CLINICAL DECISIONS
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The Guidelines Battle on Starting Statins

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

Stephen, a 52-year-old white jogger with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 25, wants you to assess his cardiovascular risks. He had scheduled his visit after taking his father to another physician to discuss his father's blindness, which is related to type 2 diabetes. Both his parents have hypertension that is controlled with medication; neither smokes.

Stephen is here to discuss the results of blood

Understanding the Cardiovascular Disease Risk Functions — Aim, Development, and Evaluation

Ralph B. D'Agostino, Sr., Ph.D.

The ACC and the AHA have formulated new guidelines regarding cholesterol levels and the risk of atherosclerotic cardiovascular disease. For primary prevention (i.e., as preventive therapy for persons who are free from cardiovascular disease), statin therapy is recommended for persons with LDL cholesterol levels higher than 190 mg per deciliter (4.90 mmol per liter) and for patients with diabetes whose LDL cholesterol level is 70 mg per deciliter (1.8 mmol per liter) or higher. For others, they recommend statins if the 10-year risk of cardiovascular disease is 7.5% or higher and the LDL cholesterol level is 70 mg per deciliter or higher.[1] The 10-year estimate of the risk of cardiovascular disease is derived from newly generated risk functions for primary cardiovascular disease developed by the Risk Assessment Work Group (RAWG),[2] of which I am a member.

The RAWG used real populations to estimate risk and selected those populations on the basis of the following specific features of the studies in which they were participants: the studies were epidemiologic studies that had high-quality, complete data; the studies had data that reflected the true natural history of cardiovascular risk (i.e., the participants had risk factors for cardiovascular disease and were not receiving intensive treatment to reduce such risk); and the studies reflected the risk profile of the general population, not of select groups such as clinical trial cohorts or selective participation groups.

Previous cholesterol guidelines (e.g., those from ATP III) used data from the Framingham Heart Study to create risk functions that assess the absolute risk of a first event of coronary death or myocardial infarction.[3] To ensure broad representativeness, the RAWG included in its data analysis the major cardiovascular studies of the National Heart, Lung, and Blood Institute: the Framingham Heart Study, the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), and the Coronary Artery Risk Development in Young Adults (CARDIA) study (collectively termed the FACC studies). These studies track epidemiologic cohorts that are representative of major U.S. populations (including both blacks and whites and both men and women), with excellent follow-up. The end point for the new risk functions was extended to include not only coronary disease but also death from coronary causes, nonfatal myocardial infarction, and stroke. The FACC studies also have good ascertainment and adjudication of risk factors and components of the end point.

The RAWG developed cardiovascular disease risk functions for the four groups (black men and women and white men and women) to estimate the 10-year risk of cardiovascular disease solely on the basis of risk factors measured at baseline; that is, they were designed to predict risk on the basis of baseline risk factors not modified by treatment and intervention made in response to these risk factors.

To achieve this aim, the RAWG deliberately chose to minimize the use of baseline data from the late 1990s, when intensive treatment came into

tests that had been performed before the day of the visit. "I'm an accountant, Doc, and I live by the numbers. I don't want to be my father in 20 years," he says. He tells you that he has recently increased his running regimen to 3 miles a day and that he smokes a half-pack a day during tax season, when he is under stress.

"So what do the numbers say, and what's this calculator thing?" he asks. His total cholesterol level is 180 mg per deciliter (4.65 mmol per liter), the high-density lipoprotein (HDL) cholesterol level is 35 mg per deciliter (0.90 mmol per liter), the triglyceride level is 150 mg per deciliter (1.70 mmol per liter), and the calculated low-density lipoprotein (LDL) cholesterol level is 115 mg per deciliter (3.00 mmol per liter). His blood pressure is 130/85 mm Hg.

You think this is a great opportunity for shared decision making and explain that although his LDL cholesterol level is not high, he has three risk factors for heart disease and stroke (he has a low HDL cholesterol level, smokes, and is a man). You explain that the new risk calculator, developed by the American College of Cardiology (ACC) and the American Heart Association (AHA), estimates his 10-year risk of an event such as a heart attack or stroke at 10.9%, and the new guidelines recommend statin treatment for that level of risk. The new guidelines assess the risks of death from atherosclerotic heart disease, nonfatal heart attack, and stroke and do not call for laboratory testing of LDL cholesterol once treatment with a statin is started.

common use, and thereafter. Functions developed with the use of data collected after statins and daily aspirin became standard therapies would be contaminated by these treatments and interventions. Such modeling would describe history as shaped by the risk factors and subsequent treatment rather than assessing the risk solely or mainly on the basis of baseline risk factors.

Even with the above considerations, it is important to investigate the application of the new functions to contemporary data, which reflect the use of intensive treatments. Such studies are under way. The RAWG report[2] includes three evaluations made with the use of recent data. They show that the new functions do overestimate risk, as was expected. Ongoing analyses of these data sets show widespread introduction of cholesterol and blood-pressure treatments in addition to increases in aspirin use and smoking cessation after the baseline measurements.

Some have complained that the RAWG did not use more contemporary data sets for developing the new risk functions.[4] In addition to the confounding treatment issues mentioned above, these data sets are not representative of broad U.S. populations, since the data are from clinical trials or from studies in which there is a substantial "healthy volunteer" effect; furthermore, some of the studies lack precise baseline measurements. It is unlikely, for example, that physicians participating in these studies who had a total cholesterol level of 260 mg per deciliter (6.70 mmol per liter) would not immediately have begun taking a statin, and thus they would have contaminated the 10-year outcome with this treatment. Furthermore, the selection of the cutoff point for risk of 7.5% actually reflects a recalibration (since recent clinical trial data indicate a possible benefit with even a 5% risk)[1] to take into account the possibility that the risk functions may still have a bias toward overestimation related to treatment and secular trends.

The cholesterol guidelines were written with all of the above in mind. It was essential to consider data that were representative of U.S. populations and that were not contaminated by the many treatments and interventions available today. The RAWG attempted to develop risk functions that were based mainly on the effects of risk factors, and the cholesterol guideline group made treatment recommendations on the basis of those risk functions.

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Choose an option and comment on your choice at NEJM.org

You also explain that the new guidelines have shifted the approach to using statins and that they have generated controversy. You tell him that, in fact, statin treatment would not be recommended under the old guidelines, which assess the risk of coronary heart disease, even though the predicted risk would be higher. You have been using the Adult Treatment Panel (ATP) III calculator in your practice, and Stephen's 10-year calculated risk according to that guideline is 13%. At that level of risk, with an LDL cholesterol level below 130 mg per deciliter (3.40 mmol per liter), statin therapy would not be advised.

You tell him that you want more time to consider the new guidelines, and the two of you agree to meet again in 2 weeks. Stephen, with his hand on the doorknob, says, "Doc, I really want to know what you would do."

After he leaves, your nurse tells you that your practice has 500 patients who may need similar reassessments if you decide to use the new calculator.

TREATMENT OPTIONS

Which one of the following three approaches would you recommend for Stephen?

1. **Do not begin statin therapy.**
2. **Begin statin therapy, and monitor LDL cholesterol.**
3. **Begin statin therapy, but do not monitor LDL cholesterol.**

To aid in your decision, three experts in the field defend these approaches in the essays below. In addition, another expert provides background information on the new guidelines regarding cholesterol levels and the risk of atherosclerotic cardiovascular disease. On the basis of your reading of the published literature, your clinical experience, your understanding of recent guidelines, your knowledge of the patient's history, and your assessment of the experts' opinions, which option would you choose? Make your choice and offer your comments at NEJM.org.

OPTION 1

Do Not Begin Statin Therapy

Benjamin J. Ansell, M.D.

Stephen is a motivated, middle-aged smoker who has a low HDL cholesterol level despite running 3 miles daily. Whether a statin would reduce his risk of cardiovascular disease is unknown, and he stands to achieve much better overall health by implementing targeted lifestyle modification, especially smoking cessation.

In the Framingham Heart Study, quitting smoking cut the risk of cardiovascular disease in half in a short time, irrespective of the extent of prior use of tobacco.[1] Consistent with this observation, the new ACC–AHA risk calculator estimates Stephen's 10-year risk of cardiovascular disease to be 10.9% if he continues to smoke, but only 5.4% if he quits smoking, with the latter risk estimate well below the recommended threshold (7.5% risk) for initiating statin therapy. His risk estimate is even lower — 5.1% — if the 5% expected increase in HDL cholesterol level associated with smoking cessation is factored in. "Kicking the habit" would also benefit Stephen by decreasing his risk of respiratory ailments, cancers, and disability. More than two thirds of smokers want to quit, and about half have had some success in doing so within the past year — results that can be substantially improved with even brief counseling by health providers, pharmacologic and other aids, and behavioral therapy.[2]

Stephen specifically wants to avoid blindness due to diabetic retinopathy, a condition that neither statins nor smoking cessation appears to prevent. In fact, one study has shown an increased incidence of diabetes among patients receiving statins, as compared with those receiving placebo.[3] The long-term implications of this risk are not yet known. The most evidence-based strategy to prevent type 2 diabetes is a multifaceted approach of ingesting less sugar, saturated fat, and alcohol while increasing the amounts of monounsaturated fats, fiber, and vegetables; engaging in regular physical activity; losing weight; and maintaining ongoing medical oversight.[4]

The primary coronary prevention trial that assessed statin treatment in persons with low HDL

cholesterol levels was the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).[5] Although lovastatin at a dose of 20 to 40 mg daily administered to persons with low HDL cholesterol levels (mean, 36 mg per deciliter [0.93 mmol per liter] in men) was associated with a 25% reduction in the risk of cardiovascular events, Stephen would not have been eligible for the study. Not only is his baseline LDL cholesterol level (115 mg per deciliter) below the entry criterion (LDL cholesterol level between 130 and 190 mg per deciliter), it already matches the mean on-treatment LDL cholesterol level in the study participants.[5] In addition, lovastatin treatment did not decrease the risk of cardiovascular disease in the cohort of participants whose LDL cholesterol levels were below the median (149 mg per deciliter [3.85 mmol per liter]; Stephen's level was 115 mg per deciliter) and whose C-reactive protein levels were below the median (P not significant; number needed to treat, infinite; Stephen's level was not reported).[6] Prescribing statins to middle-aged adults with Stephen's lipid profile would be, at best, inefficient in reducing the risk of cardiovascular disease. Other tools such as measurement of C-reactive protein levels, LDL particle analysis, and coronary-calcium screening might allow for greater risk discrimination and more targeted patient selection, but these strategies remain unproven.

Assisting Stephen with smoking cessation and adoption of other health-promoting lifestyle practices is the most evidence-based strategy to reduce his risk of cardiovascular disease, cancer, and respiratory diseases, in addition to his primary concern, diabetes. Moreover, the effects of these lifestyle measures are likely to be long-lasting. In contrast, statin treatment has not been adequately evaluated in persons with Stephen's medical profile and if initiated, would have more limited, if any, benefits. In the end, for a patient who "lives by the numbers," guiding an informed decision about therapeutic options is the most appealing approach of all.

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OPTION 2

Begin Statin Therapy, and Monitor LDL Cholesterol

Samia Mora, M.D., M.H.S.

Stephen has three risk factors for atherosclerotic cardiovascular disease and is at risk for diabetes because he meets the lipid and blood-pressure criteria for the metabolic syndrome and has a family history of diabetes. The metabolic syndrome doubles his 5-to-10-year risk of atherosclerotic cardiovascular disease and increases his risk of diabetes by a factor of 5.[7] He has atherogenic dyslipidemia (HDL cholesterol level, <40 mg per deciliter [1.0 mmol per liter]; and triglyceride level, ≥150 mg per deciliter), which is consistent with his elevated ratio of total cholesterol to HDL cholesterol (5.1; preferred ratio, <4.0) and which is nearly always associated with increased apolipoprotein B and small LDL particles, despite a nonelevated LDL cholesterol level. Hence, the LDL cholesterol level underestimates Stephen's risk of atherosclerotic cardiovascular disease. Changes in lifestyle, particularly smoking cessation, could reduce this risk by approximately 50% (from 10.9% to 5.4%) and improve his lipid profile and his control of the metabolic syndrome.[8] Exercise, weight loss, and a heart-healthy diet provide additional benefits.

If Stephen's risk remains elevated after he adopts lifestyle changes (i.e., if he has a 10-year risk ≥7.5% and LDL cholesterol level, 70 to 189 mg per deciliter [4.89 mmol per liter]), the 2013 ACC–AHA guidelines recommend moderate-to-high-intensity statin therapy.[8] Given that he smokes and that he has the metabolic syndrome — and both smoking and the metabolic syndrome are proinflammatory — his high-sensitivity C-reactive protein level is likely to be at least 2 mg per liter, and he would therefore have met the entry criteria for the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, which showed a 44% relative reduction in the risk of atherosclerotic cardiovascular disease with high-intensity statin therapy.[3] Nonetheless, the risks and benefits of statins should be discussed with him, as should the 2012 Food and

Drug Administration safety labeling changes for the class of statins.[9] The estimated incidences of statin-related diabetes associated with low-to-moderate-intensity and high-intensity statin therapy are 1 case and 3 cases per 1000 persons per year, respectively.[8] Stephen's risk is higher, however, because he has the metabolic syndrome.[3] Although statin-related diabetes has not been shown to increase the risk of atherosclerotic cardiovascular disease, the long-term macrovascular and microvascular effects remain unknown.

Dose adjustment is one reasonable approach to balancing the benefits and risks of statins. The 2013 ACC–AHA guidelines, citing the lack of randomized trials testing various goals for LDL cholesterol levels, indicate that a reduction in LDL cholesterol levels may be useful as a marker of adherence and response to treatment but should not be a goal of therapy.[8] Even so, all the statin trials monitored LDL cholesterol levels and showed that the reduction in the risk of atherosclerotic cardiovascular disease was directly proportional to the reduction in LDL cholesterol level, whereas the risk of adverse events, including diabetes, was proportional to the dose of the statin.[8] Furthermore, two of the three primary prevention trials incorporated a treat-to-target approach in their trial design. In these two trials (the AFCAPS/TexCAPS[5] and the MEGA [Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese] study[10]), statins were administered at a low dose initially, and the doses were subsequently adjusted to specific goals; the results showed reductions of approximately 20 to 30% in LDL cholesterol levels and in the relative risk of atherosclerotic cardiovascular disease. In the third trial (JUPITER), lifestyle modification was intensified and the use of lipid-lowering drugs was allowed when the LDL cholesterol level was 130 mg per deciliter or higher. Finally, prospective analyses from statin trials showed that the risk of atherosclerotic cardiovascular disease during statin therapy was related to on-treatment levels of LDL cholesterol, non-HDL cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein, among other factors.[11]

In summary, I recommend aggressive lifestyle-modification therapy for Stephen, followed by a low-to-moderate dose of a statin if his risk remains elevated. It is reasonable to monitor his lipid, glucose, and glycated hemoglobin levels while he is receiving the statin — an approach that is supported by evidence from prospective studies and indirectly by observations from randomized trials. The statin dose should be reduced if warranted by the side-effect or safety profile, and the dose should be increased, if necessary, to achieve a reduction of at least 20 to 30% in the LDL cholesterol level (there is potentially more benefit if a greater reduction is achieved). In primary prevention, drug safety is especially important, since the risks of long-term therapy should be balanced with achievable benefits, and therapy should be tailored to the individual patient.

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OPTION 3

Begin Statin Therapy, But Do Not Monitor LDL Cholesterol

Harlan M. Krumholz, M.D.

The decision about whether to take a statin is intensely personal and depends on a patient's preferences. Thus, the shared decision-making framework recognizes that different people may choose differently.[12] The best way for Stephen to reduce his risk is to quit smoking. If he will not quit, I would explain to him that a person who would choose statin treatment would be someone who is motivated by the magnitude of the benefit of statin therapy in relation to the risk, which many patients may consider to be substantial.

In a meta-analysis, statin treatment was shown to reduce the risk of cardiovascular disease and stroke by about 20%, regardless of the baseline lipid profile.[13] The evidence from the trials clearly shows that patients' overall risk, rather than their initial LDL cholesterol level, determines the magnitude of the benefit of statin treatment. The number needed to treat to avoid a cardiovascular event over the course of 10 years

in a person with Stephen's medical profile who does not stop smoking is about 50 — that is, about 50 people like him would need to be treated for 10 years for 1 person to avoid the risks detailed in the vignette. It also means that among people with his medical profile, about 98% will have the same outcome, whether or not they take a statin. There is some controversy over the risk calculator, but even if the risk calculator overestimates the risk by 20%, the number needed to treat would stay in the same ballpark (about 60).[14] To reap the benefits of statin therapy, Stephen would need to take one pill a day and incur the costs of treatment and the small risk of adverse effects, many of which are reversible.

It is important to note that if Stephen were to quit smoking, the number needed to treat would almost double. At that point, his risk would be lower than the treatment recommendation threshold of the guideline. Nevertheless, he still may decide that the magnitude of benefit is a sufficiently large motivation to choose statin therapy.

How might the discussion go? If Stephen failed to quit smoking, I might explain that his LDL cholesterol level is not very high but that he has more than a 1 in 10 chance of a major heart problem or stroke in the next decade and that statins can lower the risk. And then I would explain the magnitude of the benefit and discuss costs and potential harms. I would also emphasize that taking statins does not diminish the importance of quitting smoking and that the decision about statins can be reevaluated in the future. I would be sure that he felt supported in the decision and knew that reasonable people might make different choices.

With regard to the need for monitoring, I would tell him that he will not need to return regularly to have his cholesterol levels checked. I would explain that the new guidelines have recognized that the major studies did not include the need for monitoring lipid levels.[8] Monitoring is recommended only for assessing adherence, but I would tell him that I do not have to check his adherence by means of a blood test; we can just talk about whether he is taking the pills and wants to continue taking the pills. In these trials, patients received a particular drug at a particular dose, and the doses were not adjusted according to laboratory test results; this is the same approach that is now recommended in the Adult Treatment Panel (ATP) IV guidelines.[15] I would explain that this is good news, since he will not have to incur the cost and inconvenience of returning for this testing. I would also explain that this approach does not imply that cholesterol is not important, but that we now think about statins as risk-reduction medications in the same way that we consider aspirin. We are no longer treating to reach a target LDL cholesterol level. We are treating to lower risk, using medications and doses that have been proven effective for lowering risk, not those that are effective just for lowering the LDL cholesterol level.

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