Cholesterol Lowering in 2015
Still Answering Questions About How and in Whom

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Following the first convincing trials in humans on the benefits of cholesterol lowering for prevention of atherosclerotic-related events, in 1985, then-Director of the National Heart, Lung, and Blood Institute Robert Levy asserted that the cholesterol "question" was no longer whether to treat high cholesterol levels, but rather when, in whom, and how.1 For 30 years, it has been well known that lowering blood cholesterol concentrations by a variety of drugs and other approaches reduces cardiovascular disease (CVD) risk.2 With more trials in patient groups with lower risk, including those with relatively low levels of low-density lipoprotein cholesterol (LDL-C),3 it has become clear that atherosclerotic cardiovascular disease (ASCVD) can be prevented by lowering LDL-C levels, especially with statin drugs,2,3 in broad segments of the general population. However, the critical questions—when, in whom, and how to lower cholesterol—still remain. This Editorial, with new evidence from 2 reports in this issue of JAMA, addresses 2 of these questions: in whom and how to treat cholesterol levels in 2015.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines2 recommended consideration of statin treatment for 4 clinical scenarios: (1) patients with clinical ASCVD including those with myocardial infarction, angina, or previous coronary revascularization; (2) patients without clinical ASCVD but with an LDL-C level higher than 190 mg/dL and without secondary cause; (3) patients aged 40 through 75 years without clinical ASCVD but with diabetes mellitus and LDL-C levels from 70 through 189 mg/dL; and (4) patients aged 40 through 75 years without clinical ASCVD and diabetes, but with an LDL-C level of 70 through 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher. For the first 3 clinical scenarios there was almost universal acceptance with general agreement that the new recommendations were based on strong and consistent data.4

However, nearly immediately after release of the guidelines there was considerable scrutiny and controversy regarding the fourth clinical scenario: primary prevention in adults without diabetes but with an estimated 10-year ASCVD risk of 7.5% or higher. One group reported a set of analyses suggesting that the new ACC/AHA Pooled Cohort Equation overestimated risk in various populations,5 whereas others reported that, in properly selected cohorts, the new equation performed more accurately than previously used risk equations.6 Uncertainties about the accuracy of the risk calculator raised concerns about the wisdom of the newly lowered treatment threshold. Would the new guidelines lead to massive and unjustified overtreatment of millions of people? The question of in whom to use statins lingered.

Based on evidence from multiple clinical trials, statin drugs have been shown to lower CVD risk for primary prevention even among relatively low-risk people and even among those with relatively low LDL-C concentrations.3 Although a 10-year ASCVD risk threshold of 7.5% or higher might initially seem to be a low threshold, many, indeed most, CVD events occur among the low-risk members of the population.7 Rose first described the seeming paradox8 that relatively few ASCVD events occur in high-risk individuals simply because there are so few high-risk people in the population. The vast majority of ASCVD events occur among lower-risk persons because they comprise the greatest portion of the population.9 To prevent many more ASCVD events, it is reasonable to consider whether statin drugs should be used in lower-risk individuals, and whether risk assessment by the new Pooled Cohort Equation leads to a reasonable level of treatment of at-risk people and a rational use of medical resources, even if potentially billions of people worldwide would be recommended for statin drugs.10

In this issue of JAMA, 2 reports suggest that the new risk threshold is likely to be reasonable and cost-effective; it may not even go far enough. If true, even a risk calculator that overestimates risk might be reasonable to use in the clinical setting. In the first report, using Framingham Offspring Study data, Pursnani et al11 sought to determine whether the 2013 ACC/AHA guidelines improved identification of individuals who developed incident ASCVD, had evidence of coronary artery calcium, or had both compared with the National Cholesterol Education Program's 2004 Updated Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines. As expected, among 2435 statin-naïve people, the new Pooled Cohort Equation led to many more people being eligible for statin therapy (39% for ACC/AHA guidelines vs 14% for ATP III guidelines). However, the newly statin-eligible people were at markedly increased risk for experiencing clinical events, for having elevated levels of coronary calcium, or for having both. These findings offer assurance that the 2013 Pooled Cohort Equation can efficiently and appropriately identify those destined to develop a major ASCVD event in the near future.

However, identifying those at risk with reasonable accuracy is only part of the decision-making process. An impor-
tant consideration involves where to set the threshold for treatment.10 The findings reported by Pandya et al12 in this issue of JAMA suggest that an even lower threshold than 7.5% 10-year CVD risk may be cost-effective. Using a microsimulation model with a lifetime time horizon and a US societal perspective, a hypothetical cohort of individuals from a representative US population aged 40 through 75 years received statin treatment, experienced ASCVD events, and died from ASCVD-related or non-ASCVD-related causes based on ASCVD natural history and statin treatment parameters. In the base-case scenario, the current ASCVD threshold of 7.5% or higher, which was estimated to be associated with 48% of adults treated with statins, had an incremental cost-effectiveness ratio (ICER) of $37 000/QALY (quality-adjusted life-year) compared with a threshold of 10% or higher. More lenient ASCVD thresholds of 4.0% or higher (61% of adults treated) and 3.0% or higher (67% of adults treated) had ICERs of $81 000/QALY and $140 000/QALY, respectively. Shifting from a 7.5% or higher to a 3.0% or higher ASCVD risk threshold was estimated to be associated with an additional 161 560 cardiovascular disease events averted. These findings suggest that the currently recommended threshold of 7.5% is cost-effective, and a lower threshold might also be cost-effective. Thus, even if risk estimation overestimates risk, widespread use of the Pooled Cohort Equation should be expected to avert a large number of adverse cardiovascular events and so in a manner that is cost-effective without concerns for inappropriate over-treatment.

Based on available evidence, including the 2 reports in this issue of JAMA, answers to the questions of in whom and how regarding cholesterol lowering are now more clear than they were just 18 months ago. Available evidence indicates that statins are both effective3 and cost-effective11 for primary prevention even among low-risk individuals. Although lifestyle interventions must be employed across all segments of the population,2 for many people a statin drug will also be required to minimize risk.2 Where to set the treatment threshold and how to determine the individual’s level of risk are also becoming progressively clarified. The 2013 Pooled Cohort Equation, despite its flaws,5,6 identifies more high-risk individuals than the previously used Framingham Risk Score.13 The Pooled Cohort Equation appears to be a justifiable approach to risk assessment as a replacement for the older Framingham Risk Score, and the recommended threshold of 7.5% is also justifiable; in fact, it may even be too conservative.12 There is no longer any question as to whether to offer treatment with statins for patients for primary prevention, and there should now be fewer questions about how to treat and in whom. Rather, the next phase of research should be directed at better ways of applying lifestyle and drug treatments to the millions, and possibly billions, worldwide who could potentially benefit from a cost-effective approach to primary prevention of ASCVD.

ARTICLE INFORMATION

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REFERENCES


