New Cholesterol Guidelines for Children?

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For children and adolescents, comprehensive guidelines for the diagnosis and management of elevated cholesterol have been published once, by the National Cholesterol Education Program in 1992. Since then, substantial research on early atherosclerosis and in related clinical areas has been conducted; simultaneously, the obesity epidemic has added the metabolic syndrome and its related high-triglyceride/low–high-density lipoprotein (HDL) phenotype to the agenda of those interested in establishing a consensus approach to early cardiovascular disease prevention.

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Before assuming that new knowledge and secular trends in risk factors demand substantial revision of cardiovascular health guidelines for children, we must first consider several valuable, often prescient aspects of the 1992 report. First is an emphasis on the importance of nutritional management over pharmacological management of elevated low-density lipoprotein (LDL) cholesterol, unless levels clearly associated with premature cardiovascular disease exist and children are sufficiently old that advanced atherosclerotic lesions may be presumed to be present. Two randomized trials of dietary intervention, the DISC (Dietary Intervention Study in Children) and STRIP (Special Turku coronary Risk factor Intervention Project for babies) studies, have shown that the diet recommended by the 1992 report is safe and mildly effective in lowering LDL cholesterol and thus can be implemented in population-based strategies of cardiovascular disease risk lowering. Furthermore, the PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study has shown that advanced, irreversible atherosclerotic lesions (American Heart Association grades IV and V) are rarely present before 19 years of age and that the relationship of risk to atherosclerosis in late adolescence is with regard to reversible early lesion grades (American Heart Association grades I through III).

A second and woefully underrecognized virtue of the 1992 report is the definition of risk strata for LDL cholesterol, with borderline values being 110 to 129 mg/dL and high cholesterol defined as ≥130 mg/dL. In 2002, by Adult Treatment Panel III, these levels were accepted for adults (100 mg/dL is now the borderline threshold). The rationale was provided by natural history studies that recognized the inflection points in the LDL cholesterol distribution at which risk of cardiovascular disease increases and intervention studies that identified LDL levels below which benefit from pharmacological reduction of LDL cholesterol is not seen.

Third, the 1992 guidelines take a natural history perspective, thinking of adults as “big children” or, in scientific terms, applying inductive reasoning principles to establish prevention guidelines. The inductive approach is focused on identifying those biological and behavioral factors that are safe and both contribute to and protect from the development of early atherosclerosis. Thinking of children as “little adults,” or applying deductive reasoning to extrapolate backward from adults with cardiovascular events to what theoretically “must” be occurring in children, creates distortion. Examples include (1) the fact that cardiovascular events are related to advanced atherosclerosis, as well as thrombosis and acute factors, not to the early lesions; (2) risk factors for cardiovascular disease may also be risk factors for other diseases, so that the act of looking back starts from a biased sample (eg, obesity, low fiber intake); and (3) the incorrect idea that interventions that benefit those with established coronary artery disease must benefit those with risk but no established coronary artery disease. The last distortion is demonstrated by (1) the important criticism of many primary-prevention drug trials that all-cause mortality is not influenced by treatment and (2) the extrapolation of Adult Treatment Panel III treatment goals in those with established coronary artery disease to interpretation of screening lipid profiles in children.

Fourth, the 1992 guidelines placed an emphasis on identification of the child with multiple risk factors for more aggressive intervention. The report defined this group as those with either extreme levels of LDL cholesterol secondary to familial hypercholesterolemia or elevated cholesterol and the simultaneous presence of other major risk factors, such as hypertension, tobacco use, or diabetes mellitus. This principle is supported by vascular studies from the PDAY study and the Bogalusa Heart Study relating atherosclerosis on postmortem examination to measured cardiovascular risk factors and innovative research linking noninvasive measures of atherosclerosis in young adults to risk factors measured in youth. All these studies confirm the emphases in the 1992 report: Advanced lesions (as opposed to the earlier, lower-grade lesions) are more likely to develop and progress by the late third to fourth decade of life in the few individuals with extreme or multiple risk factors rather than the general population at modestly increased risk.

Another extremely important observation from both the pathological and imaging studies of atherosclerosis in young adulthood is that risk factors measured in youth are often
stronger predictors of future atherosclerosis than measurements made at the time imaging studies are performed.\textsuperscript{7–9} No stronger justification for paying attention to cardiovascular risk in youth can be provided. These observations serve as the rationale not only for the identification of high-risk individuals but also for the prevention of the development of risk factors in the first place through recommendations on nutrition, exercise, tobacco avoidance, and maintenance of normal body weight.\textsuperscript{11,12}

The 1992 guidelines recommend cholesterol screening, by use of a complicated algorithm, in those children with a positive family history for elevated cholesterol or premature coronary artery disease. In 2006, these recommendations are inadequate. Several studies have shown that following these recommendations results in testing $\leq 25\%$ of children presenting for well-child care and identifying only about half of those with high LDL cholesterol.\textsuperscript{13} As a consequence of the obesity epidemic, in which as much as $30\%$ of the population is above the 85th percentile of the body mass index distribution, obtaining a fasting lipid profile is now recommended for risk stratification.\textsuperscript{2} Lipid profiles are routinely measured in patients with hypertension, prior Kawasaki disease, diabetes mellitus, end-stage renal disease, postcancer chemotherapy, and HIV.

In this issue of Circulation, Jolliffe and Janssen provide for the first time age-based percentiles for the distribution of lipids and lipoproteins for US adolescents.\textsuperscript{14} The ability to account for age and gender in the interpretation of fasting lipid profiles is important. For triglycerides and HDL, percentiles may be helpful in establishing pediatric definitions of the metabolic syndrome. Because the atherosclerosis assessment studies mentioned above highlight the importance of risk in youth on the development of atherosclerosis later in life, and because lipid levels tend to track well into adulthood, individuals at higher percentiles may be at higher risk for later atherosclerosis. Age-based percentile distributions are currently used to define risk presence for both hypertension and overweight.\textsuperscript{2,15}

However, certain questions must be asked about the usefulness of a percentile-based algorithm for lipids. The rationale for using percentile-based guidelines for blood pressure and overweight in children is the demonstrated contemporary relationship of high percentiles for these distributions to related morbidities, such as the presence of left ventricular hypertrophy and the likelihood of having the metabolic syndrome. Morbidity related to LDL cholesterol occurs in the future and is related to the conventional LDL risk thresholds of 100 and 130 mg/dL.\textsuperscript{10} Because the risk for future atherosclerosis-related disease is linked to LDL levels above 100 to 110 mg/dL, is it appropriate to label children at lower levels as at risk? Furthermore, tracking is good but imperfect; there will be significant incorrect stratification in those with high percentiles but below these thresholds.\textsuperscript{16} Using the National Health and Nutrition Examination Survey (NHANES) database may also be problematic. A substantial portion of the NHANES cohort was excluded from lipid measurement because of nonfasting status at presentation.\textsuperscript{14} Finally, the authors have not considered the significant measurement variability of lipids and lipoproteins.\textsuperscript{17} Both the 1992 guidelines and the current blood pressure guidelines rely on multiple measures before risk classification.

There are a number of areas in which the 1992 guidelines are out of date. Neither triglycerides nor HDL cholesterol is adequately discussed; these have assumed increasing importance both because of the obesity epidemic and because of increasing recognition of the relationship of the high-triglyceride/low-HDL phenotype to increased atherogenicity of LDL particles. Lipoprotein biochemistry has received little attention in children.\textsuperscript{18}

The original guideline for considering pharmacological treatment, an LDL cholesterol level $\geq 190$ mg/dL in children $>10$ years of age, was based on clinical judgment and remains highly controversial. Statins were just being introduced in 1992 and thus were not included as treatment options. Well-controlled studies of efficacy, short-term safety, and benefit of the statins have now been conducted in children, and some have achieved pediatric labeling.\textsuperscript{19,20}

However, the age and precise indications for initiation of primary prevention pharmacological therapy with statins remain unknown. Adult Treatment Panel III pharmacological treatment recommendations are based on epidemiological data on proximate risk of a vascular event and results from large intervention trials; no comparable pediatric data exist.\textsuperscript{6} Noninvasive imaging now provides the ability to directly measure atherosclerosis,\textsuperscript{21,22} A PDAV risk score has recently been developed that can assist in identifying adolescents and young adults with a high likelihood of having positive imaging studies.\textsuperscript{10} It seems reasonable to consider treatment in those in whom atherosclerotic vascular changes can be demonstrated. Well-written guidelines may establish the scientific and ethical rationale for clinical trials that use these imaging modalities both to identify at-risk individuals and to demonstrate benefit of behavioral and pharmacological intervention strategies. Studies such as these are needed to limit the use of pharmacological therapies to those most likely to benefit.

Also missing from our overall knowledge is a thorough understanding of biological traits and behaviors that protect from cardiovascular disease. High HDL cholesterol, female gender (for events before 45 years of age), diet, normal body mass index, and physical fitness are known, but many others surely exist.

The core principles of the 1992 National Cholesterol Education Program report on cholesterol in children remain valid and have been confirmed by subsequent research. New research has validated the hypothesis that the origins of atherosclerosis are in childhood. However, many details of the report require revision. The scientific evidence for pharmacological treatment recommendations with regard to lipids and cardiovascular disease prevention in childhood remains incomplete. However, so much useful progress has occurred in understanding the relationship of risk factors to early atherosclerosis that an updating of the 1992 report is critical both for public education and to stimulate a new wave of research.

Disclosures
Dr Gidding has received honoraria from the University of Miami, Brown University, and the Cleveland Clinic.
References

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