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SPECIAL ARTICLE

The Use of Statins in Pediatrics: Knowledge Base, Limitations, and Future Directions

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ABSTRACT

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, effectively reduce coronary morbidity and mortality in high-risk adults. They are also some of the most widely prescribed medications in the United States. Their use in pediatrics, however, remains circumscribed. In this article we review the cholesterol hypothesis and focus on the knowledge base of the use of statins in adults and children. We pay particular attention to the known effects of statins in primary and secondary prevention of cardiovascular events. The toxicities of statins and their limitations in pediatrics are then considered. The use of statins in conjunction with noninvasive modalities of assessing atherosclerotic burden are also reviewed. Finally, we suggest methods to advance the use of statins in childhood that introduce their potential benefits to those individuals at highest risk for future events.

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Key Words
statins, pediatrics, indications, limitations

Abbreviations
HMG-CoA—3-hydroxy-3-methyl-glutaryl coenzyme A
heFH—heterozygous familial hypercholesterolemia
CVD—cardiovascular disease
LDL-C—low-density lipoprotein cholesterol
FDA—Food and Drug Administration
CVE—cardiovascular event
CRP—C-reactive protein
BAS—bile-acid sequestrant
EBCT—electron-beam computed tomography
FMD—flow-mediated dilation of the brachial artery
cIMT—carotid intima-media thickness

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THE 3-HYDROXY-3-METHYLGLUTARYL COENZYME A (HMG-CoA) reductase inhibitors (statins) have been repeatedly shown in large randomized, controlled trials to effectively reduce coronary morbidity and mortality in high-risk adults. As a result, statins have grown to become one of the most highly prescribed drugs for adults worldwide. Estimated expenditures related to the purchase of statins at the current level of use in the United Sates are from $12.5 to $20 billion per year. Fully implementing the most recent National Cholesterol Education Program treatment panel guidelines to the entire adult population of the United States would result in the treatment of millions of individuals.

In this article we review new insights into atherosclerosis and myocardial infarction relevant to the subsequent discussion of statins. We review the mechanism of action, basic pharmacology, and toxicities of the HMG-CoA reductase inhibitors and present our concerns regarding the limitations of the applicability of adult study results to children. Attention is given to the potential role of statins in childhood, with a focus on heterozygous familial hypercholesterolemia (heFH); ie, whereas studies in adults have been focused on a wide array of conditions, the pediatric literature on statin therapy has dealt mainly with children with this inherited dyslipidemia. The use of statins in conjunction with new noninvasive modalities to assess surrogate markers of cardiovascular risk status in children is also considered. We evaluate the basis on which the usage of statins remains circumscribed and suggest methods to advance their use in children at highest risk for future events as part of a primary-prevention strategy.

NEW IDEAS IN ATHEROSCLEROSIS AND THE CHOLESTEROL HYPOTHESIS

Pediatricians have long been aware that a significant body of evidence supports the concept that the antecedents of adult heart disease can be identified in childhood and that prospective studies have linked the presence of cardiovascular risk factors in childhood to early atherosclerotic lesions (fibrous plaques).[1–3] On the basis of this knowledge, the pediatric panel of the National Cholesterol Education Campaign, the American Academy of Pediatrics, and the American Heart Association have issued guidelines for the prevention of cardiovascular disease (CVD) beginning in childhood.[4–6] Guidelines for the initiation of pharmacotherapy in childhood are conservative and are based on expert consensus rather than direct evidence of efficacy. Nonetheless, these organizations and several authors have recommended that certain groups of "at-risk" children (ie, those at very high risk for future events as adults) be treated with lipid-lowering medication starting in the second decade of life (Table 1).[4–8]

Over the last 20 years some long-standing concepts regarding the development and pathogenesis of atherosclerotic lesions have been revised.[1] It is now appreciated that inflammation and the immune system are critical effectors of the atherosclerotic process.[2] The majority of occlusive (thrombotic) events that produce myocardial infarctions do not occur at areas of vessel narrowing. It is now known that as plaques develop in the coronary vessels there is a remodeling of the vessel that preserves the luminal diameter (the Glagov hypothesis).[9] The risk of thrombotic events is most often related to qualitative properties of the atherosclerotic plaque itself that make it prone either to rupture and release the highly thrombogenic contents or to suffer an erosion of its intimal surface and potentially precipitate a clot.[3,10,11] Lastly, it has been appreciated that whereas the early atherosclerotic stages are reversible, the advanced stages are not. However, new data suggest that once established, advanced plaque can vary considerably in its inherent risk to precipitate an infarction, and it can evolve into a high-risk state or alternatively regress into a lower-risk one.

TABLE 1 Conditions That Place Children at Risk for Atherosclerosis

Heterozygous familial hypercholesterolemia
Homozygous familial hypercholesterolemia
Other dyslipidemias
Nephrotic syndrome
Systemic lupus erythematosus
Solid-organ transplant recipients
Diabetes mellitus
Metabolic syndrome

On a microscopic level, the pathophysiologic process behind atherosclerosis is complex and has been reviewed recently.[12] The interplay between circulating lipoproteins, inflammatory mediators, and various cell types leads to atherosclerosis. Low-density lipoprotein cholesterol (LDL-C) particles are oxidized and accumulate beneath the arterial endothelial layer. Endothelial and smooth muscle cells then secrete chemokines that attract and activate circulating monocytes and T lymphocytes. The immune response continues to be amplified in this manner. Lipid-laden macrophages (foam cells) along with activated T cells begin to form the fatty streak along the intimal vascular surface. Subsequently, smooth muscle cells cover the luminal aspect of the fatty streak and secrete a collagen matrix that forms a fibrous cap (plaque) over the collection of cells and lipid particles. If this plaque is unstable, it may rupture and its thrombogenic contents may precipitate a clot.[10]

MECHANISMS AND PHARMACOLOGY OF STATINS

The statins decrease hepatic synthesis of cholesterol by controlling the rate-limiting step in cholesterol synthesis: HMG-CoA reductase. Sterol response elements located in the promoter regions of the genes for the LDL-C receptor respond to a decrease in the cellular sterol content and upregulate cell-surface LDL-C receptor expression. This increase in LDL-C receptor concentration and activity is predominantly responsible for the observed reductions in circulating LDL-C concentration.[13]

Beyond their direct effects stemming from LDL-C reduction, statins have other effects on biological processes that may be antiatherogenic. This phenomenon is known as statin pleiotropy. Of particular interest among the pleitropic effects is an antiinflammatory effect hypothesized to be mediated by a decrease in the concentration of farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These compounds are downstream from HMG-CoA reductase in the cholesterol biosynthetic pathway and are necessary for prenylation of proteins that have important regulatory effects on cellular proliferation (Fig 1). Cellular proliferation, in turn, is crucial to the amplification of the immune response that, in part, drives plaque maturation. Another mechanism by which statins may exert an immunomodulating or antiinflammatory effect in general relates to a decrease in cholesterol rafts within the cell membrane that are needed for clustering of T-cell antigen receptors.[14] These clustered cell-membrane–associated proteins are necessary for the cell-to-cell signaling needed for amplification of the immune response and inflammatory cell recruitment to the plaque.[15–17] Although both clinical and experimental animal data may be gathered to suggest that the antiinflammatory effects of statins are clinically important, this hypothesis is controversial and awaits the results of ongoing prospective studies that were designed to resolve this issue.[18]

Currently, there are 4 statins approved by the Food and Drug Administration (FDA) for clinical use in the United States (Table 2). All of these statins are effective in lowering LDL-C by 25% to 45%.[19] For the pediatric population, statins are approved by the FDA for the treatment of heFH in adolescent boys and postmenarcheal girls (aged 10–17) as an adjunct to diet and lifestyle modifications to reduce total cholesterol, LDL-C, and apolipoprotein-B levels if (1) LDL-C remains ≥190 mg/dL or (2) LDL-C remains ≥160 mg/dL despite adequate nonpharmacologic interventions and there is a positive family history of premature CVD or ≥2 other risk factors for CVD exist in the adolescent patient.

The approved statins vary in their lipophilicity, which may affect their capacity to cross the blood-brain barrier and the concentration of active metabolites that enter the systemic circulation after first-pass metabolism in the liver.[20] These differences are important, theoretically, if it is postulated that there are pleiotropic drug effects on atherosclerotic plaque independent of LDL-C-lowering.

CLINICAL EFFECTS OF STATINS IN ADULTS: RELEVANCE TO PEDIATRICS

There have been >40 randomized trials that examined the effects of statins on CVD prevention in adults.[21] The results of adult statin studies are so striking and favorable that one is tempted to generalize them to children, adolescents, and adults at low risk; however, there are important caveats in the extrapolation of these results to children.

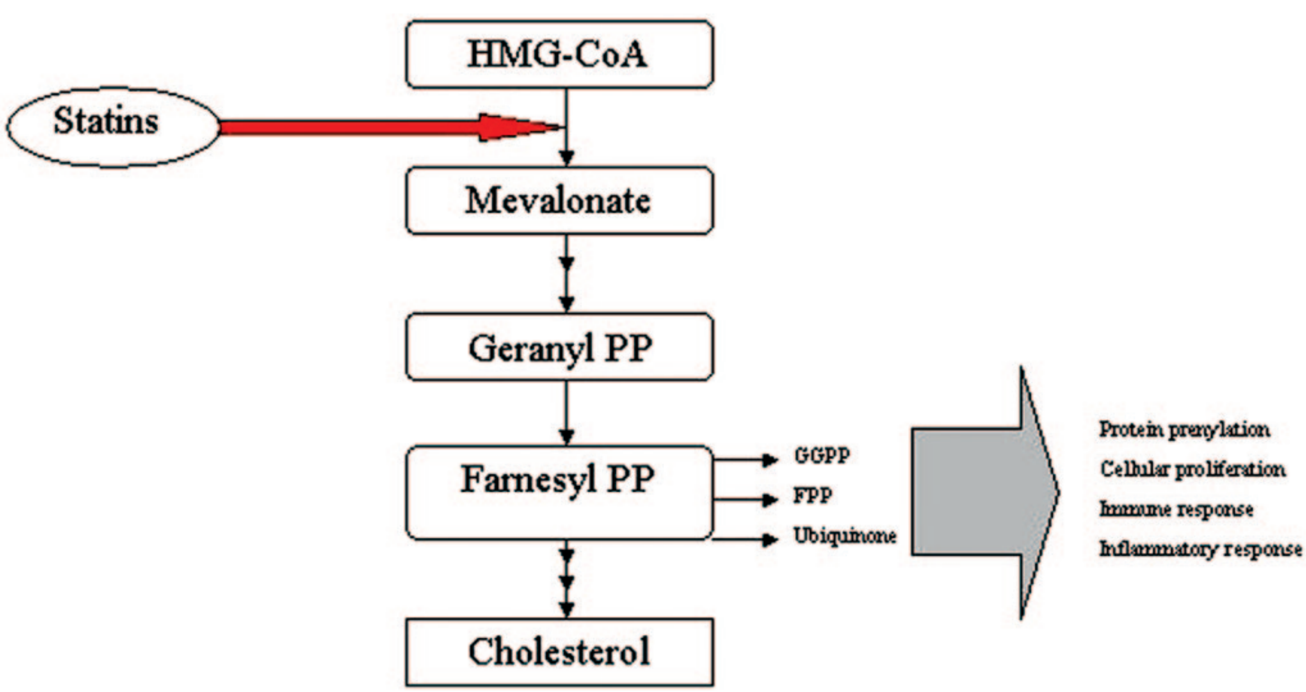

FIGURE 1
Cholesterol synthetic pathway. Critical steps in the synthesis of cholesterol are displayed, including intermediate compounds important in protein prenylation, cellular proliferation, and immune and inflammatory responses. The rate-limiting step at which statins act on HMG-CoA reductase is also shown. PP indicates pyrophosphate; GGPP, geranylgeranyl pyrophosphate; FPP, farnesyl pyrophosphate. (Reproduced with permission from Edison RJ, Muenke M. *Am J Med Genet A*. 2004;131:287–298, Wiley-Liss, Inc.)

TABLE 2 **Statins Approved for Use in Children**

Name (Trade Name)	Age Range, y	Dose, mg/d[a]	Metabolic Pathway	Lipophilicity
Simvastatin (Zocor)	10–17	10–40	CYP3A3/4 substrate	+++
Lovastatin (Mevacor)	10–17	10–40	CYP3A3/4 substrate	++
Atorvastatin (Lipitor)	10–17	10–20	CYP3A3/4 substrate; CYP3A4 inhibitor	+
Pravastatin (Pravachol)	8–13	20	CYP3A3/4 substrate; CYP3A4, CYP2C8/9, CYP2D6 inhibitor	−
	14–18	40		−

Shown are 4 FDA-approved statins for various pediatric age groups and dose ranges. CYP indicates cytochrome P450; −, nonlipophilicity.

[a] The listed doses have equivalent degrees of lipid reduction at the indicated starting dose. The degree of reduction seems to be dose dependent, and the dose-response curves for statins are sigmoidal. Doses >40 mg (20 mg for atorvastatin) have not been studied in the pediatric population for heFH. Except for pravastatin, all of the listed medications are significantly metabolized by the hepatic cytochrome P450 system. Pravastatin undergoes extensive first-pass metabolism and is minimally affected by the cytochrome P450 system. Lipophilic statins include (in order of decreasing lipophilicity) simvastatin, lovastatin, and atorvastatin.

First, the distinction between primary-prevention studies and secondary-prevention studies should be understood. Second, the application of "aggressive lipid-lowering" therapy advocated in high-risk adults is not justified by current evidence in children and adolescents. Third, whereas decreases in cardiac mortality are indisputable in primary-prevention studies, this is not true for total mortality. Finally, from a pathologic standpoint, the goal of treating at-risk children is the prevention of atherosclerotic plaque development and maturation, whereas the benefits of treating adults lie generally in mitigating the thrombogenic potential of existing plaque (Fig 2).[18]

Randomized clinical trials of statins in adults can be classified as primary prevention (ie, studies in asymptomatic adults with cardiovascular risk factors) or secondary prevention (ie, studies in adults with a history of a cardiovascular event [CVE]). The majority of studies in adults that have demonstrated the efficacy of statins in prevention of myocardial infarction have been secondary-prevention studies. Because even those children considered to be at highest risk rarely experience a CVE, the results of secondary-prevention trials in adults should be cautiously applied to children.

Early controlled studies performed in adults have demonstrated a linear relationship between achieved LDL-C levels and CVEs. This finding led to a second generation of studies in which lower LDL-C targets were associated with even more favorable results on event rates. The results of these secondary-prevention studies in adults prompted the recommendation that intensive lipid-lowering be considered in moderate and high-risk adults to LDL-C targets of <100 and <70 mg/dL, respectively.[21–25] The translation of these aggressive treatment targets to children and adolescents is not justified for primary prevention outside the context of research studies in which the risk/benefit of this approach can be monitored carefully.

Although statins have been shown to be effective in reducing cardiovascular morbidity and mortality in primary-prevention studies, these studies have not definitively demonstrated any reduction in absolute risk for total mortality (one study was not powered for this analysis,[26] and the other did not detect any significant differences[27]), and the reductions in coronary and cardiovascular mortality are modest in comparison to those observed in secondary-prevention studies.

This observation is crucial; before primary prevention with statins is undertaken on a large scale, it is critical to be certain that it is effective and that the risks for both

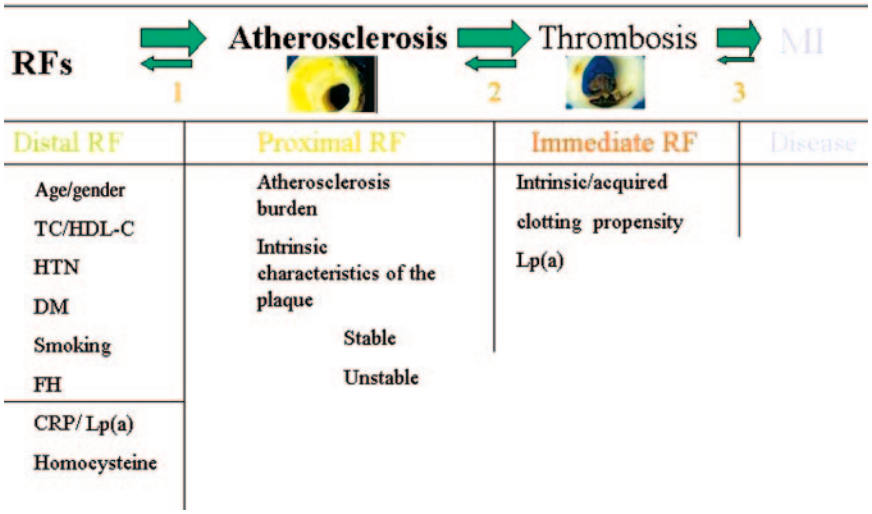

FIGURE 2
Cholesterol is a risk factor not a disease. Displayed are risk factors associated with a CVE, in this case myocardial infarction. Proceeding from left to right are distal to proximal risk factors. The modification of distal risk factors may be hypothesized to be the goal of therapy in children because many of the proximal risk factors are not evident until adulthood. The potential for reversibility of a given set of risk factors is indicated by reverse arrows. CV indicates cardiovascular; DM, diabetes mellitus; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; Lp(a), lipoprotein a; MI, myocardial infarction; RF, risk factor; TC, total cholesterol. (Photomicrographs adapted with permission from Davies MJ. *Heart*. 2000; 83:361–366, BMJ Publishing Group, Ltd.)

coronary and total mortality be reduced with statin therapy. If there is a reduction in the absolute risk for coronary mortality without a reduction in that for total mortality, then it may be postulated that the benefits of statins in reducing coronary mortality have been offset by increases in other-cause mortality.[28] This phenomenon was seen in earlier studies of bile-acid sequestrants (BASs) and fibrates and, more recently, in primary-prevention studies that focused on select groups of hypertensive adults without dyslipidemia[23] and in diabetic patients,[29] which revealed similar patterns of benefits in coronary morbidity and mortality but not in total mortality.

Next, the observed reductions in cardiovascular morbidity and mortality in statin trials may be argued to be greater than expected for the degree of lipid reduction achieved when compared with nonstatin therapies.[30–32] This potentially unexpected benefit of statin therapy has been attributed to their effects on inflammation and plaque stabilization. In this regard, the modification of the inflammatory process by statins has received considerable attention. High-sensitivity C-reactive protein (CRP) has come to be seen as an informative window into this process. The PROVE-IT study demonstrated that statins lowered CRP levels by 25%.[25] Analysis of CRP has been shown to add predictive value to cardiovascular risk assessment in adults who are treated with statins.[29,33–36]

Therefore, if these findings are related to the antiinflammatory benefits of statins on advanced atherosclerotic plaques, then it is possible that these same benefits may not be applicable to children whose plaques are at a much different stage of development. Indeed, a study of intensive lipid-lowering in adults demonstrated a modest retardation of the progression of coronary plaques as measured by intravascular ultrasound.[37] This retardation of atheroma progression correlated with both LDL-C and CRP reductions (ie, with markers of atherogenic lipids and inflammation, respectively). The relevance of these findings to adolescents is that statin treatment may particularly benefit advanced atherosclerotic lesions that are much more likely to be present in middle-aged adults. Indeed, it may be argued that the effect of statins seen in the primary-prevention studies to date relates to the subgroups of individuals who already have unstable plaques.

SUMMARY OF LIPID-LOWERING STUDIES IN CHILDREN

Traditional interventions for hypercholesterolemia in children include diet (low-fat diet and water-soluble fiber intake), exercise, fibrates, and BASs. Intensive dietary and exercise programs have been shown to mediate only modest reductions in LDL-C over a period of several months to 1 year.[38] Lifestyle interventions are appealing because of their intrinsic safety and their potential to mitigate other health risks. Their basis in empiric fact is evidenced by epidemiologic studies of societies that are largely free of CVD. BASs, however, have limited use because of their poor palatability, inconvenient dosing schedule, and adverse gastrointestinal effects.[6,39] Furthermore, BAS therapy often requires high doses and achieves only mild reductions in LDL-C (~12%).[40,41] Nonetheless, BASs have a record of safe use for >40 years.

Although several studies of varying quality have demonstrated marked reductions in LDL-C with the use of statins in certain groups of children, including those with nephrotic syndrome and kidney and heart transplants,[42–44] the focus of this section is children with heFH. Studies of statin use in this pediatric population are the most extensive and of more rigorous design. Four statins have been approved by the FDA for the treatment of children with heFH who are at markedly elevated risk of premature coronary artery disease.

heFH is a well-described autosomal-dominant condition with an estimated frequency of 1 in 500 worldwide. Children with heFH typically have total cholesterol levels in the range of 270 to 500 mg/dL with normal triglyceride levels and normal or slightly decreased levels of high-density lipoprotein cholesterol. Fifty percent of first-degree relatives are affected. It is an extraordinarily high-risk condition: it is estimated that if left untreated, up to 50% of men with this condition will have a coronary ischemic event by 50 years of age and only 15% of men will reach age 65 without experiencing a CVE.[45,46] Thus, on the basis of both consensus and individual expert opinion, children with heFH are considered to be candidates for the introduction of statins during early adolescence.[4–7,47]

The early studies of statin use in these children were often small in size and short in duration but soon gave way to larger, well-designed studies.[48–52] These studies demonstrated 30% to 50% reductions in LDL-C regardless of the statin used. Some of these children, however, did not achieve LDL-C reductions to below the 95% cutoff of 130 mg/dL. Regardless, these results were generally so favorable compared with those previously achieved in the same subjects with BAS therapy that statins quickly became standard medical care for these children. It is interesting to note that one of these studies suggested that specific LDL-C receptor mutations may have accounted for some of the variability in response to therapy.[51]

Many of these studies were limited by their restriction in patient populations by gender or ethnic background. Subsequently, however, several randomized trials, some of which were blinded, have included more diverse groups.[53–56] These studies focused on short-term safety in childhood and close monitoring of growth, pubertal progression, and hormone levels. They were generally limited by their short duration, which precludes determination of long-term efficacy, consequences, and toxicities. These shortcomings notwithstanding, these studies have confirmed the findings in adult studies of impressive reductions in LDL-C and improvements in cardiovascular risk profile.

STATIN TOXICITIES IN ADULTS

Information regarding the toxicity and adverse effects of statins in adults have been obtained from the results of clinical trials, health maintenance organization registries, and the FDA's MedWatch database. In general, statins are well tolerated and regarded as safe in adults; nonetheless fatalities have been reported in association with their use.[57] Although a spectrum of adverse effects have been reported, the majority of the literature on statin toxicities concerns their potential for hepatotoxicity and muscle toxicity.[58–60] Statins are also potent teratogens.[61–63] There is debate and differing interpretations of the literature regarding several other adverse effects including cognitive adverse effects, peripheral neuropathy, and a possible increase in the risk of cancer; these are areas that deserve mention, additional research, and a low threshold of concern for pediatricians.

Statin-Related Hepatotoxicity

Elevation of aminotransaminases, defined as >3 times the upper limit of normal on 2 consecutive measurements, is common, transient, and a "class effect" of statins. It may occur in 1% to 3% of patients using statins.[64,65] Most alanine aminotransferase elevations occur >90 days after initiation of therapy and are asymptomatic.[66,67] The propensity for hepatotoxicity may be increased with statins that are highly lipophilic and prescribed at a high dose.[68] Drug interactions involving the cytochrome P450 system that result in higher serum concentrations may also increase this risk (Table 2). Although idiosyncratic fulminant liver failure associated with statin use is extremely rare, it has been reported. The package inserts of FDA-approved statins recommend routine monitoring of liver-function tests; however, there are no data to suggest that this protocol can adequately predict or prevent acute hepatic failure.[58,69]

Statin-Related Myotoxicity

Most of the literature on statin toxicity relates to the effects of statins on skeletal muscle and their propensity to cause a spectrum of muscle complaints ranging from mild myalgias, with or without elevation of creatine kinase, to frank rhabdomyolysis resulting in renal failure and or death.[70,71] Myopathy and rhabdomyolysis are thought to be a class-effect toxicity of statins, the risk of which is increased by factors that increase serum and muscle concentrations of statins.

Statin-Related Rhabdomyolysis

Potential dangers of statins were best recognized when reports of fatal rhabdomyolysis associated with the use of cerivastatin (Baycol) led to its voluntary withdrawal by its manufacturer in 2001.[72] Subsequent analyses by the FDA suggested that the reporting rate of fatal rhabdomyolysis for cerivastatin was 16 to 80 times greater than that for other statins.[73] Rhabdomyolysis has been observed with the use of all currently approved statins. Although the exact mechanism by which statins cause rhabdomyolysis is unknown, it is thought that depletion of mevalonate, farnesol, geranylgeraniol, and especially mitochondrial ubiquinone may be responsible (Fig 1).[74]

Teratogenicty of Statins

An uncontrolled case-series analysis of all statin exposures during gestation reported to the FDA reported that among 214 determined exposures, 31 adverse birth outcomes were identified, including syndromic and nonsyndromic limb deformities, fetal demise, and intrauterine growth restriction.[61] There have also been reports of central nervous system and cardiac anomalies with lovastatin-exposed fetuses.[62,63] The teratological mechanism seems to involve inhibition of cholesterol synthesis and alterations of sterol-dependent morphogens by the lipophilic statins that cross the placenta.

Statin-Associated Cognitive Effects

Whether statins in general, or statins that cross the blood-brain barrier in particular, can adversely affect cognitive function and or mood is an area of ongoing interest and debate.[75,76] Case reports and randomized clinical trials performed in adults have reported adverse cognitive effects of statins in adults.[77,78] On the other hand, 2 large randomized, controlled trials of statins in which cognitive outcomes were assessed did not find an adverse effect of statin treatment.[79,80] There is a large, ongoing randomized trial in which the effects of statins on cognition, mood, and behavior are primary outcome measures.[81]

Statin-Associated Cancer

The relationship of cholesterol levels and cholesterol-lowering to cancer is also an ongoing area of interest. Individual randomized, controlled trials of statins have shown both increased and decreased cancer rates in statin-treated groups. A meta-analysis that pooled 29 trials and included data from 86 936 adults did not demonstrate an increase in either cancer incidence or cancer death rates.[82] Nonetheless, both in vitro and animal data justify a concern, and it remains conceivable that individual statins differ with respect to their propensity to promote or retard individual cancers.[83]

STATIN TOXICITIES IN CHILDREN

Short-term Toxicities

The safety of statins in children and adolescents is based on trials that have ranged in duration from 6 months to 2 years. Elevations in alanine aminotransferase and/or aspartate aminotransferase without clinical hepatotoxicity have been reported in 1% to 5% of children who were treated with simvastatin or atorvastatin[54,55] and in very few children treated with lovastatin or pravastatin.[52,55,84,85] These elevations were observed to be mild, asymptomatic, and reversible after discontinuation of the statin.[49,64,66] To date, clinical trials that have been performed in adolescents that have included assessments of growth, hormone synthesis, pubertal development, significant myopathy, and rhabdomyolysis have provided reassuring results; nonetheless, these studies were of relatively short duration and underpowered to detect infrequent or rare adverse effects.[54–56,82,83]

Monitoring for Statin Toxicity

Pediatricians who are using statins for primary prevention in adolescents should, in general, have a very low threshold for their discontinuation in the face of observed or incipient serious adverse effects. Current package inserts for statins call for the routine monitoring of liver-function tests with statin use; however, the utility of this approach to prevent serious idiosyncratic hepatotoxicity has been questioned.[69] Patients should be counseled to promptly report symptoms of hepatic dysfunction (fatigue, anorexia, nausea, vomiting, right upper-quadrant discomfort, and jaundice) during therapy. These reports should always be assessed promptly.[58,85] Similarly, patients should be counseled to promptly stop statin therapy for symptoms of myalgia, muscle soreness, weakness, tenderness, or dark-colored urine and inform their health care provider. Guidelines regarding the continuation or reinstatement of therapy in the case of suspected or confirmed mild adverse effects exist for adults but not for adolescents; therefore, decisions in these situations should be individualized.

Drug Interactions

Dosing of statins should be more conservative in children and adolescents to reduce the potential for dose-related adverse effects.[59] Avoiding drug interactions involving the cytochrome P450 isoenzymes, especially the 3A4 and 2C9 subtypes, may prevent increases in serum concentrations of statins and may reduce dose-related adverse effects. Lovastatin, simvastatin, and atorvastatin are primarily metabolized by the 3A4 enzymes. Medications that inhibit cytochrome P450 3A4 (macrolide antibiotics, antifungal agents, HIV-protease inhibitors, calcium channel blockers, and cyclosporine) increase the serum concentration of statins and, thus, increase the risk of toxicity. Enzyme inducers such as rifampin, barbiturates, and carbamazepine decrease statin serum concentrations. Because nonlipophilic pravastatin is the only approved statin that is not significantly affected by these mechanisms (because of its first-pass effect and metabolism by other pathways), it may be used when drug interactions preclude the use of other statins.[86,87]

Finally, it is critically important to recognize that candidates for statin use during adolescence are often still undergoing cognitive maturation, endocrinologic maturation, skeletal growth, and bone mineral accretion. Therefore, initiation of statins during adolescence incurs a risk of effects specifically related to these processes. Although the available data regarding statin use are reassuring, it is important to realize that neither adult studies (regardless of their quality and power) nor existing short-term studies of children directly address the long-term effects of statins on these processes. Patients begun on a statin during adolescence will receive a cumulative dose that far exceeds that which most adults have received. For these reasons, we strongly agree with the call for incentives for pharmaceutical companies to conduct longer-term safety trials.[88] In the interest of furthering our understanding of statin use in adolescents, pediatricians should report all statin-related adverse effects to the FDA by using the MedWatch reporting system.

STATINS AND EARLY SURROGATE MARKERS OF ATHEROSCLEROSIS IN PEDIATRICS

Recently, several noninvasive measures of atherosclerosis have been established. These measures rely on noninvasive monitoring of atherosclerosis by using changes in the function, reactivity, or ultrastructure of the vasculature. These measures serve as early proximal surrogate markers for cardiovascular end points and include coronary calcifications as measured by electron-beam computed tomography (EBCT), flow-mediated dilation of the brachial artery (FMD), mean carotid intima-media thickness (cIMT), and MRI. EBCT was assessed by Gidding et al[89] in 29 children, adolescents, and young adults with heFH, of whom 25% had elevated coronary calcium scores.

FMD relies on the observation that abnormalities in vascular dilatation and nitric-oxide response to ischemia are observed early on in the pathway to coronary artery events. Indeed, increasing severity of endothelial dysfunction has been associated with increased risk for cardiac events in a graded fashion, and such changes can be observed in the absence of any plaque formation.[90,91] Statins were previously shown to improve FMD in adults with dyslipidemia.[92] de Jongh et al[93] conducted perhaps the only pediatric study that assessed the ability of statins to reverse the early stages of endothelial dysfunction with FMD in 50 children with heFH who were randomly assigned to receive either simvastatin or placebo. After 28 weeks, FMD increased by 4% in the children in the intervention group to a level comparable to that seen in healthy controls.

Atherosclerosis can also be assessed by using the mean cIMT (ie, the mean measurement of the right and left common carotid arteries, carotid bulb, and internal carotid artery far-wall segments). The use of cIMT measurements as a marker of CVD progression was reviewed recently.[94] Increasing cIMT assessments have been shown to be associated with a stepwise increase in CVD risk profile in asymptomatic adults,[95] and atorvastatin has been demonstrated to reduce cIMT measurements in correlation with LDL-C reductions on the order of 40% to 50% in adults with heFH.[96]

To the best of our knowledge, Weigman et al[97,98] have conducted the only studies that investigated the efficacy of a statin in modulating cIMT in pediatric patients with heFH. In a randomized trial of 214 statin-naive pediatric patients with heFH, 2 years of therapy with pravastatin resulted in a 2% reduction in mean cIMT, compared with a 1% increase in the placebo group.[97] This is in comparison to the 3% to 5% reductions in the mean cIMT that have been reported in adult studies.[95,99–102] It is possible that heterogeneity within the group assignments in the Weigman et al studies (ie, not all children in the treatment group had an inflammatory atherosclerosis at baseline) could explain the relatively smaller effect on cIMT in the treatment group.

In summary, the use of cIMT, EBCT, and MRI as surrogate markers in pediatrics is promising, and long-term data need to be gathered. The negative and positive predictive values of these assessments are of paramount importance in pediatrics. Any program that uses these assessments should keep this in mind. Conversely, a recent editorial noted that in pediatric patients in whom the annual absolute risk of CVEs is low, it is precisely noninvasive monitoring techniques that may prove useful in identifying those high-risk children who might benefit from aggressive therapy.[103]

FUTURE DIRECTIONS AND STUDIES: PRACTICAL APPLICATIONS OF STATINS IN PEDIATRICS

Before statins are begun on a large scale in pediatrics, adult studies should definitively establish that statins decrease total morbidity and mortality in primary-prevention studies of middle-aged and young asymptomatic adults who are at high risk (eg, a strong family history of early CVEs). There should be a logical progression of primary-prevention studies from older to younger individuals. Whether statins are justified for primary prevention in young, healthy adults with hyperlipidemia is currently unknown. It is notable that simvastatin was recently reclassified as an over-the-counter drug in the United Kingdom as part of a primary-prevention strategy.[104] However, earlier introduction of statins offers the possibility of a greater degree of risk reduction than is currently observed in adult studies. It may be possible to regress lesions to a degree that is not possible in later adulthood when aggressive treatment is introduced earlier in the process. This would mitigate atherosclerosis risk nearly entirely. This is the most compelling argument for this type of study.

Noninvasive imaging of childhood atherosclerosis is in its infancy and encompasses the use of cIMT and, more recently, multimodal MRI to visualize and quantitate plaque burden and composition in the common carotid arteries and the abdominal aorta.[105] Both of these techniques are limited by a lack of pediatric reference values; moreover, because it is not possible to scan the coronary arteries noninvasively, these measures are proxy measures for the presence of atherosclerosis in the coronary vessels.

It will soon be possible to identify a subset of adolescents with ≥1 risk factor (hyperlipidemia, family history of premature coronary artery disease, hypertension, glucose intolerance) who, using these measures, have evidence of silent early lesions. These individuals are the logical candidates to study the early introduction of statins. Children with traditional risk factors who are shown to be free of early lesions on noninvasive assessment, however, might not be candidates for statin therapy. Noninvasive assessment used in this fashion can serve to spare traditionally at-risk children from the risk inherent in unnecessary pharmacotherapy.

Which children should be targeted for longitudinal studies? The traditional answer is that those individuals who have the most severe disease process have the most to benefit from novel and untested treatments. Some very preliminary data suggest that adolescents with type 2 diabetes and the metabolic syndrome may exceed even those adolescents with FH in their risk for advanced plaques. Within the realm of cardiovascular primary prevention, the targets of therapy are risk factors for disease; in this scenario the individual must balance the risk of treatment not against the benefits of treatment but against the reduced risk of disease. Because disease is not certain, this becomes a highly personal decision (such as with the elective mastectomy in women at high risk for breast cancer), and it demands that the treatments offsetting risk factors are extremely safe. This latter point arises because few people would accept death or serious long-term disability for themselves or their child as an adverse effect of disease prevention. Given that primary prevention with statins is still controversial in adulthood and that data are lacking for statins introduced in childhood, we do not believe that statins have met this standard.

RECOMMENDATIONS AND CONCLUSIONS

Lifestyle modification is the cornerstone of cardiovascular prevention in childhood and should remain so. When statins are prescribed for adolescents, it is important to recognize that the targets of therapy are risk factors for disease. As mentioned previously, the individual must then balance the risk of treatment not against the benefits of treatment but against the reduced risk of disease.

In view of the worldwide pediatric obesity epidemic, there will be a great temptation to empirically use these agents to attempt to mitigate the corresponding epidemic of cardiovascular risk factors.

However, we believe that our collective obligation is to design, fund, and conduct a new phase of longer-term statin studies coupled with noninvasive monitoring of atherosclerosis progression that will begin to address the potential benefits and risks of the introduction of these agents to the developing child.

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