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2013 American Cholesterol Treatment Guideline: What Was Done Well and What Could Be Done Better

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Brief title: Analysis of the 2013 Cholesterol Guideline

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Abstract

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 based on a systematic review of cholesterol treatment trials performed by the National Heart, Lung, and Blood Institute. This article 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 focus to atherosclerotic cardiovascular disease including stroke, and in emphasizing absolute cardiovascular risk to determine statin eligibility. 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 physiologic 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.

Key words: Cholesterol, Lipids, Lipoproteins, Dyslipidemia, Atherosclerosis, Coronary Heart Disease, Cardiovascular Disease, Myocardial Infarction, Stroke, Treatment, Statins, Guidelines

Abbreviations List

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
COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CTG = Cholesterol Treatment Guideline
LDL-C = Low-density lipoprotein cholesterol
NLA = National Lipid Association
Non-HDL-C = Non-high-density lipoprotein cholesterol

Introduction

Five years after it was commissioned, the document previously known as "ATP IV" was issued on November 12th, 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 based on a systematic review of cholesterol treatment trials. This article 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, in line with recommendations from our group (2) and others (3). Over the decade since the original publication of the Adult Treatment Panel III (ATP III) guideline, the Cholesterol Treatment Trialists have further expanded the extraordinary wealth of information on statin treatment (4,5). This class of medications is one of the best validated to reduce the morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD), with 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 non-statin therapy in patients not yet on maximally-tolerated statin therapy.

Expansion to Atherosclerotic Cardiovascular Disease

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 one of multiple underlying pathophysiologic mechanisms can cause a stroke, and the distinction can be challenging to adjudicate. While 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).

Emphasize Absolute Risk

The CTG emphasizes absolute risk in the allocation of statin treatment. The CTG recommends moderate- to high-intensity statin therapy in groups with high absolute risk, including those with clinical ASCVD, those 40-75 years of age with diabetes mellitus, and those with low-density lipoprotein cholesterol (LDL-C) levels ≥190 mg/dL. The CTG prioritizes these three groups based on prevailing evidence from randomized controlled trials.

For patients not in one of these groups, if the LDL-C is 70-189 mg/dL and the person is aged 40-75 years, then the CTG advises calculation of 10-year ASCVD risk from traditional risk factors using new sex- and race-stratified pooled cohort equations developed by the ACC/AHA Risk Assessment Working Group (7). Concern for 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 risk discussion between the patient and clinician. This discussion may lead to additional testing to refine the estimate of absolute risk. The CTG identifies the intermediate risk group as persons with 5-7.5% 10-year ASCVD risk, while also recommending a risk discussion in persons 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 non-statin 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 of <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 (100-130 mg/dL). Yet this group has a similar proportional risk reduction from LDL-C lowering (4). Therefore, applying a lipid goal at baseline could lead to underuse of statins in higher risk individuals.

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 in follow-up among those with clearly established ASCVD risk, while making explicitly clear that maximizing the statin dose is the first priority. Even in secondary prevention trial populations carefully selected to adhere to a high-intensity statin, 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 in 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. Since the anticipated net benefits of further lipid-lowering are clearest in those with most clearly established risk, we feel that lipid goals are best justified in high-risk secondary prevention.

It is true that there has not been a definitive randomized clinical trial of adding a second lipid-lowering agent in secondary prevention patients with residually elevated atherogenic cholesterol. There are many clinical situations, including in hypertension management, where we do not have a randomized trial of ASCVD outcomes for adding drug A onto drug B, or drug C onto drugs A and B. However, we could learn from landmark strategy trials like the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial wherein statins and non-statins were titrated to an LDL-C goal of 60-85 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 COURAGE (or similar goals such as <80 or <70 mg/dL). First, LDL-C levels in this range appear to be the evolutionarily or biologically normal. Second, those with genetically determined low LDL-C are strongly protected from ASCVD. Third, trials and observational studies have consistently shown a log-linear association of lower LDL-C with lower ASCVD risk. Fourth, populations treated to low LDL-C levels in trials were more likely to have atherosclerosis stabilization or regression. Fifth, the Cholesterol Treatment Trialists have shown that the benefit of statin therapy is tied not only to absolute ASCVD risk, but also to the absolute lowering of LDL-C, with each 39 mg/dL (1 mmol/L) reduction in LDL-C decreasing the incidence of ASCVD by about 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 Canada, we could use this information to manage residually elevated LDL-C.

Because LDL-C will not capture triglyceride-rich remnant lipoproteins, we could also consider non-HDL-C or apolipoprotein B. A previous meta-analysis of statin and nonstatin lipid-lowering drugs used as monotherapy found a ~1:1 percent lowering between non-HDL-C and CHD risk (13). Pre-specified subgroup analyses of trial participants with high triglycerides and low HDL-C (markers for remnants) are informative on the potential benefit of adding a fibrate (14) or niacin (14,15) to statin therapy. These studies have shown a consistent trend for benefit.

Therefore, "treating risk" and "treating lipids" are not mutually exclusive and actually complementary. Absolute risk places the lipids in context and can guide discussions weighing potential benefits and harms. However, lipid goals provide a marker for adequacy of lipid-lowering. They not only help ensure adherence to lifestyle improvements and statin therapy, but also help guide therapy in high-risk patients in whom these treatments are exhausted.

Enhance Guidance on Evaluation of Cholesterol

Compared with ATP III, the CTG removed "Evaluation" from its title. However, new information has become available on the evaluation of cholesterol since ATP III. Although the risk assessment guideline examines this information to some extent, cholesterol evaluation is not purely an issue of risk assessment.

For example, at baseline, the CTG recommends treatment if the LDL-C is ≥70 mg/dL, but not if it is <70 mg/dL. Therefore, accurate measurement in the individual patient is critical to management. Expanding prior evidence, we have shown that of patients who have a Friedewald-estimated LDL-C <70 mg/dL, 23% have a directly measured LDL-C ≥70 mg/dL (39% if

triglycerides 150-199 mg/dL and 59% if triglycerides 200-399 mg/dL) (16). If externally validated, a novel method for LDL-C estimation could resolve much of underestimation of LDL-C by accounting for variation in the relationship of triglycerides to very-low density lipoprotein cholesterol (17).

The next guideline could translate new knowledge on cholesterol evaluation. It could take a leadership role in guiding clinicians on not only LDL-C, but also non-HDL-C, apolipoprotein B, and LDL particle concentration. Along with the science, there are historical, financial, and logistical considerations, and an expert panel is well suited to weigh these factors.

Broaden Concept of Age

The CTG emphasizes chronologic age in treatment decisions. For example, the CTG explicitly recommends statin therapy only in patients aged 40-75 years. This same age range also determines who undergoes 10-year ASCVD risk calculation to guide treatment decisions. Age dominates the risk calculator with the 7.5% risk threshold exceeded by nearly all men in their mid to late 60s and nearly all women in their 70s despite an optimal risk factor profile.

Yet people age differently. We submit that a broader construct of age may enhance risk discussions and treatment decisions. “Heart age” and “vascular age” could help a patient better understand how his or her risk compares to their chronologic age. Moreover, the concepts of “health age” or “physiologic age” could be used to assess our patients’ non-cardiovascular comorbidities or competing risks, which could impact the net benefits from intervention. If the patient is free of competing risks, then we would suggest that the CTG could be less cautious in those aged >75. The Cholesterol Treatment Trialists’ meta-analysis included 1,872 events in individuals aged >75 years and there was no evidence of heterogeneity of treatment effect by age (4). A meta-analysis focused on elderly patients without ASCVD at baseline, involving 24,674

subjects with a mean age of 73.0±2.9 years and 3.5±1.5 years of follow-up, found a significant reduction in ASCVD outcomes with statin therapy (18).

We would also like to prevent significant accumulation of atherosclerosis earlier in life. A risk score dominated by chronologic age favors late treatment. Once atherosclerosis progresses to an advanced stage, there may be an associated degree of unmodifiable risk. Although speculative, preventing significant atherosclerosis progression in the first place may help avoid at least part of this residual risk. It is striking that the relative risk reduction associated with genetically low LDL-C is larger than that with later stage drug therapy (19).

We submit for debate – if you are stuck on a deserted island, have significant subclinical atherosclerosis or heterozygous familial hyperlipidemia with an LDL-C of 189 mg/dL, and have only enough statin to take for 20 years, would you take it from age 30-50 or 50-70?

Comprehensively Review Current Best Evidence, Build on Existing Guidelines, and Refine the CTG during Implementation

Evidence based medicine is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (20). In contrast, the CTG restricted its evaluation of the medical literature primarily to randomized controlled trials up to December, 2009. The phrase "no evidence" could be a dangerous claim (21), especially when all current best evidence has not been considered.

A search on PubMed for "cholesterol" on the day that the CTG was released yielded 219,290 published scientific reports. In answering "Critical Question 1" about lipid goals, the CTG screened 2,224 titles and abstracts, thus ~1% of the published literature.

To construct a comprehensive guideline, the writing group did not necessarily need to re-review >200,000 published scientific reports. ATP III critically appraised and synthesized

relevant literature up through 2004 (22). In addition, specialty societies such as the National Lipid Association (NLA) (23) and the American Association of Clinical Endocrinologists (AACE) (24) have issued recent recommendations for the management of cholesterol disorders.

The NLA and AACE each provided input to the NHLBI and ACC/AHA during the development of the CTG, but ultimately did not endorse the document. The reasons that the NLA and AACE each did not endorse the CTG were explained in public statements (25,26). Each group cited the highly restrictive consideration of evidence, removal of lipid targets, too little guidance on non-statin options, and insufficient consideration of special populations of patients.

Outside of the United States, guideline writers in Europe (27) and Canada (28,29) have recently provided updated guidelines. The International Atherosclerosis Society has also released a position paper on the management of dyslipidemia (30). These international efforts address many of the concerns noted by the NLA and AACE. In moving forward, we propose building upon these prior efforts. Ideally, the ACC/AHA could collaborate with professional societies around the globe to build broader consensus and produce an international consensus guideline on cholesterol treatment.

One can easily imagine potential benefits to guideline implementation from pooling resources and broadening consensus. The critical rollout phase of the CTG could leverage the influence of professional societies and engage the expertise of transdisciplinary teams inclusive of implementation scientists to help overcome barriers to guideline adherence at the bedside. For example, guideline documents like the CTG can be long, tedious and very repetitive. Although an important scholarly exercise, this form of information is far from user-friendly. Instead, implementation scientists recommend a prioritized checklist of unambiguous behaviors

organized in time and space, citing the level of evidence (31). A checklist could be printed and posted in clinic, made available online, or included in a smartphone app.

Implementation scientists have identified a number of other barriers to guideline adherence, including lack of awareness or ability, clinical inertia, disagreement with recommendations, or ambiguity of recommendations (31). Regarding the latter, while figures illustrating the flow of key guideline recommendations are valuable, their interpretation may be ambiguous when related figures are disjointed or when critical information is buried in footnotes or text. The implementation phase of the CTG could benefit from observing clinicians trying to use the guideline and striving to understand and respond to stumbling points. As such, we hope that the initial release of the CTG will function as a living document open to refinement based on feedback during its implementation.

Conclusions

We have highlighted key aspects of "What Was Done Well" by the CTG and "What Could Be Done Better." As the guideline was not released for public comment prior to its publication, we hope that a careful discussion about its content will continue, involving patients, health professionals, scientists, health systems, and payers. We offer our initial reactions, aimed at creating momentum for effective guideline implementation and timely updates that will support the application of current best evidence to the care of individual patients.

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