In 1984, the Lipid Research Clinics Program trial provided modest, if controversial, evidence that cholestyramine was associated with a reduction in the risk of coronary heart disease (CHD) in a primary prevention study of men. Other evidence for the emergence of a new treatable risk factor came from epidemiological studies, animal studies, and family studies. The National Heart, Lung, and Blood Institute (NHLBI) convened the National Cholesterol Education Program (NCEP) to develop recommendations about the detection, evaluation, and treatment of cholesterol in adults. The first Adult Treatment Panel (ATP) used levels of low-density lipoprotein (LDL) cholesterol to define both the thresholds for initiating treatment and the goals or targets of therapy.

Because LDL levels are linearly related to CHD risk, defining an LDL cholesterol threshold for starting lipid-lowering treatment was a formidable task. In 1988, the LDL level of 160 mg/dL was selected as abnormal in part because it was a value above which the risk of CHD was said to increase "steeply" and in part because it corresponded "approximately to the 75th percentile for the adult US population." While the rationale for the other thresholds for dietary and drug interventions was not provided, these recommendations declared one quarter of the adult population as having a "treatable" risk factor at a time when few safe and effective therapies were available.

Over the years, a professional circle that included investigators, clinicians, industry, funding agencies, professional societies, and journals emerged with a shared interest in the prevention of atherosclerosis and CHD. Therapeutic enthusiasm for reducing levels of LDL cholesterol sometimes led to recommendations about drug treatments, such as estrogens for postmenopausal women in 1993, that were later shown to have little or no clinical benefit. Although the first ATP report specified whether each drug treatment had been shown to reduce clinical events, this approach was later abandoned. In 2001, the ATP III recommended all the major lipid-lowering drug classes and, in the text, merely identified statins as a "usual drug" for starting therapy.

Even though the 2004 revision of ATP III reviewed 5 large statin trials, the authors avoided expressing a preference for drug choice, interpreted the trial results solely in terms of the cholesterol hypothesis, and merely emphasized the importance of initiating an "LDL-lowering drug." In other words, the lessons of the statin trials became increasingly complex over time.

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Even though the 2004 revision of ATP III reviewed 5 large statin trials, the authors avoided expressing a preference for drug choice, interpreted the trial results solely in terms of the cholesterol hypothesis, and merely emphasized the importance of initiating an “LDL-lowering drug.” In other words, the lessons of the statin trials completed in the years before the 2004 report were understood in terms of LDL levels, an interpretation that perhaps unwittingly encouraged extrapolation to other drug therapies. The inference was broadly about the expected health advantages of lipid lowering in general rather than narrowly about the risk-benefit profile of the particular statin drugs evaluated in the major trials. As a consequence of such a broad “biological” interpretation of lipid lowering, pharmaceutical manufacturers were able to market new drugs that had no proven health benefits.

All the ATP reports have used a combination of LDL levels and clinical factors to define thresholds and targets, an approach that became increasingly complex over time. In the first ATP report, there were only 2 treatment groups. By the 2004 revision of ATP III, the number of risk categories had increased from 2 to 4; for the high-risk group, there was an optional goal; and for 3 of the 4 groups, there were also optional thresholds for initiating drug therapies.

Work on new cholesterol treatment guidelines began in 2008, and in June 2013, the NHLBI announced its plan to turn over guideline development to the American College of Cardiology (ACC) and the American Heart Association (AHA). The 2013 ACC/AHA guideline was created in a new era when guidelines for the development of guidelines and recommendations for the conduct of systematic reviews have formalized the collection, evaluation, and assembly of evidence. Selecting guideline committee members is especially important for avoiding even the appearance of conflict of interest, which provoked controversy, for instance, about the lipid guidelines for children. Of course, the scientific formalism of the guidelines for guidelines largely involves methods designed to generate unbiased analyses for particular questions.

Genuine innovation resides not in the methods that are bought to bear, but in the questions for which evidence is sought. Importantly, the questions posed by the ACC/AHA task force have enabled the current guidelines to escape old frameworks and, thus, move in new directions.

In using the latest evidence-based methods, the committee members subjected to systematic review several critical questions: (1) what are the optimal LDL and high-density lipoprotein (HDL) cholesterol goals of treatment, for both primary and secondary prevention? and (2) what are the risk-benefit profiles of specific drug treatments to lower cholesterol? Several metaanalyses of up to 27 randomized clinical trials, primarily evaluating statins, were available as evidence. What shaped the new recommendations were not so much the evidence-based methods as these simple questions.

First, for the questions related to treatment targets, the task force found no scientific evidence to support specific treatment goals for either LDL or HDL cholesterol. In general, the completed trials had given patients various statins and compared their health outcomes with those
of patients in the control group. Absent evidence from clinical trials, the treatment targets that characterized the first 3 panel reports have been abandoned. Follow-up measures of LDL cholesterol are encouraged as a means of assessing medication adherence but not as a method for monitoring progress toward LDL targets.

What about thresholds for initiating treatment? Like ATP III, the new guidelines still use 4 categories: (1) adults with atherosclerotic cardiovascular disease; (2) adults with diabetes, aged 40 to 75 years with LDL levels between 70 and 189 mg/dL; (3) adults with LDL cholesterol levels of 190 mg/dL or higher; and (4) adults aged 40 through 75 years who have LDL levels 70 through 189 mg/dL and 7.5% or greater 10-year risk of atherosclerotic cardiovascular disease. While the ATP III risk equation from 2004 would identify 31.9% of patients assessed in group 4 as eligible for treatment due to 10% or higher 10-year risk of CHD, the new risk assessment tool identifies 32.9% as eligible for shared decision making about drug treatment due to a 7.5% or higher 10-year risk of atherosclerotic cardiovascular disease. The 2 groups overlap by 75%. Indeed, for all 3 of the primary prevention groups (2-4 above), the new recommendation calls appropriately for a discussion of risks, benefits, and patient preferences before starting drug therapy (see figure 4 in the guideline). Although these 4 risk groups are recognizable descended from previous reports, the authors are careful to show the clear relationship between these risk groups and the eligibility criteria of the major clinical trials. In addition, defining treatment thresholds in terms of the 10-year risk of atherosclerotic cardiovascular disease separates treatment decisions from specific baseline levels of LDL and, further, renders particular LDL targets irrelevant.

Second, the critical question about the efficacy and safety of various cholesterol-lowering drugs is carefully focused on important health outcomes—major disease end points such as coronary events and stroke—rather than the surrogate end point of levels of LDL cholesterol. By this criterion, the first-line treatment is statin therapy. The task force’s decision to use drug or drug class as the unit of analysis largely focuses attention on the risk-benefit profiles of specific drug interventions: trial findings are interpreted in terms of empirical estimates of the efficacy and safety of particular drugs rather than the hypothetical benefit associated with lipid lowering. Discussions of high- or moderate-intensity statin therapy also rely importantly on evidence about the risk-benefit profile. As a primary treatment for LDL cholesterol, the other drugs or classes—fibrates, niacin, bile acid sequestrants, ezetimibe, and omega-3 fatty acids—generally lack consistent or compelling evidence of health benefits necessary for major public health recommendations.

Overall, the revised 2013 ACC/AHA guidelines represent a strong fit with the clinical trial evidence: treatment thresholds resemble eligibility criteria of the trials; statins are clearly identified as the first-line drug therapy; and treatment targets are abandoned. With control no longer defined by LDL cholesterol levels, these recommendations also effectively abolish one traditional genre of research article: periodic reports about the awareness, treatment, and control of high cholesterol at the population level. In place of control characterized by level of cholesterol, scientists may need to redefine “control” in terms of the use of the recommended first-line therapy in an appropriate dose. The use of other drug therapies in a patient without contraindications to statins would become a novel form of uncontrolled hypercholesterolemia. Prescribing practices of clinicians, too, will be affected. The goal of therapy is not the achievement of a target level of LDL cholesterol, an approach that previously may have required multiple drugs. The primary aim of drug therapy is the use of a first-line drug among those likely to benefit, an approach designed to improve the health of the public. The interpretation of the evidence provided by the task force team has helped patients and clinicians move closer to that goal.

REFERENCES