PREVENTION

Cholesterol Screening and Management in Children and Young Adults Should Start Early — NO!

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ABSTRACT

In 2011, an expert panel from the National Heart, Lung, and Blood Institute released recommendations for universal lipid screening and treatment of high cholesterol in children. There is no evidence that universal screening will help children lead longer, healthier lives. These recommendations will, however, fuel the epidemic of overtreatment that is currently threatening our healthcare system and our patients.

The Epidemic

Universal lipid screening and management in children and young adults will be of no clear benefit, and threatens to fuel a concerning but under-recognized epidemic threatening our health system right now: overtreatment. At a time when healthcare is central to discussions about the perilous state of our economy, this epidemic of overuse is costing the United States an estimated $200 billion per year,[1] and often leads to gross violation of the most fundamental tenet of healthcare: *primum non nocere*.

Substantial harm has resulted from public health errors involving overdiagnosis and overtreatment, such as prostate cancer screening in men and hormone replacement therapy for postmenopausal women. Countless healthy men have undergone unnecessary treatment for prostate cancer,[2] and healthy women have suffered from heart disease, stroke, and breast cancer[3] directly as a result of our well-intentioned but misguided medical interventions. These examples represent mistakes made from the misinterpretation of numerous studies that were fraught with bias.

The Victims

Yet, here we are again, ready to embrace a potentially harmful and costly screening test for which there is essentially no direct evidence and that involves an even more vulnerable population: children. In 2011, an expert panel from the National Heart, Lung, and Blood Institute (NHLBI) recommended universal lipid screening for children at 2 intervals, first between 9 and 11 years of age and again between 17 and 21 years of age.[4] Targeted screening is also recommended between 2 and 8 years of age and 12 and 16 years of age. Should these recommendations be enacted, an estimated 200,000 children would qualify for drug treatment.[5] Females will be disproportionately affected. Females have higher lipid levels but lower ultimate cardiovascular disease risk than males, although the NHLBI guidelines failed to account for these sex differences.[6,7]

Screening programs should lead to longer or higher-quality lives and be cost-effective. Unfortunately, there is no evidence that universal cholesterol screening and management in children meets any of these goals.

The Evidence

There is strong evidence that high low-density lipoprotein (LDL) cholesterol levels are associated with an increased risk of atherosclerosis in adults. There is also reasonable evidence that lifestyle modification can reduce the risk of cardiovascular disease and prolong life. Some medications are successful in lowering LDL cholesterol. However, targeted modification of cholesterol levels has not always equated to better outcomes; with some drugs (clofibrate, torcetrapib), mortality risks increased despite lower

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cholesterol levels.[5] Furthermore, a recent investigation into the National Health and Nutrition Examination Survey sample demonstrated that although obesity rates continue to increase at alarming rates, adolescent lipid levels have actually decreased over the last 2 decades.[8] It is possible that public health efforts to reduce fat and cholesterol intake have been successful in reducing lipid levels but have also had the unintended effect of increasing consumption of poor quality carbohydrates.[9] Clearly, using lipid levels as a surrogate measure for overall health can be misleading. Cholesterol level is just 1 of many determinants of overall cardiac risk. Many people with heart disease have average cholesterol levels, and many people with high cholesterol will live a long life without heart disease. Healthy lifestyles can and should be promoted; a laboratory test is not necessary to do so and will prove counter-productive in many cases.

Statins are the cornerstone of lipid-lowering drug therapy. Statins, which were prescribed to 36 million adults at a cost of $17.1 billion in the United States in 2009,[10] have been demonstrated to reduce cholesterol and mortality in adults who have coronary disease. However, the vast majority of children who would potentially be treated with statins will be otherwise healthy. The efficacy of statins in reducing all-cause mortality when used for primary prevention of heart disease in adults with high cholesterol is not established.[11] There have been several recent meta-analyses on this issue. The first demonstrated no impact on all-cause mortality.[12] The second reported a small reduction in mortality, but the authors also acknowledged that there was selective reporting of outcomes, failure to report adverse events, and inclusion of patients with cardiovascular disease, and warned that "caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk."[13] In the third and most recent meta-analysis,[14] which also showed a significant reduction in mortality, the outcomes analyzed hinged on whether a chosen amount of LDL lowering (1 mmol/L or ~39 mg/dL) occurred, not on actual statin use, which makes the results less generalizable to a population of patients receiving statins. Furthermore, this meta-analysis demonstrates that adults without vascular disease who have a low 5-year risk of a major vascular event (ie, the patients who are most similar to children) do not have lower mortality rates with statin use.[14] If the benefits of statins for otherwise healthy adults with high cholesterol are uncertain, how can we justify using them on healthy children?

The Harm

Quantifying all of the potential harm and costs of universal cholesterol screening will be difficult, but doing so is important. All children would be subjected to at least 1 blood test. Needle sticks are a source of substantial anxiety in children.[15] In 1 study, nearly half of parents who did not bring their child in for follow-up of a high cholesterol level cited "child too traumatized by finger stick" as a reason for not returning.[16] For children who will need fasting lipid panels in the morning, there will be additional logistical challenges and stress on families. Although most children will have normal cholesterol levels, even a normal cholesterol result may have unintended negative consequences in some families by introducing a justification for unhealthy behaviors ("I can eat this; I have a normal cholesterol!"). Finally, adding the discussion of a cholesterol screen during a well child check puts an additional burden on pediatricians, and may come at the expense of other important evidence-based anticipatory guidance. Surprisingly, despite the recommendation by the NHLBI for universal screening, the costs of such a program (and the downstream interventions and opportunity costs) have not been analyzed.[4,7]

Harm will be greater for those children who are overdiagnosed and overtreated. If as many as 200000 children will qualify for statin use,[5] an understanding of their known and potential side effects is paramount, especially because these children are expected to receive life-long treatment.[17] Unfortunately, most trials of statins have limited long-term follow-up; the majority of trials have a mean follow-up duration of 3 to 4 years,[12] representing a very small fraction of the life expectancy of a child. The physical and psychological effects of statins in children are unknown, particularly for long-term use.

Major side effects reported in adults include myopathy and rhabdomyolysis, liver enzyme elevation, cognitive impairment, and diabetes,[11] the latter 2 having prompted a recent US Food and Drug Administration warning and modification of the labeling for statins.[18] A recent large, observational study from the Women's Health Initiative demonstrated a 48% adjusted increase in diabetes risk in women on statins.[19] Similarly, observational studies in adults have revealed higher rates of muscular symptoms associated with statins (as evidenced by comparison to control patients not on statins or by temporal association with initiation of statin therapy) than rates described in randomized trials.[20–22] This discrepancy may be explained by the exclusion in randomized trials of subjects with a history of muscle problems or elevated muscle enzymes, stricter definitions requiring more severe forms of myopathy, or insufficient follow-up periods in randomized trials.[11,20–22] All of these issues could affect results of pediatrics trials as well.

The NHLBI expert panel cites 10 randomized controlled trials to support the safety and efficacy of statins in children.[4] All of these studies are in children with familial hypercholesterolemia. Nine out of 10 of these trials described a funding source, and all 9 were funded by pharmaceutical companies.[23–31] Pharmaceutical sponsorship is also widespread in adult statin trials,[11,13] and may lead to biased reporting and biased interpretation of results.[32] Although preliminary data from trials on the safety of these medications is reassuring, long-term studies are needed. Even if statins were to prove to be safe and effective after clinical trials are done, the message that children will be receiving is nonetheless concerning and possibly damaging: "if you cannot eat right and exercise, just take this pill."

Another concern is the potential consequence of labeling. The emotional impact that a diagnosis of having a "disease" of high cholesterol will have, especially on adolescent and pre-adolescent girls (who will be diagnosed more commonly than their male counterparts), is not well studied but likely detrimental. Given concerns about the increasing prevalence of eating disorders and fear of

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fat among children, especially those of younger age, this concern should be fully explored before adopting universal screening.[33–35]

The Justification

The need to detect inherited dyslipidemias such as familial hypercholesterolemia (FH) has been cited by the authors of the NHLBI guidelines as the primary justification for the recommendation to screen lipid levels in all children.[36] This justification is predicated on data from the 2007 US Preventive Services Task Force (USPSTF) summary[37] describing poor sensitivity of family history to detect FH, leading the panel to conclude that universal screening is therefore necessary to capture all of these patients. However, all of the studies referenced examined the sensitivity of family history for the detection of cholesterol levels above a certain threshold, not for the detection of FH. The cholesterol thresholds used in these studies to define high cholesterol are quite variable and surprisingly low: 4 used LDL values of 135 mg/dL or less,[37] whereas FH is defined in the majority of pediatric drug trials as an LDL value of 160 mg/dL or higher. Even this threshold (160 mg/dL) is far below the actual mean baseline LDL values of subjects included in published trials, most of which are well over 200 mg/dL.[23–31] Does it make sense to debunk the value of family history because it fails to detect children with high cholesterol levels, the majority of which will fall way below levels that have been studied in actual drug trials? For serious cases of FH that have led to significant morbidity or mortality of immediate family members (where treatment of affected offspring, if truly effective, is most likely to be of benefit), family history would be revealing in most if not all cases. Before dismissing the value of family history, more information is needed about its sensitivity to detect cholesterol levels at thresholds where the impact of a false negative is truly consequential.

Furthermore, even though universal screening is intended to capture patients with FH, the majority of patients treated as a result of universal screening will not have FH, and the risks will outweigh any possible benefits. According to a recent study, with universal screening, 1.3% of fifth graders would meet criteria for treatment with statins,[38] which is over 6 times the reported incidence of FH (1 in 500 or 0.2%), indicating that ~85% of treated children will not carry that diagnosis.

The Answer

In summary, we agree with the prior conclusions of the USPSTF,[37] as well as multiple recent opinions[5,7,39] that universal screening of children for hypercholesterolemia is unjustified. The benefits on mortality of starting screening and treatment even in adulthood[40] are marginal at best and nonexistent at younger ages. The fact remains that no studies have evaluated the effect of screening children and adolescents on adult lipid levels or disease outcomes,[37] and long-term safety data on treatment of hypercholesterolemia in children is still lacking. As stated in the panel report, "a recommendation for universal screening requires a high burden of proof."[4] If a test or treatment has no clear benefit, then no amount of harm is acceptable. We hope that future recommendations on cholesterol screening stay true to this tenet, and that they come from expert panels that have more representation from members who are free of any potential financial conflicts of interest.[4,7]

At a time when virtually the entire elderly population is diagnosed with at least 1 chronic disease,[41] we need to protect our children from this onslaught of medicalization and concentrate instead on teaching and modeling healthy lifestyle. Rather than continuing on an unbridled quest to test and treat, let us focus on how and where we can safely do less.[42]

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