidities

All the known risk factors for accelerated atherosclerosis will occur at the same incidence as seen in the general population. In the setting of a repaired congenital defect, these may represent even more potent harbingers of premature cardiovascular disease.

Some children with repaired congenital heart defects may have limitation in their ability to perform physical activity. A sedentary lifestyle is an independent risk factor for accelerated atherosclerosis. In addition, such children may be even more prone to obesity in our current obesogenic environment. Cardiac rehabilitation has been shown to improve the exercise performance of children with congenital heart disease, even those with known residual cardiac dysfunction.<sup>343</sup> Published guidelines can be used to determine the level of exercise considered appropriate for specific congenital diagnoses.<sup>41</sup>

### Recommendations for Children With Congenital Heart Disease

Because children with congenital heart disease have other abnormalities that may make the heart more vulnerable to both the development of atherosclerosis and the adverse sequelae of a cardiovascular event, it seems prudent to be aggressive about the evaluation of their cardiovascular disease risk status. This is particularly true of those with the congenital cardiac defects presented above. Children, adolescents, and young adults with these specific congenital heart diseases are at risk (tier III) for premature cardiovascular disease. The algorithm in the Figure and Table 2 provide specific management guidelines. Future research will clarify which additional congenital cardiac diagnoses require specific attention to cardiovascular risk reduction.

## Childhood Cancer Survivors

### Introduction/Epidemiology

The prevalence of childhood cancer has been steadily increasing over the past decades, exceeded only by the adult cancers of prostate, lung, breast, colorectum, and bladder.<sup>344</sup> A newborn child is estimated to have a 1 in 325 chance of developing cancer before 20 years of age.<sup>344</sup> Progressively more effective surgical intervention, radiotherapy, and risk-stratified chemotherapeutic approaches have led to dramatic improvements in survival rates for many childhood cancers during the past 3 decades.<sup>345</sup> The overall 5-year probability of survival for children diagnosed with cancer since 1992 is >77%.<sup>346</sup>

As many childhood cancer survivors progress into adulthood, clinical and epidemiological research is now focusing on an array of long-term medical and psychosocial effects

from cancer treatment to characterize and understand the "consequences of cure."<sup>347</sup> Among 5-year or longer survivors of childhood cancer, the standardized mortality ratio for cardiac-related deaths was found to be significantly elevated at 8.2 (95% confidence interval 6.4 to 10.4).<sup>348</sup> The combination of acquired atherosclerotic disease with a previously damaged myocardium represents a serious late complication for survivors of childhood cancer. In a recent comparative study of 201 long-term childhood cancer survivors and 76 healthy siblings, Lipshultz et al<sup>349</sup> showed that overall, the cancer survivor group had increased cardiovascular risk due to the combination of reduced left ventricular mass and high prevalence of risk factors for atherosclerosis.

### Pathophysiology

Both anthracyclines used as chemotherapy for childhood cancers and direct cardiac radiation have been associated with the development of dilated cardiomyopathy. With anthracyclines, the development of cardiac dysfunction is related to cumulative dose. The cardiomyopathy that develops can be severe, with cardiac transplantation required in a small number of cases. Subclinical cardiac dysfunction has been shown to be present in 14% to 47% of patients after anthracycline therapy.<sup>350,351</sup> Late-onset clinical symptoms mandate routine serial evaluation of cardiac function for these patients. Preliminary data suggest that pretreatment with dexrazoxane, a free-radical scavenger, may prevent or reduce cardiac injury related to doxorubicin infusion, but a clinical benefit has not yet been confirmed.<sup>352</sup>

### Risk Factors/Comorbidities

#### Obesity

Obesity is very common in survivors of childhood cancer.<sup>353</sup> In adult survivors of childhood acute lymphoblastic leukemia, various factors, including female sex, genetic predisposition, exposure to steroids, and cranial radiation therapy, have been implicated in the development of excess body fat.<sup>348,354–360</sup>

Leptin, an adipocytokine produced by adipocytes, controls energy metabolism at the level of the hypothalamus by suppressing appetite and stimulating energy expenditure.<sup>361,362</sup> Leptin levels are elevated in otherwise healthy obese adults and children, which indicates resistance to the effects of leptin in these individuals.<sup>363–366</sup> Elevated leptin levels and leptin receptor abnormalities have been reported in childhood cancer survivors.<sup>367,368</sup>

Radiation exposure to the hypothalamic-pituitary axis in children can result in late-onset deficiency of growth hormone secretion and subsequent development of adult obesity.<sup>348,356,368–372</sup> Growth hormone is involved in the determination of fat cell size, fat cell differentiation,<sup>370</sup> and levels of resistin,<sup>369</sup> all of which are important determinants of insulin sensitivity.<sup>368</sup> Impaired growth hormone levels in childhood cancer survivors are potentially operative in the development of obesity, insulin resistance, and type 2 diabetes mellitus.<sup>369–373</sup>

Cachexia acutely affects ≈50% of cancer patients and is characterized by weakness, fatigue, loss of lean body mass, and abnormal metabolism. It may be associated with an increased risk for subsequent cardiovascular disease in child-

**TABLE 2. Tiers I, II, and III: Treatment Recommendations****GROWTH/DIET<sup>32-34</sup>**

- Nutritionist evaluation, diet education for all: total fat <30% of calories, saturated fat <10% of calories, cholesterol <300 mg/d, avoid *trans* fats; adequate calories for growth.
- Calculate BMI percentile for gender/height.\*
  - If initial BMI >95th percentile:
    - Step 1:
      - Age-appropriate reduced-calorie training for child and family
      - Specific diet/weight F/U every 2 to 4 weeks for 6 months; repeat BMI calculation at 6 months
      - Activity counseling (see below)
    - If F/U BMI >85th percentile for tier I, >90th percentile for tier II, or >95th percentile for tier III:
      - Step 2:
        - Weight-loss program referral plus exercise training program appropriate for cardiac status

**BLOOD PRESSURE (Tiers I, II, and III)<sup>35</sup>**

- BP measurement/interpretation for age/gender/height
  - If SBP and/or DBP=90th to 95th percentile or BP >120/80 mm Hg (3 separate occasions within 1 month):
    - Step 1: Decreased calorie intake, increased activity for 6 months
  - If initial SBP and/or DBP >95th percentile (confirmed within 1 week) OR 6-month F/U SBP and/or DBP >95th percentile:
    - Step 2: Initiate pharmacological therapy per Fourth Task Force recommendations<sup>35</sup>

**LIPIDS**

- LDL-C (tiers II and III)<sup>36</sup>
  - See Table 3 for recommendations for LDL-C for tier I.
  - If initial LDL-C ≥130 mg/dL (tier II) or >160 mg/dL (tier III):
    - Step 1: Nutritionist training for diet with <30% of calories from fat, <7% of calories from saturated fat, cholesterol <200 mg/d, avoidance of *trans* fats for 6 months
  - If repeat LDL-C >130 mg/dL in tier II or >160 mg/dL in tier III and child >10 y old:
    - Step 2: Initiate statin therapy with LDL goal of 130 mg/dL
- Triglycerides
  - If initial TG=150 to 400 mg/dL:
    - Step 1:
      - Nutritionist training for low simple carbohydrate, low-fat diet
      - If elevated TGs are associated with excess weight, nutritionist referral for weight loss management: energy balance training plus activity recommendations (see below)
    - If TG >700 to 1000 mg/dL, initial or F/U:
      - Step 2:
        - Consider fibrate or niacin if >10 y old.†
        - Weight loss recommended when TG elevation is associated with overweight/obesity.

**GLUCOSE (Tiers I, II, and III, except for patients with diabetes mellitus)<sup>37</sup>**

- If fasting glucose=100 to 126 mg/dL:
  - Step 1: Reduced-calorie diet, increased activity aimed at 5% to 10% decrease in weight over 6 months
- If repeat fasting glucose=100 to 126 mg/dL:
  - Step 2: Insulin-sensitizing medication per endocrinologist
- Casual glucose >200 mg/dL or fasting glucose >126 mg/dL=Diabetes mellitus → Endocrine referral for evaluation and management
- Maintain HbA<sub>1c</sub> <7%

**SMOKING (Tiers I, II, and III)**

- Step 1: Parental smoking history at every visit; child smoking history beginning at age 10. Active antismoking counseling for all; smoke-free home strongly recommended at each encounter.
- Step 2: Smoking cessation referral for any history of cigarette smoking.

**ACTIVITY (Tiers I, II and III)<sup>38-40</sup>**

- For children in all tiers, participation in activity is at the discretion of the physician(s) directing care. For specific cardiac diagnoses such as Kawasaki disease and congenital heart disease, activity guidelines are referenced.
  - Step 1: Specific activity history for each child, focusing on time spent in active play and screen time (television+computer+video games). Goal is ≥1 hour of active play per day; screen time limited to ≤2 h/d.
- Encourage activity at every encounter.
  - Step 2: After 6 months, if goals not met, consider referral for exercise testing, recommendations from exercise specialist.

Abbreviations: F/U indicates follow-up; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, LDL cholesterol; and TG, triglycerides.

Specific treatment goals for each risk factor and each tier are given in the algorithm (Figure). For risk factor-specific guidelines, references are provided.

\*Normal BMI values for age and sex are available at <http://www.cdc.gov/growthcharts>.

†Elevation of triglycerides to ≥1000 mg/dL is associated with significant risk for acute pancreatitis. A fasting TG of 700 mg/dL is likely to rise to >1000 mg/dL postprandially. Treatment recommendation is congruent with guidelines for management of dyslipidemia in diabetic children.<sup>30</sup>



**TABLE 3. Tier I Conditions: Specific Treatment Recommendations**

- Rigorous age-appropriate education in diet, activity, and smoking cessation for all
- Specific therapy as needed to achieve BP, LDL-C, glucose, and HbA<sub>1c</sub> goals as indicated for each tier, as outlined in algorithm; timing individualized for each patient and diagnosis. Step 1 and Step 2 therapy for all outlined in Table 2.
- For diagnosis-specific guidelines, references are provided.

**Homozygous FH<sup>41</sup>**

- LDL management: Scheduled apheresis every 1 to 2 weeks beginning at diagnosis to maximally lower LDL-C, plus statin and cholesterol absorption inhibitor
- Rx per cardiologist/lipid specialist. (Specific therapeutic goals for LDL-C are not meaningful with this diagnosis.)
- Assess BMI, BP, and FG: Step 1 management for 6 months
- If tier I goals not achieved, proceed to Step 2.

**Diabetes mellitus, type 1<sup>37,42</sup>**

- Intensive glucose management per endocrinologist, with frequent glucose monitoring/insulin titration to maintain PG <200 mg/dL, HbA<sub>1c</sub> <7%
- Assess BMI, fasting lipids: Step 1 management of weight, lipids for 6 months
- If goals not achieved, proceed to Step 2; statin Rx if >10 y old to achieve tier I treatment goals
- Initial BP >90th percentile: Step 1 management plus no added salt, increased activity for 6 months
- BP consistently >95th percentile for age/sex/height: initiate ACE inhibitor therapy with BP goal <90th percentile or <130/80 mm Hg, whichever is lower.

**CKD/ESRD<sup>44</sup>**

- Optimization of renal failure management with dialysis/transplantation per nephrology
- Assess BMI, BP, lipids, FG: Step 1 management for 6 months
- If goals not achieved, proceed to Step 2; statin Rx if >10 y old to achieve tier I treatment goals

**After heart transplantation<sup>45</sup>**

- Optimization of antirejection therapy, treatment for CMV, routine evaluation by angiography/perfusion imaging per transplant physician
- Assess BMI, BP, lipids, FG: Initiate Step 2 therapy, including statins, immediately in all patients >1 y old to achieve tier I treatment goals

**Kawasaki disease with coronary aneurysms<sup>46</sup>**

- Antithrombotic therapy, activity restriction, ongoing myocardial perfusion evaluation per cardiologist
- Assess BMI, BP, lipids, FG: Step 1 management for 6 months
- If goals not achieved, proceed to Step 2; statin Rx if >10 y old to achieve tier I treatment goals

BP indicates blood pressure; LDL-C, LDL cholesterol; Rx, prescription/treatment; FG, fasting glucose; PG, plasma glucose; ACE, angiotensin-converting enzyme; and CMV, cytomegalovirus.

hood cancer survivors in a manner similar to that of fetal malnutrition in healthy populations.<sup>374–379</sup>

The induction and intensification stages of therapy include prolonged continuous administration of high-dose steroids, which induce hunger and decrease lean body mass.<sup>354,358</sup> The combination of initial malnutrition and muscle wasting from cancer counterposed by treatment-induced intense appetite underlies the potential development of poor eating habits.

**Insulin Resistance/Type 2 Diabetes Mellitus**

Childhood cancer survivors have higher fasting plasma glucose and insulin levels than age-matched control subjects,<sup>379</sup> and type 2 diabetes is reported to be more common in childhood cancer survivors than among sibling control subjects, with an odds ratio of 1.8 (95% confidence interval 1.1 to 1.29). Cancer types associated with a statistically significant increased risk of diabetes include leukemia, Wilms' tumor, and neuroblastoma.<sup>380</sup> Impaired glucose tolerance and impaired insulin response were also found in 69% of a cohort of children who survived acute lymphoblastic leukemia, which suggests pancreatic  $\beta$ -cell dysfunction.<sup>381</sup>

Some evidence supports the hypothesis that growth hormone deficiency may play an important role in the pathogenesis of insulin resistance among survivors of childhood cancer.<sup>353,355,382</sup> Both chemotherapy and cranial radiation can

cause a variety of chronic endocrine abnormalities. In addition to its effect on growth and development, growth hormone directly and indirectly influences insulin sensitivity and lipid metabolism.

**Dyslipidemia**

As would be anticipated, obese childhood cancer survivors have the typical lipid pattern associated with obesity: elevated triglycerides and reduced HDL cholesterol.<sup>354</sup> Cyclophosphamide administration in animal models results in hypertriglyceridemia and impairment of vascular lipoprotein lipase.<sup>383,384</sup> The frequently seen constellation of obesity, insulin resistance, and dyslipidemia suggests that the cluster of findings known as the metabolic syndrome is common in survivors of childhood cancer.<sup>385</sup>

**Physical Deconditioning**

Reductions in cardiac output and cardiorespiratory fitness are prevalent among leukemia survivors, particularly those who are overweight and have features of metabolic syndrome.<sup>386–391</sup> Although resting metabolic rate does not appear to be reduced in cancer survivors, growth hormone deficiency is suggested as a potential mechanism to explain reductions in strength and in exercise capacity seen in adult survivors of childhood leukemia and in children and adults who are cancer free.<sup>392–396</sup> Because of

its effects on body composition and muscle strength, growth hormone deficiency may contribute synergistically to decreased fitness.<sup>397</sup> Lack of adequate physical activity and the approach to a survivor of childhood cancer as a “vulnerable child” may also contribute to the conditions characteristic of the metabolic syndrome, a common occurrence in this group.

Exercise may attenuate the effects of cachexia in cancer survivors by suppressing inflammatory responses and by improving insulin sensitivity, rates of protein synthesis, and antioxidant activities.<sup>398</sup> A decrease in cardiac output and a reduction in pulmonary elasticity with diminished aerobic capacity have been demonstrated in leukemia survivors, limiting their participation in tasks that require sustained or vigorous activity.<sup>386,399,400</sup>

#### **Other Factors**

A recent study in young adult survivors of disseminated testicular cancer who underwent surgery and chemotherapy reported a high prevalence of microalbuminuria and increased levels of endothelial and inflammatory marker proteins compared with both patients who underwent surgery alone and healthy control subjects.<sup>401</sup> To date, it is not clear whether the underlying mechanisms for insulin resistance in childhood cancer survivors are different from those in noncancer populations. However, there is a strong possibility that in addition to obesity, which is very common in this group, other pathways may be activated in childhood cancer survivors. These include growth hormone deficiency (a known outcome after central nervous system radiation), reduced physical activity, inflammatory mediators, and adipocytokines, which may be altered by therapies to treat cancer. Currently, data on specific anticancer drugs are insufficient to allow inferences on causality.

### **Recommendations for Childhood Cancer Survivors**

#### ***Survivors of Childhood Cancer Are at Risk for Early Cardiovascular Disease (Tier III)***

With the number of childhood cancer survivors increasing, thousands of individuals worldwide every year are faced with a

variety of long-term adverse effects. Regular evaluation of cardiac function and identification of risk factors for accelerated atherosclerosis are clearly indicated. The algorithm in the Figure and Table 2 provide specific diagnosis and treatment guidelines.

### **Conclusions**

In contrast to the normal pediatric population, children with specific underlying conditions experience accelerated atherosclerosis that leads to early CAD. In the present statement, we have reviewed what is known about coronary disease and the atherosclerotic process for 8 specific diagnoses and described current approaches to cardiovascular risk identification and treatment. A modified nominal group process was used to risk-stratify the diagnoses and to develop recommendations for risk identification and intervention.<sup>29</sup> 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 recommendations 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. When published data did not permit evidence-based practice, we suggested practical interim recommendations. As new information develops, the guidelines will need to be modified to effectively provide guidance on cardiovascular risk reduction in these high-risk pediatric settings. Finally, decisions on the management of individual patients must be tailored to their unique circumstances.

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During the time that most of the work on this paper was accomplished, Dr Kavey was employed at Children's Memorial Hospital, Northwestern University-Feinberg School of Medicine, Chicago, Ill. She had nothing to disclose at that time.

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