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Review

Incorporating Risk Stratification Into the Practice of Pediatric Preventive Cardiology

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ABSTRACT

Atherosclerosis in its earliest stages is associated with the same traditional cardiovascular disease (CVD) risk factors as are associated with manifest CVD events in adulthood. Clustering of risk factors is associated with exponential increases in atherosclerotic burden from a young age. Some medical conditions and risk behaviours occurring in children can either increase the likelihood of higher levels of risk factors (such as chronic kidney disease) or the presence of risk factor clustering (such as obesity and cardiometabolic syndrome) or are associated with acquired coronary artery pathology (such as Kawasaki

RÉSUMÉ

L'athérosclérose aux premiers stades est associée aux mêmes facteurs de risque de maladie cardiovasculaire (MCV) que ceux qui sont habituellement associés aux manifestations d'une MCV à l'âge adulte. Il existe en outre un lien entre le cumul de facteurs de risque et l'augmentation exponentielle du fardeau lié à l'athérosclérose s'installant tôt au cours de la vie. Chez les enfants, certains problèmes de santé et comportements à risque peuvent accroître la probabilité de facteurs de risque plus graves (par exemple, une néphropathie chronique) ou favoriser le cumul de plusieurs facteurs de risque (par

Atherosclerosis, evident either at autopsy or from vascular assessment, has been well documented in youth. The rate of accumulation of atherosclerosis has been shown to be influenced by traditional cardiovascular risk factors (CVRFs) in a manner similar to adults. An early longitudinal study, the Bogalusa Heart Study, showed that the extent of atherosclerosis at autopsy in youth increased geometrically when multiple CVRFs were present (Fig. 1).[1,2] This observation and others highlight the importance of evaluating and addressing the total risk profile from an early age. They also inform an imperative that the management of a particular CVRF should be intensified when other CVRFs are present.

Pediatric patients at high risk for accelerated atherosclerosis are those with extreme levels and lifetime exposure to a single CVRF such as genetic low-density lipoprotein cholesterol (LDL-C) elevation with familial hypercholesterolemia (FH); clustering of CVRFs often driven by risk behaviours and genetic predispositions such as cardiometabolic syndrome associated with obesity; and risk conditions associated with acquired structural and functional coronary artery abnormalities such as Kawasaki disease, complicated by coronary artery aneurysms. They also include conditions associated with a pathophysiological milieu that either directly affects the vessels or leads to a clustering of CVRFs for atherosclerosis, such as diabetes mellitus or inflammatory conditions.

This review will focus on surveillance, evaluation, and management of CVRFs in youth at increased risk for premature cardiovascular disease (Fig. 2). More detailed information regarding the evidence base for each risk factor and condition is provided in a recent American Heart Association (AHA) scientific statement: Cardiovascular Risk Reduction in High-Risk Pediatric Patients.[3]

Risk Factors and Risk Behaviours

CVRFs, including obesity, dyslipidemia, hypertension, and at-risk behaviours including eating habits, physical inactivity, screen time, and smoking and electronic cigarette use are common in youth (Table 1).[4] Autopsy studies have demonstrated that the presence and intensity of such CVRFs are associated with atherosclerotic development and burden in childhood and young adulthood.[2,5] Moreover,

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disease). This creates a milieu for—or increases the impact of—accelerated atherosclerosis that, in turn, increases the likelihood of premature CVD. This review highlights the importance of considering the total risk factor and risk-condition profile of pediatric patients. An algorithm is provided for stratifying patients into high-, moderate-, and at-risk categories, and practical examples are provided as to how the evaluation and management of 1 risk factor or risk condition might need to be intensified in the context of additional risk factors or risk conditions. For example, for treatment of an adolescent with familial hypercholesterolemia, the target low-density lipoprotein cholesterol level might be lowered by the concomitant presence of low high-density lipoprotein cholesterol or elevated lipoprotein(a) levels. As awareness of cardiovascular risk and atherosclerosis in pediatric patients increases, new at-risk conditions that warrant consideration are emerging. The identification and management of high-risk individuals is an important part of the overall practice of pediatric preventive cardiology.

exemple l'obésité et le syndrome cardiométabolique), ou encore sont associés à une coronaropathie acquise (par exemple, la maladie de Kawasaki). Ces facteurs accélèrent l'apparition ou augmentent les répercussions de l'athérosclérose qui, à son tour, fait augmenter le risque de MCV prématurée. Nous faisons valoir ici l'importance de tenir compte de l'ensemble des facteurs de risque et du profil de risque associé à la maladie en pédiatrie. Nous présentons un algorithme pour la stratification des patients en trois catégories (« à risque », « à risque modéré » ou « à risque élevé ») en fonction des problèmes de santé dont ils souffrent, ainsi que des exemples pratiques illustrant en quoi l'évaluation et la prise en charge d'un facteur de risque ou d'une maladie associée à un risque pourraient devoir être intensifiées en présence d'autres facteurs de risque ou maladies associées à un risque. Par exemple, chez un adolescent ayant des antécédents familiaux d'hypercholestérolémie, il pourrait être nécessaire de cibler un taux de cholestérol des lipoprotéines de basse densité plus faible si le patient présente aussi un taux de cholestérol des lipoprotéines de haute densité faible ou un taux de lipoprotéine(a) élevé. À mesure que les connaissances relatives au risque cardiovasculaire et à l'athérosclérose chez les enfants s'améliorent, de nouvelles affections associées à un risque dont il faut tenir compte sont mises au jour. Le repérage et la prise en charge des patients présentant un risque élevé constituent une part importante de la pratique globale en cardiologie préventive chez les enfants.

modifiable CVRFs—such as obesity, dyslipidemia, and hypertension— track from childhood to adulthood; for example, an overweight teen has a 75% likelihood of becoming an obese adult.[6] Thus, the timely management of CVRFs in youth has the potential to reduce or delay atherosclerotic cardiovascular disease in adulthood, particularly for youth with conditions predisposing them to increased CV risk.[3] Prospectively evaluating the impact of management of CVRF in youth on the occurrence of manifest atherosclerotic cardiovascular disease in adulthood in a randomized controlled manner would be logistically very difficult and likely unethical, given the weight of evidence to date. On this basis, the United States Preventive Services Task Force (USPSTF) has indicated that insufficient evidence exists to recommend in favour of or against screening of lipid disorders and blood pressure in youth.[7,8] Despite this, as outlined here, indirect evidence suggests that the early and effective management of CVRFs can result in improvements in manifest cardiovascular disease in adulthood and noninvasive measures of atherosclerotic burden and vascular dysfunction in youth. For example, early initiation of statins in youth with FH recently has been shown to result in significant reductions in cardiovascular disease in adulthood compared with their FH-affected parents who had not started statin therapy until adulthood.[9]

Obesity is a particularly important CVRF to consider in childhood. Along with insulin resistance, it often provides the metabolic milieu for the development of a specific form of CVRF clustering known as cardiometabolic syndrome.[10,11] Although cardiometabolic syndrome is difficult to diagnose in childhood—owing, in part, to natural age-related fluctuations in body habitus and lipid and blood pressure normative values[4]—the presence of CVRF clustering in youth is associated with endothelial dysfunction[12] and is predictive of future cardiovascular disease in adulthood.[13] Moreover, landmark autopsy studies have demonstrated that increasing CVRF clustering is associated with increased atherosclerotic burden in children and young adults.[2,14] As obesity tracks relatively strongly from childhood to adulthood,[15,16] the risk of CVRF clustering increases over time. Unfortunately, long-term effective first-line therapies for managing pediatric obesity remain elusive, as are strategies for sustained improvements in nutritional quality and physical activity.[3] The first-line strategy in obesity management remains the use of multidisciplinary subspecialty obesity programs (when available).[17]

Pediatric dyslipidemia and elevations in lipoprotein(a) have gained increasing attention in recent decades. A clear correlation exists between the presence and severity of dyslipidemia in childhood and atherosclerotic burden at autopsy.[2,5] Pediatric dyslipidemias are also associated with vascular dysfunction and increased markers of early atherosclerosis from noninvasive assessment.[18-20] FH, the most common inherited lipid disorder, is present in its heterozygous form in approximately 1:250 people,[21] with an increased prevalence in specific populations, including French Canadians.[22] It is characterized by lifelong marked elevations in low-density lipoprotein cholesterol (LDL-C) from birth, resulting in accelerated atherosclerosis and premature cardiovascular disease.[23] Etiologic mutations typically involve the LDL receptor, apolipoprotein B, or proprotein convertase subtulisin/kexin type 9 (PCSK9).[23] As heterozygous FH is clinically silent in youth, diagnostic criteria are needed to facilitate diagnosis, as indicated in a recently published Canadian definition.[24] In the pre-statin era, the median age of first myocardial infarction was significantly earlier in the FH population than the general population: approximately 50 years in men and 60 years in women,[23,25,26] with an estimated LDL-C burden in an

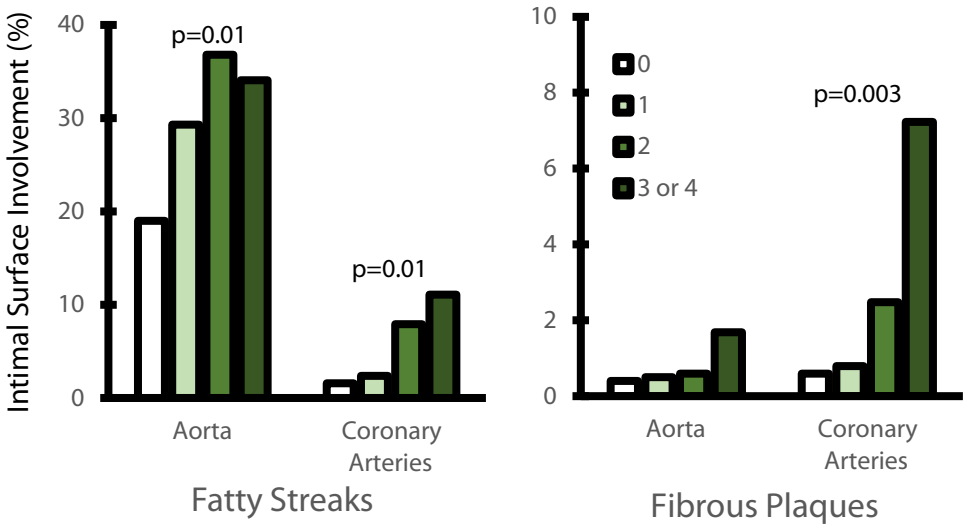

Figure 1. The effect of multiple risk factors on the extent of atherosclerosis in the aorta and coronary arteries in children and young adults; from the Bogalusa Heart Study of cardiovascular risk factors measured in youth and autopsy assessment of the extent of atherosclerosis. Values shown are the percentages of the intimal surface covered with lesions in subjects with 0, 1, 2, and 3 or 4 risk factors. Risk factors were elevated values for body-mass index, systolic blood pressure, and serum triglyceride and low-density lipoprotein (LDL) cholesterol concentrations, defined as values above the 75th percentile for the study group (specific for study period, race, sex, and age). Reproduced from Berenson et al.[2] Copyright © 1998 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

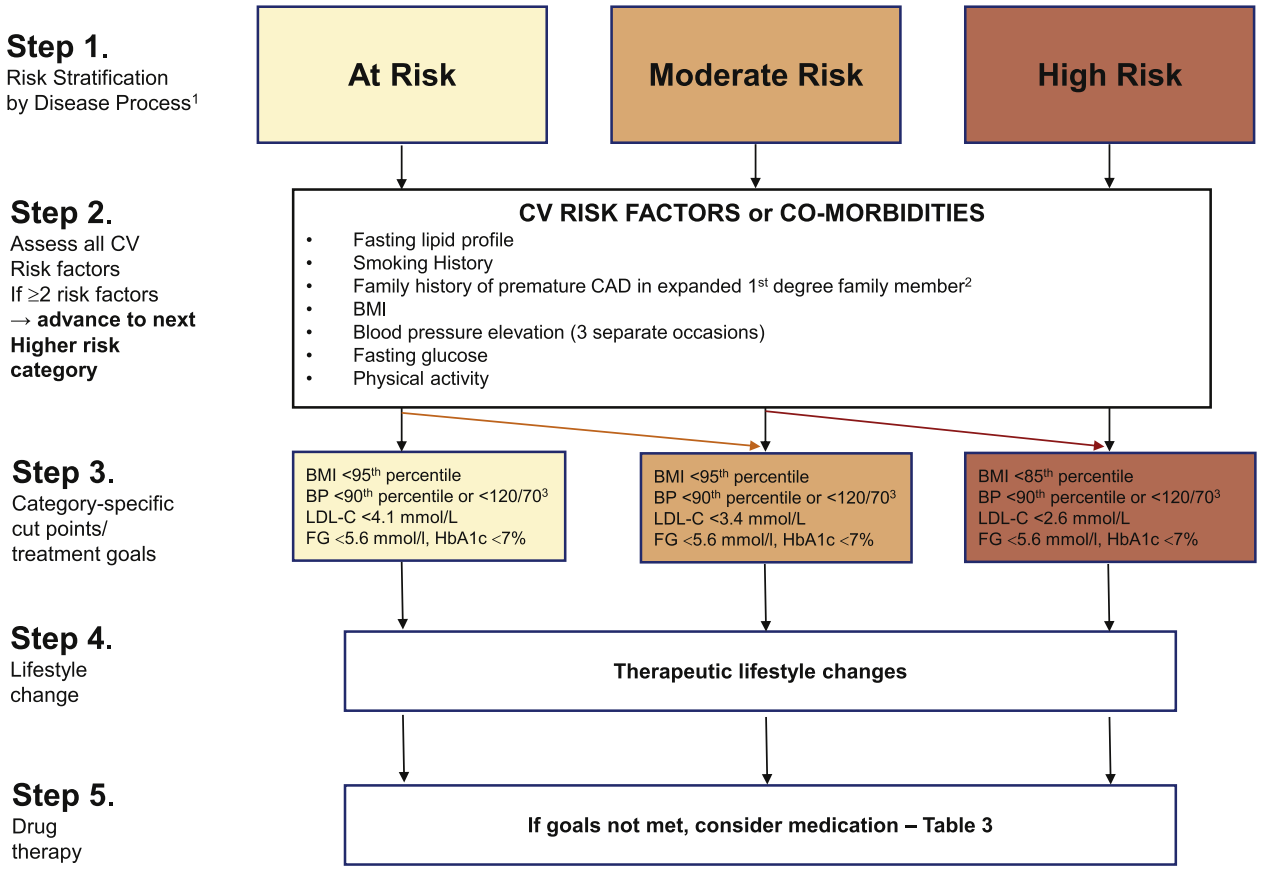

Figure 2. Risk stratification and management for children with conditions predisposing to early coronary artery disease (see Table 2). Defined as a parent, grandparent, aunt, uncle, or sibling with myocardial infarction, angina, stroke, coronary artery bypass graft, stent, or angioplasty at < 55 years in men and < 65 years in women, HbA1C > 7% in patients with diabetes mellitus. BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; FG, fasting glucose; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol. Adapted from de Ferranti et al.[3] Reprinted with permission. Circulation 2019;139:e603-34. © 2019 American Heart Association, Inc.

Table 1. Cardiovascular risk factors and behaviours and screening strategies in youth

Risk factor or behaviour	Measure	Timing of assessment
Obesity	Height percentile Weight percentile Body mass index percentile (Waist-to-height ratio)	At each clinical encounter starting at 2 years of age
Dyslipidemia	Fasting or nonfasting lipid profile	• Selective screening starting ≥ 2 years old for high-risk youths • Universal screening considered for 9- to 11-year-old and 17- to 21-year-old youths
Hypertension	Blood pressure measurement (auscultatory technique)	At least annual measurement for all children ≥ 3 years of age
	Confirmed on 3 different occasions	Screening < 3 years old in high-risk infants/toddlers
Insulin resistance/diabetes mellitus	Fasting glucose (hemoglobin A1c)	Screening in at-risk populations starting at ∼9 to 11 years of age
Family history of cardiovascular risk factors and premature cardiovascular disease	History	Updated at each clinical encounter
Physical activity and screen time	History	Each clinical encounter
Smoking and electronic cigarette use	History	Each clinical encounter

Data from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute[4] and de Ferranti et al.[3]

untreated 35-year-old with FH equivalent to that of a typical 55-year-old.[27,28] FH serves as a model for not only the impact of severe elevations of isolated CVRFs but also for the impact of CVRF clustering on youth already at increased risk. For example, a recent systematic review and meta-analysis identified the presence of CVRFs—such as hypertension, diabetes mellitus, elevated lipoprotein(a), and smoking—as strongly associated with an increased risk of cardiovascular disease events in patients with FH.[29] A large pediatric FH study showed that not only were more extreme levels of LDL-C in the affected child associated with more cardiovascular disease events in the family but that risk of events was further increased if the affected child also had low high-density lipoprotein cholesterol (HDL-C) or high lipoprotein(a).[30] To this end, risk scores to predict cardiovascular disease events in the FH population have been developed, as traditional risk stratifying tools—such as the Framingham Risk Score—are not applicable to the FH population.[31-33] Fortunately, a number of clinical trials have repeatedly shown that early use of statins in the pediatric FH population can slow or even reverse atherosclerotic progression[34-37] and may effectively normalize cardiovascular risk in this high-risk population.[9,38]

Hypertension is another established risk factor for accelerated atherosclerosis. Pediatric hypertension can either be primary (essential) or secondary to an underlying at-risk disorder.[39] Hypertension in youth is associated with evidence of cardiac (increased left-ventricular mass, systolic and diastolic dysfunction) and vascular (endothelial dysfunction, increased vascular stiffness, and increased carotid intima-media thickness) target organ damage that, in turn, is associated with progression to manifest cardiovascular disease in adulthood.[39,40] Moreover, blood pressure abnormalities track from childhood to adulthood,[39] and blood pressure trajectories in childhood are associated with hypertension in adulthood.[41] Fortunately, antihypertensive therapy can improve the left-ventricular hypertrophy (LVH) noted in pediatric[42,43] and adult[44-48] persons with hypertension, and these improvements in LVH are independently associated with improved CV outcomes.[49]

Pediatric Risk Conditions

Pediatric medical conditions identified as increased risk are categorized by the underlying disease profile and the degree of associated risk in Table 2. To demonstrate an approach to evaluation in clinical settings like these in childhood, the factors that confer added risk in 2 conditions—a medical diagnosis (diabetes mellitus) and a coronary artery diagnosis (Kawasaki disease)—are described. In addition to these established diagnoses, which are extensively reviewed in the AHA scientific statement referenced here,[3] there are other recognized conditions in which evidence of associated accelerated atherosclerosis in childhood or very early adult life is emerging or under-recognized. One of these is the association between psychiatric disorders—specifically, major depressive disorders and bipolar disorder—and increased pediatric cardiovascular risk.[50] Another risk condition is cystic fibrosis, and the emerging evidence for accelerated atherosclerosis in that population is described as an introduction to integrating CV risk assessment into management of these complex young patients. Clinicians and researchers must consider the long-term cardiovascular risk implications of various pediatric chronic diseases as their treatments and long-term prognoses continue to improve. This is particularly important and relevant for youth who have developed the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated pediatric inflammatory multisystem syndrome. The long-term vascular implications and similarities to Kawasaki disease, discussed here, remain to be determined.[51]

High-risk medical diagnosis: diabetes mellitus type 1 and type 2

Type 1 diabetes (T1DM) is a condition of absolute, lifelong insulin deficiency caused by T-cell—mediated autoimmune destruction of pancreatic β-cells. This predominant form of diabetes mellites diagnosed in childhood and early adolescence leads to chronic, recurrent hyperglycemia, even with insulin-replacement therapy. Overall, the age-adjusted relative risk for atherosclerotic cardiovascular disease in T1DM is 10 times that of the general population.[52]

Table 2. Risk conditions stratified by risk category

Category	Disease condition with accelerated atherosclerosis	Coronary artery/cardiac diagnosis associated with early coronary events
High risk	• Homozygous FH • Diabetes mellitus, type 1 and type 2 • Chronic kidney disease • Childhood cancer survivor (status post-stem cell transplant)	• Kawasaki disease with persistent aneurysms • Post-heart transplant vasculopathy
Moderate risk	• Heterozygous FH • Severe obesity • Confirmed hypertension • Childhood cancer survivor (status post-chest radiation) • Elevated lipoprotein(a) • Nephrotic syndrome • Coarctation of the aorta • Aortic stenosis	
At risk	• Obesity • Insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS) • White coat hypertension • Pulmonary hypertension • Chronic inflammatory conditions (JIA, SLE, IBD, HIV) • HCM and other cardiomyopathies • Childhood cancer survivor (status post-cardiotoxic chemotherapy only) • Psychiatric conditions (including major depressive disorders and bipolar disorder) • Cystic fibrosis	• Coronary artery translocation for ALCAPA, TGA • Kawasaki disease with regressed large coronary aneurysms

ALCAPA, anomalous left coronary artery from the pulmonary artery; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovarian syndrome; SLE, systemic lupus erythematosus; TGA, transposition of the great arteries.

Data from de Ferranti et al.[3]

Subclinical vascular abnormalities are present in youths with T1DM, even in the first decade after diagnosis.[3] When T1DM is diagnosed in childhood, cardiovascular disease is the leading cause of death beginning at age 20, at rates > 3% per year.[52]

Cardiovascular disease in patients with T1DM is the result of an accelerated atherosclerotic process. Hyperglycemia is the primary mediator and intensive glycemic control reduces cardiovascular disease events in adults and improves vascular abnormalities in adolescents.[53,54] Nephropathy complicates 30% of T1DM cases and accelerates atherosclerosis through chronic inflammation and uremia-related factors.[55] Traditional CVRFs are prevalent with elevated total and LDL-C levels inversely correlated with glycemic control and significantly elevated apolipoprotein B and small, dense LDL particle levels, regardless of glycemic control.[56] Hypertension is also common, found in 6% of T1DM youth.[52] Obesity is increasingly prevalent, present in ~40% of children with T1DM.[52] Risk clustering mediates a profoundly atherogenic state and 14% to 45% of children with T1DM have 2 or more major CVRFs.[52]

By contrast with T1DM, type 2 diabetes mellitus (T2DM) is a condition of insulin resistance secondary to excessive weight gain as visceral fat, with the resultant inability of skeletal muscle, liver, and fat to respond to normal insulin levels. T2DM is increasingly diagnosed in youth, in parallel with rising obesity rates: > 85% of adolescents with T2DM are obese. In Canada, incidence of T2DM in youth ranges from 1.54 to 12.5 per 100,000 per year, compared with a mean of 11.8 per 100,000 per year in American teenagers.[57] There is a strong genetic component; in adolescents who develop T2DM, 45% to 80% have at least 1 parent with T2DM.[58] Native American and Canadian indigenous people plus South Asians, Pacific Islanders and Latinos are at increased risk for development of T2DM.[59] In adults, both T1DM and T2DM are powerful predictors of future cardiovascular disease, equivalent to a history of previous coronary events.[60] In youth, T2DM is associated with anatomic and histologic vascular changes at autopsy, structural and functional vascular changes *in vivo*, and early cardiovascular disease events.[52]

Multiple CVRFs accelerate the atherosclerotic process in youths with T2DM. Of primary importance is diabetic nephropathy, often present at the time of diagnosis of T2DM.[61] Hyperglycemia increases cardiovascular disease risk with an 18% increase in events per 1% increase in hemoglobin A1c in adults.[62] Up to 40% of Canadian and American adolescents with T2DM have elevated triglycerides and low HDL-C, the atherogenic pattern of combined dyslipidemia.[63,64] Over a 4-year follow-up, one-third of youths with T2DM in a long-term observational study developed hypertension.[65] The cardiometabolic syndrome cluster of CVRFs described in the previous section is highly prevalent; its detection at a mean age of 12 years is an independent predictor of CV disease before 50 years of age.[13]

In adults with diabetes mellitus, management of CVRF definitively reduces cardiovascular disease events. An approach to reduction of CVRF in youth with high-risk conditions (such as T1DM and T2DM) is outlined in Table 3 and in the treatment algorithm (Fig. 2), as well as in the current Canadian guidelines.[66] In morbidly obese adolescents with T2DM, gastric bypass has been shown to significantly reduce metabolic and cardiac abnormalities.[67]

Table 3. Management of obesity, dyslipidemia, and hypertension in patients with at-risk, moderate-risk, and high- risk conditions

	Thresholds for treatment			Therapeutic targets		
	At risk	Moderate risk	High risk	At risk	Moderate risk	High risk
Obesity	First-line therapy: subspecialty program			BMI < 95th percentile		
	After 6 months of lifestyle therapy	After 3 months of lifestyle therapy	At diagnosis			
Lipids	First-line medication: statin			< 3.4 mmol/L	< 3.4 mmol/L	< 2.6 mmol/L
LDL-C*	≥ 4.1 mmol/L after 6 months of lifestyle therapy	≥ 4.1 mmol/L after 3 months of lifestyle therapy	≥ 3.4 mmol/L at diagnosis			
Lipids	Medication options: fenofibrate, omega-3 fatty acid (~ 4 g/d EPA + DHA)			TG < 1.7 mmol/L		
TG†	Statin (if TG ≥ 1.7 mmol/L and non−HDL-C ≥ 3.7 mmol/L)			Non−HDL-C < 3.7 mmol/L		
	≥ 4.5 mmol/L after 6 months of lifestyle therapy	≥ 4.5 mmol/L after 3 ≥ of lifestyle therapy	≥ 4.5 mmol/L at diagnosis			
Hypertension	Medication options: ACEi, ARB, long-acting CCB, thiazide diuretics			SBP and DBP < 90th percentile (< 13 years old) or < 130/80 (≥ 13 years old)		
	Stage 1 HTN: after 3 months of lifestyle therapy	Stage 1 HTN: after 1 month of lifestyle therapy	Stage 1 and 2 HTN: within 1 week of diagnosis			
	Stage 2 HTN: within 1 week of diagnosis	Stage 2 HTN: within 1 week of diagnosis				

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; non−HDL-C, non−high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

Data from de Ferranti et al.[3]

* To convert to mg/dL, multiply by 38.6.

† To convert to mg/dL, multiple by 88.6.

High-risk coronary artery condition: Kawasaki disease

This acute, self-limited arteritis of unknown etiology occurs primarily in children < 5 years of age. The incidence is highest in Asian (particularly Japenese) children and Pacific Islanders. The incidence in Canada and the United States is similar at 25 to 30 per 100,000 children < 5 years of age per year, compared with > 250 per 100,000 in Japan.[68,69] The acute illness is marked by dramatic inflammation of all medium-sized arteries, multiple organs, and tissues leading to a range of striking signs and symptoms. The critical problem is development of coronary artery (CA) aneurysms in 20% to 25% of untreated patients. The incidence of CA involvement is significantly lower at < 5% for children treated with intravenous immunoglobulin in the acute stage.[69]

The CA pathology involves a 3-stage arteriopathy: acute necrotizing arteritis, followed by chronic inflammation and vasculitis, and luminal myofibroblastic proliferation.[70] Outcomes depend on the severity of CA involvement, which ranges from none to dilation to aneurysms of different sizes and characteristics. Myocardial infarctions occur because of acute thrombosis of aneurysms, or stenoses caused by progressive luminal occlusion from myofibroblastic proliferation. CA aneurysms from Kawasaki disease (KD) account for 5% of acute CA syndromes in adults <40 years of age.[69]

Children with CA aneurysms require specific long-term thromboprophylaxis beginning in the acute stage, when large aneurysms are at highest risk for thrombosis, and later with the concomitant development of stenoses. CA thrombosis with actual or impending lumen occlusion is an acute emergency requiring immediate thrombolysis. With large CA aneurysms, sustained thromboprophylaxis with anticoagulation is recommended; with small CA aneurysms, only a single or dual antiplatelet agent is recommended. Children with no CA involvement are thought to have no ongoing sequelae and are typically discharged from cardiology care.[69]

Atherosclerosis is not thought to be part of the specific vasculopathic process associated with KD, but CVRF optimization is recommended empirically in all children who have had CA aneurysms of any size.[3] Statins are being evaluated in acute KD and in children with CA aneurysms in the convalescent stage. With persistent CA aneurysms, statin therapy is recommended for empiric use for its presumed pleotropic effects: specifically, its anti-inflammatory properties.[3]

At-risk condition,emerging evidence: cystic fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive disease seen in the Caucasian population. A mutation in the CF transmembrane conductance regulator gene disrupts regulation of chloride and sodium ions across epithelial cell membranes, resulting in buildup of thick mucus throughout the body. Although CF is a multiorgan disease, its effects on the pulmonary system are the leading cause of patient morbidity and mortality. Decreased right-ventricular function, paralleling the presence of pulmonary hypertension, is a well-established late complication, but, with increasing survival, there is emerging concern about CV disease.[71] Certainly, known CVRFs for accelerated

atherosclerosis are common in the CF population, including chronic inflammation, dyslipidemia (primarily low HDL-C), and nephropathy.[72,73] CF-related diabetes is the most common comorbidity, occurring in ~20% of adolescents and 40% to 50% of adults.[74] Although studies of left-ventricular function in patients with CF have been inconclusive, recent echocardiographic-strain analysis revealed significant biatrial enlargement, impaired left-atrial conduit and reservoir functions, and abnormal atrial volume indexes, which were significant predictors of mortality.[75] Evaluation of arterial flow-mediated dilation has revealed both microvascular and conduit artery endothelial dysfunction in patients with CF, potentially secondary to oxidative stress.[76] By contrast, coronary angiography performed in preparation for lung transplantation in a small series of middle-aged Canadian patients with CF revealed no evidence of luminal narrowing or focal stenosis despite the presence of diabetes in 64% and dyslipidemia in 78% of these patients.[77] Clearly, further prospective evaluation is needed, as life expectancy continues to increase for this important group of patients.

Approach to Evaluation and Management

The goal for detecting, evaluating, and managing high-risk youth is to achieve primordial and primary prevention of cardiovascular disease. To accomplish this, the clinician must ensure that any of the underlying risk conditions (Table 2) are optimally managed and that other contributing CVRFs (Table 1) are either prevented from occurring or identified early and appropriately managed. There are a number of Canadian and international guidelines providing guidance on the management of at-risk conditions such as KD,[69] diabetes mellitus,[57] and heart transplantation[78] and CVRFs such as dyslipidemia,[4,79] hypertension,[39,80] and obesity.[17] These recommendations should guide the evaluation and management of specific CVRFs and conditions, with a general theme of pursuing more aggressive management, including lower thresholds for initiating pharmacotherapy and more aggressive treatment targets in patients with higher cardiovascular risk categories (Table 3 and Fig. 2).[3]

All patients with identified CVRF or high-risk conditions should undergo thorough evaluations for other CVRFs, behaviours, and risk conditions (Tables 1 and 2),[3] beginning with a detailed history and examination with subsequent investigations, as necessary, to exclude secondary causes and consequences of various CVRFs. All medications and supplements should be reviewed for their potential to exacerbate a CVRF or interact with a potential pharmacological strategy. A detailed family history of CVRFs and cardiovascular disease should be undertaken. A family history of premature cardiovascular disease (< 55 years old in men and < 65 years old in women) in extended first-degree family members (including grandparents, aunts, and uncles) is an important consideration, both in youth at risk for autosomal dominant-codominant conditions, such as FH, and in the general population. A strong family history may indicate a polygenic predisposition toward increased risk of cardiovascular disease. To this end, a cardiovascular risk score to quantify cardiovascular disease risk in a person's family history was recently formulated and applied to youths with bipolar disorder.[81] A detailed dietary and physical activity history should be performed. Involvement of key allied health professionals, such as dieticians and exercise physiologists, should be undertaken. Access to these resources, among others, may be limited, particularly among low-socioeconomic status communities and people in geographically remote communities. To help improve access for vulnerable or at-risk communities, we encourage the exploration of unique strategies that have recently been increasingly incorporated, such as telephone or virtual assessments. These strategies, developed to help provide necessary care during the SARS-CoV-2 pandemic, should become mainstays to help widely scale the provision of comprehensive care for all Canadian youth.

The initial physical examination should be complete and systematic to evaluate both for secondary causes and complications of the CVRFs and conditions in question. Height, weight, body mass index (BMI), and blood pressure should be measured in a standardized manner and then converted to age- and sex- (for height, weight, and BMI) or age-, sex-, and height-specific normative values (for blood pressure) to allow for appropriate categorization.[4,9] Waist circumference, particularly when indexed to height (waist-to-height ratio) is a useful additional measure that is more indicative of central adiposity and associated with CVRF clustering.[82,83] A subsequent laboratory assessment should involve the confirmation of the CVRF in question (for example, ambulatory blood pressure monitoring for hypertension), evaluation of associated CVRFs or conditions (for example, fasting glucose, lipid panel, liver enzymes for nonalcoholic fatty liver disease, lipoprotein(a) for patients with FH), consequences of the CVRFs or conditions (for example, renal function and echocardiography for patients with hypertension), and secondary causes of the CVRFs or conditions. Details of recommended investigations are found in relevant guidelines.[3,4,39]

Tables 2 and 3 and the algorithm in Figure 2 demonstrate the approach to risk stratification and management for children with conditions predisposing to early cardiovascular disease. Management begins with stratification by disease process as indicated by Table 2. Assessment of all CVRFs allows further stratification: If > 2 RFs are identified, the patient is reclassified into the next highest tier (Fig. 2). Tier-specific goals for CVRFs are indicated in step 3, with defined lower thresholds for initiating pharmacotherapy, and more aggressive treatment targets in patients with higher cardiovascular risk categories (Table 3). Rigourous, age-appropriate education in diet, activity, and smoking cessation is indicated for all risk tiers. For high-risk children, intensive therapeutic lifestyle change (TLC) like this is combined with condition-specific management, as described in the following section. For children in the moderate-risk category, intensive TLC alone is indicated before initiating pharmacotherapy for up to 6 months. Children in at risk categories are managed expectantly with standard guidelines.

For high-risk conditions, specific therapy is indicated to achieve blood pressure, LDL-C, glucose, and hemoglobin A1c goals. Management of the underlying condition should be optimized in conjunction with the managing pediatric subspecialist. As an example, in patients with T1DM, hyperglycemia should be minimized with frequent glucose checks and assessment of HbA1c and insulin levels per

pediatric endocrinology. The management of dyslipidemia and the indications for pharmacotherapy are based on the patient's risk category (Table 3).[3,4] In high-risk patients with an LDL-C $\geq$ 3.4 mmol/L, consideration of concurrent statin therapy at the onset of lifestyle changes is warranted.[3] Otherwise, the timing and thresholds for initiation of statins depend on the patient's underlying cardiovascular risk categorization (Table 3). The management of hypertriglyceridemia is typically reserved for those with marked elevations in triglyceride levels in an effort to reduce the risk for pancreatitis.[4] Lifestyle modifications, including reduced intake of simple carbohydrates and added sugars and increased moderate to vigourous physical activity ($\geq$ 5 hours per week), with weight-loss counselling as appropriate, should be undertaken.[3,4] If fasting triglyceride levels remain $\geq$ 4.5 mmol/L despite lifestyle changes, medications (fenofibrate, omega-3 fatty-acid supplements, or statins if there are also elevations in non−HDL-C) can be considered with consultation with a lipid specialist.

A diagnosis of elevated blood pressure as defined by the AAP Clinical Practice Guideline does not generally require pharmacotherapy.[39] Rather, TLC should be undertaken, including incorporation of a diet rich in fruits, vegetables, other sources of fiber, and lean protein diet with reductions in salt and added sugars (for example, the Dietary Approaches to Stop Hypertension [DASH] diet).[39] Blood pressure should then be routinely assessed every 4 to 6 months. For patients with diagnosed hypertension, management is dependent on the severity of the hypertension (stage 1 vs stage 2 hypertension) and the patient's cardiovascular risk category (Table 3).[3] The presence of target organ damage (such as elevations in indexed left-ventricular mass) may also prompt initiation of pharmacotherapy.[39] First-line medications typically include angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), long-acting calcium channel blockers, and thiazide diuretics.[39] Unfortunately, head-to-head clinical trials comparing antihypertensives in pediatric hypertension do not exist, so choice of medication is largely based on clinician preference, with consideration of specific clinical circumstances (such as ACEis or ARBs in patients with chronic kidney disease or diabetes mellitus). Further details outlining the use of antihypertensive pharmacotherapy in youths are provided in the AAP Clinical Practice Guideline.[39]

A Worked Case

A 14-year-old male patient was referred for evaluation and management of dyslipidemia. He had a lipid profile checked by his primary care provider as part of a clinical evaluation of his worsening (now severe) obesity (Fig. 2, Step 1: Moderate Risk). He has no other health issues, is on no medications or supplements, and his past medical history is unremarkable. Review of systems was remarkable for snoring. His family history is remarkable in that his father is obese and is on medication for hypertension, dyslipidemia, and T2DM, and he had a myocardial infarction at 43 years of age. The paternal grandfather had a stroke at 72 years of age. The mother is obese and is on medication for T2DM, but her family history is negative for cardiovascular disease. The patient has a younger brother, 10 years of age, who has a normal BMI and is described as healthy and very active. The family history thus demonstrates the presence of premature cardiovascular disease on the paternal side and CVRFs on both the paternal and maternal sides. Physical examination showed his height to be at the 50th percentile, weight above the 95th percentile, with BMI above 120% of the 95th percentile.[84] His waist-to-height ratio was 0.65 (elevated). His blood pressure by auscultation was 142/94 mm Hg, confirmed on repeated assessments. Acanthosis nigricans was evident around his neck and axilla. Abdominal striae were present. There were no other findings on examination. His lipid profile prompting the referral showed total cholesterol of 5.85 mmol/L, LDL-C 3.78 mmol/L, HDL-C 0.92 mmol/L, triglycerides 2.54 mmol/L, and non−HDL-C 4.93 mmol/L. His fasting glucose was borderline (6.2 mmol/L), hemoglobin A1c was at the upper end of normal (5.9%), and liver enzymes were mildly elevated. Lifestyle assessment showed high levels of several risk behaviours, including physical inactivity, likely driving his increasing adiposity.

At first glance, this patient has several CVRFs, likely related to his severe obesity. He likely has at least stage 1 hypertension, a significant combined dyslipidemia, a positive family history for premature cardiovascular disease, and is at risk for the development of T2DM, nonalcoholic fatty liver disease, and obstructive sleep apnea. Given that his hypertension is likely related to his obesity, a limited evaluation for secondary causes was performed and was negative. Ambulatory blood pressure monitoring confirmed a diagnosis of sustained hypertension, showing mean daytime and night-time systolic and diastolic blood pressures above the 95th percentile, the majority of measures above the 95th percentile, and abnormal night-time dipping (percentage drop from the mean daytime to mean nighttime levels. Less than 10% is considered abnormal and indicates abnormal circadian variation in blood pressure[85]). An echocardiogram showed normal anatomy and ventricular function but evidence of increased left-ventricular mass secondary to his obesity and hypertension. A sleep study showed evidence of obstructive sleep apnea. A repeat fasting lipid profile showed similar findings to the values from referral, and it was thought that although his combined dyslipidemia was primarily related to his obesity, given the higher than expected LDL-C, there was likely also a familial component. His fasting glucose and hemoglobin A1c levels were borderline high; therefore, an oral glucose tolerance test was performed, which suggested insulin resistance but not T2DM. A liver ultrasound confirmed the presence of nonalcoholic steatohepatitis. Hence, the evaluation confirmed the presence of multiple CVRFs in the context of a positive family history. Although severe obesity placed the patient at baseline in a moderate-risk category (Table 2), the presence of multiple CVRFs escalated his risk status to high risk (Fig. 2, Step 2).

Decision making regarding coordinated management of his multiple CVRFs started with an aggressive focus on improving his risk behaviours. He was referred to an exercise medicine program for evaluation and implementation of exercise prescription with targets of achieving an accumulation of 60 minutes of moderate to vigourous physical activity per day, while cutting screen time to no more than 1 hour per day (Fig. 2, Step 4). Working with them, he developed a planned exercise program: 30 minutes per day after school using an exercise bike already in the home, walking the family dog for

15 to 20 minutes each day, walking to school, and using an exercise app each day for 15 minutes with body-weight strength-training exercises. His mother agreed to participate with him and to encourage him. A dietician worked with the family to eliminate sugar-sweetened beverages and limit junk food and eating out to no more than once a week and to emphasize selection of healthier food choices in every setting. He was to limit his intake of refined carbohydrates (white bread was his preferred snack food) and to increase his intake of vegetables. He would start preparing a healthier lunch to take to school, rather than his preferred lunch of cafeteria French fries.

Given that he had evidence of target organ damage secondary to hypertension, a decision was made to start him on an ACEi, and he achieved target blood pressure control with improvements noted in subsequent ambulatory blood pressure monitoring (Fig. 2, Step 5). His lipid profile remained unchanged after about 3 months of lifestyle changes (minimal improvement in his triglyceride level, no change in level of adiposity). Given his multiple CVRFs, a decision was made to start him on a low dose of a statin, which improved his LDL-C and non-HDL-C levels markedly to near normal. The family receives ongoing support from the exercise medicine program and dietician, and his insulin resistance has not worsened.

Conclusions

Atherosclerosis begins in youth, and its progression is accelerated by the presence of CVRFs and risk conditions. In particular, the presence of multiple CVRFs and risk conditions can increase the rate of atherosclerotic progression geometrically, reducing the time to manifest CV disease events. Preventing or slowing atherosclerosis across the lifespan, beginning in youth, is necessary to achieve primordial and primary prevention goals. The total risk profile of children should be assessed and considered in management decisions and treatment goals, beginning with identification of those with multiple CVRFs or associated risk conditions.

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