CLINICAL REPORT

Lipid Screening and Cardiovascular Health in Childhood

Guidance for the Clinician in Rendering Pediatric Care

Stephen R. Daniels, MD, PhD, Frank R. Greer, MD, and the Committee on Nutrition

ABSTRACT

This clinical report replaces the 1998 policy statement from the American Academy of Pediatrics on cholesterol in childhood, which has been retired. This report has taken on new urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension, and cardiovascular disease in older children and adults. The approach to screening children and adolescents with a fasting lipid profile remains a targeted approach. Overweight children belong to a special risk category of children and are in need of cholesterol screening regardless of family history or other risk factors. This report reemphasizes the need for prevention of cardiovascular disease by following Dietary Guidelines for Americans and increasing physical activity and also includes a review of the pharmacologic agents and indications for treating dyslipidemia in children. *Pediatrics* 2008;122:198–208

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and morbidity in the United States.[1] Most of the clinical burden of CVD occurs in adulthood. However, research over the last 40 years has increasingly indicated that the process of atherosclerotic CVD begins early in life and is progressive throughout the life span.[2] It has also become clear that there is an important genetic component to the disease process that produces susceptibility but that environmental factors, such as diet and physical activity, are equally important in determining the course of the disease process.

This statement replaces the outdated 1998 American Academy of Pediatrics (AAP) policy statement "Cholesterol in Childhood," which has been retired.[3] New data emphasize the negative effects of excess dietary intake of saturated and trans fats and cholesterol as well as the effect of carbohydrate intake, the obesity epidemic, the metabolic/insulin-resistance syndrome, and the decreased level of physical activity and fitness on the risk of adult-onset CVD. In addition, more data are now available on the safety and efficiency of pharmacologic agents used to treat dyslipidemia. Most of these data were not available at the time of the previous statement.

A number of studies have identified potential risk factors for adult CVD.[4] The strongest risk factors include a high concentration of low-density lipoprotein (LDL), a low concentration of high-density lipoprotein (HDL), elevated blood pressure, type 1 or 2 diabetes mellitus, cigarette smoking, and obesity. Research in children and adolescents has demonstrated that some of these risk factors may be present at a young age,[5] and pediatricians must initiate the lifelong approach to prevention of CVD in their patients. The focus of this report is on improving lipid and lipoprotein concentrations during childhood and adolescence to lower the lifelong risk of CVD. The current obesity epidemic among children has increased the need for pediatric health care professionals to be knowledgeable of the risk factors for CVD and to implement the changes recommended in this report in practice.

DEVELOPMENT OF ATHEROSCLEROSIS IN CHILDREN

Autopsy studies, such as the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study and the Bogalusa Heart Study, have demonstrated that the atherosclerotic process begins in childhood.[2,6–8] The earliest pathologic finding in atherosclerosis is thought to be the fatty streak. This is characterized by an accumulation of lipid-filled macrophages within the intima of an artery.[9] The progression of atherosclerosis is characterized by continued accumulation of lipid-filled macrophages and a proliferation of vascular smooth muscle cells. These

smooth muscle cells migrate into the arterial intima and form a lesion called a fibrous plaque.[9] This lesion is responsible for adverse clinical outcomes, such as myocardial infarction and ischemic stroke, by either obstructing the arterial lumen or rupture of the plaque with release of thrombogenic substances.

The PDAY study included people 15 to 34 years of age who died of accidental causes.[7,8] The PDAY investigators examined indicators of cardiovascular risk status, measured at the time of autopsy. These indicators included concentrations of cholesterol and vascular pathologic features indicative of hypertension. They evaluated the extent of fatty streaks and fibrous plaques in the aorta and coronary arteries and found that the presence of increased coverage of the arterial intimal surface, with fatty streaks and fibrous plaques, was associated with increased traditional risk factors, such as elevation of cholesterol levels and blood pressure.[7,8]

The Bogalusa Heart Study investigators followed a cohort of children who had their risk-factor status measured during examinations at school.[2,6] As this population became older, some people died of accidental causes. The investigators were able to obtain autopsies on these people and evaluate the presence and extent of atherosclerotic lesions.[6] They reported that the extent of the arterial intimal surface covered with fatty streaks and fibrous plaques increased with age. The prevalence was almost 70% in young adulthood. They also found that the extent to which the intimal surface was covered with atherosclerotic lesions was significantly associated with elevation of concentrations of total cholesterol, LDL, and triglycerides, as well as a lower concentration of HDL. Another important finding was that increased coverage of atherosclerotic lesions was positively correlated with the number of risk factors for CVD present, such as dyslipidemia, high blood pressure, and obesity.[6]

More recently, noninvasive methods of imaging have allowed for the study of atherosclerosis development. The Muscatine Study used ultrasonography of the carotid arteries to evaluate intimal medial thickness (IMT), which has been shown to be an indicator of the atherosclerotic process in adults.[10] Carotid ultrasonography in adults aged 33 to 42 years showed that increased carotid IMT was associated with increased total cholesterol concentration and other CVD risk factors, such as high blood pressure, in childhood.[10] A second study, the Cardiovascular Risk in Young Finns Study, also showed a positive relationship between adolescent risk factors and subclinical measures of atherosclerosis in adulthood.[11] In this study of >2000 young adults, CVD risk status in adolescence was predictive of increased carotid IMT in adulthood, independent of the risk factors for CVD present in adulthood.

From these studies, it is increasingly clear that cholesterol concentrations can be elevated during childhood and adolescence and that increased concentrations in childhood are associated with increased risk of atherosclerosis and CVD in adulthood.

CHOLESTEROL CONCENTRATIONS IN CHILDHOOD AND ADOLESCENCE

Data from the Lipid Research Clinics prevalence studies have shown that the concentration of serum lipids and lipoproteins increases during early childhood and reaches concentrations similar to those seen in young adults by approximately 2 years of age.[12] This knowledge is important when making recommendations regarding screening, because concentrations before 2 years of age may not reflect values in subsequent years of childhood or adult values. Population-based studies, including the National Health and Nutrition Examination Surveys (NHANESs), have provided useful data on the distribution and trends in lipids and lipoproteins during childhood and adolescence. Data from the 1988–1994 NHANES for ages 4 to 19 years showed that the mean total cholesterol concentration was 165 mg/dL.[13] Age-specific values for mean total cholesterol concentration actually peaked at 171 mg/dL at 9 to 11 years of age.[13] The values subsequently decreased during pubertal development and then increased thereafter. This has important implications for the timing of cholesterol screening and the cut points used, because lipid concentrations are age and maturation dependent.[14]

There are also differences in cholesterol concentrations related to gender. In the 1988–1994 NHANES, females had higher total cholesterol and LDL concentrations than did males. Females also tended to have higher HDL concentrations than did males after pubertal development had occurred. Investigators for the Project HeartBeat! study reported that lipid and lipoprotein concentrations changed in different ways for males and females during development.[15] These developmental patterns of puberty are complicated by ethnicity, with black girls having the earliest onset of puberty.

There are also differences in cholesterol and triglyceride concentrations according to ethnic group. In the 1988–1994 NHANES, black children had higher HDL and lower triglyceride concentrations than did children of non-Hispanic white and Hispanic descent.[13] In the Cardiovascular Health in Children Study of 8- to 10-year-olds in North Carolina, black children had the highest prevalence of having a total serum cholesterol concentration of >200 mg/dL: 18.7%, compared with 11% in white children.[16] The overall prevalence in all ethnic groups of having a total cholesterol level of >200 mg/dL was 12.6%.

As observed in adults,[17] there have been changes over time in lipid and lipoprotein concentrations in children and adolescents. Ford et al[18] compared values from the 1988–1994 and 1999–2000 NHANESs. They found that, over this 12-year time period, triglyceride concentrations decreased approximately 8.8 mg/dL in adolescents aged 12 to 17 years, and total cholesterol, LDL, and HDL concentrations remained relatively stable. Hickman et al[13] compared data from the 1966–1970 NHANES with those from the 1988–1994 NHANES in children and adolescents aged 4 to 19 years and reported a decrease in mean total cholesterol concentration of approximately 7 mg/dL during this time. The reasons for these changes are not completely understood, but they may be related

to the increased efforts to alter diet and prevent CVD that have been in effect since the 1950s.

A substantial proportion of children and adolescents have elevated concentrations of lipids and lipoproteins. In the Child and Adolescent Trial for Cardiovascular Health, 13.3% of children in the 4th grade had total cholesterol concentrations of >200 mg/dL. The prevalence of total cholesterol concentrations of >200 mg/dL was 15.6% in girls and 11.1% in boys.[5] In the 1988–1994 NHANES, approximately 10% of adolescents had total cholesterol concentrations of >200 mg/dL, which is a level of concern in adults.[13]

An important epidemiologic aspect of cardiovascular risk in children is the tracking of lipid and lipoprotein concentrations over time. Tracking indicates the likelihood that children will maintain their percentile ranking over time. Such tracking has been demonstrated in a number of studies, most notably the Muscatine Study and Bogalusa Heart Study.[19–21] In the Muscatine Study, 75% of school-aged children who had total cholesterol concentrations greater than the 90th percentile at baseline had total cholesterol concentrations of >200 mg/dL in their early 20s. In the Bogalusa Heart Study, approximately 70% of the children with elevated cholesterol levels continued to have cholesterol elevations in young adulthood. The Muscatine investigators also evaluated other factors beyond childhood cholesterol concentrations that predicted cholesterol level elevation in adulthood.[19] They found that onset of obesity in adolescence and young adulthood, cigarette smoking, and use of oral contraceptives by women may have deleterious effects on adult concentrations of lipids and lipoproteins.

CLINICAL EVALUATION

A recommendation regarding a targeted approach to cholesterol screening for children from the National Cholesterol Education Program (NCEP) of the National Heart, Lung, and Blood Institute was published in 1992 and subsequently adopted by the AAP.[22] This approach recommends screening children with a family history of premature CVD or high blood concentrations of cholesterol. They also recommend screening pediatric patients for whom family history is not known or those who had other risk factors for CVD such as obesity, hypertension, and diabetes mellitus. Since publication of that guideline, research has focused on optimizing the approach to screening children and adolescents for cholesterol elevation and the subsequent treatment of cholesterol abnormalities. However, the results of this research have not led to consensus on pediatric screening, and many continue to advocate for screening on the basis of a positive family history. Some have maintained that the evidence is insufficient to recommend for or against routine screening for lipid disorders in childhood.[23] Others have suggested that a universal screening strategy similar to that recommended for adults be used for children and adolescents, although no pediatric organizations have recommended universal screening.[23]

The optimal screening program would identify children and adolescents with progressive atherosclerosis who are most at risk of CVD in adulthood. One problem is that, currently, no noninvasive clinically applicable tools are available to adequately assess the progression of atherosclerosis in children without familial hypercholesterolemia. This means that investigators and clinicians have often relied on cholesterol concentrations as a surrogate marker for this risk. In adults, this approach is well accepted and has led to the NCEP adopting the Framingham risk score to evaluate which patients are at highest 10-year risk of CVD and would benefit from more aggressive treatment.[24] Unfortunately, no similar risk score is available for children. Also, data supporting a particular level of childhood cholesterol that predicts risk of adult CVD do not exist, which makes the prospect of a firm evidence-based recommendation for cholesterol screening for children elusive.

There are problems with the targeted approach to screening on the basis of a family history of CVD or of cholesterol level elevation.[25] The assumption for this recommendation is that the family history will provide additional information regarding the genetic predisposition and shared environmental factors that may increase risk. Unfortunately, family history may not be known, and if it is known, it may be incomplete or inaccurate. It also presumes that adult family members have had their cholesterol level measured, will know their results, and understand the significance of those results. Unfortunately, this is often not the case.

Since the NCEP recommended targeted screening, investigators have attempted to evaluate its effectiveness. Generally, studies of the targeted approach have found that 35% to 46% of children and adolescents have had their cholesterol levels measured on the basis of a positive family history of CVD or elevated cholesterol concentration.[25–29] The reasons for this variability may be that populations may differ in adult prevalence of CVD or in the implementation of the default screening strategies for children and adolescents when family history is unknown or when other risk factors, including obesity and blood pressure elevation, are present. With the prevalence of obesity increasing[30] and the possibility that the prevalence of high blood pressure is also increasing,[31] this would lead to an increase in the percentage of children and adolescents who would qualify for having their cholesterol concentration determined. The studies of screening have also shown that although it is useful for identifying children with a cholesterol level elevation, 30% to 60% of children and adolescents with high cholesterol levels will be missed by the targeted strategy.[26,32,33] An important but unanswered question is whether the lack of identification and treatment of those children leads to increased risk of CVD development.

ABNORMAL CHOLESTEROL CONCENTRATIONS

The NCEP pediatric report recommended the cut points presented in Table 1 be used to identify children and adolescents with abnormal lipid and lipoprotein concentrations.[22] It is worth noting that the same values are used for all children, from 2 to 18 years of age. After 18 years of age, the concentrations presented in the NCEP report for adults would be used. As discussed previously, cholesterol concentrations change with age in children

Cut Points for Total Cholesterol and LDL Concentrations in Children and Adolescents

Category	Percentile	Total Cholesterol, mg/dL	LDL, mg/dL
Acceptable	<75th	<170	<110
Borderline	75th–95th	170–199	110–129
Elevated	>95th	>200	>130

Adapted from NCEP guidelines for children and adolescents.[22]

TABLE 2 **Lipid and Lipoprotein Distributions in Subjects Aged 5 to 19 Years**

	Males			Females		
	5–9 y	10–14 y	15–19 y	5–9 y	10–14 y	15–19 y
Total cholesterol, mg/dL						
50th percentile	153	161	152	164	159	157
75th percentile	168	173	168	177	171	176
90th percentile	183	191	183	189	191	198
95th percentile	186	201	191	197	205	208
Triglyceride, mg/dL						
50th percentile	48	58	68	57	68	64
75th percentile	58	74	88	74	85	85
90th percentile	70	94	125	103	104	112
95th percentile	85	111	143	120	120	126
LDL, mg/dL						
50th percentile	90	94	93	98	94	93
75th percentile	103	109	109	115	110	110
90th percentile	117	123	123	125	126	129
95th percentile	129	133	130	140	136	137
HDL, mg/dL						
5th percentile	38	37	30	36	37	35
10th percentile	43	40	34	38	40	38
25th percentile	49	46	39	48	45	43
50th percentile	55	55	46	52	52	51

Adapted from the Lipid Research Clinic Pediatric Prevalence Study.[12]

and adolescents and are particularly variable during puberty. The sensitivity and specificity of these cut-point concentrations for predicting adult lipid status may vary widely according to age and sexual maturation of the pediatric patient. Friedman et al[14] showed that the lowest sensitivity occurred at 14 to 16 years of age, when cholesterol values are generally lower, whereas the highest sensitivity occurred at 5 to 10 and 17 to 19 years of age. Of interest is that the results were similar regardless of whether the population was restricted to children with a positive parental history of CVD. It is also worth noting that the NCEP did not provide pediatric cut points for concentrations of triglycerides or HDL. Measurement of these variables has become more important, because they are part of the clustering of risk factors associated with obesity and often called the metabolic syndrome. The American Heart Association has recommended that triglyceride concentrations of >150 mg/dL and HDL concentrations of <35 mg/dL be considered abnormal for children and adolescents.[34] Again, a single cut point for all pediatric age groups may be limited by the known age, sexual, and ethnic differences in the concentrations of triglycerides and HDL.

Given the concerns for using the same cut points for all children, percentile values for concentrations of total cholesterol, triglycerides, LDL, and HDL according to age and gender are presented in Table 2. These values are from the 1981 prevalence study of the Lipid Research Clinics and were measured before the increase in prevalence of obesity.[12] These percentile values could be used in a similar fashion to those for blood pressure and BMI. In this case, LDL concentrations greater than the 95th percentile (or less than the 5th percentile for HDL concentration) would be considered abnormal, particularly if the abnormality was persistent over several office visits. LDL concentrations between the 90th and 95th percentiles (5th–10th for HDL concentration) would be considered borderline. Use of these tables and percentiles would reduce the clinical effects of natural changes in lipid and lipoprotein concentrations with age.

METABOLIC SYNDROME
The metabolic syndrome is a clustering of risk factors for CVD and diabetes mellitus that seems to be related to obesity and insulin resistance. The NCEP definition of the metabolic syndrome for adults is presented in Table 3. Currently, there is no accepted definition of the metabolic syndrome for children and adolescents. However,

several definitions have been proposed using the same factors but using percentile values for the cut points.[35–37]

Prevalence of the metabolic syndrome in any group depends on the variables and cut points chosen. Nevertheless, it does seem that the metabolic syndrome, regardless of the cutoffs used for various risk factors, is more prevalent in overweight children and adolescents. It also seems that the prevalence of the metabolic syndrome has increased in children and adolescents, reflecting the increased prevalence of obesity, prediabetes, and type 2 diabetes mellitus.[38,39] In addition, pathology studies such as the Bogalusa Heart Study have clearly shown that the presence of an increasing number of risk factors (as seen in the metabolic syndrome) is associated with increased risk of fatty streaks and fibrous plaques in the aorta and coronary arteries.[6] Generally, the approach to treatment of the metabolic syndrome is focused on decreasing the BMI percentile of obese children, which is usually accomplished via lifestyle changes in diet and physical activity. Kirk et al[40] demonstrated that the components of the metabolic syndrome can be improved by effective weight management. A relatively small de-

TABLE 3 **Definition of Metabolic Syndrome for Adults[25]**

Clinical Measure	Any 3 of the Following 5 Features
Waist circumference, cm	≥102 (men) or ≥88 (women)
Lipid levels	
Triglycerides, mg/dL	≥150
HDL, mg/dL	<40 (men) or <50 (women)
Blood pressure, mm Hg	≥130/85
Fasting glucose level (includes diabetes), mg/dL	>100

Note that there is no currently accepted definition of metabolic syndrome in children.

crease in BMI percentile can be effective. In adults, a weight loss of only 5% to 7% was shown to be successful in prevention of diabetes mellitus in the Diabetes Prevention Program.[41] These results indicate that for some overweight children, maintenance of weight during growth in height can be beneficial.

CLINICAL APPROACH FOR TREATMENT OF ABNORMALITIES IN LIPID AND LIPOPROTEIN CONCENTRATIONS

The 1992 guidelines for children and adolescents published by the NCEP recommended 2 broad approaches to lowering or minimizing cholesterol levels in young people. One is a population-based approach that focuses on lifestyle issues for all children. The second is an individual approach focusing on children and adolescents at high risk.[22] This comprehensive, 2-pronged approach was adopted previously by the AAP.[3]

Population Approach

The population approach addresses the diet and levels of physical activity that are appropriate for all children and adolescents. The AAP has also addressed these issues in its policy statement on active healthy living for children.[42] The emphasis on a healthy lifestyle is key in the prevention of the development of abnormal lipid and lipoprotein concentrations. Although changes in individuals are modest, implementation of this approach can result in substantially fewer people in the higher-risk range for CVD.[43]

Dietary changes using the population approach are not recommended for children younger than 2 years, because younger children are thought to require a relatively high intake of total fat to support rapid growth and development.[22] However, some studies have examined dietary intervention at a younger age. The ongoing Special Turku Risk Intervention Program was a randomized dietary intervention study beginning at approximately 7 months of age with weaning. Children in the intervention group were maintained on a diet with total fat of <30% of calories, saturated fat of <10% of calories, and cholesterol intake of <200 mg/day, using 1.5% cow milk after 12 months of age.[44] Outcomes in this study included both growth and neurologic function. No adverse effects of the intervention diet were observed on growth or neurologic outcomes. Other significant observations included lowering the LDL concentrations of boys and decreasing the prevalence of obesity in girls in the intervention groups, compared with controls.[45]

Most studies of dietary intervention have been performed on older children aged 8 to 11 years.[46] In the Dietary Intervention Study in Children, the lower saturated fat intervention diet was safe and resulted in significantly lower LDL concentrations in the dietary intervention group. It is encouraging that in both the Special Turku Risk Intervention Program and the Dietary Intervention Study in Children, children who received the dietary intervention were more likely to select healthier foods.[44,46] The results of these studies indicate that there is no harm associated with prudent diet changes, even when they are instituted in children soon after weaning.

TABLE 4   **Daily Estimated Calories and Recommended Servings for Grains, Fruits, Vegetables, and Milk/Dairy According to Age and Gender**

	1 y	2–3 y	4–8 y	9–13 y	14–18 y
Energy, kcal[a]	900	1000	—	—	—
Female	—	—	1200	1600	1800
Male	—	—	1400	1800	2200
Fat, % kcal	30–40	30–35	25–35	25–35	25–35
Milk/dairy, cups[b]	2[c]	2	2	3	3
Lean meat/beans, oz	1½	2	—	5	—
Female	—	—	3	—	5
Male	—	—	4	—	6
Fruits, cups[d]	1	1	1½	1½	—
Female	—	—	—	—	1½
Male	—	—	—	—	2
Vegetables, cups[d]	¾	1	—	—	—
Female	—	—	1	2	2½
Male	—	—	1½	2½	3
Grains, oz[e]	2	3	—	—	—
Female	—	—	4	5	6
Male	—	—	5	6	7

Calorie estimates are based on sedentary lifestyle. Increased physical activity will require additional calories (0–200 kcal/day if moderately physically active and 200–400 kcal/day if very physically active [1 kcal = 4.2 kJ]). — indicates data not applicable.
[a] For youth 2 years and older; adapted from Table 2, Table 3, and Appendix A-2 of the 2005 *Dietary Guidelines for Americans*. (www.healthierus.gov/dietaryguidelines). Nutrient and energy contributions from each group are calculated according to the nutrient-dense forms of food in each group (eg, lean meats and fat-free milk).
[b] Milk listed is fat free (except for children younger than 2 years). If 1%, 2%, or whole-fat milk is substituted, this will use, for each cup, respectively, 19, 39, or 63 kcal of discretionary calories and add 2.6, 5.1, or 9.0 g of total fat, of which 1.3, 2.6, or 4.6 g are saturated fat.
[c] For 1-year-old children, 2% fat milk is included. If 2 cups of whole milk are substituted, 48 kcal of discretionary calories will be used.
[d] Serving sizes are> ¼ > cup for 1 year of age,> ⅓ > cup for 2 to 3 years of age, and> ½ > cup for ≥4 years of age. A variety of vegetables should be selected from each subgroup over the week.
[e] Half of all grains should be whole grains.
Adapted with permission from American Heart Association. Table: dietary recommendations for children. Available at: www.americanheart.org/presenter.jhtml?identifier=3033999.

This includes use of reduced-fat milk in children after 12 months of age.

The American Heart Association recently provided updated dietary recommendations based on the new US Department of Agriculture dietary guidelines for children (older than 2 years) and adolescents (Table 4), which have been endorsed by the AAP.[47,48] These guidelines include recommendations that children and adolescents have a balanced caloric intake with sufficient physical activity to achieve an appropriate weight and consume more fruits, vegetables, fish, whole grains, and low-fat dairy products. It is also recommended that the intake of fruit juice, sugar-sweetened beverages and foods, and salt be reduced.

At the time of the earlier NCEP recommendations, there was less concern about trans fatty acids in processed and preprepared foods. Trans fatty acids in the diet tend to increase LDL concentration and do not raise HDL concentration.[49] Therefore, the new guidelines recommend that intake of trans fatty acids be limited to <1% of total calories.[47,48] This is easier for families to implement, because the fat content, including total grams of trans fatty acids, is now required on all food

labels. The largest source of trans fatty acids is the partially hydrogenated fat used in preparation of both fried and baked products both inside and outside the home.

Individual Approach

This approach focuses on people at high risk, such as children and adolescents with a family history of CVD or high cholesterol level or who themselves have high total cholesterol and LDL concentrations or other significant CVD risk factors. Some of these children have a strong genetic basis for their dyslipidemia, including the heterozygous form of familial hypercholesterolemia. These children and adolescents require a higher level of intervention. Initially, this intervention is focused on changing the diet. However, if this approach does not lower LDL to an acceptable concentration, these children may be candidates for pharmacologic intervention (see "Pharmacologic Intervention").

Diet

The recommended diet for the high-risk group is similar to that recommended for the population but restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. Again, data from randomized clinical trials in children as young as 7 months of age have demonstrated that these dietary recommendations are safe and do not interfere with normal growth, development, and sexual maturation.[44,46,48]

The success of this diet depends on a number of factors, including the saturated-fat intake before changes are implemented. Because dyslipidemia is often a familial problem, some children will already be on a diet relatively low in saturated fat. For these children with a genetic cause of dyslipidemia and LDL concentration of ≥190 mg/dL, it is unlikely that diet alone will achieve appropriate concentrations of LDL. Nevertheless, it is important to implement dietary changes that are associated with reduction of LDL concentrations, which may allow for use of lower doses of pharmacologic agents when they are started. Dietary changes are still an important part of any long-term intervention.

Implementation of this more aggressive diet is likely to require involvement of a dietitian to help families make the appropriate changes without compromising good nutrition. There have been anecdotal reports of parents implementing a very low-fat diet without supervision, leading to nutritional insufficiency and failure to thrive.[50] The home environment is very important to help children and adolescents make the best choices and maintain a healthful diet. Parents must be empowered to choose the time and available food and drink for meals and snacks. It is most helpful if everyone in the family is consuming a healthful diet and parents act as a role model for their children.

Dietitians can also help children and their families navigate the food environment outside the house, which has become increasingly important because more children do more eating outside the home environment. Because the schedules of children and their parents are increasingly complex, these alternative venues for eating are more attractive, because they may provide more convenience and efficiency. These venues include school, the homes of friends, and restaurants. Fast-food restaurants also provide carryout foods to be eaten in the home environment. Making healthful choices in these settings is more difficult because of the myriad external cues for eating, including advertising and the choices of peers.

Other Nonpharmacologic Approaches

Some adjuncts to dietary therapy have also been recommended. Increasing the intake of soluble fiber can be helpful in reducing plasma LDL concentration. Some studies have shown a modest reduction of LDL concentration by approximately 7%, but others have been equivocal.[51] Fiber is thought to bind with cholesterol in bile acids and remove it from the enterohepatic circulation. This often requires supplements of fiber. An appropriate dose of supplemental fiber is calculated as the child's age plus 5 g/day, up to a dose of 20 g/day at 15 years of age.[34]

Plant stanols and sterols are added to a number of products, including spreads and margarine, orange juice, yogurt drinks, cereal bars, and dietary supplements. These compounds lower the absorption of dietary cholesterol and, in adults, have been shown to reduce cholesterol concentration by approximately 5% to 10% with minimal adverse effects.[52] One of the few randomized clinical trials with children showed that a margarine product resulting in 20 g/day intake of plant sterol reduced LDL concentration by 8%.[53] The most important safety concern with these products is that they also result in decreased absorption of fat-soluble vitamins and β carotene.

Increased physical activity may also be useful for improving dyslipidemia in children and adolescents. Physical activity primarily affects HDL and triglyceride concentrations, but improvement of LDL concentration has also been documented.[54,55] Although there have been few randomized clinical trials to document the effects of physical activity as a specific intervention for children and adolescents, supportive data are available from epidemiologic studies.[55]

PHARMACOLOGIC INTERVENTION

The concentrations of LDL at which pharmacologic intervention is recommended for children 8 years and older and adolescents are presented in Table 5. It is recommended that pharmacologic intervention in children younger than 8 years only be implemented if they have the dramatic elevation of LDL concentration (>500 mg/dL) as seen with the homozygous form of familial hypercholesterolemia. For children and adolescents with diabetes, renal disease, congenital heart disease, or collagen vascular diseases and those who are cancer survivors, more aggressive treatment of high LDL concentration is indicated.[56]

It is difficult to develop an evidence-based approach for the specific age at which pharmacologic treatment should be implemented. At the time of the NCEP report,

TABLE 5 Recommended LDL Concentrations for Pharmacologic Treatment of Children and Adolescents 10 Years and Older[22,56]

Patient Characteristics	Recommended Cut Points
No other risk factors for CVD	LDL concentration is persistently >190 mg/dL despite diet therapy
Other risk factors present, including obesity, hypertension, or cigarette smoking or positive family history of premature CVD	LDL concentration is persistently >160 mg/dL despite diet therapy
Children with diabetes mellitus	Pharmacologic treatment should be considered when LDL concentration is ≥130 mg/dL

there were few studies of pharmacologic intervention in children, and the degree to which such therapy would produce important adverse effects was not known.[22] More recent studies of children and adolescents have established the effectiveness and safety of the available agents, including their use in prepubertal children and children between 8 and 10 years of age. It is not known whether there is an age at which development of the atherosclerotic process is accelerated. Pathology studies have shown that the frequency of fibrous plaques increases with age.[6–8] Although these studies were performed before the recent epidemic of childhood obesity, increased BMI was an important risk factor for both fatty streaks and fibrous plaques. It is possible that if these studies were repeated, they would show an overall more aggressive atherosclerotic process in children today.

MEDICATIONS AVAILABLE FOR THE TREATMENT OF DYSLIPIDEMIA

Several classes of medication are available for treatment of dyslipidemia in children and adolescents (see Table 6).

Bile Acid–Binding Resins

Bile acid–binding resins work by binding the cholesterol in bile acids in the intestinal lumen, which prevents their reuptake as part of the enterohepatic circulation. The advantage of these medications is that they do not have systemic effects. Average lowering of cholesterol is 10% to 20% below baseline. Although adverse effects of bile acid–binding resins are limited to gastrointestinal discomfort, these adverse effects and the fact that the medication is difficult to take limits their use for young patients. They are available as either a granular powder that must be mixed with liquid or as a tablet that is large and cannot be broken. McCrindle et al[57] compared the 2 formulations in children with heterozygous familial hypercholesterolemia. They found that the tablet form was more acceptable, but gastrointestinal complaints were common for both groups, and compliance was generally poor.

TABLE 6 Classes of Medication for Treatment of Dyslipidemia in Children and Adolescents

Class	Potential Adverse Effects
Bile acid sequestrant	Gastrointestinal symptoms, constipation, cramping, bloating
Cholesterol-absorption blocker	Gastrointestinal symptoms
3-Hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors	Myopathy, rhabdomyolysis, increased hepatic transaminase levels, teratogenicity

Niacin

Niacin or nicotinic acid can be effective in lowering LDL and triglyceride concentrations while increasing HDL concentration. The mechanism of action is by decreasing hepatic production of very low-density lipoprotein (VLDL). Niacin may also lower lipoprotein(a). Because of these effects, niacin is a potentially attractive medication for treatment of dyslipidemia. Unfortunately, the adverse effects associated with niacin make it very difficult to use it in pediatric clinical practice. Adverse effects include flushing, which is quite common, as well as hepatic failure, myopathy, glucose intolerance, and hyperuricemia. In 1 pediatric study, adverse effects such as flushing occurred in 76% of the children, and elevation of hepatic transaminase concentrations occurred in 26%.[58] Because of those adverse effects, niacin should not be recommended for routine use in the treatment of pediatric dyslipidemia.

3-Hydroxy-3-methyl-glutaryl Coenzyme A Reductase Inhibitors (Statins)

Statins inhibit the rate-limiting enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A reductase for endogenous synthesis of cholesterol, which lowers the intracellular cholesterol level and upregulates the LDL receptors, resulting in increased clearance of LDL from the circulation. In general, the statins are well tolerated and result in cholesterol lowering of 20% to 50% below baseline, depending on the baseline value and the dose used.[59] In adults, a 1% reduction in LDL concentration results in a reduction of coronary events by approximately 1%. Adverse effects of statins are related to increased hepatic transaminase levels and also elevations of creatine kinase, which may be associated with rare but clinically important episodes of rhabdomyolysis. There is also a concern about the potential of statin medications to be teratogenic, so they are not recommended for women who are pregnant, seeking to become pregnant, or breastfeeding. Patients should be monitored with periodic measurement of liver transaminase and creatine kinase levels. Patients should also be instructed to report symptoms of muscle aches or cramping.

There have been a number of clinical trials of statins in children and adolescents.[60–67] Although these studies have generally been short-term, they have shown statins to be safe and effective in lowering cholesterol concentrations. More recent studies have included measures of vascular structure and function. For example, de Jongh et al[68] evaluated the response of the brachial artery to ischemia and subsequent hyperemia. This evaluation used ultrasonography and

has been found to be a measure of the function of the vascular endothelium. In adults, endothelial dysfunction has been shown to be an early marker of atherosclerosis. De Jongh et al[68] demonstrated improvement in endothelial function in children with high cholesterol levels who were treated with a statin, compared with those who were treated with placebo. Wiegman et al[69] showed that children with hypercholesterolemia treated with placebo had an increase in carotid IMT over 2 years, whereas children treated with a statin medication had regression of carotid IMT. The results of these studies are encouraging in that these noninvasive vascular measurements are thought to provide an assessment of the extent of the atherosclerotic process, which has an effect on both the structure and function of arteries. Furthermore, this study included prepubertal children as young as 8 years of age, and on the basis of these results and reassuring safety data, the US Food and Drug Administration has approved the use of pravastatin for children with familial hypercholesterolemia who are 8 years and older, regardless of pubertal status.

Cholesterol-Absorption Inhibitors

The dietary cholesterol-absorption inhibitors represent the newest class of cholesterol-lowering agents. Although they are thought to act mainly on intestinal absorption, unlike resins, these drugs are absorbed, enter the enterohepatic circulation, and may have systemic effects. Ezetimibe has been shown to reduce LDL concentrations by 20%, but in adults they are used primarily in combination with statins. These medications have not been extensively studied in children, particularly in combination with other medications such as statins. Because the adverse effects are limited to gastrointestinal discomfort and they come in a palatable, small tablet form, they represent a potentially important first-line treatment for children. Additional study will be needed to evaluate their long-term effectiveness in young patients.

Fibrates

Pharmacologic therapy for elevated triglyceride concentrations, such as the fibrates, has not been extensively studied in children. Fibric acid derivatives inhibit the synthesis and increase the clearance of the VLDL apoprotein B, which then leads to a decrease in VLDL production. These medicines also inhibit peripheral lipolysis and decrease hepatic extraction of free fatty acids, which reduces hepatic triglyceride production. These medications should be used cautiously and under the supervision of a pediatric lipid specialist. The adverse effects of fibrates are similar to those of statins. The risk of myopathy and rhabdomyolysis is markedly increased when fibrates (especially gemfibrozil) are used in combination with statins or in patients with renal insufficiency.

SUMMARY

1. The population approach to a healthful diet should be recommended to all children older than 2 years according to Dietary Guidelines for Americans. This approach includes the use of low-fat dairy products. For children between 12 months and 2 years of age for whom overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or CVD, the use of reduced-fat milk would be appropriate.

2. The individual approach for children and adolescents at higher risk for CVD and with a high concentration of LDL includes recommended changes in diet with nutritional counseling and other lifestyle interventions such as increased physical activity.

3. The most current recommendation is to screen children and adolescents with a positive family history of dyslipidemia or premature ($\leq$55 years of age for men and $\leq$65 years of age for women) CVD or dyslipidemia. It is also recommended that pediatric patients for whom family history is not known or those with other CVD risk factors, such as overweight (BMI $\geq$ 85th percentile, <95th percentile), obesity (BMI $\geq$ 95th percentile), hypertension (blood pressure $\geq$ 95th percentile), cigarette smoking, or diabetes mellitus, be screened with a fasting lipid profile.

4. For these children, the first screening should take place after 2 years of age but no later than 10 years of age. Screening before 2 years of age is not recommended.

5. A fasting lipid profile is the recommended approach to screening, because there is no currently available noninvasive method to assess atherosclerotic CVD in children. This screening should occur in the context of well-child and health maintenance visits. If values are within the reference range on initial screening, the patient should be retested in 3 to 5 years.

6. For pediatric patients who are overweight or obese and have a high triglyceride concentration or low HDL concentration, weight management is the primary treatment, which includes improvement of diet with nutritional counseling and increased physical activity to produce improved energy balance.

7. For patients 8 years and older with an LDL concentration of $\geq$190 mg/dL (or $\geq$160 mg/dL with a family history of early heart disease or $\geq$2 additional risk factors present or $\geq$130 mg/dL if diabetes mellitus is present), pharmacologic intervention should be considered. The initial goal is to lower LDL concentration to <160 mg/dL. However, targets as low as 130 mg/dL or even 110 mg/dL may be warranted when there is a strong family history of CVD, especially with other risk factors including obesity, diabetes mellitus, the metabolic syndrome, and other higher-risk situations.

REFERENCES

1. American Heart Association. *Heart Disease and Stroke Statistics: 2006 Update*. Dallas, TX: American Heart Association; 2006
2. Newman WP III, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa Heart Study. *N Engl J Med.* 1986; 314(3):138–144
3. American Academy of Pediatrics, Committee on Nutrition. Cholesterol in childhood. *Pediatrics.* 1998;101(1 pt 1):141–147
4. Ross R. The pathogenesis of atherosclerosis: an update. *N Engl J Med.* 1986;314(8):488–500
5. Webber LS, Osganian V, Luepker RV, et al. Cardiovascular risk factors among third grade children in four regions of the United States. The CATCH Study: Child and Adolescent Trial for Cardiovascular Health. *Am J Epidemiol.* 1995;141(5):428–439
6. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and the early development of atherosclerosis. Bogalusa Heart Study. *N Engl J Med.* 1998;338(23):1650–1656
7. McGill HC Jr, McMahan CA, Zieske AW, Malcom GT, Tracy RE, Strong JP. Effect of nonlipid risk factors on atherosclerosis in youth with favorable lipoprotein profile. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Circulation.* 2001;103(11):1546–1550
8. McGill HC Jr, McMahan CA, Malcolm GT, Oalmann MC, Strong JP. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. *Arterioscler Thromb Vasc Biol.* 1997;17(1):95–106
9. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol.* 1995;15(9): 1512–1531
10. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation.* 2001;104(23):2815–2819
11. Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA.* 2003;290(17):2277–2283
12. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind B. Lipid and lipoprotein distributions in white children ages 6–19 yrs: the Lipid Research Clinics Program Prevalence Study. *J Chronic Dis.* 1981;34(1):27–39
13. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. *Prev Med.* 1998; 27(6):879–890
14. Friedman LA, Morrison JA, Daniels SR, McCarthy WF, Sprecher DL. Sensitivity and specificity of pediatric lipid determinations for adult lipid status: findings from the Princeton Lipid Research Clinics Prevalence Program Follow-up Study. *Pediatrics.* 2006;118(1):165–172
15. Labarthe DR, Dai S, Fulton J. Cholesterol screening in children: insights from Project HeartBeat! and NHANES III. *Prog Pediatr Cardiol.* 2003;17(2):169–178
16. Bradley CB, Harrell JS, McMurray RG, Bangdiwala SI, Frauman AC, Webb JP. Prevalence of high cholesterol, high blood pressure, and smoking among elementary school children in North Carolina. *N C Med J.* 1997;58(5):362–367
17. Goff DC Jr, Labarthe DR, Howard G, Russell GB. Primary prevention of high blood cholesterol concentrations in the United States. *Arch Intern Med.* 2002;162(8):913–919
18. Ford ES, Mokdad AH, Ajani UA. Trends in risk factors for cardiovascular disease among children and adolescents in the United States. *Pediatrics.* 2004;114(6):1534–1544
19. Lauer RM, Lee J, Clarke WR. Factors affecting the relationship between childhood and adult cholesterol levels: the Muscatine Study. *Pediatrics.* 1988;82(3):309–318
20. Lauer RM, Clarke WR. Use of cholesterol measurements in childhood for the prediction of adult hypercholesterolemia: the Muscatine Study. *JAMA.* 1990;264(23):3034–3038
21. Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of serum and lipids and lipoproteins from childhood to adulthood: the Bogalusa Heart Study. *Am J Epidemiol.* 1991; 133(9):884–899
22. American Academy of Pediatrics. National Cholesterol Education Program: report of the expert panel on blood cholesterol levels in children and adolescents. *Pediatrics.* 1992;89(3 pt 2): 525–584
23. US Preventive Services Task Force. Screening for lipid disorders in children: US Preventive Task Force recommendation statement. *Pediatrics.* 2007;120(1). Available at: www.pediatrics.org/cgi/content/full/120/1/e215
24. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486–2497
25. Dennison BA, Jenkins PL, Pearson TA. Challenges to implementing the current pediatric cholesterol screening guidelines into practice. *Pediatrics.* 1994;94(3):296–302
26. Rifai N, Neufeld E, Ahlstrom P, Rimm E, D'Angelo L, Hicks JM. Failure of current guidelines for cholesterol screening in urban African-American adolescents. *Pediatrics.* 1996;98(3 pt 1): 383–388
27. Råstam L, Hannan PJ, Luepker RV, Mittelmark MB, Murray DM, Slater JS. Seasonal variation in plasma cholesterol distributions: implications for screening and referral. *Am J Prev Med.* 1992;8(6):360–366
28. Williams RR, Hunt SC, Barlow GK, et al. Prevention of familial

cardiovascular disease by screening for family history and lipids in youths. *Clin Chem.* 1992;38(8B pt 2):1555–1560

29. Bachman RP, Schoen EJ, Stembridge A, Jurecki ER, Imagire RS. Compliance with childhood cholesterol screening among members of a prepaid health plan. *Am J Dis Child.* 1993;147(4):382–385

30. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA.* 2006;295(13):1549–1555

31. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA.* 2004;291(17):2107–2113

32. Diller PM, Huster GA, Leach AD, Laskarzewski PM, Sprecher DL. Definition and application of the discretionary screening indicators according to the National Cholesterol Education Program for Children and Adolescents. *J Pediatr.* 1995;126(3):345–352

33. Griffin TC, Christoffel KK, Binns HJ, McGuire PA. Family history evaluation as a predictive screen for childhood hypercholesterolemia. Pediatric Practice Research Group. *Pediatrics.* 1989;84(2):365–373

34. Kavey RE, Daniels SR, Lauer RM, et al. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation.* 2003;107(11):1562–1566; copublished in *J Pediatr.* 2003;142(4):368–372

35. Cook S, Weitzman A, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med.* 2003;157(8):821–827

36. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med.* 2004;350(23):2362–2374

37. Cruz ML, Goran MI. The metabolic syndrome in children and adolescents. *Curr Diab Rep.* 2004;4(1):53–62

38. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr.* 2005;146(5):693–700

39. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin dependent diabetes mellitus among adolescents. *J Pediatr.* 1996;128(5 pt 1):608–615

40. Kirk S, Zeller M, Claytor R, Santangelo M, Khoury PR, Daniels SR. The relationship of health outcomes to improvement in BMI in children and adolescents. *Obes Res.* 2005;13(5):876–882

41. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care.* 2006;29(9):2102–2107

42. American Academy of Pediatrics, Council on Sports Medicine and Fitness, Council on School Health. Active healthy living: prevention of childhood obesity through increased physical activity. *Pediatrics.* 2006;117(5):1834–1842

43. Rose G. Sick individuals and sick populations. *Int J Epidemiol.* 1985;14(1):32–38

44. Salo P, Viikari J, Hämäläinen M, et al. Serum cholesterol ester fatty acids in 7- and 13-month-old children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet: the STRIP baby project. Special Turku Coronary Risk Factor Intervention Project for Children. *Acta Paediatr.* 1999;88(5):505–512

45. Hakanen M, Lagström H, Kaitosaari T, et al. Development of overweight in an atherosclerosis prevention trial starting in early childhood: the STRIP study. *Int J Obes (Lond).* 2006;30(4):618–626

46. Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein-cholesterol: the Dietary Intervention Study in Children (DISC). *JAMA.* 1995;273(18):1429–1435

47. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee [published corrections appear in *Circulation.* 2006;114(23):e629 and *Circulation.* 2006;114(1):e27]. *Circulation.* 2006;114(1):82–96

48. Gidding SS, Dennison BA, Birch LL, et al. Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association. *Circulation.* 2005;112(13):2061–2075

49. Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. Trans fatty acids and coronary heart disease. *N Engl J Med.* 1999;340(25):1994–1998

50. Lifshitz F, Tarim O. Considerations about dietary fat restrictions for children. *J Nutr.* 1996;126(4 suppl):1031S–1041S

51. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing. *Circulation.* 2007;115(14):1948–1967

52. Lichtenstein AH, Deckelbaum RJ; American Heart Association Science Advisory. Stanol/sterol ester-containing foods and blood cholesterol levels: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation.* 2001;103(8):1177–1179

53. Tammi A, Rönnemaa T, Miettinen TA, et al. Effects of gender, apolipoprotein E phenotype and cholesterol-lowering by plant stanol esters in children: the STRIP study. Special Turku Coronary Risk Factor Intervention Project. *Acta Paediatr.* 2002;91(11):1155–1162

54. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation.* 2004;109(22):2807–2816

55. Strong WB, Malina RM, Blimkie CJ, et al. Evidence-based physical activity for school-age youth. *J Pediatr.* 2005;146(6):732–737

56. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; 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. *Circulation.* 2006;114(24):2710–2738

57. McCrindle BW, O'Neill MB, Cullen-Dean G, Helden E. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr.* 1997;130(2):266–273

58. Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL, Newburger JW. Niacin treatment in hypercholesterolemia in children. *Pediatrics.* 1993;92(1):78–82

59. Waters DD. What the statin trials have taught us. *Am J Cardiol.* 2006;98(1):129–134

60. Ducobu J, Brasseur D, Chaudron JM, et al. Simvastatin use in children. *Lancet.* 1992;339(8807):1488

61. de Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation.* 2002;106(17):2231–2237

62. Firth JC, Marais AD, Byrnes P, Fusco RA, Bonnici F. Fluvastatin in heterozygous familial hypercholesterolemia. *Cardiol Young.* 2000;10(suppl 2):35
63. McCrindle BW, Heldon E, Cullen-Dean G, Conner WT. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. *Pediatr Res.* 2002; 51(6):715–721
64. Knipscheer HC, Boelen CC, Kastelein JJ, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res.* 1996;39(5):867–871
65. Lambert M, Lupien PJ, Gagné C, et al. Treatment of familial hypercholesterolemia in children and adults: effect of lovastatin. Canadian Lovastatin in Children Study Group. *Pediatrics.* 1996;97(5):619–628
66. Stein EA, Illingworth DR, Kwiterovich PO Jr, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA.* 1999;281(2):137–144
67. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr.* 2003;143(1): 74–80
68. de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol.* 2002;40(12):2117–2121
69. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA.* 2004;292(3):331–337