A Perspective on the New American College of Cardiology/American Heart Association Guidelines for Cardiovascular Risk Assessment

Iftikhar J. Kullo, MD; Jorge F. Trejo-Gutierrez, MD, MHS; Francisco Lopez-Jimenez, MD, MSc; Randal J. Thomas, MD, MSc; Thomas G. Allison, PhD, MPH; Sharon L. Mulvagh, MD; Adelaide M. Arruda-Olson, MD, PhD; Sharonne N. Hayes, MD; Amy W. Pollak, MD; Stephen L. Kopecky, MD; and R. Todd Hurst, MD

Abstract

The recently published American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for cardiovascular risk assessment provide equations to estimate the 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) risk in African Americans and non-Hispanic whites, include stroke as an adverse cardiovascular outcome, and emphasize shared decision making. The guidelines provide a valuable framework that can be adapted on the basis of clinical judgment and individual/institutional expertise. In this review, we provide a perspective on the new guidelines, highlighting what is new, what is controversial, and potential adaptations. We recommend obtaining family history of ASCVD at the time of estimating ASCVD risk and consideration of imaging to assess subclinical disease burden in patients at intermediate risk. In addition to the adjuncts for ASCVD risk estimation recommended in the guidelines, measures that may be useful in refining risk estimates include carotid ultrasonography, aortic pulse wave velocity, and serum lipoprotein(a) levels. Finally, we stress the need for research efforts to improve assessment of ASCVD risk given the suboptimal performance of available risk algorithms and suggest potential future directions in this regard.

Assessment of cardiovascular risk is a necessary first step to target therapy toward patients most likely to benefit. It has become evident that baseline atherosclerotic cardiovascular disease (ASCVD) risk is a better predictor of treatment benefit than the degree to which low-density lipoprotein cholesterol (LDL-C) is lowered.1,2 The recently published American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for cholesterol lowering emphasize that the intensity of risk factor management should match the risk for adverse ASCVD events. In contrast, previous guidelines have favored achieving target LDL-C levels based on the magnitude of estimated cardiovascular risk.4

The most recent ACC/AHA guidelines include a new ASCVD risk calculator for use in the clinical setting and address questions relevant to risk assessment using critical review of the available literature. The document includes a disclaimer that the recommendations are not a substitute for clinical judgment and that decisions about care must be individualized for each patient. The guidelines provide a valuable framework that can be adapted on the basis of clinical judgment and individual/institutional expertise. In this review, we provide a perspective on the new guidelines for assessing risk of ASCVD events in adults without known disease, highlighting what is new, what is controversial, and potential future directions (Table 1).

Preventive cardiologists from throughout the Mayo Foundation contributed to this document. A core writing group reviewed the guidelines and existing literature and made modifications based on foundation-wide expertise in cardiovascular risk assessment including imaging, circulating biomarkers, and genetic epidemiology. Input to the draft was provided by each author, and after several revisions, the draft was circulated to a
wider group. Feedback was incorporated iteratively until consensus was reached.

**WHAT IS NEW IN THE GUIDELINES?**

**New Equation for Estimating 10-Year Risk of ASCVD Events**
Population-based studies have identified factors associated with incident adverse cardiovascular events. These risk factors have been included in multivariate risk scores for not only coronary heart disease (CHD) but also stroke, peripheral arterial disease, and heart failure as well as composite cardiovascular disease end points. Most of these risk calculators estimate a patient’s probability of having a vascular event over 5 to 10 years. The commonly used risk scores include the Framingham CHD risk score, its derivative, the Adult Treatment Panel III (ATP-III) risk assessment profile, and the European Systematic Coronary Risk Evaluation (SCORE) algorithm for ASCVD death. These risk equations were derived from cohorts that were established decades ago and had limited ethnic diversity.

The new ASCVD risk calculator was developed from several relatively recently established population-based cohorts that included African American or non-Hispanic white participants with at least 12 years of follow-up and with adjudicated end points for fatal or nonfatal myocardial infarction and stroke (Figure 1). The cohorts include the ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham and Framingham Offspring study cohorts. The strongest predictors of the 10-year risk of “hard” ASCVD events (defined as first occurrence of nonfatal myocardial infarction or CHD death or fatal or nonfatal stroke) were age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, blood pressure treatment status, diabetes, and current smoking status. An “app” has been developed that can be used online or on a mobile device to estimate a patient’s 10-year ASCVD risk.

**Recommended Adjuncts to Refine Risk Estimates**
Additional variables were tested for inclusion in the model if they were available in the databases and could be evaluated on the basis of at least 10 years of follow-up, using the framework suggested by Hlatky et al. These variables included diastolic blood pressure, family history of ASCVD, moderate or severe chronic kidney disease (defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m²), and body mass index (continuous or categorical). None of these variables significantly improved prediction of 10-year ASCVD events when added to the final base models. The guidelines recommend 4 markers that may be considered by clinicians and patients as adjuncts for refining risk estimates—family history of ASCVD, high-sensitivity C-reactive protein, ankle-brachial index, and coronary artery calcium scoring.

**Focus on Hard ASCVD Events**
Compared with earlier guidelines, the new risk assessment guidelines attempt to take into account that atherosclerosis is a chronic disease that affects multiple vascular beds. Risk is estimated for “hard” ASCVD events including stroke, myocardial infarction, and death due to stroke or myocardial infarction. “Soft” end points such as those that might be influenced by physician preferences (eg, revascularization...
procedures) and end points that are often difficult to ascertain reliably (eg, angina and heart failure), were not included.

Recommendations for Estimating Lifetime Risk
The ACC/AHA guidelines have a primary focus on 10-year risk of ASCVD events and a secondary focus on assessing lifetime risk for adults 20 to 59 years old who are not at high short-term risk. Beginning at age 40, formal estimation of the 10-year risk for ASCVD is recommended. Long-term or lifetime risk estimation is recommended for all persons who are 20 to 39 years of age and for those 40 to 59 years old who are at low 10-year risk (<7.5%). At present, there is insufficient evidence for initiating pharmacological therapy on the basis of lifetime risk assessment.

### TABLE 1. Summary of ACC/AHA Recommendations for ASCVD Risk Assessment

<table>
<thead>
<tr>
<th>ACC/AHA recommendation</th>
<th>NHLBI grade</th>
<th>ACC/AHA LOE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The race- and sex-specific Pooled Cohort equations to predict 10-y risk for a first hard ASCVD event should be used in non-Hispanic African Americans and non-Hispanic whites aged 40-79 y</td>
<td>B (moderate)</td>
<td>B</td>
<td>Along with the use of the ASCVD risk calculator, family history of ASCVD should be obtained as first step in estimating risk of ASCVD.</td>
</tr>
<tr>
<td>2. Use of the sex-specific Pooled Cohort equations for non-Hispanic whites may be considered when estimating risk in patients from populations other than African Americans and non-Hispanic whites</td>
<td>E (expert opinion)</td>
<td>C</td>
<td>The accuracy of the ASCVD risk calculator is not established for Asian and Hispanic Americans. Among Asian Americans, those from the Indian subcontinent may be at higher risk than other ethnic groups.</td>
</tr>
<tr>
<td>3. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making</td>
<td>E (expert opinion)</td>
<td>B</td>
<td>It is reasonable to consider additional modalities as adjuncts for risk stratification. See Tables 2 and 3 for further recommendations.</td>
</tr>
<tr>
<td>4. The contribution to risk assessment for a first ASCVD event using ApoB, CKD, albuminuria, or CRF is uncertain at present</td>
<td>N (no recommendation for or against)</td>
<td>NA</td>
<td>Assessment of CRF may be useful in prescribing an exercise regimen for patients. Although CRF has limited sensitivity for detecting early coronary artery disease, it provides prognostic information independent of conventional risk factors.</td>
</tr>
<tr>
<td>5. CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event</td>
<td>N (no recommendation for or against)</td>
<td>B</td>
<td>Selective use of carotid ultrasonography for plaque detection and measurement of common CIMT is reasonable to consider as an adjunct for risk estimation; the test should be performed following standardized protocols and established guidelines.</td>
</tr>
<tr>
<td>6. It is reasonable to assess traditional ASCVD risk factors every 4-6 y in adults aged 20-79 y who are free from ASCVD and to estimate 10-y ASCVD risk every 4-6 y in adults aged 40-79 y without ASCVD</td>
<td>B (moderate)</td>
<td>B</td>
<td>Estimates of lifetime risk consider risks factors present at age 50 and therefore do not truly reflect the lifetime risk of those younger than 50 y, as their risk factors will likely change over time.</td>
</tr>
<tr>
<td>7. Assessing 30-y or lifetime ASCVD risk based on traditional risk factors may be considered in adults aged 20-59 y without ASCVD who are not at high short-term risk</td>
<td>C (weak)</td>
<td>C</td>
<td>30-y or lifetime ASCVD risk estimates should be used primarily to motivate patients regarding lifestyle changes but may also inform decisions related to statin therapy, particularly in younger individuals.</td>
</tr>
</tbody>
</table>

*ABI = ankle-brachial index; ACC = American College of Cardiology; AHA = American Heart Association; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CIMT = carotid intima-media thickness; CKD = chronic kidney disease; COR = class of recommendation; CRF = cardiorespiratory fitness; hs-CRP = high-sensitivity C-reactive protein; LOE = level of evidence; NA = not applicable; NHLBI = National Heart, Lung, and Blood Institute.

*These are expert statements not necessarily based on systematic review of evidence.
but such information may be useful in motivating younger individuals to make lifestyle changes and healthy choices, including regular physical activity, healthy dietary patterns, and smoking cessation.

**Emphasis on Shared Decision Making**

The emphasis on shared decision making is an important new feature of the guidelines. The document encourages discussion of the patient’s risk for ASCVD and potential reduction of risk with drug therapy, adverse effects from statins, cost of drug therapy, and patient preferences related to preventive measures. The document acknowledges that no data are available to document that such an approach reduces adverse cardiovascular outcomes. Risk assessment combined with counseling has been associated with favorable but modest changes in patient knowledge and intention to change and with physician prescribing behavior and risk factor control.\(^\text{22,23}\)

**LIMITATIONS AND CONTROVERSIAL AREAS**

**Relatively Small African American Cohorts**

Inclusion of race-specific estimates of ASCVD risk is a welcome new feature of the guidelines. However, in the cohorts used for deriving ASCVD risk equations, there are nearly 5 times more white individuals than African American individuals (Figure 1). Data from additional African American cohorts may be needed to increase the precision of risk estimates in African Americans.

**Lack of Multivariate Equations for Asian and Hispanic Americans**

Sufficient data were not available for additional race/ethnic groups (Asians and Hispanics) to allow development of separate risk equations. When compared with non-Hispanic whites, the risk for ASCVD differs in Hispanic American,\(^\text{24}\) Asian American,\(^\text{25}\) and American Indian populations. For example, there is considerable heterogeneity in ASCVD risk among Asian populations, and those from the Indian subcontinent are considered to be at higher risk.\(^\text{25}\) Given the absence of data, the guidelines recommend the use of equations derived from non-Hispanic whites in these ethnic groups, cautioning that the resulting risk estimates may be less accurate.

**Variable Performance of the ASCVD Risk Calculator in Other Cohorts**

Subsequent to the publication of the guidelines, investigators have tested the performance of the ASCVD calculator in several cohorts. In 2 large cohorts of nurses and physicians, respectively, the ASCVD risk calculator performed suboptimally in terms of accuracy and discrimination,\(^\text{26}\) overestimating risk by up to 100%. However, individuals in these cohorts were likely to engage
in healthy lifestyles and also to be taking lipid-
and blood pressure—lowering medications. In a
randomly sampled contemporary cohort of
30,239 adults from geographically diverse re-
gions of the United States, 10,997 were eligible
for statin drugs on the basis of the recent guide-
lines; observed and 5-year ASCVD risks predicted
using the ASCVD risk calculator were similar,
with moderate to good discrimination. Kavousi
et al applied the ACC/AHA, the ATP-III, and
the European Society of Cardiology guidelines
to a Dutch cohort of 4854 participants aged 55
years or older who were recruited between
1997 and 2001. The risk equations provided
modest discrimination; for example, in men, us-
ing the ASCVD risk calculator, the C statistic was
0.67 for hard ASCVD events, 0.67 for hard CHD
events, and 0.76 for ASCVD mortality. These
studies highlight that the ASCVD risk equations
may need to be recalibrated when used in non-
US populations as well as the need for additional
validation of the ASCVD risk equations.

### Adjunctive Measures for Risk Stratification

Although an LDL-C level 160 to 189 mg/dL and
a relatively high lifetime ASCVD risk can help in
deciding whether to start statin therapy, 4 mea-
sures are recommended by the guidelines for
use when there is uncertainty about ASCVD
risk even after the risk calculator is used
(Table 2). The following caveats should be
considered when using these adjunctive mea-
sures for cardiovascular risk estimation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Evidence</th>
<th>Threshold</th>
<th>Actionable next steps</th>
<th>Availability</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of ASCVD</td>
<td>Multiple studies have shown family history to be an independent predictor of cardiovascular risk</td>
<td>History of ASCVD in first-degree relatives: male relatives aged &lt;55 y or female relatives aged &lt;65 y</td>
<td>Shared decision making regarding statin initiation and dose. Screening of first-degree relatives</td>
<td>There is considerable variability in obtaining and documenting family history of ASCVD</td>
<td>Free</td>
</tr>
<tr>
<td>CAC</td>
<td>Increased CAC is associated with adverse outcomes, and CAC scoring leads to considerable reclassification of risk. Among available noninvasive tests, CAC provides the most incremental information in individuals at intermediate risk</td>
<td>Scores &gt;300 Agatston units or &gt;75th percentile for age and sex are considered abnormal. NRI = 23% for 5-y risk in intermediate-risk individuals</td>
<td>Shared decision making regarding statin initiation and dose. Serial measurements are not recommended</td>
<td>Widely available</td>
<td>$512 $55b</td>
</tr>
<tr>
<td>ABI</td>
<td>Associated with CHD risk and leads to considerable reclassification; among men, the effect is to down-classify high-risk men; among women, the effect is to up-classify low-risk women</td>
<td>An ABI &lt;0.9 is considered abnormal; high ABI (&gt;1.4) is also associated with increased risk</td>
<td>Shared decision making regarding statin initiation and dose. Serial measurements are not indicated</td>
<td>Widely available</td>
<td>$559 $99b</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>Multiple studies found hs-CRP to be associated with adverse ASCVD outcomes</td>
<td>Levels &gt;2 mg/L are considered to be elevated. hs-CRP is associated with other risk factors such as obesity, and its predictive value diminishes after adjustment for known risk factors</td>
<td>Lifestyle changes (diet, exercise, and weight loss) reduce levels. Individuals with hs-CRP levels &gt;2 mg/L, LDL-C levels &lt;130 mg/dL, and no history of ASCVD or diabetes benefited from statin medication in the JUPITER study</td>
<td>Widely available</td>
<td>$76 $17b</td>
</tr>
</tbody>
</table>

*ABI = ankle-brachial index; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; hs-CRP = high-sensitivity C-reactive protein; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; NRI = net reclassification index.

bMedicare reimbursement.
missing. Although additional studies are needed to establish the extent to which family history reclassifies risk, family history is meant to be routinely obtained in the clinical setting and will be useful as a supplement to the 10-year risk estimate. Increased awareness and documentation of family history of cancer and cardiovascular diseases are needed, as proposed in the Centers for Disease Control and Prevention’s Family History Public Health Initiative.31 Furthermore, documentation of family history will be necessary to be compliant with meaningful use criteria for electronic medical records.

Coronary Artery Calcium. Coronary artery calcium is considered to be the most useful of the current adjunctive measures to improve risk assessment among individuals who are at intermediate risk according to the ASCVD risk calculator. Uncertainty as to how CAC score relates to the 10-year risk of ASCVD and the limited follow-up in available cohorts that have had measurement of CAC make it a challenging to adjust ASCVD risk estimates on the basis of the CAC score.

Ankle-Brachial Index. Although noninvasive and inexpensive, the ABI is not a sensitive measure of lower extremity arterial disease. Sensitivity can be increased by measuring ABIs after exercise, but this requires a treadmill exercise test with electrocardiographic monitoring. Furthermore, the ABI is lower in women and African Americans,32 and sex- and race-specific cutoffs for defining an abnormal ABI remain to be established. In patients with diabetes, the ABI can be elevated because of medial arterial calcification. Finally, the ABI may be useful only in older persons, most of whom would already have been identified as being at higher risk by the ASCVD risk calculator.

High-Sensitivity C-Reactive Protein. The incremental predictive value of hs-CRP remains unclear.33-39 Also controversial is whether baseline hs-CRP levels predict response to statin therapy.40 Levels differ by race and sex.41 In the clinical setting, elevations in hs-CRP often represent the presence of central obesity, metabolic syndrome, estrogen use, recent infection, or trauma.42 The ordering physician should be aware of these caveats and interpret levels accordingly.

Threshold for Using Statins
The guidelines recommend statin treatment when the 10-year ASCVD risk is 7.5% or higher and consideration of therapy in those with a 10-year risk between 5.0% and less than 7.5%.3 The cut points were based on randomized controlled trials of statins that revealed reduction in adverse ASCVD outcomes at these levels of risk.3 In the analysis by Kavousi et al,28 the ACC/AHA guidelines would recommend statins for nearly all men and two-thirds of women older than 55 years, proportions exceeding those based on the ATP-III or European guidelines. When such large proportions meet the treatment threshold, risk estimation becomes redundant, and a “polypill” or universal treatment strategy comes into play.73 Certainly in making decisions on potentially lifelong therapy in mostly asymptomatic individuals, it is important to take into account patient choices.44 One option may be to expand the intermediate risk category to 5% to 10% or even 5% to 15% and use adjunctive measures to further refine and individualize risk estimates to facilitate shared decision making regarding statin use.45 Such an approach would need further investigation to determine optimal screening algorithms to minimize cost and how to use the results of adjunctive testing to refine risk estimates downward (avoid treatment) or upward (and make a stronger case for treatment).

Using Information From Adjunctive Tests to Modify 10-Year ASCVD Risk
Adjunctive tests might improve risk assessment in individuals at intermediate 10-year ASCVD risk and in those who are at low risk (<5%) but have very high levels of a single risk factor, a strong family history of ASCVD, or chronic inflammatory disease (see 2 illustrative case studies in Figure 2). Because of lack of data, no specific recommendations can be made on how these markers should be used to modify risk estimates. One proposed option is to replace the chronological age in the ASCVD risk calculator with the “vascular age” derived from imaging results.46 Another option is to multiply the baseline ASCVD 10-year risk by the hazard ratio (HR) associated with an abnormal result; for example, having a CAC score greater than the 75th percentile for age and sex could double the risk...
independent of conventional risk factors, so the 10-year risk could be multiplied by 2. The validity of this approach is uncertain because it does not take into account the prevalence of the abnormal risk marker.\(^4\) Finally, whether to downgrade a patient’s risk estimated from the ASCVD calculator on the basis of results from adjunctive testing is another area of controversy.

**Case 1**
A 47-year-old woman undergoing a general medical evaluation is concerned about her atherosclerotic cardiovascular disease (ASCVD) risk given her family history (her mother had ischemic stroke at age 53 years). The patient is asymptomatic and does not have diabetes or hypertension but smokes 5 cigarettes a day. She exercises 2 to 3 times a week on an elliptical machine. Her lipid profile includes a total cholesterol level of 198 mg/dL (to convert to mmol/L, multiply by 0.0259), high-density lipoprotein cholesterol level of 48 mg/dL (to convert to mmol/L, multiply by 0.0259), triglyceride level of 110 mg/dL (to convert to mmol/L, multiply by 0.0113), and calculated low-density lipoprotein level of 128 mg/dL (to convert to mmol/L, multiply by 0.0259). On examination, the patient’s blood pressure is 128/76 mm Hg, and cardiovascular examination findings are unremarkable. Her 10-year ASCVD risk is estimated at 4.1%, but given her family history of stroke, her physician orders carotid ultrasonography to determine the intima-media thickness and presence or absence of plaque. Her common carotid intima-media thickness is greater than the 75th percentile for her age and sex, and she also has focal intimal thickening in both carotid bulbs. After a discussion of her overall risk factor profile, family history, carotid ultrasonographic findings, and the potential benefit, cost, and adverse effects of statins, she opts for moderate-intensity statin therapy. She is also counseled to quit smoking.

**Case 2**
A 56-year-old African American man who is an executive is undergoing general medical evaluation including screening for cardiovascular disease. He is asymptomatic and exercises 4 times a week, 45 minutes each time. He is a nonsmoker and has no hypertension, diabetes, or family history of ASCVD. His cardiovascular examination yields normal findings. His blood pressure is 126/80 mm Hg. His lipid profile includes a total cholesterol level of 165 mg/dL, high-density lipoprotein cholesterol level of 60 mg/dL, triglyceride level of 125 mg/dL, and low-density lipoprotein cholesterol level of 80 mg/dL. His 10-year ASCVD risk is estimated at 6.1%. After a discussion with his preventive cardiologist, the patient remains uncertain whether he wants to take a statin and opts for additional testing. Computed tomography is performed to detect coronary calcium and reveals no evidence of calcified plaque. The patient, in consultation with his preventive cardiologist, decides to withhold statin treatment and to continue his regular exercise program and a low saturated fat diet.

**FIGURE 2. Case studies.**

**Special Populations**
There is insufficient evidence to guide management of certain patient populations who may be at increased risk of adverse cardiovascular outcomes. The additive risk of these conditions independent of conventional risk factors is uncertain. These conditions include systemic inflammatory diseases,\(^3\) a history of gestational diabetes or hypertensive disorders of pregnancy including preeclampsia,\(^4\) chronic kidney disease,\(^5\) and human immunodeficiency virus infection.\(^6\) Imaging studies to assess subclinical disease burden may be useful in these settings to better define ASCVD risk.

**USE OF ADJUNCTIVE MEASURES TO REFINE ESTIMATES OF ASCVD RISK**
We suggest the following adaptation of the ACC/AHA guidelines for the use of adjunctive tests to refine ASCVD risk estimates.

**Family History**
A family history of early-onset ASCVD (defined as occurrence of an ASCVD event in a first-degree male relative before age 55 years or in a first-degree female relative before age 65 years) should be sought from every patient who presents for cardiovascular screening.\(^3\)^\(^0\)-\(^5\)\(^4\) We recommend obtaining a family history concurrent with estimating risk using the ASCVD calculator, rather than later as an adjunctive measure. The presence of a family history of ASCVD is likely to be an important factor in shared decision making regarding lifestyle changes and statin use and also provides an opportunity to detect additional individuals in a family who may be at risk. We recognize the need for additional studies to estimate more precisely the relative risk that results from the presence of a family history of ASCVD. In the absence of robust relative risk estimates for the presence of family history, clinical judgment could be utilized in deciding how much to “adjust” the risk estimated from the ASCVD equation.

**Adjunctive Testing**
We agree that CAC scoring can be used selectively to aid decision making in situations in which the clinician is uncertain about the patient’s short-term and long-term cardiovascular risk. We recommend against the use of CAC...
scores to monitor patients longitudinally, given the unclear implications of change in CAC scores over time and the potential for additional radiation exposure. The potential for missing “soft plaque” in younger individuals (<50 years) should be recognized. Measurement of ABI could be considered for risk stratification selectively, for example in individuals with a family history of early-onset peripheral arterial disease. High-sensitivity C-reactive protein testing may be considered for refining risk estimates, recognizing the limitations stated previously. We recommend that the following additional markers also be considered as adjuncts to risk stratification (Table 3).

### Carotid Ultrasonography

Carotid ultrasonography is a relatively easily available, noninvasive imaging modality that does not involve radiation exposure. The ACC/AHA guidelines recommend against the use of carotid intima-media thickness (IMT) measurement in routine clinical practice for ASCVD risk assessment on the basis of a published meta-analysis that found that common carotid artery (CCA) IMT added only modestly to risk prediction based on traditional risk factors. This meta-analysis included 14 population-based cohorts and 45,828 patients, and found that the addition of CCA IMT was associated with modest improvement in predicting 10-year risk of incident myocardial infarction. The net reclassification index improvement with the addition of CCA IMT was 3.6% for those at intermediate risk. However, the meta-analysis did not study the predictive utility of carotid plaque detection.

Carotid plaque, a manifestation of atherosclerosis, typically forms in the carotid bifurcation and internal carotid artery. Intima-media thickness is measured in the CCA where plaque formation is uncommon. Thus, the two are independent predictors of future ASCVD events, and in observational studies, combining plaque and CCA IMT measurements performed better than CCA IMT measurement alone. A meta-analysis of 11 population-based studies that included 54,336 patients found that carotid plaque, when compared with carotid IMT, was more strongly associated with incident CHD. In the ARIC study of 13,145 participants with a mean follow-up of 15.1 years, using both plaque and CCA IMT measurements led to more accurate risk stratification of 23% of participants when

### Table 3. Additional Tests That May Be Considered for Risk Stratification

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rationale for use</th>
<th>Actionable next steps</th>
<th>Availability</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid Ultrasonography</td>
<td>Noninvasive, no radiation; relatively accessible.</td>
<td>Abnormal findings associated with both MI and stroke</td>
<td>Widely available</td>
<td>$300</td>
</tr>
<tr>
<td>aPWV</td>
<td>Noninvasive, no radiation; relatively accessible.</td>
<td>Associated with both MI and stroke</td>
<td>Widely available</td>
<td>$77</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Elevated levels are associated with increased risk of ASCVD. Mendelian randomization studies reveal that genetic variants that lead to increasing Lp(a) levels are associated with increased risk of ASCVD events, suggesting a causal role (in contrast to hs-CRP, which is a marker, not a causal risk factor).</td>
<td>Shared decision making regarding statin initiation and dose. Screening of first-degree relatives</td>
<td>Widely available</td>
<td>$17</td>
</tr>
</tbody>
</table>

**Abbreviations:** LP(a) = lipoprotein(a); MI = myocardial infarction; NA = not available; NRI = net reclassification index.
added to conventional risk factors.\textsuperscript{57} The consensus statement for use of carotid ultrasonography from the American Society of Echocardiography\textsuperscript{58} recommends screening for the presence of plaque as well as measurement of CCA IMT.

The ACC/AHA guidelines also voiced concern regarding measurement quality. Carotid ultrasonography, however, has been used in the research and clinical settings for nearly 4 decades, and considerable expertise has developed over time. The measurement of CCA IMT has high reproducibility, and consensus recommendations for use of carotid ultrasonography have been available since 2008.\textsuperscript{59,60} The use of established protocols and edge-detection methods for CCA IMT reduces the potential for variability and the concerns related to standardization. Furthermore, appropriate use criteria for carotid ultrasonography are also in place.\textsuperscript{61} We therefore believe it is reasonable to consider selective use of carotid ultrasonography for risk stratification, employing plaque screening and measurement of CCA IMT.

**Aortic Pulse Wave Velocity.** Noninvasive assessment of arterial properties remains limited to blood pressure even though newer techniques such as ultrasonography and tonometry allow measurement of several aspects of arterial function that are relevant for ASCVD risk estimation.\textsuperscript{62} Aortic pulse wave velocity (aPWV), the current gold standard for noninvasive measurement of arterial stiffness, is relatively easily measured by arterial tonometry and is predictive of ASCVD outcomes independent of conventional risk factors.\textsuperscript{62} A recent meta-analysis\textsuperscript{63} illustrated the incremental and independent predictive value of aPWV for predicting adverse ASCVD outcomes. In 17,635 individuals from 16 studies, of whom 1785 (10%) had an ASCVD event, the pooled age- and sex-adjusted HRs per 1-SD increase change in log aPWV were 1.35 (95% CI, 1.22-1.50) for CHD, 1.54 (95% CI, 1.34-1.78) for stroke, and 1.45 (95% CI, 1.30-1.61) for cardiovascular disease. After adjustment for conventional risk factors, aPWV remained a predictor of CHD events (HR, 1.23; 95% CI, 1.11-1.35), stroke (HR, 1.28; 95% CI, 1.16-1.42), and cardiovascular disease events (HR, 1.30; 95% CI, 1.18-1.43). The addition of aPWV improved the reclassification index by 13% in those with intermediate 10-year ASCVD risk.

Measurement of aPWV is highly reproducible, and the methodology is well established.\textsuperscript{62} The European Society of Hypertension recommends measurement of aPWV for assessment of target organ damage in hypertensive individuals.\textsuperscript{64} Knowledge of aPWV may also guide therapy; treatment of hypertension reduces arterial stiffness by reducing distending pressure, although drugs such as angiotensin receptor blockers may act additionally on intrinsic vascular wall properties to reduce stiffness.\textsuperscript{65} Aerobic exercise reduces arterial stiffness, and individuals with increased arterial stiffness should be motivated to start an exercise program.\textsuperscript{66}

**Lipoprotein(a) Levels.** There is considerable evidence that elevated levels of lipoprotein(a) (Lp[a]) are associated with increased risk of CHD. In contrast to several novel risk factors (including hs-CRP), Lp(a) has a causal role in ASCVD, as illustrated in a mendelian randomization study that found that genetic variants that increase Lp(a) levels are associated with adverse ASCVD events.\textsuperscript{67} Elevated levels appear to contribute to familial clustering of CHD\textsuperscript{58} and provide incremental information for risk estimation.\textsuperscript{69} Lipoprotein(a) levels are heritable and do not change considerably over the course of a lifetime. A one-time measurement of Lp(a) should be considered when there is uncertainty in the estimates of 10-year ASCVD risk, particularly in those with a family history of ASCVD. No specific therapy for reduction of Lp(a) levels is available, but lowering of LDL-C level may blunt the risk from elevated Lp(a).\textsuperscript{70} Research is ongoing to identify drugs that selectively lower Lp(a) levels.

**FUTURE DIRECTIONS**

Considerable progress has been made in identifying risk factors for ASCVD and developing multivariate risk prediction equations. Perhaps the most important limitation of risk calculators, including the new ASCVD risk calculator, is that they provide risk estimates for populations rather than individuals, are probabilistic, and tend to be only modestly accurate, with considerable variability across various populations. Thus, only 40% to 50% of individuals who experience cardiovascular events are considered high-risk candidates by most currently used risk profiles.\textsuperscript{71} In the MESA (Multi-Ethnic Study of Atherosclerosis) study, almost 60% of the events (123 of 209) occurred among individuals who were not classified as being at high risk by either traditional
risk factors or CAC score. Further research is needed to identify newer modalities to refine ASCVD risk. As more has been learned about the biology of atherosclerosis, 2 main paradigms important for ASCVD risk assessment have become apparent: (1) the complexity of ASCVD necessitates a multimodal and multimarker approach and (2) periodic assessment is needed given the dynamic nature of plaque activity and ASCVD risk. Table 4 summarizes potential future research directions in refining estimates in asymptomatic individuals. The following sections briefly discuss the potential use of imaging multiple markers, genetic susceptibility variants, and newer statistical techniques in this regard.

Imaging and Physiologic Assessment

The evidence base needs to be expanded to facilitate informed use of available noninvasive modalities for imaging and assessment of arterial function for early detection of disease and to assess subclinical plaque burden. Although the concept of “vulnerable plaque” has existed for many years, there is a need for noninvasive imaging modalities to identify vulnerable plaque and characterize temporal changes in plaque activity. Cost, availability, and radiation exposure are additional factors that require investigation to establish best practices for the use of imaging. Two risk assessment methods could also be considered—one that is low cost and widely applicable but with reduced accuracy and a second that adds cost and accuracy and may be used in patients in whom the need for intervention is less clear.

Multiple Markers

Given the complexity of ASCVD, it is unlikely that a single marker will provide sufficiently incremental predictive information about risk, and many novel risk factors have been proposed for assessing ASCVD risk. Multiple etiologic pathways lead to the development of ASCVD and to adverse cardiovascular events. Use of multiple markers will be necessary to meaningfully improve the accuracy of risk estimates.

Genetic Susceptibility Variants

Nearly 46 genetic susceptibility variants for CHD have been identified, and individuals with an excess of these variants may be at increased risk for CHD. Although the variants have modest effect sizes, most are not associated with conventional risk factors and therefore provide an orthogonal means of risk assessment, in contrast to several existing biomarkers such as hs-CRP whose incremental predictive utility is diminished because of its correlation with factors such as obesity, diabetes, and hypertension. In several cohorts with available information on incident adverse events, genetic risk scores calculated on the basis of these variants have been found to be independently predictive of adverse cardiovascular events. At Mayo Clinic in Rochester, Minnesota, a pilot clinical trial funded by the National Human Genome Research Institute, the Myocardial Infarction Genes (MI-GENES) study, is under way to test the concept of using genomic information to refine assessment of CHD risk.

New Statistical Approaches

Recently, new statistical techniques (including net reclassification improvement and integrative discrimination index) have been adopted to examine the utility of novel biomarkers in different populations and patient subgroups. Continuing work is needed to develop new statistical models to account for multiple markers, interactive effects of risk factors, and their different effects at different ages.

CONCLUSION

The availability of race- and sex-specific equations for estimating 10-year and lifetime ASCVD risk, inclusion of stroke as an adverse cardiovascular

<table>
<thead>
<tr>
<th>Table 4. Areas of Research to Improve Assessment of Atherosclerotic Cardiovascular Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establish more precise estimates of the risk due to family history; investigate utility of a family history score rather than dichotomous characterization of presence vs absence of family history; develop tools to integrate and display family history information within the electronic medical record</td>
</tr>
<tr>
<td>Develop and validate methods to adjust risk estimates based on results of adjunctive tests and data</td>
</tr>
<tr>
<td>Develop newer imaging modalities to identify vulnerable plaque and characterize temporal changes in plaque activity</td>
</tr>
<tr>
<td>Assess the impact of measuring novel risk markers on patient outcomes</td>
</tr>
<tr>
<td>Investigate the role and utility of testing for genetic susceptibility variants and develop methods to integrate genetic test results in the electronic medical record</td>
</tr>
<tr>
<td>Optimize predictive capabilities and cost-effectiveness of the use of multiple markers to refine atherosclerotic cardiovascular disease risk estimates</td>
</tr>
<tr>
<td>Validate newer statistical approaches to assess utility of novel risk markers, interactions, and other factors</td>
</tr>
<tr>
<td>Develop tools to improve communication of cardiovascular risk and motivate patients to adopt healthy lifestyle changes</td>
</tr>
</tbody>
</table>
outcome, and the emphasis on shared decision making are strengths of the new ACC/AHA guidelines for ASCVD risk assessment. There is concern, however, that the ASCVD risk calculator may overestimate risk in certain settings and that the recommended threshold for treatment will greatly increase the proportion of the US population taking statins. Conversely, it may be appropriate to expand the number of individuals taking statins because ASCVD remains the leading cause of death in the United States, and most Americans do not have ideal cardiovascular health. The guidelines recommend 4 measures that may be considered by clinicians and patients as adjuncts for refining risk estimates (family history of CHD, hs-CRP, ABI, and CAC scoring) but provide no guidance on how the results should be used to adjust risk estimated by the ASCVD calculator. Carotid ultrasonography, an established technique, is not recommended, and family history is labeled as an adjunctive measure.

Overall, we agree with the general principles of the guidelines and suggest certain adaptations for use in the clinical setting. We recommend eliciting a family history of ASCVD at the time the risk calculator is used, followed by consideration of the use of CAC score or carotid ultrasonography to assess for subclinical disease burden. Additional measures that may be useful in risk estimation include aPWV and circulating levels of Lp(a). Finally, the suboptimal performance of available ASCVD risk algorithms needs to be acknowledged, and research efforts to improve risk assessment in asymptomatic adults should to be intensified.

**Abbreviations and Acronyms.**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>ankle-brachial index</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>aPWV</td>
<td>aortic pulse wave velocity</td>
</tr>
<tr>
<td>ASCVD</td>
<td>atherosclerotic cardiovascular disease</td>
</tr>
<tr>
<td>ATP-III</td>
<td>Adult Treatment Panel III</td>
</tr>
<tr>
<td>CAC</td>
<td>coronary artery calcium</td>
</tr>
<tr>
<td>CCA</td>
<td>common carotid artery</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>high-sensitivity C-reactive protein</td>
</tr>
<tr>
<td>IMT</td>
<td>intima-media thickness</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>lipoprotein(a)</td>
</tr>
</tbody>
</table>

**Grant Support.** Dr Kullo is supported by grants HG006379 from the National Human Genome Research Institute and HL12677 from the National Heart, Lung, and Blood Institute.

**Correspondence.** Address to Iftikhar J. Kullo, MD, Division of Cardiovascular Diseases and Gonda Vascular Center, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (kullo.iftikhar@mayo.edu).

**REFERENCES**

18. Lackland DT, Ekidin MS, D’Agostino R Sr, et al. American Heart Association Stroke Council; Council on Epidemiology and Prevention; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes...
A PERSPECTIVE ON CARDIOVASCULAR RISK ASSESSMENT


22. Sheridan SL, Crespo E. Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? a systematic review of the literature. BMC Health Serv Res. 2008;6:60.


