

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

WRITING COMMITTEE MEMBERS

Philip Greenland, MD, FACC, FAHA, Chair; Joseph S. Alpert, MD, FACC, FAHA; George A. Beller, MD, MACC, FAHA; Emelia J. Benjamin, MD, ScM, FACC, FAHA*†; Matthew J. Budoff, MD, FACC, FAHA‡§||; Zahi A. Fayad, PhD, FACC, FAHA¶; Elyse Foster, MD, FACC, FAHA#; Mark A. Hlatky, MD, FACC, FAHA\$**; John McB. Hodgson, MD, FACC, FAHA, FSCAI‡§**††; Frederick G. Kushner, MD, FACC, FAHA†‡‡; Michael S. Lauer, MD, FACC, FAHA; Leslee J. Shaw, PhD, FACC, FAHA§§; Sidney C. Smith, Jr, MD, FACC, FAHA|||¶¶; Allen J. Taylor, MD, FACC, FAHA##; William S. Weintraub, MD, FACC, FAHA; Nanette K. Wenger, MD, MACC, FAHA

*ACCF/AHA Task Force on Performance Measures Liaison.

†Recused from voting on Section 2.4.5, Lipoprotein-Associated Phospholipase A2.

‡Recused from voting on Section 2.5.11, Coronary Computed Tomography Angiography.

§Recused from voting on Section 2.6.1, Diabetes Mellitus.

||SAIP Representative.

¶SCMR Representative.

#ASE Representative.

**Recused from voting on Section 2.5.10, Computed Tomography for Coronary Calcium.

††SCAI Representative.

‡‡Recused from voting on Section 2.3, Lipoprotein and Apolipoprotein Assessments.

§§ASNC Representative.

|||ACCF/AHA Task Force on Practice Guidelines Liaison.

¶¶Recused from voting on Section 2.4.2, Recommendations for Measurement of C-Reactive Protein.

##SCCT Representative.

***Former ACCF/AHA Task Force member during this writing effort.

This document was approved by the American College of Cardiology Foundation Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee and all cosponsoring organizations in September 2010.

The American Heart Association requests that this document be cited as follows: Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JMcB, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK. 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. *Circulation*. 2010;122:e584–e636.

This article has been copublished in the *Journal of the American College of Cardiology* and the *Journal of Cardiovascular Computed Tomography*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.cardiosource.org) and the American Heart Association (my.americanheart.org). A copy of the document is also available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the “topic list” link or the “chronological list” link (No. KB-0112). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <http://www.americanheart.org/presenter.jhtml?identifier=4431>. A link to the “Permission Request Form” appears on the right side of the page.

(*Circulation*. 2010;122:e584–e636.)

© 2010 by the American College of Cardiology Foundation and the American Heart Association, Inc.

ACCF/AHA TASK FORCE MEMBERS

Alice K. Jacobs, MD, FACC, FAHA, Chair, 2009–2011;
 Sidney C. Smith, Jr, MD, FACC, FAHA, Immediate Past Chair, 2006–2008***;
 Jeffrey L. Anderson, MD, FACC, FAHA, Chair-Elect;
 Nancy Albert, PhD, CCNS, CCRN; Christopher E. Buller, MD, FACC***;
 Mark A. Creager, MD, FACC, FAHA; Steven M. Ettinger, MD, FACC; Robert A. Guyton, MD, FACC;
 Jonathan L. Halperin, MD, FACC, FAHA; Judith S. Hochman, MD, FACC, FAHA;
 Frederick G. Kushner, MD, FACC, FAHA; Rick Nishimura, MD, FACC, FAHA***;
 E. Magnus Ohman, MD, FACC; Richard L. Page, MD, FACC, FAHA***;
 William G. Stevenson, MD, FACC, FAHA; Lynn G. Tarkington, RN***; Clyde W. Yancy, MD, FACC, FAHA

Table of Contents

Preamble	e587	2.3.4. Usefulness in Motivating Patients or Guiding Therapy	e596
1. Introduction	e589	2.3.5. Evidence for Improved Net Health Outcomes	e596
1.1. Methodology and Evidence Review	e589	2.4. Other Circulating Blood Markers and Associated Conditions	e596
1.2. Organization of the Writing Committee	e590	2.4.1. Recommendation for Measurement of Natriuretic Peptides	e596
1.3. Document Review and Approval	e590	2.4.1.1. General Description	e596
1.4. Magnitude of the Problem of Cardiovascular Risk in Asymptomatic Adults	e590	2.4.1.2. Usefulness in Motivating Patients or Guiding Therapy	e598
1.5. Assessing the Prognostic Value of Risk Factors and Risk Markers	e590	2.4.2. Recommendations for Measurement of C-Reactive Protein	e598
1.6. Usefulness in Motivating Patients or Guiding Therapy	e591	2.4.2.1. Association With Increased Cardiovascular Risk and Incremental Risk Prediction	e598
1.7. Economic Evaluation of Novel Risk Markers	e591	2.4.3. Metabolic: Hemoglobin A1C	e599
2. Approaches to Risk Stratification	e592	2.4.3.1. Recommendation for Measurement of Hemoglobin A1C	e599
2.1. General Approach to Risk Stratification	e592	2.4.3.2. General Description	e599
2.1.1. Recommendation for Global Risk Scoring	e592	2.4.3.3. Association With Cardiovascular Risk in Persons Without Diabetes	e599
2.1.1.1. General Description	e592	2.4.4. Urinary Albumin Excretion	e599
2.1.2. Association With Increased Risk and Incremental Risk of Additional Risk Factors	e593	2.4.4.1. Recommendations for Testing for Microalbuminuria	e599
2.2. Family History and Genomics	e594	2.4.4.2. General Description	e599
2.2.1. Recommendation for Family History	e594	2.4.4.3. Association With Cardiovascular Risk	e599
2.2.1.1. Association With Increased Cardiovascular Risk and Incremental Risk	e594	2.4.4.4. Usefulness in Motivating Patients or Guiding Therapy	e600
2.2.1.2. Usefulness in Motivating Patients or Guiding Therapy	e594	2.4.5. Lipoprotein-Associated Phospholipase A2	e600
2.2.2. Genotypes: Common Genetic Variants for Coronary Heart Disease	e595	2.4.5.1. Recommendation for Lipoprotein-Associated Phospholipase A2	e600
2.2.2.1. Recommendation for Genomic Testing	e595	2.4.5.2. General Description	e600
2.2.2.2. Association With Increased Cardiovascular Risk and Incremental Risk	e595	2.4.5.3. Association With Cardiovascular Risk	e600
2.2.2.3. Usefulness in Motivating Patients or Guiding Therapy	e595	2.4.5.4. Usefulness in Motivating Patients or Guiding Therapy	e600
2.3. Lipoprotein and Apolipoprotein Assessments	e595	2.5. Cardiac and Vascular Tests for Risk Assessment in Asymptomatic Adults	e600
2.3.1. Recommendation for Lipoprotein and Apolipoprotein Assessments	e595	2.5.1. Resting Electrocardiogram	e600
2.3.2. Assessment of Lipoprotein Concentrations, Other Lipoprotein Parameters, and Modified Lipids	e595	2.5.1.1. Recommendations for Resting Electrocardiogram	e600
2.3.3. Risk Prediction Relationships Beyond Standard Risk Factors	e596	2.5.1.2. General Description	e600

2.5.1.3. Association With Increased Risk and Incremental Risk.....	e601	2.5.7.2. Usefulness in Motivating Patients or Guiding Therapy.....	e609
2.5.1.4. Usefulness in Motivating Patients, Guiding Therapy, and Improving Outcomes.....	e602	2.5.8. Recommendation for Stress Echocardiography.....	e610
2.5.2. Resting Echocardiography for Left Ventricular Structure and Function and Left Ventricular Hypertrophy: Transthoracic Echocardiography.....	e602	2.5.8.1. General Description.....	e610
2.5.2.1. Recommendations for Transthoracic Echocardiography.....	e602	2.5.8.2. Association With Increased Risk.....	e610
2.5.2.2. Left Ventricular Function.....	e602	2.5.8.3. Usefulness in Motivating Patients or Guiding Therapy.....	e610
2.5.2.3. Left Ventricular Hypertrophy.....	e602	2.5.9. Myocardial Perfusion Imaging.....	e610
2.5.2.4. Usefulness in Motivating Patients or Guiding Therapy.....	e603	2.5.9.1. Recommendations for Myocardial Perfusion Imaging.....	e610
2.5.3. Carotid Intima-Media Thickness on Ultrasound.....	e603	2.5.9.2. Description of Myocardial Perfusion Imaging.....	e611
2.5.3.1. Recommendation for Measurement of Carotid Intima-Media Thickness.....	e603	2.5.9.3. Evidence of Association With Increased Cardiovascular Risk in Asymptomatic Adults.....	e611
2.5.3.2. General Description.....	e603	2.5.9.4. Usefulness in Motivating Patients or Guiding Therapy.....	e612
2.5.3.3. Independent Relationship Beyond Standard Risk Factors.....	e603	2.5.9.5. Changes in Patient Outcomes.....	e612
2.5.3.4. Usefulness in Motivating Patients or Guiding Therapy.....	e604	2.5.10. Computed Tomography for Coronary Calcium.....	e612
2.5.3.5. Evidence for Improved Net Health Outcomes.....	e604	2.5.10.1. Recommendations for Calcium Scoring Methods.....	e612
2.5.4. Brachial/Peripheral Flow-Mediated Dilation.....	e604	2.5.10.2. Calcium Scoring Methods.....	e612
2.5.4.1. Recommendation for Brachial/Peripheral Flow-Mediated Dilation.....	e604	2.5.10.3. Data on Independent Relationship to Cardiovascular Events.....	e613
2.5.4.2. General Description.....	e604	2.5.10.4. Usefulness in Motivating Patients.....	e613
2.5.4.3. Association With Increased Risk and Incremental Prediction.....	e605	2.5.10.5. Use as a Repeat Measure to Monitor Effects of Therapy in Asymptomatic Persons.....	e613
2.5.4.4. Usefulness in Motivating Patients or Guiding Therapy.....	e606	2.5.10.6. Usefulness of Coronary Calcium Scoring in Guiding Therapy.....	e613
2.5.4.5. Changes in Patient Outcomes.....	e606	2.5.10.7. Evidence for Improved Net Health Outcomes.....	e613
2.5.5. Pulse Wave Velocity and Other Arterial Abnormalities: Measures of Arterial Stiffness.....	e606	2.5.10.8. Special Considerations.....	e613
2.5.5.1. Recommendation for Specific Measures of Arterial Stiffness.....	e606	2.5.11. Coronary Computed Tomography Angiography.....	e614
2.5.5.2. Description of Specific Measures of Arterial Stiffness.....	e606	2.5.11.1. Recommendation for Coronary Computed Tomography Angiography.....	e614
2.5.5.3. Evidence on the Association With Increased Cardiovascular Risk and Incremental Risk.....	e606	2.5.11.2. General Description.....	e614
2.5.5.4. Usefulness in Motivating Patients or Guiding Therapy.....	e607	2.5.11.3. Association With Increased Risk and Incremental Prediction in Asymptomatic Persons.....	e614
2.5.6. Recommendation for Measurement of Ankle-Brachial Index.....	e607	2.5.11.4. Changes in Patient Outcomes.....	e614
2.5.6.1. General Description.....	e607	2.5.12. Magnetic Resonance Imaging of Plaque.....	e614
2.5.6.2. Association With Increased Risk.....	e608	2.5.12.1. Recommendation for Magnetic Resonance Imaging of Plaque.....	e614
2.5.6.3. Usefulness in Motivating Patients or Guiding Therapy.....	e608	2.5.12.2. General Description.....	e615
2.5.7. Recommendation for Exercise Electrocardiography.....	e608	2.6. Special Circumstances and Other Considerations.....	e615
2.5.7.1. Association With Increased Risk and Incremental Risk.....	e608	2.6.1. Diabetes Mellitus.....	e615
		2.6.1.1. Recommendations for Patients With Diabetes.....	e615
		2.6.1.2. General Description and Background.....	e615
		2.6.1.3. Electrocardiographic Stress Testing for Silent Myocardial Ischemia.....	e616

2.6.1.4. Noninvasive Stress Imaging for Detection of Ischemia and Risk Stratification	e616
2.6.1.5. Usefulness in Motivating Patients	e617
2.6.1.6. Evidence of Value for Risk Assessment for Coronary Atherosclerosis or Ischemia or Both to Guide Therapy or Change Patient Outcomes	e617
2.6.1.7. Diabetes and Hemoglobin A1C	e617
2.6.1.8. Association With Cardiovascular Risk	e617
2.6.1.9. Usefulness in Motivating Patients, Guiding Therapy, and Improving Outcomes	e617
2.6.2. Special Considerations: Women	e617
2.6.2.1. Recommendations for Special Considerations in Women	e618
2.6.2.2. Detection of Women at High Risk Using Traditional Risk Factors and Scores	e618
2.6.2.3. Comparable Evidence Base for Risk Stratification of Women and Men	e618
2.6.3. Ethnicity and Race	e618
2.6.4. Older Adults	e618
2.6.5. Chronic Kidney Disease	e618
3. Future Research Needs	e619
3.1. Timing and Frequency of Follow-Up for General Risk Assessment	e619
3.2. Other Test Strategies for Which Additional Research Is Needed	e619
3.2.1. Magnetic Resonance Imaging	e619
3.2.2. Genetic Testing and Genomics	e619
3.2.3. Geographic and Environmental or Neighborhood Risks	e619
3.2.4. Role of Risk Assessment Strategies in Modifying Patient Outcomes	e619
3.3. Clinical Implications of Risk Assessment: Concluding Comments	e619
Appendix 1. Author Relationships With Industry and Other Entities	e620
Appendix 2. Reviewer Relationships With Industry and Other Entities	e623
Appendix 3. Abbreviations List	e626
References	e627

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, appropriate 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 (Task Force) 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 Task Force 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

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT ➔			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> 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
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.

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 COR I and IIa, LOE 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 mem-

bers 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 and other entities (RWI) 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' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. In addition, to ensure complete transparency, writing committee members' *comprehensive disclosure information*—including RWI not pertinent to this document—is available online as a supplement to this document. Disclosure information for the ACCF/AHA Task Force on Practice Guidelines is 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 Task Force and considered current until they are updated, revised, or withdrawn from distribution. The executive summary and recommendations are published in the *Journal of the Amer-*

ican College of Cardiology, Circulation, and the Journal of Cardiovascular Computed Tomography.

Alice K. Jacobs, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

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, cardiovascular risk, risk scoring, receiver operating characteristics (ROC) curve, screening for brachial artery reactivity, stress echocardiography, subclinical atherosclerosis, subclinical and Framingham, subclinical and Multi-Ethnic Study of Atherosclerosis (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 ASE, ASNC, SAIP, SCCT, and SCMR.

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 epidemiology¹⁶ 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, 1 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 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 (eg, 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 epidemiological 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.

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

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
Age (y)	30 to 74; M: 49	19 to 80; M: 46	35 to 65; M: 47	>45; M: 52	>50; M: 63
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.nhlbi.nih.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; M, mean; MI, myocardial infarction; PROCAM, Münster Heart Study; and SCORE, Systematic Coronary Risk Evaluation.

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 $\geq 70\%$.^{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

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 no benefit of 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 (eg, 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.²⁷

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 for 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.

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	3,352	59	5.2	Major CVD (CHD death, MI, stroke, heart failure, coronary insufficiency)	CHD death: HR 1.27/SD of NT-proANP, HR 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	1,994	30 to 60	9.4	CV events (CVD death, MI, stroke)	CV events: HR 1.58/SD NT-proBNP; evidence of interaction with age
Rancho Bernardo, CA ¹¹⁰	General population without CVD	805	77	6.8	Death; CV death	Death: HR 1.74/SD of NT-proBNP; CV events: HR 1.85/SD of NT-proBNP (multivariable adjusted)
Glasgow, Scotland ¹¹¹	Random sample of general population, some with prevalent CHD	1,252	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 congestive heart failure or renal failure	2,042	62 \pm 10	5.6	All-cause mortality	Mortality somewhat assay dependent (Shionogi, Biosite, NT-proBNP), adjusted mortality ranged from HR 1.63 to 1.39, somewhat attenuated if adjusted for echocardiographic measurements
Malmö, Sweden ²⁰	General population without CVD	5,067	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; 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.

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).

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, PAD, 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 guideline, 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 (HbA1C $\geq 6.5\%$) 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 prediction¹⁵⁶ 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 persons 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 relationship 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 Caribbeans.^{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%, respectively).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 ($n = 765$), 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: C)

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: C)

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 detect-

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, US) 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 abnormalities*	DeBacquer (1998, Belgium) ²⁰⁵	CHD and CVD mortality, all-cause mortality	10	Population-based sample (5,208 men, 4,746 women)	49 (men), 48 (women)	Major ECG abnormalities 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 (5,243 men, 6,391 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 (9,141)	52-58	Predictive of CHD death (HR 4.6) and all-cause death (HR 2.7)
Minor ST-T abnormalities	Daviglus (1999, US) ²⁰⁷	All-cause, CHD, and CVD mortality	29	Men employed at an electric company (1,673)	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, US) 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.

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; MI, myocardial infarction; and US, United States.

able 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

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/m² 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 population²²⁶ 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/m² 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 (Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement) 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/m²) in patients treated with losartan compared with patients treated with atenolol (17.7 g/m²).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 hydrochlorothiazide, 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 (eg, 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 \geq 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 men²⁵⁰ 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 predic-

tor 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 \leq 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 (eg, 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 outcome (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.

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 min) 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

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

Study, Participants	Carotid IMT Measurement	Clinical Events	Patient Details			Carotid IMT Increment (mm)	OR (95% CI)
			Follow-Up (y)	Age (y)	Sex		
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	0.19	1.36 (1.23 to 1.51)
					Women	0.19	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	0.163	1.56 (1.12 to 2.18) [#]
					Women	0.163	1.44 (1.00 to 2.08) [#]
MESA, 6698 ²⁵²	CCA	Cardiovascular events	3.9	45 to 64	Men and women	0.19	1.30 (1.10 to 1.40)

*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, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and OR, odds ratio.

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 ($\leq 10\%$ 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

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 (age >70 y) (141)	87	1.19 (95% CI 1.03 to 1.37) for total CVD mortality (top decile)
Δ D (strain) as primary measure	Stork (2004, the Netherlands) ²⁶⁹	CV and all-cause mortality	4.0	Elderly men ³⁶⁷	78	No stiffness measure associated with outcomes
Aortic PWV	Sutton-Tyrrell (2005, US) ²⁷⁰	CV mortality and events	4.6	Elderly, both sexes ^{2,488} 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 70 y	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, the 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:T1 for CVD, CHD, stroke
CPP versus BPP	Roman (2007, US) ²⁷⁶	CVD, fatal and nonfatal	4.8	Healthy American Indians, both sexes, ^{2,403} 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 (age >65 y), ^{3,337} Three-City study	73.2	CD, ~2.0 (95% CI 1.27 to 3.17) for T3:T1; CPP, ~2.1 (95% CI 1.24 to 3.70) for T3:T1; BPP, ~2.1 (95% CI 1.38 to 3.40) for T3:T1
CPP and BPP	Pini (2008, Italy) ²⁷⁸	Total CV events (fatal and nonfatal)	8	Community elderly (age >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 US, United States.

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.

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

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 studies²⁷⁹ 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 (eg, 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

Table 7. Sample of Longitudinal Studies Reporting the Independent Predictive Value of Exercise Electrocardiography 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
Exercise capacity	Gulati (2003, US) 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, US) 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, US) 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; <i>P</i> <0.001); for heart rate recovery <25 bpm; HR 2.2 (95% CI 1.02 to 4.74; <i>P</i> <0.04)
Exercise capacity, heart rate recovery, and ST-segment changes	Mora (2003, US) 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 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, US) 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; <i>P</i> <0.001); for abnormal HR recovery <12 bpm 1 min postexercise; HR 1.6 (95% CI 1.04 to 2.41; <i>P</i> =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 US, United States.

Score (DTS), which incorporates exercise capacity, ST-segment changes, and exercise-induced angina.^{313,320,321} The formula for the DTS is

$$\text{exercise time} - (4 \times \text{angina index}) - (5 \times \text{maximal ST-segment depression}).$$

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.

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. (Exercise or pharmacologic stress echocardiography is primarily used for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known coronary artery disease or the assessment of patients with known or suspected valvular heart disease.) (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 (LOE: 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 or 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 computed tomography (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” (ie, 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 (eg, 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 $\geq 130/85$ 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 (eg, 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 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 health-

care 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 Net 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 women without diabetes (55 ± 10 years), 90% were classified as low risk by FRS ($\leq 9\%$), 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 ≥ 75 th 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 ≥ 75 th 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 ms versus approximately 80 to 190 ms, 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 (eg, 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 or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of 400 or greater. (*Level of Evidence: C*)

2.6.1.2. General Description and Background

CVD is the major cause of morbidity, mortality, and health-care costs for patients with diabetes.⁴⁰¹ Compared with the general population, patients with diabetes have a 4 times greater incidence of CHD⁴⁰² 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 ($48.7\% \pm 10.7\%$ versus $40.0\% \pm 12.1\%$; $P=0.03$). 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.³⁹⁷ 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 study³³⁷ 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 Therapy 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 (ie, 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 (≥ 75 th 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 (eg, hsCRP) and cardiovascular imaging modalities (eg, 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, LOE 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 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.

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

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Philip Greenland, <i>Chair</i>	Northwestern University Feinberg School of Medicine—Professor of Preventive Medicine and Professor of Medicine; Director, Northwestern University Clinical and Translational Sciences Institute	<ul style="list-style-type: none"> • GE/Toshiba • Pfizer 	None	None	None	• NHLBI (MESA)	None
Joseph S. Alpert	University of Arizona—Professor of Medicine; Head, Department of Medicine	<ul style="list-style-type: none"> • Bayer • Bristol-Myers Squibb • Exeter CME • Johnson & Johnson • King Pharmaceuticals • Merck • Novartis • Roche Diagnostics • Sanofi-aventis 	None	None	None	None	None
George A. Beller	University of Virginia Health System—Ruth C. Heede Professor of Cardiology	• BSP Advisory Board	None	• Adenosine Therapeutics	None	None	• Stress testing case, defense, 2009
Emelia J. Benjamin [†]	Boston University Schools of Medicine and Public Health—Professor of Medicine and Epidemiology; Framingham Heart Study—Director, Echocardiography/ Vascular Laboratory	None	None	None	<ul style="list-style-type: none"> • GlaxoSmithKline • Itamar[*] • NHLBI • NIH/NHLBI[*] • NIH/NIA[*] 	None	None
Matthew J. Budoff ^{†§}	Los Angeles Biomedical Research Institute—Program Director, Division of Cardiology	None	• GE Healthcare	None	None	<ul style="list-style-type: none"> • CDC • NIH/NHLBI • MESA 	None
Zahi A. Fayad	Mount Sinai School of Medicine—Professor of Radiology and Medicine (Cardiology)	<ul style="list-style-type: none"> • BG Medicine • Merck • Roche • VIA Pharmaceuticals 	None	None	<ul style="list-style-type: none"> • Merck • Roche • Siemens 	None	None
Elyse Foster	University of California San Francisco—Professor of Clinical Medicine and Anesthesia; Director, Echocardiography Laboratory	None	None	None	<ul style="list-style-type: none"> • Boston Scientific • Evalve • EBR Systems, Inc. 	None	None

(Continued)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Mark A. Hlatky [§]	Stanford University School of Medicine—Professor of Health Research and Policy; Professor of Medicine (Cardiovascular Medicine)	<ul style="list-style-type: none"> • BCBS Technology Evaluation Center Medical Advisory Panel* • California Pacific Medical Center* • CV Therapeutics • GE Medical* • The Medicines Company 	None	None	• Avir	None	None
John McB. Hodgson [§]	Geisinger Health System—Chairman of Cardiology	• Volcano*	<ul style="list-style-type: none"> • Boston Scientific • GE Medical • Pfizer • Volcano* 	• Volcano*	<ul style="list-style-type: none"> • Boston Scientific* • FAME • GE Medical* • RADI Medical* • Volcano* 	None	None
Frederick G. Kushner [†]	Tulane University Medical Center—Clinical Professor of Medicine; Heart Clinic of Louisiana—Medical Director	None	<ul style="list-style-type: none"> • Abbott • Bristol-Myers Squibb • CV Therapeutics 	None	<ul style="list-style-type: none"> • AstraZeneca • Atherogenics • Cogentus • Eli Lilly • NIH • Novartis • Pfizer 	• FDA Science Board Member	None
Michael S. Lauer	NHLBI, NIH—Director, Division of Cardiovascular Sciences	None	None	None	None	None	None
Leslee J. Shaw	Emory University School of Medicine—Professor of Medicine	None	None	None	• GE Healthcare*	None	None
Sidney C. Smith, Jr [#]	University of North Carolina at Chapel Hill—Professor of Medicine and Director, Center for Cardiovascular Science and Medicine	None	None	None	• AstraZeneca (DSMB)	None	None
Allen J. Taylor	Washington Hospital Center, Cardiology Section—Director, Advanced Cardiovascular Imaging, Cardiovascular Research Institute	<ul style="list-style-type: none"> • Abbott • Merck • Pfizer 	None	None	• Abbott	<ul style="list-style-type: none"> • SAIP • SCCT 	None
William S. Weintraub	Christiana Care Health System—Section Chief, Cardiology	<ul style="list-style-type: none"> • Bristol-Myers Squibb • Gilead • Eli Lilly • Sanofi-aventis 	None	None	<ul style="list-style-type: none"> • Abbott* • AstraZeneca* • Bristol-Myers Squibb* • Gilead* • Otsuka* • Sanofi-aventis* 	<ul style="list-style-type: none"> • AstraZeneca* • Bayer* • Pfizer* 	<ul style="list-style-type: none"> • Quetiapine case, defense, 2008 • Celebrex case, defense, 2008

(Continued)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nanette K. Wenger	Emory University School of Medicine— Professor of Medicine (Cardiology)	<ul style="list-style-type: none"> • Abbott • AstraZeneca • Boston Scientific • Genzyme • Gilead* • LCIC • Medtronic • Merck • Pfizer • Sanofi-aventis • Schering-Plough* 	None	None	<ul style="list-style-type: none"> • Gilead* • Eli Lilly* • Merck* • NHLBI* • Pfizer* • Sanofi-aventis* 	None	None

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.

*Significant relationship.

†Recused from voting on Section 2.4.5, Lipoprotein-Associated Phospholipase A2.

‡Recused from voting on Section 2.5.11, Contrast Computed Tomography Angiography.

§Recused from voting on Section 2.6.1, Diabetes Mellitus.

||Recused from voting on Section 2.5.10, Computed Tomography for Coronary Calcium.

¶Recused from voting on Section 2.3, Lipoprotein and Apolipoprotein Assessments.

#Recused from voting on 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, Multi-Ethnic 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.

Appendix 2. Reviewer Relationships With Industry and Other Entities: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Frederick G. Kushner*	Official Reviewer— ACCF/AHA Task Force on Practice Guidelines	None	<ul style="list-style-type: none"> • Abbott • Bristol-Myers Squibb • CV Therapeutics 	None	<ul style="list-style-type: none"> • AstraZeneca • Atherogenics • Cogentus • Eli Lilly • NIH • Novartis • Pfizer 	None	None
Marian C. Limacher	Official Reviewer—AHA	None	None	None	<ul style="list-style-type: none"> • NIH* 	None	None
Thomas C. Piemonte	Official Reviewer—ACCF Board of Governors	None	None	None	None	<ul style="list-style-type: none"> • Medtronic* 	None
Paul Poirier	Official Reviewer—AHA	None	None	None	<ul style="list-style-type: none"> • CDA* • CIHR* • FRSQ* 	None	None
Jane E. Schauer	Official Reviewer—ACCF Board of Trustees	None	None	None	<ul style="list-style-type: none"> • NIH 	None	None
Daniel S. Berman	Organizational Reviewer— American Society of Nuclear Cardiology	<ul style="list-style-type: none"> • Astellas • Bracco • Cedars-Sinai Medical Center* • Flora Pharma • Lantheus* • Magellan • Spectrum Dynamics* 	None	None	<ul style="list-style-type: none"> • Astellas* • GE/Amersham • Siemens 	None	None
Roger S. Blumenthal	Organizational Reviewer— Society of Atherosclerosis Imaging and Prevention	None	None	None	None	None	None
Robin P. Choudhury	Organizational Reviewer— Society for Cardiovascular Magnetic Resonance	None	None	None	None	None	None
David A. Cox	Organizational Reviewer— Society for Cardiovascular Angiography and Interventions	<ul style="list-style-type: none"> • Abbott Vascular • Boston Scientific 	<ul style="list-style-type: none"> • Abbott Vascular • Boston Scientific 	None	None	None	None
Daniel Edmundowicz	Organizational Reviewer— Society for Cardiovascular Angiography and Interventions	None	None	None	None	None	None
Steven J. Lavine	Organizational Reviewer— American Society of Echocardiography	None	None	None	None	None	None
James K. Min	Organizational Reviewer— American Society of Nuclear Cardiology	<ul style="list-style-type: none"> • GE Healthcare 	<ul style="list-style-type: none"> • GE Healthcare 	None	<ul style="list-style-type: none"> • GE Healthcare* 	None	None

(Continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kofo O. Ogunyankin	Organizational Reviewer— American Society of Echocardiography	None	None	None	None	None	None
Donna M. Polk	Organizational Reviewer— American Society of Nuclear Cardiology	• Daiichi Sankyo*	• Merck*	None	• GlaxoSmithKline • Roche	None	None
Timothy A. Sanborn	Organizational Reviewer— Society for Cardiovascular Angiography and Interventions	None	• The Medicines Company*	None	None	None	None
Gregory S. Thomas	Organizational Reviewer— American Society of Nuclear Cardiology	• Astellas • GE Medical	• Abbott • Astellas*	None	• Astellas* • GE Medical • Isis Pharmaceuticals* • Siemens	• Past President, ASNC	None
Szilard Voros	Organizational Reviewer— Society for Cardiovascular Magnetic Resonance	None	• Merck Schering- Plough*	None	• Abbott Vascular* • CardioDx* • Merck Schering- Plough* • Vital Images* • Volcano, Inc.*	None	None
Karthikeyan Ananthasubramaniam	Content Reviewer—ACCF Imaging Council	None	• Astellas Global Pharma	None	• Astellas Global Pharma*	None	None
Jeffrey L. Anderson	Content Reviewer— ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Vera Bittner	Content Reviewer— ACCF Prevention of Cardiovascular Disease Committee	None	None	None	• CV Therapeutics* • GlaxoSmithKline* • NHLBI* • NIH/Abbott* • Roche	None	None
James I. Cleeman	Content Reviewer	None	None	None	None	None	None
Mark A. Creager	Content Reviewer— ACCF/AHA Task Force on Practice Guidelines	• Genzyme Biomarin • Sanofi-aventis • Sigma Tau • Vascutek	None	None	• Merck • Sanofi-aventis	None	None
Gregg C. Fonarow	Content Reviewer	• Abbott* • AstraZeneca • BMS/Sanofi • GlaxoSmith Kline* • Medtronic* • Merck* • Novartis* • Pfizer*	• Abbott* • AstraZeneca • BMS/Sanofi* • GlaxoSmithKline* • Medtronic* • Merck* • Novartis* • Pfizer*	None	None	None	None
David C. Goff, Jr	Content Reviewer	• JAMA/Archives of Internal Medicine* • Scientific Evidence*	None	None	• Merck	None	None

(Continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Thomas A. Haffey	Content Reviewer	<ul style="list-style-type: none"> • Merck • Merck Schering-Plough 	<ul style="list-style-type: none"> • AstraZeneca • Merck • Merck Schering-Plough 	<ul style="list-style-type: none"> • Colorado Heart Institute 	<ul style="list-style-type: none"> • GlaxoSmithKline* 	None	None
Jonathan L. Halperin	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	<ul style="list-style-type: none"> • Astellas • Bayer HealthCare • Biotronik* • Boehringer Ingelheim • Daiichi Sankyo • FDA Cardiorenal Advisory Committee • Johnson & Johnson • Portola Pharmaceuticals • Sanofi-aventis 	None	None	<ul style="list-style-type: none"> • NIH (NHLBI) 	None	None
Jerome L. Hines	Content Reviewer—ACCF Imaging Council	None	None	None	None	None	None
Judith S. Hochman	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	<ul style="list-style-type: none"> • Eli Lilly • Millennium Pharmaceuticals and Schering-Plough Research Institute (TIMI 50) 	None	None	None	<ul style="list-style-type: none"> • GlaxoSmithKline 	None
Christopher M. Kramer	Content Reviewer—ACCF Imaging Council	<ul style="list-style-type: none"> • Siemens 	None	None	<ul style="list-style-type: none"> • Astellas* • GlaxoSmithKline* • NHLBI* • Merck Schering-Plough* • Siemens Medical Solutions* 	None	None
Donald M. Lloyd-Jones	Content Reviewer	None	None	None	None	None	None
Pamela B. Morris	Content Reviewer—ACCF Prevention of Cardiovascular Disease Committee	None	<ul style="list-style-type: none"> • Abbott • AstraZeneca • Merck • Merck Schering-Plough • Takeda 	None	None	None	None
Srihari S. Naidu	Content Reviewer—ACCF Cardiac Catheterization Committee	None	None	None	None	None	None
Vasan S. Ramachandran	Content Reviewer	None	None	None	<ul style="list-style-type: none"> • NIH* 	None	None
Rita F. Redberg	Content Reviewer	None	None	None	None	None	None
Charanjit S. Rihal	Content Reviewer—ACCF Cardiac Catheterization Committee	None	None	None	None	None	None
Vincent L. Sorrell	Content Reviewer—ACCF Prevention of Cardiovascular Disease Committee	<ul style="list-style-type: none"> • Lantheus* 	<ul style="list-style-type: none"> • GE Medical • Lantheus* • Phillips 	None	<ul style="list-style-type: none"> • AtCor Medical 	None	None

(Continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Laurence S. Sperling	Content Reviewer— ACCF Prevention of Cardiovascular Disease Committee	None	None	None	None	None	None
Carl L. Tommaso	Content Reviewer—ACCF Interventional Council	None	None	None	None	None	None
Uma S. Valeti	Content Reviewer	None	None	None	• Medtronic*	None	None
Christopher J. White	Content Reviewer—ACCF Interventional Council	• Baxter* • Boston Scientific*	None	None	None	None	None
Kim A. Williams	Content Reviewer— ACCF Imaging Council	• Astellas* • GE Healthcare* • King Pharmaceuticals*	• Astellas* • GE Healthcare*	None	• GE Healthcare* • Molecular Insight Pharmaceuticals*	• Molecular Insight Pharmaceuticals*	None

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 relationship.

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

Staff

American College of Cardiology Foundation

John C. Lewin, MD, Chief Executive Officer

Charlene May, Senior Director, Science and Clinical Policy

Lisa Bradfield, CAE, Director, Science and Clinical Policy

Sue Keller, BSN, MPH, Senior Specialist, Evidence-Based Medicine

Erin A. Barrett, MPS, Senior Specialist, Science and Clinical Policy

Beth Denton, Specialist, Science and Clinical Policy

American Heart Association

Nancy Brown, Chief Executive Officer

Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations

References

- ACCF/AHA Task Force on Practice Guidelines. Methodologies and Policies of the ACCF/AHA Task Force on Practice Guidelines. Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf and <http://circ.ahajournals.org/manual/>. Accessed August 27, 2010.
- Califf RM, Armstrong PW, Carver JR, et al. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;27:1007–19.
- D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham Study. *Am Heart J*. 2000;139:272–81.
- Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290:891–7.
- Ni H, Coady S, Rosamond W, et al. Trends from 1987 to 2004 in sudden death due to coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;157:46–52.
- Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119:e21–e181.
- Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–98.
- McMahan CA, Gidding SS, Viikari JS, et al. Association of Pathobiologic Determinants of Atherosclerosis in Youth risk score and 15-year change in risk score with carotid artery intima-media thickness in young adults (from the Cardiovascular Risk in Young Finns Study). *Am J Cardiol*. 2007;100:1124–9.
- Gidding SS, McMahan CA, McGill HC, et al. Prediction of coronary artery calcium in young adults using the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score: the CARDIA study. *Arch Intern Med*. 2006;166:2341–7.
- McMahan CA, Gidding SS, Malcom GT, et al. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. *Pediatrics*. 2006;118:1447–55.
- Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353:89–92.
- Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–8.
- Haapanene-Niemi N, Vuovi I, Pasanen M. Public health burden of coronary disease risk factors among middle-aged and elderly men. *Prev Med*. 2009;4:343–8.
- Vinereau D. Risk factors for atherosclerotic disease: present and future. *Herz*. 2006;31 Suppl 3:5–24.
- Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation*. 2009;119:2408–16.
- von Elm E, Altman DG, Egger M, et al. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573–7.
- Greenland P, O'Malley PG. When is a new prediction marker useful? A consideration of lipoprotein-associated phospholipase A2 and C-reactive protein for stroke risk. *Arch Intern Med*. 2005;165:2454–6.
- Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–45.
- Kathiresan S, Manning AK, Demissie S, et al. A genome-wide association study for blood lipid phenotypes in the Framingham Heart Study. *BMC Med Genet*. 2007;8 Suppl 1:S17.
- Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA*. 2009;302:49–57.
- Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007;115:928–35.
- Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297:611–9.
- Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–72.
- Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart*. 2006;92:1752–9.
- D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–7.
- Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation*. 1991;83:356–62.
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–97.
- Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–47.
- Friedmann PD, Brett AS, Mayo-Smith MF. Differences in generalists' and cardiologists' perceptions of cardiovascular risk and the outcomes of preventive therapy in cardiovascular disease. *Ann Intern Med*. 1996;124:414–21.
- Grover SA, Lowensteyn I, Esrey KL, et al. Do doctors accurately assess coronary risk in their patients? Preliminary results of the coronary health assessment study. *BMJ*. 1995;310:975–8.
- McManus RJ, Mant J, Meulendijks CF, et al. Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice: cross sectional study. *BMJ*. 2002;324:459–64.
- Montgomery AA, Fahey T, MacKintosh C, et al. Estimation of cardiovascular risk in hypertensive patients in primary care. *Br J Gen Pract*. 2000;50:127–8.
- Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation*. 2001;104:1863–7.
- Lauer MS. Clinical practice. aspirin for primary prevention of coronary events. *N Engl J Med*. 2002;346:1468–74.
- Topol EJ, Lauer MS. The rudimentary phase of personalised medicine: coronary risk scores. *Lancet*. 2003;362:1776–7.
- D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–53.
- Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.
- Diverse Populations Collaborative Group. Prediction of mortality from coronary heart disease among diverse populations: is there a common predictive function? *Heart*. 2002;88:222–8.
- Gaziano TA, Young CR, Fitzmaurice G, et al. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet*. 2008;371:923–31.
- Berry JD, Lloyd-Jones DM, Garside DB, Greenland P. Framingham risk score and prediction of coronary heart disease death in young men. *Am Heart J*. 2007;154:80–6.
- Cavanaugh-Hussey MW, Berry JD, Lloyd-Jones DM. Who exceeds ATP-III risk thresholds? Systematic examination of the effect of varying age and risk factor levels in the ATP-III risk assessment tool. *Prev Med*. 2008;47:619–23.
- Marra AK, Lloyd-Jones DM. Systematic examination of the updated Framingham heart study general cardiovascular risk profile. *Circulation*. 2009;120:384–90.
- Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–52.
- Gerszten RE, Wang TJ. The search for new cardiovascular biomarkers. *Nature*. 2008;451:949–52.
- Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557–65.
- Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the

- Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). *J Am Coll Cardiol*. 2007;50:e1–e157.
47. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *J Am Coll Cardiol*. 2007;49:1230–50.
 48. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44:E1–E211.
 49. Fletcher B, Berra K, Ades P, et al. Managing abnormal blood lipids: a collaborative approach. *Circulation*. 2005;112:3184–209.
 50. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–52.
 51. Eyre H, Kahn R, Robertson RM, et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation*. 2004;109:3244–55.
 52. Smith SC Jr, Greenland P, Grundy SM. AHA conference proceedings. Prevention conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. American Heart Association. *Circulation*. 2000;101:111–6.
 53. Grundy SM, Balady GJ, Criqui MH, et al. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. *Circulation*. 1998;97:1876–87.
 54. Pencina MJ, D'Agostino RB Sr, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:3078–84.
 55. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation*. 2002;105:310–5.
 56. Sesso HD, Lee IM, Gaziano JM, et al. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation*. 2001;104:393–8.
 57. Shih PA, O'Connor DT. Hereditary determinants of human hypertension: strategies in the setting of genetic complexity. *Hypertension*. 2008;51:1456–64.
 58. Levy D, DeStefano AL, Larson MG, et al. Evidence for a gene influencing blood pressure on chromosome 17: genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. *Hypertension*. 2000;36:477–83.
 59. Weiss LA, Pan L, Abney M, Ober C. The sex-specific genetic architecture of quantitative traits in humans. *Nat Genet*. 2006;38:218–22.
 60. Harrison TA, Hindorf LA, Kim H, et al. Family history of diabetes as a potential public health tool. *Am J Prev Med*. 2003;24:152–9.
 61. Coady SA, Jaquish CE, Fabsitz RR, et al. Genetic variability of adult body mass index: a longitudinal assessment in Framingham families. *Obes Res*. 2002;10:675–81.
 62. Munafò M, Clark T, Johnstone E, et al. The genetic basis for smoking behavior: a systematic review and meta-analysis. *Nicotine Tob Res*. 2004;6:583–97.
 63. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA*. 2004;291:2204–11.
 64. Murabito JM, Pencina MJ, Nam BH, et al. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *JAMA*. 2005;294:3117–23.
 65. Marenberg ME, Risch N, Berkman LF, et al. Genetic susceptibility to death from coronary heart disease in a study of twins. *N Engl J Med*. 1994;330:1041–6.
 66. Horne BD, Camp NJ, Muhlestein JB, Cannon-Albright LA. Identification of excess clustering of coronary heart diseases among extended pedigrees in a genealogical population database. *Am Heart J*. 2006;152:305–11.
 67. Li R, Bensen JT, Hutchinson RG, et al. Family risk score of coronary heart disease (CHD) as a predictor of CHD: the Atherosclerosis Risk in Communities (ARIC) study and the NHLBI family heart study. *Genet Epidemiol*. 2000;18:236–50.
 68. Ciruzzi M, Schargrodsky H, Rozlosnik J, et al. Frequency of family history of acute myocardial infarction in patients with acute myocardial infarction. Argentine FRICAS (Factores de Riesgo Coronario en America del Sur) Investigators. *Am J Cardiol*. 1997;80:122–7.
 69. Shiraiishi J, Kohno Y, Yamaguchi S, et al. Acute myocardial infarction in young Japanese adults. *Circ J*. 2005;69:1454–8.
 70. Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. *J Chronic Dis*. 1986;39:809–21.
 71. Williams RR, Hunt SC, Heiss G, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). *Am J Cardiol*. 2001;87:129–35.
 72. Hawe E, Talmud PJ, Miller GJ, Humphries SE. Family history is a coronary heart disease risk factor in the Second Northwick Park Heart Study. *Ann Hum Genet*. 2003;67:97–106.
 73. Murabito JM, Nam BH, D'Agostino RB Sr, et al. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med*. 2004;140:434–40.
 74. Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med*. 2003;24:128–35.
 75. Magnus P, Armstrong B, McCall M. A comparison of populations self-selected and randomly selected for coronary risk factor screening. *Prev Med*. 1983;12:340–50.
 76. Kip KE, McCreath HE, Roseman JM, et al. Absence of risk factor change in young adults after family heart attack or stroke: the CARDIA Study. *Am J Prev Med*. 2002;22:258–66.
 77. Becker DM, Yanek LR, Johnson WR Jr, et al. Impact of a community-based multiple risk factor intervention on cardiovascular risk in black families with a history of premature coronary disease. *Circulation*. 2005;111:1298–304.
 78. Cene CW, Yanek LR, Moy TF, et al. Sustainability of a multiple risk factor intervention on cardiovascular disease in high-risk African American families. *Ethn Dis*. 2008;18:169–75.
 79. Paynter NP, Chasman DI, Buring JE, et al. Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. *Ann Intern Med*. 2009;150:65–72.
 80. Scheuner MT, Sieverding P, Shekelle PG. Delivery of genomic medicine for common chronic adult diseases: a systematic review. *JAMA*. 2008;299:1320–34.
 81. Bodmer W, Bonilla C. Common and rare variants in multifactorial susceptibility to common diseases. *Nat Genet*. 2008;40:695–701.
 82. McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science*. 2007;316:1488–91.
 83. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–3.
 84. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007;357:443–53.
 85. Assimes TL, Knowles JW, Basu A, et al. Susceptibility locus for clinical and subclinical coronary artery disease at chromosome 9p21 in the multi-ethnic ADVANCE study. *Hum Mol Genet*. 2008;17:2320–8.
 86. Hinohara K, Nakajima T, Takahashi M, et al. Replication of the association between a chromosome 9p21 polymorphism and coronary artery disease in Japanese and Korean populations. *J Hum Genet*. 2008;53:357–9.
 87. Silander K, Tang H, Myles S, et al. Worldwide patterns of haplotype diversity at 9p21.3, a locus associated with type 2 diabetes and coronary heart disease. *Genome Med*. 2009;1:51.
 88. Gil J, Peters G. Regulation of the INK4b-ARF-INK4a tumour suppressor locus: all for one or one for all. *Nat Rev Mol Cell Biol*. 2006;7:667–77.
 89. Talmud PJ, Cooper JA, Palmieri J, et al. Chromosome 9p21.3 coronary heart disease locus genotype and prospective risk of CHD in healthy middle-aged men. *Clin Chem*. 2008;54:467–74.
 90. Kathiresan S, Melander O, Anefski D, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med*. 2008;358:1240–9.
 91. Marteau TM, Lerman C. Genetic risk and behavioural change. *BMJ*. 2001;322:1056–9.
 92. Sanderson SC, Michie S. Genetic testing for heart disease susceptibility: potential impact on motivation to quit smoking. *Clin Genet*. 2007;71:501–10.

93. Wright AJ, Aveyard P, Guo B, et al. Is attributing smoking to genetic causes associated with a reduced probability of quit attempt success? A cohort study. *Addiction*. 2007;102:1657–64.
94. McBride CM, Bepler G, Lipkus IM, et al. Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. *Cancer Epidemiol Biomarkers Prev*. 2002;11:521–8.
95. Offit K. Genomic profiles for disease risk: predictive or premature? *JAMA*. 2008;299:1353–5.
96. Ip S, Lichtenstein AH, Chung M, et al. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009;150:474–84.
97. El Harchaoui K, van der Steeg WA, Stroes ES, et al. Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women: the EPIC-Norfolk Prospective Population Study. *J Am Coll Cardiol*. 2007;49:547–53.
98. Duprez DA, Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. *Curr Atheroscler Rep*. 2007;9:139–44.
99. Freedman DS, Otvos JD, Jeyarajah EJ, et al. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. *Clin Chem*. 2004;50:1189–200.
100. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007;298:776–85.
101. Mora S. Advanced lipoprotein testing and subfractionation are not (yet) ready for routine clinical use. *Circulation*. 2009;119:2396–404.
102. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412–23.
103. Dati F, Tate JR, Marcovina SM, Steinmetz A. First WHO/IFCC International Reference Reagent for Lipoprotein(a) for Immunoassay—Lp(a) SRM 2B. *Clin Chem Lab Med*. 2004;42:670–6.
104. Witte DR, Taskinen MR, Perttunen-Nio H, et al. Study of agreement between LDL size as measured by nuclear magnetic resonance and gradient gel electrophoresis. *J Lipid Res*. 2004;45:1069–76.
105. DiAngelantonio E, Chowdhury R, Sarwar N, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation*. 2009;120:2177–87.
106. McKie PM, Rodeheffer RJ, Cataliotti A, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide: biomarkers for mortality in a large community-based cohort free of heart failure. *Hypertension*. 2006;47:874–80.
107. Olsen MH, Hansen TW, Christensen MK, et al. Cardiovascular risk prediction by N-terminal pro brain natriuretic peptide and high sensitivity C-reactive protein is affected by age and sex. *J Hypertens*. 2008;26:26–34.
108. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. 2004;350:655–63.
109. Kistorp C, Raymond I, Pedersen F, et al. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293:1609–16.
110. Daniels LB, Laughlin GA, Clopton P, et al. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol*. 2008;52:450–9.
111. McDonagh TA, Cunningham AD, Morrison CE, et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. *Heart*. 2001;86:21–6.
112. Laukkanen JA, Kurl S, Ala-Kopsala M, et al. Plasma N-terminal fragments of natriuretic propeptides predict the risk of cardiovascular events and mortality in middle-aged men. *Eur Heart J*. 2006;27:1230–7.
113. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. 2008;358:2107–16.
114. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–207.
115. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*. 2008;118:2243–51.
116. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–78.
117. Barzilay JI, Forsberg C, Heckbert SR, et al. The association of markers of inflammation with weight change in older adults: the Cardiovascular Health Study. *Int J Obes (Lond)*. 2006;30:1362–7.
118. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286:327–34.
119. Sesso HD, Buring JE, Rifai N, et al. C-reactive protein and the risk of developing hypertension. *JAMA*. 2003;290:2945–51.
120. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. *PLoS Med*. 2005;2:e160.
121. Balk EM, Lau J, Goudas LC, et al. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Ann Intern Med*. 2003;139:670–82.
122. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA*. 2003;289:1799–804.
123. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology*. 2002;13:561–8.
124. Ridker PM, Danielson E, Rifai N, Glynn RJ. Valsartan, blood pressure reduction, and C-reactive protein: primary report of the Val-MARC trial. *Hypertension*. 2006;48:73–9.
125. Ockene IS, Matthews CE, Rifai N, et al. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. *Clin Chem*. 2001;47:444–50.
126. Koenig W, Sund M, Frohlich M, et al. Refinement of the association of serum C-reactive protein concentration and coronary heart disease risk by correction for within-subject variation over time: the MONICA Augsburg studies, 1984 and 1987. *Am J Epidemiol*. 2003;158:357–64.
127. Glynn RJ, MacFadyen JG, Ridker PM. Tracking of high-sensitivity C-reactive protein after an initially elevated concentration: the JUPITER Study. *Clin Chem*. 2009;55:305–12.
128. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
129. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*. 2004;350:1387–97.
130. Arima H, Kubo M, Yonemoto K, et al. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol*. 2008;28:1385–91.
131. Best LG, Zhang Y, Lee ET, et al. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. *Circulation*. 2005;112:1289–95.
132. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study: Multiple Risk Factor Intervention Trial. *Am J Epidemiol*. 1996;144:537–47.
133. Albert CM, Ma J, Rifai N, et al. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. 2002;105:2595–9.
134. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation*. 2003;108:3006–10.
135. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2000;35:1628–37.
136. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med*. 1999;106:506–12.
137. Pradhan AD, Rifai N, Ridker PM. Soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, and the development of symptomatic peripheral arterial disease in men. *Circulation*. 2002;106:820–5.
138. Casas JP, Shah T, Cooper J, et al. Insight into the nature of the CRP-coronary event association using Mendelian randomization. *Int J Epidemiol*. 2006;35:922–31.
139. Casas JP, Shah T, Hingorani AD, et al. C-reactive protein and coronary heart disease: a critical review. *J Intern Med*. 2008;264:295–314.
140. Davey SG, Ebrahim S. ‘Mendelian randomization’: can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32:1–22.

141. Elliott P, Chambers JC, Zhang W, et al. Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. *JAMA*. 2009;302:37–48.
142. Pepys MB. C-reactive protein is neither a marker nor a mediator of atherosclerosis. *Nat Clin Pract Nephrol*. 2008;4:234–5.
143. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med*. 2006;145:21–9.
144. Shah T, Casas JP, Cooper JA, et al. Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. *Int J Epidemiol*. 2009;38:217–31.
145. Wilson PW, Nam BH, Pencina M, et al. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. *Arch Intern Med*. 2005;165:2473–8.
146. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation*. 2003;108:2292–7.
147. Ridker PM, Fonseca FA, Genest J, et al. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol*. 2007;100:1659–64.
148. Ridker PM, MacFadyen JG, Fonseca FA, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circ Cardiovasc Qual Outcomes*. 2009;2:616–23.
149. Hlatky MA. Expanding the orbit of primary prevention—moving beyond JUPITER. *N Engl J Med*. 2008;359:2280–2.
150. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004;141:413–20.
151. Khaw KT, Wareham N. Glycated hemoglobin as a marker of cardiovascular risk. *Curr Opin Lipidol*. 2006;17:637–43.
152. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
153. Lachin JM, Christophi CA, Edelstein SL, et al. Factors associated with diabetes onset during metformin versus placebo therapy in the diabetes prevention program. *Diabetes*. 2007;56:1153–9.
154. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141:421–31.
155. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362:800–11.
156. Pradhan AD, Rifai N, Buring JE, Ridker PM. Hemoglobin A1c predicts diabetes but not cardiovascular disease in nondiabetic women. *Am J Med*. 2007;120:720–7.
157. Bennett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of Type 2 diabetes: a systematic review. *Diabet Med*. 2007;24:333–43.
158. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33 Suppl 1:S11–S61.
159. Pencina MJ, D'Agostino RB. Evaluation of the Framingham risk score in the European Prospective Investigation of Cancer-Norfolk cohort—invited commentary. *Arch Intern Med*. 2008;168:1216–8.
160. Simmons RK, Sharp S, Boekholdt SM, et al. Evaluation of the Framingham risk score in the European Prospective Investigation of Cancer-Norfolk cohort: does adding glycated hemoglobin improve the prediction of coronary heart disease events? *Arch Intern Med*. 2008;168:1209–16.
161. Adams RJ, Appleton SL, Hill CL, et al. Independent association of HbA(1c) and incident cardiovascular disease in people without diabetes. *Obesity*. 2009;17:559–63.
162. Ibsen H, Olsen MH, Wachtell K, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension*. 2005;45:198–202.
163. Ninomiya T, Perkovic V, Verdon C, et al. Proteinuria and stroke: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2009;53:417–25.
164. Wachtell K, Ibsen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med*. 2003;139:901–6.
165. Arnlov J, Evans JC, Meigs JB, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation*. 2005;112:969–75.
166. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med*. 2008;5:e207.
167. American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care*. 2009;32 Suppl 1:S13–S61.
168. Aakre KM, Thue G, Subramanian-Haavik S, et al. Postanalytical external quality assessment of urine albumin in primary health care: an international survey. *Clin Chem*. 2008;54:1630–6.
169. McQueen MJ, Don-Wauchope AC. Requesting and interpreting urine albumin measurements in the primary health care setting. *Clin Chem*. 2008;54:1595–7.
170. Lambers Heerspink HJ, Brantsma AH, De Zeeuw D, et al. Albuminuria assessed from first-morning-void urine samples versus 24-hour urine collections as a predictor of cardiovascular morbidity and mortality. *Am J Epidemiol*. 2008;168:897–905.
171. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2005;67:2089–100.
172. Bryson CL, Ross HJ, Boyko EJ, Young BA. Racial and ethnic variations in albuminuria in the US Third National Health and Nutrition Examination Survey (NHANES III) population: associations with diabetes and level of CKD. *Am J Kidney Dis*. 2006;48:720–6.
173. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038–47.
174. Cirillo M, Senigalliesi L, Laurenzi M, et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. *Arch Intern Med*. 1998;158:1933–9.
175. Cao JJ, Biggs ML, Barzilay J, et al. Cardiovascular and mortality risk prediction and stratification using urinary albumin excretion in older adults ages 68–102: the Cardiovascular Health Study. *Atherosclerosis*. 2008;197:806–13.
176. Halimi JM, Bonnet F, Lange C, et al. Urinary albumin excretion is a risk factor for diabetes mellitus in men, independently of initial metabolic profile and development of insulin resistance: the DESIR Study. *J Hypertens*. 2008;26:2198–206.
177. Wang TJ, Evans JC, Meigs JB, et al. Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation*. 2005;111:1370–6.
178. Meigs JB, D'Agostino RB Jr, Nathan DM, et al. Longitudinal association of glycemia and microalbuminuria: the Framingham Offspring Study. *Diabetes Care*. 2002;25:977–83.
179. Papaioannou GI, Seip RL, Grey NJ, et al. Brachial artery reactivity in asymptomatic patients with type 2 diabetes mellitus and microalbuminuria (from the Detection of Ischemia in Asymptomatic Diabetics-brachial artery reactivity study). *Am J Cardiol*. 2004;94:294–9.
180. Malik AR, Sultan S, Turner ST, Kullo IJ. Urinary albumin excretion is associated with impaired flow- and nitroglycerin-mediated brachial artery dilatation in hypertensive adults. *J Hum Hypertens*. 2007;21:231–8.
181. Kshirsagar AV, Bomback AS, Bang H, et al. Association of C-reactive protein and microalbuminuria (from the National Health and Nutrition Examination Surveys, 1999 to 2004). *Am J Cardiol*. 2008;101:401–6.
182. DeZeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. *J Am Soc Nephrol*. 2006;17:2100–5.
183. Astor BC, Hallan SI, Miller ER 3rd, et al. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol*. 2008;167:1226–34.
184. Hallan S, Astor B, Romundstad S, et al. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. *Arch Intern Med*. 2007;167:2490–6.
185. Tillin T, Forouhi N, McKeigue P, Chaturvedi N. Microalbuminuria and coronary heart disease risk in an ethnically diverse UK population: a prospective cohort study. *J Am Soc Nephrol*. 2005;16:3702–10.
186. Xu J, Knowler WC, Devereux RB, et al. Albuminuria within the “normal” range and risk of cardiovascular disease and death in American Indians: the Strong Heart Study. *Am J Kidney Dis*. 2007;49:208–16.

187. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006;355:2631–9.
188. Ballantyne C, Cushman M, Psaty B, et al. Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA2 and cardiovascular diseases. *Eur J Cardiovasc Prev Rehabil*. 2007;14:3–11.
189. Daniels LB, Laughlin GA, Sarno MJ, et al. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. *J Am Coll Cardiol*. 2008;51:913–9.
190. Garza CA, Montori VM, McConnell JP, et al. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. *Mayo Clin Proc*. 2007;82:159–65.
191. Koenig W, Khuseynova N, Lowel H, et al. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. *Circulation*. 2004;110:1903–8.
192. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol*. 2005;25:923–31.
193. Persson M, Nilsson JA, Nelson JJ, et al. The epidemiology of Lp-PLA(2): distribution and correlation with cardiovascular risk factors in a population-based cohort. *Atherosclerosis*. 2007;190:388–96.
194. Brilakis ES, Khera A, McGuire DK, et al. Influence of race and sex on lipoprotein-associated phospholipase A2 levels: observations from the Dallas Heart Study. *Atherosclerosis*. 2008;199:110–5.
195. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med*. 2006;166:1368–73.
196. Tsimikas S, Willert J, Knoflach M, et al. Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study. *Eur Heart J*. 2009;30:107–15.
197. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 2000;343:1148–55.
198. Khuseynova N, Koenig W. Predicting the risk of cardiovascular disease: where does lipoprotein-associated phospholipase A(2) fit in? *Mol Diagn Ther*. 2007;11:203–17.
199. Mohler ER, III, Ballantyne CM, Davidson MH, et al. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 2008;51:1632–41.
200. DeBacquer D, DeBacker G. Electrocardiographic findings and global coronary risk assessment. *Eur Heart J*. 2002;23:268–70.
201. Okin PM, Roman MJ, Lee ET, et al. Combined echocardiographic left ventricular hypertrophy and electrocardiographic ST depression improve prediction of mortality in American Indians: the Strong Heart Study. *Hypertension*. 2004;43:769–74.
202. Ashley EA, Raxwal V, Froelicher V. An evidence-based review of the resting electrocardiogram as a screening technique for heart disease. *Prog Cardiovasc Dis*. 2001;44:55–67.
203. Schlant RC, Adolph RJ, DiMarco JP, et al. Guidelines for electrocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Electrocardiography). *J Am Coll Cardiol*. 1992;19:473–81.
204. U.S. Preventive Services Task Force. Screening for coronary heart disease: recommendation statement. *Ann Intern Med*. 2004;140:569–72.
205. DeBacquer D, DeBacker G, Kornitzer M, Blackburn H. Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart*. 1998;80:570–7.
206. Kumar A, Prineas RJ, Arnold AM, et al. Prevalence, prognosis, and implications of isolated minor nonspecific ST-segment and T-wave abnormalities in older adults: Cardiovascular Health Study. *Circulation*. 2008;118:2790–6.
207. Daviglius ML, Liao Y, Greenland P, et al. Association of nonspecific minor ST-T abnormalities with cardiovascular mortality: the Chicago Western Electric Study. *JAMA*. 1999;281:530–6.
208. Desai AD, Yaw TS, Yamazaki T, et al. Prognostic significance of quantitative QRS duration. *Am J Med*. 2006;119:600–6.
209. Kannel WB, Gordon T, Castelli WP, et al. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham Study. *Ann Intern Med*. 1970;72:813–22.
210. Larsen CT, Dahlin J, Blackburn H, et al. Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave: the Copenhagen City Heart Study. *Eur Heart J*. 2002;23:315–24.
211. Sigurdsson E, Thorgeirsson G, Sigvaldason H, et al. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris: the Reykjavik Study. *Ann Intern Med*. 1995;122:96–102.
212. Gorodeski EZ, Ishwaran H, Blackstone EH, Lauer MS. Quantitative electrocardiographic measures and long-term mortality in exercise test patients with clinically normal resting electrocardiograms. *Am Heart J*. 2009;158:61–70.
213. Okin PM, Devereux RB, Kors JA, et al. Computerized ST depression analysis improves prediction of all-cause and cardiovascular mortality: the Strong Heart Study. *Ann Noninvasive Electrocardiol*. 2001;6:107–16.
214. Prineas RJ, Rautaharju PM, Grandits G, Crow R. Independent risk for cardiovascular disease predicted by modified continuous score electrocardiographic criteria for 6-year incidence and regression of left ventricular hypertrophy among clinically disease free men: 16-year follow-up for the multiple risk factor intervention trial. *J Electrocardiol*. 2001;34:91–101.
215. Myerburg RJ, Vetter VL. Electrocardiograms should be included in preparticipation screening of athletes. *Circulation*. 2007;116:2616–26.
216. Denes P, Larson JC, Lloyd-Jones DM, et al. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. *JAMA*. 2007;297:978–85.
217. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham Study. *N Engl J Med*. 1984;311:1144–7.
218. Okin PM, Devereux RB, Nieminen MS, et al. Electrocardiographic strain pattern and prediction of cardiovascular morbidity and mortality in hypertensive patients. *Hypertension*. 2004;44:48–54.
219. Okin PM, Devereux RB, Jern S, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA*. 2004;292:2343–9.
220. Wachtell K, Okin PM, Olsen MH, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE Study. *Circulation*. 2007;116:700–5.
221. Okin PM, Devereux RB, Nieminen MS, et al. Electrocardiographic strain pattern and prediction of new-onset congestive heart failure in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. *Circulation*. 2006;113:67–73.
222. Okin PM, Devereux RB, Harris KE, et al. In-treatment resolution or absence of electrocardiographic left ventricular hypertrophy is associated with decreased incidence of new-onset diabetes mellitus in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study. *Hypertension*. 2007;50:984–90.
223. Gardin JM, Lauer MS. Left ventricular hypertrophy: the next treatable, silent killer? *JAMA*. 2004;292:2396–8.
224. Corrado D, Basso C, Pavei A, et al. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA*. 2006;296:1593–601.
225. Verdecchia P, Carini G, Circo A, et al. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. *J Am Coll Cardiol*. 2001;38:1829–35.
226. Rodriguez CJ, Lin F, Sacco RL, et al. Prognostic implications of left ventricular mass among Hispanics: the Northern Manhattan Study. *Hypertension*. 2006;48:87–92.
227. Beache GM, Herzka DA, Boxerman JL, et al. Attenuated myocardial vasodilator response in patients with hypertensive hypertrophy revealed by oxygenation-dependent magnetic resonance imaging. *Circulation*. 2001;104:1214–7.
228. Nunez E, Arnett DK, Benjamin EJ, et al. Comparison of the prognostic value of left ventricular hypertrophy in African-American men versus women. *Am J Cardiol*. 2004;94:1383–90.

229. Cuspidi C, Esposito A, Negri F, et al. Studies on left ventricular hypertrophy regression in arterial hypertension: a clear message for the clinician? *Am J Hypertens*. 2008;21:458–63.
230. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. *J Am Soc Echocardiogr*. 2005;18:1440–63.
231. Basavarajiah S, Boraita A, Whyte G, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2008;51:2256–62.
232. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–6.
233. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–72.
234. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. *JAMA*. 1996;275:1507–13.
235. Devereux RB, Palmieri V, Sharpe N, et al. Effects of once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the prospective randomized enalapril study evaluating regression of ventricular enlargement (PRESERVE) trial. *Circulation*. 2001;104:1248–54.
236. Liebson PR, Grandits GA, Dianzumba S, et al. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). *Circulation*. 1995;91:698–706.
237. Gottdiener JS, Reda DJ, Massie BM, et al. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Circulation*. 1997;95:2007–14.
238. Mathew J, Sleight P, Lonn E, et al. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation*. 2001;104:1615–21.
239. Devereux RB, Wachtell K, Gerdts E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA*. 2004;292:2350–6.
240. Nambi V, Chambless L, Folsom A, et al. Carotid intima-media thickness and the presence or absence of plaque improves prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol* 2010;55:1600–7.
241. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. *J Am Soc Echocardiogr*. 2008;21:93–111.
242. Touboul PJ, Vicaut E, Labreuche J, et al. Design, baseline characteristics and carotid intima-media thickness reproducibility in the PARC study. *Cerebrovasc Dis*. 2005;19:57–63.
243. Peretz A, Leotta DF, Sullivan JH, et al. Flow mediated dilation of the brachial artery: an investigation of methods requiring further standardization. *BMC Cardiovasc Disord*. 2007;7:11.
244. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–67.
245. Belcaro G, Nicolaidis AN, Ramaswami G, et al. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study(1)). *Atherosclerosis*. 2001;156:379–87.
246. Salonen JT, Salonen R. Ultrasound B-mode in observational studies of atherosclerotic progression. *Circ J*. 1993;87:II56–II65.
247. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol*. 1997;146:483–94.
248. Bots ML, Hoes AW, Koudstaal PJ, et al. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–7.
249. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *Cardiovascular Health Study Collaborative Research Group*. *N Engl J Med*. 1999;340:14–22.
250. Folsom AR, Chambless LE, Duncan BB, et al. Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care*. 2003;26:2777–84.
251. Kuller LH, Velentgas P, Barzilay J, et al. Diabetes mellitus: subclinical cardiovascular disease and risk of incident cardiovascular disease and all-cause mortality. *Arterioscler Thromb Vasc Biol*. 2000;20:823–9.
252. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med*. 2008;168:1333–9.
253. Newman AB, Naydeck BL, Ives DG, et al. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. *Am J Cardiol*. 2008;101:186–92.
254. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med*. 1998;128:262–9.
255. Bovet P, Perret F, Cornuz J, et al. Improved smoking cessation in smokers given ultrasound photographs of their own atherosclerotic plaques. *Prev Med*. 2002;34:215–20.
256. Kuvin JT, Mammen A, Mooney P, et al. Assessment of peripheral vascular endothelial function in the ambulatory setting. *Vasc Med*. 2007;12:13–6.
257. Takase B, Uehata A, Akima T, et al. Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. *Am J Cardiol*. 1998;82:1535–8.
258. Bots ML, Westerink J, Rabelink TJ, de Koning EJ. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurement on the FMD response. *Eur Heart J*. 2005;26:363–8.
259. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J*. 2003;146:168–74.
260. Witte DR, Westerink J, de Koning EJ, et al. Is the association between flow-mediated dilation and cardiovascular risk limited to low-risk populations? *J Am Coll Cardiol*. 2005;45:1987–93.
261. Hamburg NM, Keyes MJ, Larson MG, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. *Circulation*. 2008;117:2467–74.
262. Yeboah J, Crouse JR, Hsu FC, et al. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. *Circulation*. 2007;115:2390–7.
263. Suzuki T, Hirata K, Elkind MS, et al. Metabolic syndrome, endothelial dysfunction, and risk of cardiovascular events: the Northern Manhattan Study (NOMAS). *Am Heart J*. 2008;156:405–10.
264. Rossi R, Nuzzo A, Origliani G, Modena MG. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. *J Am Coll Cardiol*. 2008;51:997–1002.
265. Modena MG, Bonetti L, Coppi F, et al. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol*. 2002;40:505–10.
266. Kullo IJ, Malik AR. Arterial ultrasonography and tonometry as adjuncts to cardiovascular risk stratification. *J Am Coll Cardiol*. 2007;49:1413–26.
267. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–605.
268. Meaume S, Benetos A, Henry OF, et al. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol*. 2001;21:2046–50.
269. Stork S, van den Beld AW, von Schacky C, et al. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. *Circulation*. 2004;110:344–8.
270. Sutton-Tyrrell K, Najjar SS, Boudeau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005;111:3384–90.
271. Shokawa T, Imazu M, Yamamoto H, et al. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. *Circ J*. 2005;69:259–64.

272. Dolan E, Thijs L, Li Y, et al. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. *Hypertension*. 2006;47:365–70.
273. Willum-Hansen T, Staessen JA, Torp-Pedersen C, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113:664–70.
274. Hansen TW, Staessen JA, Torp-Pedersen C, et al. Ambulatory arterial stiffness index predicts stroke in a general population. *J Hypertens*. 2006;24:2247–53.
275. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–63.
276. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension*. 2007;50:197–203.
277. Leone N, Ducimetiere P, Garipey J, et al. Distension of the carotid artery and risk of coronary events: the three-city study. *Arterioscler Thromb Vasc Biol*. 2008;28:1392–7.
278. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARE Dicomano Study. *J Am Coll Cardiol*. 2008;51:2432–9.
279. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208.
280. Osthega Y, Paulose-Ram R, Dillon CF, et al. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999–2004. *J Am Geriatr Soc*. 2007;55:583–9.
281. Resnick HE, Foster GL. Prevalence of elevated ankle-brachial index in the United States 1999 to 2002. *Am J Med*. 2005;118:676–9.
282. Allison MA, Hiatt WR, Hirsch AT, et al. A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life. *J Am Coll Cardiol*. 2008;51:1292–8.
283. Criqui MH, Langer RD, Fronck A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381–6.
284. Hooi JD, Kester AD, Stoffers HE, et al. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *J Clin Epidemiol*. 2004;57:294–300.
285. Kornitzer M, Dramaix M, Sobolski J, et al. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology*. 1995;46:211–9.
286. Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation*. 1995;92:720–6.
287. Leng GC, Fowkes FG, Lee AJ, et al. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ*. 1996;313:1440–4.
288. McDermott MM, Liu K, Criqui MH, et al. Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. 2005;162:33–41.
289. Murabito JM, Evans JC, Larson MG, et al. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. *Arch Intern Med*. 2003;163:1939–42.
290. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol*. 1999;19:538–45.
291. O'Hare AM, Katz R, Shlipak MG, et al. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. *Circulation*. 2006;113:388–93.
292. van der Meer I, Bots ML, Hofman A, et al. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation*. 2004;109:1089–94.
293. Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987–2001. *BMC Cardiovasc Disord*. 2007;7:3.
294. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation*. 2004;109:733–9.
295. Abbott RD, Petrovitch H, Rodriguez BL, et al. Ankle/brachial blood pressure in men >70 years of age and the risk of coronary heart disease. *Am J Cardiol*. 2000;86:280–4.
296. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation*. 2003;108:1554–9.
297. Adabag AS, Grandits GA, Prineas RJ, et al. Relation of heart rate parameters during exercise test to sudden death and all-cause mortality in asymptomatic men. *Am J Cardiol*. 2008;101:1437–43.
298. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA*. 1999;282:1547–53.
299. Lauer M, Froelicher ES, Williams M, Kligfield P. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation*. 2005;112:771–6.
300. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation*. 1989;80:87–98.
301. Goraya TY, Jacobsen SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing in elderly persons. *Ann Intern Med*. 2000;132:862–70.
302. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol*. 2002;40:1530–40.
303. Mark DB, Lauer MS. Exercise capacity: the prognostic variable that doesn't get enough respect. *Circulation*. 2003;108:1534–6.
304. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801.
305. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301:2024–35.
306. Lauer MS, Pothier CE, Magid DJ, et al. An externally validated model for predicting long-term survival after exercise treadmill testing in patients with suspected coronary artery disease and a normal electrocardiogram. *Ann Intern Med*. 2007;147:821–8.
307. Aktas MK, Ozduran V, Pothier CE, et al. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. *JAMA*. 2004;292:1462–8.
308. Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med*. 1999;341:1351–7.
309. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. *N Engl J Med*. 2003;348:781–90.
310. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005;352:1951–8.
311. Jouven XP, Empana JP, Ducimetiere P. Ventricular ectopy after exercise as a predictor of death. *N Engl J Med*. 2003;348:2357–9.
312. Lauer MS, Francis GS, Okin PM, et al. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA*. 1999;281:524–9.
313. Nishime EO, Cole CR, Blackstone EH, et al. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*. 2000;284:1392–8.
314. Khan MN, Pothier CE, Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol). *Am J Cardiol*. 2005;96:1328–33.
315. Lauer MS, Okin PM, Larson MG, et al. Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation*. 1996;93:1520–6.
316. Imai K, Sato H, Hori M, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol*. 1994;24:1529–35.
317. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med*. 2000;132:552–5.
318. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA*. 2003;290:1600–7.

319. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol*. 2001;38:1980–7.
320. Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991;325:849–53.
321. Kwok JM, Miller TD, Christian TF, et al. Prognostic value of a treadmill exercise score in symptomatic patients with nonspecific ST-T abnormalities on resting ECG. *JAMA*. 1999;282:1047–53.
322. Douglas PS, Khandheria B, Stainback RF, et al. ACCF/AHA/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society for Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2008;51:1127–47.
323. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. 2007;50:e159–e241.
324. Marwick TH, Case C, Short L, Thomas JD. Prediction of mortality in patients without angina: use of an exercise score and exercise echocardiography. *Eur Heart J*. 2003;24:1223–30.
325. Faglia E, Manuela M, Antonella Q, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J*. 2005;149:e1–e6.
326. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol*. 2003;41:159–68.
327. Einstein AJ, Moser KW, Thompson RC, et al. Radiation dose to patients from cardiac diagnostic imaging. *Circulation*. 2007;116:1290–305.
328. Berman DS, Rozanski A, Rana JS, et al. Screening for coronary artery disease in diabetic patients: a commentary. *J Nucl Cardiol*. 2009;16:851–4.
329. Zellweger MJ, Hachamovitch R, Kang X, et al. Threshold, incidence, and predictors of prognostically high-risk silent ischemia in asymptomatic patients without prior diagnosis of coronary artery disease. *J Nucl Cardiol*. 2009;16:193–200.
330. Khandaker MH, Miller TD, Chareonthaitawee P, et al. Stress single photon emission computed tomography for detection of coronary artery disease and risk stratification of asymptomatic patients at moderate risk. *J Nucl Cardiol*. 2009;16:516–23.
331. Bax JJ, Bonow RO, Tschöpe D, et al. The potential of myocardial perfusion scintigraphy for risk stratification of asymptomatic patients with type 2 diabetes. *J Am Coll Cardiol*. 2006;48:754–60.
332. Lacourcière Y, Côté C, Lefebvre J, Dumont M. Noninvasive detection of silent coronary artery disease in patients with essential hypertension, alone or associated with type 2 diabetes mellitus, using dipyridamol stress ^{99m}Tc-tetrosestamibi myocardial perfusion imaging. *Can J Cardiol*. 2006;22 Suppl A:16A–21A.
333. Nakajima K, Yamasaki Y, Kusuoka H, et al. Cardiovascular events in Japanese asymptomatic patients with type 2 diabetes: a 1-year interim report of a J-ACCESS 2 investigation using myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging*. 2009;36:2049–57.
334. Scholte AJ, Schuijff JD, Kharagitsingh AV, et al. Prevalence and predictors of an abnormal stress myocardial perfusion study in asymptomatic patients with type 2 diabetes mellitus. *Eur J Nucl Med Mol Imaging*. 2009;36:567–75.
335. Valensi P, Paries J, Brulport-Cerisier V, et al. Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. *Diabetes Care*. 2005;28:2722–7.
336. Wackers FJ, Chyun DA, Young LH, et al. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care*. 2007;30:2892–8.
337. Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;301:1547–55.
338. Ahmadi N, Usman N, Shim J, et al. Vascular dysfunction measured by fingertip thermal monitoring is associated with the extent of myocardial perfusion defect. *J Nucl Cardiol*. 2009;16:431–9.
339. Berman DS, Wong ND, Gransar H, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol*. 2004;44:923–30.
340. Blumenthal RS, Becker DM, Yanek LR, et al. Comparison of coronary calcium and stress myocardial perfusion imaging in apparently healthy siblings of individuals with premature coronary artery disease. *Am J Cardiol*. 2006;97:328–33.
341. Rozanski A, Gransar H, Wong ND, et al. Clinical outcomes after both coronary calcium scanning and exercise myocardial perfusion scintigraphy. *J Am Coll Cardiol*. 2007;49:1352–61.
342. Rozanski A, Gransar H, Wong ND, et al. Use of coronary calcium scanning for predicting inducible myocardial ischemia: influence of patients' clinical presentation. *J Nucl Cardiol*. 2007;14:669–79.
343. Schenker MP, Dorbala S, Hong EC, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. *Circulation*. 2008;117:1693–700.
344. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J*. 2006;27:713–21.
345. Miller TD, Rajagopalan N, Hodge DO, et al. Yield of stress single-photon emission computed tomography in asymptomatic patients with diabetes. *Am Heart J*. 2004;147:890–6.
346. Rajagopalan N, Miller TD, Hodge DO, et al. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol*. 2005;45:43–9.
347. Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation*. 2005;112:1311–1316.
348. Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291:210–5.
349. Lakoski SG, Greenland P, Wong ND, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as “low risk” based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). *Arch Intern Med*. 2007;167:2437–42.
350. Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol*. 2005;46:807–14.
351. Budoff MJ, Nasir K, McClelland RL, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2009;53:345–52.
352. Nasir K, Budoff MJ, Post WS, et al. Electron beam CT versus helical CT scans for assessing coronary calcification: current utility and future directions. *Am Heart J*. 2003;146:969–77.
353. Greenland P, Kizilbash MA. Coronary computed tomography in coronary risk assessment. *J Cardiopulm Rehabil*. 2005;25:3–10.
354. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. 2006;114:1761–91.
355. Schauer DA, Linton OW. NCRP Report No. 160. Ionizing Radiation Exposure of the Population of the United States, medical exposure—are we doing less with more, and is there a role for health physicists? *Health Phys*. 2009;97:1–5.
356. Parker MS, Hui FK, Camacho MA, et al. Female breast radiation exposure during CT pulmonary angiography. *AJR Am J Roentgenol*. 2005;185:1228–33.
357. Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. *Circulation*. 2003;107:917–22.

358. Kim KP, Einstein AJ, Berrington de GA. Coronary artery calcification screening: estimated radiation dose and cancer risk. *Arch Intern Med*. 2009;169:1188–94.
359. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *J Am Coll Cardiol*. 2007;49:378–402.
360. Kalia NK, Miller LG, Nasir K, et al. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. *Atherosclerosis*. 2006;185:394–9.
361. Orakzai RH, Nasir K, Orakzai SH, et al. Effect of patient visualization of coronary calcium by electron beam computed tomography on changes in beneficial lifestyle behaviors. *Am J Cardiol*. 2008;101:999–1002.
362. O'Malley PG, Feuerstein IM, Taylor AJ. Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: a randomized controlled trial. *JAMA*. 2003;289:2215–23.
363. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. *Arterioscler Thromb Vasc Biol*. 2004;24:1272–7.
364. Taylor AJ, Bindeman J, Feuerstein I, et al. Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. *J Am Coll Cardiol*. 2008;51:1337–41.
365. Nasir K, McClelland R, Blumenthal RS, et al. Coronary artery calcium in relation to initiation and continuation of cardiovascular preventative medications: the Multiethnic Study of Atherosclerosis (MESA). *Circ Qual Care Outcomes*. 2010;3:228–35.
366. Michos ED, Nasir K, Braunstein JB, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis*. 2006;184:201–6.
367. Raggi P, Gongora MC, Gopal A, et al. Coronary artery calcium to predict all-cause mortality in elderly men and women. *J Am Coll Cardiol*. 2008;52:17–23.
368. Raggi P, Shaw LJ, Berman DS, Callister TQ. Gender-based differences in the prognostic value of coronary calcification. *J Womens Health (Larchmt)*. 2004;13:273–83.
369. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation*. 2005;112:572–7.
370. Arad Y, Spadaro LA, Roth M, et al. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol*. 2005;46:166–72.
371. Park R, Detrano R, Xiang M, et al. Combined use of computed tomography coronary calcium scores and C-reactive protein levels in predicting cardiovascular events in nondiabetic individuals. *Circulation*. 2002;106:2073–7.
372. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *J Am Coll Cardiol*. 2008;52:357–65.
373. Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention and the Council on Cardiovascular Radiology and Intervention and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. *Circulation*. 2008;118:586–606.
374. Hausleiter J, Meyer T, Hermann F, et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA*. 2009;301:500–7.
375. Choudhury RP, Fuster V, Badimon JJ, et al. MRI and characterization of atherosclerotic plaque: emerging applications and molecular imaging. *Arterioscler Thromb Vasc Biol*. 2002;22:1065–74.
376. Fayad ZA, Fuster V. Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circ Res*. 2001;89:305–16.
377. Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. *Arterioscler Thromb Vasc Biol*. 2005;25:234–9.
378. Trivedi RA, King-Im J, Graves MJ, et al. Multi-sequence in vivo MRI can quantify fibrous cap and lipid core components in human carotid atherosclerotic plaques. *Eur J Vasc Endovasc Surg*. 2004;28:207–13.
379. Kampschulte A, Ferguson MS, Kerwin WS, et al. Differentiation of intraplaque versus juxtaluminal hemorrhage/thrombus in advanced human carotid atherosclerotic lesions by in vivo magnetic resonance imaging. *Circulation*. 2004;110:3239–44.
380. Moody AR, Murphy RE, Morgan PS, et al. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. *Circulation*. 2003;107:3047–52.
381. Lindsay AC, Choudhury RP. Form to function: current and future roles for atherosclerosis imaging in drug development. *Nat Rev Drug Discov*. 2008;7:517–29.
382. Yuan C, Oikawa M, Miller Z, Hatsukami T. MRI of carotid atherosclerosis. *J Nucl Cardiol*. 2008;15:266–75.
383. Cai J, Hatsukami TS, Ferguson MS, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation*. 2005;112:3437–44.
384. Wasserman BA, Smith WI, Trout HH 3rd, et al. Carotid artery atherosclerosis: in vivo morphologic characterization with gadolinium-enhanced double-oblique MR imaging initial results. *Radiology*. 2002;223:566–73.
385. Jaffer FA, Tung CH, Gerszten RE, Weissleder R. In vivo imaging of thrombin activity in experimental thrombi with thrombin-sensitive near-infrared molecular probe. *Arterioscler Thromb Vasc Biol*. 2002;22:1929–35.
386. Li AE, Kamel I, Rando F, et al. Using MRI to assess aortic wall thickness in the Multiethnic Study of Atherosclerosis: distribution by race, sex, and age. *Am J Roentgenol*. 2004;182:593–7.
387. Wasserman BA, Sharrett AR, Lai S, et al. Risk factor associations with the presence of a lipid core in carotid plaque of asymptomatic individuals using high-resolution MRI: the Multi-Ethnic Study of Atherosclerosis (MESA). *Stroke*. 2008;39:329–35.
388. Yuan C, Zhang SX, Polissar NL, et al. Identification of fibrous cap rupture with magnetic resonance imaging is highly associated with recent transient ischemic attack or stroke. *Circulation*. 2002;105:181–5.
389. Ouhlous M, Flach HZ, de Weert TT, et al. Carotid plaque composition and cerebral infarction: MR imaging study. *AJNR Am J Neuroradiol*. 2005;26:1044–9.
390. Lin K, Zhang ZQ, Detrano R, et al. Carotid vulnerable lesions are related to accelerated recurrence for cerebral infarction magnetic resonance imaging study. *Acad Radiol*. 2006;13:1180–6.
391. Takaya N, Yuan C, Chu B, et al. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation*. 2005;111:2768–75.
392. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. *Stroke*. 2006;37:818–23.
393. Tang TY, Howarth SP, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study: evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *J Am Coll Cardiol*. 2009;53:2039–50.
394. Rudd JH, Myers KS, Bansilal S, et al. Atherosclerosis inflammation imaging with 18F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *J Nucl Med*. 2008;49:871–8.
395. Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. *Nature*. 2008;451:953–7.
396. Silvera SS, Aidi HE, Rudd JH, et al. Multimodality imaging of atherosclerotic plaque activity and composition using FDG-PET/CT and MRI in carotid and femoral arteries. *Atherosclerosis*. 2009;207:139–43.
397. Becker A, Leber AW, Becker C, et al. Predictive value of coronary calcifications for future cardiac events in asymptomatic patients with diabetes mellitus: a prospective study in 716 patients over 8 years. *BMC Cardiovasc Disord*. 2008;8:27.
398. Elkeles RS, Godsland IF, Feher MD, et al. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J*. 2008;29:2244–51.
399. Scholte AJ, Schuijff JD, Kharagitsingh AV, et al. Prevalence of coronary artery disease and plaque morphology assessed by multi-slice computed tomography coronary angiography and calcium scoring in asymptomatic patients with type 2 diabetes. *Heart*. 2008;94:290–5.
400. Becker A, Leber A, Becker C, Knez A. Predictive value of coronary calcifications for future cardiac events in asymptomatic individuals. *Am Heart J*. 2008;155:154–60.

401. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31 Suppl 1:S12–S54.
402. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. *JAMA*. 1979;241:2035–8.
403. Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–34.
404. Grundy SM, Howard B, Smith S Jr, et al. Prevention Conference VI: diabetes and cardiovascular disease: Executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. *Circulation*. 2002;105:2231–9.
405. Scholte AJ, Bax JJ, Wackers FJ. Screening of asymptomatic patients with type 2 diabetes mellitus for silent coronary artery disease: combined use of stress myocardial perfusion imaging and coronary calcium scoring. *J Nucl Cardiol*. 2006;13:11–8.
406. Pundziute G, Schuijf JD, Jukema JW, et al. Type 2 diabetes is associated with more advanced coronary atherosclerosis on multislice computed tomography and virtual histology intravascular ultrasound. *J Nucl Cardiol*. 2009;16:376–83.
407. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*. 2004;43:1663–9.
408. Hoff JA, Quinn L, Sevrukov A, et al. The prevalence of coronary artery calcium among diabetic individuals without known coronary artery disease. *J Am Coll Cardiol*. 2003;41:1008–12.
409. Schurgin S, Rich S, Mazzone T. Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care*. 2001;24:335–8.
410. Qu W, Le TT, Azen SP, et al. Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. *Diabetes Care*. 2003;26:905–10.
411. Lee DP, Fearon WF, Froelicher VF. Clinical utility of the exercise ECG in patients with diabetes and chest pain. *Chest*. 2001;119:1576–81.
412. Janand-Delenne B, Savin B, Habib G, et al. Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care*. 1999;22:1396–400.
413. Koistinen MJ, Huikuri HV, Pirttiaho H, et al. Evaluation of exercise electrocardiography and thallium tomographic imaging in detecting asymptomatic coronary artery disease in diabetic patients. *Br Heart J*. 1990;63:7–11.
414. Bacci S, Villella M, Villella A, et al. Screening for silent myocardial ischaemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol*. 2002;147:649–54.
415. Rubler S, Gerber D, Reitano J, et al. Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. *Am J Cardiol*. 1987;59:1310–3.
416. Fornengo P, Bosio A, Epifani G, et al. Prevalence of silent myocardial ischaemia in new-onset middle-aged type 2 diabetic patients without other cardiovascular risk factors. *Diabet Med*. 2006;23:775–9.
417. Sozzi FB, Elhendy A, Rizzello V, et al. Prognostic significance of myocardial ischemia during dobutamine stress echocardiography in asymptomatic patients with diabetes mellitus and no prior history of coronary events. *Am J Cardiol*. 2007;99:1193–5.
418. Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*. 2004;27:1954–61.
419. Zellweger MJ, Hachamovitch R, Kang X, et al. Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. *Eur Heart J*. 2004;25:543–50.
420. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol*. 2004;11:171–85.
421. Giri S, Shaw LJ, Murthy DR, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation*. 2002;105:32–40.
422. Ziemer DC, Kolm P, Foster JK, et al. Random plasma glucose in serendipitous screening for glucose intolerance: screening for impaired glucose tolerance study 2. *J Gen Intern Med*. 2008;23:528–35.
423. Davidson MB. Correction to the 2010 report on the diagnosis and classification of diabetes. *Diabetes Care*. 2010;33:e57.
424. Heisler M, Piette JD, Spencer M, et al. The relationship between knowledge of recent HbA1c values and diabetes care understanding and self-management. *Diabetes Care*. 2005;28:816–22.
425. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329:977–86.
426. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837–53.
427. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med*. 2007;357:28–38.
428. Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368:1096–105.
429. Stettler C, Allemann S, Juni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J*. 2006;152:27–38.
430. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129–39.
431. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–59.
432. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–72.
433. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *J Am Coll Cardiol*. 2004;43:900–21.
434. Pasternak RC, Abrams J, Greenland P, et al. 34th Bethesda Conference: task force #1—identification of coronary heart disease risk: is there a detection gap? *J Am Coll Cardiol*. 2003;41:1863–74.
435. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76–9.
436. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 2006;332:73–8.
437. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study, part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47:S4–S20.
438. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356–9.
439. Ramos RG, Olden K. The prevalence of metabolic syndrome among US women of childbearing age. *Am J Public Health*. 2008;98:1122–7.
440. Pilote L, Dasgupta K, Guru V, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ*. 2007;176:S1–44.
441. Nasir K, Michos ED, Blumenthal RS, Raggi P. Detection of high-risk young adults and women by coronary calcium and National Cholesterol Education Program Panel III guidelines. *J Am Coll Cardiol*. 2005;46:1931–6.
442. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215.
443. Mensah GA, Mokdad AH, Ford ES, et al. State of disparities in cardiovascular health in the United States. *Circulation*. 2005;111:1233–41.
444. Kwok JM, Miller TD, Hodge DO, Gibbons RJ. Prognostic value of the Duke treadmill score in the elderly. *J Am Coll Cardiol*. 2002;39:1475–81.
445. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–35.
446. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–30.

KEY WORDS: AHA Scientific Statements ■ cardiovascular risk assessment ■ asymptomatic adults ■ cardiovascular screening of asymptomatic adults ■ detection of coronary artery disease ■ risk factor assessment ■ subclinical coronary artery disease

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

Writing Committee Members, Philip Greenland, Joseph S. Alpert, George A. Beller, Emelia J. Benjamin, Matthew J. Budoff, Zahi A. Fayad, Elyse Foster, Mark. A. Hlatky, John McB. Hodgson, Frederick G. Kushner, Michael S. Lauer, Leslee J. Shaw, Sidney C. Smith, Jr, Allen J. Taylor, William S. Weintraub and Nanette K. Wenger

Circulation. 2010;122:e584-e636; originally published online November 12, 2010;
doi: 10.1161/CIR.0b013e3182051b4c

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circ.ahajournals.org/content/122/25/e584>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>