Preventing Atherosclerotic Cardiovascular Disease Using American College of Cardiology and American Heart Association Prevention Guidelines: Some Good News, But Caveats Remain

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It is axiomatic that you can be logical and factual, but if your assessment is incomplete, you can be misled.

That is why it is important to look carefully at papers that comment on the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) cholesterol and risk assessment guidelines and the use of the pooled cohort equations for risk assessment of atherosclerotic cardiovascular disease (ASCVD). An important attribute of the current ACC/AHA cholesterol guidelines is close adherence to the evidence derived from randomized controlled trials (RCTs) or meta-analyses of these RCTs. This approach emanated from important restraints imposed on the guidelines process from the start. A comprehensive literature search was undertaken in response to critical questions chosen by the panel. The literature search of RCTs and meta-analyses of these RCTs was performed by an independent contractor chosen by the National Heart, Lung, and Blood Institute. This contractor, devoid of any conflicts with industry, graded the papers that the panel could consider for quality. Poor-quality data were not considered, and the accumulated evidence was compiled into evidence tables. The cholesterol guideline recommendations were made from those tables. Importantly, >50% of the large and diverse guidelines panel reported no conflicts during this process, which focused on evidence over expert opinion.

A criticism of the method of risk assessment that surfaced after the ACC/AHA prevention guidelines were published was that the pooled cohort equations used by the ASCVD risk estimator are inaccurate for some multiethnic populations. The concern is whether this requires recalibration if a decision point of 7.5% ASCVD risk is used to determine automatic statin assignment in lower risk patients for primary prevention.\(^3\)\(^-\)\(^5\) In contrast, the usefulness of the 7.5% ASCVD 10-year risk cutoff is that investigators can look at the utility of this cutoff in predictions of ASCVD on individual and population bases.

In this issue, the Journal of the American Heart Association published 2 papers that support the guidance provided by the ACC/AHA guidelines. In addition, they provide insights useful for addressing the concern noted above. Egan et al used National Health and Nutrition Examination Survey (NHANES) data to determine the impact of treating US adults based on their estimated 10-year ASCVD risk.\(^6\) The authors determined that treating statin-eligible untreated adults could achieve more than three-quarters of the of the Healthy People 2020 ASCVD prevention goal. This benefit was accrued by treating all adults with 10-year ASCVD risk $\geq$7.5%. Cho et al looked at the application of the ACC/AHA cholesterol guidelines to 1246 asymptomatic middle-aged primary prevention Korean participants who underwent repeated coronary artery calcium score measurements during routine health examinations.\(^7\) They found that more participants were statin eligible as defined by the ACC/AHA guidelines (54.7%) than by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (20.5%).\(^8\) They then judged the performance of both guidelines by their ability to predict persons at increased risk for coronary artery calcium score progression. Participants considered statin eligible under the ACC/AHA guidelines had a significantly higher odds ratio for coronary artery calcium score progression than those considered statin eligible under the ATP III guidelines. Because coronary artery calcium score is indicative of the underlying process of atherosclerosis, the authors noted that their study showed that the method of risk estimation used in the ACC/AHA
guidelines addressed this important indicator of atherosclerotic risk better than the prior ATP III guidelines.

To put this in perspective, the following caveats are noted. It is important to emphasize that the 2013 ACC/AHA cholesterol guidelines did not mandate that all lower risk primary prevention patients with ≥7.5% ASCVD 10-year risk receive a statin. The threshold of ≥7.5% was intended to start the risk discussion and was useful in epidemiological studies for determining the potential value of statin treatment in such patients. Pencina and colleagues indicated that, based on the guidelines determination of 10-year ASCVD risk ≥7.5%, the guidelines could be projected to save 450 000 lives.\(^9\) They also correctly noted, however, that the guidelines did not equate an ASCVD risk of ≥7.5% with automatic statin assignment; the guidelines recommended a clinician–patient risk discussion (CPRD) first.

The recommendation of a CPRD before statin prescription in lower risk primary care is crucial because it helps address the potential for inaccuracy of global risk estimation. The guidelines are based on data from 3 solely primary prevention RCTs to support treating at a 10-year ASCVD risk of ≥7.5%. There was benefit down to 5%, but the guidelines panel chose the higher cutoff so that patients who had a lower risk due to ASCVD risk overestimation would still be in a statin-benefit risk group. Consequently, the guidelines advise that statin treatment should be individualized within the context of a risk discussion enabling joint decision making. The CPRD was described in the table of recommendations as well as in the explanatory text and accompanying figures. This description addresses control of other ASCVD risk factors and the need for optimal lifestyle, the potential for benefit of statin therapy versus the potential for adverse effects and drug–drug interactions, and the inclusion of informed patient preference in final decision making. Further papers described techniques for making the CPRD truly effective.\(^{10,11}\)

It should be pointed out that an ASCVD risk cutoff of 5% was not chosen to initiate statin therapy despite evidence from solely primary prevention trials reviewed by the cholesterol guidelines panel to support statin treatment at this level. This decision allows for the group with ASCVD risk in the range of 5% to 7.5%, whose exact risk estimation is less precise, to still fall within a statin-benefit zone. Furthermore, the ASCVD risk estimator provided guidance for those whose race designation was neither white nor black. The risk estimator stated that “these estimates may underestimate the 10-year and lifetime risks for persons from some race/ethnic groups, especially American Indians, some Asian Americans (eg, of South Asian ancestry) and some Hispanics (eg, Puerto Ricans) and may overestimate risk for others, including some Asian Americans (eg, of east Asian ancestry) and some Hispanics (eg, Mexican-Americans)” (http://tools.acc.org/ASCVD-Risk-Estimator/). This indicates that in the CPRD, some patients might be encouraged to start a statin at risk <7.5%, and some might have statin therapy delayed until there is a higher risk. The idea was to confine the RCT evidence with clinical judgment based on clinician assessment of the patient and inclusion of the patient’s preference for treatment.

Moreover, new data reported since the guidelines were released continue to support statin assignment in lower risk primary prevention. In the HOPE-3 trial, a global cohort of participants with an ASCVD risk of 8.7% (or 10% if including revascularization as an end point) who were treated with a moderate-intensity statin (rosuvastatin 10 mg/day) showed a significant reduction in ASCVD events compared with those treated with placebo.\(^12\) Those assigned to rosuvastatin 10 mg/day also did not show an increased incidence of new-onset diabetes mellitus, which had been seen previously when higher intensity statins were used.\(^13\)

Finally, additional studies have confirmed that patients who are eligible for statin use under the ACC/AHA guidelines are more likely to have coronary atherosclerosis, as determined by computed tomography angiography, than those selected by the ATP III guidelines.\(^14,15\) Using a contemporary multiethnic population from the Dallas Heart Study, Paixao et al showed that selection for statin treatment based on the ACC/AHA guidelines, over and above prediction for treatment by the ATP III guidelines, is efficient with a number needed to treat of <30.\(^16\) Moreover, critical observers have noted that the ACC/AHA guidelines cutoff of 7.5% is cost-effective, with benefit seen at even lower 10-year risk estimates.\(^17\)

Two natural history studies indicated that the risk estimator did a reasonably good job for those with intermediate-risk scores between 6% and 10%.\(^15,18\) Although overestimation of risk is concerning, it is important to note that overestimation of risk in the low-risk (<5%) and high-risk (>10%) groups is unlikely to affect the decision to withhold or to treat with a statin, respectively. For those for whom the risk decision was uncertain (5–7.5%), the guidelines recommended that family history of premature ASCVD; coronary artery calcium score ≥300 Agatston units or ≥75th percentile based on age, race, and sex; ankle brachial index <0.9; or high-sensitivity C-reactive protein ≥2.0 mg/L could be used to inform clinical judgment because they increased the net reclassification. The cholesterol guidelines panel also indicated that there was evidence for using low-density lipoprotein cholesterol ≥160 mg/dL and/or a strikingly increased lifetime risk in younger persons with low short-term risk.

The CPRD, as recommended by the guidelines, is crucial if we are to focus prevention efforts on those likely to benefit. Those clinicians who engage in these conversations can use the information presented in these 2 papers to inform their decisions on statin assignment in those with lower risk primary prevention. Nonetheless, for patients or clinicians
who are concerned about uncertainty after a global risk estimation is made, a coronary artery calcium score could be especially useful, particularly if the number of coronary arteries with calcified plaque—indicating increasingly “diffuse” multivessel subclinical atherosclerosis—is used to enhance the prediction of coronary heart disease and cardiovascular disease events.19

Disclosures

Dr Stone was the lead author for the 2013 ACC/AHA cholesterol guidelines and served as a member of the 2013 ACC/AHA risk assessment panel.

References


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