CLINICAL DECISIONS
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Statin Therapy for Children

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Boy with Elevated Lipid Levels, BMI, and Blood Pressure

Harleen K. Marwah, M.D.

You are a primary care pediatrician reviewing your patients' charts for the next day's clinic. In accordance with the American Academy of Pediatrics (AAP) recommendations, your clinic conducts universal cholesterol screening for children 9 to 11 years of age.[1] On the schedule for tomorrow is an appointment with a 10-year-old boy who is receiving no medications. He has a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) above the 97th percentile. You note that on a recent fasting screening test, the patient had an elevated total cholesterol level (>200 mg per deciliter [5.2 mmol per liter]; normal value, <170 mg per deciliter [4.4 mmol per liter]), an elevated low-density lipoprotein (LDL) cholesterol level (150 mg per deciliter [3.9 mmol per liter]; normal value, <110 mg per deciliter [2.8 mmol per liter]), an elevated triglyceride level (130 mg per deciliter [1.5 mmol per liter]; normal value, <90 mg per deciliter [1.0 mmol per liter] for children 10 to 19 years of age), and a high-density lipoprotein (HDL) cholesterol level within the normal range. He also had an elevated blood pressure (117/70 mm Hg) at his last clinic visit 1 year ago. The boy's 45-year-old father recently began taking a statin for hypercholesterolemia. There is no other known family history of cardiovascular disease or hyperlipidemias. You are also the physician for the patient's siblings. In the past, the parents have been hesitant about starting medications, citing concerns about adherence and adverse effects.

Given the boy's elevated weight, lipid levels, and blood pressure and the family history, you must decide whether to recommend statin therapy for this patient at this time.

TREATMENT OPTIONS

Which one of the following approaches would you take if this were your patient? Base your choice on the literature, your own experience, published guidelines, and other information.

1. **Recommend statin therapy.**
2. **Do not recommend statin therapy.**

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

OPTION 1

Recommend Statin Therapy

Ilse K. Luirink, M.D.[1]

The primary driver of atherosclerosis is the accumulation of LDL cholesterol and other apolipoprotein B–containing lipoproteins in the arterial wall. Although clinical events such as myocardial infarction and ischemic stroke typically manifest in adulthood, the disease process begins in childhood and is exacerbated by exposure to multiple cardiovascular risk factors, including obesity.[2] Timely identification and effective management of these risk factors are essential for mitigating the progression of atherosclerosis.

Assuming that the results remain consistent with those from a year ago, the 10-year-old boy in the vignette presents with at least three known cardiovascular risk factors: severe obesity (BMI >97th percentile), dyslipidemia (LDL cholesterol

level of 150 mg per deciliter), and hypertension (systolic blood pressure ≥95th percentile for his age and presumed height). Potential additional risk factors may include high lipoprotein(a) levels and insulin resistance due to his obesity. Furthermore, his father's use of a statin at 45 years of age suggests a possible genetic predisposition to hypercholesterolemia. Nevertheless, even without these potential additional risk factors, there is enough in this history to be concerned.

I assume that after the visit a year ago, a discussion took place with the boy and his parents regarding the necessary changes in diet and lifestyle. However, although lifestyle and dietary changes are essential in managing obesity in children, their effectiveness in addressing severe obesity is often limited to modest weight loss with poor long-term sustainability.[3]

I would initiate statin therapy in accordance with the latest AAP guideline on obesity,[4] which recommends considering statins for children 10 years of age or older with LDL cholesterol levels higher than 130 mg per deciliter (3.4 mmol per liter) and additional risk factors such as hypertension. I believe that the term "consider" is too cautious; statin therapy should be initiated if conservative measures fail. Several studies have shown that dyslipidemia in combination with other cardiovascular risk factors exponentially increases the risk of accelerated atherosclerosis.[2,5] That observation, combined with the mounting evidence on both absolute and cumulative effects of LDL cholesterol in the development of atherosclerosis, provides a strong rationale for starting statin therapy in this child.[6]

The patient's parents have expressed concerns about initiating medication, particularly regarding adherence and potential side effects. Although these are valid concerns, especially in the context of preventive pediatric care, extensive evidence shows that statins lead to few adverse events and few unacceptable side effects.[7] In my experience, educating both the parents and the child about the importance of treatment, along with regular monitoring for potential side effects, can substantially improve adherence and ensure the effectiveness of therapy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Do Not Recommend Statin Therapy

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Atherosclerotic cardiovascular disease remains the most common cause of death in the Western world. After age, abnormal lipid metabolism is the most important risk factor for acceleration of this disease, which progresses insidiously for several decades before symptomatic cardiovascular ischemia manifests. In the United States, the incidence of cardiovascular diseases is rising fastest among middle-aged persons.[8] Therefore, the roots of cardiovascular disease and the responsibility to identify and manage risk fall within childhood and adolescence.

This 10-year-old boy, who was screened in accordance with 2011 National Heart, Lung, and Blood Institute and AAP guidelines, presents with combined hyperlipidemia — moderate elevation of both triglyceride and LDL cholesterol levels — in the context of an elevated BMI (>97th percentile). This prevalent cardiometabolic risk phenotype is typically associated with insulin resistance and excess central adiposity. We are told that the boy's HDL cholesterol level is within the normal range; however, with elevated triglyceride levels and BMI percentile, it is probably in the low-normal range. This would increase the ratio of triglycerides to HDL cholesterol, and the increased ratio predicts an even greater total LDL particle concentration than would already be expected at an LDL cholesterol level of 150 mg per deciliter, owing to a disproportionately increased burden of atherogenic small LDL particles[9] and remnant lipoprotein cholesterol.[10]

A low HDL cholesterol level is part of the constellation of risk factors that are included in the decision of whether adjunct lipid-lowering therapy is indicated for a patient with an LDL cholesterol level of higher than 130 but less than 160 mg per deciliter. By current guidelines, at least one major risk factor and two minor risk factors, or two major risk factors, predict sufficient acceleration of atherosclerotic cardiovascular disease to warrant medication. This patient has one major risk factor: a BMI greater than the 97th percentile. There is hyperlipidemia in the family but no history of premature atherosclerotic cardiovas-

cular disease to constitute another major risk factor. We are told that the blood pressure of 117/70 mm Hg 1 year ago met hypertension thresholds, and if still present, this level of systolic hypertension would add a minor risk factor. Ultimately, this patient has one major and possibly one minor risk factor, so lifestyle intervention is the recommended treatment. The guidelines are explicit that adjunct lipid-lowering medication should be initiated only if treatment thresholds are still met after a trial of therapeutic lifestyle change.

Since 98% of U.S. youth do not meet nutritional guidelines and 75% do not meet activity guidelines,[11] there is almost always room for improvement. Combined hyperlipidemia is responsive to insulin-sensitizing nutrition, particularly upgrades in dietary carbohydrate quality (fewer simple sugars, more plants, and more fiber) and fat quality (more monounsaturated and n–3 polyunsaturated fats). This Mediterranean dietary pattern is associated with better perceived health and a higher reported level of physical activity, which together generate a positive and insulin-sensitizing feedback loop that attenuates cardiometabolic risk.[12] With time, improved insulin sensitivity might normalize or at least improve triglyceride and HDL cholesterol levels, reduce central adiposity and possibly the BMI percentile, and lower the burden of small LDL and remnant lipoprotein particle cholesterol. Larger LDL particles may transiently raise the LDL cholesterol level, but evidence suggests that with persistent lifestyle efforts that keep the ratio of triglycerides to HDL cholesterol low, the larger LDL particles are more effectively cleared by LDL receptors.

In summary, the physician should recommend a 6-month trial of lifestyle changes for this 10-year-old patient with dyslipidemia, after which he can be reassessed. Lifestyle change is powerful medicine. Even if adjunct statin therapy is indicated later, insulin-sensitizing lifestyle changes may already have increased the average LDL particle size, and additional lowering of the LDL cholesterol level may be achieved at a lower statin dose.

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