2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance

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Preamble

It is essential that the medical profession play a central role in critically evaluating the evidence related to drugs, devices, and procedures for the detection, management, or prevention of disease. Properly applied, rigorous, expert analysis of the available data documenting absolute and relative benefits and risks of these therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favorably affect the cost of care by focusing resources on the most effective strategies. One important use of such data is the production of clinical practice guidelines that, in turn, can provide a foundation for a variety of other applications, such as performance measures, appropriateness use criteria, clinical decision support tools, and quality improvement tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines is charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, and the Task Force directs and oversees this effort. Writing committees are charged with assessing the evidence as an independent group of authors to develop, update, or revise recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines in partnership with representatives from other medical practitioner and specialty groups. Writing committees are specifically charged to perform a formal literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and clinical outcomes constitute the primary basis for recommendations in these guidelines.

In analyzing the data and developing recommendations and supporting text, the writing committee used evidence-based methodologies developed by the ACCF/AHA Task Force on Practice Guidelines that are described elsewhere (1). The committee reviewed and ranked evidence supporting current recommendations, with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are

based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, where there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The schema for Classification of Recommendations (COR) and Level of Evidence (LOE) is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size as well as the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is a separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for Class of Recommendation I and IIa, Level of Evidence A or B only, have been added.

The Task Force on Practice Guidelines makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose ALL relevant relationships and those existing 24 months before initiation of the writing effort. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the members voting. Members who were recused from voting are noted on the title page of this document and in Appendix 1. Members must recuse themselves from voting on any recommendation to which their relationship with industry (RWI) and other entities applies. Any writing committee member who develops a new RWI during his or her tenure is required to notify guideline staff in writing. These statements are reviewed by the Task Force on Practice Guidelines and all members during each conference call and meeting of the writing committee and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual (1). Authors' and peer reviewers' RWIs pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. Additionally, to ensure complete transparency, writing committee members' *comprehensive disclosure information* – including RWIs not pertinent to this document – are available online at www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards.aspx. Disclosure information for the ACCF/AHA Task Force on Practice Guidelines is also available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of the writing committee was supported exclusively by the ACCF and AHA without commercial support. Writing group members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are not currently available in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough and systematic review of the available current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most situations. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to better inform patient care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles.

The guidelines will be reviewed annually by the ACCF/AHA Task Force on Practice Guidelines and considered current unless they are updated, revised, or withdrawn from distribution. The Executive Summary and recommendations are published in the _____ issue of the *Journal of the American College of Cardiology* and the _____ issue of *Circulation.* The full-text Guidelines are e-published in the same issues of these journals and are posted on the ACC (www.cardiosource.org) and AHA (my.americanheart.org) World Wide Web sites. Copies of the full-text Guidelines and the Executive Summary are available from both organizations.

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Chair, ACCF/AHA Task Force on Practice Guidelines

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* COR III: No benefit — Procedure/Test: Not Helpful — Treatment: No Proven Benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful — Treatment: Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be done; is not useful/beneficial/effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be done
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

*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.

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted for the period beginning March 2008 through April 2010. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included, but were not limited to, *African Americans, Asian Americans, albuminuria, asymptomatic, asymptomatic screening and brachial artery reactivity, atherosclerosis imaging, atrial fibrillation, brachial artery testing for atherosclerosis, calibration, cardiac tomography, compliance, carotid intima-media thickness (IMT), coronary calcium, coronary computed tomography angiography (CCTA), C-reactive protein (CRP), detection of subclinical atherosclerosis, discrimination, endothelial function, family history, flow-mediated dilation, genetics, genetic screening, guidelines, Hispanic Americans, hemoglobin A, glycosylated, meta-analysis, Mexican Americans, myocardial perfusion imaging (MPI), noninvasive testing, noninvasive testing and type 2 diabetes, outcomes, patient compliance, peripheral arterial tonometry (PAT), peripheral tonometry and atherosclerosis, lipoprotein-associated phospholipase A2, primary prevention of coronary artery disease (CAD), proteinuria, risk, risk scoring, receiver operating characteristics (ROC) curve, screening for brachial artery reactivity, stress echocardiography, subclinical atherosclerosis, subclinical and Framingham, subclinical and MESA,* and *type 2 diabetes.* Additionally, the writing committee reviewed documents related to the subject matter previously published by the ACCF and AHA, American Diabetes Association (ADA), European Society of Cardiology, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) 7. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published in the article, data from the clinical trial will be used to calculate the absolute risk difference and number needed to treat or harm; data related to the relative treatment effects will also be provided, such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio (IRR), along with confidence interval (CI) when available.

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 (2). This clinical

approach serves as a complement to the population approach to prevention of cardiovascular disease (CVD), in which population-wide strategies are used regardless of an individual's risk.

This guideline pertains to initial assessment of cardiovascular risk in the asymptomatic adult. 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. The writing committee recognizes 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 (MI), or revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery. It also excludes testing for patients with known peripheral artery disease (PAD) and cerebral vascular disease. This guideline is not intended to replace other sources of information on cardiovascular risk assessment in specific disease groups or higher-risk groups such as those with known hypertension or diabetes who are receiving treatment.

1.2. Organization of the Writing Committee

The committee was composed of physicians and others expert in the field of cardiology. The committee included representatives from the American Society of Echocardiography (ASE), American Society of Nuclear Cardiology (ASNC), Society of Atherosclerosis Imaging and Prevention (SAIP), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR).

1.3. Document Review and Approval

This document was reviewed by 2 outside reviewers nominated by the ACCF and 2 outside reviewers nominated by the AHA, as well as 2 reviewers each from ASE, ASNC, SAIP, SCAI, SCCT, and SCMR, and 23 individual content reviewers (including members from the Appropriate Use Criteria Task Force, ACCF Cardiac Catheterization Committee, ACCF Imaging Council, and ACCF Prevention of Cardiovascular Disease Committee). All reviewer RWI information was collected and distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and AHA and endorsed by the _____.

1.4. Magnitude of the Problem of Cardiovascular Risk in Asymptomatic Adults

Atherosclerotic CVD is the leading cause of death for both men and women in the United States (3). Risk factors for the development of atherosclerotic disease are widespread in the U.S. population. In 2003, approximately 37% of American adults reported having ≥2 risk factors for CVD. Ninety percent of patients with coronary heart disease (CHD) have at least 1 atherosclerotic risk factor (4). Approximately half of all coronary deaths are not preceded by cardiac symptoms or diagnoses (5). One aim of this guideline is to provide an evidence-based approach to risk assessment in an effort to lower this high burden of coronary deaths in asymptomatic adults.

CVD was mentioned on the death certificates of 56% of decedents in 2005. It was listed as the underlying cause of death in 35.3% (864 480) of all deaths (2 448 017) in 2005 or 1 of every 2.8 deaths in the U.S. (6). In every year since 1900 (except 1918), CVD accounted for more deaths than any other major cause of death in the United States (6). It is estimated that if all forms of major CVD were eliminated, life expectancy would rise by almost 7 years (6). Analyses suggest that the decrease in U.S. deaths due to CHD from 1980 to 2000 was partly attributable (approximately 47%) to evidence-based medical therapies, and about 44% of the reduction has been attributed to changes in risk factors in the population (7). The estimated direct and indirect cost of CVD for 2009 is $475.3 billion (6).

CHD has a long asymptomatic latent period, which provides an opportunity for early preventive interventions. Atherosclerosis begins in childhood and progresses into adulthood due to multiple coronary risk factors such as unfavorable levels of blood lipids, blood pressure, body weight and body fat, smoking, diabetes, and genetic predisposition (8-10). The lifetime risk of CHD and its various manifestations has been calculated for the Framingham Heart Study population at different ages. In nearly 8000 persons initially free of clinical evidence of CHD, the lifetime risk of developing clinically manifest CHD (angina pectoris, MI, coronary insufficiency, or death from CHD) at age 40 was 48.6% for men and 31.7% for women (11). At age 70, the lifetime risk of developing CHD was 34.9% for men and 24.2% for women. The lifetime risk for all CVD combined is nearly 2 of every 3 Americans (12). Thus, the problem is immense, but the preventive opportunity is also great.

1.5. Assessing the Prognostic Value of Risk Factors and Risk Markers

Many risk factors have been proposed as predictors of CHD (13, 14). New risk factors or markers are frequently identified and evaluated as potential additions to standard risk assessment strategies. The AHA has published a scientific statement on appropriate methods for evaluating the predictive value of new risk factors or risk markers (15). The scientific statement endorsed previously published guidelines for proper reporting of observational studies in epidemiology (16) but also went beyond those guidelines to

specifically address criteria for evaluation of established and new risk markers. The current writing committee endorses this scientific statement and incorporated these principles into the assessments for this guideline. The general concepts and requirements for new risk marker validation and evaluation are briefly reviewed to provide a basis for the assessments in this document.

For any new risk marker to be considered useful 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 HRs with CIs and p values (17). Although this level of basic statistical association is often regarded by researchers as meaningful in prediction of a particular outcome of interest, the AHA scientific statement called for considerably more rigorous assessments that 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 cannot be 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. For example, if a diagnostic test or a multivariable model splits patients into 3 groups with predicted risks of 5%, 10%, and 15% within each group, calibration would be considered good if in a separate group of cohorts with similar predicted risks, the actual rates of events were close to 5%, 10%, and 15%. Calibration is best presented by displaying observed versus expected event rates across quantiles of predicted risk for models that do and do not include the new risk marker.

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 ROC 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.

As an example of a risk marker that improves discrimination, MESA (Multiethnic Study of Atherosclerosis) investigators found that the addition of coronary artery calcium (CAC) scores to standard risk factors improved the area under the ROC curve from 0.77 to 0.82 ($p<0.001$) (18). In contrast, a score based on 9 genes that code for cholesterol levels added no predictive value over established risk factors and family history (19). Similarly, a study comparing the predictive capacity of conventional and newer biomarkers for prediction of cardiovascular events derived a C statistic of 0.760 for coronary events for the conventional risk factor model. Adding a number of newer biomarkers changed the C statistic by only 0.009 ($p=0.08$) (20). Small changes such as these in the C statistic suggest limited or rather modest improvement in risk discrimination with additional risk markers.

Some investigators have called for evaluating the number of subjects reclassified into other risk categories based on models that include the new risk marker (21). For example, in a model of cardiovascular risk in a large cohort of healthy women, the addition of CRP resulted in reclassification of a large proportion of subjects who were thought to be at intermediate risk based on standard risk markers alone (22). 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. Pencina and colleagues introduced 2 new approaches, namely "net reclassification improvement" and "integrated with classification improvement," which provide quantitative estimates of correct reclassifications (23). Correct reclassifications are associated with higher predicted risks for cases and lower predicted risks for noncases.

1.6. Usefulness in Motivating Patients or Guiding Therapy

In 1996 the American College of Cardiology Bethesda Conference reviewed the concept of risk stratification, an approach that is now standard for identifying the appropriate degree of therapeutic or preventive interventions (2). Patients deemed to be at low risk for clinical events are unlikely to gain substantial benefits from pharmaceutical interventions and therefore might best be managed with lifestyle modifications. Conversely, patients deemed to be at high risk for events are more likely to benefit from pharmacologic interventions and therefore are appropriate candidates for intensive risk factor modification efforts. Among patients at intermediate risk, further testing may be indicated to refine risks and assess the need for treatment. Although this model is attractive and has been shown to be appropriate in certain situations, there is no definitive evidence that it directly leads to improved patient outcomes. Further research is clearly needed, and it is appropriate to point out that the risk stratification paradigm

has not been subjected to rigorous evaluation by randomized trials. Indeed, the impact of various risk assessment modalities on patient outcomes is rarely studied and not well documented in the few studies that have been conducted (24).

1.7. Economic Evaluation of Novel Risk Markers

The progressively rising costs of medical care have increased interest in documenting the economic effects of new tests and therapies. The most basic goal is to estimate the economic consequences of a decision to order a new test. The ultimate goal is to determine whether performing the test provides sufficient value to justify its use.

A complete economic evaluation of the test has to account for all the subsequent costs induced by ordering the test, not just the cost of the test itself. The results of the test should change subsequent clinical management, which might include ordering follow-up tests, starting or stopping drug therapy, or using a device or procedure. The costs of these subsequent clinical management choices must be included in an "intention-to-test" analysis of the economic consequences of the initial decision to use the test. Ideally, the analysis should be extended to account for clinical events that are either averted or caused as a result of the strategy based on performing the test.

An example of the economic consequences of testing will illustrate the importance of these principles. Suppose a patient with diabetes who has no cardiac symptoms undergoes a computed tomography (CT) coronary angiogram, which reveals obstructive CAD but also leads to contrast-induced nephropathy. Further suppose this patient has a follow-up invasive coronary angiogram, undergoes insertion of a coronary stent, and is treated for renal insufficiency. The costs of all these "downstream events" should be included in any economic assessment of the use of CCTA because they all resulted from the initial decision to perform the test. Note that the total costs of a "test strategy" may greatly exceed the cost of the initial test itself.

The cost of any medical intervention has to be placed in the context of the clinical benefits that the intervention provides. In the example of the patient with diabetes, perhaps the aggressive use of coronary revascularization actually extended life expectancy. Cost-effectiveness analysis provides a formal framework with which to compare the clinical effectiveness of an intervention (measured in patient-centered outcomes such as length of life or quality of life) with the cost of that intervention. Cost-effectiveness analysis has been most commonly applied to the evaluation of new medical therapies that directly improve clinical outcomes (e.g., use of bypass surgery to treat CAD). Diagnostic tests do not improve clinical outcomes directly, however, and do so only indirectly by changing clinical management decisions, which in turn may improve clinical outcomes. Thus, determining the cost-effectiveness of a diagnostic test depends on how effectively the information is used and can be evaluated only in the

context of available treatments and how effective those treatments are. A test that provides accurate risk information about an untreatable disease is unlikely to be cost-effective simply because clinical outcomes cannot be improved by its use.

In general, testing strategies such as those assessed in this document have not included evaluations of the cost and cost-effectiveness of the tests. Therefore, although this general guidance is offered to the reader as a caveat, the writing committee was generally unable to find evidence to support the cost-effectiveness of any of the tests and testing approaches discussed here. Where exceptions were identified, cost-related information is included. In addition, for the uncommon examples for which clinical outcomes of testing strategies were assessed, the writing committee included that evidence in the assessment of the value of the risk assessment test.

2. Approaches to Risk Stratification

2.1. General Approach to Risk Stratification

2.1.1. Recommendation for Global Risk Scoring

Class I

1. Global risk scores (such as the Framingham Risk Score [FRS]) 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 (25). *(Level of Evidence: B)*

2.1.1.1. General Description

Prospective epidemological studies have established, primarily in studies of people ≥40 years of age, that readily measured and often modifiable risk factors are associated with the development of clinical CHD in asymptomatic individuals. There are robust prognostic data for each of the "classic risk factors," namely, cigarette smoking, cholesterol levels, blood pressure levels, and diabetes. Data obtained from the Framingham Heart Study and other population-based cohorts have demonstrated that age, sex, cigarette smoking, level of low-density lipoprotein (LDL) cholesterol or total cholesterol, diabetes, and levels of blood pressure can be combined in predictive models to estimate risk of fatal and nonfatal CHD events (26). Beginning in the 1990s, a number of global risk prediction instruments were introduced, based on multivariable models that incorporated risk factor data and clinical events (25-28). These instruments go beyond simple demographics by taking into account modifiable risk markers that are also appropriate evidence-based targets for preventive interventions. Table 2 summarizes a sample of published global risk score instruments.

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

	Framingham	SCORE	PROCAM (Men)	Reynolds (Women)	Reynolds (Men)
Sample size	5345	205,178	5389	24,558	10,724
Mean age, range (y)	49, 30 to 74	46, 19 to 80	47, 35 to 65	52, >45	63, >50
Mean follow-up (y)	12	13	10	10.2	10.8
Risk factors considered	Age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications	Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure	Age, LDL cholesterol, HDL cholesterol, smoking, systolic blood pressure, family history, diabetes, triglycerides	Age, HbA1C (with diabetes), smoking, systolic blood pressure, total cholesterol, HDL cholesterol, hsCRP, parental history of MI at <60 y of age	Age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, hsCRP, parental history of MI at <60 y of age
Endpoints	CHD (MI and CHD death)	Fatal CHD	Fatal/nonfatal MI or sudden cardiac death (CHD and CVD combined)	MI, ischemic stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)	MI, stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)
URLs for risk calculators	http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof	http://www.heartscore.org/Pages/welcome.aspx	http://www.chd-taskforce.com/coronary_risk_assessment.html	http://www.reynoldsriskscore.org/	http://www.reynoldsriskscore.org/

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; MI, myocardial infarction; PROCAM, Münster Heart Study; and SCORE, Systematic Coronary Risk Evaluation.

Global risk assessment instruments, such as the FRS, are considered valuable in medical practice because clinicians and patients may not otherwise accurately assess risk. In some survey studies, clinicians presented with scenarios were found to overestimate the likelihood of a future major clinical cardiovascular event (29). Other studies have suggested that physicians may also underestimate risk (30-32). Failure to use global quantitative risk instruments may result in physicians inappropriately informing patients that they are at high risk and inappropriately promoting therapeutic interventions of modest or questionable benefit or, alternatively, inadequately emphasizing risk when risk is actually present.

Global risk scores, although designed to estimate risk across a continuous range from 0% to 100%, have most commonly been advocated as a method by which patients can be categorized in broad terms as "low risk," "intermediate risk," and "high risk." In general, patients are deemed to be high risk if they are found to have a global risk estimate for hard CHD events of at least 20% over 10 years. The threshold for dividing low risk from intermediate risk is not uniform, with some proposing a lower cutoff

value of 6% risk over 10 years, whereas others use a value of 10% over 10 years (27, 33, 34). This document, unless otherwise noted, uses a lower cutoff value of at least 10% and a higher cutoff of <20% to designate intermediate risk.

The evidence with regard to global risk scores is most appropriate for individuals ≥40 years of age. It is important to note that there are limited data from Framingham and other long-term observational studies on 10-year risk in young adults; consequently, it is difficult to estimate 10-year risk in young adults. This is due to the fact that 10-year risk in young adults is very rarely impressively elevated, even in the face of significant risk factors, and thus there are a limited number of coronary events for calculating risk. As noted earlier in this document, the long-term or lifetime risk may be substantially raised by the presence of risk factors in young adults. Although the earliest age at which these risk scores should be used has not been rigorously established, the application of a particular risk score or test should not detract from adherence to a healthy lifestyle and identification of modifiable risk factors beginning in childhood. Therefore, to direct attention to the lifetime significance of coronary risk factors in younger adults, the writing committee considered measurement of a global risk score possibly worthwhile even in persons as young as age 20.

2.1.2. Association With Increased Risk and Incremental Risk of Additional Risk Factors

A number of global risk instruments have been developed (35). In the United States the best known is the FRS, several variants of which have been published (25-28, 34). Some include diabetes as a risk factor (25). The version published with the National Cholesterol Education Program Adult Treatment Panel (ATP III) report did not include diabetes (27), which was considered to be a CHD risk equivalent. Some versions of the FRS have focused on CHD death and nonfatal MI as endpoints, whereas a more recent version focused on more comprehensive total cardiovascular events (27, 28, 36). A European "SCORE" (Systematic Coronary Risk Evaluation) was developed based on a regression model derived from observations of >200 000 adults (37). This model differs from the Framingham model in a variety of factors, including incorporation of age into a time scale and consideration of geographic variability within European countries as the calibration metric (35).

Many of the multivariable coronary risk assessment functions have been evaluated for predictive capability (38). In a large number of different cohort studies, multivariable risk equations typically yielded ROC areas approximately equal to 0.80, indicating relatively high levels of predictive discrimination. Data from the NHANES (National Health and Nutrition Examination Surveys) prospective cohort study were used to study how well a Framingham-type risk model could predict first-time fatal and nonfatal CVD events (39). Risk factors included in the model to assess risk of CVD were age, systolic blood pressure, smoking status, total cholesterol, reported diabetes status, and current

treatment for hypertension. In women the risk model was useful for predicting events, with a C statistic of 0.829. In men the results were similar (C statistic, 0.78). Results such as these are typical for a Framingham-like risk assessment model in most populations, but there has been concern that global risk scores developed in one population may not be applicable to other populations (24). The FRS has been validated in several external populations, but in some cases it has required a "prevalence correction" to recalibrate the scores to reflect lower population prevalence of disease (25). Although global risk scores have often been found to have C statistics indicating that the score is useful for discrimination, the focus on 10-year risk estimates in clinical medicine makes many risk scores less useful for clinical decision making in most younger male patients and most women (40-42).

Some large-scale investigations have suggested that nearly 90% of the population-attributable risk for CAD can be ascribed to traditional biological and psychosocial risk factors (43). However, none of the current risk models, based only on traditional risk factors such as the FRS, are able to discriminate risk to an extent that would eliminate material uncertainty of risk for individual patients being seen by individual clinicians. Even in a global risk model such as the FRS, which predicts risk with an area under the ROC curve of as high as 80% in some studies (38), there is considerable overlap in risk scores between people who are ultimately found to be affected versus those found to be unaffected. Hence, a number of investigators argue for ongoing discovery and investigation of newer risk factors and predictive risk markers to improve the ability of clinicians to discriminate risk among their individual patients (20, 44, 45).

In summary, a FRS, or a similar type of multivariable predictive score based on traditional cardiovascular risk factors, is highly predictive of cardiovascular events. Given the familiarity of health professionals and the general public with the traditional risk factors and the proven efficacy of interventions for modifiable factors in these models, the writing committee agreed with many previous clinical practice guidelines that a "Framingham-like" risk score should be the basic risk assessment strategy to use for all asymptomatic adult patients (46-53). Additional risk markers should be assessed for their ability to improve on risk assessment beyond prediction from the multivariable global risk score. The writing committee felt that it is reasonable to advocate global risk score measures coincident with guideline-supported measurements of blood pressure or cholesterol beginning at age 20 and then every 5 years thereafter (27). The writing committee also acknowledged that some investigators advocate a shift in the risk assessment focus to 'lifetime risk" of CHD, but to date, evidence is sparse on how best to incorporate estimates of lifetime risk into clinical management (11). Another approach to the long-term risk estimation problem in younger adults was recently presented by the Framingham Study investigators as the "30-Year Risk of Cardiovascular Disease" (54).

2.2. Family History and Genomics

2.2.1. Recommendation for Family History

Class I

1. Family history of atherothrombotic CVD should be obtained for cardiovascular risk assessment in all asymptomatic adults (22, 55). ***(Level of Evidence: B)***

2.2.1.1. Association With Increased Cardiovascular Risk and Incremental Risk

A family history of premature (early-onset) atherothrombotic CVD, defined most often as occurring in a first-degree male relative <55 years of age or in a first-degree female relative <65 years of age, has long been considered a risk factor for CVD. Even a positive parental history that is not premature increases the risk of CVD in offspring (56). The importance of family history is not surprising because the risk factors for CVD, including hypertension, dyslipidemia, diabetes, obesity, and smoking behavior, are in part heritable (19, 57-62). In addition, lifestyle habits such as diet, exercise, and smoking are in part learned behaviors influenced by family patterns. However, studies examining parents, siblings, twins, and second-degree relatives have demonstrated that the 1.5- to 2.0-fold RR of family history persists even after adjusting for coexistent risk factors (56, 63-66). The risk associated with a positive family history for CVD is observed in individuals of White European, African American, Hispanic, and Japanese descent (67-69). The strength of the risk for an individual increases with younger age of onset, increasing numbers of relatives affected, and the relative's genealogical proximity (56, 63, 66, 70). Although the prevalence of a positive family history ranges from 14% to 35% in the general population, almost 75% of those with premature CHD have a positive family history, underscoring opportunities for prevention (71, 72).

The reliability of self-reported family history is imperfect (71, 73). To address recall bias, investigators from the Framingham Study used validated parental data and reported that although the negative predictive value for reports of premature MI and CHD death was superb (>90%), the positive predictive value for validated events was only fair (28% to 66%) (73). Similarly, the Health Family Tree Study found that the positive predictive value of a positive family history of CHD was 67%, but the negative predictive value was excellent at 96% (70, 71). The sensitivity of self-reported family history is ≥70% (71, 73). In addition, there has been increasing attention to improving the collection of family history through standardized questionnaires and online resources (74).

Family history modestly improves risk stratification. In the Framingham Heart Study, the inclusion of a positive family history improved ability to predict CVD (the multivariable model C statistic [ROC] increased from 0.82 to 0.83). Family history appeared to aid in reclassifying individuals and was

most useful in persons at intermediate risk (third and fourth multivariable predicted risk quintile) of CVD (63, 64).

2.2.1.2. Usefulness in Motivating Patients or Guiding Therapy

The ability of family history of CVD to motivate patients is not definitively established. Some studies have reported that persons with a positive family history of CHD were more motivated to modify their risk factors (75). In the CARDIA (Coronary Artery Risk Development in Young Adults) study, however, young adults did not self-initiate or modify their CVD risk factors after a change in family history of heart attack or stroke (76). Intensive interventions targeting those with a positive family history of CHD can improve risk factors; however, the sustainability of such interventions and their influence on CHD events has been more difficult to prove. For instance, a randomized study of black patients with a family history of premature CHD demonstrated that intensive community-based multiple risk factor intervention resulted in significant reductions in global CHD risk (improvements in cholesterol and blood pressure) compared with an enhanced primary care group (77). However, the sustainability of such efforts was disappointing; 5 years after completion, the previously observed improved risk factor profile of the intensive community-based group was no longer apparent and there was no significant difference in events (78).

2.2.2. Genotypes: Common Genetic Variants for Coronary Heart Disease

2.2.2.1. Recommendation for Genomic Testing

Class III: No Benefit

1. Genotype testing for CHD risk assessment in asymptomatic adults is not recommended (79, 80). ***(Level of Evidence: B)***

2.2.2.2. Association With Increased Cardiovascular Risk and Incremental Risk

CHD is typically due to the complex interplay between environmental factors and multiple common genetic variants (minor allele frequency >5%) with small or very modest effects (OR typically 1.2 to 1.5, and rarely >2.0) (81). The first widely replicated genetic variant for CHD was discovered by a genomewide association study on chromosome 9p21.3 (82-84). The 1.3- to 2.0-fold increased risk for MI observed with single nucleotide polymorphisms (SNPs) from the 9p21.3 genomic region has been observed in persons of various ethnicities, including European, Asian, and Hispanic descent, but thus far it has not been replicated in African Americans, which may relate to patterns of haplotype diversity in the genomic region (82-87). The mechanisms underlying the 9p21.3 association with CHD remain unclear, although the variants are adjacent to *CDKN2A, ARF*, and *CDKN2B,* which are genes thought to regulate

senescence and apoptosis (88). Variants tested in the 9p21.3 region (rs10757274, GG versus AA) were associated with a HR for incident CHD of 1.6 for incident CHD in men participating in the NPHS II (Northwick Park Heart Study II) (89). The addition of the genotype to a model based on traditional CVD risk factors did not significantly improve risk discrimination (area under the ROC, 0.62 [95% CI 0.58 to 0.66] to 0.64 [95% CI 0.60 to 0.68]; p=0.14). However, the genotype resulted in better model fit (likelihood ratio, p=0.01) and shifted 13.5% of the men into a more accurate risk category (89).

In the Women's Genome Health Study (n=22 129), an SNP at chromosome 9p21.3 was associated with an increased hazard for incident CVD; however, the SNP did not enhance model discrimination (C index, 0.807 to 0.809) or net reclassification when added to the Reynolds risk score, which includes family history (79). In another study, investigators reported that a genome score including 9 SNPs associated with serum lipid levels was associated with an increased risk of CVD events, but the score did not improve model discrimination (ROC, 0.80 for the model with and without the score). Furthermore, investigators reported that having a parent or sibling with a history of MI conferred a 50% increased risk of incident cardiovascular events (HR 1.52; 95% CI 1.17 to 1.97; p=0.002) in a model including the genotype score (90). Family history may integrate the complexity of interacting genomic and environmental factors shared by family members. Many other SNPs have been reported as risk markers for future CHD events. Given the very small OR and the small incremental risk information of the individual polymorphisms, the writing committee judged that genomic tests for CHD risk currently offer no proven benefit in risk assessment when added to a global basic risk score such as the FRS.

2.2.2.3. Usefulness in Motivating Patients or Guiding Therapy

Studies assessing whether genotype testing enhances motivation and success with adherence to recommended lifestyle and medical therapies demonstrate mixed results (80, 91). Smokers given scenarios of genotype testing information report more motivation to quit but lower levels of perceived control and similar success with smoking cessation at 1 year (92, 93). In another study, persons who agreed to receive genotype data (*GSTM1* SNP) were more likely to abstain from cigarette smoking at 12-month follow-up than those who declined the test, regardless of whether they tested positive or negative for the risk SNP (94).

Currently no data are available as to whether the results of genotype testing alter management or improve outcomes for prevention of CHD (92, 95). Despite the uncertainty about the clinical implications of most genotypic markers for CHD, there is widespread direct-to-consumer marketing of these tests (95). A concern is that advertisements and genetic information provided by for-profit genomic testing services may overstate claims and confuse or frighten consumers. In addition, regulation of the companies and provision for genetic counseling is sporadic (95). Thus, the writing committee was aware of potential

harm due to risk assessment using genotype testing, and given the limited benefit in terms of risk assessment, the writing committee concluded that these types of tests should not be done at this time.

2.3. Lipoprotein and Apolipoprotein Assessments

2.3.1. Recommendation for Lipoprotein and Apolipoprotein Assessments

Class III: No Benefit

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 (96). ***(Level of Evidence: C)***

2.3.2. Assessment of Lipoprotein Concentrations, Other Lipoprotein Parameters, and Modified Lipids

Beyond the standard fasting lipid profile (total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and triglycerides), additional measurements of lipid parameters or modified lipids have been proposed to extend the risk factor–cardiovascular prediction relationship. Each LDL particle contains 1 molecule of apolipoprotein B (often referred to as ApoB); thus, the concentration of ApoB directly reflects LDL particle numbers. The relationship between apolipoprotein A (often referred to as ApoA) and HDL is less direct. Several techniques directly measure lipid particle numbers or their size distribution. All lipid particles (e.g., LDL or HDL) are present in the circulation in a range of sizes. Oxidative modification of lipid particles occurs and appears to influence their atherogenic potential.

Non-HDL cholesterol, meaning cholesterol transported in LDL and very-low-density lipoprotein, reflects the total concentration of atherogenic particles, is closely related to particle number, and is simply calculated as the difference between total cholesterol and HDL-cholesterol blood concentrations. Particle size is similarly closely related to HDL and triglyceride concentrations. High concentrations of triglycerides lead to triglyceride enrichment of LDL or HDL. Subsequent particle modification by hepatic lipase leads to reduction of particle size and increased density, properties associated with heightened atherogenic potential. Treatment guidelines for the consideration of pharmacotherapy and the therapeutic targets for non-HDL cholesterol are 30 mg/dL higher than the thresholds for LDL cholesterol.

2.3.3. Risk Prediction Relationships Beyond Standard Risk Factors

Many so-called “advanced lipid measures” of the type discussed above, particularly apolipoprotein concentrations and particle number, have been shown by some, but not all, studies to be associated with cardiovascular outcomes comparable to standard lipid concentrations (43, 97). For example, the EPIC-Norfolk (European Prospective Investigation into Cancer and Nutrition) study among apparently healthy

individuals showed a 34% increased odds for future CHD associated with the highest quartile of LDL particle number after controlling for the FRS (97). However, this was similar to non-HDL cholesterol (38% increased odds); thus, no relative benefit of particle number determinations was found. A recent systematic review observed that no study has reported the incremental predictive value of LDL subfractions beyond that of traditional cardiovascular risk factors, nor evaluated their independent test performance (for example, sensitivity and specificity) (96). Although the distribution of advanced lipid measures is different in men and women (and is also related to menopausal status), the outcome relationships are present for both men and women in similar magnitude (98, 99).

Two studies have specifically evaluated the predictive performance of ApoB or nuclear magnetic resonance LDL-particle concentration for risk reclassification of asymptomatic individuals compared with standard lipids. In the Framingham Heart Study, little additional risk information was obtained from ApoB or ApoB/A-1 ratio compared with the total/HDL-cholesterol ratio (100). Thus, evidence that these more "advanced" lipid measures improve predictive capacity beyond standard lipid measurements is lacking (101).

The role of lipoprotein(a) [Lp(a)] in risk assessment has received attention as a potential additional risk marker. In the Emerging Risk Factors Collaboration, circulating concentration of Lp(a), a large glycoprotein attached to an LDL-like particle, was assessed for its relationship with risk of major vascular and nonvascular outcomes. Long-term prospective studies that recorded Lp(a) concentration and subsequent major vascular morbidity and/or cause-specific mortality published between January 1970 and March 2009 were identified through electronic and other means (102). Information was available from 126 634 participants in 36 prospective studies and spanned 1.3 million person-years of follow-up. Lp(a) concentration was weakly correlated with several conventional vascular risk factors and highly consistent within individuals over several years. In the 24 cohort studies, the risk ratio for CHD was 1.13 per standard deviation higher Lp(a) (95% CI 1.09 to 1.18) after adjustment for age, sex, lipid levels, and other conventional risk factors. The corresponding adjusted risk ratios were 1.10 (95% CI 1.02 to 1.18) for ischemic stroke, 1.01 (95% CI 0.98 to 1.05) for the aggregate of nonvascular deaths, 1.00 (95% CI 0.97 to 1.04) for cancer deaths, and 1.00 (95% CI 0.95 to 1.06) for nonvascular deaths other than cancer. This study demonstrated that there are continuous, independent, but modest associations of Lp(a) concentration with risk of CHD and stroke. As with previous individual reports, associations were only modest in degree, and detailed information on incremental risk prediction beyond traditional risk factors is still lacking. There have also been, and continue to be, concerns about measurement and standardization of measurement of Lp(a) in clinical settings (103). The writing committee therefore concluded that measurement of Lp(a) did not merit consideration for cardiovascular risk assessment in the asymptomatic individual.

2.3.4. Usefulness in Motivating Patients or Guiding Therapy

Additional lipid measures, beyond the standard lipid profile, vary in their interassay agreement, laboratory standardization, and established reference ranges and are generally limited by the absence of clear thresholds for initiation of treatment, therapeutic targets, or unique treatments beyond those already recommended by lipid treatment guidelines directed by the standard lipid profile (104).

2.3.5. Evidence for Improved Net Health Outcomes

There is no evidence that the assessment of additional lipid parameters leads to improved net health outcomes, and thus the cost-effectiveness of these measures cannot be assessed.

2.4. Other Circulating Blood Markers and Associated Conditions

2.4.1. Recommendation for Measurement of Natriuretic Peptides

Class III: No Benefit

1. Measurement of natriuretic peptides is not recommended for CHD risk assessment in asymptomatic adults (105). (*Level of Evidence: B*)

2.4.1.1. General Description

Atrial natriuretic peptide, B-type natriuretic peptide, and their precursors (N-terminal-proatrial natriuretic peptide) are emerging markers of prevalent CVD. Natriuretic peptides are released from the myocardium in response to increased wall stress and have been shown to be helpful in the diagnosis of heart failure among symptomatic patients, as well as having prognostic value in patients with established heart failure. Levels of natriuretic peptides have also been demonstrated to be markers of prognosis in patients with either acute coronary syndromes or stable CAD.

Recent studies have examined whether natriuretic peptides also predict the development of CVD in the asymptomatic, healthy adult population. The evidence from several prospective cohort investigations (Table 3) suggests that higher levels of natriuretic peptides predict the development of incident CVD, including heart failure, stroke, and atrial fibrillation.

There is some evidence that natriuretic peptides are stronger predictors of the development of heart failure than of incident coronary events (106-108), and other studies suggest that their prognostic value is attenuated after adjustment for echocardiographic measures such as left ventricular mass and left ventricular diameter. The mechanism for these associations is as yet undetermined, and it is possible that

natriuretic peptides are markers of left ventricular hypertrophy (LVH) or subclinical myocardial damage from hypertension, ischemia, or both.

Most prospective cohort studies (Table 3) report that natriuretic peptides predict prognosis and do so independent of other cardiac risk markers. Although these cohort studies suggest that natriuretic peptide levels convey prognostic information, the value of that information has not yet been rigorously evaluated by use of the C index or measures of risk reclassification (105). Consequently, the value of natriuretic peptide measurement in the assessment of cardiovascular risk among asymptomatic adults free of CAD or heart failure is not definitively known. Because of the absence of such data, the writing committee does not recommend measurement of natriuretic peptides for risk assessment in the asymptomatic adult.

2.4.1.2. Usefulness in Motivating Patients or Guiding Therapy

There have been no studies evaluating whether natriuretic peptides have value in motivating healthy patients, guiding treatment, or improving outcomes (there is some evidence on these points in populations of patients with heart failure but not in asymptomatic adults).

Table 3. Cardiovascular Disease Risk Assessment for B-Type Natriuretic Peptide

Study Name	Population	N	Age	Follow-Up (y)	Event	Main Findings
Framingham, MA (108)	Ambulatory adults, 3.4% with prior MI	3352	59	5.2	Major CVD (CHD death, MI, stroke, heart failure, coronary insufficiency)	CHD death: HR 1.27/SD of NT-proANP, 1.41/SD of BNP; major event: HR 1.28/SD of NT-proANP, 1.30/SD of BNP
Copenhagen, Denmark (109)	Random sample of general population without CVD	626	67.9	5.0	Death; major CVD (CHD death, MI, stroke, heart failure, unstable angina, TIA)	Death: HR 1.43/SD of NT-proBNP; CV event: HR 1.92/SD (all multivariable adjusted)
Glostrup, Denmark (107)	General population without CVD	1994	30 to 60	9.4	CV events (CVD death, MI, stroke)	CV events: 1.58/SD NT-proBNP; evidence of interaction with age
Rancho Bernardo, CA (110)	General population without CVD	805	77	6.8	Death; fatal CVD	Death: HR 1.74/SD of NT-proBNP; CV events: 1.85/SD of NT-proBNP (multivariable adjusted)

Glasgow, Scotland (111)	Random sample of general population, some with prevalent CHD	1252	50.4	4.0	All-cause mortality	Death: HR 2.2 for BNP ≥17.9 pg/mL (multivariable adjusted for age, sex, prior CHD)
Kuopio, Finland (112)	Kuopio Ischemic Heart Disease Risk Factor Study, longitudinal population-based sample of men	905	55.8 (46 to 65)	10	Death, CV death, CHD death	Multivariable-adjusted HR/SD change: proANP proBNP 1.35 1.26 1.48 1.41 1.52 1.44
Olmsted County, MN (106)	General population without CHF or renal failure	2042	62±10	5.6	All-cause mortality	Mortality somewhat assay dependent (Shionogi, Biosite, NT-proBNP), adjusted mortality ranged from 1.63 to 1.39, somewhat attenuated if adjusted for echocardiographic measurements
Malmo, Sweden (20)	General population without CVD	5067	58	12.8	CV events (CV death, MI, stroke)	Multivariable-adjusted HR/SD change for BNP 1.22, C index improvement, 0.004 (p=0.12)
Uppsala, Sweden (113)	General population without CVD	661	71	10	CV death	Multivariable-adjusted HR/SD change for NT-pro-BNP 1.58, C index improvement, 0.034 (p=0.20)

BNP indicates B-type natriuretic peptide; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NT, N-terminal; proANP, atrial natriuretic peptide; proBNP, B-type natriuretic peptide; SD, standard deviation; and TIA, transient ischemic attack.

2.4.2. Recommendations for Measurement of C-Reactive Protein

Class IIa

1. In men 50 years of age or older or women 60 years of age or older with LDL 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 (114). ***(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 (22, 115). ***(Level of Evidence: B)***

Class III: No Benefit

1. In asymptomatic high-risk adults, measurement of CRP is not recommended for cardiovascular risk assessment (116). ***(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 (22, 115). ***(Level of Evidence: B)***

2.4.2.1. Association With Increased Cardiovascular Risk and Incremental Risk Prediction

Inflammation is considered to be central to the pathogenesis of atherosclerosis, and numerous inflammatory biomarkers have been evaluated as risk factors or risk markers for CVD. The most intensively studied inflammatory biomarker associated with CVD risk is high-sensitivity CRP (hsCRP). CRP is associated with an adjusted increased risk for development of other CVD risk factors, including incident diabetes, incident weight gain, and new-onset hypertension (117-119). Interventions that improve CVD risk factors, such as exercise, weight loss, smoking cessation, statins, and antihypertensive treatments, are associated with lowering of CRP (120-124). CRP concentrations are fairly constant and repeatable over time (125, 126). In the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study participants randomly assigned to placebo, intraclass correlation was 0.54 (95% CI 0.53 to 0.55), which was similar to blood pressure and LDL cholesterol (127). Prior guidelines have recommended measuring CRP twice, particularly in persons with intercurrent illness if elevated when first measured (128).

A meta-analysis of >20 observational studies (both prospective and case-control) demonstrated that CRP levels are associated with incident CHD, with an adjusted odds ratio (comparing persons in the top versus bottom third) of 1.45 (95% CI 1.25 to 1.68) (129). CRP levels have been associated with

incident CHD in both men and women and persons of European, Japanese, and American Indian descents (22, 130-132). CRP is also associated with other forms of CVD, including incident stroke, peripheral artery disease, heart failure, atrial fibrillation, sudden death, and all-cause mortality (133-137). Despite consistent evidence that CRP levels above the population median value are associated with increased risk of CHD, it has not been determined whether CRP is causally related to CHD (138-142).

CRP modestly improved risk prediction of CVD endpoints in some studies beyond that accounted for by standard CVD risk factor testing (143). However, after accounting for standard CVD risk factors in many studies, model discrimination (area under the ROC) had no or minimal improvement (144, 145). As noted earlier in this report, statisticians recently proposed that measures of reclassification should be used to evaluate new biomarkers in addition to metrics of test discrimination, calibration, and other standard approaches to evaluate new markers. Data from the Physicians' Health Study and Framingham Heart Study have shown that CRP measurements improve reclassification of an individual's risk beyond standard risk prediction models (115, 145). However, a meta-analysis including data from the NPHS II and the Edinburgh Artery Study concluded that the ability of CRP to reclassify risk correctly was modest and inconsistent (144). As with most new biomarker tests, whether knowledge of CRP levels improves patients' motivation to adhere to CHD lifestyle or pharmacological treatments is unknown.

Recent clinical trial data provided evidence that measurement of CRP in highly preselected patients may have important clinical implications. The JUPITER trial was a randomized, double-blind, placebo-controlled trial of the use of rosuvastatin (20 mg/d) versus placebo in the primary prevention of CVD events in men and women (n=17 802) without diabetes with LDL cholesterol <130 mg/dL and CRP ≥2 mg/L (146, 147). After a median follow-up of 1.9 years, rosuvastatin was associated with a significant reduction in the primary endpoint of cardiovascular events. The HR for rosuvastatin versus placebo was 0.56 (95% CI 0.46 to 0.69; p<0.00001), and the event rate was 0.77 versus 1.36 per 100 person-years of follow-up (147). The reduction in endpoints was consistent across prespecified subgroups, including men and women, older and younger persons, whites and non-whites, and persons at higher and lower risk as measured by the FRS (147). Within JUPITER, 17 men and 31 women would need to be treated for 5 years to prevent the endpoint of MI, stroke, revascularization, or death (148). For persons at low risk (FRS ≤10), 37 persons would need to be treated for 5 years to prevent the same previous endpoints (148).

The JUPITER trial leaves a number of questions unanswered about use of CRP levels in cardiovascular risk assessment. Specifically, JUPITER was not a trial of CRP (149), because persons with unknown or low CRP concentrations were not studied. Cost-effectiveness of CRP testing in an asymptomatic population, beyond the specific patient population of JUPITER, has not yet been studied.

2.4.3. Metabolic: Hemoglobin A1C

2.4.3.1. Recommendation for Measurement of Hemoglobin A1C

Class IIb

1. Measurement of hemoglobin A1C (HbA1C) may be reasonable for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes (150-155). ***(Level of Evidence: B)***

2.4.3.2. General Description

HbA1C is a blood test useful for providing an estimate of average glycemic control over several months. The test has been shown to be predictive of new-onset diabetes (156). A systematic review and a recent international expert committee have suggested that HbA1C might be effective to screen for the presence of diabetes (157, 158). The ADA has endorsed the use of HbA1C to diagnose diabetes (HgbA1C ≥6.5%) and to identify persons at increased risk for diabetes (HbA1C, 5.7% to 6.4%) (158).

2.4.3.3. Association With Cardiovascular Risk in Persons Without Diabetes

In 1 study, in individuals without established diabetes, for every 1 percentage point higher HbA1C concentration, there was an adjusted 40% higher risk of CHD (p=0.002) (150). HbA1C was associated with an increased risk of incident stroke in the Japanese (159). Whether or not HbA1C improves CVD risk discrimination and reclassification is less certain. Some studies have reported that HbA1C does not improve prediction (156) or reclassification (160). However, other studies have observed that in persons without diabetes, higher levels of HbA1C are associated with an increased risk of CVD (161). In a 2010 report using data from the ARIC (Atherosclerosis Risk in Communities) study, it was demonstrated that in persons without diabetes, prediction models including HbA1C levels were associated with improved risk prediction, discrimination, and reclassification compared with prediction models that included standard risk factors and fasting glucose (155). This study is the strongest evidence available concerning the potential value of HbA1C for CVD risk assessment in asymptomatic people without diabetes. As with most other novel markers of CVD risk, it is unknown whether HbA1C is useful for motivating individuals to adhere to preventive interventions in the absence of diagnosed diabetes.

2.4.4. Urinary Albumin Excretion

2.4.4.1. Recommendations for Testing for Microalbuminuria

Class IIa

1. In asymptomatic adults with hypertension or diabetes, urinalysis to detect microalbuminuria is reasonable for cardiovascular risk assessment (162-164). ***(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 (165).** ***(Level of Evidence: B)***

2.4.4.2. General Description

Urinalysis for microalbuminuria is widely available, inexpensive, and associated with cardiovascular events (166). The ADA recommends annual urinalysis for detection of microalbuminuria in persons with diabetes mellitus (167). A recent meta-analysis showed that increased risk of CVD associated with microalbuminuria was present in persons both with and without diabetes (166). However, standardization of the measurement of urine albumin across laboratories is suboptimal (168, 169). It is logistically difficult for most patients to perform 24-hour urine collection, but studies have demonstrated that the first morning ("spot urine") urinary albumin–to-creatinine ratio has a similar ability to predict CVD events (170). On the basis of the urinary albumin–to-creatinine ratio on a morning spot urine sample, microalbuminuria is defined as 30 to 300 mg/g and macroalbuminuria is defined as >300 mg/g (171). Blacks and Mexican Americans have a higher prevalence of albuminuria than their Caucasian counterparts, regardless of diabetes status (172). Longitudinal data from the NHANES, between 1988-1994 and 1999-2004, found that the prevalence of microalbuminuria had increased from about 7.1% to 8.2% (p=0.01) (173).

Excretion of urinary albumin in the microalbuminuria range is considered a candidate for CVD risk biomarker for several reasons. Standard CVD risk factors are associated with microalbuminuria (174, 175). Microalbuminuria is associated with incident hypertension, progression to a higher blood pressure category, and incident diabetes (176, 177). Microalbuminuria and diabetes each appear to influence the other's progression (178). Furthermore, microalbuminuria has been associated with other novel risk factors for CVD, such as impaired endothelial function and inflammatory markers such as CRP (179-181). Microalbuminuria is considered to be an indicator of vascular dysfunction and early CVD (182).

2.4.4.3. Association With Cardiovascular Risk

A meta-analysis of 26 cohort studies with 169,949 participants reported that after accounting for standard CVD risk factors, there was a dose-response relation between albuminuria and risk of CHD (166). Compared with individuals without albuminuria, macroalbuminuria was associated with a doubling of risk (RR 2.17; 95% CI 1.87 to 2.52), and microalbuminuria was associated with a nearly 50% greater risk (RR 1.47; 95% CI 1.30 to 1.66) of CHD (166). The increased risk of CVD was present across many

different subgroups, including persons with and without hypertension, with and without diabetes, and with and without decreased estimated glomerular filtration rate (165, 166, 183). The prognostic importance of microalbuminuria also has been observed in older and younger individuals and ethnic minorities, including American Indians, South Asians, and African Carribbeans (166, 184-186).

In studies examining the incremental yield of adding urinary albumin excretion in the microalbuminuria range to standard CVD risk factors for CVD risk prediction, the Framingham Heart Study and the Cardiovascular Health Study observed only minor improvements in the C statistic (175, 187). However, the Cardiovascular Health Study observed that the urinary albumin–to-creatinine ratio did assist with risk reclassification. Persons at intermediate risk (predicted 5-year Framingham risk of 5% to 10%) with a urinary albumin–to-creatinine ratio ≥30 mg/g had a substantially higher 5-year risk of CHD than those with a ratio of <30 mg/g (20.1% versus 6.3%) (175).

2.4.4.4. Usefulness in Motivating Patients or Guiding Therapy

The writing committee is unaware of data that suggest that knowledge of albuminuria improves patient motivation or adherence to preventive therapies.

2.4.5. Lipoprotein-Associated Phospholipase A2

2.4.5.1. Recommendation for Lipoprotein-Associated Phospholipase A2

Class IIb

1. Lipoprotein-associated phospholipase A2 (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults (188-191). *(Level of Evidence: B)*

2.4.5.2. General Description

Lp-PLA2, or platelet-activating factor acetylhydrolase, is a proatherogenic enzyme produced by macrophages and lymphocytes (192). Lp-PLA2 hydrolyzes oxidized phospholipids in LDL, leading to the generation of lysophosphatidylcholine, oxidized nonesterified fatty acids, as well as other active phospholipids and inflammatory mediators (192). Reported clinical correlates of increasing Lp-PLA2 mass and activity include advanced age, male sex, smoking, and LDL; Lp-PLA2 activity also was inversely associated with HDL (193). There have been unexplained ethnic differences in Lp-PLA2 concentrations; adjusting for standard CVD risk factors, Lp-PLA2 activity was higher in white and Hispanic participants than in black participants (194).

2.4.5.3. Association With Cardiovascular Risk

In a meta-analysis of 14 studies, Lp-PLA2 was associated with an adjusted OR for CVD of 1.60 (95% CI 1.36 to 1.89) (190). Although there was moderate heterogeneity across studies in the meta-analysis, there was no significant difference between Lp-PLA2 mass and activity for risk prediction (190). A number of studies have reported that the increased CVD risk of Lp-PLA2 remains after adjusting for CRP, in addition to standard CVD risk factors (188, 189, 191). Several studies have examined whether Lp-PLA2 improves risk discrimination over and above models accounting for standard risk factors. Both the ARIC study and Rancho Bernardo study investigators observed that Lp-PLA2 was associated with a statistically significant increment in the area under the curve (AUC) ($p<0.05$), although the increments were small (for the ARIC study, 0.774, increased to 0.780 with the addition of Lp-PLA2; for the Rancho Bernardo study, change in ROC was 0.595 to 0.617) (189, 195). In a modest-sized study (n=765 patients), Lp-PLA2 was associated with a nonsignificant 9.5% net reclassification (196). These reports indicate that Lp-PLA2 has modest incremental risk prediction information, meaning its use in intermediate-risk patients might be reasonable. There is little information about the predictive capability of Lp-PLA2 in ethnic minorities, because the vast majority of studies reported to date have been conducted in whites of European ancestry (190).

2.4.5.4. Usefulness in Motivating Patients or Guiding Therapy

Presently there is no information about whether Lp-PLA2 concentrations are clinically effective for motivating patients, guiding treatment, or improving outcomes. Randomized studies have demonstrated that lipid-lowering therapies reduce Lp-PLA2, although there may be some variability by medication type (197, 198). Drugs under development that specifically inhibit Lp-PLA2 activity have been shown to lower Lp-PLA2 activity and inflammatory markers (199).

2.5. Cardiac and Vascular Tests for Risk Assessment in Asymptomatic Adults

2.5.1. Resting Electrocardiogram

2.5.1.1. Recommendations for Resting Electrocardiogram

Class IIa

1. A resting electrocardiogram (ECG) is reasonable for cardiovascular risk assessment in asymptomatic adults with hypertension or diabetes (200, 201). *(Level of Evidence: B)*

Class IIb

1. A resting ECG may be considered for cardiovascular risk assessment in asymptomatic adults without hypertension or diabetes (202-204). *(Level of Evidence: B)*

2.5.1.2. General Description

Epidemiological studies have shown that abnormalities on a resting 12-lead ECG are predictive of subsequent mortality and cardiovascular events among asymptomatic adults (200, 202, 205, 206). Specific electrocardiographic findings that have been linked to cardiovascular risk in population-based cohorts and asymptomatic patients with hypertension include LVH (especially when accompanied by repolarization changes), QRS prolongation, ST-segment depression, T-wave inversion, and pathological Q waves (202, 207-211). Several studies suggest that subtle electrocardiographic abnormalities detectable only by computer analysis may also be associated with increased risk (212-214).

The 12-lead resting ECG may provide information about other CVD, particularly cardiac arrhythmias, by documenting extra systoles, atrial fibrillation, ventricular pre-excitation, or prolonged QT interval. Many cardiomyopathies display nonspecific electrocardiographic changes. There has been interest in electrocardiographic abnormalities that may be predictive of sudden cardiac death in young, seemingly healthy athletes (215). The usefulness of screening with ECGs for these disorders is beyond the scope of the current document.

2.5.1.3. Association With Increased Risk and Incremental Risk

Table 4 presents a sample of longitudinal studies that report independent predictive value of different resting electrocardiographic measures in asymptomatic populations. A number of classification schemes have been described that may be useful for risk stratification. An example is the Novacode criteria, which divide electrocardiographic abnormalities into major and minor types (216). Major abnormalities include atrial fibrillation or atrial flutter, high-grade atrioventricular (AV) block, AV dissociation, complete bundle-branch block, pathological T waves, isolated ischemic abnormalities, LVH with accompanying repolarization abnormalities, and arrhythmias such as supraventricular tachycardia and ventricular tachycardia. Minor abnormalities include first- and second-degree AV block, borderline prolongation of the QRS interval, prolonged repolarization, isolated minor Q-wave and ST-T abnormalities, LVH by voltage only, left atrial enlargement, frequent atrial or ventricular premature beats, or fascicular blocks. Electrocardiographic findings have also been combined with echocardiography to improve risk stratification in patients with hypertension (201).

Abnormal Q waves on the ECG may indicate clinically unrecognized or “silent” MI. In the Framingham study, as many as one quarter of nonfatal MIs were found only through ECG changes (217). In a number of population studies, Q waves on the ECG indicate a higher cardiovascular risk (202, 211).

Electrocardiographic LVH and associated repolarization abnormalities have been predictive of subsequent cardiovascular risk in numerous prospective epidemiological studies, including the Framingham study. LVH on a resting ECG may indicate more severe or poorly controlled hypertension, which in turn increases cardiovascular risk (218). In 1 large randomized trial that specifically focused on patients with electrocardiographic LVH, regression of left ventricular mass as assessed by ECGs was a predictor of a lower risk of major cardiovascular events (219).

Few studies have evaluated the ability of the resting ECG to improve discrimination and reclassify risk compared with standard risk assessment. In 14 749 asymptomatic, postmenopausal women enrolled in the Women's Health Initiative, the resting ECG increased the C statistic over the FRS from 0.69 to 0.74 for prediction of CHD events (216). In 18 964 Cleveland Clinic patients without known CVD, the resting ECG similarly increased the C statistic by 0.04 and modestly improved reclassification (relative integrated discrimination improvement, 3%, $p<0.001$) (212).

2.5.1.4. Usefulness in Motivating Patients, Guiding Therapy, and Improving Outcomes

There have been no randomized trials demonstrating that findings on a resting ECG can be used to motivate better lifestyle behaviors in the asymptomatic adult. One large randomized trial offered suggestive evidence that electrocardiographic assessment of left ventricular mass may be useful for guiding antihypertensive therapy, because regression of electrocardiographic LVH was associated with reduced risk for sudden death (220), atrial fibrillation (219), heart failure (221), major CVD events (200), and diabetes (222). However, no randomized trial has directly addressed this question (223). One policy-based intervention study found that an ECG-based screening program for competitive athletes may have reduced the population risk of sudden cardiac death among young adults (224).

Table 4. Sample of Longitudinal Studies Reporting the Independent Predictive Value of Resting ECG Measures in Asymptomatic Populations

Primary Measurement(s)	First Author (Year, Country)	Type of Events	Follow-Up (y)	Population Characteristics (No.)	Mean Age (y) at Entry	Main Findings: Adjusted HR
Novacode major and minor abnormalities	Denes (2007, USA) (216)	Composite of cardiovascular events	3	Women in the Women's Health Initiative trial (14 749)	64	For minor abnormalities, HR 1.6; for major abnormalities HR 3.0; C index increased by 0.05 compared with FRS
Pooling project, major and minor	DeBacquer (1998,	CHD and CVD mortality, all-	10	Population-based sample (5208	49 (men), 48	Major ECG abnormalities

abnormalities*	Belgium) (205)	cause mortality		men, 4746 women)	(women)	predicted all-cause mortality (HR 1.8), CVD mortality (HR 3.3), and CHD mortality (HR 2.3). Minor ECG abnormalities were not predictive.
LVH with ST-depression and negative T wave	Larsen (2002, Denmark) (210)	MI, incident CHD, CVD mortality	21	Population-based sample (5243 men, 6391 women)	53	Predictive of MI (HR 1.9), incident CHD (HR 2.2), and cardiovascular mortality (HR 1.9)
Unrecognized MI	Sigurdsson (1995, Iceland) (211)	Death from CHD, stroke, and all causes	10+	Icelandic Heart Association Preventive Clinic, all men (9141)	52-58	Predictive of CHD death (HR 4.6) and all-cause death (HR 2.7)
Minor ST-T abnormalities	Daviglus (1999, USA) (207)	All-cause, CHD, and CVD mortality	29	Men employed at an electric company (1673)	48	Predictive of death due to CHD (HR 1.7), CVD (HR 1.4), and all causes (HR 1.3)
Digital ECG measures	Gorodeski (2009, USA) (212)	All-cause mortality	11	Ambulatory patients without known CVD (18 964)	51	Combined ECG measures predictive of all-cause death (HR 1.4, comparing 75th to 25th percentiles; C index increased by 0.04 compared with standard predictors; relative IDI increased by 3%)

*Major abnormalities include ST-segment depression, T-wave inversion, complete or second-degree atrioventricular block, complete left or right bundle-branch block, frequent premature beats, and atrial fibrillation or flutter. Minor abnormalities include nonpathological Q wave, a left- or right-axis deviation, QRS high voltage, borderline ST-segment depression, T-wave flattening, and QRS low voltage; and USA, United States.

CHD indicates coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; FRS, Framingham risk score; HR, hazard ratio; IDI, integrated discrimination improvement; LVH, left ventricular hypertrophy; and MI, myocardial infarction.

2.5.2. Resting Echocardiography for Left Ventricular Structure and Function and Left Ventricular Hypertrophy: Transthoracic Echocardiography

2.5.2.1. Recommendations for Transthoracic Echocardiography

Class IIb

1. Echocardiography to detect LVH may be considered for cardiovascular risk assessment in asymptomatic adults with hypertension (225, 226). *(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)*

2.5.2.2. Left Ventricular Function

Transthoracic echocardiography is a diagnostic modality widely used in cardiology practice. There are no echocardiographic findings with high sensitivity and specificity for the diagnosis of CHD in the absence of ischemia or infarction. Segmental wall motion abnormalities are the most common echocardiographic manifestation of CHD but are only present if there is active or recent (stunning) ischemia or there has been prior infarction. Moreover, segmental wall motion abnormalities do not uniformly represent ischemic territories caused by occlusive CAD, because they may also be present in patients with nonischemic cardiomyopathies. Additional manifestations of CHD include ischemic mitral regurgitation, global reduction in left ventricular systolic function, Doppler findings characteristic of diastolic dysfunction, and right ventricular dysfunction. However, none of these findings has sufficient sensitivity or specificity to be useful for screening or risk assessment in the asymptomatic patient at possible risk for CHD. Given the lack of evidence of risk assessment benefit in the general population, it was the consensus of the writing committee that echocardiography should not be performed for risk assessment in the asymptomatic adult without hypertension.

2.5.2.3. Left Ventricular Hypertrophy

LVH develops in response to varying stimuli and may be physiological in the setting of athletic training and pregnancy or pathological in response to pressure or volume overload, myocardial injury, or underlying genetic mutations. The pathophysiological mechanism for higher cardiovascular mortality in the setting of LVH is not completely understood, although studies have demonstrated decreased flow

reserve and greater susceptibility to injury associated with ischemia and infarction (227). The methodology for LVH measurement by echocardiography and the cut points for definition of LVH vary widely among studies. There is also wide variability as to whether LVH is indexed to body surface area, height, or weight (227, 228). A recent meta-analysis of 34 studies showed that 19 different criteria were used, leading to differences in the prevalence of LVH (229). The writing committee recommends the use of the methodology and cut points defined by the ASE (230). Separate cut points should be applied to men and women. Further studies may suggest that the definition of pathological LVH should be specific to race as well as sex. A recent study showed that athletic hypertrophy in African/Afro-Caribbeans (blacks) was greater than in whites (231).

LVH has been shown to be predictive of cardiovascular (including stroke) and all-cause mortality, independent of blood pressure, and across all racial groups that have been studied. In the predominantly white population of the Framingham Study, for every 50 g/m^2 higher left ventricular mass index, there was a RR of death of 1.73 (95% CI 1.19 to 2.52) independent of blood pressure level (232). In the African-American population enrolled in the ARIC study, LVH conferred an increased risk for CVD events (nonfatal MI, cardiac death, coronary revascularization, and stroke) even after adjusting for other risk factors with a HR of 1.88 in men and 1.92 in women (228). Among American Indians enrolled in the Strong Heart Study (64% female, mean age equal to 58), the prevalence of LVH on echocardiography was 9.5% and conferred a 7-fold increase in cardiovascular mortality and a 4-fold increase in all-cause mortality (201). In this study, echocardiographic evidence of LVH had additive discriminatory power over ECG evidence of LVH. Data from a Hispanic population (226) are similarly suggestive of the association of LVH and cardiovascular mortality. The association of LVH and mortality in many of these studies cannot be attributed only to the risk of developing atherosclerotic CHD, because patients with hypertrophic cardiomyopathy who die suddenly may be misclassified. Recent estimates suggest a 1 in 500 prevalence of hypertrophic cardiomyopathy in the population, which may contribute to the association between LVH and cardiovascular (including stroke) and all-cause mortality.

LVH is considered evidence of target organ damage in hypertension according to JNC 7 (233). The epidemiological association between pathological hypertrophy and CVD has also been studied in hypertensive populations (201, 226). For example, in the MAVI (MAssa Ventricolare sinistra nell'Ipertensione) study of patients with uncomplicated essential hypertension, there was a 40% higher risk of cardiovascular events for each 39 g/m^2 greater left ventricular mass index (225). Left ventricular architecture is also an important variable related to risk, with most studies suggesting that the presence of concentric rather than eccentric hypertrophy in the hypertensive population carries the highest risk.

2.5.2.4. Usefulness in Motivating Patients or Guiding Therapy

Although the finding of increased left ventricular mass on echocardiography could be envisioned to guide selection or intensity of therapy in hypertensive patients, JNC 7 recommendations do not risk stratify patients on the basis of target organ damage (233). Given the adverse prognosis associated with LVH in hypertension, further studies examined the comparative efficacy of specific antihypertensive agents in regressing LVH as well as survival benefits associated with LVH regression, but there was a lack of consistency among the trials. In a meta-analysis of 39 trials of antihypertensive therapy, angiotensin-converting enzyme inhibitors were the most effective agents, leading to a 13.3% reduction in left ventricular mass compared with 9.3% for calcium channel blockers, 6.8% for diuretics, and 5.5% for beta blockers (234). In a comparison of enalapril and long-acting nifedipine in patients with essential hypertension, the PRESERVE (Heart Failure with Preserved Systolic Function) trial, a prospective randomized enalapril study evaluating regression of ventricular enlargement, systolic and diastolic pressures as well as left ventricular mass were reduced to a similar degree with both agents (235). The LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) trial echocardiographic substudy demonstrated superior left ventricular mass reduction (21.7 g/m^2) in patients treated with losartan compared with patients treated with atenolol (17.7 g/m^2) (218). Diuretics demonstrated superiority in treating LVH regression over alternative agents in both the TOMHS (Treatment of Mild Hypertension Study) and Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents, using chlorthalidone and hydrochlorthiazide, respectively (236, 237).

LVH regression does not adversely affect cardiac function and may be associated with improvements in diastolic function. Most importantly, patients who demonstrate LVH regression on antihypertensive therapy have a lower rate of cardiovascular events than those who do not, independent of the extent of blood pressure control (238, 239).

Despite these observations, there have been no trials that target antihypertensive therapy to regress echocardiographically detected LVH, and thus the results continue to generate hypotheses.

No studies have examined whether a patient's knowledge of echocardiographic results demonstrating LVH will improve adherence to lifestyle modifications or pharmacologic treatment of hypertension.

2.5.3. Carotid Intima-Media Thickness on Ultrasound

2.5.3.1. Recommendation for Measurement of Carotid Intima-Media Thickness

Class IIa

1. Measurement of carotid artery IMT is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (240, 241). 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 (241). ***(Level of Evidence: B)***

2.5.3.2. General Description

Carotid IMT testing is a noninvasive, nonionizing radiation test using ultrasound imaging of the carotid artery wall to define the combined thickness of the intimal and medial arterial wall components. It is most commonly measured in the far wall of the common carotid artery; however, it can also be measured in the near wall and other carotid segments (bulb, internal). With well-trained operators, the test has been shown to be highly accurate with excellent intertest and interobserver reproducibility primarily in research settings and less commonly in practitioner-based settings (242). The available data on risk associated with carotid IMT are drawn almost exclusively from research settings using highly standardized protocols. The use of common carotid IMT as a standard site of measurement has been proposed due to its inherent greater reproducibility and ability to refine the cardiovascular risk prediction. Published recommendations on the required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results (241, 243). There is a need for provider competency and lab accreditation standards to ensure quality imaging. An elevated level of carotid IMT is commonly cited as a level that surpasses the population-based 75th percentile value, but this must be identified specific to a particular carotid arterial segment (e.g., common or internal carotid artery) and ultrasound methodology for which tables are available (241).

2.5.3.3. Independent Relationship Beyond Standard Risk Factors

Carotid IMT has been independently associated with future risk for ischemic coronary events and stroke in middle-aged and older individuals (244). The risk of incident CHD events increases in a continuous fashion as carotid IMT increases (RR increases approximately 15% per 0.10-mm increase in carotid IMT); thus, measurement of carotid IMT has been shown in research studies to be a marker of risk for atherosclerotic CVD. Furthermore, the finding of atherosclerotic plaque, operationally defined as a focal increase in thickness >50% of the surrounding IMT, increases the predicted CAD risk at any level of carotid IMT (245). These values were determined after adjustment for traditional CVD risk factors.

The relationship between carotid IMT and incident CHD events was initially noted in the Kuopio Ischemic Heart Disease Risk Factor study, in which risk of future MI in Finnish men increased by 11% for every 0.1-mm increment in carotid IMT (246). For carotid IMT values >1 mm, there was a 2-fold

greater risk of acute MI over 3 years. The ARIC study showed that for every 0.19-mm increment in carotid IMT, risk of death or MI increased by 36% in middle-aged patients (45 to 65 years of age) (247). CHD risk was almost 2-fold greater in men with mean carotid IMT >1 mm and even greater in women (RR 5.0). Not all studies, however, have shown differences between men and women in the predictive value of carotid IMT. For example, the Rotterdam study found that the risk of CHD events and carotid IMT was similar among men and women (248).

The association between carotid IMT and incidence of MI and stroke has been noted in older populations and other high-risk populations. In the Cardiovascular Health Study, the RR for MI, adjusted for age, gender, and standard cardiovascular risk factors, was 3.15 (95% CI 2.19 to 4.52) when an average IMT was used for the common carotid and internal carotid arteries and when comparing the highest quintile versus the lowest quintile. These differences held true for patients with and without known CVD (249). Among middle-aged adults with diabetes mellitus in the ARIC study, an IMT ≥1 mm was associated with an increase in the ROC AUC from 0.711 to 0.724 among women and 0.680 to 0.698 in men (250) when this elevated IMT was included in traditional risk factor predictive models. Similarly, in the Cardiovascular Health Study, the incidence of CAD was shown to increase from 2.5% to 5.5% per year among patients with diabetes with subclinical vascular disease (251).

Carotid IMT measurement can lead to improved cardiovascular risk prediction and reclassification. In the ARIC study, 13 145 individuals were followed for approximately 15 years for incident hard coronary events and revascularization. Carotid IMT measurements, which included both IMT and carotid plaque, were incremental to traditional risk factors for prediction of incident cardiovascular events. In particular, among intermediate-risk patients (10% to 20%, 10-year estimated risk group), the addition of carotid IMT and plaque information led to clinical net reclassification improvement of approximately 9.9% (240).

Comparisons of carotid IMT with coronary calcium scoring as methods to modify cardiovascular risk assessment have been made in both middle-aged (MESA) and older individuals (Cardiovascular Health Study). Each study showed that carotid IMT was an independent predictor of cardiovascular outcomes. Coronary calcium was a relatively stronger predictor for coronary outcomes, whereas carotid IMT was a stronger predictor of stroke in MESA (252). In contrast, significant and similar magnitude relationships to cardiovascular outcomes (HRs for fourth quartile versus first quartile for each test, approximately 2.1) were observed in the Cardiovascular Health Study for both tests (253). Given the discrepancy between these available studies, the data are insufficient to conclude whether these tests are clinically equivalent or not. Thus, at this time, test selection in clinical practice is better guided by local and patient factors such as expertise, cost, and patient preference.

Epidemiological studies demonstrate that IMT typically progresses at an average rate of ≤0.03 mm per year, and the rate of progression appears to be related to risk of cardiovascular event (254). Progression can be slowed by cholesterol-lowering drugs (statins and niacin) and other risk factor modifications (e.g., control of blood pressure). However, serial scanning of carotid IMT is challenging in individual patients across brief time horizons due to variability in measurement in relation to the rate of disease progression and is therefore not recommended in clinical settings.

Images of subclinical atherosclerosis are hypothesized to alter patient behavior, but the evidence is insufficient (255).

2.5.3.4. Usefulness in Motivating Patients or Guiding Therapy

The finding of increased carotid IMT should clinically guide selection or intensity of therapy. However, evidence is lacking regarding whether measurement of carotid IMT alters therapy (Table 5). Clinical tools integrating carotid IMT within global risk scoring systems are not available.

2.5.3.5. Evidence for Improved Net Health Outcomes

The incremental value of carotid IMT and cost-effectiveness beyond that available from standard risk assessments to improve overall patient outcomes is not established.

Table 5. Summary of Prospective Studies Evaluating Carotid IMT and Incident Coronary Events in Patients Without Known CHD

Patient Details							
Study, Participants	Carotid IMT Measurement	Clinical Events	Follow-Up (y)	Age (y)	Sex	Carotid IMT Increment (mm)	OR (95% CI)
KIHD, 905 (112)	CCA/carotid bifurcation*	Fatal/nonfatal MI	1 mo to 3 y	42 to 60	Men	0.1	1.11 (1.06 to 1.16)
ARIC, 12,841 (247)	CCA/ICA/carotid bifurcation†	Fatal/nonfatal MI	2 to 7	45 to 64	Men Women	0.19 0.19	1.36 (1.23 to 1.51) 1.69 (1.50 to 1.90)

CHS, 4476 (249)	CCA/ICA‡	MI/stroke	6.2	>65	Men and women	0.20	1.46 (1.33 to 1.60)§‖
Rotterdam Study, 7983 (248)	CCA¶	MI/stroke	2.7	>55	Men Women	0.163 0.163	1.56 (1.12 to 2.18)# 1.44 (1.00 to 2.08)#
MESA, 6698 (252)	CCA	Cardiovascular events	3.9	45 to 64	Men and women	0.19	1.3 (1.1 to 1.4)

*Mean carotid IMT; †Mean far wall, internal carotids, and bifurcation; ‡Mean of CCA and ICA; §OR is risk for MI and coronary death only; OR for MI and stroke was 1.47 (95% CI 1.37 to 1.67); ‖CCA, carotid IMT; ¶Mean CCA; #OR is for risk of MI only.

ARIC indicates Atherosclerosis Risk in Communities study; CCA, common carotid artery; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CI, confidence interval; ICA, internal carotid artery; IMT, intima-media thickness; KIHD, Kuopio Ischemic Heart Disease study; MESA, Multiethnic Study of Atherosclerosis; MI, myocardial infarction; and OR, odds ratio.

2.5.4. Brachial/Peripheral Flow-Mediated Dilation

2.5.4.1. Recommendation for Brachial/Peripheral Flow-Mediated Dilation

Class III: No Benefit

1. Peripheral arterial flow-mediated dilation (FMD) studies are not recommended for cardiovascular risk assessment in asymptomatic adults (256, 257). *(Level of Evidence: B)*

2.5.4.2. General Description

Peripheral arterial FMD is a noninvasive measure of endothelial function. Augmented flow is produced by a sustained period (typically 4 to 5 minutes) of forearm compression accompanied by vascular occlusion followed by release. In the setting of healthy endothelium, increased flow stimulates release of nitric oxide, inducing local brachial artery vasodilation. The degree of dilation can be measured using high-resolution ultrasound. The technique requires a highly skilled sonographer, highly standardized measurement conditions (including time of day, temperature, drug administration), and suitable ultrasound machine. Many examiners also use specialized computer software to semiautomatically quantitate the brachial artery diameter. Considerable variability exists for values of FMD determined by different investigators, even in similar patient populations, suggesting technical challenges with the measurement (258). Important technical factors influencing FMD are duration of forearm occlusion and the location of the occluding cuff, but many other factors are also important, as mentioned above. In

research settings, brachial artery FMD has been shown to correlate with invasive measures of coronary artery FMD after adenosine triphosphate infusion, suggesting that peripheral FMD may be a suitable substitute for invasive coronary endothelial function testing (257). FMD also correlates with other noninvasive measures of cardiovascular risk, including CRP, carotid IMT, and measures of arterial stiffness.

PAT is a second method of assessing postocclusion vasodilation. This method uses bilateral finger cuffs that sense pulse wave volume. After a 5-minute flow occlusion in 1 arm, the resulting augmentation of pulse volume in the occlusion arm is compared with the control arm, yielding a PAT ratio. The PAT ratio provides information similar to FMD (256, 259).

2.5.4.3. Association With Increased Risk and Incremental Prediction

Many studies have documented a relationship between FMD, PAT, and traditional CVD risk factors. FMD and PAT ratios are lower (abnormal) in subjects with greater numbers of risk factors or higher levels of FRS. Diabetes and smoking have the most powerful associations with abnormal FMD. A meta-regression analysis of 211 publications reported on 399 populations where both FMD and traditional risk factors were available (260). By design, many of these populations had existing CVD. The relationship between FMD and risk factors was most clear in the category with the lowest baseline risk. In this group, for each percentage point higher FRS, FMD was lower by 1.42%. In populations with an intermediate or high FRS, FMD was not related to the score. This finding fits with the hypothesis that FMD is an early marker of vascular dysfunction. Once multiple risk factors are present, FMD may become so impaired that additional risk factors do not further impair it.

PAT ratio was measured in the Framingham Third Generation Cohort (n=1957) (261). In a stepwise multivariable regression model, PAT ratio was inversely related to male sex, body mass index, total/HDL-cholesterol ratio, diabetes, smoking, and lipid-lowering treatment. In this study, hypertension was not related to PAT.

It is unclear whether these measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors. The relationship between FMD and incident cardiovascular events was reported in a population-based cohort of older adults (262). In the Cardiovascular Health Study, 2792 (2791 with complete data) adults aged 72 to 98 years underwent FMD measures (262). During 5-year follow-up, 24.1% of these subjects had events. At study entry, 76% of this population (n=2125) was free of known CVD. In the subset without known CVD at entry, the predictive value of FMD (after adjustment for age, gender, diabetes, blood pressure, cholesterol, and HMG-CoA [3-hydroxy-3-methylglutaryl-coenzyme A] reductase inhibitor use) was directionally similar to the whole population but failed to achieve statistical significance (p=0.08). The addition of brachial FMD to the

predictive model containing the classical cardiovascular risk factors increased the AUC by a net change of only 0.001, and the p value for the increase was not significant (area under receiver operating statistic 0.841 versus 0.842). NOMAS (Northern Manhattan Study), a smaller multiethnic, prospective cohort study of 842 subjects free of CVD examined the relationship of FMD to 36-month cardiovascular events (263). Although FMD was associated with the occurrence of future events (HR 1.12 for every 1% decrease in FMD), the association was no longer statistically significant when traditional cardiovascular risk factors were included in a multivariable analysis. In contrast, a study of 2264 asymptomatic postmenopausal women found that FMD was independently related to cardiovascular events (RR 1.12; 95% CI 1.04 to 2.00; $p<0.001$) when included in a model with traditional risk factors (264). No measures of reclassification were reported in this study.

2.5.4.4. Usefulness in Motivating Patients or Guiding Therapy

There is no evidence that arterial FMD studies are useful for motivating asymptomatic persons to adhere to preventive therapies.

In a study of 400 hypertensive postmenopausal women followed up for an average of 67 months (265), endothelial function was measured as FMD of the brachial artery at baseline and at 6 months after initiation of blood pressure control. After 6 months of treatment, FMD had not changed (≤10% relative to baseline) in 150 (37.5%) of the 400 women, whereas it had significantly improved (>10% relative to baseline) in the remaining 250 women (62.5%). During follow-up, failure to have an improved FMD at 6 months was an independent predictor of nonfatal cardiovascular events requiring hospitalization. This study demonstrates that a significant improvement in endothelial function may be obtained after 6 months of antihypertensive therapy and also appears to identify patients who may have a more favorable prognosis.

Due to the limited data available, the writing committee concluded that it was premature to recommend serial FMD measurements to monitor treatment effects. In addition, due to the technical challenges of standardizing measurement of FMD and the relatively modest evidence of incremental change in risk assessment, measurement for risk assessment was not regarded as appropriate for risk assessment in the asymptomatic adult.

2.5.4.5. Changes in Patient Outcomes

To date, there are no published trials evaluating the impact of specific therapy on clinical outcome in patients identified as having abnormal peripheral endothelial function.

2.5.5. Pulse Wave Velocity and Other Arterial Abnormalities: Measures of Arterial Stiffness

2.5.5.1. Recommendation for Specific Measures of Arterial Stiffness

Class III: No Benefit

1. Measures of arterial stiffness outside of research settings are not recommended for cardiovascular risk assessment in asymptomatic adults. *(Level of Evidence: C)*

2.5.5.2. Description of Specific Measures of Arterial Stiffness

Arterial stiffness is a consequence of arteriosclerosis, the process of arterial wall thickening, and loss of elasticity that occurs with onset of vascular disease and advancing age. Besides pulse pressure (the numeric difference between the systolic and diastolic blood pressures), multiple other specific measures of arterial stiffness have been described (98, 266, 267). The most commonly studied measures of arterial stiffness are aortic pulse wave velocity (PWV) and pulse wave analyses such as the aortic augmentation index (266).

Because blood is a noncompressible fluid, transmission of the arterial pressure wave occurs along the arterial wall and is influenced by the biomechanical properties of the arterial wall. When the arteries are stiffened, the pulse wave is propagated at an increased velocity, and increased PWV is therefore correlated with stiffness of the arteries. Factors associated with PWV include advancing age as well as the long-term effects of cardiovascular risk factors on the structure and function of the arterial wall. PWV is generally measured using applanation tonometry but can also be measured by Doppler ultrasound or magnetic resonance imaging (MRI). MRI is more costly and therefore is typically not used for testing in asymptomatic persons.

Pulse wave analysis is based on the concept that the pressure wave is partially reflected back toward the aorta at various points of discontinuity in arterial elasticity. Applanation tonometry is considered a relatively simple and reproducible method of collecting data for pulse wave analysis in research settings. The most commonly reported measure in pulse wave analysis is expressed as a fraction of the central pulse pressure, called the aortic augmentation index. The augmentation index is said to be most useful in patients under the age of 60 years (266). Both pulse wave analysis and PWV are typically determined by commercial devices that perform the analyses based on proprietary analytic algorithms (267).

Although predictive information (see below and Table 6) suggests a potential clinical role for measures of arterial stiffness, there are a number of technical problems that the writing committee believed would restrict the applicability of measures of arterial stiffness predominantly to research settings at this time (266, 267). For measures of arterial stiffness to be incorporated into clinical practice, measurement protocols must be well standardized, quality control procedures established, and risk-defining thresholds identified (266). Reproducibility is a problem, as is operator dependence, both of which limit the generalizability of findings derived from research studies. Additional technical concerns include the need to standardize room temperature, time of day of testing, keeping the patient at rest for at least 10 minutes before measurements are recorded, and careful attention to timing of drug and caffeine intake (267). The writing committee felt that the technical concerns make arterial stiffness tests less suitable for addition to the clinical practice of risk assessment in asymptomatic adults due to problems with measurement and data collection.

2.5.5.3. Evidence on the Association With Increased Cardiovascular Risk and Incremental Risk

From the standpoint of predictive studies within general "healthy" populations, measures that have been studied are the PWV, ambulatory arterial stiffness index, and carotid pulse pressure (versus brachial pulse pressure). Predictive results in general populations are summarized for 11 longitudinal studies in Table 6. Although a few of these studies have reported no predictive capability of these measures of arterial stiffness, most studies indicated predictive capability that is additive to standard risk factors, including (in some cases) systolic and diastolic blood pressures as well as ankle-brachial index (ABI). In some studies, but not all, HRs have been higher for stroke risk than for CAD risk. No studies have directly compared these measures of CVD risk with other measures of "subclinical" CVD such as arterial IMT or CAC score. HRs have generally been in the very modest predictive range of 1.1 to 1.3 for various measures of arterial stiffness and CHD outcomes. Information on changes in the C statistic or other measures of incremental risk stratification has generally not been reported.

2.5.5.4. Usefulness in Motivating Patients or Guiding Therapy

No information has been reported on any of these topics in well-conducted studies of populations of healthy adults.

Table 6. Longitudinal Studies Reporting the Independent Predictive Value of Arterial Stiffness in Asymptomatic Populations

Primary Measurement Type	First Author (Year, Country)	Type of Events	Follow-Up (y)	Population Characteristics (No.)	Mean Age (y) at Entry	Main Findings: Adjusted HR
Aortic PWV	Meaume (2001, France) (268)	CV mortality	2.5	Elderly men and women (>70 y) (141)	87	1.19 (95% CI 1.03 to 1.37) for total CVD mortality (top decile)
ΔD (strain) as primary measure	Stork (2004, Netherlands) (269)	CV and all-cause mortality	4.0	Elderly men (367)	78	No stiffness measure associated with outcomes
Aortic PWV	Sutton-Tyrrell (2005, USA) (270)	CV mortality and events	4.6	Elderly, both sexes (2488) in Health ABC study	55	~RR 1.15 to 1.30; p=0.019 for Q4:Q1 for CHD; ~RR 2.6; p=0.004 for stroke Q4:Q1
Aortic PWV	Shokawa (2005, Japan) (271)	CVD mortality	10	General population, both sexes (492)	63.7	Top 40%: ~4.2 (95% CI 1.39 to 12.96; p=0.01)
Ambulatory arterial stiffness index	Dolan (2006, Ireland) (272)	CVD mortality	5.3	General population, both sexes, ages 16 to 96 y (11 291)	54.6	1.16 (95% CI 1.05 to 1.27) in fully adjusted model for total CVD death
Aortic PWV	Willum-Hansen (2006, Denmark) (273)	Fatal and nonfatal CVD and CHD	9.4	General population (1678), both sexes, ages 40 to 70y	51	~HR 1.15 (95% CI 1.01 to 1.30) per 1 SD increase for all endpoints
Ambulatory arterial stiffness index	Hansen (2006, Denmark) (274)	Fatal and nonfatal CVD and stroke	9.4	General population (1678), both sexes, ages 40 to 70 y	51	~ HR 1.6 (95% CI 1.14 to 2.28; p=0.007) for stroke, but NS for CHD and CVD
Carotid-femoral PWV index	Mattace-Raso (2006, Netherlands) (275)	CVD, CHD, stroke, all-cause	4.1	Healthy elderly, both sexes (2835); Rotterdam study	71.7	~1.9 to 2.0 for T3:1 for CVD, CHD, stroke

CPP versus BPP	Roman (2007, USA) (276)	CVD, fatal and nonfatal	4.8	Healthy American Indians, both sexes (2403), Strong Heart Study	63	Aortic PP, ~ 1.12 per 10 mm Hg, p=0.008
CD, CPP, BPP	Leone (2008, France) (277)	CHD, fatal and nonfatal	4	Community elderly (>65 y) (3337), Three-City study	73.2	CD, ~2.0 (95% CI 1.27 to 3.17) for T3:1; CPP, ~ 2.1 (95% CI 1.24 to 3.70) (T3:T1); BPP, ~ 2.1 (95% CI 1.38 to 3.40) (T3:T1)
CPP and BPP	Pini (2008, Italy) (278)	Total CV events (fatal and nonfatal)	8	Community elderly (>65 y) (173)	73	BPP, NS; CPP HR 1.23 (95% CI 1.11 to 1.38; p<0.001) per 10 mm Hg

BPP indicates brachial pulse pressure; CD, carotid distension; CHD, coronary heart disease; CI, confidence interval; CPP, carotid pulse pressure; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; NS, nonsignificant; PP, pulse pressure; PWV, pulse wave velocity; Q, quartile; RR, relative risk; SD, standard deviation; T, tertile; and USA, United States.

2.5.6. Recommendation for Measurement of Ankle-Brachial Index

Class IIa

1. Measurement of ABI is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (279). *(Level of Evidence: B)*

2.5.6.1. General Description of Ankle-Brachial Index

The ABI is an office-based test to check for the presence of PAD. It is performed by Doppler measurement of blood pressure in all 4 extremities at the brachial, posterior tibial, and dorsalis pedis arteries. The highest lower-extremity blood pressure is divided by the highest of the upper-extremity blood pressures, with a value of <0.9 indicating the presence of PAD, which is defined as >50% stenosis. When defined in this way, the ABI has both a high sensitivity and specificity for anatomic stenosis. In addition to signifying PAD, an abnormally low ABI has also been shown to be a predictor of cardiovascular events. Intermediate values (0.9 to 1.1) also have a graded association with CVD risk. A high ABI (>1.3), which indicates calcified, noncompressible arteries, is also a marker of arterial disease. The prevalence of PAD as indicated by an abnormal ABI increases with age and is associated with traditional risk factors for CVD (280, 281).

2.5.6.2. Association With Increased Risk

Many epidemiological studies have demonstrated that an abnormal ABI in otherwise asymptomatic individuals is associated with cardiovascular events (279, 282-293). A recent collaborative study combined data from 16 studies (279) and included a total of 24 955 men and 23 399 women without a history of CHD. Importantly the study included data from a wide representation of the population, including blacks, American Indians, persons of Asian descent, and Hispanics as well as whites (288, 293-295). The mean age in the studies ranged from 47 to 78 years, and the FRS-predicted rate of CHD ranged from 11% to 32% in men and from 7% to 15% in women. There were 9924 deaths (25% due to CHD or stroke) over 480 325 patient-years of follow-up. For an ABI of <0.9 compared with an ABI of 1.11 to 1.4, the HR for cardiovascular mortality and major events was 3.33 for men and 2.71 for women (279). When adjusted for the FRS, the HRs were only moderately lower (2.34 in men and 2.35 in women), demonstrating the additive predictive value of the ABI beyond the FRS (279). An ABI of >1.4 was also associated with higher risk within most of the FRS categories. However, the greatest incremental benefit of ABI for predicting risk in men was in those with a high FRS (>20%), in whom a normal ABI reduced risk to intermediate (279). In women the greatest benefit was in those with a low FRS (<10%), in whom

an abnormally low or high ABI would reclassify them as high risk, and in those with an intermediate FRS, who would be reclassified as high risk with a low ABI. Reclassification occurred in 19% of men and 36% of women. Thus, an abnormally low or abnormally high ABI is associated with increased cardiovascular risk in both men and women, and the risk prediction extends beyond that of the FRS alone.

2.5.6.3. Usefulness in Motivating Patients or Guiding Therapy

There are no randomized clinical trials that demonstrate measurement of ABI is effective in motivating asymptomatic patients to comply with measures to reduce cardiovascular risk. There is also no indication that serial measurement of the ABI can be used to monitor treatment or guide treatment approaches.

2.5.7. Recommendation for Exercise Electrocardiography

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 (296-298). ***(Level of Evidence: B)***

Patients who are capable of exercising on a bicycle or treadmill with a normal resting 12-lead ECG are connected to a modified-torso 12-lead ECG and asked to exercise at increasing levels of stress until exhaustion or other milestones are met, such as a target heart rate or worrisome clinical findings (e.g., severe chest discomfort). Treadmill testing is more commonly performed in the United States; a variety of protocols are used during which both speed and grade are gradually increased in stages. Ideal exercise times are about 8 to 12 minutes. Although the best known measurement is change in ST-segment deviation during and after exercise, other important prognostic measures are exercise capacity, chronotropic response, heart rate recovery, and exercise-induced arrhythmias (299).

2.5.7.1. Association With Increased Risk and Incremental Risk

Several specific findings on exercise testing are associated with subsequent mortality and cardiovascular events (Table 7) (299). An AHA scientific statement has described in detail exercise test risk predictors in asymptomatic adults (299). Although many clinicians typically think of the exercise test as primarily a measure of ST-segment changes that may reflect ischemia, evidence has demonstrated that the ST segment is a weak marker for prevalent and incident CAD (300, 301). In contrast, non-ECG measures have emerged as stronger predictors of risk. Probably the most powerful risk marker obtained during routine exercise testing is exercise capacity; numerous investigators have consistently found that

depressed exercise capacity is associated with increased cardiovascular risk (296, 298, 299, 302-305). In a very large primary care population, adding exercise variables to clinical variables increased the C index from 0.75 to 0.83 for prediction of all-cause mortality (306). Among healthy executives, adding exercise variables to clinical variables increased the C index from 0.73 to 0.76 (307).

Markers reflective of autonomic nervous system function can predict major cardiovascular events, total mortality, and sudden cardiac death (297, 308-313). Failure of the heart rate to rise appropriately during exercise has been termed chronotropic incompetence and has been linked to adverse outcome whether or not beta blockers are being taken (299, 314, 315). The fall in heart rate immediately after exercise, also known as heart rate recovery, is thought to reflect parasympathetic tone (316). Decreased heart rate recovery has been associated with death or cardiac events in a number of populations, including those that are entirely or primarily asymptomatic (307, 309, 310, 313, 317-319). Frequent ventricular ectopy during recovery, similarly thought to reflect abnormalities of parasympathetic nervous system function, are also independently associated with long-term risk of mortality (309). The adjusted HR is 1.5 (95% CI 1.1 to 1.9; p=0.003) (309).

To synthesize the clinical importance of these measures, a number of exercise test scoring schemes have been developed and validated. Probably the best-known is the Duke Treadmill Score (DTS), which incorporates exercise capacity, ST-segment changes, and exercise-induced angina (313, 320, 321). The formula for the DTS is exercise time – (4 × angina index) – (5 × maximal ST-segment depression). The DTS has been validated in a number of populations as predictive of risk. Of note however, the only element of the DTS that has been consistently associated with increased risk has been exercise capacity (301, 313). In both younger and older adults, ST-segment changes and exercise-induced angina have not consistently appeared as risk predictors (301, 313).

The DTS has been criticized for its failure to take into account demographics and simple risk factors. A nomogram based on simple demographics, easily obtained risk factors, and standard exercise test findings was found to better discriminate risk than the DTS (C index, 0.83 versus 0.73; p<0.001); the nomogram was also successfully validated in an external cohort (306).

2.5.7.2. Usefulness in Motivating Patients or Guiding Therapy

No randomized trials have specifically addressed the role of exercise testing in these 3 areas. There is also no direct information on the role of the exercise test to monitor treatment effects in asymptomatic adults.

Table 7. Sample of Longitudinal Studies Reporting the Independent Predictive Value of Exercise Electrocardiography Measures in Asymptomatic Populations

Primary	First Author (Year,	Type of	Follow-	Population	Mean	Main Findings:

Measurement(s)	Country)	Events	Up (y)	Characteristics (No.)	Age (y) at Entry	Adjusted HR
Exercise capacity	Gulati (2003, USA) (296)	All-cause death	8.4	Women with mean FRS of 6 (5721)	52	Compared with >8 METs, HR 1.9 (95% CI 1.3 to 2.9) for 5 to 8 METs and 3.1 (95% CI 2.0 to 4.7) for <5 METs
Exercise capacity	Wei (1999, USA) (298)	CVD death and all-cause death	10	Men in preventive medicine clinic (25,714)	44	For CVD death, HR 3.1 (95% CI 2.5 to 3.8); for all-cause death, HR 2.2 (95% CI 1.4 to 3.8); all in normal weight; similar in overweight and obese men
Exercise capacity and heart rate recovery	Adabag (2008, USA) (297)	Sudden death, CHD death, nonfatal CHD, all-cause death	7	Men in MRFIT Study (12,555)	46	For all-cause death, HR 0.85 (95% CI 0.7 to 0.9) for >8 min of Bruce protocol compared with <6 min HR 0.90 (95% CI 0.82 to 0.99) for heart rate recovery >65 bpm 3 min after exercise compared with <50 bpm
Chronotropic response and heart rate recovery	Jouven (2005, France) (310)	Sudden death	23	Men in Paris civil service (5713)	47	For chronotropic response <89 bpm; HR 6.18 (95% CI 2.30 to 16.11; p<0.001) For heart rate recovery <25 bpm; HR 2.2 (95% CI 1.02 to 4.74; p<0.04)
Exercise capacity, heart rate recovery, and ST-segment	Mora (2003, USA) (318)	CVD death and all-cause death	20	Women in LRC prevalence study (2994)	46	For CVD death, exercise capacity below median HR 2.0 (95% CI

changes						1.29 to 3.25); heart rate recovery below median HR 2.9 (95% CI 1.85 to 4.39); ST-segment depression >1 mm, HR 1.0 (95% CI 0.59 to 1.80); similar for all-cause death
Exercise capacity, heart rate recovery, and ST-segment changes	Aktas (2004, USA) (307)	All-cause death	8	Men in preventive medicine clinic (3554)	57	For impaired exercise capacity, HR 3.0 (95% CI 1.98 to 4.39; p<0.001); for abnormal HR recovery <12 bpm 1 min postexercise; HR 1.6 (95% CI 1.04 to 2.41; p=0.03); not significant for ST-segment depression
Exercise capacity	Kodama (2009, International) (305)	All-cause death and CHD/CVD events	1.1 to 26	Healthy men and women in meta-analysis (102,980)	37 to 57	For all-cause mortality, 1-MET increase; HR 0.87 (95% CI 0.84 to 0.90); for CHD/CVD

bpm indicates beats per minute; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; FRS, Framingham Risk Score; HR, hazard ratio; LRC, Lipid Research Clinics; MET, metabolic equivalent; MRFIT, Multiple Risk Factor Intervention Trial; and USA, United States.

2.5.8. Recommendation for Stress Echocardiography

Class III: No Benefit

1. Stress echocardiography is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults. ***(Level of Evidence: C)***

2.5.8.1. General Description

Stress echocardiography can be performed with dynamic forms of exercise, including treadmill and bicycle, as well as with pharmacologic stress, most often using dobutamine. The manifestations of ischemia on echocardiography include segmental and global left ventricular dysfunction. The use of

echocardiography during treadmill testing is indicated for those patients with an abnormal resting ECG, including findings of left bundle-branch block, electronically paced rhythm, and LVH, as well as for patients taking digoxin. The diagnostic performance of the test is highly dependent on the availability of skilled acquisition and interpretation of the images and should be performed according to best practices (322). MPI with echocardiographic contrast agents has not been widely used, and there are no currently approved agents available in the United States, so this technique is not addressed here.

The current guideline focuses on the use of tests and procedures that may be employed for assessment of cardiovascular risk in the asymptomatic adult. In several sections of this document the writing committee has also assessed the evidence for applying conventional diagnostic testing with or without imaging. It is important to realize the vast difference in concepts between use of a diagnostic test, usually in the symptomatic patient, to define a patient's likelihood of obstructive CAD compared with stratification of risk in an asymptomatic patient to serve as a basis for cardiovascular preventive strategies. Stress echocardiography is a test predominantly used in symptomatic patients to assist in the diagnosis of obstructive CAD. There is very little information in the literature on the use of stress echocardiography in asymptomatic individuals for the purposes of cardiovascular risk assessment. Accordingly, the Class III (Level of Evidence: C) recommendation for stress echocardiography reflects a lack of population evidence of this test for risk assessment purposes. This contraindication to testing must be placed within the concept of accepted indications for testing asymptomatic patients for diagnosis of CAD, such as for asymptomatic individuals undergoing preoperative risk assessment (323), patients with new-onset atrial fibrillation, or a clinical work-up after episodes of ventricular tachycardia or syncope. In contrast, the current guideline focuses on risk assessment in the asymptomatic adult, which must not be confused with evaluation of the patient without chest pain with ischemic equivalents such as dyspnea, where in some cases, stress testing may be considered appropriate. The focus of these latter evaluations is to assess a patient's ischemic burden and the ensuing likelihood of obstructive CAD. There are clinical practice guidelines and appropriate use criteria that focus on the quality of evidence for assessment of asymptomatic patients or those with ischemic equivalents and clinical indications for the use of stress echocardiography. The current guideline is not applicable in this setting of diagnosis of CAD.

2.5.8.2. Association With Increased Risk

In a cohort of 1832 asymptomatic adults with no history of CHD (mean age, 51 years; 51% male), the predictive value of exercise echocardiography was examined at a mean of almost 5 years of follow-up (324). The incidence of significant ST-segment depression was 12%, and the incidence of inducible wall motion abnormalities was 8%. The presence of inducible wall motion abnormalities was not an

independent predictor of cardiac events in the entire population or those with ≥2 risk factors (324). There are additional clinical studies in patients with type 2 diabetes mellitus. One small series compared screening with combined exercise electrocardiography and dobutamine stress echocardiography to a no-screening strategy in 141 patients with type 2 diabetes. The series found that the screening strategy was associated with reduced cardiac events when those with inducible wall motion abnormalities (21%) underwent revascularization (325).

No information is currently available to assess the role of exercise echocardiography in addition to conventional risk factors for risk assessment in asymptomatic adults. Because of the lack of information on the role of risk assessment in the asymptomatic adult, the writing committee thought that there was no basis to recommend stress echocardiography for routine risk assessment in this type of patient.

2.5.8.3. Usefulness in Motivating Patients or Guiding Therapy

There have been no randomized trials on exercise echocardiography to suggest that it can be used to motivate lifestyle behavior changes in asymptomatic adults. One small pilot trial in patients with type 2 diabetes is cited above (325). No other trials have investigated the use of echocardiography to guide therapy in asymptomatic adults. Thus, there is no clear indication that an exercise echocardiogram can be used to motivate asymptomatic adults or guide their therapy.

2.5.9. Myocardial Perfusion Imaging

2.5.9.1. Recommendations for Myocardial Perfusion Imaging

Class IIb

1. Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CHD when previous risk assessment testing suggests high risk of CHD, such as a 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 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 CAD.). (326). ***(Level of Evidence: C)***

2.5.9.2. Description of Myocardial Perfusion Imaging

Exercise or pharmacologic stress MPI using single-photon emission CT (SPECT) or positron emission tomography (PET) is predominantly considered appropriate for the clinical evaluation of symptoms suggestive of myocardial ischemia or for determination of prognosis in patients with suspected or previously known CAD. As noted in the stress echocardiography section, it is important to recognize the distinction between the use of a diagnostic test to define the likelihood of obstructive CAD in a symptomatic patient and the possible role of a diagnostic test in risk assessment of an asymptomatic individual, for whom the results of testing would be used in decision making about strategies for prevention of CVD. This guideline is not intended to address the evaluation of patients presenting with possible cardiovascular symptoms or signs such as dyspnea, syncope, or arrhythmia, nor does this guideline address the preoperative assessment of a high-risk patient. These patient evaluations are the topics of other guidelines, and the reader is referred to other guidelines when confronted with such symptomatic patients.

Stress myocardial perfusion SPECT and PET involve exposure to ionizing radiation. The effective radiation dose for SPECT and PET considerably exceeds that of a CAC score (median effective dose: 2.3 millisievert [mSv]), and therefore the use of these modalities should be limited to patients in whom clinical benefit exceeds the risk of radiation exposure, for example, higher-risk or older patients. Use of these procedures must be performed with the guiding principle of applying effective doses that are "As Low as Reasonably Achievable" (i.e., ALARA). The estimated effective dose for stress myocardial perfusion SPECT is ~14.6 mSv, whereas that of Rb82 PET is ~5 mSv (327). For all patients, dose-reduction strategies should be used whenever possible (e.g., stress-only imaging), and these approaches may reduce SPECT doses to as low as 5 to 8 mSv (328). The clinician is strongly urged to consider radiation exposure when deciding whether the benefit of testing an asymptomatic patient outweighs the potential risks.

2.5.9.3. Evidence of Association With Increased Cardiovascular Risk in Asymptomatic Adults

There are few studies on the role of stress MPI for risk assessment in asymptomatic persons. The writing committee did not identify any studies in population-based (relatively unselected) asymptomatic individuals. Reported studies of stress perfusion imaging in asymptomatic persons have involved selected higher-risk patients who were referred for cardiac risk evaluation. In 1 large series of patients referred to a stress perfusion imaging laboratory (n=3664 asymptomatic patients), those with >7.5% myocardial ischemia had an annual event rate of 3.2%, which was consistent with high risk. High-risk findings were noted in <10% of asymptomatic patients who were referred. Limitations of the study include the absence

of clear indications for referral and absence of prior global risk assessment as a basis for advanced risk assessment (329). A second study, from the Mayo Clinic, selected 260 asymptomatic patients from a nuclear cardiology database (67±8 years, 72% male) without known CAD who were at moderate risk for CHD by FRS (330). SPECT MPI images were categorized using the summed stress score. Mean follow-up was nearly 10 years. Abnormal SPECT MPI scans were present in 142 patients (55%). By summed stress score categories, SPECT scans were low risk in 67% of patients, intermediate risk in 20%, and high risk in 13%. Survival was 60% for patients with high-risk scans (95% CI 45% to 80%), 79% with intermediate-risk scans (95% CI 69% to 91%), and 83% with low-risk scans (95% CI 77% to 88%) (p=0.03), including 84% (95% CI 77% to 91%) with normal scans. In asymptomatic intermediate- to higher-risk patients, these available data suggest a possible role for stress perfusion imaging in advanced risk assessment of selected asymptomatic patients.

Risk stratification using MPI has also been studied in asymptomatic patients with diabetes (331-337). In 1 multicenter study of 370 asymptomatic persons with diabetes recruited from departments of diabetology (335), abnormality was defined as a fixed or reversible perfusion defect or a positive stress ECG. These abnormalities (compared with patients with normal study results) were associated with a 2.9-fold (1.3 to 6.4) higher risk for cardiovascular events in patients >60 years of age but not for those <60 years of age. In the DIAD (Detection of Ischemia in Asymptomatic Diabetics) trial, asymptomatic, relatively low-risk patients with diabetes were randomized to screening for "silent" myocardial ischemia using adenosine stress MPI as an initial screening test versus "usual care"(337). The DIAD study found evidence of effective risk stratification, with annual cardiovascular event rates of 0.4% for those with normal- or low-risk scans compared with 2.4% for those with a moderate to large perfusion defect (p=0.001)(337). However, the overall result of the DIAD study was no significant difference in clinical outcomes in the screened group versus the usual care group (see further on this point below).

Stress perfusion imaging tests have been studied in a limited way when used as a secondary test following an initial evaluation with exercise ECG, carotid IMT, or CAC (333, 338-343). A summary of the literature from the ASNC synthesized published reports in patients who had these first-level indications of higher risk. Results suggested that as many as 1 in 3 of higher-risk patients with a CAC score of ≥400 had demonstrable ischemia. The prevalence of ischemia can be quite high in patients with diabetes, especially those with a family history of CHD (340, 344). In a series of 510 asymptomatic patients with type 2 diabetes recruited from 4 London diabetes clinics, the incidence of myocardial ischemia was 0%, 18.4%, 22.9%, 48.3%, and 71.4% for those with CAC scores of 0 to 10, 11 to 100, 101 to 400, 401 to 1000, and >1000, respectively (p<0.0001).

Three studies have reported the prognosis for patients referred to either initial CAC screening or combined CAC scanning with stress MPI (333, 341, 343). In 1 series that included a mixed sample of asymptomatic patients and patients with chest pain, high-risk CAC scores did not confer an elevated cardiovascular event risk. In another series of 621 patients who underwent hybrid PET-CT imaging with CAC scoring, one third of whom were asymptomatic, cardiovascular event-free survival was worse for patients with ischemia on PET plus a CAC score ≥1000 ($p<0.001$). In another study using a patient registry, data on asymptomatic patients with type 2 diabetes were reported (333). The inclusion criteria for the latter prospective registry included patients with diabetes who were ≥50 years of age with either prior carotid IMT ≥1.1 mm, urinary albumin rate ≥30 mg/g creatinine, or 2 of the following: abdominal obesity, HDL cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or hypertension ≥130/85 mm Hg. One-year event-free survival ranged from 96% to 76% for those with a summed stress score ranging from <4 to ≥14 ($p<0.0001$). These results suggest that stress perfusion imaging may have a role in the advanced testing of asymptomatic patients who have been evaluated with other modalities and found to be at high risk of silent ischemia. Such patients might include patients with a high-risk CAC score of ≥400 or higher-risk patients with diabetes, including those with a strong family history of CHD.

2.5.9.4. Usefulness in Motivating Patients or Guiding Therapy

There are limited data to demonstrate that stress-induced evidence of silent ischemia in asymptomatic patients will have an impact on patient management. These data are limited to the use of follow-up testing in the DIAD trial. Patients enrolled in the DIAD trial who were randomized to screening with stress MPI had a higher rate of follow-up coronary angiography and revascularization. These data are consistent with single-center studies that have shown that demonstration of high-risk myocardial perfusion scans in asymptomatic patients with diabetes leads to diagnostic cardiac catheterization to identify high-risk anatomy (e.g., 3-vessel CAD or left main CAD) with a view toward revascularization (345, 346). One nonrandomized observational study showed that asymptomatic patients with diabetes with high-risk stress MPI scans had a better outcome with revascularization than medical therapy (347).

2.5.9.5. Changes in Patient Outcomes

There is evidence from 1 randomized trial on the utility of stress MPI to screen for CVD in persons with diabetes (337). The DIAD trial randomized 1123 patients to no screening compared with screening with adenosine stress MPI. The trial results revealed that stress MPI performed as an initial screening test had no impact on 5-year outcomes compared with nonscreening or usual care of asymptomatic patients with diabetes (337). The relative hazard was 0.88 (95% CI 0.44 to 1.88) for those who were screened with

stress myocardial perfusion SPECT compared with those who were not screened (p=0.73). Notable limitations to this trial are its small, underpowered sample size, the high crossover rate (n=170/562 nonscreening arm undergoing nonprotocol stress testing), and the high incomplete follow-up rate (n=81/1123) exceeding the 49 observed cardiovascular events. Importantly, the enrolled patients were low risk with an annual cardiovascular event rate of 0.6% and included patients with a normal resting 12-lead ECG.

2.5.10. Computed Tomography for Coronary Calcium

2.5.10.1. Recommendations for Calcium Scoring Methods (see Section 2.6.1)

Class IIa

1. Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk) (18, 348). *(Level of Evidence: B)*

Class IIb

1. Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk) (348-350). *(Level of Evidence: B)*

Class III: No Benefit

1. Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for cardiovascular risk assessment (18, 348, 351). *(Level of Evidence: B)*

2.5.10.2. Calcium Scoring Methods

Cardiac CT, using either multidetector row CT or electron beam tomography, enables the acquisition of thin slices of the heart and coronary arteries gated to diastole to minimize coronary motion. Both are sensitive noninvasive techniques that can detect and quantify coronary calcium, a marker of atherosclerosis (352, 353). The test is typically performed in a prospectively ECG-triggered scanning mode with 2.5- to 3.0-mm thick axial images obtained through the heart. The quantity of calcium within the coronary arteries is typically scored as the area affected on the scan, multiplied by a weighting factor depending on the Hounsfield unit density of the calcium deposits (352). The radiation dose in a prospectively triggered acquisition is low, with a typical effective dose of <1.5 mSv (354). Due to the radiation exposure and general low prevalence of calcification in men <40 years of age and women <50 years of age, patient selection is an important consideration. CT scanning should generally not be done in

men <40 years old and women <50 years old due to the very low prevalence of detectable calcium in these age groups.

The widespread use of CCTA has also raised concerns about radiation dose for patients. The National Council on Radiation Protection NCRP Report No. 160 stated that radiation exposure to the U.S. population due to medical sources increased >7 times between 1986 and 2006 (355). CT calcium scoring produces the same amount of radiation as 1 to 2 mammograms performed on each breast (356). The radiation dose in a prospectively triggered acquisition is low, with a typical effective dose of 0.9 to 1.1 mSv (354, 357), but doses can be higher if retrospective imaging is used (358). All current recommendations suggest prospective triggering be used for CAC scoring. CT personnel must be constantly aware of the risks of radiation and strive to apply the lowest dose to the patient consistent with the clinical study. Because of radiation exposure and the general low prevalence of calcification in men <40 years of age and women <50 years of age, CT scanning should generally not be done in these younger-age patients.

2.5.10.3. Data on Independent Relationship to Cardiovascular Events

The majority of published studies have reported that the total amount of coronary calcium (usually expressed as the Agatston score) provides information about future CAD events over and above the information provided by standard risk factors. Intermediate-risk patients with an elevated CAC score (intermediate FRS and CAC >300) had a 2.8% annual rate of cardiac death or MI (roughly equivalent to a 10-year rate of 28%) that would be considered high risk (352). Pooled data from 6 studies of 27 622 asymptomatic patients were summarized in an ACCF/AHA clinical expert consensus document that examined predictors of the 395 CHD deaths or MIs (359). The 11 815 subjects who had CAC scores of 0 had a low rate of events over the subsequent 3 to 5 years (0.4%, based on 49 events). Compared with a CAC score of 0, a CAC score between 100 and 400 indicated a RR of 4.3 (95% CI 3.5 to 5.2; $p<0.0001$), a score of 400 to 1000 indicated a RR of 7.2 (95% CI 5.2 to 9.9; $p<0.0001$), and a score >1000 indicated a RR of 10.8 (95% CI 4.2 to 27.7; $p<0.0001$). The corresponding pooled rates of 3- to 5-year CHD death or MI rates were 4.6% (for scores from 400 to 1000) and 7.1% (for scores >1000), resulting in a RR ratio of 7.2 (95% CI 5.2 to 9.9; $p<0.001$) and 10.8 (95% CI 4.2 to 27.7; $p<0.0001$).

Since the ACCF/AHA expert consensus document was published, other prospective confirmatory studies have been published (18, 348, 351, 353, 354). These studies have demonstrated that the relationships between CAC outcomes are similar in men and women and different ethnic groups (353, 354). Each of these studies demonstrated that the AUC to predict coronary artery events is significantly higher with CAC than either Framingham or PROCAM (Münster Heart Study) risk stratification alone. In

MESA, the C statistic with traditional risk factors was 0.79 for major coronary events in the risk factor prediction model and 0.83 in the risk factor plus CAC model (p=0.006) (18).

2.5.10.4. Usefulness in Motivating Patients

To understand the clinical utility of CAC testing as a risk assessment tool, it is imperative to demonstrate that it alters clinical management (such as the use of preventive medications). In an observational survey study, Kalia et al. showed that self-reported lipid-lowering medication provision increased from 44% over 3 years to >90% in those with baseline calcium scores in the top 75th percentile for age and sex (p<0.001) (360). This finding was independent of underlying cardiovascular risk factors, age, and sex. Other cardiovascular risk behaviors were reported to be beneficially affected, specifically showing that higher baseline CAC was strongly associated with initiation of aspirin therapy, dietary changes, and increased exercise (361).

A randomized controlled study suggested that although a calcium scan did not in itself improve net population healthy behaviors, the post-test recurring interactions with a healthcare provider can be useful to reinforce lifestyle and treatment recommendations that could ensue from calcium testing (362).

2.5.10.5. Use as a Repeat Measure to Monitor Effects of Therapy in Asymptomatic Persons

Coronary calcium progresses at typically 10% to 20% of the baseline value per year, and among persons >45 years of age, approximately 7% per year of those without calcium develop detectable coronary calcium. The value of repeat calcium scanning is governed by the interscan interval, rate of coronary calcium progression, variability in repeated measurements, and independent association to shifts in prognosis and management based on the observed calcium progression rate. Although preliminary data suggest that a calcium scan progression rate of >15% per year is associated with a 17-fold increased risk for incident CHD events (363), there are no data demonstrating that serial CAC testing leads to improved outcomes or changes in therapeutic decision making (354).

2.5.10.6. Usefulness of Coronary Calcium Scoring in Guiding Therapy

Calcium scores >100 to 300 are associated with a high rate of incident CHD events over the ensuing 3 to 5 years, so that persons with calcium scores in this range are a suitable target group for stringent lifestyle recommendations, selection of evidence-based therapeutic agents to reduce cardiovascular risk, and focus on adherence to medical recommendations. In the Prospective Army Coronary Calcium study, among 1640 participants followed up for 6 years, use of statin and aspirin was independently 3.5- and 3-fold greater in those with any coronary calcium over 6 years, suggesting management changes can occur

following calcium screening in community-based cohorts (364). Multiple logistic regression analysis, controlling for National Cholesterol Education Program (NCEP) risk variables, showed that CAC was independently associated with a significantly higher likelihood of use of statin, aspirin, or both (OR 6.97; 95% CI 4.81 to 10.10; p<0.001) (364). The OR for aspirin and statin use based on NCEP risk factors alone was dramatically lower (OR 1.52; 95% CI 1.27 to 1.82; p<0.001). Recent data from MESA suggest similar effects of CAC visualization on lipid-lowering and aspirin therapy (365).

2.5.10.7. Evidence for Improved Health Outcomes

Evidence is not available to show that risk assessment using CAC scoring improves clinical outcomes by reducing mortality or morbidity from CAD.

2.5.10.8. Special Considerations

2.5.10.8.1. Coronary Calcium Scoring in Women

A vast majority of women <75 years of age are classified by FRS to be low risk. In 1 study of 2447 consecutive asymptomatic females without diabetes (55±10 years), 90% were classified as low risk by FRS (≤9%), 10% as intermediate risk (10% to 20%), and none had a high-risk FRS >20% (366). CAC was observed in 33%, whereas moderate (CAC ≥100), a marker of high risk, was seen in 10% of women. Overall, 20% of women had CAC ≥75th percentile for age and gender, another marker for future CHD events. However, when FRS was used, the majority (84%) of these women with significant subclinical atherosclerosis ≥75th percentile were classified as low risk, whereas only 16% were considered intermediate risk. Thus, FRS frequently classifies women as being low risk, even in the presence of significant CAC. Based on this 1 substudy from MESA, it is possible that CAC scoring may provide incremental value to FRS in identifying which asymptomatic women may benefit from targeted preventive measures (349). A recent report noted net reclassification improvement with CAC in relation to risk factors for all-cause mortality in women <60 years of age (367). In terms of the overall predictive capacity of high calcium scores, several studies have demonstrated that CAC-associated outcomes are similar in men and women (368, 369).

For a discussion of the utility of CAC testing in persons with diabetes, see Section 2.6.1.

2.5.10.8.2. Comparison of Coronary Artery Calcium Scoring With Other Risk Assessment Modalities

Several studies have compared multiple techniques for cardiovascular risk stratification (350, 369-371). Four studies comparing the predictive abilities of hsCRP with CAC have demonstrated that CAC remains an independent predictor of cardiovascular events in multivariable models, whereas CRP no longer retains a significant association with incident CHD (350, 369-371). This has recently been confirmed in MESA as well (18, 351). The CAC score was also shown to be a better predictor of subsequent CVD events than carotid IMT. Multivariable analysis revealed HRs for CHD of 1.7 (95% CI 1.1 to 2.7; p=0.07) for carotid IMT and 8.2 (95% CI 4.5 to 15.1; p<0.001) for CAC score (quartile 4 versus quartiles 1 and 2) (252).

2.5.11. Coronary Computed Tomography Angiography

2.5.11.1. Recommendation for Coronary Computed Tomography Angiography

Class III: No Benefit

1. Coronary computed tomography angiography is not recommended for cardiovascular risk assessment in asymptomatic adults (372). ***(Level of Evidence: C)***

2.5.11.2. General Description

CCTA has been widely available since around 2004, when 64-detector scanners were produced by multiple vendors. Two basic scanning protocols may be used; both require ECG monitoring and gating. Helical (or spiral) scanning uses continuous image acquisition while the patient moves slowly through the scanner plane. Axial scanning incorporates a scanning period, followed by a patient movement period, followed by another scanning period (step-and-shoot). Compared with invasive coronary angiography using a cine system, both the temporal and spatial resolution of CCTA are far less (spatial: 200 microns versus 400; temporal: 10 milliseconds versus approximately 80 to 190 milliseconds, depending on the type of scanner). CCTA provides the best quality images when the heart rate is regular and slow (<60 bpm if possible).

CCTA has been compared with invasive coronary angiography for detection of atherosclerosis (typically defined as a 50% diameter stenosis) (373). Sensitivities and specificities from >40 studies are consistently in the range of 85% to 95%, and the most important test feature is the high negative predictive value (>98%) (373). In addition, CCTA can image mild plaque (<50%) in the vessel wall. Plaques may be roughly characterized according to their density (Hounsfield units) as calcified or noncalcified. CCTA requires a CT scanner with at least 64 detector rows and specialized software (approximate cost, $1 million). Concern has been raised that CCTA uses ionizing radiation. CCTA studies using unmodulated, helical scanning deliver 12 to 24 mSv of radiation per examination (373). Methods to reduce the radiation dose, including ECG dose modulation or prospective ECG-triggered axial

scanning, have resulted in doses of less than 3 mSv in selected patients (estimated radiation dose associated with CCTA) (374).

2.5.11.3. Association With Increased Risk and Incremental Prediction in Asymptomatic Persons

Very limited information is available on the role of CCTA for risk assessment in asymptomatic persons. In a study from Korea, 1000 middle-aged patients underwent CCTA as a component of a general health evaluation (372). Patients were either self-referred to this examination or referred by a physician. Patients with chest discomfort or known CAD were excluded from the analysis. Clinical follow-up was obtained at 17±2 months in >97% of patients. Coronary calcium was detected in 18% of patients, and 22% had identifiable atherosclerotic plaque. Significant (>50%) stenoses were found in 5% of patients. CCTA results were compared with the NCEP ATP III risk classification. The majority of patients were classified as low risk (55.7%) by NCEP criteria. Only 10.2% were classified as high risk. The prevalence of significant coronary stenoses in the low-, moderate- and high-risk groups was 2%, 7%, and 16%, respectively. During follow-up, 15 patients had "cardiac events," although 14 of these were revascularization procedures prompted by the CCTA results. There were no deaths or MIs. Additional diagnostic testing was performed in 14% of patients identified as having coronary atherosclerosis, representing 3.1% of the entire screened population. On the basis of the small number of nonprocedural events in this study, the authors could not compare CCTA results with the NCEP risk assessment data for risk prediction purposes. No other studies have been reported to date on the potential utility of CCTA results for risk assessment in asymptomatic adults with coronary events as the outcome.

2.5.11.4. Changes in Patient Outcomes

There are no published trials evaluating the impact of specific therapy on clinical outcome in patients identified as having noncalcified atheroma by CCTA.

2.5.12. Magnetic Resonance Imaging of Plaque

2.5.12.1. Recommendation for Magnetic Resonance Imaging of Plaque

Class III: No Benefit

1. MRI for detection of vascular plaque is not recommended for cardiovascular risk assessment in asymptomatic adults. (*Level of Evidence: C)*

2.5.12.2. General Description

MRI is a noninvasive method of plaque measurement that does not involve ionizing radiation. Studies of the aorta and the femoral and carotid arteries have demonstrated the capability of MRI for detection and quantification of atherosclerosis and suggested its potential for risk assessment and evaluation of the response to treatment in asymptomatic patients. MRI seems to offer the greatest role for plaque characterization as distinct from lesion quantification. Examination of plaque under different contrast weighting (black blood: T1, T2, proton density-weightings, and magnetization prepared rapid gradient echocardiography or bright blood: time of flight) allows characterization of individual plaque components (375, 376), including lipid-rich necrotic core (377), fibrous cap status (378), hemorrhage (379, 380), and calcification (377, 381, 382). Although most magnetic resonance plaque imaging studies do not require exogenous contrast administration, gadolinium-based contrast agents can further improve delineation of individual plaque components such as the fibrous cap and lipid-rich necrotic core (383, 384).

Several studies have demonstrated that MRI findings are correlated with atherosclerosis risk factors. Aortic MRI scanning in 318 patients participating in the Framingham Heart Study found that after age adjustment, plaque prevalence and burden correlated with FRS for both women and men (385). In another Framingham Heart Study, subclinical aortic atherosclerosis was seen in nearly half of subjects and increased with advancing age. Hypertension was associated with increased aortic plaque burden. In the MESA study, aortic wall thickness measured with MRI increased with age, but males and blacks had the greatest wall thickness (386). In another MESA study, it was found that thickened carotid walls and plasma total cholesterol, but not other established CHD risk factors, were strongly associated with lipid core presence by MRI (387).

A few small prospective studies have been done to investigate characteristics of carotid artery plaque on MRI that are associated with disease progression and future cardiovascular events. One study examined patients with symptomatic and asymptomatic carotid disease to determine whether fibrous cap thinning or rupture as identified on MRI were associated with a history of recent transient ischemic attack or stroke. When compared with patients with a thick fibrous cap, patients with a ruptured cap were 23 times more likely to have had a recent transient ischemic attack or stroke (388). In a separate study of symptomatic carotid disease, patients with lipid cores in carotid plaque by MRI had ipsilateral cerebral infarctions more often than those without lipid cores (68% versus 31%; p=0.03) (389). Another study performed carotid MRI on 53 patients within 7 days of a second cerebrovascular accident. Patients with "vulnerable" carotid lesions, as defined by eccentric shape and heterogeneous signal on MRI, had an 8 times greater risk of a third cerebrovascular accident compared with those without vulnerable lesions (24% versus 3%; p=0.023) (390).

Prospective studies demonstrated that hemorrhage within carotid atherosclerotic plaques was associated with an accelerated increase in subsequent plaque volume over a period of 18 months (391). An increased risk of ipsilateral cerebrovascular events has also been reported over a mean follow-up period of 38.2 months in asymptomatic patients who had 50% to 79% carotid stenosis and the presence of a thin or ruptured fibrous cap, intraplaque hemorrhage, or a larger lipid-rich necrotic core (392). These studies support the hypothesis that the presence of intraplaque hemorrhage is a potent atherogenic stimulus.

At this time there are no published prospective population data to evaluate the role of MRI findings in risk assessment of asymptomatic adults. A number of large-scale studies are ongoing. It is recommended that additional large-scale multicenter trials be conducted to evaluate the possibility of using MRI in the detection of atherosclerosis in asymptomatic patients.

Rapid technological progress is transforming the imaging of atherosclerotic CVD at the molecular level using nanoparticles (393). In addition, a new generation of hybrid technology is now becoming available; this technology combines multiple imaging modalities, including PET in a single platform (e.g., PET/CT and MR/PET), using 1 machine for >1 type of imaging to measure atherosclerotic plaque metabolic activity with anatomical special resolution and contrast (394-396). There is no information available yet on the role of these newer tests for risk assessment in the asymptomatic adult.

2.6. Special Circumstances and Other Considerations

2.6.1. Diabetes Mellitus

2.6.1.1. Recommendations for Patients With Diabetes

Class IIa

1. In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment (344, 397-399). *(Level of Evidence: B)*

Class IIb

1. Measurement of HbA1C may be considered for cardiovascular risk assessment in asymptomatic adults with diabetes (400). *(Level of Evidence: B)*

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

2.6.1.2. General Description and Background

CVD is the major cause of morbidity, mortality, and healthcare costs for patients with diabetes (401). Compared with the general population, patients with diabetes have a 4 times greater incidence of CHD (402) and a 2- to 4-fold higher risk of a cardiovascular event (307). The risk of MI in patients with diabetes without prior documented CHD is similar to the risk of reinfarction in patients without diabetes with known CHD (403). Women with type 2 diabetes are particularly prone to developing cardiovascular complications (the age-adjusted risk ratio of developing clinical CHD among people with diabetes was 2.4 in men and 5.1 in women compared with patients without diabetes) (403).

The prevalence of significant coronary atherosclerosis in a truly representative population of patients with type 2 diabetes has not been ascertained. One estimate is that 20% of patients with diabetes have coronary atherosclerosis (404). However, in an asymptomatic and uncomplicated cohort of patients with type 2 diabetes, 46.3% had evidence of coronary artery calcification reflective of coronary atherosclerosis (344). The prevalence of CAD on multislice CT was 80% in a group of 70 asymptomatic patients with type 2 diabetes (399). The majority of these patients had diffuse involvement of all 3 coronary arteries. In another study by this group, 60% of asymptomatic patients with diabetes had evidence of coronary calcification, of which 18% had calcium scores of >400 (405). Seventy percent had coronary luminal narrowing of 1 or more coronary arteries on multislice CT coronary angiography, patients with diabetes showed more plaques on multislice CT than patients without diabetes (7.1±3.2 versus 4.9±3.2; p=0.01) with more calcified plaques (52% versus 24%) (406). On invasive grayscale intravascular ultrasound, patients with diabetes in this study had a larger plaque burden (48.7%±10.7% versus 40.0%±12.1%; p=0.03). Asymptomatic patients with diabetes have more coronary calcification than patients without diabetes even when controlling for other variables (407-409), and for every increase in CAC on CT scanning, mortality for patients with diabetes is higher than in patients without diabetes (407). However, patients with diabetes with no coronary calcium have a survival rate similar to that of subjects without diabetes and with no identifiable coronary calcium (407). The overall rate of death or MI was 0%, 2.6%, 13.3%, and 17.9% (p<0.0001) in patients with diabetes with a CAC score of ≤100, 100 to 400, 401 to 1000 and >1000, respectively (344). ROC curve analysis showed by AUC that the CAC (AUC: 0.92; 95% CI 0.87 to 0.96) was superior to the UKPDS (United Kingdom Prospective Diabetes Study Risk Score) (AUC, 0.74; 95% CI 0.65 to 0.83) and FRS (AUC, 0.60; 95% CI 0.48 to 0.73; p<0.0001) for predicting cardiac events, with a risk ratio of 10.1 (95% CI 1.68 to 61.12) for patients with a score of 100 to 400 and 58.1 (95% CI 12.28 to >100) for scores >1000 (344).

The CAC score has been found to be predictive beyond conventional risk factors in several studies in patients with diabetes. In the PREDICT (Patients with Renal Impairment and Diabetes Undergoing Computed Tomography) study, 589 patients with type 2 diabetes underwent CAC

measurement (398). At a median of 4 years' follow-up, in a predictive model that included CAC score and traditional risk factors, the CAC score was a highly significant independent predictor of CHD events or stroke. The model found that a doubling in calcium score was associated with a 32% increase in risk of events (29% after adjustment). Only the homeostasis model assessment of insulin resistance predicted primary endpoints independent of the CAC score. In another study, after adjusting for CHD risk factors, the CAC score was significantly associated with occurrence of coronary events in patients without diabetes but not in patients with diabetes (410). Another study performed CAC measurement in 716 asymptomatic patients with diabetes and no history of CHD (397). During 8 years of follow-up, 40 patients had MI and 36 additional patients experienced cardiac death. The CAC score was significantly higher in those with events compared with those without events, 5.6% per year for patients with scores of >400 versus 0.7% per year for those with lower scores. The area under the ROC curve with CAC in the model was significantly higher (0.77) for prediction of MI than the FRS (0.63).

2.6.1.3. Electrocardiographic Stress Testing for Silent Myocardial Ischemia

(See Section 2.5.7)

The value of exercise ECG testing to detect silent ischemia and assess prognosis has been evaluated in a few small studies of asymptomatic patients with diabetes (411-416). ECG stress testing has an approximate 50% sensitivity and 80% specificity (401). The positive predictive value for detecting CAD using coronary angiography as the gold standard ranges between 60% and 94% and was higher in men than women (401, 416). Recommendations for exercise stress testing for risk assessment do not appear to be different in patients with diabetes and patients without diabetes.

2.6.1.4. Noninvasive Stress Imaging for Detection of Ischemia and Risk Stratification

(See Section 2.5.9)

The prevalence of asymptomatic ischemia as determined by noninvasive imaging in patients with diabetes ranges from 16% to 59% (345, 346, 417-419) and depends on the pretest clinical risk of CAD in the population. The DIAD study (337) was composed of a group of patients with type 2 diabetes who were at lower risk than those undergoing stress imaging in other studies, with only 6% of the 522 patients manifesting large defects on adenosine MPI. All had a normal resting ECG, whereas in a separate Mayo Clinic cohort, 43% had abnormal Q waves on the ECG and 28% had peripheral vascular disease (346).

Approximately 50% of the Mayo Clinic study patients were referred for preoperative testing for risk assessment. In another report from the same group, 58.6% of asymptomatic patients with diabetes had an abnormal scan, and 19.7% had a high-risk scan (345). In another retrospective study, 39% of asymptomatic patients with diabetes had an abnormal stress scan (419). Of those presenting with dyspnea, 51% had an abnormal perfusion study. The annual hard event rate at follow-up (7.7%) was highest in those presenting with dyspnea compared with 3.2% in those presenting with angina. Using contrast dipyridamole echocardiography, approximately 60% of asymptomatic patients with diabetes who were ≤60 years of age had abnormal myocardial perfusion with vasodilator stress.

Asymptomatic patients with diabetes who have high CAC scores have a high prevalence of inducible ischemia on stress imaging (339). In a prospective study, 48% of patients with diabetes with a CAC score of >400 had silent ischemia on SPECT imaging, and in those with a score of >1000, 71.4% had inducible ischemia (344). The majority of the defects were moderate to severe. Patients with diabetes with inducible ischemia have a higher annual death or nonfatal infarction rate compared with patients without diabetes with similar perfusion abnormalities on stress imaging (10% versus 6%) (420). Also, the greater the degree of ischemia, the worse the outcome during follow-up in both asymptomatic and symptomatic patients with diabetes (344, 421). The risk ratio for cardiac events was 12.27 (95% CI 3.44 to 43.71; $p<0.001$) for patients with >5% ischemic burden on stress SPECT (344). These observations should be tempered by the recent report that 16% of patients with no coronary calcium had inducible ischemia by rest-stress rubidium-82 PET imaging (343). The prevalence of diabetes was 28% in that study. These data, in aggregate, suggest that coronary calcium measurement in patients with diabetes may justify different approaches to risk assessment compared with patients without diabetes. The writing committee therefore judged it reasonable to perform coronary calcium measurement for cardiovascular risk assessment in asymptomatic patients with diabetes who were >40 years of age.

2.6.1.5. Usefulness in Motivating Patients

To date there is no evidence that performing coronary calcium imaging by CT scanning is effective in motivating patients to better adhere to lifestyle changes, medical therapy of diabetes, or primary prevention measures to reduce the risk of developing coronary atherosclerosis or future ischemic events.

2.6.1.6. Evidence of Value for Risk Assessment for Coronary Atherosclerosis or Ischemia or Both to Guide Treatment or Change Patient Outcomes

Because of the high risks associated with diabetes, diabetes has been designated as a CHD risk equivalent by the NCEP (27). One study randomized 141 patients with type 2 diabetes without known CAD to receive exercise ECG/dipyridamole stress echocardiographic imaging or a control arm (325). If a test result was abnormal, coronary angiography was performed with subsequent revascularization as indicated by anatomic findings. At a mean follow-up of 53.5 months, 1 major event (MI) and 3 minor events (angina) occurred in the testing arm, and 11 major and 4 minor events occurred in the control arm. Numbers in the study were too small to be considered definitive. In the DIAD study, 561 low-risk asymptomatic patients were randomized to screening with adenosine SPECT perfusion imaging; 562 patients were randomized to no testing (337). All patients had a normal resting ECG and no prior history of CAD. Over a mean follow-up of 4.8 years, the cumulative event rate was 2.9% (0.6% per year), and there was no difference in event rates between the 2 groups. In the tested group, those with moderate or large defects had a higher cardiac event rate than those with a normal scan or small defects (337).

2.6.1.7. Diabetes and Hemoglobin A1C

HbA1C is used to integrate average glycemic control over several months and predict new-onset diabetes (156). A systematic review has suggested that HbA1C might be effective to screen for the presence of diabetes (157). Some experts have noted that screening with HbA1C might be advantageous because it can be performed in nonfasting individuals (422). The ADA now endorses the use of HbA1C to diagnose diabetes and assess for future risk of diabetes in higher-risk patients (158, 423).

2.6.1.8. Association With Cardiovascular Risk

Higher HbA1C concentrations have been associated with elevated risk of CVD in asymptomatic persons with diabetes (154). In a meta-analysis by Selvin, et al., adjusted RR estimates for glycosylated hemoglobin (total glycosylated hemoglobin, hemoglobin A1, or HbA1C levels) and CVD events (CHD and stroke) were pooled by using random-effects models (154). Three studies involved persons with type 1 diabetes (n=1688), and 10 studies involved persons with type 2 diabetes (n=7435). The pooled RR for CVD was 1.18; this represented a 1% higher glycosylated hemoglobin level (95% CI 1.10 to 1.26) in persons with type 2 diabetes. The results in persons with type 1 diabetes were similar but had a wider CI (pooled RR 1.15 [95% CI 0.92 to 1.43]). Important concerns about the published studies included residual confounding, the possibility of publication bias, the small number of studies, and the heterogeneity of study results. The authors concluded that, pending confirmation from large, ongoing clinical trials, this

analysis suggests that chronic hyperglycemia is associated with an increased risk for CVD in persons with diabetes.

2.6.1.9. Usefulness in Motivating Patients, Guiding Therapy, and Improving Outcomes

It is unknown whether knowledge of HbA1C is associated with better cardiovascular clinical outcomes in asymptomatic patients with diabetes. In persons with established diabetes, knowledge of HbA1C concentration was associated with better understanding of diabetes care and glucose control (424). However, such knowledge was unaccompanied by objective evidence of better clinical outcomes (424). It is unknown whether HbA1C is useful for motivating persons without diabetes.

Although the beneficial effects of glycemic control for microvascular complications have been demonstrated by numerous studies, the benefits for macrovascular complications, particularly CVD, remain controversial (425-427). Prevention trials have demonstrated that persons with impaired glucose tolerance have less progression to overt diabetes with lifestyle and pharmacologic interventions but without accompanying reductions in CVD complications (428). A meta-analysis of randomized controlled trials of persons with diabetes reported that improved glycemic control was associated with an improved IRR for macrovascular complications – mainly CVD – for both type 1 (IRR 0.38, 95% CI 0.26 to 0.56) and type 2 (IRR 0.81, 95% CI 0.73 to 0.91) diabetes (429). However, the meta-analysis did not demonstrate a reduction in cardiac events in persons with type 2 diabetes (IRR 0.91, 95% CI 0.80 to 1.03) (429).

Recent large, randomized, controlled studies have also failed to demonstrate that intensive blood glucose control and a lower HbA1C level is accompanied by a reduction in macrovascular events (430-432).

2.6.2. Special Considerations: Women

The rationale for providing a separate section for risk assessment considerations in women was based on reports of underrepresentation of females within the published literature and clinicians who considered women at lower risk when their profiles were comparable to those of men. Moreover, the focus on special considerations in testing women has been put forward as a result of frequent reporting of underutilization of diagnostic and preventive services and undertreatment in women with known disease (433).

2.6.2.1. Recommendations for Special Considerations in Women

Class I

1. **A global risk score should be obtained in all asymptomatic women (22, 434).** ***(Level of Evidence: B)***

2. **Family history of CVD should be obtained for cardiovascular risk assessment in all asymptomatic women (22, 55).** ***(Level of Evidence: B)***

2.6.2.2. Detection of Women at High Risk Using Traditional Risk Factors and Scores

Nearly 80% of women >18 years of age have 1 or more traditional CHD risk factors (435). Diabetes and hypertriglyceridemia are associated with increases in CHD mortality in women more so than in men (436, 437). In women, traditional and novel risk factors are prevalent and frequently cluster (i.e., metabolic syndrome) (438-440). CHD risk accelerates greatly for women with multiple risk factors, and CHD risk notably increases after menopause.

Global risk scores, such as the FRS, classify the majority of women (>90%) as low risk, with few assigned to high-risk status before the age of 70 years (434, 441). Several reports have examined the prevalence of subclinical atherosclerosis in female FRS subsets (349, 366). In a recent study of 2447 women without diabetes, 84% with significant coronary artery calcification (≥75th percentile) were classified with a low FRS (366). The lack of sensitivity of FRS estimates in women was presented in several reports, suggesting lower utility of FRS in female patients (366, 441). The Reynolds risk score in women improved risk reclassification when compared with the FRS by including hsCRP, HbA1C (if the patient has diabetes), and family history of premature CHD (22). This finding has not been uniformly confirmed in other studies that included women.

2.6.2.3. Comparable Evidence Base for Risk Stratification of Women and Men

Within the past decade, high-quality, gender-specific evidence in CHD risk stratification of women has emerged for novel risk markers (e.g., hsCRP) and cardiovascular imaging modalities (e.g., carotid IMT, CAC). This evidence reveals effective and, importantly, similar risk stratification for women and men as based on relatively large female cohorts or a sizeable representation of females. Detailed discussions and recommendations for each of the tests are provided in Sections 2.4.2 for hsCRP, 2.5.1 for resting ECG, 2.5.3 for carotid IMT, 2.5.6 for ABI, 2.5.7 for exercise ECG, and 2.5.10 for CAC. In the case of hsCRP, carotid IMT, ABI, CAC, resting ECG, and exercise ECG, the recommendations for men apply similarly to women. Limited female-specific evidence is also available for FMD, thus warranting a Class III, Level of Evidence B recommendation similar to that for men.

2.6.3. Ethnicity and Race

A variety of disparities exist in different ethnic groups with respect to cardiovascular risk factors, incidence, and outcomes (442). In 2002, age-adjusted death rates for diseases of the heart were 30% higher among African Americans than among whites of both sexes. Disparities were also common with respect to the presence of atherosclerotic risk factors, with Hispanics and black women demonstrating the highest rates of obesity. Blacks also had the highest rates for hypertension, whereas hypercholesterolemia was highest among white and Mexican-American males and white women. Lower educational level and socioeconomic status conferred a greater risk of dying from heart disease in all ethnic groups (443).

Minimal information is available at this time with regard to differing risk assessment strategies in ethnic groups other than whites. The writing committee did not find evidence to suggest that ethnic groups other than whites should undergo selective risk assessment approaches based on ethnicity.

2.6.4. Older Adults

Although increasing age is a risk factor for CVD, with progression of age, the prevalence of traditional risk factors also rises. Conceptually, risk intervention could be anticipated to have greater benefit at an elderly age, due to the increased absolute risk for coronary events; however, age comparisons for risk interventions have not been rigorously tested. Furthermore, the term "elderly" is used to describe a range of age subgroups from 65 to 74, 75 to 84, and >85 years in different studies. Elderly patients in the community also vary substantially from those in clinical trials, with greater comorbidity, renal dysfunction, traditional risk factors, etc., and with very limited data available for the oldest of the old.

In the Cardiovascular Health Study, subclinical markers (increased carotid IMT, decreased ABI, ECG, history of MI, echocardiographic left ventricular dysfunction, coronary calcium) predicted CVD events more than traditional risk scores. The DTS does not predict cardiac survival beyond age 75, with a 7-year cardiac survival for those classified as low, intermediate, and high risk being 86%, 85%, and 69%, respectively (444). Elderly patients have a more adverse prognosis than younger patients with the same Duke risk score. Based on information drawn largely from the Cardiovascular Health Study, application of traditional risk factors for risk assessment in the elderly, as well as selected other tests, can be considered an evidence-based approach.

2.6.5. Chronic Kidney Disease

Chronic kidney disease, the permanent loss of kidney function, is considered a coronary risk equivalent in various observational studies. However, data are insufficient to define differences in outcomes in populations with different degrees of renal insufficiency versus normal renal function. Data for lipid lowering with statins in the TNT (Treating to New Targets) study, a population with documented CAD,

suggest serial improvement in renal function and clinical outcome, but extrapolation to an asymptomatic healthy population is inappropriate (445). Lipid lowering restricted to the elderly in the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study failed to show benefit. Similarly, lipid lowering in a dialysis population failed to show benefit (446). In TNT, patients with diabetes with mild to moderate chronic kidney disease demonstrated marked reduction in cardiovascular events with intensive lipid lowering in contrast to previous observations in patients with diabetes with end-stage renal disease. It is important to note that TNT was not a study of asymptomatic adults (the focus of this guideline) but rather was focused on a CAD population.

3. FUTURE RESEARCH NEEDS

3.1. Timing and Frequency of Follow-Up for General Risk Assessment

There is little information available in the research literature to suggest the optimal timing to initiate risk assessment in adults. There is also limited information to inform decisions about frequency of risk assessment in persons who are determined to be at low or intermediate risk on initial risk assessment. High-risk persons are likely to initiate treatment strategies, and repeat risk assessment is likely to be a standard component of patient follow-up. More research on the optimal timing to begin risk assessment and repeat risk assessment in the asymptomatic patient is warranted.

3.2. Other Test Strategies for Which Additional Research Is Needed

3.2.1. Magnetic Resonance Imaging

Although MRI is an established cardiovascular imaging modality, its use in risk assessment studies to date is very limited. Research questions to be answered should focus on 1) which MRI parameters are the best for predicting major macro- and microvascular disease in the asymptomatic patient, 2) whether such parameters add to existing risk scores, and 3) what is the cost-effectiveness of such imaging according to risk strata.

3.2.2. Genetic Testing and Genomics

At present the plethora of genetic tests available for assessing cardiovascular risk has not reached the point of being able to add to the general risk assessment approach using global risk scoring with traditional risk factors and addition of careful family history. Additional research on the role of genetic

testing, with specific attention to the value for incremental risk prediction in asymptomatic people, is needed.

3.2.3. Geographic and Environmental or Neighborhood Risks

Much research indicates that socioeconomic factors play a role in cardiovascular risk. It remains unclear how this information should best be measured and incorporated into individual risk assessment or whether this area of research applies primarily at the population and policy levels. Attention to this area of research for individual risk assessment was deemed to be warranted by the writing committee.

3.2.4. Role of Risk Assessment Strategies in Modifying Patient Outcomes

Although the concept of individual risk assessment as a means of properly targeting intensity of risk treatments is now engrained in the practice of medicine and cardiology, data to support the clinical benefits of alternative testing strategies are very limited. For example, would risk assessments that use images of abnormal vessels be able to motivate patients and achieve better patient outcomes than testing strategies that use only historical information or blood tests? Studies that evaluate the specific testing strategy against a specific patient-centered outcome are needed. In addition, comparative effectiveness of various test strategies is needed to determine costs, benefits, and comparative benefits of competing testing approaches.

3.3. Clinical Implications of Risk Assessment: Concluding Comments

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.

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Appendix 1. Author Relationships With Industry and Other Entities: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

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This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Indicates significant relationship; †Recused from Section 2.4.5., Lipoprotein-Associated Phospholipase A2; ‡Recused from Section 2.5.11., Contrast Computed Tomography Angiography; §Recused from Section 2.6.1., Diabetes Mellitus; ‖Recused from Section 2.5.10., Computed Tomography for Coronary Calcium; ¶Recused from Section 2.3., Lipoprotein and Apolipoprotein Assessments; #Recused from Section 2.4.2., Recommendations for Measurement of C-Reactive Protein.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; BCBS, Blue Cross Blue Shield; BSP, Biological Signal Processing; CDC, Centers for Disease Control and Prevention; CME, continuing medical education; DSMB, Data Safety Monitoring Board; FAME, Fractional flow reserve (FFR) vs. Angiography in Multivessel Evaluation; FDA, Food and Drug Administration; LCIC, Leadership Council for Improving Cardiovascular Care; MESA, Multiethnic Study of Atherosclerosis; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIH, National Institutes of Health; SAIP, Society of Atherosclerosis Imaging and Prevention; and SCCT, Society of Cardiovascular Computed Tomography.
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Appendix 2. Reviewer Relationships With Industry and Other Entities: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

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This table represents the relevant relationships with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

*Significant (greater than $10,000) relationship; †Recused from Section 2.4.5., Lipoprotein-Associated Phospholipase A2; ‡‡Recused from Section 2.3., Lipoprotein and Apolipoprotein Assessments.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; ASNC, American Society of Nuclear Cardiology; CDA, Canadian Diabetes Association; CIHR, Canadian Institutes of Health; FDA, Food and Drug Administration; FRSQ, Fonds de la recherche en santé du Québec; NHLBI, National

Heart, Lung, and Blood Institute; NIH, National Institutes of Health; JAMA, Journal of the American Medical Association; and TIMI, Thrombolysis In Myocardial Infarction.

Appendix 3. Abbreviations List

ABI = ankle-brachial index
ApoB = apolipoprotein B
AUC = area under the curve
AV = atrioventricular
CABG = coronary artery bypass graft
CAC = coronary artery calcium
CAD = coronary artery disease
CCTA = coronary computed tomography angiography
CHD = coronary heart disease
CRP = C-reactive protein
CT = computed tomography
CVD = cardiovascular disease
DTS = Duke treadmill score
ECG = electrocardiogram
FMD = flow-mediated dilation
FRS = Framingham risk score
HbA1C = hemoglobin A1C
HDL = high-density lipoprotein
hsCRP = high-sensitivity C-reactive protein
IMT = intima-media thickness
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
Lp-PLA2 = lipoprotein-associated phospholipase A2
LVH = left ventricular hypertrophy
MI = myocardial infarction
MPI = myocardial perfusion imaging
MRI = magnetic resonance imaging
PAD = peripheral artery disease
PAT = peripheral arterial tonometry
PET = positron emission tomography
PWV = pulse wave velocity
ROC = receiver operating characteristics
SNP = single nucleotide polymorphism
SPECT = single-photon emission computed tomography

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