Contemporary Evidence-Based Guidelines: Practice Based on the Strongest Evidence

In this issue of Mayo Clinic Proceedings, 2 articles written by 2 different (but overlapping) groups of Mayo Clinic experts (Kullo et al1 and Lopez-Jimenez et al2) provide critiques of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults and the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. These 2 guidelines are hereafter referred to as the 2013 ACC/AHA cholesterol guideline and the 2013 ACC/AHA risk assessment guideline, respectively. Although, Lopez-Jimenez et al2 focus on the 2013 ACC/AHA cholesterol guideline and Kullo et al1 focus on the 2013 ACC/AHA risk assessment guideline, both articles comment on aspects of both 2013 ACC/AHA guidelines. The Mayo Clinic authors also add their own recommendations for clinical practice. The purpose of this editorial is 3-fold: (1) to provide a clear and concise summary of the 2013 ACC/AHA cholesterol guideline (which incorporated recommendations from the 2013 ACC/AHA risk assessment guideline), (2) to address the main criticisms by the 2 Mayo Clinic expert reports, and (3) to comment on the limitations of their recommendations.

The 2013 ACC/AHA cholesterol guideline was first published online ahead of print in November 2013, with the final print version with updated figures published in July 2014. This guideline largely adhered to the contemporary approach to evidence-based guideline development recommended by the Institute of Medicine and was based on a rigorous systematic review of randomized controlled trials (RCTs) with arteriosclerotic cardiovascular disease (ASCVD) outcomes and meta-analyses of those trials. In addition, the 2013 ACC/AHA cholesterol guideline incorporated recommendations from the 2013 ACC/AHA risk assessment guideline, published simultaneously with the 2013 ACC/AHA cholesterol guideline. The 2013 ACC/AHA risk assessment guideline was based on a similarly rigorous review of epidemiologic studies of lifetime ASCVD risk, biomarkers, and noninvasive cardiovascular imaging, in addition to developing new risk prediction equations using contemporary data from 5 National Heart, Lung, and Blood Institute cohort studies. For lifestyle recommendations, the 2013 ACC/AHA cholesterol guideline refers readers to the 2013 ACC/AHA Guideline on Lifestyle Management to Reduce Cardiovascular Risk (published at the same time), which also resulted from a rigorous systematic review of RCTs. The lifestyle recommendations did not receive comment from Kullo et al1 or Lopez-Jimenez et al2 and so are not commented on further in this editorial. Thus, as a result of the rigorous systematic review approach undertaken and the development of new risk prediction equations, the 2013 ACC/AHA cholesterol guideline is not simply an extension of previous Adult Treatment Panel III guidelines.

What the 2013 ACC/AHA Cholesterol Guideline Recommends

Much of the discussion by Lopez-Jimenez et al2 and Kullo et al1 can be better understood by providing an overview of the 2013 ACC/AHA cholesterol recommendations and understanding the strength of the evidence supporting the recommendations. The major recommendations for initiating statin therapy are summarized in the Figure. In brief, the 2013 ACC/AHA cholesterol guideline makes the following major recommendations:

- Lifestyle change is the foundation of ASCVD risk reduction. Statin therapy reduces ASCVD risk in the setting of lifestyle advice. In addition, smoking and obesity should be avoided and blood pressure controlled.
- Strong evidence from RCTs supports the use of moderate- or high-intensity statin therapy in 4 major groups of patients most likely to experience a net ASCVD risk reduction benefit: (1) clinical ASCVD; (2) low-density lipoprotein cholesterol (LDL-C) level of 190 mg/dL or greater (to convert to mmol/L, multiply by 0.0259); (3) diabetes mellitus type 1 or 2 in individuals aged 40 to 75 years with LDL-C levels of 70 to 189 mg/dL; and (4)
FIGURE. Summary of statin therapy initiation recommendations from the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline. (See Figures 3, 4, and 5 in Stone et al1 for more detailed management information.) Assessment of the potential for benefit and risk from statin therapy for atherosclerotic cardiovascular disease (ASCVD) prevention provides the framework for clinical decision making incorporating patient preferences.* Percentage reduction in low-density lipoprotein cholesterol (LDL-C) levels can be used as an indication of response and adherence to therapy but is not in itself a treatment goal.

The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes mellitus (DM). The estimator in this application should be used to inform decision making in primary prevention patients not taking a statin.

Consider moderate-intensity statin therapy as more appropriate in low-risk individuals. For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C levels of 160 mg/dL or greater or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset at younger than 55 years in a first-degree male relative or younger than 65 years in a (continued on next page)
primary prevention with an estimated 7.5% or greater 10-year ASCVD risk (using the Pooled Cohort Equations, later herein) in individuals aged 40 to 75 years with LDL-C levels of 70 to 189 mg/dL.

- Moderate evidence supports the use of moderate-intensity statin therapy in primary prevention patients with 5% to less than 7.5% 10-year ASCVD risk, age 40 to 75 years, and LDL-C levels of 70 to 189 mg/dL.

- Statin therapy may also be used in other patients, but there is little or no RCT evidence to determine the net benefit.

The decision to initiate statin therapy for primary prevention should be individualized as part of a clinician-patient discussion, which includes consideration of the potential for an ASCVD risk reduction benefit based on estimation of 10-year ASCVD risk and intensity of statin therapy, adverse effects, drug-drug interactions, and patient preferences.

The Pooled Cohort Equations developed by the 2013 ACC/AHA risk assessment guideline should be used to estimate 10-year risk of nonfatal and fatal myocardial infarction and stroke for most primary prevention patients with LDL-C 70-189 mg/dL. The 10-year ASCVD risk estimate should be used as the starting point for clinician-patient discussions.

- In selected individuals, consideration may be given to family history, lifetime risk of ASCVD, high-sensitivity C-reactive protein (CRP) level, coronary artery calcium (CAC) level, and ankle-brachial index (ABI) because these factors may provide additional information about ASCVD risk.

- There are 2 groups of patients who do not seem to benefit from initiation of statin therapy: those with heart failure and those undergoing maintenance hemodialysis. Continuation of existing statin therapy in these patients should be individualized.

- Patients and their physicians should regularly monitor adherence to lifestyle and drug therapy. Reductions in LDL-C levels from baseline can provide a guide for the adequacy of therapy (≥50% for high-intensity statins and 30%–50% for moderate-intensity statins; an LDL-C level <100 mg/dL may be used if the baseline LDL-C level is unknown).

- Nonstatin therapy may be considered for additional LDL-C level lowering in high-risk patients, such as those with genetic hypercholesterolemia, clinical ASCVD, or diabetes, who cannot tolerate the recommended intensity of statin therapy.

The major recommendations for initiating statin therapy are summarized in the Figure. Because statin therapy was found to reduce ASCVD risk across a range of LDL-C levels greater than 70 mg/dL in secondary and primary prevention, there was not sufficient evidence to support the continued use of the LDL-C threshold for drug treatment initiation. Neither were any RCTs with ASCVD outcomes identified that titrated therapy to specific LDL-C or non–high-density lipoprotein cholesterol (HDL-C) goals.

The most extensive evidence supported the use of statins to reduce ASCVD risk. A few RCTs used nonstatins as monotherapy in restricted populations (eg, men only, coronary heart disease only) and statin-nonstatin combination
therapy vs placebo or active control. There was little RCT evidence that nonstatin therapy, when added to statin therapy, further reduced ASCVD risk and no evidence that combination statin/nonstatin therapy was equivalent or superior to high-intensity statin therapy in terms of ASCVD risk reduction or safety.

**Criticisms by the Mayo Clinic Experts**

First, note that the reports developed by the Mayo Clinic authors reflect expert consensus rather than a rigorous systematic review process. Second, the main criticisms of the 2 Mayo expert groups can be more clearly understood by referring to the Figure. The 2013 ACC/AHA cholesterol guideline recommendations are color-coded based on the strength of the recommendation (which reflects the level of evidence): green is class I (strong evidence, “should do”) and yellow is class Ila (moderate evidence, “reasonable to do”). Note that for primary prevention, selected patients in categories in which there is no RCT evidence (white boxes) may still be considered for statin therapy. Orange represents class Iib evidence (expert recommendation, “may consider”).

The Mayo expert group of Kullo et al focused on risk assessment in primary prevention. They consider the 2013 ACC/AHA risk assessment and cholesterol guidelines to be “a valuable framework” and make a series of expert recommendations for the use of biomarkers and noninvasive testing to further refine risk estimation in primary prevention. They propose a variety of tests in addition to the 6 characteristics recommended in the 2013 ACC/AHA risk assessment (listed previously herein).

Kullo et al also provide a helpful tabulation of the availability and cost of several biomarkers and noninvasive tests that clinicians may find useful when considering the value of these tests in selected patients. To put both sets of recommendations in context, note that none of the studies reviewed either for the 2013 ACC/AHA risk assessment guideline or by Kullo et al determined the incremental information added by any test to the new 10-year ASCVD risk cutoff points (which include stroke as well as coronary heart disease) recommended by the 2013 ACC/AHA cholesterol guideline. Therefore, the value of any of these tests for guiding the decision to initiate statin therapy is unknown. Future updates of the ACC/AHA prevention guidelines will no doubt address this issue on the basis of new data.

The Mayo Clinic Task Force of Lopez-Jimenez et al supports several aspects of the 2013 ACC/AHA guidelines, including statins as first-line agents for ASCVD risk reduction, the 4 groups of patients most likely to benefit from statin therapy, and the shared decision-making process for primary prevention. They also agreed that there is insufficient evidence at this time to support the use of LDL-C or non–HDL-C as goals.

Collectively, Kullo et al and Lopez-Jimenez et al provide numerous criticisms and recommendations, of which the major ones are commented on in the following subsections. The criticisms and recommendations are attributed to the specific groups of authors, as appropriate.

**Criticism 1: Need to Consider Non-RCT Evidence.** The 2013 ACC/AHA cholesterol guideline developers, which included this author, who was vice chair, well understood that the RCTs reviewed did not address all clinical questions, as noted by Lopez-Jimenez et al. However, we, the 2013 ACC/AHA cholesterol guideline developers, considered it important to minimize expert opinion and instead strongly emphasize the groups of patients likely to experience a net benefit from cholesterol treatment to reduce ASCVD risk with a good margin of safety. We were aware of a variety other treatments thought to be beneficial on the basis of observational studies that were subsequently shown to provide no additional benefit, and so we elected a more cautious approach to expert recommendations without a basis in RCT evidence. The RCTs that have failed to demonstrate a benefit include those with niacin for alterations beyond LDL-C level, postmenopausal hormone therapy, torcetrapib to raise HDL-C levels, and antioxidant and folic acid/B vitamins among others.

**Criticism 2: Trial of Lifestyle Changes Before Starting Statin Therapy.** Lopez-Jimenez et al propose that 10-year ASCVD risk be recalculated based on risk factors after lifestyle changes and that the decision to initiate statin therapy be based on the new recalculated level of risk. The epidemiologists in the Risk Assessment Panel do not consider this an appropriate use of the Pooled Cohort Equations. Atherosclerosis is a process of many decades, and a few months of improved...
lifestyle risk factors will not influence the estimate of 10-year or long-term ASCVD risk. Long-term adherence to healthy lifestyle habits is desirable for many reasons, but most individuals are unable to maintain lifestyle changes long-term without participation in a structured program. Moreover, RCTs have also shown that a low-fat dietary pattern does not decrease ASCVD events in women aged 50 to 79 years, nor does an intensive diet, physical activity, and weight-loss intervention reduce CVD events over 11 years in patients with diabetes. Notably, the 2013 ACC/AHA cholesterol panel found that statin therapy reduced ASCVD risk in the setting of lifestyle advice delivered in all the trials and agreed that smoking cessation, blood pressure control, and prevention of obesity are important components of ASCVD prevention.

Criticism 3: Use Non-HDL-C and LDL-C Levels as Criteria for Treatment Initiation. Lopez-Jimenez et al recommend using non-HDL-C and LDL-C levels to guide treatment initiation. In contrast, the 2013 ACC/AHA cholesterol guideline recommends treatment on the basis of the risk of ASCVD because statin therapy was shown to reduce ASCVD events regardless of LDL-C levels greater than 70 mg/dL in secondary and primary prevention. Except for the results of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, the RCTs reviewed for the 2013 ACC/AHA cholesterol guideline did not report on-treatment non-HDL-C levels, so no comment was made.

Lopez-Jimenez et al made a recommendation to initiate statin therapy for primary prevention only for LDL-C levels of 100 mg/dL or greater. This is not entirely discordant with the 2013 ACC/AHA cholesterol guideline recommendation for a clinician-patient discussion that includes many factors. Patients with LDL-C values of 70 to 99 mg/dL deserve consideration of the potential for an ASCVD risk reduction benefit based on their estimated 10-year ASCVD risk, and additional factors could be considered, including a CRP concentration of at least 2 mg/L (to convert to nmol/L, multiply by 9.524) (which, along with an LDL-C level < 130 mg/dL [median, 108 mg/dL], was an eligibility criterion in JUPITER), family history of premature ASCVD, CAC level, -ABI, and lifetime ASCVD risk. In older patients whose age is the primary contributor to ASCVD risk, a calcium score could be particularly useful, with the caveats that none of these 6 factors has been evaluated in the setting of the lower treatment thresholds using the 10-year risk of coronary and stroke events.

Criticism 4: Do Not Initiate Statin Therapy in Patients With Diabetes Unless 10-Year ASCVD Risk Is 5% or Greater. Lopez-Jimenez et al considered there to be a lack of clinical trial evidence to support statin treatment in individuals with diabetes mellitus type 1 or 2 aged 21 to 75 years unless 10-year ASCVD risk was 5% or greater. In contrast, the 2013 ACC/AHA cholesterol guideline made a strong recommendation for moderate-intensity statin dosing in individuals with diabetes mellitus aged 40 to 75 years, and a high-intensity statin is reasonable to consider when 10-year ASCVD risk is 7.5% or greater. Note that the Pooled Cohort Equations predict risk only in individuals aged 40 to 79 years, so the 2013 ACC/AHA cholesterol guideline simplified the clinical recommendation. In addition, the lifetime risk of ASCVD in individuals with types 1 and 2 diabetes mellitus is high. Thus, the 2013 ACC/AHA cholesterol guideline recommendation is more consistent with a later Lopez-Jimenez et al recommendation to use statins for primary prevention on the basis of high lifetime ASCVD risk. The 2 Lopez-Jimenez et al recommendations are inconsistent: wait to treat cholesterol in individuals with diabetes until 10-year ASCVD risk reaches 5%, but use statins for primary prevention based on lifetime ASCVD risk. Note that lifestyle modification is recommended as the first-line response for individuals at low 10-year but high lifetime ASCVD risk by the 2013 ACC/AHA cholesterol guideline. Kullo et al, and Lopez-Jimenez et al.


Note that an earlier non-peer-reviewed commentary critical of the accuracy of the Pooled Cohort Equations has not been supported in a
subsequent analysis of contemporary data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. This later study found that the Pooled Cohort Equations had very good calibration and discrimination for ASCVD events in the population-based REGARDS cohort of 30,000 white and black US adults. Thus, the Pooled Cohort Equations should be considered as appropriate for use in the general US population.

After reviewing the epidemiologic evidence for a variety of biomarkers (including apolipoprotein B, creatinine and glomerular filtration rate, microalbuminuria, carotid intimal medial thickness, and cardiorespiratory fitness), the 2013 ACC/AHA risk assessment guideline found evidence that only family history, CRP level, CAC level, and ABI improved risk prediction over traditional risk factors in terms of discrimination, calibration, and reclassification. Unfortunately, no data were available to determine whether these 4 risk factors improved risk prediction using the new 5% and 7.5% 10-year risk of nonfatal and fatal stroke as well as myocardial infarction. Clearly, this is a direction for future research. In the absence of such data, however, there does not seem to be compelling evidence for the general use of additional tests. Indeed, there are significant limitations in terms of availability and costs, as indicated by Kullo et al.

**Criticism 6: Treat Groups of Patients at Increased ASCVD Risk Who Were Not Included in RCTs.** Lopez-Jimenez et al recommend initiating statin therapy in patients with rheumatologic inflammatory diseases or human immunodeficiency virus infection with 5% or greater 10-year ASCVD risk. This is reasonable and consistent with the 2013 ACC/AHA cholesterol guideline, where moderate-intensity statins provide a net ASCVD risk reduction benefit in individuals with 5% or greater 10-year ASCVD risk. Unfortunately, because the magnitude of ASCVD event reduction and the rates of statin-related adverse events are unknown for groups of patients excluded from RCTs, the net benefit for ASCVD risk is unknown. Supplemental material in the 2013 ACC/AHA cholesterol guideline full report discusses treatment of other high-risk patient groups. Lopez-Jimenez et al additionally provide a useful discussion of choosing drug regimens to enhance the safety of statin therapy in these populations.

**Conclusion**

The 2013 ACC/AHA cholesterol and risk assessment guidelines, Kullo et al, and Lopez-Jimenez et al, have many important areas of agreement, including the importance of statin therapy for reducing ASCVD risk in individuals most likely to benefit. All agree that more research is needed to more accurately predict ASCVD risk and that more RCTs are needed to guide the treatment of individuals who largely have been excluded from RCTs to date, including patients older than 75 years without clinical ASCVD, those infected with human immunodeficiency virus, and other high-risk populations. Ongoing RCTs are evaluating whether a second lipid-modifying drug added to maximally tolerated statin therapy further reduces ASCVD events with an acceptable level of safety. Future ACC/AHA guidelines will provide updated recommendations based on the results of these investigations. In the meantime, clinicians using the 2013 ACC/AHA cholesterol and risk assessment guidelines can feel confident that they are offering their patients evidence-based care strongly grounded in the data available to date.

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Potential Competing Interests: Dr Robinson was the vice chair for the 2013 ACC/AHA cholesterol guideline and a co-author of the 2013 ACC/AHA risk assessment guideline. She has served as the principal investigator for research grants to the institution from Amarin, Amgen, AstraZeneca, Daiichi Sankyo, Genentech/Hoffman La Roche, GlaxoSmithKline, Merck, Regeneron/Sanoﬁ, and Zinfandel/Takeda. Since completion of the guidelines she has served as a consultant to Amgen, Hoffman LaRoche, Merck, Pfizer, and Sanoﬁ.

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**REFERENCES**
