

Storm over Statins — The Controversy Surrounding Pharmacologic Treatment of Children

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In July of this year, the American Academy of Pediatrics (AAP) released revised recommendations for the management of hypercholesterolemia in children (see table).¹ Within days after publication,

the new policy statement had elicited a firestorm of controversy — including hundreds of print and broadcast news stories, editorials in the *New York Times* and the *Boston Globe*, and thousands of Internet postings — that took many members of the pediatrics community by surprise. The AAP and the National Cholesterol Education Program have advocated targeted screening and pharmacologic treatment for nearly two decades. What sparked this sudden flurry of media attention?

The AAP report was motivated by growing evidence that atherosclerosis begins at an early age and

that treatment of hypercholesterolemia in children may reduce the lifetime risk of cardiovascular disease. For example, recent analyses in the Muscatine Study and the Cardiovascular Risk in Young Finns Study found significant associations between cardiovascular risk factors in childhood and carotid intima-media thickness in young adulthood. The new recommendations represent, for the most part, incremental change from previous practice: more comprehensive screening, an emphasis on improving the quality of dietary fat rather than reducing total fat consumption, and a low-

ering of the age at which drug therapy may be instituted, from 10 to 8 years (see table for a comparison of the 1998 and 2008 recommendations). The most controversial change appears to have been the inclusion of statins as potential first-line pharmacologic agents.

Cholesterol is a lipid present in the cell membrane and subcellular organelles of tissues throughout the body. Because of its amphipathic nature, cholesterol plays a key role in maintaining membrane fluidity, thereby influencing transmembrane signaling and other fundamental cellular functions. Cholesterol in the brain, which accounts for about 25% of total body stores, promotes myelin formation, synaptogenesis, and neuronal plasticity.² In addition, cholesterol serves as the building

Comparison of AAP Recommendations on Hypercholesterolemia in 1998 and 2008.*		
Recommendation	1998	2008
Screening		
	Measure nonfasting total cholesterol or fasting lipids according to algorithm	Assess fasting lipid profile
	Recommended with family history of high cholesterol or early atherosclerosis	(Unchanged)
	Optional with unknown family history	Recommended with unknown family history
	Optional given personal risk factors	Recommended given personal risk factors
	Screen at least every 5 yr	Screen every 3–5 yr beginning at 2 yr of age
	Use same cutoff points for all ages and both sexes	Use age- and sex-specific cholesterol norms (>95th percentile considered abnormal)
	No specific recommendations for high triglyceride levels and low HDL cholesterol levels	Measure triglyceride and HDL cholesterol levels, with age- and sex-specific norms
Diet and exercise		
	Begin nutritional therapy at 2 yr of age	Begin nutritional therapy with reduced-fat milk at 1 yr for children at risk owing to obesity or family history
	Initiate treatment with NCEP Step-One Diet (total fat 20 to 30% of total calories consumed, saturated fat <10%, dietary cholesterol <300 mg/day); if diet is not effective after 3 mo, progress to Step-Two Diet: (total fat 20 to 30%, saturated fat <7%, dietary cholesterol <200 mg/day)	Follow Dietary Guidelines for Americans, with saturated fat <7%, trans fat <1%, dietary cholesterol <200 mg/day, and suggested fiber intake equal to child's age plus 5 g/day, up to 20 g/day at 15 yr of age
	Encourage regular exercise	Encourage physical activity for weight management and for treatment of high triglyceride levels and low HDL cholesterol levels
Pharmacology		
	Use bile acid-binding agents as first-line agent; statins not recommended	Include statins among potential first-line agents
	10-yr minimum age for pharmacotherapy	8-yr minimum age for pharmacotherapy
	Initiate pharmacotherapy for LDL cholesterol level of ≥ 190 mg per deciliter or ≥ 160 mg per deciliter with positive family history or two additional risk factors	Use new LDL cholesterol treatment cutoff point of ≥ 130 mg per deciliter if diabetes mellitus present

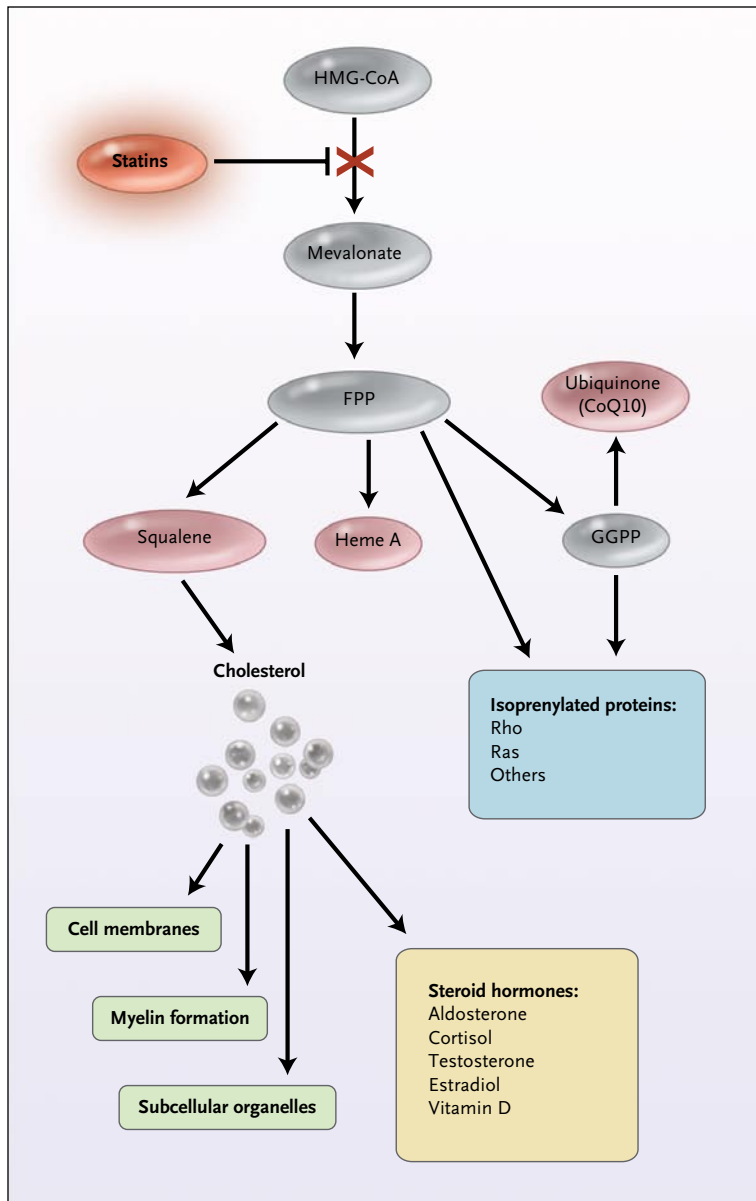
* AAP denotes American Academy of Pediatrics, HDL high-density lipoprotein, LDL low-density lipoprotein, and NCEP National Cholesterol Education Program.

block for all steroid hormones, including cortisol, aldosterone, estrogen, and testosterone. The critical importance of cholesterol to health is demonstrated by Smith-Lemli-Opitz syndrome, a disorder resulting from decreased cholesterol biosynthesis that causes devastating multiorgan failure.

Before this year's policy statement, the AAP recommended only

one class of lipid-lowering drugs, bile acid-binding resins such as cholestyramine and colestipol that bind cholesterol in the gut and have no clinically significant systemic side effects. Statins work through a novel mechanism, the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme involved in the synthesis of cho-

lesterol (see diagram). Statins also inhibit production of mevalonate and other cholesterol intermediates in the isoprenoid pathway. These compounds, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, participate in the post-translational modification of small guanosine triphosphate-binding proteins involved in cell proliferation and other functions,



Steroid Synthesis Pathway.

Inhibition of this steroid pathway by a statin (red) may have pleiotropic effects, influencing antioxidant activity (pink); intracellular processes (blue), including signal transduction, cell proliferation, and apoptosis; structural components (green); and steroid hormones (yellow). FPP denotes farnesyl pyrophosphate, GGPP geranylgeranyl pyrophosphate, and HMG-CoA 3-hydroxy-3-methylglutaryl coenzyme A. Arrows may reflect more than one enzymatic reaction.

providing a molecular explanation for the pleiotropic effects of statins that are observed both in vitro and in vivo.³ Though the primary site of action for statins

is the liver, some agents in this class inhibit cholesterol synthesis in other tissues, including the brain.

Statins have been extensively

studied and have a reasonable safety and side-effect profile in adults. Their main side effects, elevated serum aminotransferase concentrations and myopathy, occur relatively infrequently. Primary prevention trials have shown decreased rates of cardiovascular events but not decreased mortality among adults. There are limited, short-term data showing that statins appear safe in children, though long-term follow-up is completely lacking. At 8 years of age, a child's brain and other organ systems remain in dynamic stages of growth and development, raising concern that long-term pharmacotherapy initiated at this age may adversely affect the central nervous system, immune function, hormones, energy metabolism, or other systems in unanticipated ways.

The subtext for this controversy is, of course, the epidemic of childhood obesity in the United States and, increasingly, around the world. Indeed, the word "obese" or "obesity" appears more than 20 times in the AAP's 2008 report, as compared with just twice in its previous report. During the past 25 years, the prevalence of pediatric obesity has tripled; in some minority-group populations, the majority of adolescents are overweight or obese. Recent research suggests that increasing body weight in childhood, even within the range considered normal, is strongly associated with the risk of cardiovascular disease in adulthood.⁴ Case reports have identified renal failure requiring dialysis, limb amputation, and death before 30 years of age among persons who developed type 2 diabetes during adolescence. Because of such effects,

some experts have predicted that life expectancy will decrease in the United States for the first time in more than a century unless something is done about childhood obesity. Given the urgency of this situation, the expert committee formulating the new AAP guidelines faced the unenviable task of balancing the unknown risks associated with pharmacologic therapy in children against the prospect that myocardial infarction would become a common condition of young adulthood. In this scenario, the pediatrics community has no good choices.

The recommendation to use statins in childhood seems to have hit a collective nerve, perhaps awakening us to the fuller implications of the obesity epidemic. It's one thing to treat the rare child who has an inherited defect in cholesterol metabolism and quite another to extend treatment to children who are at risk for cardiovascular disease because of modifiable lifestyle factors.

At present, we do not know how many children or adolescents will meet the criteria for statin treatment because of the effects of obesity, poor diet, or physical inactivity. High levels of low-density lipoprotein cholesterol represent just one of many risk factors resulting from an unhealthy

lifestyle, and among lipid abnormalities, low levels of high-density lipoprotein cholesterol and high triglyceride levels appear to be more strongly associated with excess body weight. Regardless of how many additional children may receive statin treatment under these new guidelines, the broader, more important question is whether we intend to treat pediatric obesity with an ever-increasing array of powerful adult drugs — beta-blockers and diuretics for hypertension, aspirin for coagulopathy, insulin sensitizers for the metabolic syndrome, and of course insulin for diabetes. Once this door has been opened, the pharmaceutical industry will happily walk through it. Instead of fewer advertisements for junk food, are we destined to see new commercials promoting the use of cholesterol-lowering medications in children?

The intense media coverage of the new statin policy may have shined a light on the profound cultural disconnect between our willingness to treat disease with drugs and our reluctance to institute preventive public health measures. These measures would include regulating food marketing to children, improving the quality of nutrition at school, promoting physical activity at school

and elsewhere, and providing greater funding for obesity prevention and treatment programs.⁵ If the AAP recommendations have helped bring this disconnect to light, then their greatest effect may be not on the children who will receive pharmacologic treatment for hypercholesterolemia but rather on the adults who are responsible for the world in which our children live.

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1. Daniels SR, Greer FR, Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008;122:198-208.
2. Valenza M, Cattaneo E. Cholesterol dysfunction in neurodegenerative diseases: is Huntington's disease in the list? *Prog Neurobiol* 2006;80:165-76.
3. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med* 2008;14:37-44.
4. Baker JL, Olsen LW, Sørensen TIA. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med* 2007;357:2329-37.
5. Lavizzo-Mourey R. Childhood obesity: what it means for physicians. *JAMA* 2007;298:920-2.

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