The 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol
Questions, Questions, Questions

Henry N. Ginsberg

When I was asked to write this Perspective on the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, I wondered why any reasonable person would agree to do so? It is nice to have your thoughts and opinions in a prestigious journal read by your closest peers, but could it be anything more than a lose-lose situation? I decided, therefore, to preface the perspective with several disclosures. First, I was a member of the original Adult Treatment Panel (ATP) guidelines committee—on the Drug Treatment Subcommittee. I was never again asked to be on the committee, but that rejection has had no effect on what I have written here. Second, I think that physician–scientists have the responsibility to integrate all available data, with appropriate priorities, and draw conclusions that can be offered to patients, clinicians, and the world-at-large. So let me state that, based on what I have integrated from a variety of sources for the past 40 years, I have concluded that lowering low-density lipoprotein cholesterol (LDL-C) reduces the risk for atherosclerotic cardiovascular disease (ASCVD), and that the level of LDL-C is important—lower is better. Third, as someone who led a major clinical trial—Action to Control Cardiovascular Risk in Diabetes Lipid—I know that although randomized clinical trials (RCTs) provide the best evidence for the efficacy and safety of an intervention, each and every RCT has deficiencies. We must avoid, therefore, the tyranny of RCT evidence-based dogma. Fourth, at the end of this piece is my official Disclosure, a listing of my pharmaceutical company relationships. Suffice it to say that all of us who have such relationships must carefully look in the mirror when we evaluate guidelines. However, the same is true for our colleagues who avoid, as part of their career paths, all such industry relationships. Finally, I want to say how much I respect the effort that the panel made for the past several years in generating these new guidelines.

Historical Perspective
Anyone who has not read the series of 5 reviews by Steinberg in the Journal of Lipid Research (published between 2004 and 2006) or his book, The Cholesterol Wars: The Skeptics versus the Preponderance of Evidence, should do so to place the new guidelines within the framework of the preceding 100 years of preclinical and clinical science, demonstrating both the link between LDL-C and ASCVD, and our ability to reduce the incidence of the latter by lowering blood levels of the former. But individuals who are seriously considering the value and validity of the new guidelines should also review the publications summarizing the first 3 National Cholesterol Education, Adult Treatment Panel guidelines, as well as the modification of those guidelines published in 2004 and the AHA/ACC guidelines published in 2006. A close examination of how the guidelines matured during the previous 25 years will facilitate greatly your interpretation of the 2013 version.

Questions, Questions, Questions
After reading the entire guidelines several times, I had to decide the depth of my critique. As I formulated my approach, I realized that Passover, the Jewish holiday commemorating the escape of the Israelites from Egypt, could serve as a structure for my perspective. It seems to me that the AHA/ACC panel viewed as their goal an escape from a past filled with LDL-C cut points and targets, paring the waters so to speak, as they moved us from 5 prior guideline statements into a new era of strictly evidence-based medicine, which will ensure that only those most likely to benefit will be treated. So picture yourself at the Passover Seder where, at a long table with too many people seated around too much food, the youngest family member, instead of asking the traditional 4 questions about the Passover holiday, asks about the guidelines.

Grandpa, Why Are These Guidelines Different From All the Previous Guidelines?
Some say it is because these new guidelines, unlike the previous guidelines, are strictly and rigorously evidence based, but I am not sure that is completely true. In ATP I, published in 1988, the opening paragraph states, as facts, that LDL causes coronary heart disease (CHD), that risk for CHD increases as total cholesterol and LDL-C levels rise, and that lowering LDL reduces the incidence of CHD. The first 2 statements derived from a large base of preclinical and clinical/observational evidence. The last point was based on the results of the Coronary Primary Prevention Trial, the first large (n=3600) RCT demonstrating that lowering LDL-C (with cholestyramine, a bile acid sequestrant) reduced CHD risk. Indeed, the impetus to develop the guidelines was the outcome of that iconic RCT. ATP II, published in 1993, did not have additional RCTs to support major changes, so the panel chose only to refine the first guidelines.
In several ways, including the identification of people with existing CHD as being at particularly high risk for additional events. ATP II also introduced the terms Primary and Secondary Prevention to the guidelines. The identification of a high-risk group with existing CHD and the division of people into those with and without pre-existing disease are key components of the new guidelines. In ATP III, published in 2001, the opening paragraph noted that “The full ATP III document is an evidence-based and extensively referenced report...” ATP III was supported by the results of 5 major statin RCTs: Scandinavian Simvastatin Survival Study,10 West of Scotland Coronary Prevention Study,11 Cholesterol and Recurrent Events,12 Long-Term Intervention with Pravastatin in Ischemic Disease,13 and Air Force/Texas Coronary Atherosclerosis Prevention Study.14 Those studies provided the panel with the evidence they needed to increase the level of intensity of treatment recommendations. In addition, ATP III introduced the Framingham Score as a refinement to counting risk factors; the new guidelines use the Pooled Cohort Equation. The stimulus for Implications as a refinement to counting risk factors; the new guidelines to increase the level of intensity of treatment recommendations is unique, or novel, to the new guidelines. Rather, the new guidelines differ from all the previous ones because the panel decided on a unique interpretation of essentially the same body of evidence used previously. In particular, the same evidence used as the basis for the 2006 AHA/ACC Guidelines led the new panel to change our approach dramatically to the treatment of LDL-C to prevent ASCVD.

In All Previous Guidelines, We Used LDL-C Cut Points to Initiate Treatments: Why Are We Now Focusing on 4 Groups of Patients?

Although this seems to be a significant change, it is actually an aspect of the new guidelines that makes sense as a natural evolution of our approach to treatment. In ATP I, levels of total cholesterol were chosen as cut points to initiate diet and, if necessary, drug therapy, based on risk estimates for ASCVD derived from the Multiple Risk Factor Intervention Trial study. The LDL-C levels for each risk-group were approximated from levels of total cholesterol. Because these cut points for starting treatments have been iteratively modified based on a series of RCTs that showed efficacy with lower and lower starting LDL-C levels, it seems reasonable to move from 3 or 4 LDL-C cut points to 4 groups of individuals based on risk for having a CHD or ASCVD event (Table). I think that the new guidelines make it easier to identify individuals requiring treatment and should, as the panel hopes, lead to treatment of those “most likely to benefit.” Not everyone agrees with this new approach, with some saying it will double the number of individuals receiving statins. My sense, as well as that of the panel, is that about the same number of individuals will be treated under the new guidelines (I am ignoring the debate about the accuracy of the risk calculator—way above my pay scale). Overall, I support the panels approach to identify risk, rather than the level of LDL-C, as the key determinant of treatment.

In All Previous Guidelines, We Had LDL-C Targets for Therapies: Why Are We Now Just Treating People With Statins and Not Worrying About Where Their LDL-C Levels End Up?

As much as I agree with the shift from LDL-C cut points for starting treatment to 4 risk groups, I disagree completely with moving from LDL-C targets to a strategy that says “since statins work regardless of the starting LDL-C, why worry about the final levels of these atherogenic lipoproteins” (my quotes). The conclusion by the panel that because they could not find evidence from any RCT that titration of LDL-C to a specific target further reduced CHD or ASCVD events beyond that achieved by just giving a statin when compared with placebo is a clear example of the tyranny of evidence-based dogma (ie, because there has not been a titration trial targeting a specific LDL-C level that would be the same for every individual in the treatment group, we should not have LDL-C targets). I agree that RCTs most often test drugs, not strategies, but you cannot ignore the meta-analysis of 169 138 participants in 26 statin trials published by the Cholesterol Treatment Trialists (CTT) Collaboration, demonstrating continuously lower event rates with progressively lower achieved LDL-C concentration. You cannot ignore TNT, PROVE IT-TIMI 22, and IDEAL, which demonstrated directly that achieving a greater reduction in LDL-C, which equated to a lower LDL-C, was associated with greater reductions in events. Panel members decided that those studies simply proved that high intensity was better than low- or moderate-intensity statin therapy: I find that wrong-headed. In the opening paragraph of TNT, the authors state “We prospectively assessed the efficacy and safety of lowering LDL cholesterol levels below 100 mg per deciliter (2.6 mmol per liter) in patients with stable coronary
Not perfect, targets are crucial components of our approach to treatment of LDL-C to prevent CHD.

In All Previous Guidelines, Different Statin Intensity Was Linked to LDL-C Levels Cut Points and Targets; If We No Longer Use Either of Those, Why Do We Still Have Different Levels of Statin-Treatment Intensity?

I do not understand this one at all. If the panel chose not to have targets for LDL-C and yet did refer to the CTT meta-analysis several times as evidence that you both get benefit irrespective of the starting LDL-C and that lower absolute rates of events are observed at lower levels of LDL-C, why did they not at least support high intensity, maximal LDL-C lowering to all 4 groups. I think that our colleagues in Canada, who offered either a goal of ≥80 mg/dL or ≥50% LDL-C lowering made better choices.

In All Previous Guidelines, There were No Hard Cutoffs for Age; Why Do We Now Have 75 Years as a Defined Upper Limit for the Guidelines Main Recommendations?

The matzoh-ball soup is getting cold so I will be brief. When I look at HPS, PROSPER, and the CTT meta-analysis, and when I consider that there is no age limit for revascularization procedures, I will treat higher risk individuals at all ages.

What the Future Holds

At the Seder, we leave the door open for the Prophet Elijah to join us for a glass of wine. The new guidelines also left the door open (Section 9, Gaps and Future Research Needs). In my view, however, they also left themselves and the guidelines process exposed to a drastic reversal when results of studies presently underway are available. I am not sure if Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin will be positive, but it is likely that trials with cholesteryl ester transfer protein inhibitors or proprotein convertase subtilisin/kexin type 9 inhibitors will show significant benefit of further lowering of LDL-C on the background of statin therapy. Because the new guidelines have abandoned LDL-C targets, the next panel will either have to reintimate them or be forced to develop an algorithm where some patients will receive these new agents on top of statins irrespective of LDL-C levels. It is unfortunate that by deciding not to recommend LDL-C targets even as Expert Opinion, the panel opened the door so little that Elijah may have to knock it completely down to enter and drink his wine.

Disclosures

The author has had, during the past 12 months, relationships (grant funding, consulting, lectures) with the following pharmaceutical companies: AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Genentech/Roche, Genzyme, ISIS, Janssen, Kowa, Merck, Novartis, Pfizer, Regeneron, and Sanofi.

References


Key Words: cardiovascular disease ■ cholesterol ■ diabetes ■ guidelines ■ low-density-lipoprotein ■ risk ■ treatment
The 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol: Questions, Questions

Henry N. Ginsberg

Circ Res. 2014;114:761-764
doi: 10.1161/CIRCRESAHA.114.303398

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/114/5/761

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/