EDITORIAL COMMENT

Lipid Screening in Children*

Stephen R. Daniels, MD, PhD

Screening for lipid disorders in childhood and adolescence has been controversial. Although it is well documented that atherosclerotic cardiovascular disease is the number 1 cause of death in the United States and that elevated cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), is a major risk factor for the development of disease (1), many issues regarding screening in children remain in question.

Various entities, such as the National Heart, Lung, and Blood Institute; the National Cholesterol Education Program; the American Academy of Pediatrics; and the National Lipid Association and the American Heart Association, have recommended some form of screening for lipid disorders in children (2). However, the U.S. Preventive Services Task Force has found insufficient evidence for or against cholesterol screening in childhood (3). Clearly, there is a need for more evidence to make the best clinical decisions.

Several approaches to screening for lipid disorders in children have been proposed, including screening on the basis of family history, which is sometimes referred to as cascade screening, universal screening of all children, or no screening at all later in adulthood. Even if one accepts that screening has merit, many questions remain, such as what is the goal of screening, what is the best age for screening, which lipid measure is most useful, and what cut point would be used to indicate abnormality?

In lipid screening for adults, it is generally assumed that all measures in the lipid profile, including triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C, are important. It is also generally assumed that there is a continuous risk function so that for LDL-C, as the value increases, so does the risk of atherosclerosis. Epidemiological data in adults allow risk factors to be combined in a way that estimates the risk of an adverse cardiovascular event in the subsequent 10 years (4). This estimate of risk is then used to make clinical decisions.

Unfortunately, such epidemiological data in children, which could be used to calculate a lifetime risk of the development of cardiovascular disease for individual patients, are lacking. This means that lipid screening in children is fundamentally different from that in the adult population. The primary focus of lipid screening in children should be on how to identify young individuals with genetic causes of dyslipidemia, such as familial hypercholesterolemia (FH). FH results in LDL-C, which is elevated substantially above the 95th percentile for age and is a clearly elevated lifetime risk of cardiovascular disease (5). However, even if one accepts genetic dyslipidemia as the target for screening, a number of questions remain regarding the best approach to accomplishing this in practice.

In lipid screening for children, it is generally assumed that all measures in the lipid profile, including triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C, are important. It is also generally assumed that there is a continuous risk function so that for LDL-C, as the value increases, so does the risk of atherosclerosis. Epidemiological data in adults allow risk factors to be combined in a way that estimates the risk of an adverse cardiovascular event in the subsequent 10 years (4). This estimate of risk is then used to make clinical decisions.

Unfortunately, such epidemiological data in children, which could be used to calculate a lifetime risk of the development of cardiovascular disease for individual patients, are lacking. This means that lipid screening in children is fundamentally different from that in the adult population. The primary focus of lipid screening in children should be on how to identify young individuals with genetic causes of dyslipidemia, such as familial hypercholesterolemia (FH). FH results in LDL-C, which is elevated substantially above the 95th percentile for age and is a clearly elevated lifetime risk of cardiovascular disease (5). However, even if one accepts genetic dyslipidemia as the target for screening, a number of questions remain regarding the best approach to accomplishing this in practice.

In this issue of the Journal, the study by Klänčar et al. (6) provides some useful information. They took advantage of a universal lipid screening process in children that was adopted in Slovenia, which has a population of ~2 million citizens. The country adopted a universal lipid screening program in children 5 years of age in 1995. By 2013, this screening program was reaching 20,000 children at 5 years of age. Evaluation of this experience is important as there are few studies of universal pediatric lipid screening in practice.

For children born between 1989 and 2009, they identified 272 children with either total cholesterol >231.7 mg/dl or total cholesterol >193.1 mg/dl and a positive family history of premature cardiovascular disease. These individuals were then genotyped for variants in the LDL receptor, apolipoprotein (apo) B, apo E, and proprotein convertase subtilisin/kexin type 9 (PCSK9) to evaluate whether they had known
disease-causing mutations. Of 272 individuals identified, 155 (57%) had disease-causing mutations: 38.6% in the LDL receptor and 18.4% in apo B, with none in PCSK9. In the individuals without disease-causing mutations, 51 (18.7%) were carriers of a hypercholesterolemia-associated apo E E4 isoform. No known genetic abnormality was identified in the remaining 66 individuals (24.3%).

These screening results from Slovenia are most consistent, with a prevalence of heterozygous FH of 1 in 500 individuals. Studies from other countries have estimated the prevalence to range from 1 in 200 to 1 in 500 (7). This is a range for prevalence that indicates that heterozygous FH is a relatively common genetic abnormality and the most common monogenic disorder leading to coronary heart disease. This high prevalence and low rate of early clinical detection would support a screening strategy to identify affected individuals.

The question of family history as a potential identifier of high-risk children is important. Klankar et al. reported that a negative family history was found in one-half to three-fourths of patients with a disease-causing or disease-associated genetic variant. This supports the concept that the family history is not a reliable indicator of pediatric patients with FH. This result would also tend to support the universal approach to screening for individuals with FH as opposed to cascade screening.

There were some limitations to the data collected by Klankar et al. (6). For example, the percentage of children not screened for dyslipidemia at 5 years of age, or later if they were missed at age 5, is unknown. It does appear that awareness of this screening approach increased with time as the number of children screened increased over time. Only total cholesterol was measured in the universal screening program. Thus, it is not possible to compare the performance of different lipid measures at the initial screening. Patients referred from the primary care physician to a tertiary clinic did have more complete lipid testing. However, it is also not possible to know how many with an elevated total cholesterol at screening were not referred or refused the visit to a tertiary clinic and would not have had further testing. Finally, family history was collected via questionnaire but was not verified via medical records. Thus, there could have been substantial misclassification of family history, but the extent of that is not known.

Although the work of Klancar et al. (6) is helpful in elucidating some aspects of universal screening, there are many practical aspects of this approach to screening in childhood for FH that remain unclear. Some of the important unanswered issues include the age of 5 years chosen for screening in Slovenia. The optimal age for screening remains unknown. It is of interest that even though screening was done at 5 years of age, the mean age at referral to an appropriate clinic for further evaluation and treatment was 7.3 years. The current recommended age for screening in the United States is between 9 and 11 years of age (2). This was designed to avoid the decrease in LDL-C, which occurs during puberty. However, it is not clear how quickly individuals who are screened in the United States and have a positive result are then seen for further evaluation and treatment.

The experience with lipid screening in Slovenia raises some other important practical questions. It took more than a decade and a half to fully implement the universal screening program. It would be useful to know more about the barriers to full implementation. Although it is helpful to know the prevalence of those with known disease-causing mutations using the screening approach used in Slovenia, questions remain regarding the optimal lipid measure to use in screening (total cholesterol, LDL-C, or non-HDL-C) and what cut point to use. It also is not clear whether lipid values alone or a combination of lipid values and family history would perform best in identifying children with FH. The role of genetic testing in clinical practice also remains unclear.

More evidence is required to determine the optimal approach to screening for children with FH. Experience with screening programs such as the one in Slovenia is useful, but well-designed prospective studies to evaluate the screening process will be even more important to provide the needed answers.

Reprint Requests and Correspondence: Dr. Stephen R. Daniels, Department of Pediatrics, University of Colorado School of Medicine, 13123 East 16th Avenue, B065, Aurora, Colorado 80045. E-mail: Stephen.Daniels@childrenscolorado.org.

References


**KEY WORDS** atherosclerosis, cardiovascular disease, dyslipidemia, familial hypercholesterolemia, lipid screening