

## 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 of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing

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**Abstract**—Despite compliance with lifestyle recommendations, some children and adolescents with high-risk hyperlipidemia will require lipid-lowering drug therapy, particularly those with familial hypercholesterolemia. The purpose of this statement is to examine new evidence on the association of lipid abnormalities with early atherosclerosis, discuss challenges with previous guidelines, and highlight results of clinical trials with statin therapy in children and adolescents with familial hypercholesterolemia or severe hypercholesterolemia. Recommendations are provided to guide decision-making with regard to patient selection, initiation, monitoring, and maintenance of drug therapy. (*Circulation*. 2007;115:000-000.)

**Key Words:** AHA Scientific Statements ■ lipids ■ pediatrics ■ drugs ■ hypercholesterolemia

Drug therapy of high-risk lipid abnormalities, particularly lowering of low-density lipoprotein (LDL) cholesterol levels, has resulted in great advances in the prevention and treatment of atherosclerotic cardiovascular disease in adults. Definitive evidence now indicates that the atherosclerotic disease process begins in childhood and that the rate of progression is greatly increased by lipid abnormalities and their severity. The prevalence of lipid abnormalities in children is increasing, primarily in association with the concomitant epidemic of obesity and the metabolic syndrome. Because overweight and associated lipid abnormalities in children have been shown to persist or track into adulthood, the epidemic of increased cardiovascular risk may soon burgeon into an epidemic of premature cardiovascular disease. Although effective population-based strategies are essential and the first priority to reversing this trend, selected individuals with more extreme lipid abnormalities or associated high-risk conditions or risk factors may be identified for whom lifestyle interventions are not sufficiently effective and drug therapy may be of benefit.

Although there has been a general reluctance to use drug therapy to treat lipid abnormalities in children,<sup>1</sup> increasing evidence suggests effectiveness and short-term safety similar to those in adults. The purposes of this statement are (1) to examine the atherosclerotic process in children and its relationship to lipid abnormalities, (2) to review and discuss existing screening and management guidelines and their limitations, (3) to highlight current knowledge specific to drug therapy in children, and (4) to provide general recommendations for pharmacological management of high-risk lipid abnormalities in children and adolescents. We define high-risk lipid abnormalities as primary and secondary conditions associated with extreme lipid abnormalities or conditions with an underlying high risk of cardiovascular disease whereby the presence and severity of lipid abnormalities may further exacerbate that risk. The statement is not meant to imply advocacy of widespread use of medications to treat the epidemic of lipid abnormalities associated with childhood obesity, for which strategies aimed at achieving sufficient weight loss are the cornerstone of therapy.

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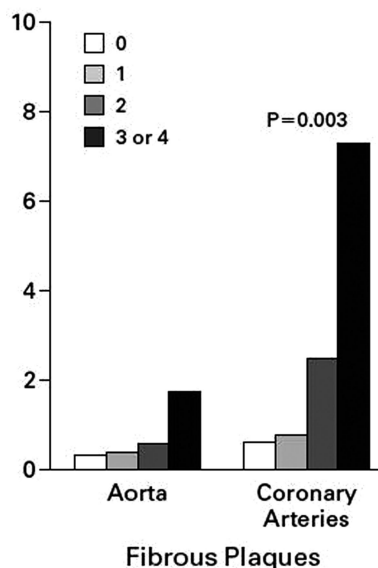
### The Atherosclerotic Process in Children

It has become clear that atherosclerotic cardiovascular disease begins in childhood and is progressive. This provides the strongest rationale for aggressive treatment of risk factors in individuals at greater risk for cardiovascular disease at an early age. The earliest pathological abnormality in atherosclerosis is the fatty streak, which is an accumulation of lipid-filled macrophages within the intima of the artery. With increasing age, lipid may continue to accumulate. In response to this lipid accumulation, macrophages and smooth muscle cells proliferate and migrate into the intima and media to form a fibrous plaque lesion. Advanced and complicated fibrous plaques are vulnerable to rupture, which initiates a cascade of events leading to the formation of thrombus. This can lead to occlusion of the artery and subsequent myocardial infarction or stroke. Complications also can occur when there is vascularization of the plaque, which can lead to hemorrhage and swelling within the plaque and occlusion of the arterial lumen. The American Heart Association Committee on Lesions has described the gross and microscopic aspects of the development of atherosclerosis.<sup>2,3</sup>

### Pathology Studies

It is well known that most clinically apparent atherosclerotic disease occurs in adulthood. The understanding of the early stages of the development of atherosclerosis has been hampered by the lack of simple, noninvasive methods to measure the presence and progression of atherosclerotic lesions. Thus, research in this area has had to rely on autopsies done on individuals who have died accidentally or in combat. The first such studies were done during the Korean War<sup>4</sup> and subsequently the war in Vietnam.<sup>5</sup> McNamara et al<sup>5</sup> found that of 105 soldiers killed in Vietnam at a mean of 22 years of age who had an autopsy, 45% had some evidence of coronary atherosclerosis, and 5% had gross evidence of severe coronary artery atherosclerosis. The limitation of these early autopsy studies was that the risk factor status of the soldiers examined was not known. Therefore, it was not possible to determine whether lipid abnormalities, hypertension, or other cardiovascular risk factors were associated with the presence or severity of the atherosclerotic lesions.

Subsequent studies of pathology were able to evaluate the relationship between risk factors and the presence of atherosclerotic lesions. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study is a multicenter autopsy study.<sup>6</sup> Subjects were individuals 15 to 34 years of age who were the victims of accidental trauma, suicide, or homicide. Subjects underwent autopsy in forensic laboratories within 48 hours of death. Examination of the risk factor status was inferred at the time of autopsy from serum analysis for cholesterol, renal artery intimal thickness for hypertension, and weight and length for body mass index. The PDAY investigators found that cardiovascular risk factors such as elevated cholesterol levels and blood pressure were associated with the extent of fatty streaks and fibrous plaques in the arteries of these young subjects.<sup>6,7</sup> McMahan et al<sup>8</sup> recently derived a predictive equation using multiple traditional risk factors that accurately predicted advanced atherosclerotic lesions noted at autopsy in young adults. This approach may



**Figure 1.** The effect of multiple risk factors on the extent of atherosclerosis in the aorta and coronary arteries in children and young adults. Values shown are the percentages of the intimal surface covered with fibrous plaques in subjects with 0, 1, 2, and 3 or 4 risk factors. Reproduced from Berenson et al<sup>10</sup> with permission from the Massachusetts Medical Society. Copyright 1998 Massachusetts Medical Society. All rights reserved.

be considered similar to the current approach of risk stratification in adults and may prove to be a useful adjunct to guide screening and treatment recommendations in youth.

The Bogalusa Heart Study also has included a pathology component in its investigation.<sup>9</sup> This community-based epidemiological study collected a large amount of information on cardiovascular risk factors during childhood. In the pathology study, individuals who died of accident or homicide and had previously been studied as part of the Bogalusa Heart Study underwent autopsy. The Bogalusa investigators found that the prevalence and extent of the arterial surface covered with fatty streaks in the coronary arteries increased with age, as did the prevalence of fibrous plaques. Fatty streaks were present in  $\approx 50\%$  of individuals during childhood and in  $\approx 85\%$  of young adults. The prevalence of fibrous plaques increased from 8% in childhood to 69% in young adulthood.<sup>9,10</sup> The extent of atherosclerotic lesions was significantly correlated with elevations in serum total and LDL cholesterol, triglycerides, blood pressure, and body mass index during childhood and has been shown to rise exponentially with increasing number of risk factors (Figure 1).<sup>9,10</sup>

Tuzcu et al<sup>11</sup> studied the coronary arteries of heart transplant recipients using intravascular ultrasound  $\approx 1$  month after transplantation. The average age of the heart donors was  $33 \pm 13$  years. The prevalence of atherosclerotic lesions in these transplanted donor hearts varied from 17% in donors  $< 20$  years of age to 85% in donors  $> 50$  years of age.

Napoli et al<sup>12</sup> identified early atherosclerotic lesions on postmortem examination of fetuses delivered from hypercholesterolemic mothers. In addition, autopsies of young infants and children showed that the extent of involvement of the abdominal aorta with atherosclerotic lesions was much higher and increased more rapidly with age in those who were born

to mothers who were hypercholesterolemic compared with normocholesterolemic mothers, despite normal lipid levels in the children. This suggests that passive in utero exposure to a hyperlipidemic environment may have programmed these children for accelerated atherosclerosis.

These pathology data suggest that the process of atherosclerosis begins in childhood with the development of fatty streaks. The lesions then appear to progress to fibrous plaque lesions, which may occur as early as adolescence and increase in prevalence and severity into adulthood. It is clear that lipid abnormalities are associated with this process and contribute to the synergy of multiple risk factors.<sup>8</sup> This suggests that aggressive treatment of lipid abnormalities may be beneficial in appropriate patients for preventing or slowing the progression of atherosclerosis.

### In Vivo Studies

Although pathology studies are useful, they are limited by the low mortality rate among pediatric subjects and the feasibility and degree of rigor with which risk factors can be assessed. The importance of identifying and treating children with elevated levels of cardiovascular risk factors is evident from studies relating risk factors measured in childhood to noninvasive studies of vascular structure and function both in childhood and later in life.

Ultrasound has been used to noninvasively assess the thickness of the intima-media complex at standardized locations within the carotid arteries as an indicator of atherosclerotic vascular involvement. Not only are risk factors in childhood associated with increased carotid intima-media thickness,<sup>13</sup> but the cumulative burden of risk factors such as increasing levels of LDL cholesterol help to predict carotid intima-media thickness in young adults.<sup>14</sup> Clustering of risk factors also affects carotid intima-media thickness, which increases with increasing numbers of risk factors even in healthy adolescents.<sup>15,16</sup> These increases in carotid intima-media thickness, seen in children with familial hypercholesterolemia and in normal children, may be mediated through both traditional risk factors such as LDL and high density lipoprotein (HDL) cholesterol and nontraditional ones such as apolipoprotein B, fibrinogen, homocysteine,<sup>17</sup> and levels of inflammation as indicated by C-reactive protein.<sup>18</sup> Family history is important; increased carotid intima-media thickness has been found in adolescents with a family history of premature myocardial infarction.<sup>19</sup>

Ultrasound also can be used to assess functional properties of arteries, including mechanical properties such as stiffness and distensibility and adaptive properties such as vasomotion or dilation, in response to provocative stimulus. Impaired vascular function related to risk factor levels also is found in children. Children with familial hypercholesterolemia have increased carotid artery stiffness that is independent of blood pressure.<sup>20</sup> Functional abnormalities may be seen in hyperlipidemic children without familial hypercholesterolemia, with reports of an inverse relationship between LDL cholesterol and C-reactive protein levels and brachial artery distensibility.<sup>18,21</sup> Furthermore, even small increases in blood pressure across the normal range leads to decreased brachial distensibility in normotensive adolescents and young adults,<sup>22</sup>

thus underscoring the importance of identifying at-risk children. Decreased levels of cardiovascular fitness and increased body adiposity also have been found to impair vascular function in asymptomatic youth,<sup>23</sup> and the increased carotid artery stiffness seen in overweight children appears to be associated with insulin resistance.<sup>24</sup> This is anticipated because children with type 1 diabetes mellitus have been shown to have abnormal forearm vascular reactivity, which is related to elevated fasting glucose levels.<sup>25</sup> Interestingly, obesity may have effects on vascular function that are independent of the metabolic syndrome because elevations in leptin levels are associated with impaired vascular function in children independent of the metabolic and inflammatory disturbances associated with increased adiposity.<sup>26</sup> Finally, family history and environment affect vascular function, with family history of premature myocardial infarction<sup>19</sup> and passive smoking linked to abnormalities in brachial artery flow-mediated dilation in adolescents.<sup>27</sup>

Fortunately, interventional studies in children with familial hyperlipidemia have been able to demonstrate reversal of vascular functional abnormalities with early therapy with statins<sup>28,29</sup> and supplementation with antioxidant vitamins<sup>30</sup> and omega-3 fatty acids.<sup>31</sup> Therefore, early identification and treatment of children with elevated levels of risk factors who are at risk of developing abnormal vascular structure and function may be paramount in the prevention of manifest cardiovascular diseases.

### Existing Guidelines for Screening and Managing Lipoprotein Abnormalities in Children and Adolescents

Existing pediatric guidelines are based on a consensus report originally published in 1992 by the National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents.<sup>32</sup> The panel examined the large body of available laboratory, clinical, pathological, and epidemiological evidence in both children and adults. The panel then sought to develop guidelines on the basis of the rationale that (1) there was a strong relationship between elevated LDL cholesterol levels and the development of coronary artery disease in adults, (2) there was a growing body of pathological evidence from autopsy studies in children and adolescents, and (3) family history had been shown to have some predictive value in identifying children and adolescents with elevated serum cholesterol levels, particularly high LDL cholesterol levels. Therefore, to lower elevated cholesterol levels in children and adolescents, the panel recommended 2 strategies: a population-based approach aimed at shifting the population distribution of cholesterol levels and a targeted screening approach aimed at identifying those individuals with elevated LDL cholesterol levels who needed further monitoring and management.

The cornerstone of the population-based approach involved the recommendation that all healthy children >2 years of age adopt a fat- and cholesterol-restricted diet that had the appropriate number of calories to support growth and development and to maintain a "desirable" body weight. Consumption of a wide variety of foods was recommended to achieve nutrient needs and with a goal to achieve an average daily

intake of  $\leq 10\%$  of total calories from saturated fat with  $\leq 30\%$  from total fat and intake of  $\leq 300$  mg/d dietary cholesterol.

With regard to the high-risk individual approach, the panel specifically recommended against universal cholesterol screening for several reasons. Tracking of cholesterol levels into adulthood was imperfect in that not all children with high cholesterol levels will have high enough cholesterol levels as adults to warrant treatment. Concerns were raised that universal cholesterol screening could lead to labeling children as having a "disease." The panel believed that for children who were not from high-risk families, cholesterol-lowering therapies could wait until adulthood. Concerns existed that there was insufficient evidence on the long-term safety and efficacy of treating children to reduce coronary heart disease morbidity and mortality in adulthood. However, the panel did feel that for children at high risk because of a family history of premature cardiovascular disease and/or parental hypercholesterolemia, it was prudent to initiate therapy at an early age.

Therefore, selective screening in the context of regular health care was recommended. The screening algorithm primarily used family history as an entry point for detection of children and adolescents with elevated LDL cholesterol levels. Children and adolescents who have a parent or grandparent  $< 55$  years of age who had evidence of coronary atherosclerosis, peripheral vascular disease, or cerebrovascular disease; who had a coronary artery procedure; or who suffered a myocardial infarction or sudden cardiac death were thought to have a positive family history for premature cardiovascular disease. These children should be screened by a fasting blood lipoprotein analysis. Children and adolescents without such a family history but with a parent with a history of high blood cholesterol levels ( $\geq 6.2$  mmol/L; 240 mg/dL) should be screened by measuring total cholesterol level. If the child's total cholesterol level is borderline high (4.4 to 5.2 mmol/L; 170 to 200 mg/dL), the cholesterol measurement should be repeated. If the average of the 2 cholesterol levels is  $\geq 4.4$  mmol/L ( $\geq 170$  mg/dL), the child should have a fasting lipoprotein analysis performed. If the initial total cholesterol level is high ( $\geq 5.2$  mmol/L;  $\geq 200$  mg/dL), a fasting lipoprotein analysis should be obtained. Whenever a fasting lipoprotein analysis is performed, 2 measurements should be made and the LDL cholesterol levels should be averaged because of intraindividual variability. Recommendations for further evaluation and treatment are then based on the averaged LDL cholesterol value, with LDL cholesterol levels between 2.85 and 3.34 mmol/L (110 and 129 mg/dL) defined as borderline high and those  $\geq 3.35$  mmol/L ( $\geq 130$  mg/dL) defined as high.

The guidelines recommend dietary and lifestyle interventions for children identified as having elevated LDL cholesterol levels. For children whose LDL cholesterol level remains  $> 3.35$  mmol/L ( $> 130$  mg/dL) while compliant with the fat- and cholesterol-restricted diet recommended for the general population, a more restrictive diet is implemented. This diet further limits saturated fat intake to  $< 7\%$  of total caloric intake and cholesterol intake to  $< 200$  mg/d. LDL cholesterol-lowering drug therapy is recommended only in

those children  $\geq 10$  years of age whose LDL cholesterol remains extremely elevated after an adequate 6- to 12-month trial of diet therapy. Drug therapy was to be considered for children with LDL cholesterol levels  $\geq 4.9$  mmol/L ( $\geq 190$  mg/dL), which is similar to currently existing guidelines for primary prevention in adults. In addition, those children whose levels are  $\geq 4.1$  mmol/L ( $\geq 160$  mg/dL), together with either the presence of  $\geq 2$  other cardiovascular disease risk factors or a positive family history of premature cardiovascular disease, also merit treatment.

### Familial Hypercholesterolemia

These existing guidelines for drug therapy in children with very high LDL cholesterol levels with or without a family history of premature cardiovascular disease target predominantly those patients with more extreme lipid elevations and who are most likely to have familial hypercholesterolemia. Familial hypercholesterolemia is inherited as an autosomal-dominant condition resulting in deficient or defective LDL receptors and hence impaired clearance of circulating LDL particles. A similar phenotype may be caused by abnormalities of the LDL particle surface apolipoprotein B100 recognized by the LDL receptor. Familial hypercholesterolemia results in extreme elevations in LDL cholesterol that may distinguish the condition from other primary and most secondary causes of hyperlipidemia. The diagnosis usually can be made clinically by observation of more extreme abnormalities of the fasting lipoprotein levels in family members, combined with a positive family history of premature atherosclerotic cardiovascular disease and events. However, genetic testing remains the criterion standard, although it is not widely available. Wiegman and colleagues<sup>33</sup> studied 1034 children from kindreds with familial hypercholesterolemia, including assessment of LDL receptor mutations, and noted that an LDL cholesterol level  $> 3.5$  mmol/L ( $> 135$  mg/dL) predicted the presence of familial hypercholesterolemia with a 0.98 posttest probability, differentiating affected individuals from their unaffected family members. Some children with known mutations in the LDL receptor and thus definite familial hypercholesterolemia had LDL cholesterol levels below the NCEP-accepted guidelines of 4.1 mmol/L (160 mg/dL) and in the absence of other risk factors might not meet current criteria for drug therapy. The elevated presence of a family history of premature cardiovascular disease was noted to be further exacerbated by the presence of more extreme elevations of LDL cholesterol, elevated lipoprotein(a) levels, and decreased HDL cholesterol levels. The authors advocated that in the absence of genetic testing, a clinical diagnosis of familial hypercholesterolemia could be made if the LDL cholesterol level was above the 95th percentile for age and gender in a family with a history of premature cardiovascular disease in conjunction with tendon xanthomata. It is not known what proportion of children and adolescents in the general population whose LDL cholesterol levels are above the 95th percentile will have familial hypercholesterolemia.

### Challenges With These Existing Guidelines

Since publication of the NCEP Pediatric Expert Panel recommendations, studies have challenged several of the as-

sumptions made, more so recently in light of newer data.<sup>34</sup> The panel estimated that 25% of children and adolescents would be targeted for cholesterol screening (19.5% because of parental hypercholesterolemia, 5.6% because of family history of premature cardiovascular disease), yet a number of population-based studies report that between 36% and 46% of children and adolescents would be targeted for screening. Among 10 457 primarily white children and adolescents, 38% met the criteria for cholesterol screening: 27% because of a family history of premature cardiovascular disease and another 11% because of parental hypercholesterolemia.<sup>35</sup> A study of 260 black adolescents found that 37% of children would be targeted for screening<sup>36</sup>: 19% with a family history of hypercholesterolemia, 26% with a history of premature cardiovascular disease, and 8% with both a family history of premature cardiovascular disease and hyperlipidemia.<sup>37</sup> In a study among high school students in Utah and Texas, 36% and 38%, respectively, met the criteria for cholesterol screening.<sup>38</sup> A study of 1160 children and adolescents in a prepaid health plan in California found that 46% had a family history of premature cardiovascular disease or parental hypercholesterolemia.<sup>39</sup> Thus, the panel clearly underestimated the number of children who would be targeted for screening.

Several studies have reported relatively low efficacy of the targeted screening of children based on family history. In several studies, only 50% of children and adolescents with an elevated LDL cholesterol level would have been selected for screening with the guidelines.<sup>36,40,41</sup> The low efficacy might be due in part to incomplete or unavailable family health history, which is more common among children from single-parent households and children whose parents have not had their cholesterol levels checked.<sup>35</sup> Furthermore, studies have shown that total cholesterol levels are inefficient as a screening test for identifying children with increased levels of LDL cholesterol.<sup>42,43</sup> When a cut point of total cholesterol level at or above the 95th percentile ( $\approx 5.2$  mmol/L; 200 mg/dL) is used,  $\approx 45\%$  to 60% of children with elevated LDL cholesterol levels would be detected, with a false-positive rate of 50%. When the 75th percentile ( $\approx 4.4$  mmol/L; 170 mg/dL) is taken as the cut point,  $\approx 95\%$  of children with elevated LDL cholesterol would be identified, but the false-positive rate is  $>80\%$ .

In setting cut points for screening, the guidelines do not take into account variability in total cholesterol and HDL cholesterol levels based on race, gender, and sexual maturation.<sup>44</sup> This has an important impact on the sensitivity and specificity of screening. Black children tend to have higher levels of total cholesterol and higher levels of HDL cholesterol. Therefore, sensitivities for any given total cholesterol cut point will be higher in black children than in white children, whereas the specificities will be lower. Because girls tend to have higher total cholesterol levels than boys, the sensitivity will be higher for girls, whereas the specificity will be lower.<sup>43</sup> Total cholesterol levels tend to be higher during the prepubertal period than during puberty, leading to higher sensitivity in screening prepubertal children. Recent data from the National Health and Nutrition Examination Survey have highlighted changes in percentile cut points from 12 to 20 years of age with differences between male and female

subjects.<sup>45</sup> Use of these percentile cut points will lower LDL cholesterol level criteria for some adolescents while raising it for others, depending on age and sex.

Other threats to the sensitivity and specificity of screening include measurement error and intraindividual variation. Variability within individuals with regard to lipoprotein levels may be due to measurement error, regression to the mean, day-to-day variability, seasonal variability, and in children, change with age, growth, and pubertal status. In a study of 646 children 3 to 19 years of age, only 41% of children with a total cholesterol level  $\geq 5.2$  mmol/L ( $\geq 200$  mg/dL) had a cholesterol level that high 1 year later.<sup>46</sup> The higher the initial cholesterol level, the more likely it was for the repeat value also to be high, and the greater the number of measurements, the smaller the confidence interval around the estimated value. Assessment of 95% confidence limits for predicting a total cholesterol level in 1 year suggests that individuals with total cholesterol levels of  $\geq 5.9$  mmol/L ( $\geq 230$  mg/dL) from a single measurement or  $\geq 5.6$  mmol/L ( $\geq 215$  mg/dL) averaged from 2 measurements would have a total cholesterol level of  $\geq 5.2$  mmol/L ( $\geq 200$  mg/dL).<sup>46</sup> In adults, seasonal variation in total cholesterol levels also has been described, with maximal values obtained during the winter months and minimal values obtained during the summer months.<sup>37</sup> Peak-to-trough changes were 2.6% to 6.3% in men and 1.0% to 4.6% in women. In addition, the presence of intercurrent illness has been shown to influence the variability of levels.<sup>47</sup>

Limited compliance with the guidelines may affect their effectiveness. Noncompliance with screening recommendations is seen at all levels because of physician and family determinants. Multiple visits and blood draws in children are barriers. The variability in cholesterol levels is not well understood by parents, who are likely to believe that differences are due to errors. Balancing a desire to identify children with elevated LDL cholesterol levels with avoiding unnecessary testing of children has led to recommendations for selective cholesterol screening and a 2-level approach. The complicated scheme and multiple blood draws may have inadvertently led to confusion and lower compliance levels. Two studies, reported  $\approx 10$  years apart, have shown that only two thirds of pediatric healthcare providers self-report that they selectively screen children for high cholesterol on the basis of family history of cardiovascular disease.<sup>1,48</sup> Low levels of parental compliance with both cholesterol screening and intervention have been reported. In a study in which routine total cholesterol screening of children 2 through 15 years of age was offered in their pediatrician's office, only 70% of parents chose to have their child screened.<sup>49</sup> Of children screened and noted to have total cholesterol levels  $>4.4$  mmol/L ( $>170$  mg/dL), only 47% of their parents complied with recommendations to have their child have a repeat measurement or a fasting lipoprotein profile performed. In a school-based screening program, parents were notified if a child's total cholesterol level exceeded 5.2 mmol/L (200 mg/dL).<sup>49</sup> Follow-up of these families showed that only 20% of parents had contacted their child's physician. In a study of children in a prepaid health plan, only 70% of parents whose child was identified with a positive

family history complied with the recommendation to have their child's total cholesterol level determined.<sup>39</sup> Of those children initially screened and noted to have a total cholesterol level that was moderately high ( $\geq 4.9$  mmol/L;  $\geq 190$  mg/dL), only 62% had the recommended second measurement. Children whose LDL cholesterol level was found to be moderately high ( $\geq 3.25$  mmol/L;  $\geq 125$  mg/dL) were offered the opportunity to participate in a 3- to 6-week nutrition program, yet only 36% of parents enrolled. Thus, acceptance and implementation of the guidelines have been problematic.

The existing guidelines have a number of other important limitations. The primary focus of the existing guidelines is on elevated LDL cholesterol levels. They do not address other lipoprotein abnormalities such as decreased HDL cholesterol levels or hypertriglyceridemia, which may be more prevalent lipid abnormalities associated with obesity and the metabolic syndrome.<sup>50,51</sup>

The recommended fat- and cholesterol-restricted diet, which by default results in an increase in carbohydrate intake, has been shown to have only a limited effect on LDL cholesterol levels and may be associated with decreases in HDL cholesterol and increases in triglyceride levels.<sup>52,53</sup> Thus, many children will not achieve target LDL cholesterol levels but may also transition to combined hyperlipidemia. In addition, the recommended diet does not address the prevention and management of overweight and obesity, which have reached epidemic proportions in children and adolescents worldwide.

For those children meeting recommendations for drug treatment, the guidelines advocate the primary use of the bile acid-binding resins. This class of drugs has been shown to be poorly tolerated and accepted in children, contributing to poor compliance and effectiveness, with only modest decreases in LDL cholesterol levels that are unlikely to result in target levels being reached. Since publication of the existing guidelines, there have been more well-controlled studies in children and adolescents documenting the excellent short-term safety and effectiveness of the HMG CoA reductase inhibitors or statins than have ever been performed with the resins.

In summary, >10 years have passed since publication of the guidelines for children and adolescents from the NCEP expert panel. Evaluation and new knowledge have clearly highlighted the limitations and shortcomings of these existing guidelines and mandate a reevaluation and update.<sup>34</sup>

### Screening and Management Guidelines for Adults: A Comparison

The NCEP has distinct guidelines for screening and managing lipoprotein abnormalities in adults as outlined by the Adult Treatment Panel III (ATP III) ([http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3\\_rpt.htm](http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm)) and an update (<http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.htm>). There are few similarities with the pediatric guidelines. The ATP III evaluates and incorporates a large body of evidence not available for children and adolescents. In contrast to selective screening, the ATP III recommends universal screening of all adults with a fasting lipoprotein profile every 5 years. Risk categorization and treatment guidelines focus on LDL cholesterol as the primary target for treatment but are further refined on the basis of the presence

of clinical atherosclerotic disease or multiple major risk factors (gender, cigarette smoking, hypertension, diabetes, low HDL cholesterol levels, family history of premature cardiovascular disease, and age). The Framingham tables are used to incorporate the presence of these risk factors and to allow calculation of an individual's predicted subsequent 10-year risk for a cardiovascular disease event. The guidelines consider the presence of diabetes to be equivalent to having cardiovascular disease and recognize the need for more aggressive management in the setting of the metabolic syndrome. Risk levels are defined for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Treatment thresholds and targets are modified by the calculated 10-year risk and the presence of either diabetes or existing cardiovascular disease. In those adults without cardiovascular disease, a threshold LDL cholesterol level of 4.9 mmol/L (190 mg/dL) is set for considering drug therapy. Those with lower levels may be considered for drug therapy if additional factors are present, including life habits (ie, obesity, sedentary lifestyle, atherogenic diet) and emerging risk factors and markers [ie, elevated lipoprotein(a), elevated homocysteine, impaired glucose tolerance, and elevation of prothrombotic and proinflammatory factors]. In addition to drug therapy, use of plant stanols and sterols is recommended as adjunctive therapy. A more recent review of clinical trial evidence has further confirmed some aspects of the guidelines and suggested lower LDL cholesterol target levels for very high-risk individuals and the addition of specific drug therapy for those with concomitant high triglyceride or low HDL cholesterol levels.<sup>54</sup> Thus, the recommendations for adults focus on multiple risk factors in addition to LDL cholesterol levels, advocate the identification and treatment of other lipoprotein abnormalities, and are regularly updated on the basis of the best available critically appraised evidence. Recent work from the PDAY study suggests that a similar approach may be feasible for children and adolescents and that a multiple risk scoring system aimed at pathological changes in youth has been shown to have similar predictive capability for pathology in middle-aged adults.<sup>55,56</sup>

### Specific and Important Gaps in the Guidelines for Children and Adolescents

#### Obesity and the Metabolic Syndrome

The metabolic syndrome, also known as the insulin resistance syndrome, is widely recognized as an important risk for diabetes and cardiovascular disease in adults. In children, this constellation of conditions—obesity (particularly central adiposity), hyperinsulinemia/insulin resistance, hypertension, and lipoprotein abnormalities—may be overlooked as a syndrome but is no less important. The metabolic syndrome in children confers a significantly increased risk for cardiovascular disease. A postmortem study of young men 15 to 34 years of age who died accidentally showed accelerated coronary atherosclerosis and unfavorable cholesterol profiles associated with obesity.<sup>57</sup> Other studies have confirmed the strong association of childhood obesity with the development of insulin resistance and increased cardiovascular risk.<sup>58–60</sup> A compelling recent autopsy study of 204 young persons 2 to 39 years of age has shown that the severity and extent of asymptomatic coronary and aortic atherosclerosis were di-

rectly related to the number of cardiovascular risk factors clustered under the metabolic syndrome.<sup>10</sup> Obesity seems to have a central role in the development of this cluster.

The epidemic of obesity among children, which has been recognized and reported regularly during the past 10 to 15 years, is worsening. A recent study reported that the prevalence of overweight in children has increased by 3% to 5% in the past decade, with a current prevalence of 15.5% among 12- to 19-year-olds, 15.3% among 6- to 11-year-olds, and 10.4% among 2- to 5-year-olds.<sup>61</sup>

Overweight and obesity increase the risk for type 2 diabetes. Formerly dubbed “maturity-onset diabetes” because it occurred most frequently in obese, middle-aged adults, type 2 diabetes is currently on the rise in younger patients. The pathophysiology of the development of type 2 diabetes mellitus is complex and multifactorial. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time. It appears that at some point a loss of control of blood glucose levels begins to emerge, resulting in dietary glucose intolerance. This ultimately results in type 2 diabetes. It is known that obese individuals may develop different degrees of insulin resistance and that not all individuals develop glucose intolerance.

A number of studies have addressed the association between insulin and blood pressure in children and adolescents. Interactions similar to those identified in adults also may be found at a young age. The Bogalusa Heart Study has shown a positive correlation between blood pressure and fasting insulin, even after adjustment for body mass index, as early as 5 years of age.<sup>62</sup> Insulin resistance has been found in young black male subjects with only borderline hypertension that is independent of body mass index.<sup>63</sup> Several mechanisms through which blood pressure may be linked to insulin resistance have been proposed. In adolescents, the resistance to insulin has been associated with chronic sodium retention<sup>64</sup> and sodium sensitivity,<sup>65</sup> and this is reversible with weight loss and exercise.<sup>66</sup> Moreover, obese, insulin-resistant adolescents have increased forearm vascular resistance that is reversible with weight loss.<sup>67</sup>

Insulin resistance has been hypothesized to play a major role in lipoprotein abnormalities in individuals with normal glucose tolerance and in those with impaired glucose tolerance and type 2 diabetes.<sup>68,69</sup> Lipoprotein abnormalities also have been reported in obese adults who have elevated triglycerides and LDL cholesterol levels and low levels of HDL cholesterol.<sup>70–74</sup> Similar lipoprotein profiles have been reported in obese and nonobese adults with type 2 diabetes, in obese normoglycemic adults, and in nonobese adults with impaired glucose tolerance.<sup>75–77</sup> The association between obesity and abnormal lipoproteins observed in adults also has been documented in the pediatric population. In the adolescent population included in the *Lipid Research Clinics Population Studies Data Book*, obese adolescents had an abnormal “atherogenic” lipid profile consisting of elevated LDL cholesterol and triglycerides and low HDL cholesterol levels. In more recent studies in children, insulin resistance also was implicated in the association between obesity and lipoprotein abnormalities. In a study of insulin resistance and lipids in children, 82 normoglycemic, obese adolescents were

compared with 40 lean adolescents, and abnormalities consistent with an “atherogenic” lipid profile were present in the obese adolescents. The lipoprotein abnormalities correlated with the degree of insulin resistance in the obese children, and the degree of insulin resistance explained a significant portion of the variance in the levels of triglycerides, LDL cholesterol, and HDL cholesterol.<sup>78</sup> Investigators from the Bogalusa Heart Study reported that in comparison with their lean counterparts, overweight schoolchildren were between 2.4 and 7.1 times more likely to have elevated total cholesterol, LDL cholesterol, and triglyceride levels and 12.6 times more likely to have hyperinsulinemia.<sup>58</sup>

Several mechanisms whereby insulin resistance could cause an alteration in lipid metabolism have been described. Hyperinsulinemia is known to enhance hepatic synthesis of very-low-density lipoprotein (VLDL) and thus may directly contribute to the increased plasma triglyceride and LDL cholesterol levels.<sup>79</sup> Resistance to the action of insulin on lipoprotein lipase in peripheral tissues also may contribute to elevated triglyceride and LDL cholesterol levels.<sup>80,81</sup> It has been suggested that insulin resistance may be responsible for the reduced levels of HDL cholesterol observed in type 2 diabetes patients and that despite enhanced HDL cholesterol synthesis, the plasma HDL cholesterol concentration was significantly reduced in patients with type 2 diabetes compared with control subjects. This decrease in plasma HDL cholesterol was entirely accounted for by an increase in the rate of apolipoprotein A1/HDL cholesterol degradation, which exceeded the enhanced rate of its synthesis.<sup>82</sup>

Thus, from current knowledge, it is reasonable to suggest that weight control and lifestyle modification could alter the prevalence of the syndrome of insulin resistance and improve the risk profiles for cardiovascular disease as children make the transition toward adolescence and young adulthood.

### Non-LDL Cholesterol Lipid Disorders and Their Management

The existing NCEP guidelines for children and adolescents did not make specific recommendations with regard to screening or management of lipid abnormalities other than elevated LDL cholesterol levels, particularly abnormalities associated with elevated triglycerides and/or decreased HDL cholesterol levels. Sufficient data are not available to inform evidence-based guidelines for screening and management of disorders other than those associated with elevated LDL cholesterol level. Nonetheless, some primary lipid disorders merit comment. Familial combined hyperlipidemia is associated with elevated LDL and apolipoprotein B, elevated triglycerides and decreased HDL levels, or both. It is associated with autosomal-dominant inheritance, and many phenotypes may be present within the same family pedigree. The mechanism underlying the abnormalities is the overproduction of VLDL particles, reduced free fatty acid trapping, and decreased clearance of chylomicrons and remnants. This disorder is associated with a moderately increased risk of premature cardiovascular disease. A cornerstone of management in children should be aimed at a fat-, cholesterol-, and simple carbohydrate-restricted diet, together with attention to other cardiovascular lifestyle changes. The presence of con-

comitant overweight can exacerbate the lipid abnormalities. The NCEP guidelines for drug therapy for LDL cholesterol elevations should apply. In addition, for those with both elevated LDL cholesterol and triglycerides, the level of non-HDL cholesterol or apolipoprotein B might be substituted into the guidelines to guide decisions about initiation of drug therapy. The fibrates and nicotinic acid are ideal in treating the combined lipid abnormalities associated with this disorder. However, there has been very little published experience in children.<sup>83,84</sup> Use of statins and therapeutic lifestyle modifications would be reasonable, with the addition of a fibrate or nicotinic acid for more extreme elevations of triglycerides or very low HDL cholesterol. Recommended levels at which to initiate drug therapy for hypertriglyceridemia or low HDL cholesterol levels have not been established in children. However, patients with persistent extreme elevations of triglycerides  $>4$  mmol/L ( $>350$  mg/dL) or who have random levels  $>8$  mmol/L ( $>700$  mg/dL) might benefit from therapy aimed primarily at preventing an episode of pancreatitis.

Dysbetalipoproteinemia or type III hyperlipoproteinemia, characterized by elevations of cholesterol and triglycerides, may be rarely or incompletely expressed during childhood. It is associated with autosomal-recessive inheritance, and physical manifestations, when presenting in the pediatric age group, may include palmar xanthomas and tuberous and eruptive xanthomata. It is associated with a moderately increased risk of cardiovascular disease. The phenotype is evident in the presence of homozygosity for apolipoprotein E2 or other polymorphisms, together possibly with the presence of familial combined hyperlipidemia or other metabolic abnormalities such as hypothyroidism, diabetes, or obesity. Recommendations similar to those for managing the combined hyperlipidemia as noted for familial combined hyperlipidemia apply here.

Familial hypoalphalipoproteinemia is associated with isolated low HDL cholesterol levels. It is associated with autosomal-dominant inheritance and has been associated with a mild to moderately increased risk of premature cardiovascular disease. The underlying mechanism is decreased production of HDL or a mutation in apolipoprotein A1. Although specific drug therapy is not routinely recommended in the pediatric age groups, initiation of a fat- and cholesterol-restricted diet, together with attention to other lifestyle factors, is important. Because recommended dietary therapy may further lower HDL, as in adults, the most effective way to reduce cardiovascular risk in such patients is to maintain low LDL cholesterol levels.

### High-Risk Individuals

A number of other medical conditions make the pediatric patient at high risk for both lipoprotein abnormalities and cardiovascular disease. Some of these conditions include diabetes, transplantation, HIV infection, systemic lupus erythematosus, and nephrotic syndrome.

In diabetic patients,  $>50\%$  of the mortality is the result of coronary artery disease. It is clear in adults that lipoprotein-lowering treatment is effective in reducing this long-term complication. In the child and adolescent with insulin-dependent

diabetes, all would agree that aggressive nutritional therapy should be instituted to improve the patient's metabolic profile (ie, to reduce LDL cholesterol and triglycerides and increase HDL cholesterol levels). However, the use of drug therapy to treat lipoprotein abnormalities in the child or adolescent with diabetes is much more controversial. Most physicians would recommend that if dietary therapy alone is unsuccessful in lowering LDL cholesterol levels to  $<3.35$  mmol/L ( $<130$  mg/dL), then drug therapy should be started.<sup>85</sup>

Elevated total cholesterol and triglyceride levels are commonly observed in pediatric patients after all types of solid organ transplantations. Immunosuppressive therapy is the most likely explanation for lipoprotein abnormalities. In renal transplantation patients, important reductions in lipoprotein levels are observed only after the first year, and persistent lipoprotein abnormalities beyond this period necessitate therapy.<sup>86</sup> In heart transplantation patients, not only is there a high prevalence of lipoprotein abnormalities after transplantation, but these abnormalities have been implicated as a risk factor for the development of graft coronary artery disease. In addition, in adult transplantation trials, therapy with statins has been shown to reduce the development of graft coronary artery disease. Therefore, most pediatric heart transplantation patients are recommended to receive drug therapy with a statin regardless of the baseline lipoprotein levels.<sup>87</sup> Statin therapy also may be considered at a younger age than presently recommended for the general population.

Twenty percent to 50% of HIV-infected children treated with highly active antiretroviral therapy that includes protease inhibitors have been shown to develop lipoprotein abnormalities, most commonly increased total and LDL cholesterol levels. In adults, lipoprotein abnormalities have been shown to be associated with an increased risk of cardiovascular disease. Currently, other than dietary treatment, no consensus exists as to what lipoprotein levels should be treated in the pediatric patient in whom treatment with protease inhibitors is necessary.<sup>88</sup> One should be cautious in prescribing statins, especially at higher doses, in this group of patients because of the increased risk of myositis/myolysis when statins are given in conjunction with protease inhibitors or azole antifungal drugs.

Finally, lipoprotein abnormalities are a common finding in individuals with systemic lupus erythematosus. Several different mechanisms have been proposed for systemic lupus erythematosus-related lipoprotein abnormalities: multifactorial related to both kidney disease and corticosteroid therapy or immune mediated. In the adult, lipoprotein abnormalities have been documented to be associated with early-onset cardiovascular disease. Dietary modifications and fish oil supplementation, along with statin therapy, have been shown to improve the lipoprotein abnormalities in the pediatric systemic lupus erythematosus patient.<sup>89,90</sup>

### Clinical Studies of Drug Therapy in Children

Several drugs in a limited number of therapeutic classes are currently available for treatment of high-risk lipid abnormalities (Table 1). Randomized clinical trials are being performed in the pediatric age groups to determine the safety and effectiveness of currently available lipid-lowering drugs.



**TABLE 1. Drugs for Managing Hyperlipidemia**

Type of Drug	Mechanism of Action	Major Effects	Example(s)	Adverse Reactions
HMG CoA reductase inhibitors (statins)	Inhibits cholesterol synthesis in hepatic cells, resulting in upregulation of hepatic LDL receptors	Lowers LDL cholesterol and triglyceride, raises HDL-C	Atorvastatin, lovastatin, pravastatin, simvastatin, fluvastatin, rosuvastatin	Raised hepatic enzymes, raised CPK, myopathy possibly progressing to rhabdomyolysis
Bile acid-binding resins	Binds intestinal bile acids interrupting enterohepatic recirculation, which in turn results in LDL receptor upregulation	Lowers LDL-C, raises triglycerides	Cholestyramine, colestipol, colesevelam	Limited to gastrointestinal tract: gas, bloating, constipation, cramps
Fibric acid derivatives	Probably inhibits hepatic synthesis of VLDL	Mainly lowers triglycerides and raises HDL-C, with less effect on LDL-C	Gemfibrozil, fenofibrate	Dyspepsia, constipation, myositis, anemia
Nicotinic acid (extended release)	Upregulates hepatic LDL receptors	Lowers triglycerides and LDL-C	Niacin	Flushing, hepatic toxicity
Cholesterol absorption inhibitors	Inhibits intestinal absorption of cholesterol and plant sterols	Lowers LDL-C	Ezetimibe	Myopathy, gastrointestinal upset

HDL-C indicates HDL cholesterol; LDL-C, LDL cholesterol; and CPK, creatine phosphokinase.

Although these studies have been short term in nature, they have shown degrees of safety and effectiveness similar to those in studies<sup>23,24,29,91-101</sup> performed in adults (Table 2). It

should be noted that all of these studies have been performed in children and adolescents with primary high-risk lipid abnormalities such as familial hypercholesterolemia.

**TABLE 2. Clinical Trials of Lipid-Lowering Drug Therapy in Children and Adolescents**

Study	Daily Drug	Effect on Lipid Profile, subjects/gender	Dose	Total Cholesterol, %	LDL, %	HDL, %	Triglycerides, %
<b>Bile acid-binding resins</b>							
Tonstad et al <sup>91</sup>	Cholestyramine	96 both	8 g	-12	-17	8	NA
McCrindle et al <sup>92</sup>	Cholestyramine	40 both	8 g	-7 to -11	-10 to -15	2-4	6-9
Tonstad et al <sup>93</sup>	Colestipol	27 both	2-12 g	-17	-20	-7	-13
McCrindle et al <sup>94</sup>	Colestipol	36 both	10 g	-7	-10	2	12
<b>HMG CoA reductase inhibitors (statins)</b>							
de Jongh et al <sup>95</sup>	Simvastatin	173 both	10-40 mg	-31	-41	3	-9
Knipscheer et al <sup>96</sup>	Pravastatin	72 both	5 mg	-18	-23	4	2
			10 mg	-17	-24	6	7
			20 mg	-25	-33	11	3
			40 mg	-29	-36	3	-9
Wiegman et al <sup>99</sup>	Pravastatin	214 both	20-40 mg	-19	-24	6	-17
Lambert et al <sup>97</sup>	Lovastatin	69 males	10 mg	-17	-21	9	-18
			20 mg	-19	-24	2	9
			30 mg	-21	-27	11	3
Stein et al <sup>98</sup>	Lovastatin	132 males	10 mg	-13	-17	4	4
			20 mg	-19	-24	4	8
			40 mg	-21	-27	5	6
Clauss et al <sup>99</sup>	Lovastatin	54 females	40 mg	-22	-27	-23	3
McCrindle et al <sup>100</sup>	Atorvastatin	187 both	10-20 mg	-30	-40	6	-13
<b>Other agents</b>							
Wheeler et al <sup>83</sup>	Bezafibrate	14 both	10-20 mg	-22	Not calculated	15	-23
Colletti et al <sup>84</sup>	Niacin	21 both	500				
			2200 mg	-13	-17	4	13
McCrindle et al <sup>94</sup>	Pravastatin and colestipol	36 both	Pravastatin 10 mg with colestipol 5 g	-13	-17	4	8

### Bile Acid–Binding Resins

The present NCEP guidelines, released in 1992 and not updated since, advocate the use of the bile acid–binding resins as initial drug therapy in children. These agents bind bile acids in the intestinal lumen and prevent their enterohepatic reuptake, thus removing them from the cholesterol pool. This leads to an upregulation of LDL receptors on the hepatic cell surface and increased clearance of LDL from the circulation. These agents are thought to be preferential in children because they are not systemically absorbed. Dosing starts at 4 to 5 g/d and can be titrated up to 20 g/d as tolerated. However, these drugs are associated with very poor palatability, leading to poor compliance. Adverse effects are mainly gastrointestinal upset. They may cause increases in triglyceride levels and may interfere with the absorption of fat-soluble vitamins and some medications. In selected patients, an association with increased homocysteine levels has been noted. Average LDL cholesterol lowering in clinical studies has ranged from 13% to 20%. Tonstad and colleagues<sup>101</sup> performed a randomized clinical trial in 66 children with familial hypercholesterolemia using colestipol granules at a dose of 10 g/d. An open-treatment period of 44 to 52 weeks was preceded by an 8-week placebo-controlled phase. Compliance was poor in the long term, and vitamin levels were reduced in the colestipol group. No safety concerns were raised, although it was recommended that folate and vitamin D be supplemented. These investigators also performed a clinical study of cholestyramine powder in 72 children with familial hypercholesterolemia.<sup>91</sup> Again, compliance was poor, and many patients withdrew from the study. Nonetheless, there were no safety concerns, although a reduction in vitamin D levels was seen. Elevated homocysteine levels were noted in 1 patient who showed a low folate level. Investigators further recommended that folate and vitamin D be supplemented. A recent placebo-controlled trial in adults after acute myocardial infarction showed no cardiovascular benefit and possible harm with folate and B complex vitamin supplementation despite significant reductions in homocysteine levels.<sup>102</sup> McCrindle and colleagues<sup>92</sup> compared cholestyramine powder with a tablet formulation in 40 children with familial hypercholesterolemia. This randomized crossover trial at a dose of 8 g/d showed that study subjects preferred the tablet, but overall compliance was low with both formulations. Gastrointestinal complaints were common. In summary, given the high prevalence of high gastrointestinal complaints, poor palatability, low compliance, and limited effectiveness, it is unlikely that the bile acid–binding resins will be sufficient to achieve target LDL cholesterol levels in children who meet the criteria for lipid-lowering drug therapy. A more recent tablet nonresin form of bile acid sequestrant, colesevelam, is currently in clinical trials in children with familial hypercholesterolemia, in combination with statin therapy, and may be better tolerated.<sup>103</sup>

### HMG CoA Reductase Inhibitors

The HMG CoA reductase inhibitors, or statins, have led to significant reductions in cardiovascular and all-cause mortality for adults at risk or with manifested atherosclerotic cardiovascular disease.<sup>104</sup> In addition, they are increasingly

becoming the preferred agent for treating elevated LDL levels in children and adolescents who meet the criteria for drug therapy. The statins work by inhibiting the rate-limiting enzyme HMG CoA reductase for the endogenous synthesis of cholesterol. This leads to depletion of the intracellular cholesterol pool, which triggers an upregulation of LDL surface receptors, leading to increased clearance of LDL from the circulation. In general, when statins are initiated in children, the lowest dose is preferred and is usually associated with the greatest increment in LDL lowering. Further upward titrations in the dose will result in further, although less impressive, reductions in LDL cholesterol, and there is a log-linear dose response with 6% more LDL cholesterol reduction for every doubling of dose, as seen in adults. Adverse effects are related to infrequent gastrointestinal upset, elevations of liver transaminases, and elevation of creatine kinase, with rare episodes of rhabdomyolysis. Patients should be advised of their contraindication with pregnancy, and care should be taken to prevent drug interactions that might increase the risk of rhabdomyolysis such as the concomitant use of cyclosporine, gemfibrozil, and erythromycin. Patients should be monitored for symptoms of muscle cramps, with periodic monitoring of creatine kinase and liver transaminases.

There has been increasing experience with statins in the context of clinical trials in children. Ducobu and colleagues<sup>105</sup> performed a study of simvastatin in 32 children with hyperlipidemia. Patients were titrated up to doses as high as 40 mg/d. Excellent LDL lowering with few adverse effects was noted over a follow-up period of at least 24 months. Only 1 patient showed an increase in liver transaminases, and 2 patients had transient elevations in creatine kinase levels. Growth and development remained normal. De Jongh and colleagues<sup>95</sup> performed a clinical trial of simvastatin in 173 children with familial hypercholesterolemia. After a placebo run-in period, patients were randomized to placebo or an initial dose of simvastatin 10 mg with titration up to 40 mg/d during a 24-week period, with the dose remaining 40 mg for a 24-week extension. Drug-related clinical adverse events and laboratory abnormalities were slightly increased in the simvastatin group, although not statistically significantly. Only 3 patients had transient elevations of creatine kinase, one of whom had been concomitantly taking erythromycin. Growth and maturation were not different from those in patients taking placebo. Both boys and girls on simvastatin had significantly lesser degrees of increase in dehydroepiandrosterone sulfate levels, although the magnitude of these differences was thought not to be clinically important.

Knipscheer and colleagues<sup>96</sup> performed a randomized clinical trial of pravastatin in 72 children with familial hypercholesterolemia with varying doses of the pravastatin administered over a 12-week period. Adverse effects were equally distributed among the groups taking placebo and the different dosage levels of the pravastatin. Wiegman and colleagues<sup>29</sup> performed a clinical trial of pravastatin in 214 children with familial hypercholesterolemia. Patients were randomized to placebo or pravastatin at a daily dose of 20 mg if <14 years of age and 40 mg if older for a period of 2 years. No effects on growth, maturation, or hormone levels were observed. Transient elevations in creatine kinase and hepatic transami-

nases were infrequent and occurred equally in both groups, with only 1 patient who was taking placebo having an asymptomatic episode of extreme elevation of creatine kinase levels, which resolved when the study therapy was stopped for 1 week and did not recur. A recent non-placebo-controlled study of 30 children and adolescents with familial hypercholesterolemia treated with pravastatin to achieve a target LDL cholesterol level showed sustained efficacy and safety over a period of 24 months.<sup>106</sup>

Firth and colleagues<sup>107</sup> presented data from an open-label dosage-titration study of fluvastatin in 29 boys with familial hypercholesterolemia. The majority had been titrated up to 80 mg/d, and an interim analysis after 2 years showed marked reductions in LDL with excellent tolerance. Although transient asymptomatic increases in creatine kinase were noted, other laboratory abnormalities were absent.

Lambert and colleagues<sup>97</sup> from the Canadian Lovastatin in Children Study Group performed a clinical trial of lovastatin in boys with familial hypercholesterolemia. Patients were enrolled in an initial 4-week placebo period, followed by randomization to 10, 20, 30, or 40 mg/d lovastatin for a treatment period of 8 weeks. Some transient increases in liver transaminases were noted, although they did not exceed twice the upper limit of normal. Asymptomatic increases in creatine kinase were rarely noted and resolved spontaneously. Hormonal status was monitored, and increases in cortisol and dehydroepiandrosterone levels were noted, the clinical significance of which is questionable. Stein and colleagues<sup>98</sup> also performed a clinical trial of lovastatin in 132 boys with familial hypercholesterolemia. Patients were randomized to either placebo or 10 mg lovastatin; the lovastatin was titrated to 20 and then 40 mg/d. Growth and sexual maturation were not affected, and biochemical nutritional parameters and serum hormone levels remained within the normal range. No differences between the placebo and lovastatin dose groups were seen with regard to liver transaminases, although infrequent and sporadic increases in creatine kinase occurred, not significantly different between the treatment groups. Elevations in creatine kinase were generally asymptomatic and associated with vigorous or unusual activity. Clauss and colleagues<sup>99</sup> performed a clinical trial of lovastatin in 54 postmenarchal girls with familial hypercholesterolemia. Patients were randomized to either placebo or 20 mg followed by 40 mg lovastatin for 24 weeks. No differences from placebo were seen with regard to any safety parameter, including a comprehensive assessment of hormone levels, and no differences in menstrual cycle length.

McCrimdle and colleagues<sup>100</sup> performed a clinical trial of atorvastatin in 187 male and female children with familial or severe hypercholesterolemia. A 6-month phase comparing subjects taking placebo with those taking 10 to 20 mg atorvastatin showed excellent safety and tolerance with significant reductions in LDL cholesterol, triglycerides, and apolipoprotein B, together with significant increases in HDL cholesterol. An open-label 6-month extension in which all subjects took atorvastatin 10 mg/d showed ongoing safety and tolerance with no effect on growth and development.

Only 1 study in children has been performed using a combination of a bile acid-binding resin and a statin.

McCrimdle and colleagues<sup>94</sup> performed a randomized cross-over clinical trial of colestipol 10 g/d versus a low-dose combination of colestipol 5 g/d with pravastatin 10 mg/d given for two 18-week intervals separated by an 8-week washout period. Forty children with familial or severe hypercholesterolemia were studied, and it was noted that acceptability was better for the low-dose combination, although compliance was equally poor for both regimens. LDL cholesterol was lowered 17% with the combination, with no effect on HDL cholesterol or triglycerides.

The efficacy and safety profile of the statins for children and adolescents appears similar to that for adults. A new statin, rosuvastatin, is currently being studied in children with familial hypercholesterolemia but has been shown to have an excellent efficacy and safety profile in adults.<sup>108</sup> Practitioners should be aware that recommended monitoring of creatine kinase levels is more likely to result in numerous mild to severe sporadic increases that may not be attributable to the statin. Vigorous exercise, particularly contact sports or weightlifting, may cause physiological increases, and it is important that not all increases are immediately attributed to the statin. In addition, the reported clinical trials have been short term; thus, long-term adverse effects remain unknown. Particularly important are concerns about any potential impact on development. The reported clinical trials have spanned the age range of pubertal development, with no impact on sexual or physical maturation, but these trials have not included measures of psychological and intellectual development. Another important concern is the impact of exposure during pregnancy for patients of child-bearing potential; patients must be counseled extensively, and an effective contraception strategy should be implemented.

Many families and their healthcare providers continue to be concerned about the prospect of a lifetime of drug therapy and the potential impact on quality of life and anxiety. De Jongh and colleagues<sup>109</sup> studied children with familial hypercholesterolemia being treated with statins and their parents. The families reported no problems with quality of life and anxiety, although they had some concerns specific to their disease. Limitations and concerns related to their disease were reported by 44% of the children, but 62% reported that taking medication made them feel safer. Concerns appeared to be related more to the underlying condition than to its therapy.

In summary, encouraging results have been obtained from clinical trials of statins in children and adolescents with familial or severe hypercholesterolemia. Adverse effects do not appear to be increased over those noted in clinical studies in adults; however, ultra-long-term safety and compliance remain of concern, as does demonstration of an impact on clinical disease. Currently, lovastatin, simvastatin, pravastatin, and atorvastatin have pediatric labeling from the US Food and Drug Administration on the basis of clinical trials performed in children with familial hypercholesterolemia. Guidelines for initiation, titration, and monitoring of statin therapy in children are given in Table 3.

### Niacin or Nicotinic Acid

Niacin or nicotinic acid is rarely used to treat the pediatric population. Its lipid-lowering effect is to lower LDL cholesterol and triglycerides while increasing HDL cholesterol. It is

**TABLE 3. Recommendations for the Use of HMG CoA Reductase Inhibitors (Statins) in Children and Adolescents With Hyperlipidemia****Patient selection**

1. Begin with the present criteria of the expert panel of the NCEP for drug initiation.
2. The age and LDL level at which statin therapy is initiated may be influenced by the presence, magnitude, and number of other cardiovascular risk factors, as well as by the presence of cutaneous xanthomas.
3. Include the preferences of patient and family in the decision making.
4. In general, do not start before 10 y of age in boys and preferably after onset of menses in girls. Patients should ideally be at Tanner stage II or higher.
5. Ensure that there are no contraindications for statin therapy (eg, important hepatic disease).

**Initiation and titration**

1. The choice of the particular statin is a matter of preference.
2. Start with the lowest dose given once daily, usually at bedtime. Measure baseline CK, ALT, and AST.
3. Instruct the patient to report all potential adverse effects, especially myopathy (muscle cramps, weakness, asthenia, and more diffuse symptoms), immediately. If myopathy is present, its relation to recent physical activity should be assessed, the medication stopped, and CK assessed. The patient should be monitored for resolution of the myopathy and any associated increases in CK. Consideration can be given to restarting the medication once symptoms and laboratory abnormalities have resolved.
4. Advise female patients about concerns with regard to pregnancy and the need for appropriate contraception if warranted.
5. Advise about drug interactions, especially cyclosporine, fibric acid derivatives, niacin, erythromycin, azole antifungals, nefazodone, and many HIV protease inhibitors.
6. After 4 wk, measure fasting lipoprotein profile, CK, ALT, and AST and compare with laboratory-specific reported normal values.

The threshold for worrisome level of CK is 10 times above the upper limit of reported normal; consider impact of physical activity.

The threshold for worrisome level of ALT or AST is 3 times above the upper limit of reported normal.

Target levels for LDL: minimal, <3.35 mmol/L (130 mg/dL); ideal, <2.85 mmol/L (110 mg/dL)

7. If target LDL levels are achieved and there are no laboratory abnormalities, continue therapy and recheck in 8 wk and then 3 mo.
8. If laboratory abnormalities are noted or symptoms are reported, temporarily withhold the drug and repeat the blood work in  $\approx$ 2 wk. When abnormalities return to normal, the drug may be restarted with close monitoring.
9. If target LDL levels are not achieved, double the dose, and repeat the blood work in 4 wk. Continue stepped titration up to the maximum recommended dose until target LDL levels are achieved or there is evidence of toxicity.

**Monitoring**

1. Monitor growth (height, weight, and body mass index and relate to normal growth charts), sexual maturation, and development (Tanner staging).
2. Monitor fasting lipoprotein profile, CK, ALT, and AST every 3 to 6 mo.
3. Monitor and encourage compliance with lipid-lowering dietary and drug therapy. Serially assess and counsel for other risk factors, such as weight gain, smoking, and inactivity.
4. Counsel adolescent females about statin contraindications in pregnancy and the need for abstinence or use of appropriate contraceptive measures. Seek referral to an adolescent medicine or gynecologic specialist as appropriate.

CK indicates creatine kinase; ALT, alanine aminotransferase; and AST, aspartate aminotransferase.

thought to do this by decreasing hepatic production and release of VLDL. It also is known to be the only medication to lower lipoprotein(a) levels. Initiation at a low dose is followed by uptitration to a daily dose of 2 to 6 g/d. Adverse effects, predominantly flushing, are very common. Several serious adverse effects are a concern, including glucose intolerance, myopathy, hyperuricemia, and fulminant hepatic failure. Only 1 observational study has been performed in 21 children treated with niacin 500 to 2250 mg/d an average duration of 8.1 months.<sup>84</sup> Reversible adverse effects occurred in 76% of children, with elevations of liver transaminases in 29%. Symptoms of flushing, abdominal pain, vomiting, and headache, together with elevated liver transaminases, led to discontinuation of therapy in 8 children. Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients.

**Fibric Acid Derivatives**

Fibric acid derivatives or fibrates have the effect of both raising HDL and lowering triglycerides. The underlying mechanism of

action is complex. Gastrointestinal upset can occur, together with an increased predisposition to cholelithiasis. Elevated liver transaminases and creatine kinase can occur but are much less common than with statins. However, the risk of myopathy and possible rhabdomyolysis is markedly increased if the fibric acid derivatives are combined with other agents, particularly statins, or used in the presence of renal insufficiency. Wheeler and colleagues<sup>83</sup> performed a 6-month randomized crossover trial of bezafibrate in 14 children with familial hypercholesterolemia. One patient had transient elevations in liver transaminases, and 1 patient had elevation of alkaline phosphatase. The medication, however, was well tolerated, with no impact on growth or development. This class of drugs should be used preferentially for children with severe elevations in triglyceride levels who are at risk for pancreatitis.

**Cholesterol Absorption Inhibitors**

A new class of lipid-lowering agents known as cholesterol absorption inhibitors has recently emerged. Ezetimibe prevents the intestinal absorption of cholesterol and plant sterols

at the level of the brush border of the small intestine. This includes both dietary cholesterol and resorption of cholesterol derived from intestinal cell breakdown and contained in secretions such as bile. Ezetimibe has been studied and marketed predominantly as adjunctive therapy with other lipid-lowering medications for patients with severe hyperlipidemia who do not reach target LDL cholesterol levels primarily with a statin alone. Ezetimibe has been shown to reduce LDL cholesterol levels by  $\approx 20\%$  either alone or in addition to reductions caused by concomitant medications. Although there have not yet been published studies of ezetimibe in children, a study of 50 patients with severe LDL cholesterol elevations resulting from homozygous familial hypercholesterolemia included an unspecified number of children  $\geq 12$  years of age.<sup>110</sup> Ezetimibe was safe and well tolerated. Studies of ezetimibe coadministered with a statin are currently in progress in children with heterozygous familial hypercholesterolemia. It is likely that ezetimibe will be used predominantly in children with persistent elevations of LDL cholesterol after treatment with other drugs, although its use as monotherapy has yet to be explored. A recent study in adults has suggested that ezetimibe alone may be insufficient to improve endothelial dysfunction.<sup>111</sup>

## Adjuvant Therapies

### The Role of Physical Activity in Management

Data from studies of adults over the past 50 years have supported regular, vigorous physical activity as an independent protective factor in the development of cardiovascular disease. Most recent data indicate that this protection is likely due in large part to the impact of exercise on the lipoprotein profile. Studies have shown favorable impact on multiple lipoprotein factors, including LDL cholesterol, HDL cholesterol, and apolipoprotein AI, as well as total cholesterol levels. However, study results have been inconsistent with regard to the changes seen in various lipoproteins.<sup>112</sup>

Data from the pediatric and adolescent populations are far more limited than data from adult populations. However, these studies show a similar pattern for lipoprotein profile modification by exercise in the pediatric population. In a recent review by Tolfrey et al,<sup>113</sup> it was noted that cross-sectional studies provided the strongest support for the role of exercise in the modification of lipoprotein profiles in children. These included improvements in HDL cholesterol levels, the ratio of total to HDL cholesterol, and the ratio of LDL cholesterol to HDL cholesterol, with little effect on total cholesterol levels. Methodological issues, especially selection bias and imprecise measures of physical activity, are problems in most of these studies, making it difficult to establish a clear cause-and-effect relationship between physical activity and lipoprotein profiles.

Correlational studies assessing the impact of exercise training programs on lipoprotein profiles generally have shown a positive but inconsistent impact on lipoproteins. Again, this may be due primarily to methodological issues, with important variations in populations and study design. Studies that have assessed the impact of increased routine physical activity generally have shown a positive effect on lipoprotein profiles with increasing

physical activity. The unique variance in the lipoprotein profile resulting from physical activity ranged from 5% to 30% in various studies.<sup>112–116</sup>

The data on aerobic fitness are more equivocal. Some studies show no relationship between the lipoprotein profile and aerobic fitness; others show changes that are gender specific or are similar to the variance seen in physical activity. Some of these differences may be due to different methods of assessing aerobic capacity and maximal oxygen consumption ( $\dot{V}O_2$ ). However, the major determinant of maximal  $\dot{V}O_2$  is genetics, and this may make this a less sensitive marker of the effects of exercise on the lipoprotein profile.<sup>112,113,115,117</sup>

Long-term longitudinal studies of the effects of exercise on lipoprotein profiles in children are few. They also suffer from relatively low numbers of study subjects. A recent report from the Muscatine Study examined 125 children as they progressed through adolescence. This study found that 11% of the variance in the ratio of total to HDL cholesterol levels and 5% of the variance in LDL cholesterol levels were due to aerobic fitness.<sup>118,119</sup>

From current pediatric data, it would appear that an exercise program should be included as part of a comprehensive risk factor modification program for the prevention of cardiovascular disease in children and adolescents. Emphasis on regular physical activity rather than improvement in aerobic capacity appears to be the best approach for structuring such a program. More long-term data are needed to completely assess the role of physical activity in risk factor modification for the pediatric population.

### Nonpharmacological Therapies

Fat- and cholesterol-restricted diets have been well studied in infants, children, and adolescents.<sup>52,53,120–123</sup> They have been shown to be safe but result in only modest improvements in hyperlipidemia. A recent study has suggested that changes in the quality of dietary fat consumption with substitution of products predominating in saturated fat for those predominating in polyunsaturated fats, without altering total fat intake, may result in an  $\approx 15\%$  reduction in LDL cholesterol levels.<sup>124</sup> There have been some concerns whether the fat- and cholesterol-restricted diet adversely alters HDL cholesterol, LDL particle properties, and triglycerides, but clinical trials performed in children have shown no significant adverse effects.<sup>53,123</sup> In general, dietary recommendations should be consistent with good nutrition, aimed at a proper caloric balance to ensure optimal growth and development while preventing obesity.<sup>125</sup>

There has been a great deal of interest in dietary supplements and complementary medicines, although few have been subjected to rigorous clinical study. The use of omega-3 fatty acids has been advocated. Engler and colleagues<sup>126</sup> performed a clinical trial of docosahexaenoic acid in 20 children with hyperlipidemia. They noted significant and favorable changes in lipoprotein subclasses, with shifts toward less dense LDL particles and more buoyant HDL particles.

Dietary fiber has been shown to have a variable impact on lipid levels. Dennison and colleagues<sup>127</sup> performed a cross-over clinical trial in 20 hyperlipidemic children of a psyllium-enriched cereal and did not show any benefit on lipid levels.

In contrast, Davidson and colleagues<sup>128</sup> performed a similar crossover clinical trial in 26 hyperlipidemic children and showed a modest LDL cholesterol reduction of 7% with the psyllium-enriched cereal versus control.

Small studies of dietary alterations in hyperlipidemic children have shown that substitution with soy-based protein may increase HDL cholesterol and lower VLDL levels and triglycerides<sup>129</sup> and may lower LDL cholesterol levels.<sup>130</sup> Dietary enrichment with rapeseed or canola oil has been shown to lower triglyceride and VLDL levels.<sup>131</sup>

Plant stanol and sterol esters have been incorporated into dietary spreads and act through inhibition of cholesterol absorption.<sup>132</sup> A clinical trial of plant stanol ester margarine in 81 children showed that LDL cholesterol levels were lowered by a mean of 7.5%, with good tolerance.<sup>133</sup> Gylling and colleagues<sup>134</sup> performed a crossover trial in 15 children with familial hypercholesterolemia of partial dietary fat substitution with sitostanol ester dissolved in a rapeseed oil margarine. They showed that LDL cholesterol levels were reduced by a mean of 15%, and ratios of HDL cholesterol to LDL cholesterol levels were improved by a mean of 27%.

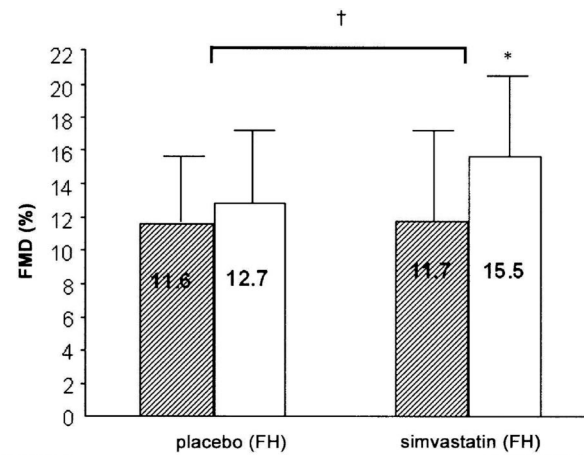
Garlic preparations have been marketed for the treatment of hyperlipidemia, although evidence of a beneficial effect on the lipid profile has not been noted in independent clinical trials.<sup>135–137</sup> McCrindle and colleagues<sup>138</sup> performed a placebo-controlled, double-blind clinical trial in 30 children with familial hyperlipidemia of a commercially available garlic extract. They noted no clinically important effect on the lipid profile or any other cardiovascular risk factor. Complementary medicines and dietary supplements and modifications should be supported by rigorous clinical trial evidence before being adopted as acceptable therapies for the management of hyperlipidemia in children.

### Impact on Vascular End Points

Optimally, the screening and management of hyperlipidemia in children should be aimed at making an impact on the atherosclerotic disease process itself, with an aim of preventing cardiovascular morbidity and mortality in adulthood. Although a clinical study spanning childhood through adulthood will likely never be performed, some evidence is now being acquired to suggest an impact on vascular function and structure in children.

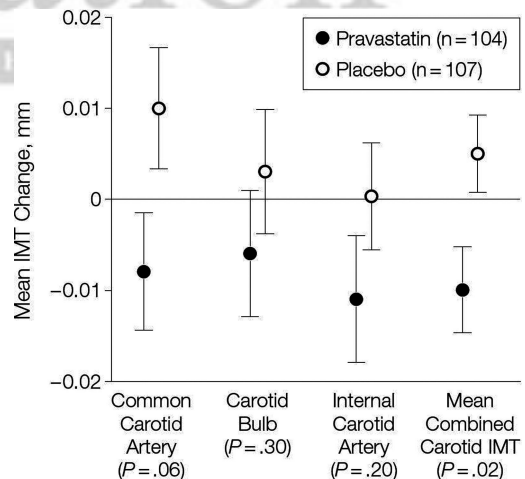
A clinical trial of dietary intervention in infancy aimed at altering fat consumption to reduce saturated fat intake (the Special Turku Coronary Risk Factor Intervention Project) evaluated participants at 11 years of age for flow-mediated dilatation as assessed by vascular ultrasound of the brachial artery.<sup>139</sup> The investigators noted greater dilation for boys but not girls in the intervention group relative to the control group, which they attributed to reduced LDL cholesterol levels.

A clinical trial of simvastatin in 50 children with familial hypercholesterolemia was performed by de Jongh and colleagues.<sup>28</sup> After a treatment period of 28 weeks, flow-mediated dilatation as assessed by vascular ultrasound of the brachial artery was noted to have improved to normal levels in the patients treated with 40 mg simvastatin compared with no improvement in the placebo group (Figure 2). Wiegman and colleagues<sup>29</sup> assessed carotid intima-media thickness as



**Figure 2.** Changes from baseline (striped bar) to 28 weeks (white bar) in flow-mediated dilatation (FMD) in the placebo and simvastatin groups of children with familial hypercholesterolemia (FH). \* $P < 0.0001$  vs baseline; † $P < 0.05$  for change in placebo vs change in simvastatin groups. Reproduced from de Jongh et al<sup>28</sup> with permission from the American College of Cardiology Foundation. Copyright 2002 American College of Cardiology Foundation.

part of a clinical trial of pravastatin in children with familial hypercholesterolemia. They noted that those in the placebo group showed progression of intima-media thickness over a 2-year period, whereas those treated with pravastatin demonstrated regression (Figure 3). A further study by Koeijvoets et al<sup>140</sup> in the pravastatin-treated group showed greater intima-media thickness in those children with heterozygous familial hypercholesterolemia who had a null allele for LDL receptor genotype (compared with receptor-defective mutations). The null allele also was associated with higher LDL cholesterol levels. There was a nonsignificant tendency toward less LDL cholesterol lowering in this group also. They concluded that genotyping of patients with familial hypercholesterolemia will identify patients with null alleles who may require more aggressive interventions.



**Figure 3.** Mean carotid intima-media thickness (IMT) changes from baseline for the different carotid arterial wall segments in the pravastatin and placebo groups of children with familial hypercholesterolemia. Reproduced from Wiegman et al<sup>29</sup> with permission from the American Medical Association. Copyright 2004 American Medical Association.

**TABLE 4. Recommendations for Drug Therapy of High-Risk Hyperlipidemia in Children and Adolescents**

**Original recommendations of the NCEP Expert Panel**

1. Consider drug therapy in children  $\geq 10$  y of age (usually wait until menarche for females) and after a 6- to 12-mo trial of fat- and cholesterol-restricted dietary management.
2. Consider drug therapy if
  - LDL level remains  $\geq 4.90$  mmol/L (190 mg/dL) or
  - LDL remains  $> 4.10$  mmol/L (160 mg/dL) and
    - there is a positive family history of premature cardiovascular disease
    - $\geq 2$  other risk factors are present in the child or adolescent after vigorous attempts to control these risk factors.
3. Referral to specialized lipid center may be deemed appropriate.
4. Treatment goal
  - Minimal, LDL  $< 3.35$  mmol/L (130 mg/dL)
  - Ideal, LDL  $< 2.85$  mmol/L (110 mg/dL)

**Current modifications**

1. In addition to family history, overweight and obesity should trigger screening with a fasting lipid profile.
2. Overweight and obese children with lipid abnormalities should be screened for other aspects of the metabolic syndrome (ie, insulin resistance and type 2 diabetes, hypertension, or central adiposity).
3. For children meeting criteria for starting lipid-lowering drug therapy, a statin is recommended as first-line treatment.
4. For children with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may also lower the recommended cutpoint LDL cholesterol level for initiation of drug therapy, lower the desired target LDL cholesterol levels, and in selected cases, may prompt consideration for initiation below the age of 10 years. These risk factors and high-risk conditions may include:
  - Male gender
  - Strong family history of premature cardiovascular disease or events
  - Presence of associated low HDL, high triglycerides, small dense LDL
  - Presence of overweight or obesity and aspects of the metabolic syndrome
  - Presence of other medical conditions associated with an increased atherosclerotic risk such as diabetes, HIV infection, systemic lupus erythematosus, organ transplantation, survivors of childhood cancer
  - Presence of hypertension
  - Current smoking and passive smoke exposure
  - Presence of novel and emerging risk factors and markers, eg, elevated lipoprotein(a), homocysteine, C-reactive protein
5. Ongoing research of drug therapy of high-risk lipid abnormalities in children is needed, particularly with regard to long-term efficacy and safety, and impact on the atherosclerotic disease process.



The impact of adjuvant therapies on vascular structure and function also has been explored. Engler and colleagues<sup>141</sup> performed a double-blind randomized crossover trial in 15 children with familial or familial combined hypercholesterolemia, comparing placebo with 500 mg/d vitamin C and 400 U vitamin E given over a 6-week period. Although flow-mediated dilatation as assessed by vascular ultrasound of the brachial artery was similarly reduced at baseline in the diet-only phase and in the placebo phase, it returned toward near normal with intake of the antioxidant vitamins. Nonetheless, it is difficult to make a recommendation for their use because long-term efficacy trials in adults, often with cardiovascular disease or other medical conditions, have not shown benefit.<sup>142–145</sup>

Engler and colleagues<sup>31</sup> studied 20 hyperlipidemic children in a 6-week crossover clinical trial of docosahexaenoic acid supplementation. Endothelial function as assessed by flow-mediated dilation of the brachial artery was significantly improved while the patients were taking docosahexaenoic acid, without affecting biomarkers for oxidative stress, inflammation, or nitric oxide metabolism.

Although not yet studied in children, Engler and colleagues<sup>146</sup> performed a clinical trial in healthy adults of high-flavanoid

versus low-flavanoid dark chocolate bars. Those subjects who consumed the high-flavanoid dark chocolate were noted to have improved endothelial function as assessed by brachial artery reactivity. One can imagine the popularity of this therapy in children if proven in a clinical trial.

Although plant sterols have been shown to significantly lower LDL cholesterol levels in hyperlipidemic children, a recent study did not show an impact on endothelial function. De Jongh and colleagues<sup>147</sup> studied 41 children with familial hypercholesterolemia in a crossover clinical trial of a plant sterol spread taken for a 4-week period. Although LDL cholesterol was reduced by a mean of 14%, there was no improvement in flow-mediated dilation of the brachial artery. A similar clinical trial incorporating the plant stanol into low-fat yogurt likewise showed reductions in LDL cholesterol levels without improvement in endothelial function.<sup>148,149</sup>

These studies give preliminary evidence for an impact on the actual atherosclerotic disease process with treatment of familial hypercholesterolemia in children. Similar studies are required for other types of high-risk lipid abnormalities. Increasingly, these types of indicators will be used as surrogate end points in clinical trials of atherosclerotic risk reduction therapy in children.

## Modifications to the Existing NCEP Guidelines

Evidence on drug therapy of high-risk lipid abnormalities, notably familial hypercholesterolemia, in children has been accumulating, showing efficacy and safety similar to those in adults, with some evidence of an impact on the atherosclerotic disease process. The existing guidelines had limitations evident from the time of their publication, which have been magnified by an epidemic of overweight and obesity in children and adolescents, which add an additional risk factor to those youth who may already have a high-risk lipid abnormality.<sup>34</sup> From the above discussion, modifications to the existing guidelines are badly needed and are supported by increased evidence of benefit with availability of effective drugs since the original guidelines were published in 1992 (Table 4).

It should, however, be recognized that the evidence base underlying these recommendations is supported by indirect evidence, evidence extrapolated from studies in adults, studies performed in the setting of familial hypercholesterolemia, and expert consensus. Therefore, these recommendations and their implementation should be the subject of ongoing study and

modification. Further refinement of guidelines should incorporate new evidence on multiple risk factor scoring and its association with atherosclerotic pathology. They also should incorporate means to individualize cut points on the basis of gender, race, age, pubertal status, and other potential modulating factors. They should be influenced by further studies on the long-term safety and efficacy of lipid-lowering drug therapy and studies of drug therapy for high-risk conditions and abnormalities other than familial hypercholesterolemia. It must be realized that direct evidence of an impact of interventions during childhood and adolescence on later cardiovascular morbidity and mortality will likely always be lacking. It also must be emphasized that drug therapy should be targeted only toward individuals with high-risk lipid abnormalities or high-risk conditions who have not reached target lipid levels with lifestyle modification and should not be used as a first-line therapy for those whose lipid abnormalities are primarily lifestyle related. Effective lifestyle interventions need to be developed, evaluated, and implemented as the primary modality to reduce overall population risk, to prevent and treat obesity, and to prevent and treat exacerbation of high-risk lipid abnormalities and high-risk conditions.

## Disclosures

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\*Modest.

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