NHLBI Integrated Guidelines on Cardiovascular Disease Risk Reduction: Can We Clarify the Controversy about Cholesterol Screening and Treatment in Childhood?

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On November 15, 2011, the National Heart, Lung, and Blood Institute (NHLBI)12 released the report of its Expert Panel on Integrated Guidelines for Cardiovascular Risk Reduction. The evidence was reviewed and graded in the full document (>400 pages), and recommendations were made on a broad range of relevant topics. The most controversial aspect of this report by far seems to be the guidelines for lipid screening and treatment in children and adolescents. This topic had been addressed in previous statements going back 3 decades, most recently by the American Academy of Pediatrics in 2008, the National Lipid Association in 2011, and the US Preventive Services Task Force report and commentaries in 2007. The controversy in both the scientific literature and the lay press seems to center around whether these new guidelines would increase pharmacotherapy of children and suggests that many are concerned about the advisability of medicating children who have acquired risk related to obesity and lifestyle issues. To better understand the issues surrounding this important topic, we have asked several experts in this and related fields to address some questions on the topic. The experts include a pediatric preventive cardiologist and member of the guideline committee, an epidemiologist and also a member of the guideline committee, a primary care pediatrician, an adult lipidologist, and a pediatric advanced-practice nurse.

The recommendation to add universal screening to selective screening is probably the most controversial part of the new NHLBI guidelines on lipids in children. What do you think is the most important potential benefit? What is the most important potential harm?

Stephen R. Daniels: The most important benefit from universal screening is better identification of children with genetic dyslipidemia, such as familial hypercholesterolemia. This condition is common (1/500) and is associated with premature cardiovascular disease. This universal approach will also lead to the identification of adult family members with genetic dyslipidemia who are at a more immediate risk of cardiovascular disease. A secondary benefit is the identification of children with dyslipidemia based on lifestyle. These children will benefit from more intensive diet and physical-activity intervention. There is no evidence that there is any harm related to cholesterol screening.

Matthew Gillman: The most important potential benefit is the identification of children who really need statins, because their LDL cholesterol is extremely high but their family history is unknown. However, the guideline calls for expanded screening (selective vs universal) along...
with relatively low cutpoints for action. So, the most important potential harms relate to performing identification and intervention (mostly lifestyle, some meds) on a huge number of children, with very uncertain benefit and high cost.

**Louis Vernacchio:** In my understanding, the most proven benefit of universal screening will be in identifying the occasional child suffering from familial hypercholesterolemia; for such children evidence is good that early identification and treatment are effective in reducing cardiovascular disease morbidity and that not all these children would be identified by a selective screening approach. It is possible that there will be additional benefit in identifying children with mild to moderate hypercholesterolemia, although the research on any benefit to such children is inconclusive and the recommendations for them (i.e., diet and physical activity) are essentially identical to the recommendations that pediatric primary care providers should be giving to all families.

I see the potential harms of universal screening in 3 areas: (1) The economic costs of universal screening (which, as far as I can tell, were not considered by the NHLBI expert panel) may outweigh the benefits and contribute to already escalating healthcare costs; (2) the identification of biochemical abnormalities, such as mild hypercholesterolemia, that may never progress to clinically significant disease can produce parental anxiety and other forms of subtle harm that are difficult to measure (e.g., “vulnerable child syndrome,” eating disorders); (3) universal lipid screening will compete with other priorities for the limited time that primary care providers have with their patients. Since it is currently nearly impossible for a primary care provider to carefully deliver all the care that is recommended in the context of a well-child visit, the addition of new recommendations necessarily means that less attention will be paid to other recommended areas of care (e.g., immunizations, developmental screening, mental health screening, injury prevention, family violence screening, etc.).

I would add that screening almost always seems like a wonderful idea up front, but as the examples of screening for prostate cancer, breast cancer, and newborn metabolic abnormalities have shown, the benefits of screening are easy to imagine, but the costs and harms are often hidden and become apparent only after long experience.

**Annette L. Baker:** I think the most important potential benefit from adding universal screening will be to increase awareness about the presence of lipid disorders in children and hopefully increase our attention to preventive practices in general. The “old” guidelines did recommend a universal/population-based approach to a heart-healthy lifestyle for all American children, but obviously this approach was not effective, as demonstrated by the increasing obesity epidemic in this country. By screening all children intermittently, one would hope to provide targeted lifestyle counseling to affected children and referral of the most severely affected for further treatment. The benefit of screening all children would be to find those children with abnormal lipid profiles who might not have been screened solely on the basis of family history, since family history is often incomplete or unknown.

The most important harm that I can see is that we need to be careful not to cause “cardiac nondisease” in children who are healthy. Finding out that a child has high cholesterol may increase anxiety in families and label a child as “sick.” Coronary disease is a long way off for most children, and although there is obviously a lot of documentation about the benefits of a heart-healthy lifestyle, there are little long-term data regarding the individual benefit of initiating treatment in any one child. In addition, parents need to understand that we do not have long-term data regarding the benefit of statin use at 8 vs 10 vs 12 years old.

**Jorge Plutzky:** As long as universal screening is coupled with education and appropriate caution, it can be a very powerful way to identify issues early on. Such identification is not coupled to pharmacologic therapy, but it does help define risk early and allow attention to be directed to important lifestyle interventions. In the absence of education and caution, universal screening can lead...
to unnecessary anxiety, unnecessary testing, and overtreatment.

For the first time in the history of pediatric cholesterol guidelines, the concept of residual risk is included in management. The guidelines say, “Children aged ≥10 years with non-HDL cholesterol ≥145 mg/dL after LDL cholesterol goal is achieved may be considered for additional treatment with statins, fibrates, or niacin in conjunction with a lipid specialist consultation.” In your practice, do you intensify pharmacologic treatment in a patient with residual risk, as represented by non-HDL?

Stephen R. Daniels: From my perspective, this concept is still quite speculative and needs further research. The evidence for this received a grade of D, indicating that this derives from opinion. This leads to a recommendation that is optional. Non-HDL cholesterol is a measure of atherogenic particles and may turn out to be an important risk marker, but current evidence does not support a cutpoint that would indicate more intensive therapy in children and adolescents. I use non-HDL cholesterol in my practice only as a screening tool.

Matthew Gillman: In general, I do not intensify treatment based on non-HDL. The long-term benefits, much less risks, of intensifying pharmacologic treatment are not fully understood. Fibrates and niacin are not proven to lower cardiovascular disease risk/mortality in adults, and statins may indeed be diabetogenic.

Annette L. Baker: In our clinical practice, we look at each parameter in the lipid profile separately, but these parameters definitely have an additive effect when determining the overall concern . . . i.e., if a child had an HDL of 16 mg/dl, we would be more aggressive in terms of LDL lowering, if the LDL was high, but we wouldn’t initiate a statin if the triglycerides were high and the LDL was not over the cutpoint for therapy. We make decisions regarding medications on the basis of triglycerides separately from LDL, rather than on “non-HDL cholesterol.” We do take into consideration residual risk in patients who have multiple risk factors.

Jorge Plutzky: In treating adults, we do consider non-HDL targets and the rationale they provide for intensification of statin therapy, as well as, in some scenarios, the addition of other interventions such as niacin and fibrates. The enthusiasm for the addition of fibrates and niacin has been tempered by somewhat disappointing results in cardiovascular outcomes in clinical trials with these agents. But with fibrates, we do see some signal for benefit in subgroups where they are most likely to be used by lipid specialists, namely those with significantly increased triglycerides and lower HDL. With niacin, prior suggestion of benefit has been offset by negative data in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study. But there were potential issues with that study, and other large clinical trials are ongoing. Pushing to intensify therapy is easier to rationalize in individuals in which the risk is higher, such as those who have known cardiovascular disease.

How much pediatric lipid evaluation and management should be done in the primary care setting, as compared to the subspecialist office?

Stephen R. Daniels: More identification and management of lipid disorders should be done in the primary care pediatric setting. Primary care pediatricians and family physicians should be prepared to take on routine lifestyle management and initial pharmacologic management based on the guidelines. Referral to lipid specialists should be reserved for pediatric patients who are more complex and difficult to manage.

Matthew Gillman: As training gets better, more and more could be done in primary care, including screening (when/if warranted) and risk prognostication. For now, I’m guessing most pediatric primary care physicians will be uncomfortable prescribing medications, but that could change over time.

The big uncertainties are about behavior change. If LDL is the main goal, then diet change has limited effect. If triglycerides are the goal, then diet may have a large effect, but its relation with cardiovascular disease is uncertain. Behavior change in the pediatric office is difficult to achieve without resources that many offices don’t have or can’t afford. Put these all together and the role of primary care practices is currently uncertain. This could be an area for research.

Louis Vernacchio: I do not see why nearly all pediatric lipid management could not be handled in the primary care setting, with the exception of extreme cases, such as homozygous familial hypercholesterolemia and children with very high-risk conditions, such as heart or kidney transplants or Kawasaki disease. Since management of lipid disorders will invariably involve long-term lifestyle changes, primary care providers are best situated to work with the family longitudinally and enlist the help of nutritionists, exercise programs, and other community resources as needed. To do so successfully, however, pediatric primary care providers will require adequate professional education in the nuts and bolts of lipid evaluation and management and also will have to embrace the concept of chronic-disease
management (in addition to episodic acute-disease management that has dominated pediatric primary care).

Annette L. Baker: I think that, ideally, the majority of lipid evaluation and management would be done in the primary care setting, reserving subspecialist referrals for those most severely affected. Almost all patients with lipid disorders (except homozygous patients) are initially managed with lifestyle counseling for at least 6 months. It therefore seems this type of counseling would be most cost-effective if done in the primary care setting. I believe that this approach would be the least stress provoking and the most convenient for families, rather than referring to a tertiary setting. Having said this, I understand the challenges and the cost of providing individualized lifestyle modification counseling along with the follow-up that would be needed, and it might be unrealistic to expect primary care practices to provide this level of care when they are stretched as it is for time/resources. I am most concerned about the inability of our current system to support this type of preventive healthcare. There would need to be a lot of support, both in terms of economics and education, to make sure that the people involved in this type of counseling had the resources available, as well as a good understanding about the various types of lipid disorders and the nutritional recommendations, etc. The reality is that even tertiary care centers will not be able to handle the volume of patients referred with borderline values, as one would expect 25% of the population to have values that fall over the 75th percentile and as most states have few designated preventive cardiology programs.

No published clinical guideline is ever left unrevised. What do you think will be next in terms of pediatric screening for atherosclerotic risk?

Stephen R. Daniels: It is important to emphasize that guidelines should be “living” documents. They should be implemented, but they also need to be updated and revised as new evidence becomes available. An important advance for guideline development would come from a better ability to image and track the early development of atherosclerotic plaque in the coronary arteries.

Matthew Gillman: Pediatric screening for atherosclerotic risk will involve more integration with adult guidelines, perhaps a more integrated multiple-risk factor approach within childhood, and (I hope) waiting for better evidence before being aggressive with screen-and-treat approaches.

Louis Vernacchio: I think controversy about universal screening will remain until there is further clinical evidence as to whether early identification and treatment of mild to moderate hypercholesterolemia in childhood modify lifelong cardiovascular disease morbidity. Unfortunately, such evidence will be daunting to obtain, given the long latency period from detection of biochemical abnormalities to disease. I am hopeful that research into the prevention (as opposed to treatment) of obesity and metabolic syndrome in children will continue to progress, as I believe a preventive approach has a greater chance of achieving a cost-effective reduction in lifelong cardiovascular disease.

Annette L. Baker: We need clinical evidence regarding the benefits of early intervention, but unfortunately these types of longitudinal studies are unlikely to happen, in view of the length of time needed from intervention to clinical event. I would also like to see longer-term data on the use of statin therapy in young children (age 8 and above), as most studies have been quite short-term. I think the focus of future guidelines will continue to be geared to decreasing overall cardiovascular risk—primarily obesity, hypertension, insulin resistance, etc., in addition to lipid disorders—as these are much more common problems than the small number of children with familial hyperlipidemia that we will pick up with expanded screening.

Jorge Plutzky: In preventive cardiology among adults, we are wrestling with multiple issues and waiting to see how they will be addressed in the next iteration of guidelines expected relatively soon. One issue is whether or not C-reactive protein will be included as a tool for risk stratification. Another question is whether we should move to non-HDL as a primary target for treating lipid issues. Given the increasing incidence of obesity and type 2 diabetes in pediatric populations, what is the relevance of hemoglobin A1c determination to identify prediabetes, and what changes in therapy should be instituted once prediabetes has been found?

What types of data are necessary to move forward our understanding of the role of pediatric lipid abnormalities and pharmacotherapy for the same? If you were in charge of the NHLBI’s budget on this topic, what types of projects would you look to fund?

Stephen R. Daniels: We need more data on the long-term safety and efficacy of statins. We need more studies of the screening process itself, and we need to learn more about implementing the guidelines in practice. We especially need research on the optimum methods to improve lifestyle in clinical practice. We need more data on the cost of screening and treatment in relation to benefits of disease prevention. We also need more research on improved approaches to imaging the atherosclerotic process noninvasively.
Matthew Gillman: I would like to see: (1) more comprehensive approaches to assessing long-term benefit/risk/cost (e.g., by decision analysis); (2) the inclusion of multiple risk factors in such assessments; (3) shorter-term randomized controlled trials of screening itself; (4) more on the benefits and risks of medications; (5) for items 1–4 above, examining of higher cutpoints for action (i.e., identifying a small very high-risk group) and examining of the extent to which positive family history raises predictive values; and (6) information on the feasibility of implementing these guidelines and the acceptance of the guidelines by parents and providers.

Louis Vernacchio: I would love to see a long-term randomized controlled trial of universal lipid screening vs targeted lipid screening in children with a primary clinical outcome of cardiovascular disease morbidity, but I imagine such a study is nearly impossible to do. Perhaps a trial of the 2 approaches that uses intermediate biochemical outcomes, such as plaque development, would be more realistic. It would also be helpful to quantify the benefits and risks of statin therapy in children with moderate hypercholesterolemia who fail lifestyle interventions, especially because I fear that the long-term risks of statin therapy on children are poorly known.

Furthermore, I would like to see more research into the effectiveness of preventive approaches to childhood obesity and lipid disorders, starting in infancy and young childhood. Such approaches may be more cost-effective in the long run than treating children with pharmacologic therapy after they develop obesity and lipid disorders.

Annette L. Baker: I would put the majority of funding into education related to diet and exercise for clinicians/schools. I would also fund schools so that they would have a mandatory daily-exercise requirement year round, along with heart-healthy lunches in the school systems. Some funding would also need to be allotted to provide targeted program-based counseling for patients with known risk factors and education of medical providers who are interpreting results and hopefully providing first-line counseling.

Do you have any additional comments?

Stephen R. Daniels: The guidelines are the result of an extensive and systematic review of the evidence based on rules that were developed prospectively. Those who are critical of the guidelines must come to the discussion with data. For example, some have discussed the potential harm related to screening but are unable to show any evidence of harm. Others are concerned about cost but have no data to indicate that costs outweigh benefits.

Matthew Gillman: The ethical standard for screening is higher than for diagnosis, because we are offering a test (and all follow-up management) to asymptomatic individuals. Until evidence is more certain, it’s often best not to screen.

Louis Vernacchio: In areas of controversy among experts, such as we have with universal lipid screening, I believe there is an opportunity for shared decision-making by the physician and patient/family. I find most families capable of engaging in a brief thoughtful discussion when a summary of the evidence is presented and the discussion is framed in the context of the patient’s or family’s tolerance for risk and approach to healthcare. Some families are strongly proactive and prefer a more interventionist approach, while others fear the potential downsides of unnecessary testing. When the experts disagree, we should honor the informed patient and family’s decisions.