EVIDENCE REPORT

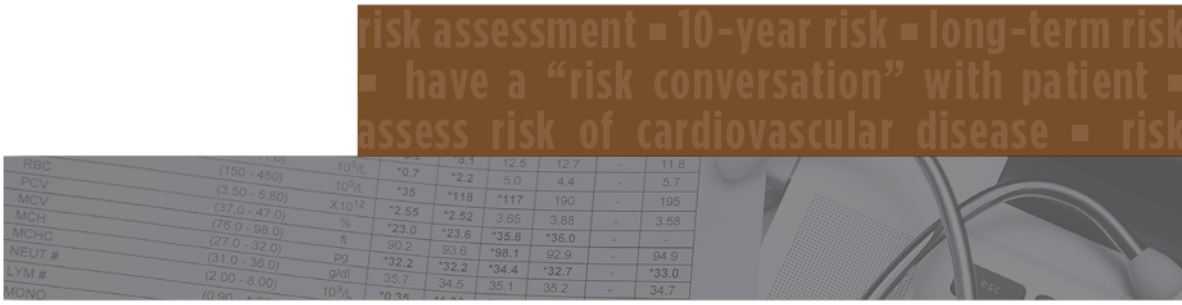
Assessing Cardiovascular Risk

Systematic Evidence Review From the Risk Assessment Work Group, 2013

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

EVIDENCE REPORT



Assessing Cardiovascular Risk

Systematic Evidence Review From the Risk Assessment Work Group, 2013

U.S. Department of Health and Human Services
National Institutes of Health

National Heart, Lung, and Blood Institute

Contents

List of Tables

List of Figures

Foreword

In 1977, the National Heart, Lung, and Blood Institute (NHLBI) issued the first of several clinical practice guidelines (CPGs) as part of its core mission, which is to provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. Guidelines from the National High Blood Pressure Education Program, the National Cholesterol Education Program, the Obesity Education Initiative, as well as from other similar programs and initiatives, have addressed a variety of topics, including, but not limited to, cholesterol, blood pressure, obesity, asthma, and von Willebrand disease. Over the years, health care systems and providers have used these guidelines for the prevention, detection, evaluation, and treatment of cardiovascular disease risk factors, and lung and blood diseases.

In 2008, NHLBI convened expert panels to update the existing clinical guidelines on cholesterol, blood pressure, and overweight/obesity, by conducting rigorous systematic evidence reviews. At the same time, three crosscutting work groups—on lifestyle, risk assessment, and implementation—were convened to develop additional systematic evidence reviews to support the work of the expert panels. The impetus for these guidelines was the recognition that despite the enormous progress over the last 60 years, cardiovascular disease remains the leading cause of death in the United States.

While the updates were underway, the Institute of Medicine (IOM) issued two reports that established new "best practice" standards for generating systematic evidence reviews and developing clinical guidelines. The reports underscore that these are two distinct, yet related, activities that require careful intersection and coordination. Accordingly, NHLBI's role in the guidelines updates transitioned to completing a systematic evidence review for each topic and collaborating with other organizations to prepare and issue the related clinical guidelines.

Since implementing the new collaborative partnership model for developing guidelines based upon NHLBI-sponsored systematic evidence reviews, four of the five Expert Panels/Work Groups have worked successfully with the American Heart Association (AHA), the American College of Cardiology (ACC), The Obesity Society (TOS), and other professional societies to develop new cardiovascular disease prevention CPGs for lifestyle, risk assessment, cholesterol, and obesity. The new guidelines—published in November 2013 by the AHA, ACC, and TOS, and endorsed by other professional societies—provide a valuable updated roadmap to help clinicians and patients manage CVD prevention and treatment challenges.

We appreciate the outstanding work and dedication of the expert panels and work groups that developed the systematic evidence reviews that formed the basis for the guidelines. These systematic evidence reviews are the products of one of the most rigorous evidence-based systematic reviews conducted to date. We look forward to continuing to develop accurate and timely evidence reviews, fueled by our investment in primary research on the prevention and treatment of cardiovascular disease as well as implementation science, to improve public health.

The following systematic evidence report is available as a public resource.

Gary H. Gibbons, M.D.
Director
National Heart, Lung, and Blood Institute

Risk Assessment Work Group

Co-Chairs

David C. Goff, Jr., M.D., Ph.D.
Colorado School of Public Health
Denver, CO

Donald M. Lloyd-Jones, M.D., Sc.M.
Northwestern University
Evanston, IL

Members

Ralph B. D'Agostino, Sr., Ph.D.
Boston University
Boston, MA

Raymond Gibbons, M.D.
Mayo Clinic
Rochester, MN

Philip Greenland, M.D.
Northwestern University
Evanston, IL

Frank Hu, M.D., Ph.D., M.P.H.
Harvard School of Public Health
Cambridge, MA

Daniel T. Lackland, Dr.P.H.
Medical University of South Carolina
Columbia, SC

Jennifer Robinson, M.D., M.P.H.
University of Iowa
Iowa City, IA

Sidney C. Smith, Jr., M.D.
University of North Carolina at Chapel Hill
Chapel Hill, NC

J. Sanford Schwartz, M.D.
University of Pennsylvania
Philadelphia, PA

Neil J. Stone, M.D.
Northwestern University
Evanston, IL

Peter W.F. Wilson, M.D.
Emory University School of Medicine
Atlanta, GA

National Heart, Lung, and Blood Institute (NHLBI) Work Group Members
Sean Coady, M.S.
Daniel Levy, M.D.
Christopher O'Donnel, M.D.
Paul Sorlie, Ph.D.

NHLBI Staff
Glen Bennett, M.P.H.
Susan Shero, M.S., R.N.
Denise Simons-Morton, M.D., Ph.D.

Methodology Team

RTI International
Harmon Jordan, Sc.D.
Michael G. Trisolini, Ph.D., M.B.A.

Science Applications International Corporation
Lev Nevo, M.D.
Janusz Wnek, Ph.D.

Section 1. Background and Description of the NHLBI Cardiovascular Risk Reduction Project

Background

Since the 1970s, the National Heart, Lung, and Blood Institute (NHLBI) has sponsored the development of clinical practice guidelines that have helped to accelerate the application of health research to strategies and programs for the prevention, detection, and treatment of cardiovascular, lung, and blood diseases. In 2005, NHLBI recognized the need to update the most recent cardiovascular guidelines, namely those on high blood cholesterol, high blood pressure, and overweight/obesity in adults. NHLBI convened stakeholder groups to provide input on the development process for the next generation of clinical practice guidelines.

The stakeholders emphasized the following needs:

- Maintain cardiovascular clinical practice guidelines that focus on specific risk factors
- Take a standardized and coordinated approach to updating risk factors
- Take a more evidence-based approach to development and implementation
- Give more attention to dissemination and implementation issues
- Work closely with stakeholders in health care and community systems to translate and disseminate the evidence base

In 2008, NHLBI established three expert panels that used a rigorous systematic evidence review process to update the guidelines for high blood cholesterol,[1] high blood pressure,[2] and overweight/obesity.[3] In addition, three work groups were formed around risk assessment, lifestyle, and implementation to develop recommendations and provide crosscutting input to the expert panels. A Guidelines Executive Committee comprising co-chairs from the expert panels and work groups coordinated the work of the expert panels and work groups. Efforts resulted in six topic-specific yet complementary reports on blood cholesterol, blood pressure, overweight/obesity, lifestyle, risk assessment, and implementation. While the expert panels and work groups were undertaking the rigorous, systematic, evidence-based approach to updating the guidelines, in 2011 the Institute of Medicine (IOM) issued two reports that established new "best practices" for generating systematic evidence reviews[4] and developing clinical practice guidelines[5]. The reports from IOM stress that these are two distinct but related activities that require careful intersection and coordination.

Because of these developments and the changing approaches to developing guidelines, in June 2012, the NHLBI Advisory Council recommended that the Institute transition to a new model in accordance with the best practice standards established by IOM. In mid-2013, NHLBI adopted a new collaborative partnership model whereby it will focus on generating high-quality systematic reviews that can be used by professional societies and other organizations to develop clinical practice guidelines.[6] To date, the American Heart Association and the American College of Cardiology have used four of the evidence reviews on adult cardiovascular disease (CVD)

to spearhead a collaborative effort to develop clinical practice guidelines on CVD risk reduction.[7-10] This evidence report is a public resource that summarizes the findings of the Risk Assessment Work Group (RAWG).

Overview of the Evidence-Based Methodology

To continually improve the quality and impact of the evidence reviews sponsored by NHLBI, the evidence review process was updated to ensure rigor and minimize bias. This new effort involved the use of a rigorous evidence-based methodology and the development of evidence statements that are based on a systematic review of the biomedical literature for specific periods of time.

The process followed most of the standards from the IOM report, *Clinical Practice Guidelines We Can Trust*,[5] which states that trustworthy guidelines should:

- Be based on a systematic review of the existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patient preferences, as appropriate
- Be based on an explicit and transparent process that minimizes distortion, biases, and conflicts of interest
- Provide a clear explanation of logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of the recommendations
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations

All of the expert panels and work groups followed the same methods, aside from variations needed to reflect the evidence in the field. The methodology involved numerous components and followed a prespecified development process. Expert panels and work groups consisting of cardiologists, primary care providers, and other clinical and nonclinical experts were convened to develop the evidence review. Directed by NHLBI, with support from a methodology contractor and a systematic review and general support contractor, the expert panels and work groups:

- Constructed CQs most relevant to clinical practice. CQs followed the "PICOTSS" (population, intervention/exposure, comparison group, outcome, time, setting, and study design) format.
- Identified (a priori) inclusion/exclusion (I/E) criteria for each CQ.

Directed by NHLBI, with input from the expert panels and work groups, the contractor staff:

- Developed a search strategy, based on I/E criteria, for each CQ.
- Executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ.
- Screened—by two independent reviewers—thousands of abstracts and full-text articles returned from the search to identify relevant original articles, systematic reviews, and/or meta-analyses. Rigorous validation procedures were applied to ensure that the selected articles met the preestablished detailed I/E criteria before being included in the final review.
- Determined—by two independent raters—the quality (good, fair, or poor) of each included study. With input from NHLBI, the methodology staff adapted study-rating instruments and trained study raters on the use of these instruments.
- Abstracted relevant information from the included studies into an electronic database.

- Supported abstractions by constructing templates with lists of data elements that were pertinent to I/E criteria.
- Constructed detailed evidence tables as a way of organizing data from the abstraction database.
- Analyzed the evidence tables and constructed summary tables, which display the evidence in a manageable format to answer specific parts of each CQ.

The expert panels and work groups:

- Used summary tables to develop evidence statements for each CQ. The quality of evidence for each evidence statement was graded as high, moderate, or low. The grade was based on scientific methodology, scientific strength, and consistency of results.
- Drafted a report that was reviewed by external Federal agencies and a group of experts selected by NHLBI.

i. System for Grading the Body of Evidence

NHLBI adapted a system developed by the U.S. Preventive Services Task Force (USPSTF) to grade the body of the evidence and the strength of the recommendations. Evidence statements were graded as high, moderate, or low quality.

Evidence Quality Grading System

Type of Evidence	Strength of Evidence Grade
■ Well-designed, well-executed RCTs that adequately represent populations to which the ■ Meta-analyses of such studies. ■ High confidence that the evidence reflects the true effect. Further research is unlikely to	**High**
■ RCTs with minor limitations that affect confidence in, or applicability of, the results; including minor flaws in design or execution. ■ Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies. ■ Meta-analyses of such studies. ■ Moderate confidence that the evidence reflects the true effect. Further research may change the moderate confidence in the estimate of effect and may change the estimate.	**Moderate**
■ RCTs with major limitations. ■ Nonrandomized intervention studies and observational studies with major limitations ■ Uncontrolled clinical observations without an appropriate comparison group (e.g., case ■ Physiological studies in humans. ■ Meta-analyses of such studies. ■ Low confidence that the evidence reflects the true effect. Further research is likely to	**Low**

The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. Appendix A describes how four domains of the body of evidence—risk of bias, consistency, directness, and precision—were used to grade the strength of evidence.

ii. Peer-Review Process

A formal peer-review process was undertaken that included inviting several scientific experts and representatives from multiple Federal agencies to review and comment on the draft documents. NHLBI selected scientific experts with diverse perspectives to review the reports. Potential reviewers were asked to sign a confidentiality agreement, but NHLBI did not collect COI information from the reviewers. DARD staff collected reviewers' comments and forwarded them to the respective panels and work groups for consideration. Each comment received was addressed—either by a narrative response and/or a change to the draft document. A compilation of the comments received and the panels' and work groups' responses was submitted to the NHLBI Advisory Council working group; individual reviewers did not receive responses.

iii. Critical Question-Based Approach

The two questions addressed by the Risk Assessment Work Group are as follows:

Risk Assessment Work Group—Critical Questions

No.	Question
CQ1.	**What is the evidence regarding reclassification or contribution to risk assessment when high-sensitivity C-reactive protein, apolipoprotein B, glomerular filtration rate, microalbuminuria, family history, cardiorespiratory fitness, ankle-brachial index, coronary artery calcium score, or carotid intima-media thickness are considered in addition to the variables that are in the traditional risk scores?**
CQ2.	**Are models constructed to assess the long-term (≥15 years or lifetime) risk for a first CVD event in adults effective in assessing variation in long-term risk among adults at low and/or intermediate short-term risk, whether analyzed separately or combined? [As described in appendix B, the draft version of CQ2, including I/E criteria, had an initial phrasing that was revised by the RAWG after additional discussion and deliberation and application of the PICOTSS framework.]**

The body of this report is organized by CQ. For each CQ, the Risk Assessment Work Group (RAWG):

- Provides the rationale for its selection and describes the methods used to address the CQ
- Summarizes the body of evidence and presents evidence statements that include a rating for quality; a narrative summary supports each evidence statement

A detailed description of methods is provided in the appendixes. The appendixes present all tools used to develop the present systematic reviews as well as documentation for search strategies and results from the search of the published literature.

Charge to the Risk Assessment Work Group

The RAWG was asked to examine the scientific evidence on risk assessment for initial atherosclerotic cardiovascular disease (ASCVD) events and to develop an approach for risk assessment that could be used in practice and used or adapted by the expert panels on cholesterol, hypertension, and obesity. Specifically, the RAWG was charged with two tasks:

1. To develop or recommend an approach to quantitative risk assessment that could be used to guide care
2. To pose and address a small number of questions judged to be critical to refining and adopting risk assessment in clinical practice using systematic review methodology

In addressing this charge, members of the RAWG recognized the need for a risk assessment tool that was based on the types of data that primary care providers could easily collect and that could be implemented in routine clinical practice. Given the modification and adoption of the Framingham 10-year risk score (Framingham Risk Score, or FRS) for coronary heart disease (CHD) risk assessment by the Third Report of the National Cholesterol Education Program Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (Third Adult Treatment Panel, or ATP III),[1] and the uptake of this algorithm by practice sites across the United States, the RAWG began its work by discussing the value of retaining this algorithm. With guidance from the Guideline Executive Committee, composed of the co-chairs from the three expert panels and three work groups, the RAWG decided to focus on first hard ASCVD events (defined as occurrence of coronary death or fatal stroke or first occurrence of nonfatal myocardial infarction (MI) or stroke) rather than CHD alone as the outcome of interest because it was deemed to be of greater relevance than CHD alone to both patients and providers. The focus on hard ASCVD, rather than CHD, also is consistent with recent evidence reviewed in a statement from the American Heart Association/American Stroke Association calling for the inclusion of ischemic stroke in the outcome of interest for cardiovascular disease (CVD) risk assessment.[11]

Considerations in Developing the Approach to Risk Assessment

The RAWG sought a simple, unifying approach to clinical decisionmaking that would not force clinicians to check an individual patient's profile against the I/E criteria for each RCT in the area of CVD prevention. After deliberation, the RAWG endorsed the existing and widely employed paradigm of matching the individual's absolute risk with the intensity of preventive efforts.[1,12] The RAWG judged that this approach balances an understanding of an individual's absolute risk for CVD against potential absolute risks of harm from therapy. Using this framework, treatment can be targeted to those most likely to benefit without undue risk for harm, in the context of a "risk discussion." Likewise, the RAWG recognized that there is an opportunity cost for clinicians and patients in discussing CVD prevention measures when absolute risk for CVD is low (i.e., the limited time during a clinical visit may be better spent focusing on other issues if absolute CVD risk is shown to be low by quantitative assessment). By its nature, such an approach requires a platform for reliable estimation of absolute risk based upon data from representative cohort samples. It is important to note that risk estimation is based on group averages that are then applied to individual patients in practice. By its nature, this process is imperfect. No one has 10 percent or 20 percent of a heart attack during a 10-year period. Individuals with the same estimated risk will either have or not have the event of interest, and only those patients who are destined to have an event can have their event prevented by therapy. This criticism of the risk estimation approach to treatment decisionmaking also applies to the alternative and much less efficient approach of checking the patient's characteristics against the I/E criteria for each pertinent trial. Only a small fraction of trial participants have events, and only a fraction of these events are prevented by therapy. Using either approach, the clinician must apply the average results obtained from groups of patients to the individual patient in practice.

Data are sparse regarding current usage and impact of using absolute risk scores in clinical practice in primary prevention settings.[13,14] Two systematic reviews, based on few studies, support the conclusion that risk assessment combined with counseling is associated with small, favorable changes in provider prescribing behavior and risk factor control. The RAWG notes that the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Performance Measures for the Primary Prevention of CVD[15] have specifically recommended use of global risk estimation in clinical practice. Likewise, the USPSTF recommendations for aspirin,[16] ATP III panel recommendations,[1] and European[17] and Canadian[18] guidelines for primary prevention of CVD, among others, have all recommended use of absolute risk assessment for decisionmaking about the intensity of lifestyle and pharmacologic preventive interventions. Risk scores have been estimated with scoring sheets, calculators, and computers. The electronic medical record can be adapted to

estimate risk for outcomes, and it is anticipated that risk estimation using this technology will become a mainstream application.

Some data exist about the utility of absolute risk assessment algorithms in clinical practice. In brief, use of absolute risk estimation in clinical practice has been shown to have significant but modest effects on prescribing preventive therapies and on intermediate end points, such as risk factor levels.[19-21] No data are available on hard event outcomes. As noted below, the RAWG specifically calls for research in this area.

Methods for Modeling Risk and Developing Algorithms

Risk prediction equations based on the Framingham Heart Study have been used extensively in scientific publications, international and U.S. prevention guidelines, and in the ATP III risk calculator available on the NHBLI's Web site.[1] Use of these risk prediction equations raises a number of issues, including generalizability to non-White populations; statistical performance in terms of discrimination, calibration, and appropriate classification of risk in diverse groups; lack of inclusion of novel risk markers beyond traditional risk factors; and the focus solely on a hard CHD end point, which does not account for risk for stroke and other atherosclerotic events that may be more important in women and non-White groups. The ATP III considered diabetes mellitus (hereinafter referred to as diabetes) to be a CHD risk equivalent and did not include diabetes in its multivariable risk equations.[1] A large meta-analysis failed to support the hypothesis that diabetes is a CHD risk equivalent,[22] and it is judged that appropriate CVD risk estimates should consider inclusion of diabetes as an independent predictor variable in this setting.

Numerous other risk scores and equations have been derived and published in the past decade (tables 1a and 1b).[1,19,23-28]

Table 1a. Characteristics of Previously Published Risk Scores and Current NHLBI Pooled Cohort Risk Scores, Including Data Sources and Covariates

Risk Score: Study Group	Risk Score: Study and Region	Risk Score: Data Source	Risk Score: Publication Year	Risk Factor:* Age	Risk Factor:* Sex	Risk Factor:* Total Chol	Risk Factor:* LDL-Chol	Risk Factor:* HDL-Chol	Risk Factor:* CRP	Risk Factor:* Systolic BP	Risk Factor:* BP Rx	Risk Factor:* Diabetes	Risk Factor:* HbA1c†	Risk Factor:* Smoking	Risk Factor:* Family Hx CVD‡	Risk Factor:* Body Mass Index	Risk Factor:* Social	Risk Factor:* Region
Framingham CHD[28]	Framingham MA, USA	EAF, EAM	1998	X	X	X	X	X		X		X		X				
ATP III[1]	Framingham MA, USA	EAF, EAM	2001	X	X	X		X		X	X			X				
Framingham Global[19]	Framingham MA, USA	EAF, EAM	2008	X	X	X		X		X	X	X		X				
PRO-CAM[23]	Muenster, Germany	EM	2002	X			X	X		X		X		X	X			
QRISK[25]	QRESEARCH, United Kingdom	EF, EM	2007	X	X	X		X		X	X			X	X	X	X‡	X
Reynolds Men[27]	Phys Health Study USA	EAF	2008	X		X		X	X	X				X	X			
Reynolds Women[26]	Women's Health Study USA	EAM	2007	X		X		X	X	X			X	X	X			
EURO-SCORE[24]	12 cohorts Europe	EF, EM	2003	X	X	X		X		X				X				X
NHLBI	CARDIA, Framingham, ARIC, CHS,USA	EAF, EAM AAF, AAM		X	X	X		X		X	X	X		X				

* Covariates Included
† Only among those with diabetes
‡ Definitions of a positive family history vary
¥ Measure of social deprivation
Note: AAF=African American females; AAM=African American males; EF=European females; EM=European males; EAF=European American females; EAM=European American males.

Table 1b. Characteristics of Previously Published Risk Scores and Current NHLBI Pooled Cohort Risk Scores, Including Data Sources and Outcomes

Risk Score: Study Group	Risk Score: Study and Region	Risk Score: Data Source	Risk Score: Publication Year	CVD Event: Coronary Revasc *	CVD Event: Angina Pectoris *†	CVD Event: Unstable Angina *†	CVD Event: Myocardial Infarct *†‡¥§	CVD Event: CHD Death *†‡¥§	CVD Event: Stroke ‡¥§	CVD Event: Stroke Death ‡¥§	CVD Event: Cardiac Failure §	CVD Event: TIA
Framingham CHD[28]	Framingham MA, USA	EAF, EAM	1998		X	X	X	X				
ATP III[1]	Framingham MA, USA	EAF, EAM	2001				X	X				
Framingham Global[19]	Framingham MA, USA	EAF, EAM	2008				X	X	X	X	X	
PRO-CAM[23]	Muenster, Germany	EM	2002				X	X				
QRISK[25]	QRESEARCH, United Kingdom	EF, EM	2007	X	X	X	X	X	X	X		X
Reynolds Men[27]	Phys Health Study USA	EAF	2008	X			X	X	X	X		
Reynolds Women[26]	Women's Health Study USA	EAM	2007	X			X	X	X	X		
EURO-SCORE[24]	12 cohorts Europe	EF, EM	2003					X		X		
NHLBI	CARDIA, Framingham, ARIC, CHS,USA	EAF, EAM AAF, AAM					X	X	X	X		

* Total CHD including revascularization
† Total CHD
‡ Hard CHD
¥ Hard ASCVD
§ Hard CVD including cardiac failure

Note: AAF=African American females; AAM=African American males; ARIC = Atherosclerosis Risk in Communities; ASCVD=atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; BP=blood pressure; CARDIA = Coronary Artery Risk Development in Young Adults; Chol=cholesterol; CHD=coronary heart disease; CHS = Cardiovascular Health Study; CRP=C-reactive protein; CVD=cardiovascular disease; EF=European females; EM=European males; EAF=European American females; EAM=European American males; HbA1c=hemoglobin A1c;Hx=history; HDL-Chol = high-density lipoprotein cholesterol; LDL-Chol = low-density lipoprotein cholesterol; PROCAM = Prospective Cardiovascular Munster study; Revasc=revascularization; TIA=transient ischemic attack.

Some of these equations address the limitations identified above. Therefore, the RAWG considered use of previously published risk scores with validation in NHLBI cohort data as one possible approach. However, the RAWG identified a number of persistent concerns with existing risk equations, including the following:

Some scores used samples for derivation that were not representative of the general U.S. population (for example, the participants were European or had been selected for inclusion in a clinical trial).[23-27]

Most scores had been derived in exclusively or overwhelmingly White samples, without adequate representation of or sufficient events in non-White groups.[1,19,23-28] The RAWG judged that it would be important to include data on African Americans and to produce sex- and race-specific equations, given known differences in event rates and possible differences in coefficients for Whites and African Americans. The work group recognizes that data are limited for followup of Hispanic and Asian American samples and calls for further research in these and other groups.

Many scores used end points that the RAWG judged to be suboptimal. Existing scores have examined a number of different composite outcomes, some of which were deemed too narrow, such as CVD death only without nonfatal events;[24] or CHD events only without other types of ASCVD;[1,23,28] or composite end points, including CVD events that are less severe or difficult to diagnose reliably (e.g., angina or transient ischemic attack)[25,28] or that are subject to significant variability depending on practice patterns (e.g., revascularization).[25-27]

Some of the risk scores include data from older population samples derived from earlier birth cohorts. Participants in these studies may have lived during eras when exposure to risk factors and prevention strategies differed from those of contemporary patients.[1,19,28]

Validation and calibration of existing risk scores in NHLBI cohorts also was deemed to be a suboptimal approach, given that some covariates were unavailable in NHLBI cohorts (as described below) and some end points were not collected or were defined differently than in the original scores.

The ideal population from which to derive a risk prediction algorithm would be a contemporary, population-based cohort that closely reflects the general population in racial, geographic, and lifestyle or environmental factors but is largely unaffected by new or alternate interventions during followup to provide a predicted risk estimate associated with risk in the absence of treatment. Given the absence of such an ideal population from which to derive a risk prediction algorithm and the inherit limitations of existing scores, the RAWG deemed that a new risk score was needed. A new risk score could address some of the deficiencies of existing scores with a population sample that approaches the ideal sample, to the degree possible.

The RAWG created a new risk assessment algorithm using pooled NHLBI community-based cohort data. The score estimates risk for fatal and nonfatal hard ASCVD events and is based on data from biracial, community-based population samples. This approach allowed inclusion of relatively contemporary cohorts whose event rates more closely approximate the current patient population in the United States.

Development of ASCVD Risk Equations

The RAWG desired to build upon experience with prior Framingham 10-year *CHD* risk prediction equations[1,20,28,29] and the more recent Framingham 10-year *general CVD* risk prediction equations,[19] while also expanding the utility and generalizability of new equations. Therefore, the RAWG elected to capitalize on the extensive data from several large NHLBI-sponsored cohort studies to derive a more geographically and racially diverse database. Specifically, baseline data from the Atherosclerosis Risk in Communities (ARIC) study[21] and Cardiovascular Health Study (CHS),[30] along with applicable data from the Coronary Artery Risk Development in Young Adults (CARDIA) study[31] (including participants ages 40 or older who attended the year 10 examination) were combined with data from the Framingham Original Cohort and the Framingham Offspring Cohort.

A total of 11,240 White women (902 ASCVD events), 9,098 White men (1,259 events), 2,641 African American women (290 events), and 1,647 African American men (238 events) who met the following criteria were included: ages 40 to 79; apparently healthy; African American or White; and free of a previous history of MI (recognized or unrecognized), stroke, heart failure, percutaneous coronary intervention, coronary bypass surgery, or atrial fibrillation. Participants with atrial fibrillation at baseline were excluded because these participants have a clear need for risk reducing therapies due to the strong relationship between atrial fibrillation and stroke. Participants older than age 79 were excluded due to complex age-covariate interactions. Data from the included participants were used to develop sex- and race-specific equations to predict 10-year risk for a first hard ASCVD event. Due to the growing health burden of heart failure, the work group examined the possibility of including heart failure as an outcome. However, study-by-study ascertainment and adjudication of heart failure varied considerably; therefore, heart failure could not be included in the risk estimation. Due to self-selection and physician recommendation biases,[32-36] coronary revascularization was not an included end point. The ASCVD risk estimates were developed from sex-and race-specific proportional hazards models that included the covariates of age, treated or untreated systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), current smoking (Y/N), and diabetes (Y/N). A variable representing lipid treatment was considered but not retained in the final model because lipid therapy was relatively uncommon in the cohorts, and statistical significance was lacking. Baseline characteristics of the participants included in the equation derivation model are shown in tables 2a and 2b. Interactions with age were tested for each risk factor and retained in final models if the *p* value for the interaction term was less than.01, or the *p* value was .01 to .05 and the continuous net reclassification improvement for nonevents was 15 percent or greater, or the integrated discrimination improvement index (IDI) was statistically significant.[37,38] End points were censored at 12 years, and model fit was evaluated through the area under the receiver operating curve (*C*-statistic)for discrimination[39] and the calibration chi-squared statistic.[40]

In developing the new 10-year ASCVD risk model, the RAWG also addressed the CQ regarding the value of novel risk factors in risk assessment (CQ1). Based on the availability of data across cohorts at applicable examination cycles, additional risk markers were evaluated for potential improvement in model performance based on the framework of Hlatky et al., 2009[41] (table 3).

Table 2a. Baseline Characteristics (Unadjusted) of the Risk Estimation Population of Women by Study Cohort and Race (Age Criterion 40 to 79)

Women	African American ARIC: Mean or %	African American ARIC: Std	African American CARDIA: Mean or %	African American CARDIA: Std	African American CHS: Mean or %	African America n CHS: Std	White ARIC: Mean or %	White ARIC: Std	White CARDIA: Mean or %	White CARDIA: Std	White CHS: Mean or %	White CHS: Std	White Fram: Mean or %	White Fram: Std
Sample Size	*n*=2,137	*n*=2,137	*n*=110	*n*=110	*n*=394	*n*=394	*n*=5,508	*n*=5,508	*n*=131	*n*=131	*n*=2,131	*n*=2,131	*n*=3,470	*n*=3,470
Age Range	(44–66)	(44–66)	(40–45)	(40–45)	(65–79)	(65–79)	(44–65)	(44–65)	(40–42)	(40–42)	(65–79)	(65–79)	(40–74)	(40–74)
Age (years)	53.1	5.7	40.4	1.0	71.2	4.0	53.9	5.7	40.1	0.3	70.8	3.8	53.5	8.7
Total Chol (mg/dL)	216.4	45.1	181.3	35.4	215.4	38.2	218.1	42.2	181.2	28.9	223.3	37.7	224.2	43.1
HDL Chol (mg/dL)	58.4	17.3	53.2	14.6	60.9	14.8	57.9	17.0	54.1	12.8	59.6	15.9	58.0	15.7
Untreated SBP (mmHg)	124.2	19.6	111.4	15.0	136.7	19.8	114.3	16.4	104.5	10.5	130.4	20.0	126.7	18.8
Treated SBP (mmHg)	132.5	21.3	129.7	19.4	146.3	24.6	129.1	18.0	108.0	4.4	140.8	19.9	147.9	19.7
BP Meds (%)	39.3%		9.1%		58.1%		16.7%		2.3%		32.9%		13.2%	
Current Smoker (%)	24.0%		27.3%		14.2%		24.5%		17.6%		13.7%		32.8%	
Diabetes (1) (%)	17.1%		6.4%		22.3%		6.1%		1.5%		9.9%		4.7%	
10-yr KM CVD Rate	7.2%		0.9%		23.0%		3.6%		0.0%		18.0%		3.8%	

Note: ARIC = Atherosclerosis Risk in Communities study; BP = blood pressure; CARDIA = Coronary Artery Risk Development in Young Adults study; Chol = cholesterol; CHS = Cardiovascular Health Study; Fram = Framingham Heart Study; Std = standard.

Table 2b. Baseline Characteristics (Unadjusted) of the Risk Estimation Population of Men by Study Cohort and Race (Age Criterion 40 to 79)

Men	African American ARIC: Mean or %	African American ARIC: Std	African American CARDIA: Mean or %	African American CARDIA: Std	African American CHS: Mean or %	African American CHS: Std	White ARIC: Mean or %	White ARIC: Std	White CARDIA: Mean or %	White CARDIA: Std	White CHS: Mean or %	White CHS: Std	White Fram: Mean or %	White Fram: Std
Sample Size	*n*=1,364	*n*=1,364	*n*=64	*n*=64	*n*=219	*n*=219	*n*=4,692	*n*=4,692	*n*=103	*n*=103	*n*=1,308	*n*=1,308	*n*=2,995	*n*=2,995
Age Range	(44–66)	(44–66)	(40–45)	(40–45)	(65–79)	(65–79)	(44–65)	(44–65)	(40–42)	(40–42)	(65–79)	(65–79)	(40–74)	(40–74)
Age (years)	53.6	5.9	40.3	0.8	70.9	3.9	54.5	5.7	40.2	0.4	71.2	3.8	52.8	8.5
Total Chol (mg/dL)	210.8	44.0	187.0	39.1	200.1	35.7	210.3	38.1	186.2	33.6	200.3	34.9	216.6	38.8
HDL Chol (mg/dL)	51.0	16.9	46.8	17.2	52.2	13.6	43.1	12.4	42.8	11.1	47.5	12.5	45.0	12.4
Untreated SBP (mmHg)	127.8	21.2	117.3	13.7	134.0	17.8	118.3	15.0	112.5	13.2	131.5	19.1	129.9	17.4
Treated SBP (mmHg)	133.5	19.4	127.7	8.6	143.7	24.0	128.6	16.7	114.0	11.3	142.0	22.4	145.8	19.9
BP Meds (%)	30.2%		10.9%		43.8%		16.6%		1.9%		30.4%		11.9%	
Current Smoker (%)	37.3%		37.5%		23.7%		24.5%		23.3%		10.7%		33.6%	
Diabetes (1) (%)	15.0%		3.1%		25.6%		7.8%		2.9%		15.4%		7.7%	
10-yr KM CVD Rate	11.1%		4.7%		24.9%		9.0%		1.0%		28.5%		9.5%	

Note: ARIC = Atherosclerosis Risk in Communities study; BP = blood pressure; CARDIA = Coronary Artery Risk Development in Young Adults study; Chol = cholesterol; CHS = Cardiovascular Health Study; Fram = Framingham Heart Study; Std = standard.

Table 3. Considerations for Evaluating New Risk Factors When Assessing Clinical Utility for Risk Assessment (Derived From Hlatky 2009[41])

Considerations
1. **Association:** Has a statistically significant prospective association been demonstrated with the end point of
2. **Discrimination:** Does addition of the new marker lead to significant improvement in discrimination (typically assessed by the *C*-statistic) after addition of the marker to a model with traditional risk factors? Information on the likelihood ratio or sensitivity and specificity would inform this consideration as well.
3. **Calibration:** Does addition of the new factor to a traditional risk factor model result in improved calibration,
4. **Net reclassification improvement (categorical or category free):** Does the addition of the new risk factor to a traditional risk model result in net reassignment of events to higher risk status and nonevents to lower risk status?
5. **Integrated discrimination index:** The improvement in the *r*-square for the model, which is also a representation of how far a reclassified individual moves along the predicted risk spectrum, on average, when a new risk marker
6. **Improvement in clinical outcomes:** Does use of the new risk factor result in changes in clinical decisionmaking that leads to improved clinical outcomes (especially hard clinical outcomes)? Has this utility been demonstrated through use of the marker in a clinical trial?
7. **Safety:** Are any risks outweighed by the benefits, overall and in subgroups of interest?
8. **Cost and cost-effectiveness:** Are the benefits worth the costs of the new assessment?

The additional risk markers that were evaluated included diastolic blood pressure (DBP); family history of ASCVD (defined in the ARIC, CARDIA, and Framingham Offspring study as a parent with an MI before age 55 or a stroke before age 65, and in the CHS study as a sibling with an MI before age 55 or a stroke before age 65); moderate or severe chronic kidney disease (CKD, defined as an estimated glomerular filtration rate (GFR)of less than 60 mL/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation[42]); and BMI(continuous and categorical, modeled separately).None of these variables significantly improved discrimination for 10-year hard ASCVD risk prediction when added to the final base models. Improvement in discrimination was defined as a relative IDI (rIDI) of 6 percent or more. Moderate or severe CKD in African American women was the closest variable to the threshold, with an rIDI of 5.4 percent. None of the other potential risk factors had an rIDI above 2 percent. Other risk markers (high-sensitivity C reactive protein (hs-CRP), apolipoprotein B (ApoB), microalbuminuria, cardiorespiratory fitness, coronary artery calcium (CAC) score, carotid artery intima-media thickness (CIMT), and ankle-brachial index (ABI)) could not be evaluated in creating this new model due to absence of data or lack of inclusion in the appropriate examination cycle of one or more of the studies.

The RAWG also addressed the potential utility of novel risk markers in addition to established risk factors by reviewing existing systematic reviews and meta-analyses identified by the methodologists for CQ1. That evidence is reviewed below. Further research using state-of-the art statistical techniques (including net reclassification improvement and IDI[37,38]) will be needed to examine the utility of novel biomarkers when added to the new pooled cohort risk equations in different populations and patient subgroups. RCTs demonstrating the utility of screening with novel risk markers would represent the best evidence for their inclusion in future risk assessment algorithms. In the absence of evidence from trials, methodologically rigorous observational studies should be conducted to evaluate utility.

The equations for calculating an estimate of an individual's 10-year risk for incident hard ASCVD are provided in tables 4a and 4b, and an example based on a specific risk profile is shown in table 5. As can be seen from the *C*-statistics (tables 6a and 6b), these estimating equations have good to excellent[43] ability to discriminate those who will experience hard ASCVD events from those who will not experience hard ASCVD events over a 10-year followup interval in these population samples.

Table 4a. Example of Estimation of 10-Year Risk for Hard ASCVD, Defined as Occurrence of Coronary Death or Fatal Stroke or First Occurrence of Nonfatal MI or Stroke; Equation Parameters and Specific Example for Women of Each Race

Women	White: Coefficient	White: Ind. Value	White: Coefficient × Value*	African American: Coefficient	African American: Ind. Value	African American: Coefficient × Value*
Log Age (yr)	–29.799	55	–119.41	17.114	55	68.58
Log Age Squared	4.884		78.44	NA	NA	NA
Log Total Cholesterol (mg/dL)	13.540	213	72.59	0.940	213	5.04
Log Age×Log Total Cholesterol	–3.114		–66.91	NA	NA	NA
Log HDL Cholesterol (mg/dL)	–13.578	50	–53.12	–18.920	50	–74.01
Log Age×Log HDL Cholesterol	3.149		49.37	4.475	NA	70.15
Log Treated SBP (mmHg)	2.019	–	–	29.291	–	–
Log Age×Log Treated SBP	NA	NA	NA	–6.432	–	–
Log Untreated SBP (mmHg)	1.957	120	9.37	27.820	120	133.19
Log Age×Log Untreated SBP	NA	NA	NA	–6.087		–116.79
Current Smoker (1=Yes, 0=No)	7.574	0	0	0.691	0	0
Log Age×Current Smoker	–1.665		0	NA	NA	NA
Diabetes (1=Yes, 0=No)	0.661	0	0	0.874	0	0
Individual Sum			–29.67			86.16
Mean (Coefficient×Value)			–29.18			86.61
Baseline Survival			0.9665			0.9533
Estimated 10-Yr Risk			2.1%			3.0%

* Parameter × Value: For age, lipids, and blood pressure, defined as the natural log of the value multiplied by the parameter estimate. When an age interaction is present with lipids or blood pressure, the natural log of age is multiplied by the natural log of the lipid or blood pressure, and the result is multiplied by the parameter estimate.

Note: HDL-Cholesterol = high-density lipoprotein cholesterol; Ind = individual.

Table 4b. Example of Estimation of 10-Year Risk for Hard ASCVD, Defined as Occurrence of Coronary Death or Fatal Stroke or First Occurrence of Nonfatal MI or Stroke; Equation Parameters and Specific Example for Men of Each Race

Men	White: Coefficient	White: Ind. Value	White: Coefficient × Value*	African American: Coefficient	African American: Ind. Value	African American: Coefficient × Value*
Log Age (yr)	12.344	55	49.47	2.469	55	9.89
Log Total Cholesterol (mg/dL)	11.853	213	63.55	0.302	213	1.62
Log Age×Log Total Cholesterol	–2.664		–57.24		NA	NA
Log HDL Cholesterol (mg/dL)	–7.990	50	–31.26	–0.307	50	–1.20
Log Age×Log HDL Cholesterol	1.769		27.73			
Log Treated Systolic BP (mmHg)	1.797	–	–	1.916	–	–
Log Untreated Systolic BP (mmHg)	1.764	120	8.45	1.809	120	8.66
Current Smoker (1=Yes, 0=No)	7.837	0	0.00	0.549	0	0.00
Log Age×Current Smoker	–1.795		0.00		NA	NA
Diabetes (1=Yes, 0=No)	0.658	0	0	0.645	0	0
Individual Sum			60.69			18.97
Mean (Coefficient×Value)			61.18			19.54
Baseline Survival			0.9144			0.8954
Estimated 10-Yr Risk			5.3%			6.1%

* Parameter × Value: For age, lipids, and blood pressure, defined as the natural log of the value multiplied by the parameter estimate. When an age interaction is present with lipids or blood pressure, the natural log of age is multiplied by the natural log of the lipid or blood pressure, and the result is multiplied by the parameter estimate.

Note: HDL-Cholesterol = high-density lipoprotein cholesterol; Ind = individual.

Table 5. Estimating an Individual's 10-Year Risk for Incident Hard ASCVD

The hypothetical profile provided in tables 4a and 4b (the "Ind. Value" column) is identical for each race and sex group and is based on the overall sample mean. The profile assumes an individual age 55, with a total cholesterol of 213 mg/dL, HDL cholesterol of 50 mg/dL, and an untreated SBP of 124 mmHg. This individual is a current smoker and does not have diabetes. For the equations, the values for age, lipids, and SBP are log transformed. Interactions between age and lipids or age and SBP use the natural log of each variable (e.g., Ln[Age]×Ln[Total Cholesterol]).

Calculation of the 10-year risk estimate can best be described as a series of steps. The natural log of age, total cholesterol, HDL-C, and SBP are first calculated with SBP being either a treated blood pressure or untreated blood pressure. Any appropriate interaction terms are then calculated. These values are then multiplied by the coefficients for the equation ("Coefficient" column of tables 4a and 4b). The "Coefficient×Value" column in the table provides the results of the multiplication for the risk profile described above.

The sum of the "Coefficient×Value" column is then calculated. For the profile above, this value is shown in table 4as "Individual Sum" for each race and sex group.

The estimated probability of an incident hard ASCVD event within 10 years is formally calculated as 1 minus the survival rate at 10 years ("Baseline Survival" in tables 4a and 4b), raised to the power of the exponent of the "Coefficient×Value" sum minus the race and sex specific overall mean "Coefficient×Value" sum, or in equation form:

$$1 - S_{10}^{e^{(IndX'B - MeanX'B)}}$$

Using White men as an example:

$$1 - 0.9144^{e^{(60.69 - 61.18)}}$$

equates to a 5.3 percent probability of an incident hard ASCVD event within 10 years.

i. Internal Validation

The RAWG evaluated the internal consistency of the discrimination and calibration performance measures using a 10x10 cross-validation technique. The 10x10 cross-validation is an extension of a 10-fold cross-validation in which the 10-fold cross-validation is repeated a total of 10 times, beginning with a new group randomization. In brief, each sex and race population was randomly divided into 10 equal groups. One group was used as the validation sample while the other nine groups represented the training sample. The model was run using the training sample, and the resulting prediction equation was then applied to the validation sample. The discrimination *C*-statistic, calibration chi-squared statistic, and the calibration slope (defined as the beta coefficient from a model with the linear predictor as the sole covariate, the linear predictor being the sum of the beta coefficients times the risk factor value) from the validation run were then collected. A single 10-fold cross-validation was completed after each group served a turn as the validation sample while the other nine groups served as the training sample (10 model performance observations). The process was repeated an additional nine times, beginning with a new randomization to create a total of 100 observed performance statistics, which were then averaged to provide summary statistics regarding the internal consistency of how the models performed.

For the hard ASCVD end point, the internal validation results yielded average discrimination *C*-statistics and calibration chi-squared statistics that were in agreement with the full model (tables 6a and 6b). The calibration slope was near 1 for all race-sex groups, but highest in African American females, with a slight tendency to

underestimate risk. Variation in the discrimination *C*-statistic, calibration chi-squared, and calibration was notably higher in African American men compared to the other race-sex groups.

Table 6a. Summary of Internal Validation of Risk Prediction of Hard ASCVD and the Components of ASCVD Within 10 Years Using a 10x10 Cross-Validation for People Classified as White

White	Women: Original	Women: Mean	Women: Std	Women: P5†	Women: Median	Women: P95†	Men: Original	Men: Mean	Men: Std	Men: P5†	Men: Median	Men: P95†
N	11,240	1,124	0	1,124	1,124	1,124	9,098	909.8	0.402	909	910	910
C-statistic	0.8058	0.8040	0.025	0.7625	0.8012	0.8449	0.7462	0.7443	0.023	0.7060	0.7444	0.7841
Calib. Chi-sq.	6.43	7.29	3.89	2.40	6.62	14.70	4.86	8.31	3.44	3.47	7.97	15.24
Calib. Slope*	1.00	1.024	0.131	0.824	1.010	1.250	1.00	1.029	0.130	0.829	1.027	1.262

* Calibration slope: Beta coefficient from a proportional hazards model using the linear predictor as the sole independent variable.
† P5 and P95 represent the 5th and 95th percentiles, respectively.
Note: Calib = calibration; Chi-sq = Chi-squared; Std = standard.

Table 6b. Summary of Internal Validation of Risk Prediction of Hard ASCVD and the Components of ASCVD Within 10 Years Using a 10x10 Cross-Validation for People Classified as African American

African American	Women: Original	Women: Mean	Women: Std	Women: P5†	Women: Median	Women: P95†	Men: Original	Men: Mean	Men: Std	Men: P5†	Men: Median	Men: P95†
N	2,641	264.1	0.302	264	264	265	1,647	164.7	0.461	164	165	165
C-statistic	0.8182	0.8142	0.037	0.7467	0.8206	0.8661	0.7130	0.7036	0.051	0.6201	0.7040	0.7875
Calib. Chi-sq.	7.25	5.30	2.95	1.56	4.81	10.68	6.71	6.25	3.25	2.59	5.57	13.79
Calib. Slope*	1.00	1.058	0.220	0.722	1.083	1.456	1.00	0.991	0.314	0.486	0.960	1.577

* Calibration slope: Beta coefficient from a proportional hazards model using the linear predictor as the sole independent variable.
† P5 and P95 represent the 5th and 95th percentiles, respectively.
Note: Calib = calibration; Chi-sq = Chi-squared; Std = standard.

ii. External Validation

The Work Group also evaluated the performance of the algorithms in predicting ASCVD events in two external cohorts and in the most contemporary available data from the derivation cohorts (specifically, the most recent examination cycles from ARIC and Framingham for which 10 years of followup is available). The external cohorts consisted of Whites and African Americans from the Multi-Ethnic Study of Atherosclerosis (MESA)[44] and the Reasons for Geographic And Racial Differences in Stroke study (REGARDS).[45] The MESA and REGARDS studies were approached for external validation due to their large size, contemporary nature, and comparability of end points. Both studies have less than 10 years of followup. Validation using "most contemporary cohort" data also was conducted using ARIC visit 4, Framingham original cohort (cycle 22 or 23), and Framingham offspring cohort (cycles 5 or 6) data. The events that occurred during this followup period included 4.4 percent of the events included in the algorithm derivation period.

After restricting the validation samples to Whites and African Americans ages 40 to 79, free of a history of MI, stroke, congestive heart failure (CHF), coronary revascularizations, or atrial fibrillation and with complete data, 13,652 contemporary cohort participants, 4,234 MESA participants, and 18,675 REGARDS participants were available for validation. For MESA and REGARDS, the algorithm was adjusted for the reduced followup time

by calculating a new baseline survival rate (S_{10} in the equation). For MESA, a 6-year rate was used, and a 4-year rate was used for REGARDS. All other equation parameters remained the same as for the 10-year prediction function.

For the hard ASCVD end point, the external validation results yielded discrimination *C*-statistics that were lower than those observed for the 10-year prediction in the derivation data (tables 7a and 7b).

Table 7a. Number of Events, *C*-Statistic, and Calibration Chi-Squared Statistic of the Combined Studies Hard CVD Risk Prediction Equation as Applied to the Validation Cohorts of a Contemporary Cohort Studies Population, MESA and REGARDS Studies for People Classified as White

White	Women: Algorithm Derivation Cohort	Women: Validation Cohort Contemporary (4)	Women: Validation Cohort MESA (5)	Women: Validation Cohort REGARDS (6)	Men: Algorithm Derivation Cohort	Men: Validation Cohort Contemporary (4)	Men: Validation Cohort MESA (5)	Men: Validation Cohort REGARDS (6)
Total *N*	11,240	6,509	1,273	5.914	9,098	5,041	1,184	4,970
Events (1)	683	400	37	85	1,032	539	57	175
Events (2)	722.9	426.7	38.4	90.8	1,095.2	580.9	59.7	186.8
Exp Events (3)	723.5	549.4	49.9	105.4	1,098.5	798.9	94.9	242.2
C-statistic	0.8058	0.7377	0.7109	0.7503	0.7462	0.6843	0.7044	0.6605
Calib. Chi-sq	6.43	45.50	14.56	7.03	4.86	84.45	21.43	31.50

(1) Actual number of events through followup window.
(2) Observed number of events after Kaplan-Meier adjustment through followup window.
(3) Expected number of events based on the combined cohort studies global CVD equation, calibrated for the individual components where appropriate, through follow up window.
(4) Based on 10-year prediction. Includes ARIC V4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended).
(5) Based on 6-year prediction.
(6) Based on 4-year prediction.
Note: Calib = calibration; Chi-sq = Chi-squared; Exp = expected; MESA = Multi-Ethnic Study of Atherosclerosis; REGARDS = Reasons for Geographic and Racial Differences in Stroke study.

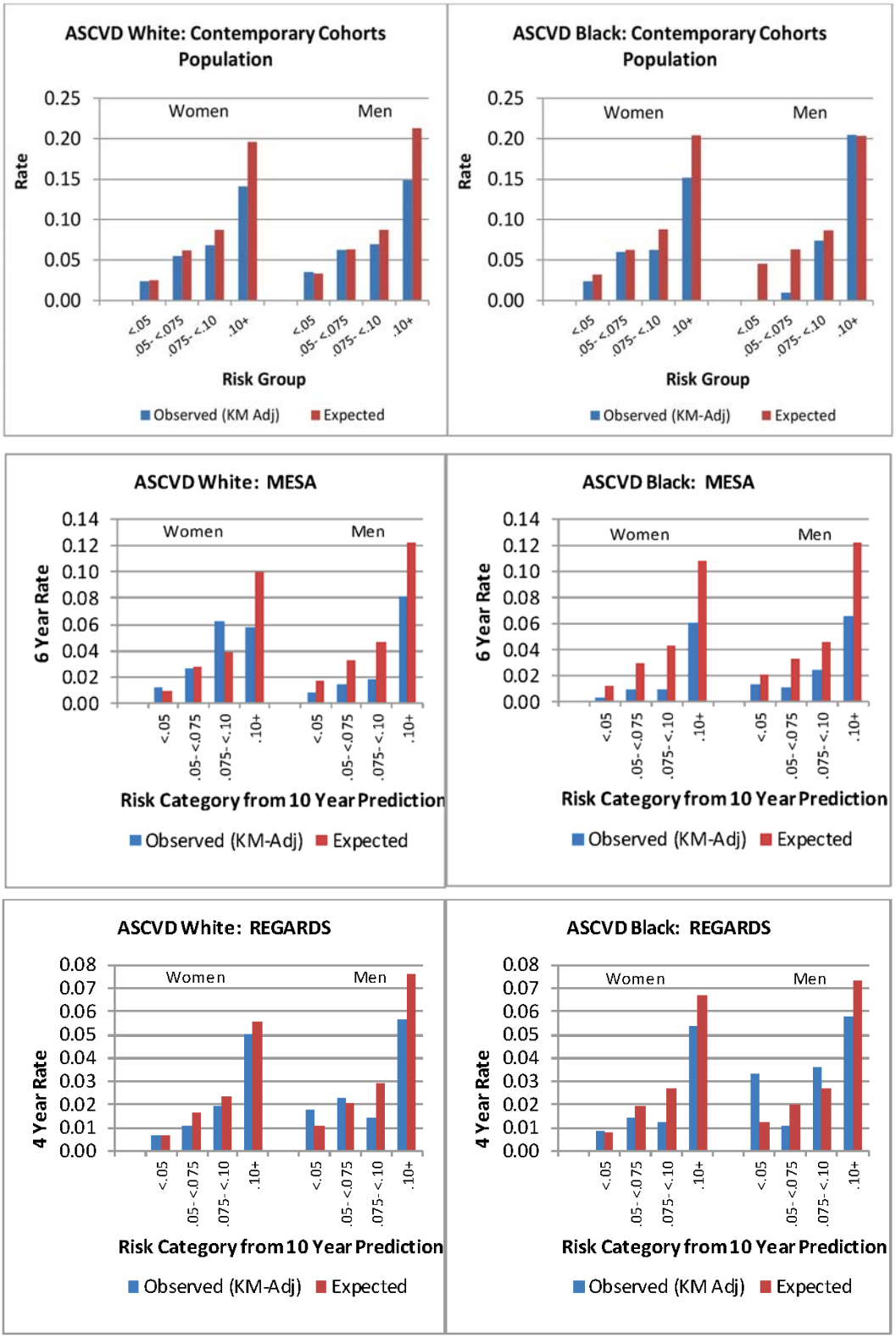
Table 7b. Number of Events, *C*-Statistic, and Calibration Chi-Squared Statistic of the Combined Studies Hard CVD Risk Prediction Equation as Applied to the Validation Cohorts of a Contemporary Cohort Studies Population, MESA and REGARDS Studies for People Classified as African American

African American	Women: Algorithm Derivation Cohort	Women: Validation Cohort Contemporary (4)	Women: Validation Cohort MESA (5)	Women: Validation Cohort REGARDS (6)	Men: Algorithm Derivation Cohort	Men: Validation Cohort Contemporary (4)	Men: Validation Cohort MESA (5)	Men: Validation Cohort REGARDS (6)
Total *N*	2,641	1,367	978	4,957	1,647	735	799	2,834
Events (1)	235	127	28	117	194	107	36	100
Events (2)	248.7	131.3	30.1	129.0	213.8	114.0	38.3	110.1
Exp Events (3)	250.6	173.5	59.4	161.0	212.5	120.8	72.3	145.2
C-statistic	0.8182	0.7068	0.7684	0.7193	0.7130	0.7109	0.6689	0.6260
Calib. Chi-sq	7.25	15.96	18.51	15.64	6.71	12.62	24.40	16.95

(1) Actual number of events through followup window.
(2) Observed number of events after Kaplan-Meier adjustment through followup window.
(3) Expected number of events based on the combined cohort studies global CVD equation, calibrated for the individual components where appropriate, through follow up window.
(4) Based on 10-year prediction. Includes ARIC V4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended).
(5) Based on 6-year prediction.
(6) Based on 4-year prediction.
Note: Calib = calibration; Chi-sq = Chi-squared; Exp = expected; MESA = Multi-Ethnic Study of Atherosclerosis; REGARDS = Reasons for Geographic and Racial Differences in Stroke study.

Overprediction of events was noted in all validation cohorts, particularly for persons at higher risk in MESA and REGARDS (tables 7a and 7b). Calibration chi-squared statistic was above the threshold of 20 for White men in REGARDS due to low observed event rates at higher predicted risk. Calibration charts for each race-sex group in each validation cohort are shown in figure 1 for the ASCVD end point. As opposed to traditional charts that show observed and predicted events in deciles, these calibration charts use clinically meaningful cutpoints in specific predicted risk categories (<.05, .05–<.075, .075–<.10, .10+) to illustrate prediction and also to help avoid categories with just a few events. An estimated 10-year prediction was calculated in MESA and REGARDS in order to classify participants into the clinical risk groups; however, the observed and expected rates were based on the 6-year (MESA) or 4-year (REGARDS) prediction results. Overestimation of risk was more pronounced at higher risk than at lower risk. The reasons for this overestimation are not known. However, the clinical implications of risk overestimation would be more important in lower risk individuals, who might be treated unnecessarily as a result of overestimation of risk, than in higher risk individuals, who are likely to be well above risk-based treatment thresholds.

Figure 1. Kaplan-Meier Observed Event Rate and Predicted Event Rate for the ASCVD Outcome in the External Validation Samples From the Most Contemporary Cohort Studies Dataset, MESA, and REGARDS, by Race, Sex, and Selected Predicted Risk Groupings



The external validation has limitations that should be noted. Although the "most contemporary" cohort sample is later in time than the derivation sample (approximately 9 years later for ARIC, 20 years later for the Framingham cohort, and 8 to 12 years later for the Framingham offspring), a small amount of overlap in terms of events does exist between this validation sample and the derivation sample. MESA is a particularly low-risk population that excluded participants who would have been eligible for risk estimation if the study entry criteria had been less restrictive.

External validation is also hampered by the recent rise in lipid-lowering therapy. Statin use was just being introduced at the time of the derivation sample (<3 percent prevalence), and by the time of MESA, more than 15 percent of that cohort was on cholesterol-lowering medications. A sensitivity analysis was conducted excluding participants in the validation samples that were on lipid-lowering therapy at the time of examination. Excluding these participants resulted in modest improvements in both discrimination and calibration (on average, the *C*-statistic was .0135 higher and the calibration chi-squared statistic was lower in all cases, with the exception of the "most contemporary cohort's" African American women). However, the overall inferences were unchanged in terms of lower discrimination and overprediction in the validation samples. Furthermore, at present, we have not accounted for uptake of statin or blood pressure lowering therapy during followup in any of the validation cohorts. Whereas the purpose of the risk prediction equation is to estimate risk in the absence of future treatment, initiation of statins or blood pressure lowering therapy in higher risk cohort members during the followup periods may have significantly reduced events rates, and therefore impaired performance of the prediction equation in the manner observed.

iii. Limitations

Some remaining limitations of these models should be considered. The number of African Americans, particularly men, is relatively low, creating a somewhat greater level of uncertainty with respect to these estimates. The absence of other ethnicities limits the applicability of the equations to other populations, in particular to lower risk populations, such as Asians or Hispanics/Latinos. Application of the risk scores to these and other patient subgroups should be performed with caution, as it may lead to unpredictable over- and underestimation in these and other patient subgroups. As previously mentioned, there are also limitations with respect to incorporating novel risk markers or risk stratifiers. Finally, although the cohorts from which the risk equations are derived contain more contemporary data, secular trends of declining ASCVD incidence may lead to an overestimation of the predicted risks. In the ARIC communities, analysis of trends in incident acute myocardial infarction (AMI) and fatal CHD found significant declines in both African Americans and Whites from 1997 to 2008, whereas rates were fairly stable from 1987 to 1996.[46] In a large Kaiser Permanente population, Yeh et al., 2010, found a small increase in AMI incidence from 1999 to 2000 but significant declines in incidence from 2000 to 2008.[47] Public smoking bans, lower targets for blood pressure and cholesterol levels, and greater uptake in cardio-protective medications are potential contributors to recent declines in AMI incidence. These secular trends in incidence also present challenges for risk prediction in which quantitative assessment for risk will continue to be an evolving process.

Implications for Risk Assessment

Tables 8a–11b illustrate the range of estimated risk for an incident hard ASCVD event within 10 years across a broad range of risk factor burden for selected combinations of the risk factors in sex-race groups (African American and White women and men). The risk factor values were chosen to represent clinically meaningful ranges. The tables can be read in a relatively straightforward manner. Columns are first grouped according to diabetes status (Diabetes=No, then Diabetes=Yes), and each diabetes group has columns for "Current Smoker=No" and "Current Smoker=Yes." Finally, each smoking group has column groups for specific SBP

levels, with the first set of blood pressures being untreated systolic and then treated SBP. Rows are first grouped by a specific age, followed by specific total cholesterol levels and, within each total cholesterol level, specific HDL-C levels.

Table 8a. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic African American Women Without Diabetes

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	<.01	<.01	<.01	<.01	0.013	0.027	<.01	<.01	0.010	0.011	0.026	0.054
40	160	**55**	<.01	<.01	<.01	<.01	0.020	0.041	<.01	<.01	0.015	0.017	0.039	0.080
40	160	**45**	<.01	<.01	0.012	0.014	0.032	0.065	<.01	0.010	0.024	0.027	0.062	0.126
40	**200**	**65**	<.01	<.01	<.01	<.01	0.016	0.034	<.01	<.01	0.012	0.014	0.032	0.066
40	200	**55**	<.01	<.01	<.01	0.010	0.024	0.050	<.01	<.01	0.018	0.020	0.047	0.097
40	200	**45**	<.01	<.01	0.015	0.017	0.039	0.080	<.01	0.013	0.029	0.033	0.076	0.153
40	**240**	**65**	<.01	<.01	<.01	<.01	0.019	0.040	<.01	<.01	0.014	0.016	0.038	0.078
40	240	**55**	<.01	<.01	0.011	0.012	0.029	0.059	<.01	<.01	0.021	0.024	0.056	0.114
40	240	**45**	<.01	<.01	0.017	0.020	0.046	0.094	<.01	0.015	0.034	0.039	0.089	0.179
50	**160**	**65**	<.01	<.01	0.018	0.017	0.032	0.055	<.01	0.019	0.035	0.034	0.062	0.106
50	160	**55**	<.01	0.012	0.022	0.021	0.040	0.069	0.012	0.024	0.044	0.042	0.078	0.132
50	160	**45**	<.01	0.016	0.029	0.028	0.053	0.090	0.015	0.031	0.058	0.056	0.103	0.171
50	**200**	**65**	<.01	0.012	0.022	0.021	0.039	0.067	0.011	0.023	0.043	0.041	0.076	0.129
50	200	**55**	<.01	0.015	0.027	0.026	0.049	0.084	0.014	0.029	0.054	0.052	0.096	0.160
50	200	**45**	<.01	0.020	0.036	0.035	0.065	0.110	0.019	0.039	0.070	0.068	0.125	0.207
50	**240**	**65**	<.01	0.014	0.026	0.025	0.046	0.079	0.013	0.027	0.050	0.049	0.090	0.151
50	240	**55**	<.01	0.018	0.032	0.031	0.058	0.099	0.017	0.035	0.063	0.061	0.113	0.187
50	240	**45**	0.011	0.023	0.043	0.041	0.076	0.129	0.022	0.046	0.083	0.081	0.147	0.241
60	**160**	**65**	0.019	0.032	0.049	0.042	0.065	0.095	0.037	0.062	0.095	0.081	0.125	0.180
60	160	**55**	0.021	0.035	0.054	0.046	0.071	0.104	0.041	0.068	0.104	0.090	0.137	0.197

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.023	0.039	0.060	0.052	0.080	0.117	0.046	0.077	0.117	0.100	0.154	0.219
60	**200**	**65**	0.023	0.039	0.060	0.051	0.079	0.116	0.045	0.076	0.116	0.099	0.152	0.217
60	200	**55**	0.025	0.043	0.066	0.056	0.087	0.127	0.050	0.083	0.127	0.109	0.167	0.237
60	200	**45**	0.029	0.048	0.074	0.063	0.098	0.142	0.056	0.094	0.142	0.122	0.186	0.263
60	**240**	**65**	0.027	0.046	0.071	0.060	0.094	0.136	0.054	0.089	0.136	0.117	0.178	0.252
60	240	**55**	0.030	0.050	0.078	0.066	0.103	0.149	0.059	0.098	0.149	0.128	0.195	0.275
60	240	**45**	0.034	0.057	0.087	0.075	0.115	0.166	0.066	0.110	0.167	0.143	0.217	>.30
70	**160**	**65**	0.061	0.085	0.114	0.088	0.117	0.149	0.117	0.163	0.214	0.168	0.220	0.276
70	160	**55**	0.060	0.084	0.112	0.087	0.115	0.147	0.116	0.161	0.211	0.165	0.217	0.272
70	160	**45**	0.059	0.083	0.110	0.085	0.113	0.145	0.114	0.158	0.208	0.163	0.213	0.268
70	**200**	**65**	0.074	0.104	0.138	0.107	0.142	0.181	0.143	0.197	0.257	0.202	0.264	>.30
70	200	**55**	0.073	0.103	0.136	0.106	0.140	0.178	0.141	0.195	0.254	0.200	0.260	>.30
70	200	**45**	0.072	0.101	0.134	0.104	0.138	0.175	0.138	0.191	0.250	0.196	0.256	>.30
70	**240**	**65**	0.087	0.122	0.162	0.126	0.167	0.211	0.167	0.230	0.297	0.235	>.30	>.30
70	240	**55**	0.086	0.121	0.160	0.124	0.164	0.208	0.164	0.226	0.293	0.232	>.30	>.30
70	240	**45**	0.085	0.119	0.157	0.122	0.161	0.205	0.162	0.223	0.289	0.229	0.296	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 8b. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic African American Women With Diabetes

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	<.01	<.01	0.012	0.013	0.031	0.064	<.01	0.010	0.023	0.026	0.061	0.124
40	160	**55**	<.01	<.01	0.018	0.020	0.046	0.095	<.01	0.015	0.035	0.039	0.090	0.180
40	160	**45**	0.005	0.012	0.028	0.032	0.074	0.149	<.01	0.025	0.056	0.063	0.142	0.275
40	**200**	**65**	<.01	<.01	0.014	0.016	0.038	0.079	<.01	0.013	0.029	0.032	0.075	0.151
40	200	**55**	<.01	0.010	0.022	0.024	0.057	0.115	<.01	0.019	0.043	0.048	0.110	0.217
40	200	**45**	<.01	0.015	0.035	0.039	0.090	0.181	0.012	0.030	0.068	0.077	0.172	>.30
40	**240**	**65**	<.01	<.01	0.017	0.019	0.045	0.093	<.01	0.015	0.034	0.038	0.088	0.177
40	240	**55**	<.01	0.011	0.026	0.029	0.067	0.136	<.01	0.022	0.050	0.057	0.129	0.252
40	240	**45**	<.01	0.018	0.041	0.047	0.106	0.211	0.014	0.036	0.080	0.091	0.201	>.30
50	**160**	**65**	0.011	0.023	0.041	0.040	0.074	0.126	0.022	0.045	0.081	0.078	0.143	0.235
50	160	**55**	0.014	0.028	0.052	0.051	0.093	0.156	0.027	0.056	0.101	0.098	0.178	0.288
50	160	**45**	0.018	0.038	0.069	0.067	0.122	0.202	0.036	0.074	0.132	0.128	0.229	>.30
50	**200**	**65**	0.013	0.028	0.051	0.049	0.091	0.153	0.027	0.055	0.099	0.096	0.173	0.281
50	200	**55**	0.017	0.035	0.064	0.062	0.114	0.189	0.034	0.069	0.124	0.120	0.214	>.30
50	200	**45**	0.023	0.046	0.084	0.081	0.148	0.243	0.044	0.090	0.161	0.156	0.274	>.30
50	**240**	**65**	0.016	0.033	0.060	0.058	0.107	0.178	0.032	0.064	0.116	0.113	0.202	>.30
50	240	**55**	0.020	0.041	0.075	0.073	0.134	0.220	0.040	0.081	0.145	0.141	0.249	>.30
50	240	**45**	0.027	0.055	0.099	0.096	0.173	0.282	0.053	0.106	0.188	0.182	>.30	>.30
60	**160**	**65**	0.044	0.074	0.113	0.097	0.148	0.212	0.086	0.142	0.213	0.184	0.274	>.30
60	160	**55**	0.049	0.081	0.124	0.107	0.163	0.232	0.095	0.156	0.232	0.201	0.298	>.30

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.055	0.091	0.139	0.119	0.181	0.257	0.106	0.174	0.258	0.224	>.30	>.30
60	**200**	**65**	0.054	0.090	0.137	0.118	0.180	0.255	0.105	0.172	0.256	0.222	>.30	>.30
60	200	**55**	0.060	0.099	0.151	0.130	0.197	0.277	0.116	0.188	0.278	0.242	>.30	>.30
60	200	**45**	0.067	0.111	0.168	0.145	0.219	>.30	0.130	0.210	>.30	0.268	>.30	>.30
60	**240**	**65**	0.064	0.106	0.161	0.139	0.210	0.295	0.124	0.201	0.295	0.257	>.30	>.30
60	240	**55**	0.071	0.117	0.176	0.152	0.229	>.30	0.136	0.219	>.30	0.280	>.30	>.30
60	240	**45**	0.079	0.131	0.196	0.170	0.254	>.30	0.152	0.244	>.30	>.30	>.30	>.30
70	**160**	**65**	0.139	0.193	0.251	0.198	0.258	>.30	0.258	>.30	>.30	>.30	>.30	>.30
70	160	**55**	0.137	0.190	0.248	0.195	0.254	>.30	0.255	>.30	>.30	>.30	>.30	>.30
70	160	**45**	0.135	0.187	0.244	0.192	0.250	>.30	0.251	>.30	>.30	>.30	>.30	>.30
70	**200**	**65**	0.169	0.232	0.300	0.238	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
70	200	**55**	0.166	0.229	0.296	0.235	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
70	200	**45**	0.163	0.225	0.292	0.231	0.299	>.30	0.300	>.30	>.30	>.30	>.30	>.30
70	**240**	**65**	0.197	0.269	>.30	0.276	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
70	240	**55**	0.194	0.265	>.30	0.272	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
70	240	**45**	0.191	0.261	>.30	0.268	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 9a. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic White Women Without Diabetes

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	<.01	<.01	<.01	<.01	<.01	<.01	<.01	0.010	0.013	0.013	0.018	0.023
40	160	**55**	<.01	<.01	<.01	<.01	<.01	<.01	<.01	0.013	0.018	0.018	0.025	0.032
40	160	**45**	<.01	<.01	<.01	<.01	<.01	0.011	0.014	0.020	0.027	0.027	0.036	0.047
40	**200**	**65**	<.01	<.01	<.01	<.01	<.01	0.009	0.011	0.015	0.021	0.021	0.028	0.036
40	200	**55**	<.01	<.01	<.01	<.01	<.01	0.012	0.015	0.021	0.028	0.028	0.038	0.050
40	200	**45**	<.01	<.01	<.01	0.010	0.010	0.018	0.022	0.031	0.042	0.042	0.057	0.073
40	**240**	**65**	<.01	<.01	<.01	<.01	<.01	0.013	0.016	0.022	0.030	0.030	0.040	0.052
40	240	**55**	<.01	<.01	0.010	0.010	0.010	0.018	0.022	0.031	0.041	0.041	0.055	0.072
40	240	**45**	<.01	0.011	0.015	0.015	0.015	0.026	0.032	0.045	0.060	0.060	0.081	0.105
50	**160**	**65**	<.01	<.01	<.01	<.01	<.01	0.016	0.013	0.019	0.025	0.025	0.034	0.045
50	160	**55**	<.01	<.01	0.011	0.011	0.011	0.019	0.016	0.023	0.031	0.031	0.042	0.055
50	160	**45**	<.01	0.010	0.014	0.014	0.014	0.025	0.021	0.030	0.040	0.040	0.054	0.070
50	**200**	**65**	<.01	<.01	0.012	0.012	0.012	0.021	0.018	0.025	0.034	0.034	0.046	0.060
50	200	**55**	<.01	0.011	0.015	0.015	0.015	0.026	0.022	0.031	0.042	0.042	0.057	0.074
50	200	**45**	0.010	0.014	0.019	0.019	0.019	0.034	0.028	0.040	0.054	0.054	0.072	0.094
50	**240**	**65**	<.01	0.011	0.015	0.015	0.015	0.027	0.023	0.032	0.044	0.043	0.059	0.076
50	240	**55**	0.010	0.014	0.019	0.019	0.019	0.033	0.028	0.040	0.054	0.053	0.072	0.093
50	240	**45**	0.013	0.018	0.024	0.024	0.024	0.043	0.036	0.051	0.068	0.068	0.092	0.118
60	**160**	**65**	0.015	0.022	0.029	0.029	0.029	0.052	0.032	0.046	0.062	0.061	0.083	0.107
60	160	**55**	0.017	0.024	0.033	0.033	0.033	0.058	0.036	0.051	0.069	0.069	0.093	0.119

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.020	0.028	0.038	0.038	0.038	0.066	0.042	0.059	0.079	0.078	0.105	0.136
60	**200**	**65**	0.018	0.026	0.035	0.035	0.035	0.061	0.039	0.055	0.073	0.073	0.098	0.127
60	200	**55**	0.020	0.029	0.039	0.039	0.039	0.069	0.043	0.061	0.082	0.081	0.109	0.141
60	200	**45**	0.023	0.033	0.045	0.045	0.045	0.078	0.049	0.070	0.093	0.093	0.124	0.160
60	**240**	**65**	0.021	0.030	0.040	0.040	0.040	0.071	0.044	0.063	0.084	0.084	0.112	0.145
60	240	**55**	0.024	0.034	0.045	0.045	0.045	0.079	0.050	0.070	0.094	0.093	0.125	0.161
60	240	**45**	0.027	0.038	0.052	0.051	0.051	0.090	0.057	0.080	0.107	0.106	0.142	0.182
70	**160**	**65**	0.054	0.076	0.102	0.101	0.101	0.174	0.088	0.123	0.162	0.161	0.214	0.270
70	160	**55**	0.056	0.079	0.105	0.105	0.105	0.179	0.090	0.127	0.167	0.166	0.220	0.278
70	160	**45**	0.058	0.082	0.109	0.109	0.109	0.186	0.094	0.131	0.173	0.173	0.228	0.287
70	**200**	**65**	0.058	0.082	0.109	0.108	0.108	0.185	0.094	0.131	0.173	0.172	0.227	0.286
70	200	**55**	0.060	0.084	0.112	0.112	0.112	0.191	0.097	0.135	0.178	0.177	0.234	0.294
70	200	**45**	0.062	0.087	0.116	0.116	0.116	0.198	0.100	0.140	0.185	0.184	0.242	>.30
70	**240**	**65**	0.061	0.086	0.115	0.114	0.114	0.195	0.099	0.138	0.182	0.181	0.239	0.300
70	240	**55**	0.063	0.089	0.118	0.118	0.118	0.201	0.102	0.142	0.187	0.187	0.246	>.30
70	240	**45**	0.066	0.092	0.123	0.122	0.122	0.208	0.106	0.148	0.194	0.193	0.254	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 9b. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic White Women With Diabetes

Age	Total Cholesterol	HDL-Cholesterol	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	<.01	<.01	<.01	<.01	<.01	0.011	0.013	0.019	0.025	0.025	0.034	0.044
40	160	**55**	<.01	<.01	<.01	<.01	0.011	0.015	0.018	0.026	0.035	0.035	0.047	0.061
40	160	**45**	<.01	<.01	0.012	0.012	0.017	0.022	0.027	0.038	0.051	0.051	0.069	0.089
40	**200**	**65**	<.01	<.01	0.010	0.010	0.013	0.017	0.021	0.029	0.040	0.039	0.053	0.069
40	200	**55**	<.01	0.010	0.013	0.013	0.018	0.023	0.029	0.041	0.054	0.054	0.073	0.095
40	200	**45**	0.010	0.015	0.020	0.020	0.027	0.035	0.042	0.059	0.080	0.079	0.107	0.137
40	**240**	**65**	<.01	0.010	0.014	0.014	0.019	0.025	0.030	0.042	0.057	0.057	0.077	0.099
40	240	**55**	0.010	0.014	0.019	0.019	0.026	0.034	0.041	0.058	0.078	0.078	0.105	0.135
40	240	**45**	0.015	0.021	0.028	0.028	0.038	0.050	0.061	0.085	0.114	0.113	0.151	0.193
50	**160**	**65**	<.01	0.013	0.017	0.017	0.023	0.030	0.025	0.036	0.049	0.048	0.065	0.085
50	160	**55**	0.011	0.016	0.021	0.021	0.028	0.037	0.031	0.044	0.060	0.059	0.080	0.104
50	160	**45**	0.014	0.020	0.027	0.027	0.037	0.048	0.040	0.057	0.076	0.076	0.102	0.131
50	**200**	**65**	0.012	0.017	0.023	0.023	0.031	0.041	0.034	0.049	0.065	0.065	0.088	0.113
50	200	**55**	0.015	0.021	0.028	0.028	0.038	0.050	0.042	0.060	0.080	0.079	0.107	0.138
50	200	**45**	0.019	0.027	0.036	0.036	0.049	0.064	0.054	0.076	0.102	0.101	0.135	0.174
50	**240**	**65**	0.015	0.022	0.029	0.029	0.040	0.052	0.044	0.062	0.083	0.082	0.111	0.142
50	240	**55**	0.019	0.027	0.036	0.036	0.049	0.064	0.054	0.076	0.101	0.101	0.135	0.173
50	240	**45**	0.024	0.035	0.046	0.046	0.063	0.081	0.069	0.097	0.128	0.128	0.170	0.217
60	**160**	**65**	0.030	0.042	0.056	0.056	0.076	0.098	0.062	0.087	0.116	0.116	0.154	0.197
60	160	**55**	0.033	0.047	0.063	0.063	0.084	0.109	0.069	0.097	0.129	0.129	0.171	0.218

Age	Total Cholesterol	HDL-Cholesterol	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.038	0.054	0.072	0.071	0.096	0.124	0.079	0.111	0.147	0.146	0.194	0.246
60	**200**	**65**	0.035	0.050	0.067	0.066	0.090	0.116	0.073	0.103	0.137	0.136	0.181	0.230
60	200	**55**	0.039	0.056	0.075	0.074	0.100	0.129	0.082	0.115	0.152	0.152	0.201	0.255
60	200	**45**	0.045	0.064	0.085	0.085	0.114	0.146	0.093	0.131	0.173	0.172	0.227	0.286
60	**240**	**65**	0.040	0.057	0.077	0.076	0.103	0.132	0.084	0.118	0.156	0.156	0.206	0.261
60	240	**55**	0.045	0.064	0.086	0.085	0.114	0.147	0.094	0.132	0.174	0.173	0.228	0.288
60	240	**45**	0.052	0.073	0.098	0.097	0.130	0.167	0.107	0.149	0.197	0.196	0.257	>.30
70	**160**	**65**	0.102	0.142	0.188	0.187	0.246	>.30	0.163	0.224	0.290	0.289	>.30	>.30
70	160	**55**	0.105	0.147	0.193	0.193	0.253	>.30	0.168	0.231	0.298	0.297	>.30	>.30
70	160	**45**	0.109	0.152	0.200	0.200	0.262	>.30	0.174	0.239	>.30	>.30	>.30	>.30
70	**200**	**65**	0.109	0.152	0.200	0.199	0.261	>.30	0.173	0.238	>.30	>.30	>.30	>.30
70	200	**55**	0.112	0.157	0.206	0.205	0.269	>.30	0.178	0.245	>.30	>.30	>.30	>.30
70	200	**45**	0.117	0.162	0.213	0.212	0.278	>.30	0.185	0.253	>.30	>.30	>.30	>.30
70	**240**	**65**	0.115	0.160	0.210	0.209	0.274	>.30	0.182	0.250	>.30	>.30	>.30	>.30
70	240	**55**	0.119	0.165	0.216	0.215	0.282	>.30	0.188	0.257	>.30	>.30	>.30	>.30
70	240	**45**	0.123	0.171	0.224	0.223	0.291	>.30	0.195	0.266	>.30	>.30	>.30	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 10a. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic African American Men Without Diabetes

Age	Total Cholesterol	HDL-Cholesterol	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	0.018	0.025	0.033	0.041	0.055	0.071	0.031	0.043	0.056	0.071	0.094	0.119
40	160	**55**	0.019	0.027	0.035	0.044	0.059	0.075	0.033	0.046	0.060	0.075	0.099	0.127
40	160	**45**	0.021	0.029	0.038	0.047	0.063	0.081	0.036	0.049	0.065	0.081	0.107	0.136
40	**200**	**65**	0.019	0.027	0.035	0.044	0.059	0.076	0.033	0.046	0.060	0.075	0.100	0.127
40	200	**55**	0.021	0.028	0.037	0.047	0.063	0.080	0.035	0.049	0.064	0.080	0.106	0.135
40	200	**45**	0.022	0.031	0.040	0.051	0.068	0.086	0.038	0.053	0.069	0.086	0.114	0.145
40	**240**	**65**	0.020	0.028	0.037	0.047	0.062	0.080	0.035	0.048	0.064	0.080	0.105	0.134
40	240	**55**	0.022	0.030	0.040	0.050	0.066	0.085	0.037	0.051	0.067	0.084	0.112	0.142
40	240	**45**	0.023	0.032	0.043	0.054	0.071	0.091	0.040	0.055	0.073	0.091	0.120	0.152
50	**160**	**65**	0.031	0.043	0.057	0.071	0.094	0.120	0.053	0.073	0.096	0.119	0.157	0.198
50	160	**55**	0.033	0.046	0.060	0.075	0.100	0.127	0.057	0.078	0.102	0.127	0.166	0.209
50	160	**45**	0.036	0.049	0.065	0.081	0.107	0.136	0.061	0.084	0.109	0.136	0.178	0.224
50	**200**	**65**	0.033	0.046	0.060	0.076	0.100	0.127	0.057	0.078	0.102	0.127	0.167	0.210
50	200	**55**	0.035	0.049	0.064	0.080	0.106	0.135	0.060	0.083	0.108	0.135	0.177	0.222
50	200	**45**	0.038	0.053	0.069	0.086	0.114	0.145	0.065	0.089	0.116	0.145	0.189	0.238
50	**240**	**65**	0.035	0.049	0.064	0.080	0.106	0.134	0.060	0.083	0.108	0.134	0.176	0.221
50	240	**55**	0.037	0.052	0.068	0.085	0.112	0.142	0.064	0.088	0.114	0.142	0.186	0.233
50	240	**45**	0.040	0.056	0.073	0.091	0.120	0.153	0.069	0.094	0.123	0.152	0.199	0.249
60	**160**	**65**	0.048	0.067	0.087	0.109	0.143	0.181	0.082	0.113	0.146	0.181	0.235	0.293
60	160	**55**	0.051	0.071	0.092	0.115	0.152	0.192	0.087	0.119	0.155	0.191	0.248	>.30

Age	Total Cholesterol	HDL-Cholesterol	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.055	0.076	0.100	0.124	0.163	0.205	0.094	0.128	0.166	0.205	0.265	>.30
60	**200**	**65**	0.052	0.071	0.093	0.116	0.153	0.193	0.088	0.120	0.156	0.192	0.249	>.30
60	200	**55**	0.055	0.076	0.099	0.123	0.162	0.203	0.093	0.127	0.165	0.203	0.263	>.30
60	200	**45**	0.059	0.081	0.106	0.132	0.173	0.218	0.100	0.137	0.176	0.217	0.281	>.30
60	**240**	**65**	0.055	0.075	0.098	0.122	0.161	0.202	0.093	0.126	0.164	0.202	0.261	>.30
60	240	**55**	0.058	0.080	0.104	0.129	0.170	0.214	0.098	0.134	0.173	0.213	0.276	>.30
60	240	**45**	0.062	0.086	0.112	0.139	0.182	0.229	0.106	0.144	0.185	0.228	0.294	>.30
70	**160**	**65**	0.070	0.096	0.125	0.155	0.203	0.254	0.118	0.160	0.206	0.253	>.30	>.30
70	160	**55**	0.074	0.102	0.132	0.164	0.214	0.267	0.125	0.170	0.218	0.267	>.30	>.30
70	160	**45**	0.080	0.110	0.142	0.176	0.229	0.285	0.135	0.182	0.233	0.285	>.30	>.30
70	**200**	**65**	0.075	0.102	0.133	0.165	0.215	0.269	0.126	0.171	0.219	0.268	>.30	>.30
70	200	**55**	0.079	0.109	0.141	0.175	0.227	0.283	0.133	0.180	0.231	0.283	>.30	>.30
70	200	**45**	0.085	0.117	0.151	0.187	0.243	>.30	0.143	0.193	0.247	>.30	>.30	>.30
70	**240**	**65**	0.079	0.108	0.140	0.174	0.226	0.282	0.133	0.179	0.230	0.281	>.30	>.30
70	240	**55**	0.084	0.114	0.148	0.183	0.238	0.297	0.140	0.190	0.243	0.296	>.30	>.30
70	240	**45**	0.090	0.123	0.159	0.197	0.255	>.30	0.151	0.203	0.259	>.30	>.30	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 10b. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic African American Men With Diabetes

Age	Total Cholesterol	HDL-Cholesterol	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	0.034	0.047	0.062	0.078	0.103	0.131	0.058	0.080	0.105	0.130	0.171	0.215
40	160	**55**	0.036	0.050	0.066	0.082	0.109	0.138	0.062	0.085	0.111	0.138	0.181	0.227
40	160	**45**	0.039	0.054	0.071	0.089	0.117	0.149	0.067	0.092	0.119	0.148	0.194	0.243
40	**200**	**65**	0.037	0.050	0.066	0.083	0.110	0.139	0.062	0.086	0.112	0.139	0.182	0.229
40	200	**55**	0.039	0.054	0.070	0.088	0.116	0.147	0.066	0.091	0.118	0.147	0.192	0.241
40	200	**45**	0.042	0.058	0.076	0.094	0.125	0.158	0.071	0.098	0.127	0.158	0.206	0.258
40	**240**	**65**	0.039	0.053	0.070	0.087	0.115	0.146	0.066	0.090	0.118	0.146	0.191	0.240
40	240	**55**	0.041	0.056	0.074	0.092	0.122	0.155	0.070	0.096	0.125	0.155	0.202	0.253
40	240	**45**	0.044	0.061	0.080	0.100	0.131	0.166	0.075	0.103	0.134	0.166	0.216	0.270
50	**160**	**65**	0.059	0.080	0.105	0.131	0.172	0.216	0.099	0.135	0.175	0.215	0.278	>.30
50	160	**55**	0.062	0.085	0.111	0.138	0.181	0.228	0.105	0.143	0.185	0.227	0.293	>.30
50	160	**45**	0.067	0.092	0.120	0.149	0.194	0.244	0.113	0.154	0.198	0.243	>.30	>.30
50	**200**	**65**	0.062	0.086	0.112	0.139	0.182	0.229	0.106	0.144	0.186	0.228	0.294	>.30
50	200	**55**	0.066	0.091	0.119	0.147	0.193	0.242	0.112	0.152	0.196	0.241	>.30	>.30
50	200	**45**	0.071	0.098	0.127	0.158	0.206	0.258	0.120	0.163	0.210	0.258	>.30	>.30
50	**240**	**65**	0.066	0.090	0.118	0.146	0.192	0.240	0.111	0.151	0.195	0.240	>.30	>.30
50	240	**55**	0.070	0.096	0.125	0.155	0.202	0.253	0.118	0.160	0.206	0.253	>.30	>.30
50	240	**45**	0.075	0.103	0.134	0.166	0.217	0.271	0.127	0.172	0.221	0.270	>.30	>.30
60	**160**	**65**	0.090	0.123	0.160	0.197	0.256	>.30	0.151	0.204	0.260	>.30	>.30	>.30
60	160	**55**	0.096	0.131	0.169	0.208	0.269	>.30	0.160	0.215	0.274	>.30	>.30	>.30

Age	Total Cholesterol	HDL-Cholesterol	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.103	0.140	0.181	0.223	0.288	>.30	0.172	0.230	0.292	>.30	>.30	>.30
60	**200**	**65**	0.096	0.131	0.170	0.209	0.271	>.30	0.161	0.216	0.275	>.30	>.30	>.30
60	200	**55**	0.102	0.139	0.180	0.221	0.285	>.30	0.170	0.228	0.290	>.30	>.30	>.30
60	200	**45**	0.110	0.149	0.192	0.237	>.30	>.30	0.182	0.244	>.30	>.30	>.30	>.30
60	**240**	**65**	0.101	0.138	0.178	0.220	0.284	>.30	0.169	0.227	0.288	>.30	>.30	>.30
60	240	**55**	0.108	0.146	0.189	0.232	0.299	>.30	0.179	0.240	>.30	>.30	>.30	>.30
60	240	**45**	0.116	0.157	0.202	0.248	>.30	>.30	0.192	0.256	>.30	>.30	>.30	>.30
70	**160**	**65**	0.129	0.175	0.225	0.275	>.30	>.30	0.213	0.284	>.30	>.30	>.30	>.30
70	160	**55**	0.137	0.185	0.237	0.290	>.30	>.30	0.225	0.299	>.30	>.30	>.30	>.30
70	160	**45**	0.147	0.198	0.253	>.30	>.30	>.30	0.241	>.30	>.30	>.30	>.30	>.30
70	**200**	**65**	0.138	0.186	0.238	0.291	>.30	>.30	0.226	0.300	>.30	>.30	>.30	>.30
70	200	**55**	0.146	0.197	0.251	>.30	>.30	>.30	0.239	>.30	>.30	>.30	>.30	>.30
70	200	**45**	0.156	0.211	0.269	>.30	>.30	>.30	0.255	>.30	>.30	>.30	>.30	>.30
70	**240**	**65**	0.145	0.196	0.250	>.30	>.30	>.30	0.237	>.30	>.30	>.30	>.30	>.30
70	240	**55**	0.153	0.207	0.264	>.30	>.30	>.30	0.250	>.30	>.30	>.30	>.30	>.30
70	240	**45**	0.165	0.221	0.281	>.30	>.30	>.30	0.267	>.30	>.30	>.30	>.30	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 11a. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic White Men Without Diabetes

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	<.01	<.01	<.01	<.01	<.01	0.011	0.013	0.018	0.024	0.022	0.028	0.036
40	160	**55**	<.01	<.01	0.010	<.01	0.011	0.014	0.018	0.025	0.032	0.029	0.038	0.048
40	160	**45**	<.01	0.011	0.014	0.012	0.016	0.021	0.026	0.035	0.046	0.041	0.054	0.068
40	**200**	**65**	<.01	<.01	0.011	0.010	0.013	0.017	0.021	0.029	0.038	0.034	0.044	0.056
40	200	**55**	<.01	0.012	0.015	0.014	0.018	0.023	0.028	0.038	0.050	0.045	0.059	0.074
40	200	**45**	0.012	0.017	0.022	0.019	0.026	0.032	0.040	0.055	0.072	0.064	0.084	0.105
40	**240**	**65**	<.01	0.012	0.016	0.015	0.019	0.024	0.030	0.041	0.054	0.048	0.063	0.080
40	240	**55**	0.012	0.017	0.022	0.019	0.026	0.032	0.040	0.055	0.072	0.064	0.084	0.105
40	240	**45**	0.017	0.024	0.031	0.028	0.037	0.047	0.058	0.079	0.102	0.091	0.119	0.149
50	**160**	**65**	0.015	0.020	0.027	0.024	0.031	0.040	0.033	0.046	0.059	0.053	0.069	0.087
50	160	**55**	0.018	0.025	0.033	0.029	0.039	0.049	0.041	0.056	0.073	0.065	0.085	0.107
50	160	**45**	0.024	0.033	0.043	0.038	0.050	0.064	0.053	0.073	0.094	0.085	0.110	0.138
50	**200**	**65**	0.020	0.028	0.037	0.033	0.043	0.054	0.045	0.062	0.081	0.072	0.094	0.118
50	200	**55**	0.025	0.035	0.045	0.040	0.053	0.067	0.056	0.076	0.099	0.089	0.116	0.144
50	200	**45**	0.033	0.045	0.059	0.052	0.069	0.086	0.073	0.099	0.128	0.115	0.148	0.185
50	**240**	**65**	0.026	0.036	0.047	0.042	0.055	0.070	0.059	0.080	0.103	0.093	0.121	0.151
50	240	**55**	0.033	0.045	0.058	0.052	0.068	0.086	0.072	0.098	0.127	0.114	0.147	0.183
50	240	**45**	0.042	0.058	0.075	0.068	0.088	0.111	0.093	0.126	0.162	0.146	0.188	0.233
60	**160**	**65**	0.043	0.059	0.076	0.069	0.089	0.112	0.069	0.094	0.121	0.109	0.141	0.176
60	160	**55**	0.050	0.068	0.088	0.079	0.103	0.129	0.080	0.108	0.140	0.126	0.162	0.202

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.060	0.081	0.105	0.095	0.123	0.154	0.095	0.129	0.166	0.150	0.192	0.238
60	**200**	**65**	0.053	0.072	0.094	0.084	0.109	0.137	0.085	0.115	0.148	0.133	0.172	0.213
60	200	**55**	0.061	0.083	0.108	0.097	0.126	0.157	0.098	0.132	0.170	0.153	0.196	0.243
60	200	**45**	0.073	0.100	0.129	0.116	0.150	0.186	0.116	0.157	0.201	0.181	0.232	0.285
60	**240**	**65**	0.062	0.085	0.110	0.099	0.128	0.160	0.100	0.135	0.173	0.156	0.200	0.248
60	240	**55**	0.072	0.098	0.127	0.114	0.148	0.184	0.115	0.155	0.198	0.179	0.229	0.281
60	240	**45**	0.086	0.117	0.151	0.136	0.175	0.217	0.137	0.184	0.234	0.212	0.269	>.30
70	**160**	**65**	0.104	0.140	0.180	0.162	0.208	0.256	0.126	0.170	0.217	0.196	0.250	>.30
70	160	**55**	0.113	0.153	0.196	0.177	0.226	0.278	0.138	0.185	0.236	0.213	0.271	>.30
70	160	**45**	0.127	0.170	0.217	0.197	0.251	>.30	0.154	0.206	0.261	0.237	0.300	>.30
70	**200**	**65**	0.116	0.156	0.200	0.180	0.231	0.284	0.141	0.189	0.241	0.218	0.277	>.30
70	200	**55**	0.127	0.170	0.217	0.197	0.251	>.30	0.154	0.206	0.261	0.237	0.300	>.30
70	200	**45**	0.142	0.190	0.241	0.218	0.278	>.30	0.172	0.229	0.289	0.262	>.30	>.30
70	**240**	**65**	0.127	0.171	0.218	0.197	0.251	>.30	0.154	0.206	0.262	0.237	0.300	>.30
70	240	**55**	0.139	0.186	0.237	0.214	0.273	>.30	0.168	0.225	0.284	0.258	>.30	>.30
70	240	**45**	0.155	0.207	0.263	0.238	>.30	>.30	0.188	0.249	>.30	0.285	>.30	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

Table 11b. Predicted Probability of Incident ASCVD Within 10 Years by Specific Combinations of Total Cholesterol, HDL-Cholesterol, Systolic Blood Pressure and Current Smoking for Non-Hispanic White Men With Diabetes

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
40	**160**	**65**	<.01	0.011	0.014	0.012	0.016	0.021	0.026	0.035	0.046	0.041	0.054	0.068
40	160	**55**	0.010	0.014	0.019	0.017	0.022	0.028	0.034	0.047	0.061	0.055	0.072	0.090
40	160	**45**	0.015	0.020	0.027	0.024	0.031	0.040	0.049	0.067	0.087	0.078	0.102	0.128
40	**200**	**65**	0.012	0.017	0.022	0.019	0.026	0.032	0.040	0.055	0.071	0.064	0.083	0.105
40	200	**55**	0.016	0.022	0.029	0.026	0.034	0.043	0.053	0.073	0.095	0.085	0.110	0.138
40	200	**45**	0.023	0.032	0.042	0.037	0.049	0.062	0.076	0.104	0.134	0.120	0.155	0.193
40	**240**	**65**	0.017	0.024	0.031	0.028	0.037	0.046	0.057	0.078	0.102	0.091	0.118	0.148
40	240	**55**	0.023	0.032	0.042	0.037	0.049	0.062	0.076	0.104	0.134	0.120	0.156	0.193
40	240	**45**	0.033	0.046	0.060	0.053	0.070	0.088	0.108	0.146	0.187	0.169	0.217	0.267
50	**160**	**65**	0.028	0.039	0.051	0.046	0.060	0.075	0.063	0.086	0.111	0.100	0.130	0.162
50	160	**55**	0.035	0.048	0.063	0.056	0.073	0.092	0.078	0.105	0.136	0.122	0.158	0.197
50	160	**45**	0.046	0.063	0.081	0.073	0.095	0.119	0.100	0.136	0.174	0.157	0.202	0.249
50	**200**	**65**	0.039	0.053	0.069	0.062	0.081	0.102	0.086	0.116	0.150	0.135	0.174	0.216
50	200	**55**	0.048	0.066	0.085	0.076	0.100	0.125	0.105	0.142	0.182	0.164	0.211	0.260
50	200	**45**	0.062	0.085	0.110	0.099	0.128	0.160	0.135	0.182	0.232	0.210	0.267	>.30
50	**240**	**65**	0.050	0.069	0.089	0.080	0.104	0.130	0.110	0.148	0.190	0.172	0.220	0.271
50	240	**55**	0.062	0.084	0.109	0.098	0.127	0.159	0.134	0.181	0.230	0.208	0.265	>.30
50	240	**45**	0.080	0.109	0.141	0.126	0.163	0.203	0.172	0.229	0.290	0.263	>.30	>.30
60	**160**	**65**	0.081	0.110	0.142	0.128	0.165	0.205	0.129	0.173	0.221	0.200	0.255	>.30
60	160	**55**	0.094	0.127	0.163	0.147	0.189	0.234	0.148	0.199	0.252	0.228	0.290	>.30

Age	Total Cholesterol	HDL-C	Current Smoking (No) Untreated Systolic: 100	Current Smoking (No) Untreated Systolic: 120	Current Smoking (No) Untreated Systolic: 140	Current Smoking (No) Treated Systolic: 120	Current Smoking (No) Treated Systolic: 140	Current Smoking (No) Treated Systolic: 160	Current Smoking (Yes) Untreated Systolic: 100	Current Smoking (Yes) Untreated Systolic: 120	Current Smoking (Yes) Untreated Systolic: 140	Current Smoking (Yes) Treated Systolic: 120	Current Smoking (Yes) Treated Systolic: 140	Current Smoking (Yes) Treated Systolic: 160
60	160	**45**	0.112	0.151	0.194	0.175	0.224	0.275	0.176	0.234	0.296	0.269	>.30	>.30
60	**200**	**65**	0.099	0.135	0.173	0.156	0.200	0.247	0.157	0.210	0.266	0.241	>.30	>.30
60	200	**55**	0.115	0.155	0.198	0.178	0.228	0.281	0.180	0.239	>.30	0.274	>.30	>.30
60	200	**45**	0.137	0.183	0.233	0.211	0.269	>.30	0.213	0.281	>.30	>.30	>.30	>.30
60	**240**	**65**	0.117	0.158	0.202	0.182	0.233	0.286	0.183	0.244	>.30	0.279	>.30	>.30
60	240	**55**	0.135	0.181	0.230	0.208	0.265	>.30	0.210	0.277	>.30	>.30	>.30	>.30
60	240	**45**	0.160	0.214	0.271	0.246	>.30	>.30	0.247	>.30	>.30	>.30	>.30	>.30
70	**160**	**65**	0.190	0.253	>.30	0.289	>.30	>.30	0.229	>.30	>.30	>.30	>.30	>.30
70	160	**55**	0.207	0.274	>.30	>.30	>.30	>.30	0.249	>.30	>.30	>.30	>.30	>.30
70	160	**45**	0.230	>.30	>.30	>.30	>.30	>.30	0.276	>.30	>.30	>.30	>.30	>.30
70	**200**	**65**	0.212	0.280	>.30	>.30	>.30	>.30	0.254	>.30	>.30	>.30	>.30	>.30
70	200	**55**	0.230	>.30	>.30	>.30	>.30	>.30	0.276	>.30	>.30	>.30	>.30	>.30
70	200	**45**	0.255	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
70	**240**	**65**	0.231	>.30	>.30	>.30	>.30	>.30	0.277	>.30	>.30	>.30	>.30	>.30
70	240	**55**	0.251	>.30	>.30	>.30	>.30	>.30	0.300	>.30	>.30	>.30	>.30	>.30
70	240	**45**	0.277	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30

Note: ASCVD = atherosclerotic cardiovascular disease; HDL-Cholesterol = high-density lipoprotein cholesterol.

The estimated risk probabilities shown are specific to defined combinations of risk factors, and the tables demonstrate how the estimated probabilities vary over a broad spectrum of potential profiles. Risk factor levels that are more adverse than those shown in the following tables should always be associated with a higher estimated risk. For example, if a given risk factor combination indicates a 10-year risk for hard ASCVD of 8 percent but a patient has a higher level of systolic blood pressure or total cholesterol or a lower level of HDL-47C than shown for that cell, then the estimated risk would be at least 8 percent. Because the estimated probabilities can become unstable when approaching the limits of the sample data, the risk probabilities are truncated at 1 percent and 30 percent.

The proportion of the U.S. adult population in selected strata of estimated 10-year risk for hard ASCVD are shown overall and by sex and race (table 12), and by sex and age group (table 13), by applying the risk equations to data from the most recent National Health and Nutrition Examination Surveys (NHANES, 2007–2010). Note that, at present, the risk equations apply most accurately to non-Hispanic Whites and African Americans. For Hispanics and other groups, the equations for Whites of the same sex were used, which may provide overestimation of risk for some groups (e.g., East Asian Americans) and underestimation in others (e.g., South Asian Americans).

Tables 14a–14c display a cross-tabulation of results from NHANES 2007–2010, using the same individuals ages 40 to 79, to show the different risk classification that is achieved using the ATP III 10-year risk assessment equations[1] for hard CHD (coronary death or nonfatal MI) as the end point, compared with use of the new 10-year risk equations with hard ASCVD as the end point. Overall, approximately two-thirds of individuals remain in the same estimated risk stratum with either approach. As can be seen, some individuals are up-classified by the new equations, meaning they are in a higher risk category using the new equations than using the older ATP III 10-year risk equations. Likewise, some individuals are down-classified using the newer risk equations. One might expect that most of the reclassification would have been upward given the expanded end point that includes stroke in addition to hard CHD. However, a number of issues lead to differential reclassification, indicating that simple multiplication of the older ATP III risk estimate would be an unreliable means for assessing risk under the new algorithm. For example, the new risk estimates are based on race- and sex-specific coefficients, which differ from the older ATP III coefficients. Furthermore, men tend to be at somewhat lower risk for stroke compared with CHD, whereas for women the opposite tends to be true. Down-classification in risk occurred among those younger than age 55, when stroke is at low risk, and also potentially due to secular changes in age at onset. Thus, when men are reclassified by the new equations, more tend to be down-classified, whereas women who are reclassified are more often up-classified. In addition, diabetes was considered a coronary risk equivalent in ATP III, so all individuals with diabetes were considered to be in the highest risk category in the ATP III algorithm.[1] In the new algorithm, individuals with diabetes may have a risk estimate of less than 10 percent.

Table 12. Distribution of 10-Year Risk for Hard ASCVD in the CVD-Free, Nonpregnant U.S. Population Ages 40 to 79 (NHANES 2007–2010), by Sex and Race (*N*=5,367, Weighted to 100,542,000 U.S. Population)

Group	<2.5%	2.5–4.9%	5.0–7.4%	Predicted 10-Year Risk for Hard ASCVD Event: 7.5–9.9%	Predicted 10-Year Risk for Hard ASCVD Event: 10.0–14.9%	Predicted 10-Year Risk for Hard ASCVD Event: 15.0–19.9%	Predicted 10-Year Risk for Hard ASCVD Event: ≥20.0%
Total People: % (95% CI)	33.4 (31.2-35.5)	21.0 (19.4-22.7)	12.7 (11.4-14.0)	7.4 (6.5-8.3)	8.9 (8.1-9.6)	6.3 (5.6-7.1)	10.2 (9.5-11.0)
Total People: *n*	33,534,000	21,151,000	12,766,000	7,470,000	8,940,000	6,380,000	10,300,000
Total Men: % (95% CI)	17.4 (15.2-19.7)	22.7 (20.3-25.1)	15.6 (13.8-17.4)	10.1 (8.5-11.6)	12.1 (10.7-13.5)	8.8 (7.4-10.2)	13.3 (12.1-14.4)
Total Men: *n*	8,386,000	10,950,000	7,511,000	4,847,000	5,849,000	4,248,000	6,388,000
Total Women: % (95% CI)	48.0 (44.8-51.3)	19.5 (17.3-21.6)	10.0 (8.3-11.8)	5.0 (3.8-6.2)	5.9 (5.1-6.7)	4.1 (3.4-4.7)	7.5 (6.5-8.4)
Total Women: *n*	25,148,000	10,200,000	5,256,000	2,622,000	3,091,000	2,131,000	3,912,000
White Men: % (95% CI)	18.0 (15.0-21.1)	22.4 (19.4-25.3)	15.7 (13.3-18.1)	10.0 (8.2-11.8)	11.7 (9.9-13.5)	8.7 (7.0-10.4)	13.6 (12.3-14.9)
White Men: *n*	6,467,000	8,016,000	5,616,000	3,584,000	4,189,000	3,112,000	4,870,000
White Women: % (95% CI)	47.1 (43.0-51.1)	20.4 (17.7-23.0)	10.7 (8.6-12.8)	5.1 (3.6-6.7)	5.5 (4.6-6.5)	4.1 (3.4-4.9)	7.1 (5.9-8.2)
White Women: *n*	18,175,000	7,863,000	4,136,000	1,984,000	2,132,000	1,596,000	2,725,000
African American Men: % (95% CI)	1.4 (0.3-2.6)	23.9 (19.9-28.0)	20.6 (17.0-24.2)	11.8 (8.8-14.8)	17.4 (14.3-20.5)	11.1 (8.2-13.9)	13.8 (11.0-16.7)
African American Men: *n*	60,000	1,008,000	866,000	495,000	731,000	466,000	583,000
African American Women: % (95% CI)	36.5 (32.4-40.6)	18.7 (15.6-21.8)	10.9 (8.6-13.2)	6.5 (5.0-7.9)	9.4 (7.2-11.7)	5.7 (4.2-7.2)	12.3 (9.5-15.0)
African American Women: *n*	1,921,000	985,000	572,000	339,000	496,000	300,000	645,000
Hispanic Men: % (95% CI)	24.0 (19.8-28.1)	22.1 (17.9-26.2)	13.2 (10.8-15.6)	10.6 (8.1-13.0)	11.4 (9.9-12.9)	6.2 (4.6-7.9)	12.6 (9.4-15.7)
Hispanic Men: *n*	1,303,000	1,200,000	718,000	574,000	619,000	339,000	683,000
Hispanic Women: % (95% CI)	59.4 (54.3-64.4)	14.5 (11.5-17.5)	7.5 (5.4-9.6)	4.5 (2.6-6.4)	4.9 (3.4-6.5)	3.0 (2.0-3.9)	6.3 (4.7-7.9)
Hispanic Women: *n*	3,293,000	803,000	418,000	248,000	273,000	164,000	347,000
Other Men: % (95% CI)	20.8 (10.8-30.7)	27.1 (18.0-36.3)	11.6 (4.9-18.2)	7.2 (0.6-13.8)	11.5 (4.5-18.6)	12.3 (5.9-18.8)	9.4 (3.0-15.8)
Other Men: *n*	555,000	726,000	310,000	193,000	309,000	330,000	251,000
Other Women: % (95% CI)	59.8 (50.2-69.3)	18.6 (10.8-26.5)	4.4 (0-8.7)	1.7 (0-3.5)	6.4 (2.1-10.7)	2.4 (0.4-4.5)	6.7 (2.3-11.0)
Other Women: *n*	1,757,000	548,000	128,000	49,000	188,000	71,000	195,000

Note: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey.

Table 13. Distribution of 10-Year Risk for Hard ASCVD in the CVD-Free, Nonpregnant U.S. Population Ages 40 to 79 (NHANES 2007–2010), Stratified by Age and Sex Groups (*N*=5,367, Weighted to 100,542,000 U.S. Population)

Group	10-Year Hard ASCVD Risk Estimate <2.5%, % (*n*)	10-Year Hard ASCVD Risk Estimate 2.5–4.9%, % (*n*)	10-Year Hard ASCVD Risk Estimate 5.0–7.4%, % (*n*)	10-Year Hard ASCVD Risk Estimate 7.5–9.9%, % (*n*)	10-Year Hard ASCVD Risk Estimate 10.0–14.9%, % (*n*)	10-Year Hard ASCVD Risk Estimate 15.0–19.9%, % (*n*)	10-Year Hard ASCVD Risk Estimate ≥20.0%, % (*n*)
Total: Age 40–50 (*n*=1,684, weighted to 37,263,000 U.S. pop.)	63.9 (23,812,000)	22.7 (8,473,000)	6.6 (2,480,000)	3.1 (1,164,000)	2.0 (746,000)	1.0 (378,000)	0.6 (209,000)
Men: Age 40–50 (*n*=1,684, weighted to 37,263,000 U.S. pop.)	42.7 (8,018,000)	35.4 (6,632,000)	10.6 (1,985,000)	5.4 (1,013,000)	3.4 (636,000)	1.8 (333,000)	0.7 (138,000)
Women: Age 40–50 (*n*=1,684, weighted to 37,263,000 U.S. pop.)	85.3 (15,794,000)	9.9 (1,840,000)	2.7 (495,000)	0.8 (150,000)	0.6 (110,000)	0.2 (45,000)	0.4 (71,000)
Total: Age 50–60 (*n*=1,435, weighted to 32,569,000 U.S. pop.)	28.5 (9,286,000)	28.8 (9,366,000)	19.3 (6,280,000)	9.4 (3,050,000)	8.1 (2,644,000)	4.1 (1,319,000)	1.9 (622,000)
Men: Age 50–60 (*n*=1,435, weighted to 32,569,000 U.S. pop.)	2.3 (368,000)	26.8 (4,278,000)	29.2 (4,648,000)	16.6 (2,643,000)	14.5 (2,317,000)	7.9 (1,253,000)	2.7 (434,000)
Women: Age 50–60 (*n*=1,435, weighted to 32,569,000 U.S. pop.)	53.6 (8,918,000)	30.6 (5,088,000)	9.8 (1,632,000)	2.4 (406,000)	2.0 (327,000)	0.4 (65,000)	1.1 (188,000)
Total: Age 60–70 (*n*=1,375, weighted to 19,927,000 U.S. pop.)	2.2 (436,000)	16.6 (3,312,000)	19.5 (3,894,000)	14.8 (2,953,000)	20.2 (4,027,000)	13.6 (2,704,000)	13.1 (2,602,000)
Men: Age 60–70 (*n*=1,375, weighted to 19,927,000 U.S. pop.)	0	0.4 (40,000)	9.7 (876,000)	13.1 (1,186,000)	28.9 (2,606,000)	24.5 (2,213,000)	23.3 (2,105,000)
Women: Age 60–70 (*n*=1,375, weighted to 19,927,000 U.S. pop.)	4.0 (436,000)	30.0 (3,272,000)	27.7 (3,017,000)	16.2 (1,767,000)	13.0 (1,421,000)	4.5 (490,000)	4.6 (497,000)
Total: Age 70–79 (*n*=873, weighted to 10,782,000 U.S. pop.)	0	0	1.0 (110,000)	2.8 (302,000)	14.1 (1,523,000)	18.4 (1,979,000)	63.7 (6,866,000)
Men: Age 70–79 (*n*=873, weighted to 10,782,000 U.S. pop.)	0	0	0	0.1 (5,000)	6.5 (291,000)	10.1 (449,000)	83.3 (3,710,000)
Women: Age 70–79 (*n*=873, weighted to 10,782,000 U.S. pop.)	0	0	1.8 (110,000)	4.7 (298,000)	19.5 (1,232,000)	24.2 (1,530,000)	49.9 (3,156,000)

Note: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey; U.S. pop. = U.S. population.

Table 14a. Distribution of 10-Year Risk for Hard CHD (Per ATP III Risk Equation) vs. 10-Year Risk for Hard ASCVD (Per NHLBI Risk Equations) in the Total CVD-Free, Nonpregnant U.S. Population Ages 40 to 79 (NHANES 2007–2010)

10-Year Risk for Hard CHD (ATP III)[1]	10-Year Risk for Hard ASCVD (NHLBI Equations) <5% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) 5.0–7.4% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) 7.5–9.9% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) ≥10.0% % of total *N* (*N*)	
0–< 5%	44.1 (44,310,000)	3.5 (3,540,000)	1.2 (1,184,000)	1.2 (1,200,000)	50.0% (50,236,000)
5–7.4%	6.3 (6,380,000)	3.0 (3,046,000)	0.9 (864,000)	1.8 (1,849,000)	12.1% (12,139,000)
7.5–9.9%	1.0 (1,043,000)	2.2 (2,211,000)	1.0 (1,031,000)	1.8 (1,847,000)	6.1% (6,132,000)
≥10% or DM	2.9 (2,951,000)	3.9 (3,969,000)	4.4 (4,390,000)	20.6 (20,724,000)	31.9% (32,035,000)
	54.4% (54,685,000)	12.7% (12,766,000)	7.4% (7,470,000)	25.5% (25,620,000)	

Note: ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; CVD = cardiovascular disease; DM = diabetes mellitus; NHANES = National Health and Nutrition Examination Survey.

Table 14b. Distribution of 10-Year Risk for Hard CHD (Per ATP III Risk Equation) vs. 10-Year Risk for Hard ASCVD (Per NHLBI Risk Equations) in the CVD-Free, U.S. Male Population Ages 40 to 79 (NHANES 2007–2010)

10-Year Risk for Hard CHD (ATP III)[1]	10-Year Risk for Hard ASCVD (NHLBI Equations) <5% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) 5.0–7.4% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) 7.5–9.9% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) ≥10.0% % of total *N* (*N*)	
0–< 5%	24.0 (11,535,000)	0.6 (296,000)	0.1 (24,000)	0	24.6% (11,855,000)
5–7.4%	11.8 (5,672,000)	4.2 (2,026,000)	0.4 (209,000)	0.1 (37,000)	16.5% (7,944,000)
7.5–9.9%	2.0 (960,000)	4.2 (2,003,000)	2.0 (967,000)	1.2 (561,000)	9.3% (4,491,000)
≥10% or DM	2.4 (1,169,000)	6.6 (3,186,000)	7.6 (3,647,000)	33.0 (15,887,000)	49.6% (23,889,000)
	40.1% (19,336,000)	15.6% (7,511,000)	10.1% (4,848,000)	34.2% (16,486,000)	

Note: ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; CVD = cardiovascular disease; DM = diabetes mellitus; NHANES = National Health and Nutrition Examination Survey.

Table 14c. Distribution of 10-Year Risk for Hard CHD (Per ATP III Risk Equation) vs. 10-Year Risk for Hard ASCVD(Per NHLBI Risk Equations) in the CVD-Free, Nonpregnant U.S. Female Population Ages 40 to 79 (NHANES 2007–2010)

10-Year Risk for Hard CHD (ATP III)[1]	10-Year Risk for Hard ASCVD (NHLBI Equations) <5% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) 5.0–7.4% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) 7.5–9.9% % of total *N* (*N*)	10-Year Risk for Hard ASCVD (NHLBI Equations) ≥10.0% % of total *N* (*N*)	
0–< 5%	62.6 (32,775,000)	6.2 (3,245,000)	2.2 (1,160,000)	2.3 (1,200,000)	73.3% (38,80,000)
5–7.4%	1.4 (709,000)	1.9 (1,020,000)	1.3 (655,000)	3.4 (1,811,000)	8.0% (4,195,000)
7.5–9.9%	0.2 (83,000)	0.4 (208,000)	0.1 (63,000)	2.4 (1,128,000)	3.1% (1,640,000)
≥10% or DM	3.4 (1,782,000)	1.5 (783,000)	1.4 (743,000)	9.2 (4,838,000)	15.6% (8,145,000)
	67.5% (35,349,000)	10.0% (5,256,000)	5.0% (2,622,000)	17.4% (9,134,000)	

Note: ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; CVD = cardiovascular disease; DM = diabetes mellitus; NHANES = National Health and Nutrition Examination Survey.

Section 2. Critical Questions

A. CQ1

CQ1:

What is the evidence regarding reclassification or contribution to risk assessment when high-sensitivity C-reactive protein, apolipoprotein B, glomerular filtration rate, microalbuminuria, family history, cardiorespiratory fitness, ankle-brachial index, coronary artery calcium score, or carotid intima-media thickness are considered in addition to the variables that are in the traditional risk scores?

The RAWG applied the PICOTSS paradigm to ensure that the CQ and the I/E criteria were well stated with regard to the seven PICOTSS dimensions. Following are the high-level elements of CQ1 that were assessed using PICOTSS (table B–1):

- **Population:** Adult primary prevention populations with no clinical manifestation of CVD
- Intervention/Assessment:
  - Total cholesterol, non-HDL-C, low-density lipoprotein cholesterol (LDL-C), or ApoB
  - HDL-C
  - Assessed smoking, diabetes, blood pressure level or hypertension, age, sex
  - Family history, hs-CRP, ApoB, microalbuminuria, GFR, cardiorespiratory fitness, CAC, CIMT, or ABI
- **Comparator:** Comparison to the variables that are in the traditional risk scores
- **Outcomes:** One or more of CVD mortality, fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for or death from arrhythmia; hospitalization for or death from CHF; composite CVD outcomes that include any of the previous outcomes
- **Timing:** Longer than 1year
- **Setting:** Any geographic location (single or multicenter); any clinical, diagnostic, or research setting
- **Study design:** Systematic reviews, prospective or retrospective cohort studies

Appendix B describes the PICOTSS analysis in more detail.

i. Selection of the I/E Criteria

In addition to using the PICOTSS analysis to refine the CQ, the RAWG used the analysis to refine the I/E criteria. In addition to the seven PICOTSS dimensions, the work group added criteria for:

- Measures of association: Quantitative assessment of model performance, such as relative risk (RR), *C*-statistic, reclassification, and model fit
- Language: Articles must be available in English text
- Publications: Published articles only

The final I/E criteria do not completely correspond to the PICOTSS analysis due to subsequent refinements. Table B–2 presents the detailed I/E criteria.

ii. Rationale for Selecting This CQ and I/E Criteria and Identifying Them as a Priority

The concept of matching the intensity of risk factor management to the estimated risk for CVD has been well established since at least the 27th Bethesda Conference in 1996.[12] As a consequence, great attention has been placed on the accuracy and reliability of risk assessment. The claim (subsequently disproved)[48] that only 50 percent of the risk for CVD can be explained by the major traditional risk factors has helped to stimulate and maintain interest in the search for new risk factors for CVD. Recently, a general CVD risk profile for use in primary care has been published that is associated with *C*-statistics of 0.763 in men and 0.793 in women.[19] As good as this level of discrimination is, the pursuit of even better risk prediction has sustained interest in identifying new risk markers that might enhance risk assessment.

This CQ was developed to address whether new risk markers have been identified that actually improve risk assessment enough to warrant routine measurement in clinical practice. This CQ is meant to apply to risk assessment in the general population; that is, the typical asymptomatic adult in routine clinical practice. This CQ does not address other highly selected patient subgroups, such as those with symptoms suggestive of CVD.

Members of the RAWG proposed new risk markers of potential interest, and the initial list was prioritized based on several rounds of discussion within the RAWG and with the Guidelines Executive Committee. In selecting the final list, the RAWG gave priority to factors that have engendered substantial discussion in the scientific community and that could be reasonably considered as potentially feasible for widespread population use by primary care providers in routine clinical settings in the United States. Issues of availability, cost, assay reliability, and risks of the test or downstream testing were considered in these deliberations. The final list of new risk markers to be evaluated by the RAWG included several blood and urine biomarkers (hs-CRP, ApoB, creatinine (or estimated GFR), and microalbuminuria), several measures of subclinical CVD (CAC, CIMT, and ABI), family history, and cardiorespiratory fitness. When considering the utility of incorporating these new risk factors into routine risk assessment, the RAWG was guided by the considerations published by Hlatky (2009)[41] shown in table 3.

The RAWG addressed this CQ using two independent approaches. First, the work group developed a risk prediction model (described above) for hard ASCVD using data from a multicohort database (Framingham Heart Study, Framingham Offspring Study, ARIC, CHS, and CARDIA) at NHLBI. In the process of developing the risk model, the additional new risk markers were tested for inclusion in the model if they were available in the databases and could be evaluated on the basis of at least 10 years of followup. Second, a review of meta-analyses and systematic reviews published before April 26, 2011, was conducted. Resources were not available to support de novo systematic reviews of the nine new risk factors; hence, individual original scientific reports were not evaluated. Pertinent published meta-analyses were examined, a general approach that was adopted across the workgroups and panels. The reliance on published meta-analyses to evaluate novel biomarkers is a conservative approach that helps avoid the influence of positive publication bias that can occur early in the evaluation of a novel association and assures that the work group relied on a mature body of evidence.

iii. Methods for CQ1

The RAWG identified and reviewed published systematic reviews and meta-analyses (see appendix B for more detail). These articles were screened according to the I/E criteria noted previously. Given the relatively small amount of detailed information reported for an overall systematic review or meta-analysis, in a few instances the articles might have contained a small number of individual studies that do not strictly conform to the individual CQ1 criteria. Formal evidence and summary tables were not constructed. Rather, the workgroup developed the "Systematic Review Evidence Conclusion" document shown in table B–3 for this purpose.

iv. Evidence Summaries

Summary Table for CQ1

Eight systematic review articles met the I/E criteria. Five were meta-analyses; one was an individual-level meta-analysis. Publication dates ranged from 2008 to 2011. Two of the articles were products of the Emerging Risk Factor Coalition Study and two were by the USPSTF.

Summary of Systematic Reviews and Meta-Analyses for CQ1

Formal evidence and summary tables were not generated for this CQ. The work group reviewed the eight systematic reviews and meta-analyses and created a table to list their key findings, as shown in table B–3. The following paragraphs summarize the available evidence for each of the nine novel risk markers considered.

hs-CRP

The work group was not able to evaluate hs-CRP in the risk prediction model development process due to the lack of data in the appropriate examination cycle of one or more of the studies. The work group examined several published systematic reviews pertinent to hs-CRP.

A review by Buckley et al., 2009, for the USPSTF provided evidence rated by the methodology staff as good quality.[49] This review focused on the potential risk related to CRP greater than 3.0 mg/L versus CRP less than 1.0 mg/L. The authors concluded the following:

> *Strong evidence indicates that CRP is associated with CHD events. Moderate, consistent evidence suggests that adding CRP to risk prediction models among initially intermediate-risk persons improves risk stratification. Few studies directly assessed the effect of CRP on risk reclassification in intermediate-risk persons.*[49]

No evidence was provided in the review pertinent to discrimination, calibration, net reclassification index, IDI, improvement in clinical outcomes, safety, or cost-effectiveness.

The 2009 USPSTF report on CRP and eight other risk factors authored by Helfand et al. provided evidence rated by the methodology staff as good quality.[50] The authors concluded the following:

> *The current evidence does not support the routine use of any of the nine risk factors for further risk stratification of intermediate-risk persons.*[50]

This report was based on the same evidence reviewed in more detail by the Buckley 2009paper[49] and provided no new evidence pertinent to this issue.

Kaptoge et al., 2010, published an individual-level meta-analysis pertinent to CRP under the auspices of the Emerging Risk Factor Collaboration.[51] This meta-analysis was rated by the methodology staff as fair quality evidence. The authors concluded the following:

> *CRP concentration has continuous associations with the risk for coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to such a range of disorders is unclear. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.*[51]

No evidence was provided in this meta-analysis pertinent to discrimination, calibration, net reclassification index, IDI, improvement in clinical outcomes, safety, or cost-effectiveness.

Schnell-Inderst et al., 2010, published a systematic review-based modeling evaluation of the utility of hs-CRP screening in asymptomatic adults.[52] This review was rated by the methodology staff as air quality evidence. The authors concluded the following:

> *Adding hs-CRP to traditional risk factors improves risk prediction, but the clinical relevance and cost-effectiveness of this improvement remain unclear.*[52]

The authors reported a small increase in the *C*-statistic from 0.00 to 0.027 and provided some evidence of cost-effectiveness in some modeling scenarios characterized by intermediate- and higher-risk populations and lower cost (generic) statins of at least moderate efficacy. Although the authors did not provide interpretation ranges for CRP, they quoted the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study[53] for high levels equal to or greater than 2 mg/L. This review provided no evidence pertinent to calibration, net reclassification improvement, IDI, or safety.

The RAWG concluded that this review provided evidence that hs-CRP is associated with risk independent of traditional risk factors and results in some net reclassification compared with models containing only traditional risk factors. The JUPITER trial[53] provides evidence that clinical outcomes can be influenced in those with CRP greater than 2 mg/L, but it did not evaluate the utility of CRP screening per se (because it did not include those with hs-CRP less than 2 mg/L). The Schnell-Inderst modeling exercise provides some evidence of cost-effectiveness in some risk subgroups.[52] The work group did not review evidence pertinent to calibration, net reclassification index, IDI, or safety, and the evidence it did review on improvement of clinical outcomes or cost-effectiveness was not applicable to the general population that composes the target population for this report.

The RAWG is aware of individual scientific reports evaluating the utility of hs-CRP that have provided evidence supporting the value of assessing hs-CRP. The RAWG encourages additional research on this risk marker, including attention to the considerations elaborated by Hlatky 2009[41] in studies evaluating the addition of hs-CRP to the new NHLBI risk equations in the context of updated prevention guideline recommendations and in representative populations, and when updating pertinent systematic reviews.

ApoB

The RAWG was not able to evaluate ApoB in the risk prediction model development process due to the lack of data in the appropriate examination cycle of one or more of the studies. The work group examined several published systematic reviews pertinent to ApoB. It is important to note that ApoB has most often been discussed as a substitute for total cholesterol, non-HDL-C, or LDL-C in risk assessment, rather than as an additional variable to be incorporated along with traditional lipid measurements in risk assessment. The RAWG did not need to evaluate the potential additional value of non-HDL-C to risk assessment because non-HDL-C is already in the traditional risk equation. The inclusion of total cholesterol and HDL cholesterol in a model is equivalent to the inclusion of total cholesterol and non-HDL-C. The only way that HDL-C can differ between two individuals with the same level of total cholesterol is if non-HDL-C also differs by an equivalent and offsetting amount.

Di Angelantonio et al., 2009, published an individual-level meta-analysis pertinent to ApoB under the auspices of the Emerging Risk Factor Collaboration.[54] This meta-analysis was rated by the methodology staff as fair quality evidence. The authors concluded that the associations of CVD with non-HDL-C and ApoB were roughly equivalent after full adjustment (including HDL-C). By inference, the RAWG concluded that this result means ApoB and total cholesterol also are roughly equivalent with similar full adjustment.

Sniderman et al., 2011, provided a study-level meta-analysis that focused on the question of whether ApoB was more strongly related to risk for CVD than either LDL-C or non-HDL-C.[55] This meta-analysis was rated by the

methodology staff as fair quality evidence. The authors concluded that ApoB was more strongly related to risk for CVD than was either non-HDL-C or LDL cholesterol in substitution models. By inference, the RAWG concluded that these results may mean that ApoB is more strongly related to risk than is total cholesterol. Whereas the relative risks evaluated in this meta-analysis were adjusted for some baseline covariates at the study level, the adjustments were judged by the RAWG to be incomplete, leaving substantial potential for residual confounding.

The RAWG is aware of individual scientific reports evaluating the utility of ApoB that have provided evidence supporting its value. However, little evidence was found from systematic reviews that directly assessed the considerations outlined by Hlatky 2009 (e.g., discrimination, calibration, net reclassification index, or IDI),[41] nor was the evidence reviewed on improvement of clinical outcomes or cost-effectiveness applicable to the general population. The RAWG encourages additional research on this marker, including attention to the considerations elaborated by Hlatky 2009,[41] in studies evaluating substitution of ApoB in the new NHLBI risk equations in the context of updated prevention guideline recommendations, in representative populations, and when updating pertinent systematic reviews.

CKD

The RAWG was able to examine moderate CKD (defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation[42]) in its risk prediction model development process. It is important to note that very few participants with CKD in this database had stage 4 or worse CKD. When added to the final base models, moderate CKD (eGFR<60 vs. ≥60) did not significantly improve model discrimination. The RAWG is aware of individual scientific reports evaluating the utility of incorporating information about CKD into risk assessment, but the work group found no pertinent systematic reviews. The RAWG encourages additional research on this marker, including attention to the considerations elaborated by Hlatky 2009,[41] in studies evaluating the addition of measures of CKD to the new risk equations in the context of updated prevention guideline recommendations, in representative populations, and when producing pertinent systematic reviews.

Microalbuminuria

The RAWG was not able to evaluate microalbuminuria (30 to 300 mg albumin/gm creatinine in urine) in the risk prediction model development process due to the lack of data in the appropriate examination cycle of one or more of the studies. The work group found no pertinent systematic reviews. The RAWG is aware of individual scientific reports evaluating the utility of incorporating information regarding microalbuminuria into risk assessment, especially for population subgroups, such as Native Americans and individuals with diabetes. The RAWG encourages additional research on this marker, including attention to the considerations elaborated by Hlatky 2009,[41] in studies evaluating the addition of albuminuria to the new risk equations in the context of updated prevention guideline recommendations, in representative populations, and when updating pertinent systematic reviews.

Family history of premature CVD

The RAWG was able to examine family history of premature CVD in its risk prediction model development process. Family history was defined in the ARIC, CARDIA, and Framingham Offspring studies as a parent with an MI before age 55 or a stroke before age 65 and in the CHS study as a sibling with an MI before age 55 or a stroke before age 65. When added to the final base models, family history did not significantly improve model discrimination. The RAWG is aware of individual scientific reports evaluating the utility of incorporating information about family history into risk assessment, but it found no pertinent systematic reviews.

Assessing family history of multiple medical conditions remains a best practice in clinical medicine. The RAWG encourages additional research on this characteristic, including attention to the considerations elaborated by Hlatky 2009,[41] in studies evaluating the addition of family history to the new NHLBI risk equations in the context of updated prevention guideline recommendations, in representative populations, and when producing pertinent systematic reviews.

Cardiorespiratory fitness

The RAWG was not able to evaluate cardiorespiratory fitness in the risk prediction model development process due to the lack of data in the appropriate examination cycle of one or more of the studies. The work group is aware of individual scientific reports evaluating the utility of incorporating information about cardiorespiratory fitness into risk assessment. The work group found one pertinent systematic review by Kodama et al., 2009.[56] In that review, better fitness was associated with a lower risk for all-cause mortality and CVD. In studies with complete adjustment for other risk factors, evidence of association was weak but still significant. Utility in risk prediction was not assessed in a comprehensive manner. That is, Kodama 2009 did not discuss discrimination, calibration, reclassification, or cost-effectiveness. The RAWG encourages additional research on this marker, including attention to the considerations elaborated by Hlatky 2009,[41] in studies evaluating the addition of cardiorespiratory fitness to the new NHLBI risk equations in the context of updated prevention guideline recommendations, in representative populations, and when producing pertinent systematic reviews.

ABI

The RAWG was not able to evaluate ABI in the risk prediction model development process due to lack of data in the appropriate examination cycle in one or more studies. The RAWG examined one meta-analysis on ABI for prediction, rated by the methodology staff as fair quality and an additional meta-analysis graded as good quality. In a meta-analysis by Fowkes et al., 2008,[57] 16 population cohort studies were included. During 480,325 person-years of followup of 24,955 men and 23,339 women, the risk for all-cause death had a reverse J-shaped distribution, with the group having a normal ABI of 1.11 to 1.40 at lowest risk for death. A J-shaped distribution was not observed for CVD death. The hazard ratio for 10-year CVD mortality in men with a low ABI (≤0.90) compared to men with normal ABI (1.11–1.40) was 4.2(95 percent confidence interval (CI): 3.3–5.4). The hazard ratio in women (low ABI vs. normal) was 3.5 (95 percent CI: 2.4–5.1). Overall, the FRS, as applied by the investigators, showed relatively poor discrimination in this meta-analysis, with *C*-statistics of 0.646 (95 percent CI: 0.643–0.657) in men and 0.605 (95 percent CI: 0.590–0.619) in women. When ABI was added to a model with FRS, the *C*-statistic improved in both men, 0.655 (95 percent CI: 0.643–0.666) and women, 0.658 (95 percent CI: 0.644–0.672). The improvement in the *C*-statistic was greater and significant in women but was not significant in men. ABI also was associated with significant risk reclassification when added to the FRS, and the pattern of reclassification was different by sex. Inclusion of ABI tended to down-classify higher risk men to lower risk groups. Among women, the addition of ABI tended to increase the predicted risk for women initially predicted to be at low risk. No evidence on calibration, net reclassification improvement, or cost-effectiveness was provided in this meta-analysis.[57]

The USPSTF performed systematic reviews of nine risk markers, including ABI.[50] ABI was associated with CHD and some reclassification, but it is uncertain how much and how valuable this reclassification is. Evidence suggests some improvement in discrimination, but the document provides little evidence about calibration and cost-effectiveness.

The RAWG concluded that ABI is associated with total CHD risk and leads to some reclassification and some improvement in discrimination for prediction of CHD (strength of evidence: Moderate). Nevertheless, there is insufficient evidence on calibration, net reclassification improvement, or cost of the screening strategy to determine whether routine assessment of ABI adds value to risk assessment for CVD events. The RAWG

encourages additional research on this characteristic, including attention to the considerations elaborated by Hlatky 2009.[41]

CAC

The RAWG was not able to evaluate CAC in the risk prediction model development process due to lack of data in several of the cohort studies. The work group examined the USPSTF systematic reviews of nine risk markers, one of which was CAC.[50] In this review of papers published before 2009, CAC was associated with CHD risk and with some reclassification, but it was unclear how much and how valuable this reclassification is. The document provides little evidence about discrimination, calibration, and cost-effectiveness. The RAWG also was concerned about radiation exposure,[58,59] and relatively limited information was available on how incidental findings from CAC testing are actually handled in routine clinical practice.[60-62]

The RAWG recognizes that individual study results have been published since 2009 and concludes that updated systematic reviews addressing discrimination, calibration, reclassification, cost, and safety issues in the context of the newer NHLBI risk equations are needed. The RAWG encourages additional research on this characteristic, including attention to the considerations elaborated by Hlatky 2009.[41]

CIMT by Ultrasound

The RAWG was not able to evaluate CIMT in the risk prediction model development process due to lack of data in several of the cohort studies. The RAWG examined the USPSTF systematic reviews of nine risk markers, one of which was CIMT.[50] In this review of papers published before 2009, CIMT was associated with CHD, but the USPSTF document provides little evidence about reclassification, discrimination, calibration, and cost-effectiveness. The RAWG also has concerns about measurement of CIMT. Specifically, standardization of CIMT measurement from laboratory to laboratory is a major challenge.[63] The RAWG recognizes that individual study results since 2009 have been published. Updated systematic reviews addressing discrimination, calibration, reclassification, cost, and measurement (standardization) issues in the context of the new risk equations are needed.

B. CQ2

CQ2:

Are models constructed to assess the long-term (≥15 years or lifetime) risk for a first CVD event in adults effective in assessing variation in long-term risk among adults at low and/or intermediate short-term risk, whether analyzed separately or combined? As described in appendix B, the draft version of CQ2, including I/E criteria, had an initial phrasing that was revised by the RAWG after additional discussion and deliberation and application of the PICOTSS framework.

The work group applied the PICOTSS paradigm to ensure that CQ2 and the I/E criteria were well stated with regard to the seven PICOTSS dimensions. Following are the high-level elements of CQ2 that were assessed using PICOTSS (table B–4):

- **Population:** Adults at low and/or intermediate short-term risk without CHD/CVD or CHD risk equivalents as defined by ATP III
- **Intervention/Assessment:** Short-term risk (defined as 5-year or 10-year risk estimate) assessed by a risk factor model with at least the following risk factors: age, sex, smoking, and either blood pressure measure or hypertension variable

- **Comparator:** Long-term (≥15 years or lifetime) risk models
- **Outcomes:** Risk for a first CVD event
- **Timing:** Minimum average followup of 15 years
- **Setting:** Any geographic location—single or multicenter
- **Study design:** Prospective or retrospective cohort studies, RCTs, or systematic reviews; appropriate statistical significance reporting

Appendix B describes the PICOTSS analysis in more detail.

i. Selection of the I/E Criteria

In addition to using the PICOTSS analysis to refine the CQ, the RAWG used the analysis to refine the I/E criteria. The work group added several criteria to the seven PICOTSS dimensions:

- **Study design:** Prospective or retrospective cohort studies, RCTs, or systematic reviews, appropriate statistical significance reporting
- **Measures of association:** Quantitative assessment of model performance, such as *C*-statistics and reclassification results
- **Language:** Articles must be available in English text
- **Publications:** Published studies and brief research communications with sufficient information

Table B–5 presents the detailed I/E criteria.

ii. Rationale for Selecting This CQ and I/E Criteria and Identifying Them as a Priority

As noted above, the most widely accepted current paradigm for preventing CVD was first described by the 27th Bethesda Conference in 1996.[12] The central concept is that, for a given patient or group, the intensity of prevention efforts (including lifestyle modification and pharmacologic therapy) should match the absolute risk for developing CHD or CVD. A number of U.S. and international guidelines[1,17,18] have adopted this perspective, which requires estimation of absolute risk levels, most often using multivariable equations derived from population-based cohorts to estimate short-term (5- or 10-year) predicted risk for development of CHD.

The ATP III[1] operationalized this concept by employing a modified version of the FRS to predict 10-year absolute risk for development of coronary death or nonfatal MI, so-called "hard CHD" events. These 10-year risk estimates were used (with or without first counting major traditional risk factors) in an algorithm to define thresholds of LDL-C for initiation of drug therapy and targets for LDL-C reduction on therapy. At the time, short-term (rather than long-term) risk estimates were deemed most useful in that they would help to identify individuals at highest risk in the near term, who were most likely to benefit from costly cholesterol-lowering therapies (i.e., branded statin medications) and in whom the cost-effectiveness and risk/benefit ratios would be most favorable. In addition, safety data about use of statin medications for longer than 5- to 10-years' duration were limited. Quantitative risk estimates have been used to guide decisions regarding lipid-lowering therapy, and the risk assessment approach also can be used to guide management of hypertension. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[2] adopted a less quantitative approach to risk assessment. Nevertheless, more intensive blood pressure treatment thresholds and goals were recommended for subgroups of patients at higher risk (e.g., patients with diabetes or CKD).

A number of studies have noted that younger men and most women may have low (e.g., <5 percent or 10 percent) predicted 10-year risks despite the presence of significant risk factor burden.[64-68] In part, this

observation is expected. Given the importance of age in the clinical appearance of ASCVD events and, hence, the generalized risk equations, it is unusual for younger individuals to exceed risk thresholds of 10 percent or 20 percent predicted risk, corresponding to treatment thresholds selected by several previous guidelines. However, extensive epidemiologic, pathologic, and basic science data indicate that the development of atherosclerosis—the precursor of ASCVD—occurs over decades and is related to long-term and cumulative exposure to causal, modifiable risk factors. Thus, a life course perspective to risk assessment and prevention must be considered, especially among younger individuals.

A consistent observation in a number of studies has been that individuals who have lower predicted 10-year risks may still be at very high risk for developing CHD or ASCVD in the long-term or over their remaining lifespan. Indeed, the Bethesda Conference[12] and ATP III[1] panels anticipated this issue by suggesting clinicians consider long-term and lifetime risk in addition to short-term risk estimates in evaluating patients and making decisions regarding intensity of prevention therapy.

In the past decade, novel means for considering long-term risk assessment for ASCVD (including use of life table methods and competing Cox models that account for the risk for CHD or ASCVD and also adjust for the competing risk for death from other causes) have increasingly been employed to assess long-term risk for ASCVD. Long-term risk assessment requires consideration of these competing risks because traditional survival methods (Kaplan-Meier analysis and standard Cox proportional hazards regression models) may overestimate long-term risks for ASCVD substantially, especially for younger individuals over the long term or when the competing risks from non-ASCVD death are high.

When posing this CQ, the RAWG did not anticipate that long-term or lifetime risk would replace 10-year risk assessment as the foundation for absolute risk assessment. Rather, longer-term risk estimates, if found to be useful, could provide adjunctive information for risk communication. This additional risk information could assist with treatment decisions for selected subgroups of patients at very high risk over the long term. The primary value of risk factor measurement and quantitative long-term risk estimation in younger adults is twofold: first, to identify risk in individuals with extreme values of risk factors (e.g., familial hypercholesterolemia); second, to provide risk information and context regarding the potential benefits of lifestyle modification.

The RAWG developed this CQ to assess the utility of long-term and lifetime risk assessment as an adjunct to short-term (10-year) risk assessment. The RAWG recognized that there is little "disconnect" regarding approaches to prevention when the 10-year risk estimate is high (e.g., >10 percent predicted 10-year risk); such patients clearly merit intensive prevention efforts and should be considered for drug therapy to reduce or modify adverse levels of causal risk factors. The RAWG selected this CQ for evaluation to determine whether quantitative or semi-quantitative long-term risk assessment would provide differential information that could be useful in risk communication, specifically to patients estimated to be at lower short-term risk. However, it has been unclear what the long-term predicted and observed risks for CHD and ASCVD are among individuals who are at low predicted 10-year risk. This CQ was designed to identify studies that assessed both short- and long-term risk, particularly focusing on those studies that provide long-term outcomes data for groups predicted to be at low 10-year risk. If a sufficiently large proportion of the population is at high long-term risk despite being at low short-term risk, then incorporating long-term risk assessment into routine clinical practice might have value for informing risk conversations with patients and guiding therapeutic lifestyle counseling and other aspects of care.

iii. Methods for CQ2

All of the CQ2 articles were original research publications and did not include systematic reviews or meta-analyses because none were identified (see appendix B for more detail). The methods used to summarize these studies in evidence and summary tables are described in appendix A. Because the articles often used different techniques for summarizing results, the work group judged it more useful to primarily present summary text statements in the tables rather than comparing summary statistics.

iv. Evidence Summaries

Summary Table for CQ2

Table B–6 shows the Risk Assessment CQ2 Summary Table.

Summary Text for CQ2

Ten articles met the CQ2 I/E criteria. Publication dates ranged from 1999 to 2009. Five of these articles reported results from the Framingham Heart Study. Average ages of participants were as young as their late thirties, although many studies did not report overall mean ages. Followup times ranged from 23 to 35 years. All of the studies were observational, which is consistent with the data requirements of the statistical modeling approach for risk assessment.

v. Evidence Statements for CQ2

The following evidence statements are derived solely from studies that met I/E criteria for CQ2 and reflect the findings from these studies. All of the studies were considered in developing the evidence statements and recommendations, although some were deemed by the RAWG to be more or less relevant to the CQ. Because of the nature of this CQ, all evidence is derived from observational studies. Therefore, although there may be consistent, reproducible evidence from large, well-designed studies, the highest grade of evidence possible is "moderate," given that randomized clinical trial data are not appropriate to answer this CQ.

ES1. **No evidence assessing variations in long-term or lifetime risk for CVD outcomes among persons at low or intermediate short-term risk in race/ethnic groups other than non-Hispanic Whites in the United States and Europe was found.**

ES2. **Traditional CVD risk factors measured in young and middle-aged adults, considered singly or jointly, generally are associated with short-term (≤10 years), long-term (≥15 years), and lifetime risk for CVD.**

Strength of evidence: ***Low (for diabetes and metabolic syndrome) to Moderate (for BMI, cholesterol, systolic blood pressure, and smoking)***

It is important to note that the strength of evidence assignments provided above are based on the evidence reviewed that was pertinent to CQ2 and do not reflect the totality of the available evidence regarding risk factor associations. In the included studies, diabetes was associated with both short-term and longer-term CVD risk (strength of evidence: Low). Berry et al., 2008, examined 33-year followup in 16,608 participants of the Chicago Heart Association Detection Project in Industry (CHA Study) ages 40 to 59 at baseline.[69] Compared to participants of the same sex without diabetes at the baseline examination, men with diabetes consistently had approximately twofold elevations in risk for death occurring between 0 to 10 years, between 10 and 20 years, and with >20 years' followup. Women with diabetes had a nearly fourfold increased hazard for CVD death in the short term (<10 years); relative hazards remained significant but decreased to 1.6 for events occurring after >20 years' followup.[69] Data from the FHS indicate that diabetes is associated with the highest lifetime risk for

any single CVD risk factor. Remaining lifetime risks for ASCVD events through age 75 in men and women with diabetes who are age 50 were 67.1 percent and 57.3 percent, respectively, compared with 30.2 percent and 16.3 percent for men and women who do not have diabetes.[70] Clear differences were seen in cumulative risks for ASCVD between those with and without diabetes in the short term (<10 years), and differences increased over time. Metabolic syndrome does not add additional utility beyond traditional risk factors in short- and long-term multivariable CVD risk estimation (strength of evidence: Low).[71]

BMI or categorical obesity is not associated independently with short-term CVD risk but is generally associated with long-term or lifetime risk even after adjustment for major traditional risk factors (strength of evidence: Moderate). There was a significant trend of increasing risk for CVD death, with greater duration of followup associated with higher baseline BMI among middle-aged men in the CHA Study.[69] For women, the independent risks associated with higher baseline BMI were similar across 0 to 10, 10 to 20, and greater than 20 years' followup, but they became significant only with CVD deaths occurring after greater than 20 years' followup. In a similar analysis of 14,403 men ages 40 to 49 by Håheim et al., 2007,[72] baseline BMI was not significantly associated with fatal CHD events occurring before 15 years of followup but was associated with fatal CHD events occurring 16 to 21 years after baseline. In another similarly designed analysis of 1,622 men followed for CHD death for up to 35 years, BMI was not significantly associated with CHD death during any 5-year followup interval. Data from the FHS including younger and middle-aged adults confirm the association of higher BMI with increased 30-year (but not short-term) risk for hard CVD events and associations of overweight and obesity with higher lifetime risks for ASCVD events, even after considering competing outcomes of non-CVD death.[70,73]

Total cholesterol is associated with short-term, long-term, and lifetime CVD risk (strength of evidence: Moderate). All three studies that examined baseline total cholesterol levels in association with fatal CVD events found generally consistent associations without evidence for trend in the magnitude of effect of total cholesterol levels across different followup intervals.[69,72,74] Pencina et al., 2009,[73] and Lloyd-Jones et al., 2006[70] also observed associations of total cholesterol levels with 30-year competing risks and lifetime risks for CVD events using Framingham data.

In all of the identified studies, SBP is associated with short-term, long-term, and lifetime CVD risk (strength of evidence: Moderate). The association of baseline SBP with ASCVD events remains significant during all followup intervals[69,72,74] and in the context of 30-year competing risks for CVD as well as lifetime risk for CVD in Men and women.[70,73]

Current smoking is consistently associated with short-term and longer-term CVD risk (strength of evidence: Moderate). As expected, baseline current smoking is associated with CVD events throughout diverse followup intervals.[69,72,75] In a 30-year competing Cox model analysis, current smoking at baseline was associated with approximately a twofold greater risk for CVD events over 30 years.[73] Remaining lifetime risks for ASCVD were similar for smokers and nonsmokers among men and women ages 50 through 95. However, smokers had CVD events at substantially younger ages and substantially shorter median survival compared with nonsmokers, who survived longer and had their CVD events much later in life.[70]

The above studies generally considered the individual associations of risk factors across different followup time intervals but also tended to perform multivariable adjustment for other risk factors or stratify by aggregate risk factor burden. These findings suggest the need for continued clinical screening efforts for these short-term and long-term modifiable risk factors.

ES3. Multivariable short-term (10-year) CHD risk prediction models underestimate absolute lifetime risk for CHD but may stratify relative lifetime risk for CHD in women and older men.*

Strength of evidence: ***Low***

* CHD is defined as all manifestations of CHD, or as CHD death/nonfatal MI

The Framingham investigators[76] examined the ability of the FRS[28]—designed to predict 10-year risk for CHD—to predict observed levels of lifetime risk for CHD. As expected, 10-year predicted risks were substantially lower than observed lifetime risks, especially for younger men and women. At older ages (70 or 80), as remaining lifespan approached 10 years, predicted 10-year risks were more similar to observed lifetime risks. When participants were stratified into tertiles based on their 10-year predicted risks, the Framingham 10-year CHD risk score did stratify relative CHD lifetime risk fairly well for women at all ages. For example, for 40-year-old women in the lowest, middle, and highest tertiles of predicted 10-year CHD risk, the remaining lifetime risks for CHD through age 84 were 12.2 percent, 25.4 percent, and 33.2 percent, respectively. Ten-year predicted CHD risks stratified remaining lifetime risks less well in younger men: At age 40, lifetime risks through age 84 were 38.4 percent, 41.7 percent, and 50.7 percent, respectively. Overall, there were 1.5-fold to 3.0-fold gradients in lifetime risk across FRS tertiles among younger women and 1.2-fold to 1.3-fold gradients in younger men.

Thus, the RAWG judged that 10-year risk estimates do not serve as a reliable estimate of absolute lifetime risk for CVD for younger men and women and they may not adequately represent the full spectrum of risk information regarding CHD. Likewise, the RAWG had limited confidence that younger individuals, particularly younger men, with lower predicted 10-year risks would consistently "track" in the lower strata of risk over the long term. This lack of tracking may be due to changes in risk factor profiles with aging or due to the influence of competing risks.[76]

ES4. Long-term (30-year) risk equations based on traditional risk factors* provide more accurate prediction of long-term ASCVD† risk than do extrapolations of short-term (10-year) risk equations among individuals ages 20 to 59 free from ASCVD.

Strength of evidence: ***Low***

* Age, sex, total and HDL-C, SBP, use of antihypertensive therapy, diabetes, current smoking
† CHD death, nonfatal MI, or fatal/nonfatal stroke; or all ASCVD

An important question addressed by the included studies is whether extrapolation of 10-year risk equations provides the same estimate of absolute long-term risk as models designed specifically to predict long-term risk. Pencina 2009 addressed this question in their study estimating 30-year competing risks for CVD.[73] They compared the results of 30-year risk estimates obtained by diverse methods: (1) tripling a 10-year risk estimate ("naïve approach"); (2) estimating three separate models based on the baseline age, age plus 10 years, and age plus 20 years, maintaining the same risk factor levels in all three models ("combined approach"), and calculating the 30-year risk as 1 minus the product of these three 10-year probabilities; (3) a 30-year risk estimate not accounting for competing risks ("unadjusted approach"); and (4) a 30-year risk estimate accounting for competing risks ("adjusted approach"). The naïve approach of tripling the 10-year risk estimate consistently underestimated observed 30-year risks. As expected, the unadjusted approach overestimated 30-year risks somewhat, given that it does not account for competing risks that would constrain CVD rates. Estimates from the combined approach tended to be the highest, although correlation with the adjusted approach was unpredictable and varied with risk factor burden. Thus, the adjusted approach provided the most appropriate and reliable estimates of 30-year risk.[73]

On the basis of the evidence reviewed (for Evidence Statements 3 and 4), long-term or lifetime risk estimation models adjusting for competing causes of mortality are more valid than is extrapolation of results from 10-year risk equations.

ES5. The presence and severity of traditional CVD risk factors* stratify absolute levels of lifetime risk for ASCVD† among non-Hispanic White adults ages 45 to 50 who are free of ASCVD and not at high short-term risk.

Strength of evidence: ***Low***

* Risk factors were considered in five mutually exclusive strata encompassing the full spectrum of risk levels as follows: (1) two or more major risk factors (defined as total cholesterol ≥240 mg/dL or treated, SBP ≥160 or DBP ≥100 mmHg or treated, or diabetes, or current smoking); (2) one major risk factor only; (3) one or more elevated risk factors (defined as untreated total cholesterol 200 to 239 mg/dL, or untreated SBP 140 to 159 or DBP 90 to 99 mmHg, and no diabetes and no current smoking); (4) one or more risk factors at nonoptimal levels (untreated total cholesterol 180 to 199 mg/dL, or untreated SBP 120 to 139 or DBP 80 to 89 mmHg, and no diabetes and no current smoking); and (5) all optimal levels of risk factors (defined as untreated total cholesterol <180 mg/dL, and untreated BP <120/<80 mmHg, and no diabetes, and no current smoking).

† CHD death, MI, coronary insufficiency, angina, fatal/nonfatal atherothrombotic stroke, claudication, other CVD death

Participants in the FHS were stratified by their aggregate risk factor burden at ages 45 to 50, and the remaining lifetime risk for ASCVD was evaluated.[70] The data allowed for comparisons of short- and long-term risks by aggregate risk factor burden. In the Lloyd-Jones et al., 2006, paper, the following prevalences and short-term and lifetime risks were noted for the selected strata of aggregate risk factor burden in non-Hispanic White men and women in Framingham:

- Approximately 20 percent had two or more major traditional risk factors, with an average 10-year ASCVD risk for 10 to 25 percent and an average lifetime risk for ASCVD exceeding 50 percent.
- Approximately 40 percent had one major traditional risk factor, with an average 10-year ASCVD risk ofapproximately10 percent and an average lifetime risk for ASCVD of 39 to 50 percent.
- Approximately 23 percent had one or more elevated traditional risk factors, with an average 10-year ASCVD risk of approximately 5 percent and an average lifetime risk for ASCVD of 39 to 46 percent.
- Approximately 12 percent had nonoptimal levels of traditional ASCVD risk factors, with an average10-year ASCVD risk of less than 5 percent and an average lifetime risk for ASCVD of 27 to 36 percent.
- Approximately 4 percent had optimal levels of all traditional ASCVD risk factors, with an average 10-year ASCVD risk of less than 5 percent and lifetime risk for ASCVD of less than 10 percent.[70]

The RAWG reviewed another study that was not included in the 10 manuscripts for the evidence base for CQ2 because it did not include observed lifetime risk outcomes. It did include predicted lifetime risks, and the report merits some discussion. In this study, Marma et al., 2010,[65] examined the nationally representative sample from NHANES 2003–2006 and predicted 10-year risks using the ATP III risk estimator for hard CHD and the updated general risk score for total CVD published by D'Agostino et al., 2008.[19] Lifetime risk was estimated using the algorithm (discussed immediately above) developed in the FHS and subsequently validated in other studies. Marma 2010 stratified participants into three groups: (1) those with low 10-year (<10 percent)/low lifetime (<39 percent) predicted risk; (2) those with low 10-year (<10 percent)/high lifetime (≥39 percent) predicted risk; and (3) those with high 10-year (≥10 percent) predicted risk or diagnosed diabetes. Overall, 82 percent of U.S. adults had low 10-year predicted risk for hard CHD. However, most of those with low 10-year CHD risk had a high lifetime risk for ASCVD (56 percent, or 87 million individuals). A further 18 percent (28 million individuals) had high short-term predicted risk. The addition of lifetime risk estimation to 10-year risk estimation identified large subgroups of women and younger men in particular as being at low short-term but high lifetime risk.[65] Thus, although this study did not include observed outcomes, the magnitude

of predicted short-term and lifetime risks differed substantially for the majority of individuals with 10-year risk of less than 10 percent.

ES6. Long-term (≥15 years) risk prediction models based on traditional risk factors* predict CHD death with good discrimination and calibration, and better in women than men, in U.S. non-Hispanic White populations.

Strength of evidence: ***Low***

* Age, sex, total cholesterol, SBP, diabetes, smoking

Liao et al., 1999, created risk-prediction models for CHD death using short-term traditional risk factors as covariates for 15 to 24 years' followup in the Framingham Heart Study and NHANES I and NHANES II mortality followup cohorts.[77] When applied to the same cohorts from which they were derived, or to the other cohorts, the models had similar ability to rank-order risk (discrimination), with *C*-statistics of 0.71 to 0.75 for men and 0.76 to 0.81 for women. The Framingham equations for women predicted CHD death rates well (were well calibrated) for women in the NHANES I and II cohorts; the Framingham equations tended to over predict 15-year risk for men somewhat.[77]

ES7. Measuring and updating ASCVD risk factors every 4 to 6 years improves short- and long-term risk prediction.

Strength of evidence: ***Moderate***

Using FHS data, Karp et al., 2004,[78] sought to compare the predictive utility of risk equations based on covariates updated at intervals rather than on single baseline measurements, and to establish the optimal frequency of updating. They used two approaches to examine risk estimates for 10-, 14- and 30-year followup for all CHD events: a "prognostic" approach, using current (baseline) and/or subsequent risk covariate measures, and a "lagged" approach, which incorporated baseline and earlier examination data at different intervals to attempt to optimize model fit. In brief, they found that assessment of short-term coronary risk was improved by using updated risk factor values to calculate the multivariable risk score. Whereas the optimal frequency and utility of updating varied somewhat across subgroups, they suggest that updating risk factor values every 6 years led to the best predictive utilities.[78]

In the aforementioned Pencina 2009 study[73] from Framingham that generated 30-year risk competing risk prediction models for hard CVD events, the authors compared the results of models using baseline levels of covariates alone with models using time-dependent covariates for the risk factors, with updating of values every 4 years. For some of the risk factors, the hazard ratios associated with 30-year CVD events were similar whether baseline or time-dependent covariates were used. However, the association was stronger for smoking and weaker for BMI when 4-year risk factor updating was used.[73]

Taken together, these findings suggest that, in the context of short-term and long-term risk assessment, use of updated covariate values, rather than single baseline long-term values, may enhance validity.

Research Gaps

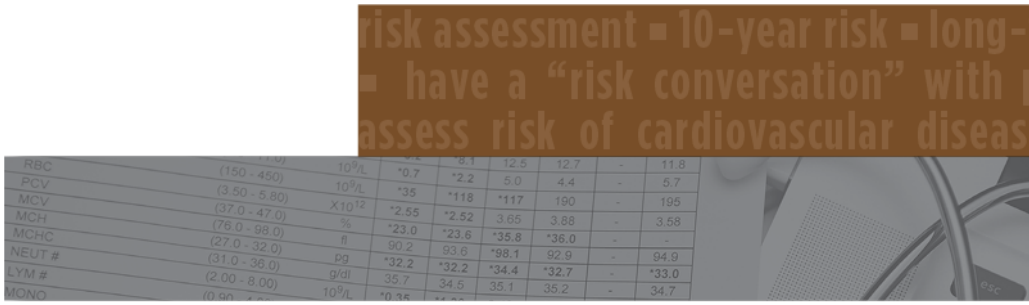
The RAWG strongly recommends continued research to fill gaps in knowledge regarding short- and long-term ASCVD risk assessment and outcomes in all race/ethnic groups, across the age spectrum, and in women and men. Future research should include analyses of:

- Short- and long-term risk in diverse groups
- Optimal communication of ASCVD risk information
- Utility of short-and long-term risk assessment for motivating behavioral change and adherence to therapy
- Utility of short-and long-term risk assessment for influencing risk factor levels and clinical outcomes
- Utility of differential information conveyed by short- and long-term risk assessment
- Utility of novel risk markers in short- and long-term risk assessment

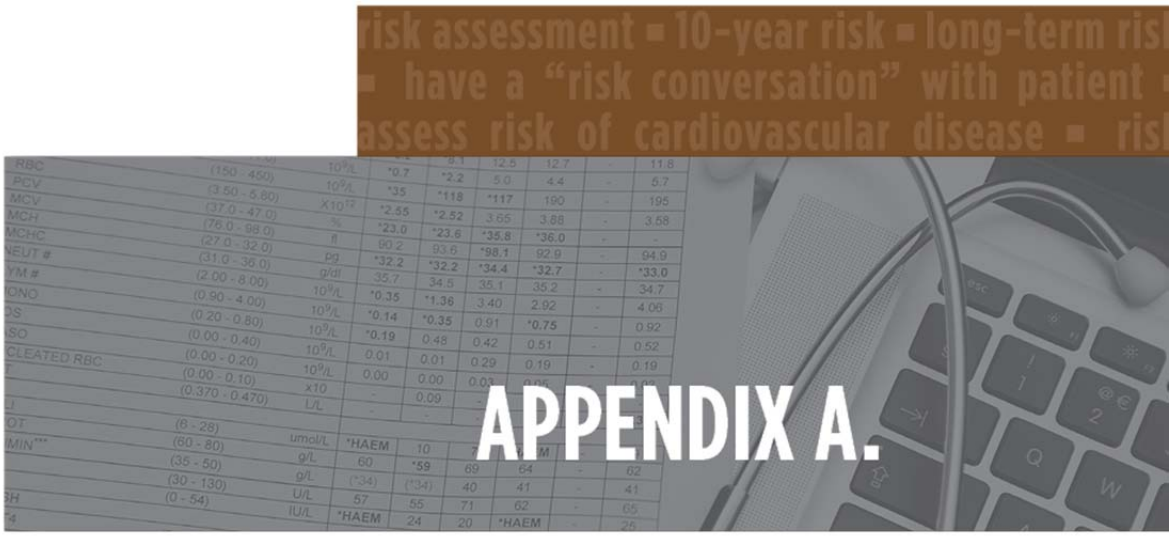
Section 3. Abbreviations and Acronyms

ABI	ankle-brachial index
AMI	acute myocardial infarction
ApoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
ATP III	Adult Treatment Panel III
ATP IV	Adult Treatment Panel IV
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcium
CHD	coronary heart disease
CHF	congestive heart failure
CHO	carbohydrate
CI	confidence interval
CIMT	carotid artery intima-media thickness
CKD	chronic kidney disease
CQ	critical question
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
ES	evidence statement
FRS	Framingham Risk Score
GFR	glomerular filtration rate
GLIA	GuideLine Implementability Appraisal
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
IDI	integrated discrimination improvement index
I/E	inclusion/exclusion
IOM	Institute of Medicine
ITT	intent-to-treat
LDL-C	low-density lipoprotein cholesterol
MeSH	Medical Subject Headings
MI	myocardial infarction
NHANES	National Health and Nutrition Examination Surveys
NHLBI	National Heart, Lung, and Blood Institute
PICOTSS	population, intervention/exposure, comparison group, outcome, time, setting, study design

RCT	randomized controlled trial
RAWG	Risk Assessment Work Group
SBP	systolic blood pressure
TG	triglycerides
VCW	virtual collaborative Workspace
USPSTF	U.S. Preventive Services Task Force


risk assessment ▪ 10-year risk ▪ long-
▪ have a “risk conversation” with
assess risk of cardiovascular diseas

Appendixes



APPENDIX A.

Detailed Methods Applying to All Critical Questions

Appendix A. Detailed Methods Applying to All Critical Questions

i. Description of How Expert Panel Members Were Selected

NHLBI initiated a public call for nominations for panel membership to ensure adequate representation of key specialties and stakeholders and appropriate expertise among expert panel and work group members. A nomination form was posted on NHLBI's Web site for several weeks and distributed to a guidelines leadership group that had given advice to NHLBI on its guideline efforts. Information from nomination forms, including contact information and areas of clinical and research expertise was entered into a database.

After the close of the call for nominations, NHLBI staff reviewed the database and selected a potential chair and co-chair for each expert panel and work group. The potential chairs and co-chairs provided to NHLBI conflict of interest disclosures and a copy of their curriculum vitae. NHLBI's Ethics Office reviewed the disclosures and cleared or rejected persons being considered as chairs and co-chairs. The selected chairs were then formed into a Guidelines Executive Committee, which worked with NHLBI to select panel members from the list of nominees. Beginning in September 2011, the GEC set up its own approach to manage relationships with industry and other potential conflicts of interest (see http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm).

NHLBI received 440 nominations for potential panel members with appropriate expertise for the task. Panel selection focused on creating a diverse and balanced composition of members. Panel members were selected based on their expertise in the specific topic area (e.g., high BP, high blood cholesterol, obesity) as well as in such specific disciplines as primary care, nursing, pharmacology, nutrition, exercise, behavioral science, epidemiology, clinical trials, research methodology, evidence-based medicine, guideline development, guideline implementation, systems of care, or informatics. The panels also included, as voting ex officio members, senior scientific staff from NHLBI and other Institutes from the National Institutes of Health who are recognized experts in the topics under consideration.

ii. Description of How Expert Panels Developed and Prioritized Critical Questions

After panels were convened, members were invited to submit topic areas or questions for systematic review. Members were asked to identify topics of the greatest relevance and impact for the target audience of the guideline, primary care providers.

Proposed questions and topic areas were collected from panel members over a period of several months. The number of CQs was scoped, and questions were prioritized based on available resources. After group discussion, panel members ranked priority CQs through a combination of collaborative dialogue and voting. The rationale for each priority CQ is addressed in the sections on CQ1 and CQ2.

With support from the methodologist and systematic review team, priority CQs were formulated. I/E criteria were defined and formatted using the PICOTSS framework. PICOTSS is a framework for a structured research question. It includes the following components in the statement of the CQ or in the question's I/E criteria:

P person, population
I intervention, exposure
C comparator
O outcome
T timing
S setting
S study design

I/E criteria define the parameters for the selection of literature for a particular CQ. I/E criteria were developed with help from the methodologist and systematic review team to ensure that criteria were clear and precise and could be applied consistently across literature identified in the search.

The final CQs and criteria were submitted to the literature search team for search strategy development.

iii. Literature Search Infrastructure, Search Strategy Development, and Validation

The literature search was performed using an integrated suite of search engines that explored a central repository of citations and full-text journal articles. The central repository, search engines, search results, and Web-based modules for literature screening and data abstraction were integrated within a technology platform called the Virtual Collaborative Workspace (VCW). The VCW was custom-developed for NHLBI's guidelines initiative.

The central repository consisted of 1.9 million citations and 71,000 full-text articles related to CVD risk reduction. Citations were acquired from several databases: PubMed, Embase, CINAHL®, Cochrane, PsycINFO®, Wilson Science, and Biological Abstracts®. Literature searches were conducted using a collection of search engines, including TeraText®, Content Analyst, Collexis, and Lucene. The first three engines were used for executing search strategies, and Lucene was used to correlate the search with literature screening results.

For every CQ, the literature search and screening were conducted according to the understanding of the question and the I/E criteria that provided specific characteristics of studies relevant to the question. Criteria were framed in the PICOTSS format, and the question and PICOTSS components were translated into a search strategy involving Boolean and conceptual queries.

A Boolean query encodes both inclusion and exclusion rules. It grants access to the maximum quantity of citations, which are then analyzed by text analytics tools and ranked to produce a selection for literature screening. Two independent reviewers conducted this screening in the VCW's Web-based module. Boolean queries select citations by matching words in titles and abstracts as well as medical subject headings (MeSH) and subheadings. The number of citations resulting from Boolean queries has ranged from a few hundred to several thousand, depending on the question. The text analytics tools suite included:

- A natural language processing module for automated extraction of data elements to support the application of I/E criteria. Frequently extracted and utilized data elements were study size and intervention followup period.
- Content Analyst for automatically expanding vocabulary of queries, conceptual retrieval, and conceptual clustering. The conceptual query engine employed in Content Analyst leverages word frequency features and co-occurrence in similar contexts to index, select, and rank results. The indexing uses the singular value decomposition (SVD) algebraic method.
- TeraText for ranking search results and executing operations on literature collections.

Search strategy development was intertwined with the results of literature screening, which provided feedback on search quality and context. Screened literature was categorized into two subsets: relevant or not relevant to the question. Next, results were analyzed to determine the characteristics of relevant versus not relevant citations. Additional keywords and MeSH terms were used to expand or contract the scope of the query as driven by characteristics of relevant citations. If the revised search strategy produced citations that did not undergo the

screening process, then a new batch of citations was added for review. The search strategy refinement/literature review cycle was repeated until all citations covered by the most recent Boolean query had been screened.

Each search strategy was developed and implemented in the VCW. The search strategy was reviewed by the methodologist and panel members and was available for viewing and printing at any time by panel members and staff collaborating on the systematic review. It was available for execution and for supplying literature updates until the literature search and screening cut-off date.

Search strategies for a sample of questions were validated by an independent methodology team. This validation process involved developing and executing a separate search strategy and screening a random sample of citations against I/E criteria. These results were compared with the search and screening results developed by the systematic review team. As an additional validation method, studies identified in systematic reviews and meta-analyses were cross-checked against a CQ's "include" list to ensure completeness of the search strategy.

iv. Process for Literature Review

Using results of the search strategy, criteria were applied to screen literature for inclusion or exclusion in the evidence base for the CQ. I/E criteria address the parameters in the PICOTSS framework and determine what types of studies are eligible and appropriate to answer the CQ. Additional criteria, such as sample size restrictions, were included by the panel to fit the context of the CQ.

a. Pilot Literature Screening Mode

In the pilot literature screening mode, two reviewers independently screened the first 50 titles/abstracts in the search strategy results by applying I/E criteria. Reviewers voted to include or exclude the publication for full-text review. Reviewers compared their results to ensure that I/E criteria were applied consistently. Discrepancies in votes were discussed, and clarification on criteria was sought from the panel when appropriate. For example, if criteria were not specific enough to be clearly applied to include or exclude a citation, then guidance was sought to word criteria more explicitly.

During this phase, reviewers provided feedback to the literature search team about the relevance of search strategy results; this feedback was used to further refine and optimize the search.

Phase 1: Title and Abstract Screening Phase

After completing the pilot mode phase, two reviewers independently screened search results at the title and abstract levels by applying I/E criteria. Reviewers voted to include or exclude the publication for full-text review.

Titles and abstracts that one or both reviewers voted to include advanced to phase 2, full-text screening. Titles and abstracts that both reviewers voted to exclude were excluded and not reviewed further; these citations are maintained in the VCW and marked as "excluded at title/abstract phase."

Phase 2: Full-Text Screening Phase

Titles and abstracts that at least one reviewer voted to include were reviewed at the full-text level in phase 2. In this phase, two reviewers independently applied I/E criteria to the full-text article and voted for "include," "exclude," or "undecided." The reviewer had to specify the rationale for exclusion (e.g., population, intervention, etc.) in this phase.

Articles that both reviewers voted to include were moved to the "include" list. Articles that both reviewers voted to exclude were moved to the "exclude" list; these citations were maintained in the VCW and identified as "excluded at the full article phase," and the rationale for exclusion was noted. Any article with discrepant votes (i.e., one include and one undecided, one include and one exclude) advanced to phase 3.

Phase 3: Resolution and Consultation Phase

In this phase, reviewers discussed their vote for "include," "exclude," or "undecided" and cited the relevant criteria for their decision. The two reviewers attempted to achieve consensus through collaborative discussion. If a decision was not reached between the two reviewers, input was sought from the methodologist. If a decision was not reached after consultation with the methodologist, then input was sought from the panel; however, the methodologist had the final decision. The final disposition of the article ("include" or "exclude") was recorded in the VCW along with comments from the adjudication process.

Similarly to search strategies being posted and available for viewing on the VCW, all citations screened for a CQ were maintained in the VCW with their reviewer voting status and all collected comments.

v. Description of Methods for Quality Assessment of Individual Studies

The methodology team assessed the quality (internal validity) of all studies meeting the I/E criteria after the three-phase literature review process. Separate quality rating tools were used for each study design.

a. Design of the Quality Assessment Tools

Appraisal of individual study quality was based on six quality assessment tools developed jointly by NHLBI and the methodology team. The tools were based on quality assessment methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers, the Cochrane Collaborative, the USPSTF, the National Health Service Centre for Reviews and Dissemination, as well as consulting epidemiologists and others working in evidence-based medicine, with adaptations by methodology and NHLBI staff for this project.

The tools were designed to assist reviewers in focusing on concepts that are key for critical appraisal of the internal validity of a study. The tools were not designed to provide a list of factors comprising a numeric score. The tools were specific to individual types of included study designs and are described in more detail below.

The tools included items for evaluating potential flaws in study methods or implementation, including sources of bias (e.g., patient selection, performance, attrition, and detection), confounding, study power, the strength of causality in the association between interventions and outcomes, and other factors. Quality reviewers could select "yes," "no," or "cannot determine (CD)/not reported (NR)/not applicable (NA)" in response to each item in the tool. For each item where "no" was selected, reviewers were instructed to consider the potential risk of bias that could be introduced by that flaw in the study design or implementation. CD and NR also were noted as representing potential flaws.

Each of the six quality assessment tools has a detailed guidance document (except for the tool for case series studies), which was also developed by the methodology team and NHLBI. The guidance documents are specific to each tool and provided detailed descriptions and examples about how to apply the items, as well as justifications for including each item. For some items, examples were provided to clarify the intent of the question and the appropriate rater response. The four quality assessment tools and guidance documents used in this evidence review are included in tables A–1 through A–4 below.

b. Significance of the Quality Ratings of Good, Fair, or Poor

Reviewers used the study ratings on the range of items included in each tool to judge each study to be of "good," "fair," or "poor" quality. The ratings on the different items were used by the reviewers to assess the risk of bias in the study due to flaws in study design or implementation.

In general terms, a "good" study has the least risk of bias and results are considered to be valid. A "fair" study is susceptible to some bias deemed not sufficient to invalidate its results. The fair quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses.

A "poor" rating indicates significant risk of bias. Studies rated poor were excluded from the body of evidence to be considered for each CQ. The only exception to this policy was if there was no other evidence available, then poor quality studies could be considered. However, this exception was not applied in this project because no situations occurred in which only poor quality studies were available for a body of evidence for a particular CQ.

c. Training for Application of the Quality Assessment Tools

The methodology team conducted a series of training sessions on the use of four of the quality assessment tools. Initial training consisted of two 2-day, in-person training sessions. Reviewers trained in the quality rating were master's or doctorate-level staff with a background in public health or health sciences. Training sessions provided instruction on identifying the correct study designs, the theory behind evidence-based research and quality assessment, explanations and rationales for the items in each tool, and methods for achieving overall judgments regarding quality ratings of "good," "fair," or "poor." Participants engaged in interactive evaluation of multiple example articles, both with the instructors and during group work. Reviewers also were instructed to refer to related articles on study methods if such papers were cited in the articles being rated.

Following the in-person training sessions, the methodology team assigned several articles with pertinent study designs to test the abilities of each reviewer. The reviewers were asked to individually identify the correct study design, complete the appropriate quality assessment tool, and submit it to the methodology team for grading against a methodologist-developed key. A second round of training sessions was then conducted by telephone to review the results and resolve any remaining misinterpretations. Based on the results of these evaluations, a third round of exercises and training sessions was sometimes convened.

d. Quality Assessment Process

For all studies except for systematic reviews and meta-analyses, each article that met the CQ's inclusion criteria was rated independently for quality by two reviewers using the appropriate tool. If the ratings differed, the reviewers discussed the article in an effort to reach consensus. When consensus was not achieved, the article was forwarded to a methodologist for quality adjudication.

Quality rating of systematic reviews and meta-analyses was performed independently by two methodologists. If ratings differed, then the reviewers discussed the article in an effort to reach consensus. When consensus was not achieved, the article was forwarded to a third methodologist for adjudication.

Panel members could appeal the quality of a particular study or publication after the initial rating was reported to the panel members. However, to enhance the objectivity of the quality rating process, the final decision on quality ratings was made by the methodology team, and not by panel members.

vi. Quality Assessment Tool for Controlled Intervention Studies

The quality assessment tool for controlled intervention studies is included in table A–1. The guidance document for that tool is also included in table A–1. This tool was developed by the methodology team and NHLBI based in part on criteria from the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers, the USPSTF, and the National Health Service Centre for Reviews and Dissemination.

This tool addresses 14 elements of quality assessment. They include randomization and allocation concealment, similarity of compared groups at baseline, use of intent-to-treat analysis (i.e., analysis of all randomized patients

even if some were lost to followup), adequacy of blinding, the overall percentage of subjects lost to followup, the differential rates of loss to followup between the intervention and control groups, and other factors.

Table A–1. Quality Assessment Tool for Controlled Intervention Studies

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?			
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			
4. Were study participants and providers blinded to treatment group assignment?			
5. Were the people assessing the outcomes blinded to the participants' group assignments?			
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?			
7. Was the overall dropout rate from the study at its endpoint 20% or less than the number originally allocated to treatment?			
8. Was the differential drop-out rate between groups at the study's endpoint 15% or less?			
9. Was there high adherence to the intervention protocols for each treatment group?			
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			
14. Were all randomized participants analyzed in the group to which they were originally assigned (i.e., did they use an intention-to-treat analysis)?			

Quality Rating (Good, Fair, Poor) (see guidance):
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

Note: CD = cannot determine; NA = not applicable; NR = not reported.

vii. Guidance for Assessing the Quality of Controlled Intervention Studies

The guidance document below is organized by question number from the tool for quality assessment of controlled intervention studies.

Question 1. Described as randomized

Literally, was the study described as randomized? A study does not satisfy quality criteria as randomized simply because the authors call it *randomized*. But as a first step, did the authors of the study say it was randomized?

Questions 2 and 3. Treatment Allocation—two interrelated pieces

- Adequate randomization: The randomization is adequate if it occurred according to the play of chance (e.g., computer-generated sequence in more recent studies, or random number table in older studies).

Inadequate randomization: "Randomization" is inadequate if there is a preset plan (e.g., alternation where every other subject is assigned to treatment arm or another method of allocation is used such as time or day of hospital admission or clinic visit, ZIP Code, phone number, etc.). In fact, this is not randomization at all—it is another method of assignment to groups. If assignment is not by the play of chance then the answer is *no*.

There may be some tricky scenarios that will require careful reading and consideration for the role of chance in assignment. For example, sites are randomized to receive treatment or not so all individuals at the site are thereby assigned to a treatment group. This scenario is used for group-randomized trials, which can be truly randomized, but often are "quasi-experimental" studies with comparison groups rather than true control groups. (Few, if any, group-randomized trials are anticipated in this evidence review.)

Allocation concealment: This means that one does not know in advance, or cannot guess accurately, to what group the next person eligible for randomization will be assigned. Methods include sequentially numbered opaque sealed envelopes, numbered or coded containers, central randomization by a coordinating center, computer-generated randomization that is not revealed ahead of time, etc.

Questions 4 and 5. Blinding

Blinding means that one does not know to which group—intervention or control—the participant is assigned. It is also sometimes called "masking." You are looking to see if each of the following is blinded to knowledge of treatment assignment: (1) the person assessing the primary outcome(s) for the study (e.g., taking the measurements, examining medical records to determine type of event as in an adjudication committee, etc.); (2) the person receiving the intervention (e.g., the patient or volunteer participant); and (3) the person providing the intervention (e.g., the physician, nurse, or behavioral interventionist).

Generally placebo-controlled medication studies are blinded to patient, provider, and outcome assessors; behavioral or lifestyle studies may often be blinded only to the outcome assessors. Sometimes the person providing the intervention is the same person doing the outcome assessment. If so, make note of it in your comments section.

Question 6. Similarity of groups at baseline

This question relates to whether the intervention and control groups have similar characteristics on average. The whole point of doing a randomized trial is to create similar groups to enable valid comparisons of intervention effects between groups. If there is a significant difference, you should see it when you abstract baseline characteristics. Baseline characteristics for intervention groups are usually presented in a table in the article (often Table 1).

Groups can differ at baseline without raising red flags if: (1) the differences would not be expected to have any bearing on the interventions and outcomes; or (2) the differences are not statistically significant. If you have any concerns about baseline difference in the groups, write them down in the comments section and consider them in your overall determination of the study quality.

Questions 7 and 8. Dropout

Here "dropout" means participants for whom there are no endpoint measurements—the most common reason being that they dropped out of the study (for whatever reason) and were lost to followup.

Generally, an acceptable overall dropout rate is considered 20 percent or less of participants who were randomized or allocated into each group, and an acceptable *differential dropout* is considered an absolute difference between groups of 15 percentage points at most (calculated by subtracting the dropout rate of one group minus the dropout rate of the other group). However, these are general rates. Higher overall dropout rates may be acceptable. If you are conducting a systematic review on comparative efficacy of antidepressants, then setting the cap at 20 percent for overall dropout makes sense. On the other hand, if you are looking at joint space narrowing for targeted immune modulators, you may be able to raise the cap for what you define as an overall acceptable dropout rate. Studies comparing targeted immune modulators for this outcome are going to be of longer duration which means dropouts are more likely. This is the kind of thing that should be decided by the experts for your systematic review. It may or may not be the same cap for all expert panels for NHLBI's systematic reviews.

Differential dropout, however, is not flexible. Stick with the 15 percent cap. If you have a differential dropout rate of 15 percent or higher between arms, then you have serious potential for bias and this constitutes a fatal flaw resulting in a *poor* quality rating for the study.

Question 9. Adherence

Did participants in each treatment group adhere to the protocols for assigned interventions? For example, if Group 1 was assigned to 10 mg/day of Drug A, did most of them take 10 mg/day of Drug A? Another example is a study evaluating the difference between a 30-pound weight loss and a 10-pound weight loss on specific clinical outcomes (e.g., heart attacks), but the 30-pound weight loss group did not achieve its intended weight loss target. A third example is whether a large percentage of participants assigned to one group "crossed over" and got the intervention provided to the other group. A final example is when one group that was assigned to receive a particular drug at a particular dose had a large percentage of participants who did not end up taking the drug or the dose as designed in the protocol.

Question 10. Avoid other interventions

Changes that occur in the study outcomes being assessed should be attributable to the interventions being compared in the study. If participants in any of the groups receive other interventions that are not part of the study protocol and that could affect the outcomes being assessed, and they receive these interventions differentially, there is cause for concern, as it could bias the results. For example, if a study is comparing two different dietary interventions on serum cholesterol, but one of the groups had a significantly higher percentage of participants taking statin drugs, it could unduly influence the results of the study because you would not know whether the difference in outcome was due to the dietary intervention or the drugs.

Question 11. Outcome measures assessment

What tools or methods were used to measure outcomes in the study? Were the tools/methods accurate and reliable—for example, have they been validated, or are they objective? This is important because it indicates the confidence you can have in the reported outcomes. Perhaps even more important is whether the outcomes

were assessed in the same manner within groups and between groups. One example is that a self-report of dietary salt intake is not as valid and reliable as testing urine for sodium content. Another example is measurement of BP that only uses clinicians' usual measurement approaches rather than measurers being trained on a standard approach using the same instrument and taking BP multiple times. In each of these cases, the question would get a "no" for the former and a "yes" for the latter scenario. Another example of a "no" is when an intervention group is seen much more often, enabling more opportunities to report clinical events, than the control group.

Question 12. Power calculation

Generally, a paragraph in the methods section of the study will explain sample size needed to detect differences in primary outcomes. The current standard is at least 80 percent power to detect a clinically relevant difference in an outcome using a two-sided alpha of 0.05. Often, however, older studies will not report anything about power.

Question 13. Prespecified outcomes

Outcomes reported in the study must have been prespecified in order to be hypothesis testing, which is the whole purpose of doing a RCT. If they are not prespecified, then the study may be reporting ad hoc analyses, simply looking for differences that support the findings they wanted. In addition to outcomes, the subgroups being examined should be prespecified in order to be considered hypothesis testing. Most RCTs conduct numerous post-hoc analyses as a way of exploring findings and generating additional hypotheses. The intent of this question is to give more weight to reports that are not simply exploratory in nature.

Question 14. Intent-to-treat (ITT) analysis

ITT means everybody who was randomized is analyzed according to the original group to which they are assigned. This is an extremely important concept, because doing an ITT analysis preserves the reason for doing a randomized trial—that is, to compare groups that differ only in the intervention being tested. Once the ITT analysis philosophy is not followed, you are not really sure that the main reason for doing an RCT is upheld because the groups being compared may no longer be the same. If a study does not use an ITT analysis, it should probably be rated as "poor." However, if some other analysis is used and you think it is valid, explain that in the "other" box of the quality review form. Some studies will use a *completers analysis* (which analyzes only the participants that completed the intervention and the study); this introduces significant potential for bias. Characteristics of participants who do not complete the study are unlikely to be the same as those who do. The likely impact of participants who withdraw from the study treatment must be considered carefully. ITT analysis provides a more conservative (and potentially less biased) estimate of effectiveness.

General guidance for determining the overall quality rating

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity is the extent to which the results (effects) reported in a study can truly be attributed to the intervention being evaluated and not to flaws in the design or conduct of the study—in other words, the ability for the study to make causal conclusions about the effects of the intervention being tested. Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk for potential for allocation bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other. Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above). High potential for risk of bias translates to a rating of poor quality. Low potential for risk of bias translates to a rating of good quality. (Again, the greater the risk of bias, the lower the quality rating of the study.)

Fatal flaws: If a study has a "fatal flaw," then the risk of bias is significant and the study is of poor quality. Examples of fatal flaws in RCTs include high dropout, high differential dropout, no ITT analysis or unsuitable statistical analysis (e.g., completers-only analysis).

Generally, when you evaluate a study, you will not see a fatal flaw, but you will find some risk of bias. By focusing on the concepts underlying the questions in the tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask what the potential for bias is as a result. That is, does this factor cause you to doubt the results that are reported in the study?

Although some background reading on critical appraisal can be provided for you, the best approach is for you to think about the questions in the tool and how each tells you something about the potential for bias for any study. It is not advisable to give you general rules as each study has nuances. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal.

Some examples of studies that fall into each of the categories good, fair, and poor will be provided to you. But again, these will be examples. Each study must be assessed on its own given the details that are reported.

viii. Quality Assessment Tool for Systematic Reviews and Meta-Analyses

The quality assessment tool for systematic reviews and meta-analyses is included in table A–2. The guidance document for that tool is also included in table A–2. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers and the Cochrane Collaborative.

This tool addresses eight elements of quality assessment. They include use of prespecified eligibility criteria, use of a comprehensive and systematic literature search process, dual review for abstracts and full-text articles, quality assessment of individual studies, assessment of publication bias, and other factors.

Table A–2. Quality Assessment Tool for Systematic Reviews and Meta-Analyses

Criteria	Yes	No	Other (CD, NR, NA)
1. Is the review based on a focused question that is adequately formulated and described?			
2. Were eligibility criteria for included and excluded studies predefined and specified?			
3. Did the literature search strategy use a comprehensive, systematic approach?			
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?			
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?			
6. Were the included studies listed along with important characteristics and results of each study?			
7. Was publication bias assessed?			
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)			

Quality Rating (Good, Fair, or Poor):
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

Note: CD = cannot determine; NA = not applicable; NR = not reported.

A systematic review is a study that attempts to answer a question by synthesizing the results of primary studies using strategies to limit bias and random error.[79] These strategies include a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles included in the review. Research designs and study characteristics are appraised, data are synthesized, and results are interpreted using a predefined systematic approach that adheres to evidence-based methodological principles.

Systematic reviews can be qualitative or quantitative. A qualitative systematic review summarizes the results of the primary studies but does not combine the results statistically. A quantitative systematic review, or *meta-analysis*, is a type of systematic review that employs statistical techniques to combine the results of the different studies into a single pooled estimate of effect, often given as an odds ratio.

ix. Guidance for Quality Assessment of Systematic Reviews and Meta-Analyses

The guidance document below is organized by question number from the tool for quality assessment of systematic reviews and meta-analyses.

Question 1. Focused question

The review should be based on a question that is clearly stated and well formulated. An example would be a question that uses the PICO (population, intervention, comparator, outcome) format, with all the components clearly described.

Question 2. Eligibility criteria

The eligibility criteria used to determine whether studies were included or excluded from the review should be clearly specified and predefined. It should be clear to the reader why studies were included or excluded.

Question 3. Literature search

The search strategy should employ a comprehensive, systematic approach in order to capture all of the evidence possible that pertains to the question of interest. At a minimum, a comprehensive review should have the following attributes:

- Electronic searches were conducted using multiple scientific literature databases such as MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PsychLit, and others as appropriate for the subject matter.
- Manual searches of references found in articles and textbooks should supplement the electronic searches.

Additional search strategies that may be used to improve the yield include the following:

- Studies published in other countries

- Studies published in languages other than English
- Identification by experts in the field of studies and articles that may have been missed
- Search of the grey literature, which includes technical reports and other papers from government agencies or scientific groups or committees, presentations and posters from scientific meetings, conference proceedings, unpublished manuscripts, etc. A search of the grey literature is important (whenever feasible) because sometimes only positive studies with significant findings are published in the peer-reviewed literature, which can bias the results of a review.

The literature search strategy should be described clearly in the review and be reproducible by others with similar results.

Question 4. Dual review for determining which studies to include and exclude

Titles, abstracts, and full-text articles (when indicated) should be reviewed by two independent reviewers to determine which studies to include and exclude in the review. Disagreements between the reviewers should be resolved by discussion and consensus or with third party involvement. The process for review, including methods for adjudicating disagreements, should be clearly stated.

Question 5. Quality appraisal for internal validity

Each included study should be appraised for internal validity (study quality assessment) using a standardized approach for rating the quality of the individual studies. Ideally, this should be done by at least two independent reviewers. However, because there is not one commonly accepted, standardized tool for rating the quality of studies, the goal is to show that individual study quality was assessed, and details as to how this was done should be clearly stated by the authors.

Question 6. List and describe included studies

All of the included studies should be listed in the review, along with descriptions of their key characteristics. This can be presented in narrative or table format.

Question 7. Publication bias

Publication bias is when studies with positive results have a higher likelihood of being published, being published rapidly, being published in higher impact journals, being published in English, being published more than once, or being cited by others.[80,81] Publication bias can be linked to favorable or unfavorable treatment of research findings due to the investigators, editors, industry, commercial interests, or peer reviewers. A strategy that can minimize the potential for publication bias is to conduct a very comprehensive literature search that includes the strategies discussed in Question 3.

A funnel plot is a commonly used graphical method for detecting publication bias. The funnel plot is a scatter plot of component studies in a meta-analysis. The graph looks like a symmetrical inverted funnel if there is no significant publication bias.

The likelihood of publication bias should be assessed in the review. This can be done in a number of different ways, but an assessment should be conducted and clearly described.

Question 8. Heterogeneity

Heterogeneity is used to describe important differences in the included studies of a meta-analysis that may make it inappropriate to combine the studies.[82] Heterogeneity can be clinical (e.g., important differences between study participants, baseline disease severity, interventions), methodological (e.g., important differences in the design and conduct of the study), or statistical (e.g., important differences in the quantitative results or reported effects).

Clinical or methodological heterogeneity is usually assessed qualitatively by determining whether it makes sense to combine studies.

For example:

- Should a study evaluating the effects of an intervention on CVD risk that involves elderly male smokers with hypertension be combined with a study that involves healthy adults ages 18 to 40? (Clinical Heterogeneity)
- Should a study that uses a randomized controlled trial design be combined with a study that uses a case-control study design? (Methodological Heterogeneity)

Statistical heterogeneity describes the degree of variation in the effect estimates from a set of studies and is assessed quantitatively. The two most common methods used to assess statistical heterogeneity are the Q test (also known as the χ^2or chi-square test) or I^2 test.

An assessment for heterogeneity should be conducted and clearly described. If the studies are found to be heterogeneous, the investigators should explore and explain the causes of the heterogeneity, and they should determine what influence, if any, the study differences had on the overall study results.

x. Quality Assessment Tool for Cohort and Cross-Sectional Studies

The quality assessment tool for cohort and cross-sectional studies is included in table A–3. The guidance document for that tool is also included in table A–3. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers, the USPSTF, consultation with epidemiologists, and other sources.

This tool addresses 13 elements of quality assessment. They include the clarity of the research question or research objective; the definition, selection, composition, and participation of the study population; the definition and assessment of exposure and outcome variables; the measurement of exposures before outcome assessment; the study timeframe and followup; study analysis and power; and other factors.

Table A–3. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this study clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this study, were the exposures of interest measured prior to the outcome(s) being measured?			
7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			

Criteria	Yes	No	Other (CD, NR, NA)
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as a continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Were the exposures assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposures and outcomes?			

Quality Rating (Good, Fair, or Poor):
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

Note: CD = cannot determine; NR = not reported; NA = not applicable.

xi. Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of individuals from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcome of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan

Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is *crucial* that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50 percent of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies—which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for CVD than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same I/E criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of individuals included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It simply may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question(i.e., it may have been an exploratory, hypothesis-generating study).

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham use this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data)where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 5 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than

recommended consumption, between the two)? Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes; the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable—for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care—where clinicians measure BP however it is done is their practice setting (which can vary considerably)—and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If individuals with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Multiple measurements also enable investigators to look at changes in exposure over time (e.g., individuals who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout). Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable? For example, have they been validated or are they objective? This issue is important because it influences

confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death—the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., individuals with high BP) is seen more frequently than another group (e.g., individuals with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is "no," then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which would be stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup Rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, and lower overall followup rates are often seen in studies of longer duration. Usually an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to a randomized controlled trial where the randomization process controls for potential confounders.

All key factors that may be associated both with the exposure of interest and the outcome—that are not of interest to the research question—should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

General guidance for determining the overall quality rating

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study—in other words, the ability for the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk for potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of "poor" quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding—all concepts reflected in the tool.

Generally, when you evaluate a study you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

xii. Quality Assessment Tool for Case-Control Studies

The quality assessment tool for case-control studies is included in table A–4. The guidance document for that tool is also included in table A–4. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers, consultation with epidemiologists, and other factors.

This tool includes 12 items for assessment of study quality. They include clarity of the research objective or research question; definition, selection, composition, and participation of the study population; definition and assessment of case or control status; exposure and outcome variables; use of concurrent controls; confirmation that the exposure occurred before the outcome; statistical power; and other factors.

Table A–4. Quality Assessment Tool for Case-Control Studies

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this study clearly stated and appropriate?			
2. Was the study population clearly specified and defined?			
3. Was an appropriate target population clearly defined per the research question? Did the cases adequately represent the cases that arose in the target population?			
4. Did the authors include a sample size justification?			
5. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same time frame)?			
6. Were the definitions, inclusion and exclusion criteria, algorithms, or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
7. Were the cases clearly defined and differentiated from controls?			
8. If not all eligible cases and/or controls (e.g., fewer than 100 percent) were selected for the study, were the cases and/or controls randomly selected from those that were eligible?			
9. Was there use of concurrent controls?			
10. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
11. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
12. Were the assessors of exposure/risk blinded to the case or control status of participants?			
13. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

Quality Rating (Good, Fair, or Poor):
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

Note: CD = cannot determine; NR = not reported; NA = not applicable

xiii. Guidance for Assessing the Quality of Case-Control Studies

The guidance document below is organized by question number from the tool for quality assessment of case-control studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Question 2. Study population

Did the authors describe the group of individuals from which the cases and controls were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know exactly who to recruit, from where, and from what time period?

Case-control study populations are determined by the location, time period, and inclusion criteria for cases (individuals with the disease or problem) and controls (individuals without the disease or health problem). An example population for a study of lung cancer and chemical exposure would be all incident cases of lung cancer diagnosed in patients ages 35 to 79 years from January 1, 2003 to December 31, 2007, in 6 regions of northern France, as well as lung cancer-free controls recruited from the same population during that time. The population is clearly described as: (1) who (men and women ages 35 to 79 with (cases) and without (controls) incident lung cancer); (2) where (6 regions of northern France); and (3) when (between January 1, 2003 and December 31, 2007).

Other studies may use disease registries or data from cohort studies to identify cases, in which case the populations are individuals in the area covered by the disease registry or included in a cohort study (i.e., nested case-control or case-cohort). For example, a study of the relationship between vitamin D intake and MI might use patients identified via the GRACE registry, a database of heart attack patients.

You may need to look at prior papers on methods in order to make this assessment. Those papers are usually in the reference list.

Question 3. Target population and case representation

IN order for a study to truly address the research question, the target population—the population from which the study population is drawn, and to which study results are believed to apply—should be carefully defined. Some authors may compare characteristics of the study cases to characteristics of cases in the target population, either in text or in a table. When study cases are shown to be representative of cases in the appropriate target population, it increases the likelihood that the study was well-designed per the research question.

However, because these statistics are frequently difficult or impossible to measure, publications should not be penalized if case representation is not shown. For most papers, the response to question 3 will be "NR." These subquestions are combined because the answer to the second subquestion—case representation—determines the response to this item. However, it cannot be determined without considering the response to the first subquestion. For example, if the answer to the first subquestion is "yes," and the second, "CD," then the response for item 3 is "CD."

Question 4. Sample size justification

Did the authors discuss their reasons for selecting or recruiting the number of participants included? Do they discuss the statistical power of the study? This question concerns whether or not the study was sufficiently sized to see an association if one exists.

Generally, a paragraph in the methods section of the article will explain sample size needed to detect differences in exposures. However, you may also find a discussion of power in the discussion section.

Question 5. Groups recruited from the same population

In order to determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control was to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls are recruited from hospitals in a given region. It may be reasonable to assume that controls in the catchment area for the hospitals, or those already in the hospitals for a different reason, would attend those hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If controls are recruited or selected from a different region or time period, then the cases and controls are recruited from different populations.

Another example: Eligible cases may be men and women between the ages of 18 and 39 who were diagnosed with atherosclerosis at hospitals in Perth, Australia between July 1, 2000 and December 31, 2007. Appropriate controls for these cases might be sampled using voter registration information for men and women ages 18 to 39 living in Perth (population-based controls); they could also be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are individuals that would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls are considered to be selected appropriately from the same source population as cases.

In a prospective case-control study, participants are enrolled as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. In this type of study, controls may be recruited or selected from the population without the outcome of interest at the time the case is diagnosed. Cases may be identified or recruited through a surveillance system, with controls selected from the population covered by that surveillance system; this would be an example of population-based controls. Controls may also be sampled from a cohort study population, in which cases should be the cases that are identified in that cohort study population, and controls should be selected from outcome-free individuals in the same cohort study. This is known as a nested case-control study.

Question 6. Inclusion and exclusion criteria prespecified and applied uniformly

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the groups involved? The same selection criteria should be used except, of course, for whether or not they had the disease/condition, which by definition would be different for cases and controls. Often, therefore, the same age (or age range), gender, race, etc., is used to select cases and controls. This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Question 7. Case and control definitions

Was a specific description of "case" and "control" provided? Is there a discussion of the validity of the case and control definitions and the processes or tools used to identify study participants as such? Were the tools or methods accurate, reliable, and objective? For example, cases might be identified as "adult patients admitted to a VA hospital from January 1, 2000 to December 31, 2009, with an ICD–9 discharge diagnosis code of AMI and at least one of the following confirmatory findings in their medical records: at least 2mm of ST elevation changes in 2 or more ECG leads, an elevated troponin level." Investigators might also use ICD–9 or CPT codes

to identify patients. All cases should be identified using the same methods. Study results cannot be used to draw valid conclusions unless the distinction between cases and controls is accurate and reliable.

Question 8. Random selection of study participants

If a case-control study did not use 100 percent of eligible cases and controls (e.g., not all *disease-free participants* were included as controls), did the authors indicate that random sampling was used to select controls? When it is possible to identify the source population fairly explicitly (e.g., in a nested case-control study, or in a registry-based study), then random sampling of controls is preferred. If consecutive sampling was used, as frequently occurs for cases in prospective studies, then study participants were not randomly selected, so the answer would be "no." This would not be considered a fatal flaw.

If all eligible cases and controls were included as study participants, then mark "NA."

Question 9. Concurrent controls

A concurrent control is a control selected at the time another person became a case, usually on the same day. This means that one or more controls are recruited or selected from the population without the outcome of interest at the time a case is diagnosed. This can be done in both prospective case-control studies and retrospective case-control studies. For example (assuming our study of adenocarcinoma of the colon was performed retrospectively using data from hospital records), if hospital records indicate that Person A was diagnosed with adenocarcinoma of the colon on June 22, 2002, then one or more controls would be selected from the population of patients *without* adenocarcinoma of the colon on June 22, 2002. One might also imagine this study to have been performed using patient records from a cohort study instead of from a hospital database, in which case it would be a nested case-control study.

The use of concurrent controls can be done in the presence or absence of matching, and vice versa. Just because a study incorporates matching does not mean that concurrent controls were used.

Question 10. Exposure assessed prior to outcome measurement

Because case or control status is determined first (based on presence or absence of outcome of interest), and then exposure history of the case or control is assessed, it is important to make sure that the exposure preceded the outcome. For example, if tissue samples were used to determine exposure, were the tissue samples collected from patients prior to their diagnosis? If hospital records were used, did investigators verify that the date that a patient was exposed (e.g., received medication for atherosclerosis) occurred prior to the date that a person became a case (e.g., was diagnosed with type 2 diabetes)? In order for an association between an exposure and an outcome to be considered causal, the exposure *must* occur prior to the outcome.

Question 11. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable? For example, have they been validated, or are they objective? This is important as it influences confidence in the reported exposures. As important is whether the exposures were assessed in the same manner within groups and between groups.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP in a study assessing BP as an exposure potentially affecting a particular outcome. There may be quite a difference in BP measurements between usual care—where clinicians measure BP however it is done is their practice setting—and use of trained BP assessors using standardized equipment (e.g., the same BP device which

has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged).

Question 12. Blinding of exposure assessors

Blinding means that persons assessing the exposure status of study participants did not know whether the participant was a case or control. It is also sometimes called "masking." The objective is to look for evidence in the article that the person assessing the exposure(s) (for example, examining medical records to determine the exposures that occurred in the cases and controls) is masked to the case/control status of the participant. Sometimes the person measuring the exposure is the same person conducting case ascertainment. If so, make a note of that in the comments section.

One way to ensure good blinding of exposure assessment is to have a separate committee, whose members have no information about the study participants' status as cases or controls. As you assess this criterion, think about whether it is likely that the person doing the exposure assessment would know whether the study participant was a case or control. If the answer is "no," then the blinding should be adequate. For example, if the investigators were using medical records to assess exposure, you would want them to: (1) Not be directly involved in the care of the study subjects, since they would probably have knowledge of the conditions of their patients; and (2) If the medical record contained information on the patient's condition that identified him/ or her as a case (which is likely), that information would have to be removed before the exposure assessors reviewed the records.

If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Statistical analysis

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in case-control studies, because the statistical analyses need to control for potential confounders, in contrast to a randomized controlled trial where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome should be controlled for in the analyses. For example, in a study of the relationship between smoking and CVD events (heart attacks and strokes), the investigators need to control for age, gender, and body weight, because those are all associated both with smoking and with CVD events. Well-done case-control studies control for multiple potential confounders.

Matching is a technique used in an effort to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, one might identify cases that have had a heart attack or stroke and then select controls of similar age, gender, and body weight to the cases. For case-control studies, it is important that if matching was performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) *should be controlled for in the analysis*.

General guidance for determining the overall quality rating

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for case-control studies is the extent to which the associations between disease and exposure reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study. In other words, what is the ability of the study to draw associative conclusions about the

effects of the exposures being studied on outcomes? Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk for potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other. Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality; low risk of bias translates to a rating of good quality. Thus, the greater the risk of bias, the lower the quality rating of the study.

If a study has a "fatal flaw," then risk of bias is significant and the study is deemed to be of poor quality. An example of a fatal flaw in case-control studies is a lack of a consistent standard process to identify cases and controls.

Generally, when you evaluate a study you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. Specific rules are not useful, as each study has nuances that are a bit different. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

xiv. Description of Data Abstraction and Review Process

Articles rated "good" or "fair" during the quality rating process were abstracted into the VCW using a Web-based data entry form. Requirements for abstraction were specified in an evidence table template that was developed by the methodologist for each CQ. The evidence table template included data elements relevant to the CQ, such as study characteristics, interventions, population demographics, and outcomes.

The abstractor carefully read the article and entered the required information into the Web-based tool. Once abstraction was complete, an independent quality control review was conducted. During this review, data were checked for accuracy, completeness, and the use of standard formatting.

xv. Development of Evidence Tables and Summary Tables

a. Evidence Tables

For each CQ, methodologists worked with the expert panel or work group members to identify the key data elements needed to answer the question. Using the PICOTSS criteria as the foundation, expert panel or work group members determined what information was needed from each study to be able to understand the design, sample, and baseline characteristics in order to interpret the outcomes of interest. A template for a standard evidence table was created and then populated with data from several example studies for review by the expert panel or work group to ensure that all of the appropriate study characteristics were being considered. Once a final template was agreed upon, evidence tables were generated by pulling the appropriate data elements from the master abstraction database for those studies that met the inclusion criteria for the CQ.

Only studies rated "good" and "fair" were included in the evidence tables.

Templates varied by each individual CQ but generally provided the following information:

- **Study characteristics:** Author, year, study name, country and setting, funding, study design, research objective, year study began, overall study *N*, quality rating
- **Criteria and end points:** I/E criteria, primary outcome, secondary outcome, composite outcomes
- **Study design details:** Treatment groups, descriptions of interventions, duration of treatment, duration of followup, run-in, wash-out, intervention *N*
- **Baseline population characteristics:** Demographics, biomarkers, other measures relevant to the outcomes
- **Results:** Outcomes of interest for the CQ with between-group *p* values or confidence intervals for risk ratios, adverse events, attrition, and adherence

Studies are presented in alphabetical order by the study name (if none, the first author's last name was used). Some expert panels combined all of the articles for a study and presented it as a single entry, but for those that did not, the articles were presented in chronological order within the group for the same study.

b. Summary Tables

To enable a more targeted focus on the specific aspects of a CQ, methodologists developed summary tables, or abbreviated evidence tables, in concert with the expert panels or work groups. A summary table might be designed to address a general population or a specific subpopulation, such as individuals with diabetes, women, or the elderly, but it presents only concise data elements. All of the available data in the evidence tables were reviewed to determine a consistent format to present the specific outcome of interest. For example, some lifestyle interventions have lengthy descriptions in the evidence tables, but only the key features would be concisely stated in the summary tables. Within an outcome, the time periods were clearly identified and the order of the different measures was consistently applied. For example, weight loss was always listed in order of percentage change, followed by kilogram change, and lastly by number of subjects losing a certain percent of their body weight. Templates varied by each aspect of the CQ being addressed but generally provide the following information:

- **Study characteristics:** Study name, author/year, design, overall study *N*, quality rating
- **Sample characteristics:** Relevant inclusion criteria
- **Study design details:** Intervention doses and duration
- **Results:** Change in outcomes by time periods, attrition, and adherence

Each expert panel or work group determined its own ordering of studies to present the evidence within each summary table. For some, trials were listed in chronological order; for others it was by the type or characteristics of the intervention.

xvi. Development of Evidence Statement sand Expert Panel Voting

Using the summary tables (and evidence tables as needed), evidence statements were collaboratively written by expert panel members with input from methodology staff and oversight of the process by NHLBI staff. Evidence statements aimed to summarize key messages from the evidence that could be provided to primary care providers and other stakeholders. In some cases, the evidence was too limited or inconclusive, so no evidence statement was developed, or a statement of insufficient evidence was made.

Methodology staff provided the expert panels with overarching guidance on how to grade the level of evidence (i.e., high, moderate, low), and the expert panels used this guidance to grade each evidence statement. This guidance is documented in the following section.

Expert panel members who have relationships with industry or other possible conflicts of interest were allowed to participate in discussions leading up to voting as long as they declared their relationships, but they recused themselves from voting on any issue relating to their relationships with industry or potential conflicts of interest. Voting occurred by the panel or work group chair asking each member to signify his or her vote. Beginning in September 2011, the GEC set up its own approach to manage relationships with industry and other potential conflicts of interest (see http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm.) NHLBI project staff and contractors did not vote.

xvii. Description of Methods for Grading the Body of Evidence

The NHBLI Adult Cardiovascular Disease project team applied related but distinct processes for grading the bodies of evidence for CQs, and for bodies of evidence for different outcomes included within CQs. Each of these processes is described in turn below.

In developing the system for grading the body of evidence, NHLBI reviewed a number of systems, including GRADE (Grading of Recommendations Assessment, Development, and Evaluation), USPSTF, AHRQ Evidence-based Practice Centers, American College of Cardiology/American Heart Association (ACC/AHA), American Academy of Pediatrics, Strength of Recommendation Taxonomy, Canadian Task Force on Preventive Health Care, Scottish Intercollegiate Guidelines Network, and Centre for Evidence-Based Medicine in Oxford. In particular, GRADE, USPSTF, and ACC/AHA were considered at length. However, none of those systems fully met the needs of NHLBI's project. NHLBI therefore developed its own hybrid version that incorporated features of those systems. The resulting system was strongly supported by expert panel and work group members. In using the system, decisions about evidence rating were made by the expert panel and work group members and the methodology team working collaboratively to apply the system and guidance in a thoughtful manner.

Two approaches were used for summarizing the body of evidence for each CQ. The first process was to conduct a de novo literature search and literature review for all of the individual studies that met a CQ's I/E criteria. This approach was used for most of the CQs. The second process, developed in response to resource limitations for the overall project, was to focus the literature search on existing systematic reviews and meta-analyses, that themselves summarized a broad range of the scientific literature. This was used for several CQs across expert panels and work groups. Additional information on the use of systematic reviews and meta-analyses is provided in the following section.

Once the expert panel and work group members reached consensus on the wording of the evidence statement, the next step was to assign a grade to the strength of the body of evidence to provide guidance to primary care providers and other stakeholders on how much support the evidence provided for the evidence statement. Three options were identified for grades for the strength of evidence: high, moderate, or low.

The table below describes the types of evidence that were used to grade the strength of evidence as high, moderate, or low by the expert panel and work group members, with assistance from methodologists.

Table A–5. Evidence Quality Grading System

Type of Evidence	Strength of Evidence Grade
■ Well-designed, well-executed RCTs that adequately represent populations to which the ■ Meta-analyses of such studies. ■ High confidence that the evidence reflects the true effect. Further research is unlikely to	
■ RCTs with minor limitations that affect confidence in, or applicability of, the results; including minor flaws in design or execution. ■ Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies. ■ Meta-analyses of such studies. ■ Moderate confidence that the evidence reflects the true effect. Further research may change the moderate confidence in the estimate of effect and may change the estimate.	**Moderate**
■ RCTs with major limitations. ■ Nonrandomized intervention studies and observational studies with major limitations ■ Uncontrolled clinical observations without an appropriate comparison group (e.g., case ■ Physiological studies in humans. ■ Meta-analyses of such studies. ■ Low confidence that the evidence reflects the true effect. Further research is likely to	**Low**

The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. It is important to assess the strength of the evidence as objectively as possible. For rating the overall strength of evidence, the entire body of evidence for a particular summary table and its associated evidence statement was used.

Methodologists provided guidance to the expert panels and work groups on assessing the body of evidence for each outcome or summary table of interest using four domains: (1) risk of bias, (2) consistency, (3) directness, and (4) precision. Each domain was assessed and discussed, and the aggregate assessment was used to increase or decrease the strength of the evidence, as determined by NHLBI's Evidence Quality Grading System shown above. The four domains are explained in more detail below.

a. Risk of Bias

Risk of bias refers to the likelihood that the body of included studies for a given question or outcome is biased due to flaws in the design or conduct of the studies. Risk of bias and internal validity are similar concepts that are inversely correlated. A study with a low risk of bias has high internal validity and is more likely to provide correct results than one with high risk of bias and low internal validity. At the individual study level, risk of bias is determined by rating the quality of each individual study using standard rating instruments, such as NHLBI's study quality rating tools presented and discussed in the previous section of this report. Overall risk of bias for the body of evidence regarding a particular question, summary table, or outcome is then assessed by the aggregate quality of studies available for that particular question or outcome. Expert panel and work group members reviewed the individual study quality ratings with methodologists to determine the aggregate quality of the studies available for a particular question, summary table, or outcome. If the risk of bias was low, then it

increased the strength of evidence rating for the strength of the overall body of evidence. If the risk of bias was high, then it decreased the strength of evidence rating.

b. Consistency

Consistency is the degree to which reported effect sizes are similar across the included studies for a particular question or outcome. Consistency enhances the overall strength of evidence and is assessed through effect sizes being in the same direction (i.e., multiple studies demonstrate an improvement in a particular outcome) and the range of effect sizes across studies being narrow. Inconsistent evidence is reflected in (1) effect sizes that are in different directions, (2) a broad range of effect sizes, (3) non-overlapping confidence intervals, or (4) unexplained clinical or statistical heterogeneity. Studies included for a particular question or outcome can have effect sizes that are consistent, inconsistent, or unknown (or not applicable). The latter occurs in situations where only a single study is available. For NHLBI's project, consistent with the approach of AHRQ's Evidence-Based Practice Centers, evidence from a single study generally was considered insufficient for a high strength of evidence rating because a single trial, no matter how large or well designed, may not provide definitive evidence of a particular effect until confirmed by another trial. However, a very large, multicentered, well-designed, well-executed RCT that performs well in the other domains could in some circumstances be considered high-quality evidence after thoughtful consideration.

c. Directness

Directness has two aspects: the direct line of causality and the degree to which findings can be extended from a specific population to a more general population. The first defines directness as whether the evidence being assessed reflects a single direct link between the intervention (or service, approach, or exposure) of interest and the ultimate health outcome under consideration. Indirect evidence relies on intermediate or surrogate outcomes that serve as links along a causal pathway. Evidence that an intervention results in changes in important health outcomes (e.g., mortality, morbidity) increases the strength of the evidence. Evidence that an intervention results in changes limited to intermediate or surrogate outcomes (e.g., a blood measurement) decreases the strength of the evidence. However, the importance of each link in the chain should be considered, including existing evidence that a change in an intermediate outcome affects important health outcomes.

Another example of directness involves whether the bodies of evidence used to compare interventions are the same. For example, if Drug A is compared to placebo in one study and Drug B is compared to placebo in another study, using those two studies to compare Drug A with Drug B yields indirect evidence and provides a lower strength of the evidence than direct head-to-head studies of Drug A versus Drug B.

The second aspect of directness refers to the degree to which participants or interventions in the study are different from those to whom the study results are being applied. This concept is referred to as applicability. If the population or interventions are similar, then the evidence is direct and strengthened. If they are different, then the evidence is indirect and weakened.

d. Precision

Precision is the degree of certainty about an estimate of effect for a specific outcome of interest. Indicators of precision are statistical significance and confidence intervals. Precise estimates enable firm conclusions to be drawn about an intervention's effect relative to another intervention or control. An imprecise estimate is where the confidence interval is so wide that the superiority or inferiority of an intervention cannot be determined. Precision is related to the statistical power of the study. An outcome that was not the primary outcome or not prespecified will generally be less precise than the primary outcome of a study. In a meta-analysis, precision is reflected by the confidence interval around the summary effect size. For systematic reviews, which include multiple studies but no quantitative summary estimate, the quantitative information from each study should be

considered in determining the overall precision of the body of included studies because some studies may be more precise than others. Determining precision across many studies without conducting a formal meta-analysis is challenging and requires judgment. A more precise body of evidence increases the strength of evidence, and less precision reduces the strength of a body of evidence.

Following discussion of the four criteria for the strength of evidence grading options, the expert panels and work groups also considered other factors in some cases. For example, the objectivity of an outcome measure can be an issue in some cases. Total mortality is a very objective measure because it is usually recorded accurately. Determination of angina is less objective and may be considered to result is lower strength of evidence. Similarly, urinary sodium excretion is a more objective measure than is dietary sodium intake reported by study subjects through recall. Another example is measured height and weight used to calculate a study subject's BMI versus self-reported weight and height, which provide less reliable data.

Following the conclusion of review and discussion of this range of factors, the expert panel or work group members voted on the final grade for the strength of evidence for each evidence statement. Methodologists provided analysis and recommendations regarding strength of evidence grading, but did not participate in the voting process. A simple majority vote was sufficient to identify the strength of evidence grade, although in most cases the expert panels and work groups discussed the results if there were dissenting opinions until consensus or large majorities were achieved for the votes on the strength of evidence.

xviii. Policy and Procedures for the Use of Existing Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses are routinely used in evidence reviews, and well-conducted systematic reviews or meta-analyses of RCTs are generally considered to be among the highest forms of evidence. As a result, systematic reviews and meta-analyses could be used to inform guideline development in the NHLBI CVD adult systematic review project if certain criteria were met. Guidance on using existing systematic reviews has been published by AHRQ as a chapter of the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and helped to inform the development of the NHLBI criteria.[83]

To use existing systematic reviews or meta-analyses to inform NHLBI's guideline recommendations, the project needed to identify: (1) those relevant to the topic of interest, (2) those where the risk of bias was low, and (3) those that were recent. Examining the research question and component studies in the systematic reviews and meta-analyses as they related to the NHLBI CQs addressed the first issue; using a quality assessment tool addressed the second; and examining publication dates addressed the third.

In general, for this project:

- Eligibility of systematic reviews and meta-analyses was determined by the methodologists, consulting with expert panels and workgroups as needed.
- Data were not abstracted from systematic reviews and meta-analyses, so they were not included in evidence tables. However, if a systematic review or meta-analysis was used to make a recommendation, a summary of the evidence was provided in the text, information from the systematic review or meta-analysis was included in a summary table or appendix, and the citation was included in the reference list.
- Systematic reviews and or meta-analyses were rated using the quality assessment tool for this project. Systematic reviews and meta-analyses were used to develop recommendations if they were rated "good" or "fair" or were comprehensive reviews commissioned by the Federal Government. Systematic reviews and meta-analyses rated as "poor" were used only when there were no eligible "good" or "fair" publications; this occurred for the Obesity Expert Panel's CQ2.

If an existing systematic review or meta-analysis was used to develop recommendations:

- Multiple eligible systematic reviews and meta-analyses addressing the same topic were identified through a systematic search to minimize bias. The systematic reviews and meta-analyses used were summarized in text, a table, or an appendix.
- Rating the body of evidence followed the same system used for the de novo systematic reviews conducted for this project and resulted in a high (systematic reviews/meta-analyses rated "good" only), moderate, or low rating based on number, type, and quality of the studies in the systematic review or meta-analysis.

Three criteria were used to determine when systematic reviews or meta-analyses could be used. They are described in Situations 1–3 below.

SITUATION #1—When a systematic review or meta-analysis addressed a topic relevant to NHLBI's CVD guidelines that was not covered by an existing CQ (e.g., effects of physical activity on CVD risk):

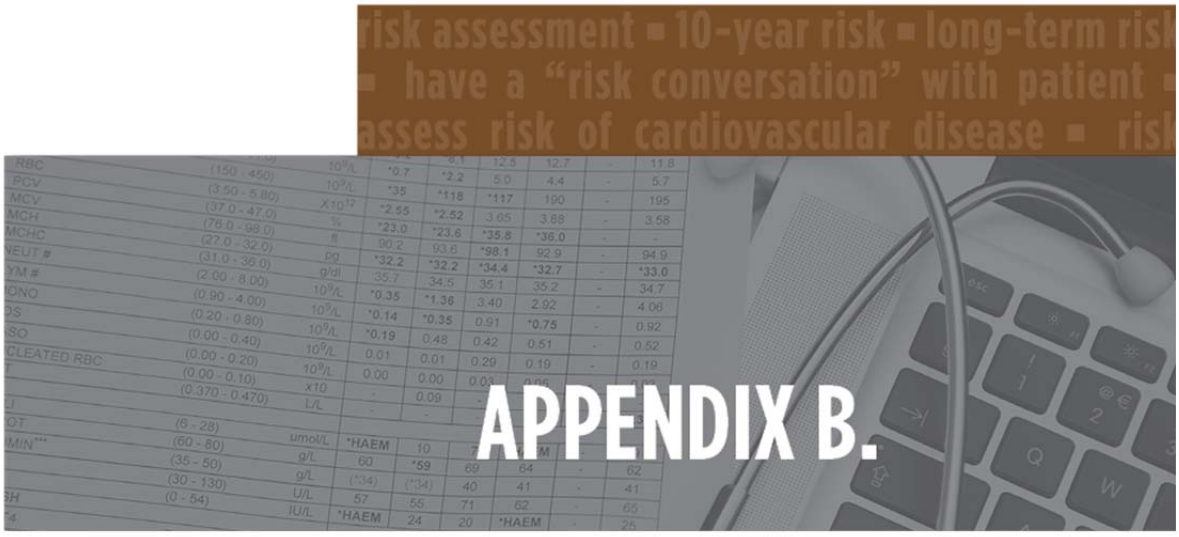
- In order for a systematic review or meta-analysis to be examined for relevance to the topic of interest, the topic needed to be prespecified in the form of a CQ using the PICOTSS structure. If only portion(s) of a systematic review were relevant, those relevant portions that were reported separately could be used. Systematic reviews or meta-analyses could be used if they were recent, (i.e., published within 3 years of the end date of NHLBI's systematic review publication window of December 31, 2009) or identified by the expert panel or work group if published after the end date of the project literature search and before the expert panel began deliberations on the evidence. If the end date of the systematic review or meta-analysis literature search was before December 31, 2009, expert panels or work groups had the option of conducting a bridging literature search through December 31, 2009, if the members believed it was necessary because relevant studies were published after the end date. In this situation, the bridging literature search could cover only the time period up to 1 year before the literature search cut-off date of the systematic review or meta-analysis and extend to no later than December 31, 2009.

SITUATION #2—If the NHLBI literature review identified an existing systematic review or meta-analysis that could possibly replace NHLBI's review of a CQ or subquestion:

- The systematic review or meta-analysis was examined for consistency between the studies included in the systematic review and meta-analysis and the CQI/E criteria. Component studies had to meet the I/E criteria. However, smaller sample sizes were allowed, as were studies published before the beginning of the project's search date window, as long as a truly systematic approach was used.
- Systematic reviews or meta-analyses could be used if they were recent (i.e., published within 3 years of the end date of the NHLBI systematic review publication window) or identified by the expert panel or work group if published after the end date of the project literature search and before the panel began deliberations on recommendations. If the end date of the systematic review or meta-analysis literature search was before December 31, 2009, expert panels or work groups could conduct a bridging literature search through December 31, 2009, if the expert panel or work group members believed it was necessary because relevant studies were published after the end date. In this situation, the bridging literature search could cover the time period only up to 1 year before the literature search cut-off date of the systematic review or meta-analysis and extend to no later than December 31, 2009.

SITUATION #3—If the NHLBI literature review identified an existing systematic review or meta-analysis that addressed the same or a similar CQ or subquestion as one undergoing NHLBI review:

- Systematic review or meta-analysis component articles that *met all the I/E criteria for the CQ* but were not identified in NHLBI's literature search could be added to the included studies in NHLBI's review and treated the same way (i.e., abstracted, quality rated, and added to evidence and summary tables).



APPENDIX B.

Question-Specific Methods

Appendix B. Question-Specific Methods

i. Search Strategy: Risk Assessment Critical Question 1

What is the evidence regarding reclassification or contribution to risk assessment when high-sensitivity C-reactive protein, apolipoprotein B, glomerular filtration rate, microalbuminuria, family history, cardiorespiratory fitness, ankle-brachial index, coronary artery calcium score, or carotid intima-media thickness are considered in addition to the variables that are in the traditional risk scores?

a. Study Type Query

Study types eligible for this question: Published studies, research letters, and brief research communications where sufficient data on the population, intervention, and results are presented and adequate information is available for quality assessment.

- {RCT} OR {Systematic Review} OR (subject=("Cohort Studies" OR "Longitudinal Studies" OR "Follow Up Studies" OR "Prospective Studies" OR "Retrospective Studies" OR "Multivariate Analysis" OR "Prognosis" OR "Epidemiologic Methods" OR "Randomized Controlled Trials as Topic") OR qualifier,subject,abstract,title=(epidemiol? or etiology) or prospective cohort stud? or retrospective cohort stud?)

b. Boolean Search

- (
- publicationYear>1997 and language=eng and {Cardiovascular Diseases}
- **AND** (predict? or estimat? or title,abstract,subject=prognosis or (association %3 risk factors %3 (cardiovascular disease? or CVD)))
- **AND** subject,title,abstract=risk
- **AND** (subject,title,abstract=("Risk Assessment" OR "Actuarial Analysis" OR "Life Tables" OR "Quality Adjusted Life Years" OR "Analysis of Variance" OR "Multivariate Analysis" OR "Bayes Theorem" OR "Markov Chains" OR "Regression Analysis" OR "Stochastic Processes" OR "Models Statistical" OR "Likelihood Functions" OR "Linear Models" OR "Logistic Models" OR "Proportional Hazards Models" OR "Multilevel Analysis") or (lifetime %3 risk) or subject,abstract,title="life expectancy" or risk score or risk estimation or ((risk or CHD or CVD or coronary or cardiovascular) %2 predict?) or Framingham or ATP III or Kannel or NORA or QRisk? or Cuore or SCORE model or Systemic Coronary Risk Evaluation or Reynolds or PROCAM or Northern Manhattan or ASSIGN score or risk assessment model)
- **AND** (subject=("age factors" or "age distribution" or "age groups" or "age of onset") or age or ages or aged)
- **AND** (subject=("sex factors" or "sex distribution") or sex? or gender? or male? or female? or men or women)
- **AND** (qualifier,subject,abstract,title=(epidemiol? or etiology or mortality))
- **AND** (subject,title,abstract="middle aged")

)

  OR (
- ((long-term or lifetime or 20-year or 30-year or 40-year or 50-year) and (short-term or 5-year or 10-year))
- **AND** subject,title,abstract="Risk Assessment"
- **AND** (qualifier,subject,abstract,title=(epidemiol? or etiology or mortality))

- **AND** (subject,title,abstract="middle aged")
)

c. Boolean Filter

- ((CVD or CHD or cardiovascular or coronary) %2 event?)
- or subject,qualifier,title,abstract=mortality or death?
- or subject,title,abstract=(myocardial infarction) or subject,title,abstract=(heart failure) or subject,title,abstract=stroke or subject,title,abstract=(myocardial revascularization)
- or subject=(outcome assessment health care) or subject=(fatal outcome) or hospitalization
- or peripheral vascular disease or abdominal aortic aneurism repair or coronary revascularization or peripheral revascularization or surgical revascularization or extremity revascularization
- or (lifetime %3 risk) or "coronary risk assessment"

d. Risk Assessment CQ1 Search Strategy Results and PRISMA Diagram

Risk Assessment CQ1 was initially intended to be a de novo systematic review of original studies plus systematic reviews and meta-analyses. In 2011, CQ1was de-scoped and restricted to systematic reviews and meta-analyses only. The initial search included the following bibliographic databases:

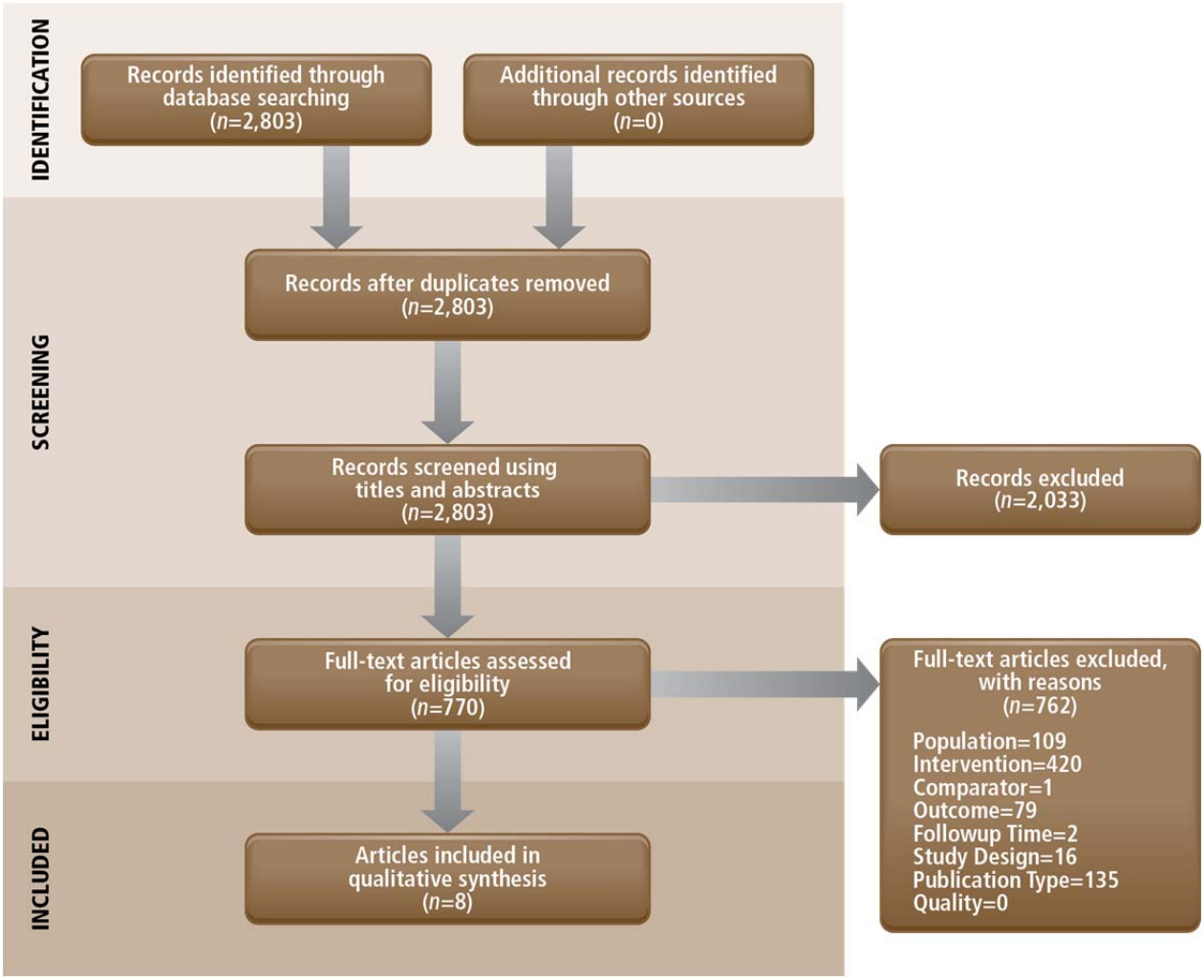
- PubMed from January 1998 to December 2009, later extended to April 2011
- CINAHL from January 1998 to July 2008
- Embase from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

On April 27, 2011, a supplemental PubMed search was executed that sought exclusively systematic reviews and meta-analyses. The search strategy presented above is the final strategy, which queries for systematic reviews and meta-analyses.

Duplicate citations that arose from the same citation being found in more than one database were removed from the central repository before screening. (More information on the central repository is available in appendix A.) The search produced 2,803 citations; this number includes the search for original studies and systematic reviews and meta-analyses sought from the initial search plus results from the supplemental search that was restricted to systematic reviews and meta-analyses.

The titles and abstracts of these 2,803 publications were independently screened against the I/E criteria by two reviewers, which resulted in the retrieval of 770 full-text papers. These papers were independently screened by two reviewers, and 762 of these publications were excluded on one or more of the I/E criteria. The most common reason for exclusion was that the intervention did not meet specified criteria. The eight included systematic reviews and meta-analyses were quality rated using NHLBI's quality assessment tool for systematic reviews and meta-analyses; two were rated as "good" and six were rated as "fair." Thus, eight systematic reviews and meta-analyses were eligible for inclusion in the evidence base for CQ1;six of these were published after December 2009 and captured by the supplemental search.

Figure B–1. PRISMA Diagram Showing Selection of Articles for Risk Assessment Question 1



ii. Search Strategy: Risk Assessment Critical Question 2

Are models constructed to assess the long-term (≥15 years or lifetime) risk for a first CVD event in adults effective in assessing variation in long-term risk among adults at low and/or intermediate short-term risk whether analyzed separately or combined?

a. Study Type Query

Study types eligible for this question: Systematic reviews and meta-analyses.

- {Systematic Review}

b. Boolean Search

- (
- publicationYear>1997 and language=eng and {Cardiovascular Diseases}
- **AND** (((CVD or CHD or HF or cardiovascular or coronary or heart or cardiac) %3 event?) or subject,qualifier,title,abstract=mortality or death? or fatal? or subject,title,abstract="myocardial infarction" or subject,title,abstract="heart failure" or subject,title,abstract=stroke or heart attack or CHF or subject="fatal outcome" or ((CVD or CHD or HF or cardiovascular or coronary or heart or cardiac) and (hospitaliz? or subject,abstract,title=inciden?)) or subject="survival rate" or (lifetime %3 risk) or

((subject=(Cardiovascular or Coronary or Heart or Carotid or Myocardial)) with (qualifier=etiology)) or subject="area under curve" or "Framingham Heart Study" or "net reclassification")

- **AND** (((subject=(cholesterol or Apolipoprotein or Apolipoproteins)) with (qualifier=blood)) or cholesterol or modifiable risk or traditional risk or standard risk or Framingham risk or vascular risk or "net reclassification")
- **AND** (
- subject,abstract,title="body mass index" or BMI or (weight and height) or subject,abstract,title=("Waist-Hip ratio" or "Waist Circumference")
- OR "Family History" or "Parental history" or familial or personal history
- OR ((subject="C-Reactive Protein") with (qualifier=(metabolism or analysis))) or hs-CRP or CRP or "C-reactive protein"
- OR apoB or ((subject="Apolipoproteins B") with (qualifier=(blood or metabolism))) or Lp(a) or ((subject="Lipoprotein (a)") with (qualifier=blood)) or "Lipoprotein (a)" or Apolipoprotein?
- OR microalbuminuria or subject=Albuminuria
- OR GFR or subject,abstract,title=("Glomerular Filtration Rate" or Creatinine)
- OR (cardiorespiratory fitness OR subject,title,abstract=("Physical Fitness" OR "Exercise Tolerance" OR "Metabolic Equivalent" OR "Exercise Test" or "Oxygen Consumption") OR ((subject=Exercise) with (qualifier=physiology)) OR VO2? OR "maximal MET" OR (METs not "metabolic syndrome mets") OR "maximal metabolic" OR metabolic equivalent? or graded exercise test? OR GXT) or physical activity or physical inactivity
- OR CAC or "coronary artery calcium" or coronary calc?
- OR IMT or intima-media thickness
- OR subject=(Ankle Brachial Index) or ABI or ABPI or AAI or (ankle %2 brachial) or (ankle %2 arm)
- OR ((modifiable or traditional or combination?) %5 risk factors)
- OR "net reclassification"
-)
-)
- **NOT** journalTitle="ACP journal club"
- **NOT** recordStatus=delete

c. Boolean Filter

- None

d. Risk Assessment CQ2 Search Strategy Results and PRISMA Diagram

The following databases were searched for prospective or retrospective cohort studies, RCTs, and systematic reviews to answer CQ2:

- PubMed from January 1998 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

Duplicate citations that arose from the same citation being found in more than one database were removed from the central repository before screening. (More information on the central repository is available in appendix A.)The search produced 2,338 citations. An additional 10 citations published after December 2009 were retrieved from PubMed for review for a total of 2,348 publications.

The titles and abstracts of these 2,348 publications were independently screened against the I/E criteria by two reviewers, which resulted in the retrieval of 348 full-text papers. These papers were independently screened by two reviewers, and 338 of these publications were excluded on one or more of the I/E criteria. The most common reason for exclusion was that the intervention did not meet specified criteria. The 10 included publications were quality rated using NHLBI's quality assessment tool for cohort or cross-sectional studies; 8 were rated as good quality and 2 were rated as fair quality. Thus, 10 publications were eligible for inclusion in the evidence base for CQ2.

None of the 10 citations published after December 2009 that were reviewed met the inclusion criteria.

Figure B–2. PRISMA Diagram Showing Selection of Articles for Risk Assessment Question 2

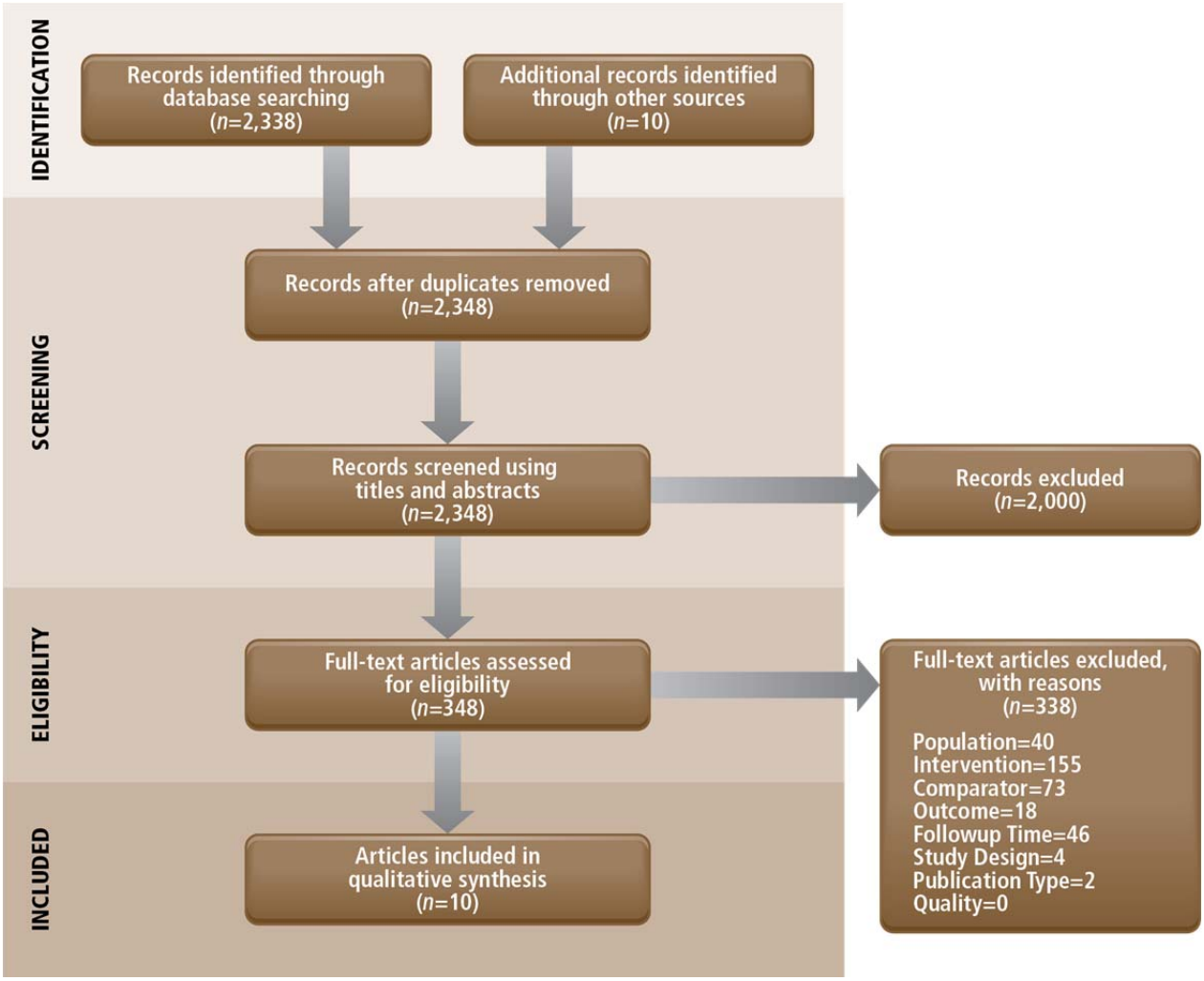


Table B–1. Risk Assessment Work Group CriticalQuestion1 PICOTSS

PICOTSS	From Inclusion/Exclusion Criteria	Notes
Population	Include: ■ Adults ≥18 ■ Primary prevention populations: No clinical manifestation of CVD Exclude: ■ Studies of children ■ Studies of animals	
Intervention/ Exposure	All of the following: ■ One or more of the following: measured or calculated total cholesterol, non-HDL-C, LDL-C, or ApoB ■ Measured HDL-C ■ Traditional risk factors included in assessment: smoking, diabetes, BP level or hypertension, age, sex ■ Data include at least one of the following: Family history, hs-CRP, ApoB, microalbuminuria, GFR, cardiorespiratory fitness, CAC, CIMT, or ABI	This is an assessment intervention, not a therapeutic intervention
Comparator	Comparison to the variables that are in the traditional risk scores (Reynolds, Framingham, ARIC, Cardiovascular Health Study, PROCAM, AUGSBURG, ROTTERDAM)	
Outcomes/Events	Studies must report one or more of the following outcomes: ■ CVD mortality ■ Fatal or nonfatal MI ■ Fatal or nonfatal stroke ■ Hospitalization for or death from arrhythmia ■ Hospitalization for or death from CHF ■ Composite CVD outcomes that include any of the above outcomes	
Timing	>1 year	
Setting	■ Any geographic location—single or multicenter ■ Any clinical, diagnostic, or research setting	
Study Design	Systematic reviews, prospective or retrospective cohort studies	

Note: ABI=ankle-brachial index; ApoB = apolipoprotein B; ARIC = Atherosclerosis Risk in Communities Study; CAC = coronary artery calcium; CVD = cardiovascular disease; CHF = congestive heart failure; CIMT = carotid intima-media thickness; GFR = glomerular filtration rate; HDL-C = high density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

Table B–2. Risk Assessment Work Group Critical Question1 Inclusion/Exclusion Criteria

PICOTSS	From Inclusion/Exclusion Criteria
Population	■ Adults older than or equal to 18 ■ Primary prevention populations: No clinical CVD
Intervention—Diagnosis or Assessment or Therapy	All of the following: ■ One or more of the following: measured or calculated total cholesterol, non-HDL-C, LDL-C, or ApoB ■ Measured HDL-C ■ Traditional risk factors included in assessment: Smoking, diabetes, BP level or hypertension, age, sex ■ Data include at least one of the following: family history, hs-CRP, ApoB, microalbuminuria, GFR, cardiorespiratory fitness, CAC, CIMT, or ABI
Outcomes/Events	All major initial CVD events, specifically any or all of the following: ■ Fatal or nonfatal MI ■ Stroke ■ CVD death (including CHD and stroke death ■ Congestive heart failure (hospitalized CHF or fatal CHF)
Setting	■ Any geographic location—single or multicenter ■ Any clinical, diagnostic, or research setting
Study Design	■ Systematic reviews, prospective or retrospective cohort studies ■ Sample size: No restrictions ■ Exclusions: Followup less than 12 months; case series; case reports
Measures of association	Examples: ■ Relative risk ■ Hazards ratio ■ Odds ratio ■ AUC/C statistic ■ Reclassification ■ Measures of model fit (e.g., R^2, pseudo-R^2, AIC, BIC, LR or Wald chi^2)
Followup Interval	More than 1 year
Language	■ Full text must be available in English ■ Exclusions: Studies for which abstract only is available in English
Publication	■ Published studies ■ Exclusions – Unpublished literature – Theses – Studies published only as abstracts – Letters, unless sufficient data on the population, intervention, and results are presented and adequate information is available for quality assessment – Commentaries and opinion pieces ■ Nonsystematic reviews

Notes: The following variables were given consideration as risk predictors but their contribution awaits further consideration at a later time: BMI, waist circumference, lipoprotein (a), left bundle branch block, sleep apnea, erectile dysfunction, systemic lupus erythematosus, rheumatoid arthritis, and physical activity.

ABI = ankle-brachial index; ApoB = apolipoprotein B; BP = blood pressure; CVD = cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CHF = congestive heart failure; CIMT = carotid artery intima-media thickness; GFR = glomerular filtration rate; HDL-C = high density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a).

Table B–3. Risk Assessment Work Group Critical Question 1 Systematic Reviews Evidence Conclusions

#	Article	Factor	Evidence Statement/Conclusion
1	USPSTF[49]	hs-CRP	"Strong evidence indicates that CRP is associated with CHD events. Moderate, consistent evidence suggests that adding CRP to risk prediction models among initially intermediate-risk persons improves risk stratification." "Few studies directly assessed the effect of CRP on risk reclassification in intermediate-risk persons." hs-CRP was associated with risk and results in some reclassification in intermediate-risk persons, but it was not clear whether this reclassification led to a net improvement in prediction. Values of receiver operating curve *C*-statistics, measures of discrimination, are mentioned but not reported; hence, no evidence on discrimination, calibration, net reclassification index or cost-effectiveness was provided. Reports some impact on reclassification, probably modest (pp. 488–491).
2	Helfand et al., 2009[50]	hs-CRP, CAC, CIMT, ABI	With respect to risk assessment for major CHD, the authors concluded that, "The current evidence does not support the routine use of any of the 9 risk factors for further risk stratification of intermediate-risk persons." The nine risk factors examined were: hs-CRP, CAC score as measured by electron-beam computed tomography, lipoprotein (a) level, homocysteine level, leukocyte count, fasting blood glucose, periodontal disease, ABI, and CIMT. hs-CRP was associated with CHD and led to some reclassification. The authors cite the JUPITER results to support the conclusion that hs-CRP testing may be useful in intermediate-risk patients to drive statin therapy. The RAWG recognizes that more recent individual study results have been published. Updated systematic reviews addressing discrimination, calibration, reclassification, and cost issues in the context of the newer ASCVD risk assessment model proposed in this document are needed. CAC was associated with CHD and with some reclassification, but it is uncertain how much and how valuable this reclassification is. The document provides little evidence regarding discrimination, calibration, and cost-effectiveness. The RAWG also is concerned about radiation and incidental findings. The RAWG recognizes that more recent individual study results have been published. Updated systematic reviews addressing discrimination, calibration, reclassification, cost, and safety issues in the context of the newer ASCVD risk assessment model proposed in this document are needed. CIMT was associated with CHD, but the document provides little evidence regarding reclassification, discrimination, calibration, and cost-effectiveness. The RAWG also has concerns about measurement issues. Standardization of CIMT measurement is a major challenge. The RAWG recognizes that more recent individual study results have been published. Updated systematic reviews addressing discrimination, calibration, reclassification, cost, and measurement (standardization) issues in the context of the newer ASCVD risk assessment model proposed in this document are needed. ABI was associated with CHD and some reclassification, but it is uncertain how much and how valuable this reclassification is. Evidence suggests some improvement in discrimination, but the document provides little evidence regarding calibration and cost-effectiveness. The RAWG members are uncertain whether more recent individual study results have been published relevant to ABI. Updated systematic reviews addressing discrimination, calibration, reclassification, and cost issues in the context of the newer ASCVD risk assessment model proposed in this document are needed.

#	Article	Factor	Evidence Statement/Conclusion
3	Emerging Risk Factors Collaboration[51]	hs-CRP	"CRP concentration has continuous associations with the risk for coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to such a range of disorders is unclear. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation." hs-CRP is associated with risk for CVD. This analysis did not directly assess value in risk prediction. No additional evidence was provided regarding discrimination, calibration, reclassification, or cost-effectiveness.
4	Schnell-Inderst et al., 2010[52]	hs-CRP	For MI and cardiovascular mortality, "Adding hs-CRP to traditional risk factors improves risk prediction, but the clinical relevance and cost-effectiveness of this improvement remain unclear." Absolute differences in *C*-statistics between models including and not including hs-CRP ranged from 0.00 to 0.027. Some evidence was provided to support the cost-effectiveness of hs-CRP testing in some modeling scenarios, characterized by intermediate- and higher-risk populations and lower cost (generics) statins of at least moderate efficacy.
5	Emerging Risk Factors Collaboration[54]	ApoB	This paper provided evidence of rough equivalence of associations of CVD with non-HDL-C and ApoB after multivariable adjustment (including HDL-C). See figure 3 for CHD and the text for stroke. By inference, this finding means there would be rough equivalence between ApoB and total cholesterol with similar adjustment.
6	Sniderman et al., 2011[55]	ApoB	ApoB was more strongly related to risk for ASCVD than either non-HDL-C or LDL-C in a substitution model that also included HDL-C. No evidence was presented pertinent to an addition model in which ApoB might be added to a model that included total cholesterol, LDL-C or non-HDL-C. Additional models are the type of model of interest to this question. By inference, these results may mean that ApoB is more strongly related to risk than is total cholesterol. This paper did not address directly the value of adding ApoB to a model with traditional risk factors. No information was presented regarding discrimination, calibration, reclassification, or cost. The relative risks evaluated in the meta-analysis were adjusted for various sets of covariates in the various primary reports, and the adjustments were judged to be incomplete. Furthermore, studies of varying designs and quality were included, leaving the RAWG members concerned regarding the validity of the evidence.
7	Kodama et al., 2009[56]	Cardiorespiratory fitness	Better cardiorespiratory fitness was associated with lower risk for all-cause mortality and CHD/CVD. Based on the sensitivity analyses in table 2, evidence of association was weaker for CHD/CVD, but still significant, when based on studies with more complete adjustment for other risk factors. The utility of assessing cardiorespiratory fitness in risk prediction was not assessed (discrimination, calibration, reclassification, and cost).
8	Ankle Brachial Index Collaboration[57]	ABI	ABI is associated with total CHD risk and leads to significant reclassification, and the pattern of reclassification is different by sex. Among men, the effect is to down-classify high-risk men. Among women, the effect is to up-classify low-risk women. Overall, the FRS, as applied by the investigators, showed relatively poor discrimination in this meta-analysis, with *C*-statistics of 0.646 (95%CI: 0.643–0.657) in men and 0.605 (0.590–0.619) in women. There was an improvement in *C*-statistic in both men, 0.655 (0.643–0.666) and women, 0.658 (0.644–0.672) when ABI was added to a model with FRS. The improvement in the *C*-statistic was greater and significant in women but was not significant in men. No evidence on, calibration, net reclassification index, or cost-effectiveness was provided.

Note: ABI = ankle-brachial index; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CIMT = carotid intima-media thickness; FRS = Framingham Risk Score; HDL-C = high density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; RAWG = Risk Assessment Work Group.

Table B–4. Risk Assessment Work Group Critical Question 2 PICOTSS

PICOTSS	From Inclusion/Exclusion Criteria	Notes
Population	Include: ■ Adults ages 18 and older at low and/or intermediate short-term risk separately without CHD/CVD or CHD risk equivalents (other than diabetes including when HbA1c is ≥6.5%) as defined by ATP III (*other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)…multiple risk factors that confer a 10-year risk for CHD >20%)* Exclude: ■ Studies with individuals at high risk (≥20%) or with CHD risk equivalents unless the studies stratify the risk levels ■ Studies of children ■ Studies of animals	
Intervention/Exposure	Include: ■ Short-term risk (defined as 5-year or 10-year risk estimate) assessed by a risk factor counting method, stratification method, or multivariable risk score or equation ■ Minimum set of risk factors to be considered in the model are age, sex, smoking measure, and either BP measure or hypertension variable Exclude: ■ Any model that does not include these four risk factors: age, sex, smoking measure, BP measure or hypertension variable	This is an assessment intervention, not a therapeutic intervention
Comparator	Include: ■ Long-term risk (≥15 years, or lifetime) assessed by a risk factor counting method, stratification method, or multivariable risk score or equation. ■ Minimum set of risk factors to be considered in the model are age, sex, smoking measure, and either BP measure or hypertension variable Exclude: ■ Any model that does not include these four risk factors: age, sex, smoking measure, BP measure or hypertension variable	
Outcomes	Studies have to report one or more of the following outcomes: ■ CVD mortality ■ Fatal or nonfatal MI ■ Fatal or nonfatal stroke ■ Hospitalization for or death from arrhythmia ■ Hospitalization for or death from CHF ■ Composite CVD outcomes that include any of the above outcomes	Exclusions: None
Timing	Minimum average followup: 15 years	
Setting	Any geographic location—single or multicenter	
Study Design	■ RCTs or systematic reviews; appropriate statistical significance reporting ■ Prospective or retrospective cohort studies	

Note: ATP III = Adult Treatment Panel III;BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; CVD = cardiovascular disease; MI = myocardial infarction; RCT = randomized controlled trial.

Table B–5. Risk Assessment Work Group Critical Question 2 Inclusion/Exclusion Criteria

PICOTSS	From Inclusion/Exclusion Criteria
Population	■ Adults older than age 18 years of age without CHD/CVD or CHD risk equivalents as defined by ATP III (but including individuals with diabetes) ■ With or without risk factors or comorbid conditions (excluding CHD risk equivalents, but including individuals with diabetes)
Intervention—Diagnosis or Assessment or Therapy	■ Short-term risk (defined as 5-year or 10-year risk estimate) assessed by risk factor counting/stratification method or multivariable risk score or equation; AND ■ Longer-term risk (>10 years, or lifetime) assessed by risk factor counting/stratification method or multivariable score or equation
Outcomes/Events	All CVD events, including any or all of the following: ■ CVD death (including CHD and stroke deaths) ■ Fatal or nonfatal MI ■ Fatal or nonfatal stroke ■ Hospitalized CHF ■ Peripheral vascular disease (defined as abdominal aortic aneurysm repair, surgical revascularization of upper/lower extremity, or amputation) ■ Total mortality
Setting	■ Any geographic location—single or multicenter ■ Any clinical, diagnostic, or research setting
Study Design	■ Prospective or retrospective cohort studies, RCTs or systematic reviews with or without a comparison group ■ Sample size: No restrictions ■ Exclusions: Case reports
Measures of Association	Comparison (qualitative or quantitative) of short-term and long-term risk estimates
Followup Interval	N/A
Language	■ Full text must be available in English ■ Exclusions: Studies for which abstract only is available in English
Publication	■ Published studies ■ Exclusions – Unpublished data – Theses – Studies published only as abstracts – Letters, unless sufficient data on the population, intervention, and results are presented, and adequate information is available for quality assessment

Note: ATP III = Adult Treatment Panel III; CHD = coronary heart disease; CHF = congestive heart failure; CVD = cardiovascular disease; MI = myocardial infarction; N/A = not applicable; RCT = randomized controlled trial.

Table B–6. Risk Assessment Work Group Critical Question 2 Summary Table

CQ2: Are models constructed to assess the long-term (≥15 years or lifetime) risk for a first CVD event in adults effective in assessing variation in long-term risk among adults at low and/or intermediate short-term risk whether analyzed separately or combined?

Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
The Framingham Heart Study (FHS)[77] Fair To compare predictive functions derived from the major risk factors for CHD from Framingham and two more recent national cohorts, the First and Second NHANES I and NHANES II. To test the quantitative predictive capacity of regression models on CHD mortality rates. To examine whether the model from the Framingham Study can rank individual risk as well as predict absolute risk for death in the new cohorts.	*N*: FHS: 4,169 NHANES I: 6,611 NHANES II: 5,705 24 years max	1. Multiple linear regression used to calculate and compare the age-adjusted means among groups 2. Cox proportional hazards model used to examine the relations between risk factors and CHD death 3. **Primary Outcome:** Rank order of risk for individuals in the U.S. White population.	FHS 1948 NHANES I epidemiologic followup study 1971 NHANES II mortality followup study 1976 Inclusion/ exclusion NR	Candidate risk factors: Age, SBP, DBP, serum cholesterol, smoking ■ The age-adjusted mortality rate from all causes and CHD was the highest in the Framingham cohort and the lowest in NHANES II. ■ With a few exceptions, the major risk factors were significantly and independently related to CHD death for both sexes in all three cohorts: – The magnitude of the coefficients across cohorts, especially in men, was heterogeneous. – The greatest variation was in smoking and the least in SBP. – Cholesterol had a greater effect in Framingham relative to both national samples; smoking was much weaker. – When the analyses accounted for the complex sampling design (NHANES I and II), the difference in SBP across cohorts was no longer statistically significant. – Interactions between age and other risk factors occurred: age-SBP in men in NHANES I; age-cholesterol in women in NHANES I and II; age-smoking in women in NHANES I. – A quadratic relation between serum cholesterol and CHD mortality rate was found only in women in NHANES I. ■ The percentage distributions (*y*-axis) of the observed (actual) CHD deaths in 15 years were plotted by each quintile of risk: – For men, only 7.4% to 12.6% of the observed CHD deaths appeared in the lower two quintiles compared with 72.4% to 77.1% in the upper two. – For women, the corresponding proportions were 5.3% to 8.2% of the observed CHD deaths in the lower two quintiles compared with and 82.7% to 87.7% in the upper two. – The ratios of the number of cases in the highest two quintiles to the number of cases in the lowest two quintiles were 6 to 10 in men and 12 to 16 in women – All models had similar levels of accuracy in ordering risk; goodness-of-fit tests comparing observed versus predicted number of CHD deaths were mostly statistically significant ($p < .05$), except among women in NHANES II, who were ranked by their own population equation and among women in NHANES I, who were ranked by the equation from the Framingham Study. ▪ These results suggest poor fit of the models in predicting absolute number of deaths, especially in men. ▪ ROC areas suggest that all the mortality equations predict better than chance. ■ The percentage distributions (*y*-axis) of the observed (actual) CHD deaths in 15 years were plotted by each quintile of risk: – The performance of different risk functions when applied to a second population (either NHANES I or NHANES II cohort) was nearly identical, as assessed by area under the ROC. ▪ Applied to the 15-year followup of men in NHANES I, the area under the curve (AUC) was 0.71 by use of either the Framingham or NHANES I model; for women, the corresponding AUCs were 0.80

Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				and 0.81, respectively. ▪ When models from Framingham and NHANES II were applied to the NHANES II cohort, the AUCs were 0.74 and 0.75, respectively, for men, and 0.76 and 0.77, respectively, for women. ▪ Summary: All the models had similar ability to rank risk. – With the Framingham equation to predict 15-year CHD death in NHANES I, when the false-positive rate was 33%, the true-positive rate was 67% in men and 83% in women. – Applying the Framingham equation to NHANES II, the true-positive rate was 71% in men and 77% in women. – These equations correctly predict two-thirds to three-fourths of cases, while mistakenly classifying one-third of non-cases as cases. – The predicted probability of CHD death was calculated in the NHANES I cohort using the NHANES I equation. – Appreciable overlap occurs in the distribution of the predicted probabilities between those who died from CHD in 15 years and those who did not. ▪ Among men, median predicted probability of CHD death was 16.2% in cases and 7.1% in noncases. ▪ Among women, the median was 12.8% in cases and 18% in non-cases. ▪ The interquartile differences in cases versus non-cases were 13.5% versus 11.2% in men and 12.6% versus 6.6% in women. ■ The percentage distributions (*y*-axis) of the observed (actual) CHD deaths in 15 years were plotted by each quintile of risk: – Using the Framingham equation to predict absolute survival rate of CHD in the two more recent cohorts, the observed and predicted survival curves were very close for women. Framingham overpredicted CHD mortality rates in men for both cohorts. – The predicted 15-year cumulative NHANES I CHD mortality in men was 11.6%, vs. observed rate of 10.4%. ▪ For men in NHANES II, the CHD mortality rate was 11.4% predicted vs. 7.4% observed.
Framingham Heart Study[76] Good To investigate whether Framingham 10-year risk equations could reliably stratify lifetime risk for CHD in men and women free of CHD at selected ages. See p. 7 in evidence table	*N*: 6,216 25 years max	1. Stratification by age- and sex-specific tertiles of Framingham risk score (FRS) 2. Lifetime risk for CHD estimated 3. Risk score calculated at each exam and assigned FRS based on mean of subject's calculated risk scores in 5 years before each index age of 40, 50, 60, 70, and 80 4. Men and women stratified separately into tertiles of risk score for each index age 5. **Primary Outcome:** Lifetime risk for CHD by tertile of	Subjects examined between 1971 and 1976 Ages 40 to 94, without CHD	■ 10-year risk score: Categorical values of age, total cholesterol, HDL-C, BP, smoking, and diabetes. ■ For women at all ages, the 10-year risk score appeared to discriminate lifetime risk well, with 1.5- to 3-fold gradients in remaining lifetime risk between the highest and lowest tertiles. ■ In men, the 10-year risk score discriminated lifetime risk less well at younger ages, but it performed better at older ages as remaining life expectancy approached 10 years. – In men and women, overall lifetime risk for CHD decreased with advancing index age because of increasing competing risk for death and depletion of susceptible individuals at younger ages. – Lifetime risks for hard CHD events, excluding angina pectoris as an initial CHD event, showed similar patterns of risk discrimination, but absolute lifetime risk for hard CHD was slightly lower. – The FRS stratified 10-year cumulative risk well, even in the context of the competing risk for death free of CHD, for men and women at all ages. – At older ages, the 10-year and lifetime risks more closely approximated each other. – Younger subjects in the lowest risk tertiles, who had very low 10-year risks of CHD, still had a

Study/ Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
		FRS at specific ages. CHD events included angina pectoris, coronary insufficiency, MI, and death due to CHD.		substantial lifetime risk for CHD. – At ages 40 and 50, no group had a 10-year cumulative risk of>20%. – In men, only the highest tertile at ages 60, 70, and 80 was >20% risk threshold in 10 years; in women, only the highest tertile at age 80 was at >20% risk threshold in 10 years.
The Framingham Heart Study[78] Good To systematically assess the potential advantages of using the multivariate risk score based on updated, instead of baseline, risk factors in CHD prediction and to establish the optimal frequency of updating. See p.9 in evidence table	*N*:4,962 30 years max	1. "Prognostic" approach: Current and/or subsequent risk factor values were used for CHD prediction 2. "Lagged" approach: Risk factor values from the preceding 2 years (current) and earlier examinations were assessed for their relation to the development of CHD at a given examination 3. **Primary Outcome:** Predictive ability of three multivariable risk scores for 10, 14, and 30 years of followup. End point was the first occurrence of CHD, defined as MI, angina pectoris, coronary insufficiency, or CHD death	Study began 1948 Subjects with no CHD Ages 28 to 62 44.8% male	Candidate risk factors: age, current smoking, SBP, BMI, glucose intolerance, and serum total cholesterol. Study reports on Multiple Risk Score models, but only lagged models (6, 10, and 20 years) are included here. ■ For younger men, current risk factor values (R^2 =.024; c=0.63) yield statistically significantly higher R^2 and C-statistics than do the values observed 10 (R^2 $_{difference}$= 0.016 and $c_{difference}$= 0.05 higher) or 20 (R^2 $_{difference}$=0.015 and $c_{difference}$ = 0.05 higher) years earlier. ■ For younger women, current risk factor values (R^2 =.022; c=0.63) perform significantly better than do the values lagged by 20 (R^2 $_{difference}$= 0.012 and $c_{difference}$ = 0.06 higher) years only ■ In contrast, for older women, compared with current values, (R^2 =.002; c=0.53) 6-year lagging *improved* significantly the R^2 and C-statistics(R^2 $_{difference}$=–0.009 and $c_{difference}$ =–0.05 lower), compared with current values. ■ For older men, the current values yielded better results than did any of the lagged values, but the differences were not significant. ■ In most of these cases, similar differences were observed for the corresponding deviances, but they were not statistically significant.
The Framingham Heart Study[70] Good To estimate the lifetime risk for ASCVD and to examine overall survival in the presence and absence of established factors See p. 10 in evidence table	*N*: NR Followup time NR	1. A modified survival analysis used with information provided about the incidences of ASCVD and death free of ASCVD for each age patients attained during followup 2. **Primary Outcome:** Lifetime risk for ASCVD	Study began 1971 Subjects examined between 1971 and 2002 No ASCVD, age 50+	Risk factors: BMI, smoking, BP, total cholesterol, diabetes, SBP, DBP: ■ Increasing BP and total cholesterol were associated with increased lifetime risk for ASCVD and with shorter median survival in both men and women. ■ The presence of diabetes at age 50 conferred the highest lifetime risk for ASCVD of any single risk factor, at 67.1% for diabetic men and 57.3% for diabetic women through age 75. ■ Median survival was substantially lower among men with and without diabetes compared to women. Overweight and obesity were associated with modest increases in lifetime risk and reductions in survival compared with normal weight. ■ Stratification by burden of risk factors at age 50, the magnitude of lifetime risk rose steeply from those with optimal risk factor levels to those with ≥2 major risk factors; median survival declined substantially. ■ Compared with participants with ≥2 major risk factors, participants with optimal levels had substantially lower lifetime risks (5.2% versus 68.9% in men, 8.2% versus 50.2% in women) and markedly longer median survivals (by >11 years in men, >8 years in women). ■ For both men and women older than 50, the adjusted cumulative incidence curves across aggregate risk strata separated early and continued to diverge throughout the remaining lifespan. ■ When low HDL cholesterol (<1.03 mmol/L [(<40 mg/dL] in men, <1.29 mmol/L [<50 mg/dL] in women) and obesity (BMI≥30 kg/m^2) were included as major risk factors, lifetime risks for ASCVD were similar to those

Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				shown in figure 2, indicating that low HDL cholesterol and obesity were equivalent to major risk factors. ■ Lifetime risk for ASCVD was similar for smokers and nonsmokers. ■ Among men free of ASCVD at age 50, lifetime risk to age 95 for developing ASCVD was 51.7% (95% CI, 49.3 to 54.2); median overall survival in men was 30 years. ■ Among women, lifetime risk to age 95 was 39.2% (95% CI, 37.0 to 41.4), with median overall survival of 36 years. ■ Lifetime risks for hard ASCVD to age 95 were 41.2% (95% CI, 38.8 to 43.7) in men and 28.8% (95% CI, 26.6 to 30.8) in women. ■ The relative effect of some risk factors on lifetime risks for ASCVD differed through age 75 compared with effects through age 95: – Smoking and elevated BP at age 50 were associated with greater relative increases in lifetime risk for ASCVD through age 75 than through age 95. – Elevated cholesterol was associated with a fairly constant relative effect on lifetime risk for ASCVD.
The Framingham Heart Study[73] Good To develop a tool for estimating 30-year risk for hard ASCVD events among individuals free of the condition at baseline See p. 14 in evidence table	*N*: 4,506 Median 32 years	1. Used Cox regression to assess effect of risk factors measured at baseline on the long-term risk for hard ASCVD. 2. Second model used full ASCVD as outcome. 3. **Primary Outcome:** "Hard" ASCVD events defined as a composite of hard CHD events, such as coronary death, MI, stroke (fatal and nonfatal)	Study began 1971 Offspring of original Framingham cohort, ages 20 to 59 with complete risk factor profile, no ASCVD or cancer 48.2% male	Candidate risk factors: Age, SBP, DBP, antihypertensive treatment, total and HDL-C, LDL-C, smoking, diabetes, triglycerides, BMI ■ The 30-year rate of hard ASCVD adjusted for the competing risk for non-ASCVD death (Kaplan-Meier) was 7.6% for women and 18.3% for men: – Male sex, age, SBP, antihypertensive treatment, total and HDL cholesterol, smoking, and diabetes were highly significant (0.01 level) in the multivariable model. – DBP and triglycerides were not statistically significant. – Inclusion of LDL-C in place of total cholesterol did not improve model performance. – BMI was weakly significant in the final model (p=.04); it did not increase the *C*-statistic and had a nonsignificant net reclassification improvement of <1%, and was not included in the main risk prediction model. In a simplified office-based risk model BMI replaced lipids and was highly significant with all other risk factors (p<0.01). ■ The 30-year risk model offered excellent discrimination (cross-validated *C*-statistic=0.803; 95% CI, 0.786 to 0.820; internally validated *C*-statistic=0.802; 95% CI, 0.772 to 0.832) and calibration (cross-validated Nam-D'Agostino χ^2=4.25; p=.894; internally validated χ^2=3.98; p=.913) (adjusting for the competing risk for non-CVD death, improved the model). ■ Contrast of estimated 30-year risks of hard ASCVD adjusted for the competing risk for non-CVD death with 10-year risks: – 10-year models suggest negligible risk levels (<2.5% in women and 5% in men). – 30-year model estimates are almost 10 times higher (e.g., 10-year risk for a 25-year-old smoking woman with adverse lipid profile and hypertension is only 1.4%, but the corresponding 30-year risk reaches 12%). ■ In time-dependent analysis updating all variables approximately every 4 years, all standard risk factors remained significantly related to the hard ASCVD outcome with hazard ratios similar to those obtained in 30-year risk models:

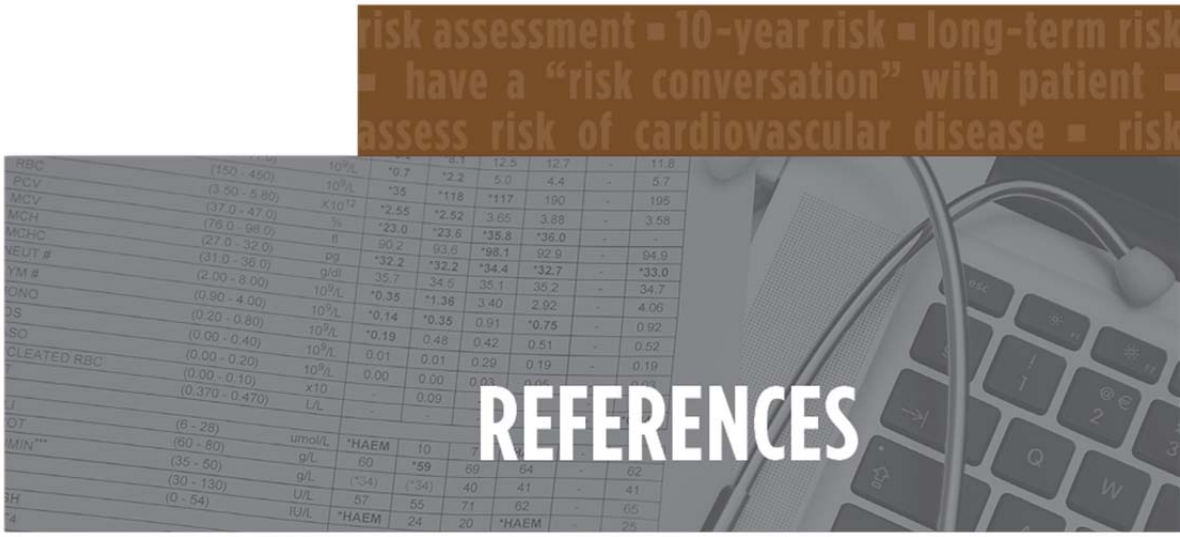
Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				– The hazard ratio for smoking increased by approximately one-third in the time-dependent model. – For hard ASCVD, BMI was weakly significant in the long-term, 30-year model (hazard ratio=1.10 per 1 SD; *p*=.04) but lost its entire impact (hazard ratio=0.99; *p*=.82) in the time-dependent model. ■ Comparison with alternative approaches for risk prediction: – Mean estimated 30-year risks based on "adjusted" approach were 7.9% for women and 18.0% for men. – "Naive" approach risks were 4.1% for women and 13.3% for men. – Ignoring competing risk for non-CVD death ("unadjusted" approach), the mean risks increased to 8.6% for women and 20.4% for men. – Risks based on the "combined" approach averaged across the cohort were even higher, but the relationship varied across individuals with different levels of risk factors. – Calculated 30-year risks for individuals with different combinations of risk factors, the unadjusted approach consistently overestimated the correct predictions based on the adjusted model: ▪ The combined approach underestimated the true risk for those with lower risk (younger and with fewer risk factors) and overestimated the risk in those with higher risk (older with several risk factors). ▪ Differences were larger for higher risk levels (>20%). – There was a 10% (95% CI, 6% to 14%) net reclassification improvement from using adjusted 30-year risk estimates over the tripled 10-year risks (naive approach) but no improvement when compared with the unadjusted or combined approaches.
Headache and the Risk for Stroke[84] Good To find out whether self-reported chronic headache predicts stroke or a particular type of stroke event in a large prospective cohort. To determine whether this association was independent of other cardiovascular risk factors, such as BP, smoking, diabetes, obesity, and serum cholesterol. See p. 16 in evidence table	*N*: 35,056 23 years max	1. Standard *t* and chi-squared tests were used to assess the cardiovascular risk factor distribution at baseline 2. Multivariate analyses were performed using Cox proportional hazards model 3. The association of chronic headache with the risk for stroke was analyzed for 1, 5, and a maximum of 23 years of followup 4. **Primary Outcome:** Predictive value of chronic unspecified headache for stroke	Study began 1972 Finnish men and women, ages 25 to 64 with completed data, no history of stroke 48.5% male	Candidate risk factors: Age, smoking, SBP, BMI, diabetes, cholesterol, oral contraceptive use ■ During the 1st year of followup, men with headache had a 4-times higher risk for stroke compared with men without headache. ■ The association of headache with the risk for stroke decreased markedly when followup time was extended: – During the 5-year followup, the age-adjusted hazard ratio was 1.86. – During the 23-year followup, the age-adjusted hazard ratio was 1.24. – Adjustment for smoking, SBP, BMI, diabetes, and serum cholesterol level slightly decreased the hazard ratios. ■ Among women, the headache-associated hazard ratios of stroke also increased, although not significantly.

Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
The Seven Countries Study[74] Good To study the time-related association of a single measurement of coronary risk factors with CHD deaths occurring during a very long followup period in a population sample of middle-aged men. See p. 20 in evidence table	*N*: 1,622 35 years max	1. Cox proportional hazards model using the BMDP standard statistical package 2. A model was produced using all events that occurred during the 35 years of followup, as a function of baseline risk factor measurements 3. Seven results were computed, each dealing with events occurring in subsequent and independent blocks of five years—for a total of 35 years—corresponding to the so called partitioned or segmented modeling approach 4. **Primary Outcome:** To predict risk for CHD death	Study began 1960 Men, no CHD, all six risk factor measurements were available	Candidate risk factors: Age, SBP, serum total cholesterol, physical activity at work, BMI, and cigarette smoking ■ Seven proportional hazards analyses with CHD death as end point, each for an independent 5-year interval of followup, showed that coefficients for SBP were significant on four occasions, age and cholesterol three times, physical activity and cigarette smoking twice, and BMI on no occasion. ■ Time trends of cumulated hazard ratio scores for age, SBP, and cholesterol increased at each subsequent 5-year interval of followup, suggesting relatively regular and constant association of risk factors with events during the whole followup period. ■ The 95% lower confidence limits for age and SBP become >0 around year 10, while that of serum cholesterol was always >0. ■ The regression lines suggest good fits, but the impression is that the curve for SBP tended to flatten after year 20 and for cholesterol became a little less steep after year 10. ■ There was little relation between BMI and CHD deaths at any followup point. ■ The curve for cigarette smoking increased during the 35 years of followup but rather irregularly and mainly during the first 20 years: – There were large average increases in mean levels of most risk factors: ▪ SBP increased from 143.6 mmHg at baseline to 153.2 mmHg at year 10 and 166.7 mmHg at year 25 and stabilized or declined thereafter, ▪ Serum cholesterol increased from 5.21 mmol/L (201.6 mg/dL) to 5.58 mmol/L (215.8 mg/dL) after 10 years and 5.84 mmol/L (225.8 mg/dL) after 25 years and then stabilized or declined thereafter ▪ There was a steady decline in cigarette consumption and in mean levels of physical activity, with slight changes in BMI. – SBP and serum cholesterol coefficients were adjusted for interim changes and derived from independent models for the 6 to 10 and 11 to 15 year periods: ▪ Partitioned coefficients in models adjusted for risk factor changes were, on average, larger than disregarded changes, except for cholesterol during the third 5-year period. ■ In general, all the curves of the cumulated hazard ratio scores were set at a higher level. Curves of the hazard function adjusted for changes and limited to the first 15 years, for SBP and serum cholesterol shape of the curves were approximately the same.
The British Regional Heart Study[71] Fair To compare MetS with the FRS as predictors of CHD, stroke, and type 2 diabetes in middle-aged men. Seep. 1 in evidence table	*N*: 5,128 21.3 years mean followup	1. Cox proportional hazard model assessed the adjusted relative risks 2. ROC curves and their respective AUC were used to compare the ability of the FRS and the number of metabolic abnormalities to predict CHD and DM2 3. **Primary outcome:** Prediction of CHD using MetS and FRS	Study began 1978 Men ages 40 to 59 with no history of ASCVD (CHD or stroke) or DM2	Candidate risk factors: Age, current cigarette smoker, inactive, manual social class, nondrinker, heavy drinker, BMI, SBP, DBP, triglycerides, HDL-C, cholesterol, glucose, hypertension, MetS and its components (high triglycerides, low HDL-C; high glucose, obesity) ■ Men with MetS at baseline (26%) showed significantly higher relative risk (RR) than men without MetS (adjusted for age, smoking status, social class, physical activity level, and alcohol intake) for: – CHD (RR, 1.64; 95% CI, 1.41–1.90) – Stroke (RR, 1.61 95% CI, 1.26–2.06) ■ The probability of developing ASCVD or diabetes over 20 years increased from 11.9% in those with no abnormalities to 31.2 % in those with three abnormalities and to 40.8% in those with four or more abnormalities. ■ The subjects in the top quintile of the FRS showed higher probability of developing CHD than those with four or more abnormalities for both 10- and 20-year followup. ■ FRS was a significantly better predictor of CHD than number of metabolic abnormalities at both 10 and 20 years, but less predictive of diabetes (p<.001 for all differences).

Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				■ MetS provided no additional predictive value for CHD when FRS was included in the multivariate model but remained strongly associated with diabetes (adjusted RR, 1.14; 95% CI, 0.96–1.35 for CHD). ■ MetS had a higher sensitivity for diabetes than for CHD at both 10 and 20 years' followup. ■ For a given specificity (fixed at the specificity levels for MetS), the FRS was more sensitive than MetS in identifying CHD cases for both 10- and 20-year events but less sensitive than MetS in identifying diabetes. ■ The FRS also was a significantly better discriminator of CHD than the number of metabolic abnormalities (AUC, 0.73; 95% CI, 0.71–0.75 vs. AUC, 0.63; 95% CI, 0.61–0.65 for 10 years and AUC, 0.68; 95% CI, 0.66–0.70 vs. AUC, 0.59; 95% CI, 0.57–0.61 for 20 years; p<.001 for all). ■ The FRS also was a significantly better discriminator of stroke than the number of metabolic abnormalities (AUC, 0.71; 95% CI, 0.65–0.77 vs. AUC, 0.54; 95% CI, 0.48–0.60 for 10 years and AUC, 0.66; 95% CI, 0.62–0.70 vs. AUC, 0.55; 95% CI, 0.51–0.59 for 20 years; p<.001 for all).
The Oslo Study[72] Good To examine the predictive role of BMI and other CHD risk factors at prespecified periods of followup using a test for trend See p. 18 in evidence table	*N*: 14,403 21 years mean followup	1. Cox proportional hazards regression analyses were used to analyze the predictive ability of risk factors for CHD mortality for 5-year periods 2. **Primary Outcome:** Trends for risk factor's predictiveness of fatal CHD	Study began 1972 Men, ages 40 to 49, no CHD	Candidate risk factors: Age, total cholesterol, SBP, DBP, glucose, triglycerides, BMI, smoker, sedentary, physical activity at leisure (sedentary, moderate, vigorous), mental stress variables (chooses high activity rather than a peaceful life, increased psychic tension or irritation during recent years, increased pressure due to deadlines at work) ■ The number of CHD deaths during followup was 485. The cumulative 21 years fatal CHD rate was 1.78/1,000 person-years. ■ Examined unadjusted rate ratios of CHD risk according to quintiles of BMI for 1 to 10 years and 11 to 21 years of followup. ■ A U-shaped relationship was observed during the first 10 years. During the subsequent 10 years of followup, CHD risk was higher for every BMI quintile compared with the first 10 years, most markedly for the highest quintile. ■ The risk curve resembled a J- rather than a U-shape. ■ Levels of total serum cholesterol, triglycerides, glucose, SBP, BMI, cigarette smoking, and physical activity were significant predictors of fatal CHD after age adjustment in univariate analyses. ■ In multivariate analyses, in addition to age, serum cholesterol, SBP, and cigarette smoking remained significant predictors of fatal CHD, but not BMI. ■ Relation between risk factors and risk for fatal CHD by prespecified periods of followup: age, cigarette smoking, serum cholesterol, and SBP were significant predictors of CHD during all four periods of followup, though the effect of cigarette smoking weakened significantly with time (p for trend =.01). Physical activity was protective for 10 years (p for trend =.053). ■ Questions on mental stress did not predict the fatal CHD at any time point, though the trait variable tended to predict this end point during the first 5 years of followup, but not subsequently (p for trend =.03) ■ Increasing BMI was predictive of increased risk in the Cox analyses only after 15 years of followup (p for trend =.002). ■ Moderate risk increase from the second quintile of BMI during the second 10-year period of followup. An elevation in BMI of one unit (kg/m^2) was associated with a multivariate relative risk for fatal CHD of 1.02 (95% CI, 1.00–1.05) over 21 years. When each 5-year period was examined separately, the relative risk was 0.96 (95% CI, 0.89–1.04) during the first 5 years of followup, 0.99 (95% CI, 0.93–1.06) during the

Study/Grade/ Objective	Sample/ Duration	Analysis/ Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				second 5 years, 1.03 (95% CI, 0.98–1.08) during the third 5 years, and 1.06 (95% CI, 1.01−1.10) during the final 5 years.
The Chicago Heart Association study[69] Good To assess the associations of traditional risk factors with CVD; To determine the relative strength of the association between a single measurement of traditional risk factors at baseline and CVD death across three unique followup periods—0 to 10, 10 to 20, and >20 years followup periods See p. 2 in evidence table	*N*: 16,608 33 years mean followup	1. Cox proportional hazards models constructed for each followup period; indicate periods: 0 to 10, 10 to 20, >20 years 2. Models included age, some physical characteristic, and electrocardiographic abnormalities 3. Standardized coefficients and standard errors for risk factors were compared across three followup intervals 4. **Primary Outcome:** Strength of the association between traditional risk factors and CVD death	Study began 1967 Ages 40 to 59, free of CHD 54.4% male	Candidate risk factors: Age, SBP, serum total cholesterol, BMI, smoking, diabetes, major electrocardiographic abnormalities, and minor electrocardiographic abnormalities ■ The results demonstrate a progressive increase in unadjusted mortality rates across each period of followup for both men and women for CVD, CHD, and non-CVD mortality. ■ Rates for CVD and CHD death were low for women in the initial decade of followup. ■ SBP, total cholesterol, current smoking, and diabetes were independently associated with CVD death during nearly all followup intervals in men and women. ■ The HR for CVD death associated with SBP differed significantly across followup periods and decreased in later followup periods in both men and women. ■ The HR for total cholesterol did not differ across followup periods. – There were gender differences for other risk factors in association with CVD death. ■ In men, the HR for diabetes remained consistent across the followup periods. ■ In women, the HR for diabetes showed a decrease in strength across the distinct followup periods. ■ Sex differences for smoking showed a similar pattern. ■ For BMI in men, the HR increased across the followup periods but not in women. ■ The association of baseline major and minor electrocardiographic abnormalities with CVD death in men was strong in the initial followup period, with marked attenuation in the subsequent followup periods. ■ In women, there was no consistent association. – Results were similar for CHD death as the end point.

Note: ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; CHD = coronary heart disease; DBP = diastolic blood pressure; FHS = Framingham Heart Study; FRS = Framingham Risk Score; HDL-C = high density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; ROC = receiver operator characteristic; SBP = systolic blood pressure.


risk assessment ▪ 10-year risk ▪ long-term risk
▪ have a "risk conversation" with patient ▪
assess risk of cardiovascular disease ▪ risk
REFERENCES

References

1. 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) final report. *Circulation.* 2002;106(25):3143-421.

2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003 December 1;42(6):1206-52.

3. National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. Bethesda, MD: National Institutes of Health, 1998.

4. Eden J, Levit L, Berg A, Morton S, editors. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington: National Academies Press; 2011.

5. Graham R, Mancher M, Wolman DM. *Clinical Practice Guidelines We Can Trust*. Washington (DC): National Academies Press; 2011.

6. Gibbons GH, Harold JG, Jessup M, Robertson RM, Oetgen W. Next steps in developing clinical practice guidelines for prevention. *Circulation.* 2013 Aug 8;128(15):1716-7.

7. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *Circulation.* 2013 [Epub ahead of print].

8. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2013 [Epub ahead of print].

9. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013 [Epub ahead of print].

10. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee IM, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013 [Epub ahead of print].

11. Lackland DT, Elkind MS, D'Agostino R Sr, Dhamoon MS, Goff DC Jr, Higashida RT, et al. Inclusion of stroke in cardiovascular risk prediction instruments: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2012 Jul;43(7):1998-2027.

12. 27th Bethesda Conference. Matching the intensity of Risk Factor Management with the Hazard for Coronary Disease Events. September 14–15, 1995. *J Am Coll Cardiol.* 1996 Apr;27(5):957-1047.

13. Shillinglaw B, Viera AJ, Edwards T, Simpson R, Sheridan SL. Use of global coronary heart disease risk assessment in practice: a cross-sectional survey of a sample of U.S. physicians. *BMC Health Serv Res.* 2012;12:20.

14. Sheridan SL, Viera AJ, Krantz MJ, Ice CL, Steinman LE, Peters KE, et al. The effect of giving global coronary risk information to adults: a systematic review. *Arch Intern Med.* 2010 Feb 8;170(3):230-9.

15. Redberg RF, Benjamin EJ, Bittner V, Braun LT, Goff DC, Jr., Havas S, et al. AHA/ACCF 2009 performance measures for primary prevention of cardiovascular disease in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on performance measures (writing committee to develop performance measures for primary prevention of cardiovascular disease): developed in collaboration with the American Academy of Family Physicians; American Association of Cardiovascular and Pulmonary Rehabilitation; and Preventive Cardiovascular Nurses Association: endorsed by the American College of Preventive Medicine, American College of Sports Medicine, and Society for Women's Health Research. *Circulation.* 2009 Sep 29;120(13):1296-336.

16. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2009 Mar 17;150(6):396-404.

17. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J.* 2012 Jul;33(13):1635-701.

18. Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *Can J Cardiol.* 2009 Oct;25(10):567-79.

19. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008;117(6):743-53.

20. 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 Jul 11;286(2):180-7.

21. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC Investigators. *Am J Epidemiol.* 1989;129(4):687-702.

22. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet Med.* 2009 Feb;26(2):142-8.

23. 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 Münster (PROCAM) study. *Circulation.* 2002;105(3):310-5.

24. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J.* 2003 Jun;24(11):987-1003.

25. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ.* 2007 Jul 21;335(7611):136.

26. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* 2007 Feb 14;297(6):611-9.

27. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation.* 2008;118(22):2243-51.

28. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998 1998/05/12/;97(18):1837-47.

29. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J.* 1991 Jan;121(1 Pt 2):293-8.

30. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* 1991 Feb;1(3):263-76.

31. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol.* 1988;41(11):1105-16.

32. Rose KM, Foraker RE, Heiss G, Rosamond WD, Suchindran CM, Whitsel EA. Neighborhood socioeconomic and racial disparities in angiography and coronary revascularization: the ARIC surveillance study. *Ann Epidemiol.* 2012 Sep;22(9):623-9.

33. Mumma BE, Baumann BM, Diercks DB, Takakuwa KM, Campbell CF, Shofer FS, et al. Sex bias in cardiovascular testing: the contribution of patient preference. *Ann Emerg Med.* 2011 Jun;57(6):551-60 e4.

34. Takakuwa KM, Shofer FS, Limkakeng AT Jr, Hollander JE. Preferences for cardiac tests and procedures may partially explain sex but not race disparities. *Am J Emerg Med.* 2008 Jun;26(5):545-50.

35. Epstein AM, Weissman JS, Schneider EC, Gatsonis C, Leape LL, Piana RN. Race and gender disparities in rates of cardiac revascularization: do they reflect appropriate use of procedures or problems in quality of care? *Med Care.* 2003 Nov;41(11):1240-55.

36. Ibrahim SA, Whittle J, Bean-Mayberry B, Kelley ME, Good C, Conigliaro J. Racial/ethnic variations in physician recommendations for cardiac revascularization. *Am J Public Health.* 2003 Oct;93(10):1689-93.

37. 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 Jan 30;27(2):157-72; discussion 207-12.

38. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med.* 2011 Jan 15;30(1):11-21.

39. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat Med.* 2011 May 10;30(10):1105-17.

40. D'Agostino RB, Nam BH. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan N, Rao CR, editors. *Handbook of Statistics 23: Advances in Survival Analysis.* New York: Elsevier; 2004. p. 1-25.

41. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation.* 2009 May 5;119(17):2408-16.

42. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009 May 5;150(9):604-12.

43. Hosmer DW, Lemeshow S. *Applied Logistic Regression, Second Edition*. New York: John Wiley & Sons; 2000.

44. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol.* 2002 Nov 1;156(9):871-81.

45. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-43.

46. Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008. *Circulation.* 2012 Apr 17;125(15):1848-57.

47. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med.* 2010 Jun 10;362(23):2155-65.

48. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA.* 2003 Aug 20;290(7):891-7.

49. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2009;151(7):483-95.

50. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2009;151(7):496-507.

51. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet.* 2010;375(9709):132-40.

52. Schnell-Inderst P, Schwarzer R, Göhler A, Grandi N, Grabein K, Stollenwerk B, et al. Prognostic value, clinical effectiveness, and cost-effectiveness of high-sensitivity C-reactive protein as a marker for major cardiac events in asymptomatic individuals: a health technology assessment report. *Int J Technol Assess Health Care.* 2010;26(1):30-9.

53. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008 Nov 20;359(21):2195-207.

54. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA.* 2009;302(18):1993-2000.

55. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes.* 2011;4(3):337-45.

56. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, 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(19):2024-35.

57. Fowkes FGR, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008;300(2):197-208.

58. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? *J Am Coll Cardiol.* 2012 Feb 7;59(6):553-65.

59. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. *Arch Intern Med.* 2009 Jul 13;169(13):1188-94.

60. Iribarren C, Hlatky MA, Chandra M, Fair JM, Rubin GD, Go AS, et al. Incidental pulmonary nodules on cardiac computed tomography: prognosis and use. *Am J Med.* 2008 Nov;121(11):989-96.

61. Burt JR, Iribarren C, Fair JM, Norton LC, Mahbouba M, Rubin GD, et al. Incidental findings on cardiac multidetector row computed tomography among healthy older adults: prevalence and clinical correlates. *Arch Intern Med.* 2008 Apr 14;168(7):756-61.

62. Killeen RP, Cury RC, McErlean A, Dodd JD. Noncardiac findings on cardiac CT. Part II: spectrum of imaging findings. *J Cardiovasc Comput Tomogr.* 2009 Nov-Dec;3(6):361-71.

63. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, 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. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr.* 2008 Feb;21(2):93-111; quiz 89-90.

64. Ford ES, Giles WH, Mokdad AH. The distribution of 10-Year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. *J Am Coll Cardiol.* 2004 May 19;43(10):1791-6.

65. Marma AK, Berry JD, Ning H, Persell SD, Lloyd-Jones DM. Distribution of 10-year and lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes.* 2010;3(1):8-14.

66. Marma AK, Lloyd-Jones DM. Systematic examination of the updated Framingham heart study general cardiovascular risk profile. *Circulation.* 2009 Aug 4;120(5):384-90.

67. Berry JD, Lloyd-Jones DM, Garside DB, Greenland P. Framingham risk score and prediction of coronary heart disease death in young men. *American Heart Journal.* 2007 Jul;154(1):80-6.

68. 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 Dec;47(6):619-23.

69. Berry JD, Dyer A, Carnethon M, Tian L, Greenland P, Lloyd-Jones DM. Association of traditional risk factors with cardiovascular death across 0 to 10, 10 to 20, and >20 years follow-up in men and women. *Am J Cardiol.* 2008;101(1):89-94.

70. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PWF, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation.* 2006;113(6):791-8.

71. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs. Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med.* 2005;165(22):2644-50.

72. Håheim LL, Tonstad S, Hjermann I, Leren P, Holme I. Predictiveness of body mass index for fatal coronary heart disease in men according to length of follow-up: a 21-year prospective cohort study. *Scand J Public Health.* 2007;35(1):4-10.

73. Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham heart study. *Circulation.* 2009;119(24):3078-84.

74. Menotti A, Lanti M. Coronary risk factors predicting early and late coronary deaths. *Heart.* 2003;89(1):19-24.

75. Menotti A, Lanti M, Puddu PE, Mancini M, Zanchetti A, Cirillo M, et al. First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study. *Ital Heart J.* 2000;1(6):394-9.

76. Lloyd-Jones DM, Wilson PWF, Larson MG, Beiser A, Leip EP, D'Agostino RB, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. *Am J Cardiol.* 2004;94(1):20-4.

77. Liao Y, McGee DL, Cooper RS, Sutkowski MB. How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts. *Am Heart J.* 1999;137(5):837-45.

78. Karp I, Abrahamowicz M, Bartlett G, Pilote L. Updated risk factor values and the ability of the multivariable risk score to predict coronary heart disease. *Am J Epidemiol.* 2004;160(7):707-16.

79. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997 Mar 1;126(5):376-80.

80. Dubben HH, Beck-Bornholdt HP. Systematic review of publication bias in studies on publication bias. *BMJ.* 2005 Aug 20;331(7514):433-4.

81. The Cochrane Collaboration. Publication Bias: The Cochrane Collaboration; 2002 [cited 2012 July 20]. Available from: http://www.cochrane-net.org/openlearning/HTML/mod15-2.htm.

82. Shaneyfelt T, Ortiz E. Applying evidence to the care of a patient with heart failure and chronic obstructive pulmonary disease: how to find and use a systematic review. *Semin Med Pract.* 2006 2006/08/01;9:29-40.

83. White CM, Ip S, McPheeters M, Carey TS, Chou R, Lohr KN, et al. Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Rockville (MD): Agency for Healthcare Research and Quality; 2008.

84. Jousilahti P, Tuomilehto J, Rastenyte D, Vartiainen E. Headache and the risk of stroke: a prospective observational cohort study among 35,056 Finnish men and women. *Arch Intern Med.* 2003;163(9):1058-62.

U.S. Department of Health and Human Services
National Institutes of Health

NIH
National Heart, Lung,
and Blood Institute