Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

November 2010

ACCF/AHA Writing Committee

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Atherosclerotic cardiovascular disease (CVD) is the leading cause of death for both men and women in the United States. It is estimated that if all forms of major CVD were eliminated, life expectancy would rise by almost 7 years. Coronary heart disease (CHD), in particular, has a long asymptomatic latent period that provides an opportunity for early preventive interventions. The focus of this guideline is the initial assessment of the apparently healthy adult for risk of developing cardiovascular events associated with atherosclerotic vascular disease. The goal of this early assessment of cardiovascular risk in an asymptomatic individual is to provide the foundation for targeted preventive efforts based on that individual’s predicted risk. It is based on the long-standing concept of targeting the intensity of drug treatment interventions to the severity of the patient’s risk. This clinical approach serves as a complement to the population approach to prevention of CVD, in which population-wide strategies are used regardless of an individual’s risk.

Although there is no clear age cut point for defining the onset of risk for CVD, elevated risk factor levels and subclinical abnormalities can be detected in adolescents as well as young adults. To maximize
the benefits of prevention-oriented interventions, especially those involving lifestyle changes, the writing committee advises that these guidelines be applied in asymptomatic persons beginning at age 20, recognizing that the decision about a starting point is an arbitrary one.

This document specifically excludes from consideration patients with a diagnosis of CVD or a coronary event, for example, angina or anginal equivalent, myocardial infarction, or revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery. It also excludes testing for patients with known peripheral artery disease and cerebral vascular disease. This guideline is not intended to replace other sources of information on cardiovascular risk assessment in specific disease groups or in higher-risk groups such as those with known hypertension or diabetes on treatment.
### Table 1. Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>LEVEL B</th>
<th>LEVEL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple populations evaluated*&lt;br&gt;Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Limited populations evaluated*&lt;br&gt;Data derived from a single randomized trial or nonrandomized studies</td>
<td>Very limited populations evaluated*&lt;br&gt;Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS I</th>
<th>Benefit &gt;&gt;&gt; Risk</th>
<th>Procedure/Treatment SHOULD be performed/administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS IIa</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Additional studies with focused objectives needed&lt;br&gt;IT IS REASONABLE to perform procedure/administer treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S I Z E O F</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL A</td>
</tr>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
</tr>
<tr>
<td>Recommendation in favor of treatment or procedure being useful/effective&lt;br&gt;■ Some conflicting evidence from multiple randomized trials or meta-analyses</td>
</tr>
<tr>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful&lt;br&gt;■ Sufficient evidence from multiple randomized trials or meta-analyses</td>
</tr>
</tbody>
</table>

Suggested phrases for writing recommendations:

- Treatment/strategy A is recommended/indicated
- Treatment/strategy A is probably recommended/indicated

Comparative effectiveness phrases:

- Treatment/strategy A is probably recommended(indicated in preference to treatment B)
- Treatment A should be chosen over treatment B
- It is reasonable to choose treatment A over treatment B
**CLASS IIb**

Benefit ≥ Risk

Additional studies with broad objectives needed; additional registry data would be helpful

Procedure/Treatment MAY BE CONSIDERED

- Recommendation’s usefulness/efficacy less well established
- Greater conflicting evidence from multiple randomized trials or meta-analyses

**CLASS III**

No Benefit or CLASS III Harm

<table>
<thead>
<tr>
<th>Procedure/Treatment</th>
<th>COR III: No Benefit</th>
<th>COR III: Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure/Test</td>
<td>Not Helpful</td>
<td>Excess Cost w/o Benefit or Harmful</td>
</tr>
<tr>
<td>Treatment</td>
<td>No Proven Benefit</td>
<td>Harmful to Patients</td>
</tr>
</tbody>
</table>

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses

May/might be considered

May/might be reasonable

Usefulness/effectiveness is unknown/unclear/uncertain or not well established

---

* Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

† For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
II. Assessing the Prognostic Value of Risk Factors and Risk Markers: Basis for Recommendations in this Guideline

New risk factors or markers are frequently identified and evaluated as potential additions to standard risk assessment strategies. For any new risk marker to be considered a useful candidate for risk prediction, it must, at the very least, have an independent statistical association with risk after accounting for established readily available and inexpensive risk markers. This independent statistical association should be based on studies that include large numbers of outcome events. Traditionally, reports of novel risk markers have only gone this far, reporting adjusted hazard ratios with confidence intervals and p-values. Although this level of basic statistical association is often regarded by researchers as meaningful in prediction of a particular outcome of interest, more rigorous assessments include analysis of the calibration, discrimination, and reclassification of the predictive model. Many of the tests reviewed in this guideline fail to provide these more comprehensive measures of test evaluation, and for this reason, many tests that are statistically associated with clinical outcomes were not judged to be useful beyond a standard risk assessment profile. In the absence of this evidence of “additive predictive information,” the writing committee generally concluded that a new risk marker was not ready for routine use in risk assessment.
Calibration and discrimination are 2 separate concepts that do not necessarily track with each other. Calibration refers to the ability to correctly predict the proportion of subjects within any given group who will experience disease events. Among patients predicted to be at higher risk, there will be a higher number of events, whereas among patients identified as being at lower risk, there will be fewer events.

Discrimination is a different concept that refers to the probability of a diagnostic test or a risk prediction instrument to distinguish between patients who are at higher compared with lower risk. For example, a clinician sees 2 random patients, one of whom is ultimately destined to experience a clinical event. A diagnostic test or risk model discriminates well if it usually
correctly predicts which of the 2 subjects is at higher risk for an event. Mathematically this is described by calculating a C index or C statistic, parameters that are analogous to the area under the receiver operating characteristics curve. These statistics define the probability that a randomly selected person from the “affected group” will have a higher test score than a randomly selected person from the “nonaffected group.” A test with no discrimination would have a C statistic of 0.50 and a perfect test would have a C statistic of 1.0. Throughout this document, C statistic information is cited where available.

Some investigators have called for evaluating the number of subjects reclassified into other risk categories based on models that include the new risk marker. One problem with this approach is that not all reclassification is necessarily clinically useful. If a patient is deemed to be at intermediate risk and is then reclassified as being at high or low risk, the clinician might find that information helpful. It may not be known, however, whether or not these reclassifications are correct for individual subjects. Two new approaches to risk reclassification have been introduced, namely “net reclassification improvement” and “integrated discrimination improvement,” which provide quantitative estimates of correct reclassifications. Correct reclassifications are associated with higher predicted risks for cases and lower predicted risks for noncases.
III. Risk Stratification and Genomics

A. Global Risk Scoring Recommendation

Class I 1. Global risk scores (such as the Framingham Risk Score) that use multiple traditional cardiovascular risk factors should be obtained for risk assessment in all asymptomatic adults without a clinical history of CHD. These scores are useful for combining individual risk factor measurements into a single quantitative estimate of risk that can be used to target preventive interventions. (Level of Evidence: B)
Table 2 summarizes a sample of published global risk score instruments that take into account modifiable risk markers that are also appropriate evidence-based targets for preventive interventions.

**Table 2. Comparison of a Sample of Global Coronary and Cardiovascular Risk Scores**

<table>
<thead>
<tr>
<th></th>
<th>Framingham</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>5345</td>
<td>205,178</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>30 to 74; M:49</td>
<td>19 to 80; M:46</td>
</tr>
<tr>
<td><strong>Mean follow-up (y)</strong></td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td><strong>Risk factors considered</strong></td>
<td>Age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications</td>
<td>Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>CHD (MI and CHD death)</td>
<td>Fatal CHD</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CVD, cardiovascular disease; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; M, Mean; MI, myocardial infarction; PROCAM, Münster Heart Study; and SCORE, Systematic Coronary Risk Evaluation.
## Risk Scores

<table>
<thead>
<tr>
<th>PROCAM (Men)</th>
<th>Reynolds (Women)</th>
<th>Reynolds (Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5389</td>
<td>24,558</td>
<td>10,724</td>
</tr>
<tr>
<td>35 to 65; M:47</td>
<td>&gt;45; M:52</td>
<td>&gt;50; M:63</td>
</tr>
<tr>
<td>10</td>
<td>10.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Age, LDL cholesterol, HDL cholesterol, smoking, systolic blood pressure, family history, diabetes, triglycerides</td>
<td>Age, HbA1C (with diabetes), smoking, systolic blood pressure, total cholesterol, HDL cholesterol, hsCRP, parental history of MI at &lt;60 y of age</td>
<td>Age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, hsCRP, parental history of MI at &lt;60 y of age</td>
</tr>
<tr>
<td>Fatal/nonfatal MI or sudden cardiac death (CHD and CVD combined)</td>
<td>MI, ischemic stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)</td>
<td>MI, stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CVD, cardiovascular disease; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; M, Mean; MI, myocardial infarction; PROCAM, Münster Heart Study; and SCORE, Systematic Coronary Risk Evaluation.
B. Family History Recommendation

**Class I**

1. Family history of atherothrombotic CVD should be obtained for cardiovascular risk assessment in all asymptomatic adults. (Level of Evidence: B)

C. Genotypes Recommendation

**Class III:**

1. Genotype testing for CHD risk assessment in asymptomatic adults is not recommended. (Level of Evidence: B)
IV. Lipoproteins and Circulating Blood Markers

A. Lipoprotein and Apolipoprotein Assessments

Recommendation

Class III: 1. Measurement of lipid parameters, including lipoproteins, apolipoproteins, particle size, and density, beyond a standard fasting lipid profile is not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: C)

B. Natriuretic Peptides Recommendation

Class III: 1. Measurement of natriuretic peptides is not recommended for CHD risk assessment in asymptomatic adults. (Level of Evidence: B)

C. C-Reactive Protein Recommendations

Class IIa 1. In men 50 years of age or older or women 60 years of age or older with low-density lipoprotein cholesterol less than 130 mg/dL; not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy. (Level of Evidence: B)
Class IIb 1. In asymptomatic intermediate-risk men 50 years of age or younger or women 60 years of age or younger, measurement of CRP may be reasonable for cardiovascular risk assessment. (Level of Evidence: B)

Class III: No Benefit 1. In asymptomatic high-risk adults, measurement of CRP is not recommended for cardiovascular risk assessment. (Level of Evidence: B)

2. In low-risk men younger than 50 years of age or women 60 years of age or younger, measurement of CRP is not recommended for cardiovascular risk assessment. (Level of Evidence: B)
D. Hemoglobin A1C Recommendation

Class IIb 1. Measurement of hemoglobin A1C may be reasonable for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes. (Level of Evidence: B)

E. Lipoprotein-Associated Phospholipase A2 Recommendation

Class IIb 1. Lipoprotein-associated phospholipase A2 might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults. (Level of Evidence: B)
V. Microalbuminuria Recommendations

**Class IIa** 1. In asymptomatic adults with hypertension or diabetes, urinalysis to detect microalbuminuria is reasonable for cardiovascular risk assessment. (Level of Evidence: B)

**Class IIb** 1. In asymptomatic adults at intermediate risk without hypertension or diabetes, urinalysis to detect microalbuminuria might be reasonable for cardiovascular risk assessment. (Level of Evidence: B)
VI. Cardiac and Vascular Tests

A. Resting Electrocardiogram Recommendations

Class IIa 1. A resting electrocardiogram (ECG) is reasonable for cardiovascular risk assessment in asymptomatic adults with hypertension or diabetes. (Level of Evidence: C)

Class IIb 1. A resting ECG may be considered for cardiovascular risk assessment in asymptomatic adults without hypertension or diabetes. (Level of Evidence: C)

B. Transthoracic Echocardiography Recommendations

Class IIb 1. Echocardiography to detect left ventricular hypertrophy may be considered for cardiovascular risk assessment in asymptomatic adults with hypertension. (Level of Evidence: B)

Class III: No Benefit 1. Echocardiography is not recommended for cardiovascular risk assessment of CHD in asymptomatic adults without hypertension. (Level of Evidence: C)
C. Carotid Intima-Media Thickness Recommendation

Class IIa 1. Measurement of carotid artery intima-media thickness is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk. Published recommendations on required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results. (Level of Evidence: B)

D. Brachial/Peripheral Flow-Mediated Dilation Recommendation

Class III: 1. Peripheral arterial flow-mediated dilation studies are not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: B)

E. Specific Measures of Arterial Stiffness Recommendation

Class III: 1. Measures of arterial stiffness outside of research settings are not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: C)
**F. Ankle-Brachial Index Recommendation**

**Class IIa**
1. Measurement of ankle-brachial index is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk. (Level of Evidence: B)

**G. Exercise Electrocardiography Recommendation**

**Class IIb**
1. An exercise ECG may be considered for cardiovascular risk assessment in intermediate-risk asymptomatic adults (including sedentary adults considering starting a vigorous exercise program), particularly when attention is paid to non-ECG markers such as exercise capacity. (Level of Evidence: B)

**H. Stress Echocardiography Recommendation**

**Class III: No Benefit**
1. Stress echocardiography is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults. (Exercise or pharmacological stress echocardiography is primarily used for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known CAD or the assessment of patients with known or suspected valvular heart disease.) (Level of Evidence: C)
I. Myocardial Perfusion Imaging Recommendations

**Class IIb**
1. Stress myocardial perfusion imaging (MPI) may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CHD or when previous risk assessment testing suggests a high risk of CHD, such as a coronary artery calcium (CAC) score of 400 or greater. (Level of Evidence: C)

**Class III: No Benefit**
1. Stress MPI is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults. (Exercise or pharmacologic stress MPI is a technology primarily used and studied for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known coronary artery disease.) (Level of Evidence: C)
J. Calcium Scoring Methods Recommendations

Class IIa  
1. Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk). (Level of Evidence: B)

Class IIb  
1. Measurement of CAC may be reasonable for cardiovascular risk assessment persons at low to intermediate risk (6% to 10% 10-year risk). (Level of Evidence: B)

Class III:  
1. Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for cardiovascular risk assessment. (Level of Evidence: B)

K. Coronary Computed Tomography Angiography Recommendation

Class III:  
1. Coronary computed tomography angiography is not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: C)

L. Magnetic Resonance Imaging of Plaque Recommendation

Class III:  
1. Magnetic resonance imaging for detection of vascular plaque is not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: C)
VII. Additional Considerations

A. Patients With Diabetes Recommendations

Class IIa  
1. In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment. (Level of Evidence: B)

Class IIb  
1. Measurement of hemoglobin A1C may be considered for cardiovascular risk assessment in asymptomatic adults with diabetes. (Level of Evidence: B)

2. Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of 400 or greater. (Level of Evidence: C)

B. Women Recommendations

Class I  
1. A global risk score should be obtained in all asymptomatic women. (Level of Evidence: B)

2. Family history of CVD should be obtained for cardiovascular risk assessment in all asymptomatic women. (Level of Evidence: B)
VIII. Clinical Implications of Risk Assessment: Summary and Conclusions

The assessment of risk for development of clinical manifestations of atherosclerotic CVD is designed to aid the clinician in informed decision making about lifestyle and pharmacologic interventions to reduce such risk. Patients are broadly categorized into low-, intermediate-, and high-risk subsets, and level of intensity and type of treatments are based on these differing assessments of risk.

The initial step in risk assessment in individual patients involves the ascertainment of a global risk score (Framingham, Reynolds, etc.) and the elucidation of a family history of atherosclerotic CVD. These Class I recommendations, which are simple and inexpensive, determine subsequent strategies to be undertaken. Persons at low risk do not require further testing for risk assessment, as more intensive interventions are considered unwarranted, and those already documented to be at high risk (established CHD or coronary risk equivalents) are already candidates for intensive preventive interventions, so that added testing will not provide incremental benefit.
For the intermediate-risk patient, this guideline should help the clinician select appropriate test modalities that can further define risk status. Tests classified as Class IIa are those shown to provide benefit that exceeds costs and risk. Selection among these will vary with local availability and expertise, decisions regarding cost, and potential risks such as radiation exposure, etc. Tests classified as Class IIb have less robust evidence for benefit but may prove helpful in selected patients. Tests classified as Class III are not recommended for use in that there is no, or rather limited, evidence of their benefit in incrementally adding to the assessment of risk; therefore, these tests fail to contribute to changes in the clinical approach to therapy. In addition, a number of Class III tests discussed in this guideline require additional efforts to standardize the measurement or make the test more commonly available on a routine clinical basis. Furthermore, some of the Class III tests also pose potential harm (radiation exposure or psychological distress in the absence of a defined treatment strategy) and are therefore to be avoided for cardiovascular risk assessment purposes in the asymptomatic adult. Until additional research is accomplished to justify the addition of Class III tests, the writing committee recommends against their use for cardiovascular risk assessment.