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VIEWPOINT

2013 ACC/AHA Cholesterol Treatment Guideline

What Was Done Well and What Could Be Done Better

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Five years after convening the expert panel, the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was released. The American College of Cardiology and American Heart Association issued the guideline on the basis of a systematic review of cholesterol treatment trials performed by the National Heart, Lung, and Blood Institute. This report critically appraises the guideline and provides our view of what was done well and what could be done better. In particular, we propose that the guideline succeeds in prioritizing statin therapy, expanding the focus to atherosclerotic cardiovascular disease (including stroke), and emphasizing absolute cardiovascular risk to determine eligibility for statin therapy. We contend that the guideline could be enhanced by refining the use of lipid goals rather than removing them, enhancing guidance on evaluation of cholesterol, and broadening the concept of age underpinning risk-based decision making to include vascular and physiological age. We further suggest that the next guideline panel could comprehensively review current best evidence, build on existing guidelines, and cultivate broader national and international consensus. Overall, we aim to continue discussions about the important contributions and shortfalls of the guideline and create momentum for effective implementation and timely updates. (J Am Coll Cardiol 2014;63:2674–8) © 2014 by the American College of Cardiology Foundation

Five years after it was commissioned, the document previously known as "ATP IV" was issued on November 12, 2013, under a revised name, "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" (henceforth abbreviated as "CTG" for "Cholesterol Treatment Guideline") (1). The American College of Cardiology and American Heart Association (ACC/AHA) issued the CTG on the basis of a systematic review of cholesterol treatment trials. This report critically appraises the CTG and provides our view of what was done well and what could be done better in future iterations.

What Was Done Well

Prioritizing statin therapy. The CTG succeeds in prioritizing statin therapy, which is in line with recommendations from our group (2) and others (3). Over the decade since the original publication of the Adult Treatment Panel (ATP) III guideline, the Cholesterol Treatment Trialists' Collaboration has further expanded the extraordinary wealth of information on statin therapy (4,5). This class of medications is 1 of the best validated to reduce the morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD) and has an excellent safety profile (1,2,4). Moreover, generic options for moderate- and high-intensity statin formulations are now available. We anticipate that prioritizing statins will lead to much less use of nonstatin therapy in patients not yet on maximally tolerated statin therapy.

Expanding the focus to ASCVD. Cerebrovascular disease and coronary heart disease (CHD) share risk factors and the underlying disease process of atherosclerosis. Lipid-lowering interventions reduce clinical events related to ASCVD, not only CHD. Therefore, addressing the broader disease construct is justified and more efficient.

There are complexities to this expanded paradigm, not limited to the fact that 1 of multiple underlying pathophysiological mechanisms can cause a stroke, and the distinction can be challenging to adjudicate. Although we must carefully scrutinize and understand how to manage such complexities, on balance, expanding the framework from CHD to ASCVD is an important and welcome change (6).

Emphasizing absolute cardiovascular risk. The CTG emphasizes absolute risk in the allocation of statin therapy. The CTG recommends moderate- to high-intensity statin

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therapy in groups with high absolute risk, including patients with clinical ASCVD, those 40 to 75 years of age with diabetes mellitus, and those with low-density lipoprotein cholesterol (LDL-C) levels ≥190 mg/dl. The CTG prioritizes these 3 groups on the basis of prevailing evidence from randomized controlled trials.

For those not in one of these groups, if the patient has an LDL-C level of 70 to 189 mg/dl and is 40 to 75 years of age, then the CTG advises calculation of 10-year risk of ASCVD on the basis of traditional risk factors using new sex- and race-stratified pooled cohort equations developed by the ACC/AHA Risk Assessment Working Group (7). Concern about overestimation of risk by these equations is being debated (8,9), and further validation studies are necessary. Nevertheless, we appreciate the intention to address absolute risk in primary prevention. In the CTG, the risk calculator does not mandate drug prescription but rather serves as a starting point for a discussion about risk between the patient and the clinician. This discussion may lead to additional testing to refine the estimate of absolute risk. The CTG identifies the intermediate-risk group as people with a 5% to 7.5% 10-year risk of ASCVD and recommends a discussion about risk in people with ≥7.5% risk.

What Could Be Done Better

Refine the use of lipid goals rather than remove them. There are potential downsides to lipid goals. They could lead to overuse of nonstatin agents and combination regimens instead of maximizing statin therapy. This could increase the propensity for adverse effects, which could be problematic specifically in primary prevention patients with less certain absolute ASCVD risk and, therefore, less certain benefits. Moreover, lipid goals could conceivably result in withholding of efficacious treatment in a person with an LDL-C level <100 mg/dl. Prior guidelines may not have recommended intensive statin therapy, or a statin at all, in higher-risk patients with low or average off-treatment levels of LDL-C (100 to 130 mg/dl), yet this group has a similar proportional risk reduction from lowering of LDL-C levels (4). Therefore, applying a lipid goal at baseline could lead to underuse of statins in higher-risk patients.

We could address these issues without abandoning lipid goals. To do so, we could refocus the use of lipid goals as an option to guide residual risk discussions on follow-up among those with a clearly established risk of ASCVD while making it explicitly clear that maximizing the statin dose is the first priority. Even in secondary prevention trial populations carefully selected to adhere to high-intensity statin therapy, many patients did not attain optimal levels of atherogenic cholesterol. In statin-treated patients, LDL-C, non–high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B are markers of residual risk (10). Considering LDL-C and non–HDL-C on follow-up in relation to explicit goals, as was done in ATP III, could alert the patient and provider that levels are still suboptimal. This does not need to trigger automatic addition of drug therapy. Rather, it could prompt a discussion of residual risk and options for further intensification of lifestyle improvements and add-on drug therapy, particularly in the setting of an elevated triglyceride level and a low HDL-C level. Because the anticipated net benefits of further lipid lowering are clearest in those with the most clearly established risk, we believe that lipid goals are best justified in high-risk secondary prevention.

Abbreviations and Acronyms

ACC/AHA = American College of Cardiology and American Heart Association

AACE = American Association of Clinical Endocrinologists

ASCVD = atherosclerotic cardiovascular disease

ATP III = Adult Treatment Panel III

CHD = coronary heart disease

CTG = Cholesterol Treatment Guideline

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

NLA = National Lipid Association

It is true that there has not been a definitive randomized clinical trial of the addition of a second lipid-lowering agent in secondary prevention patients with residually elevated atherogenic cholesterol levels. There are many clinical situations, including in the management of hypertension, in which there are no randomized trials of ASCVD outcomes with the addition of drug A to drug B or the addition of drug C to drugs A and B. However, we could learn from landmark strategy trials such as the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, in which statins and nonstatins were titrated to an LDL-C goal of 60 to 85 mg/dl. The central test of the trial was optimal medical therapy with or without percutaneous coronary intervention, and it forms part of the foundation for management of patients with stable CHD. A COURAGE-like strategy to medical management includes an LDL-C goal.

As previously reviewed (11,12), complementary lines of evidence support the low LDL-C goal used in the COURAGE trial (or similar goals such as <80 or <70 mg/dl). First, LDL-C levels in this range appear to be evolutionarily or biologically normal. Second, those with genetically determined low LDL-C levels are strongly protected from ASCVD. Third, trials and observational studies have consistently shown a log-linear association of lower LDL-C level with lower risk of ASCVD. Fourth, populations treated to low LDL-C levels in trials were more likely to have stabilization or regression of atherosclerosis. Fifth, the Cholesterol Treatment Trialists' Collaboration has shown that the benefit of statin therapy is tied not only to absolute ASCVD risk but also to the absolute lowering of LDL-C levels, with each 39-mg/dl (1-mmol/l) reduction in LDL-C level decreasing the incidence of ASCVD by approximately one-fifth. Finally, subgroups of patients attaining the lowest LDL-C levels in these trials had the best outcomes without any significant increases in major adverse effects. Therefore, like COURAGE, ATP III, and guidelines in Europe and