2013 Report on the Assessment of Cardiovascular Risk:

Full Work Group Report Supplement

Based on a Systematic Review From the National Heart, Lung, and Blood Institute

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PREAMBLE AND TRANSITION TO ACC/AHA GUIDELINES TO REDUCE CARDIOVASCULAR RISK

The goals of the American College of Cardiology (ACC) and the American Heart Association (AHA) are to prevent cardiovascular (CV) diseases, improve the management of people who have these diseases through professional education and research, and develop guidelines, standards and policies that promote optimal patient care and cardiovascular health. Toward these objectives, the ACC and AHA have collaborated with the National Heart, Lung, and Blood Institute (NHLBI) and stakeholder and professional organizations to develop clinical practice guidelines for assessment of CV risk, lifestyle modifications to reduce CV risk, and management of blood cholesterol, overweight and obesity in adults.

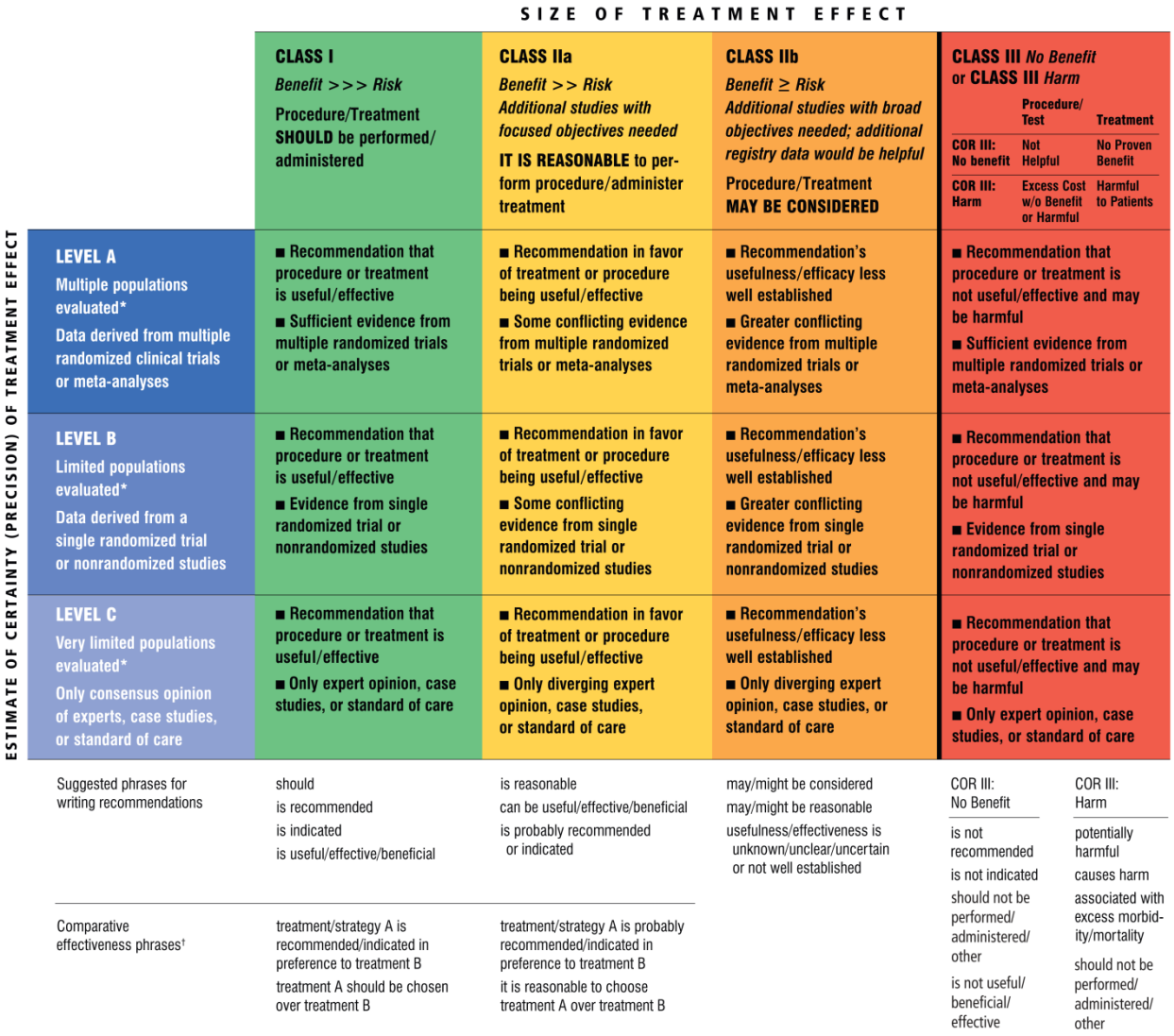
In 2008, the NHLBI initiated these guidelines by sponsoring rigorous systematic evidence reviews for each topic by expert panels convened to develop critical questions, interpret the evidence and craft recommendations. In response to the 2011 report of the Institute of Medicine on the development of trustworthy clinical guidelines (1), the NHLBI Advisory Council (NHLBAC) recommended that the NHLBI focus specifically on reviewing the highest quality evidence and partner with other organizations to develop recommendations (2,3). Accordingly, in June 2013 the NHLBI initiated collaboration with the ACC and AHA to work with other organizations to complete and publish the 4 guidelines noted above and make them available to the widest possible constituency. Recognizing that the expert panels did not consider evidence beyond 2011 (except as specified in the methodology), the ACC, AHA, and collaborating societies plan to begin updating these guidelines starting in 2014.

The joint ACC/AHA Task Force on Practice Guidelines (Task Force) appointed a subcommittee to shepherd this transition, communicate the rationale and expectations to the writing panels and partnering organizations and expeditiously publish the documents. The ACC/AHA and partner organizations recruited a limited number of expert reviewers for fiduciary examination of content, recognizing that each document had undergone extensive peer review by representatives of the NHLBAC, key Federal agencies and scientific experts. Each writing panel responded to comments from these reviewers. Clarifications were incorporated where appropriate, but there were no substantive changes as the bulk of the content was undisputed.

Although the Task Force led the final development of these prevention guidelines, they differ from other ACC/AHA guidelines. First, as opposed to an extensive compendium of clinical information, these documents are significantly more limited in scope and focus on selected critical questions in each topic, based on the highest quality evidence available. Recommendations were derived from randomized trials, meta-analyses, and observational studies evaluated for quality, and were not formulated when sufficient evidence was not available. Second, the text accompanying each recommendation is succinct,

summarizing the evidence for each question. The Full Panel Reports include more detailed information about the evidence statements that serves as the basis for recommendations. Third, the format of the recommendations differs from other ACC/AHA guidelines. Each recommendation has been mapped from the NHLBI grading format to the ACC/AHA Class of Recommendation/Level of Evidence (COR/LOE) construct (Table 1) and is expressed in both formats. Because of the inherent differences in grading systems and the clinical questions driving the recommendations, alignment between the NHLBI and ACC/AHA formats is in some cases imperfect. Explanations of these variations are noted in the recommendation tables, where applicable.

Table 1. Applying Classification of Recommendation and Level of Evidence



A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even when

randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

In consultation with NHLBI, the policies adopted by the writing panels to manage relationships of authors with industry and other entities (RWI) are outlined in the methods section of each panel report. These policies were in effect when this effort began in 2008 and throughout the writing process and voting on recommendations, until the process was transferred to ACC/AHA in 2013. In the interest of transparency, the ACC/AHA requested that panel authors resubmit RWI disclosures as of July 2013. Relationships relevant to this guideline are disclosed in Appendix C.

Systematic evidence reports and accompanying summary tables were developed by the expert panels and NHLBI. The guideline was reviewed by the ACC/AHA Task Force and approved by the ACC Board of Trustees, the AHA Science Advisory and Coordinating Committee, and the governing bodies of partnering organizations. In addition, ACC/AHA sought endorsement by other stakeholders, including professional organizations. It is the hope of the writing panels, stakeholders, professional organizations, NHLBI, and the Task Force that the guidelines will garner the widest possible readership for the benefit of patients, providers and the public health.

Guidelines attempt to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate. These considerations notwithstanding, in caring for most patients, clinicians can employ the recommendations confidently to reduce the risks of atherosclerotic cardiovascular disease events.

See Tables B and C for an explanation of the NHLBI recommendation grading methodology.

Table B. NHLBI Grading of the Strength of Recommendations

Grade	Strength of Recommendation*
A	**Strong recommendation** There is high certainty based on evidence that the net benefit† is substantial.
B	**Moderate recommendation** There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.
C	**Weak recommendation**

	There is at least moderate certainty based on evidence that there is a small net benefit.
D	**Recommendation against** There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
E	**Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Panel recommends.")** Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Panel thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	**No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.")** Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Panel thought no recommendation should be made. Further research is recommended in this area.

*In most cases, the strength of the recommendation should be closely aligned with the quality of the evidence; however, under some circumstances, there may be valid reasons for making recommendations that are not closely aligned with the quality of the evidence (e.g., strong recommendation when the evidence quality is moderate, like smoking cessation to reduce CVD risk or ordering an ECG as part of the initial diagnostic work-up for a patient presenting with possible MI). Those situations should be limited and the rationale explained clearly by the Panel.
†Net benefit is defined as benefits minus risks/harms of the service/intervention.
CVD indicates cardiovascular risk; ECG, electrocardiography; MI, myocardial infarction; and NHLBI, National Heart, Lung, and Blood Institute.

Table C. NHLBI Quality Rating of the Strength of Evidence

Type of Evidence	Quality Rating*
• Well-designed, well-executed† RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. • MAs of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect.	High
• RCTs with minor limitations‡ affecting confidence in, or applicability of, the results. • Well-designed, well-executed nonrandomized controlled studies§ and well-designed, well-executed observational studies‖. • MAs of such studies. Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate.	Moderate
• RCTs with major limitations. • Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). • Physiological studies in humans.	Low

• MAs of such studies. Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	

*In some cases, other evidence, such as large all-or-none case series (e.g., jumping from airplanes or tall structures), can represent high or moderate quality evidence. In such cases, the rationale for the evidence rating exception should be explained by the Workgroup and clearly justified.
†Well-designed, well-executed refers to studies that directly address the question, use adequate randomization, blinding, allocation concealment, are adequately powered, use ITT analyses, and have high follow-up rates.
‡Limitations include concerns with the design and execution of a study that result in decreased confidence in the true estimate of the effect. Examples of such limitations include, but are not limited to: inadequate randomization, lack of blinding of study participants or outcome assessors, inadequate power, outcomes of interest are not prespecified or the primary outcomes, low follow-up rates, or findings based on subgroup analyses. Whether the limitations are considered minor or major is based on the number and severity of flaws in design or execution. Rules for determining whether the limitations are considered minor or major and how they will affect rating of the individual studies will be developed collaboratively with the methodology team.
§Nonrandomized controlled studies refer to intervention studies where assignment to intervention and comparison groups is not random (e.g., quasi-experimental study design)
‖Observational studies include prospective and retrospective cohort, case-control, and cross sectional studies.

ITT indicates intention-to-treat, MA, meta-analysis; and RCT, randomized controlled trial.

Introduction

Organization of the Work Group

The Risk Assessment Work Group (Work Group) was composed of 11 members and 5 ex-officio members, which includes internists, cardiologists, endocrinologists, and experts in cardiovascular epidemiology, biostatistics, healthcare management and economics, and guideline development.

Document Review

A formal peer review process was initially completed under the auspices of the NHLBI which included 12 expert reviewers and representatives of Federal agencies. This document was also reviewed by 3 expert reviewers nominated by the ACC and the AHA when the management of the guideline transitioned to the ACC/AHA.

PROCESS AND METHODS OVERVIEW

BACKGROUND AND DESCRIPTION OF THE PROJECT

To address its mission to accelerate the application of health research to strategies and programs to prevent, detect, and treat cardiovascular, lung, and blood diseases, and to narrow the discovery-delivery gap, the National Heart, Lung, and Blood Institute (NHLBI) has sponsored the development of clinical practice guidelines since the 1970s. Recognizing the need to update the most recent cardiovascular guideline reports, beginning in 2005 NHLBI convened stakeholder groups to help develop the next generation of guidelines.

Resulting recommendations were used to design the process for subsequent versions of the guidelines. The recommendations emphasized the need to:

- Maintain cardiovascular clinical practice guidelines for specific risk factors
- Take a standardized and coordinated approach to risk factor guidelines updates
- Take a more evidence-based approach to development and implementation
- Give focused attention to implementation issues and work closely with stakeholders in health care and community systems to translate and disseminate the evidence base

In 2008, the NHLBI established expert panels to develop updates of the guidelines for high blood cholesterol, (4) high blood pressure, (5) and overweight/obesity (6). Three crosscutting work groups on risk assessment, lifestyle, and implementation were formed to develop their own recommendations or to provide crosscutting input to the expert panels. The six topics were seen as integral and complementary. A guidelines executive committee composed of all expert panel and work group co-chairs and NHLBI staff coordinated the work of the expert panels and work groups.

OVERVIEW OF EVIDENCE-BASED METHODOLOGY

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

The process followed most of the standards from the Institute of Medicine (IOM) report, *Clinical Practice Guidelines We Can Trust*,(7) 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 preference, 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, with variations as needed to reflect the evidence in the field. The methodology implemented for this project involved numerous components and followed a prespecified development process. Expert panels and work groups consisting of cardiologists and other clinical and nonclinical experts were convened to develop the guidelines. Directed by NHLBI, with support from a methodology contractor and a systematic review and general support contractor, the expert panels and work groups:

- Constructed questions most relevant to clinical practice that followed the "PICOTSS" (population, intervention/exposure, comparison group, outcome, time, setting, and study design) format

- Identified (a priori) inclusion and exclusion (I/E) criteria for each Question

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

- Developed a search strategy, based on I/E criteria, for each Question

- Executed a systematic electronic search of the published literature from relevant bibliographic databases for each Question.

- Screened, by two independent reviewers, thousands of abstracts/full text articles returned from the search to identify relevant original articles, systematic reviews (SRs), and/or meta-analyses (MA), and applied rigorous validation procedures to ensure that the selected articles met the pre-established detailed I/E criteria before being included in the final review results

- Determined, by two independent raters, the quality of each included study. The methodology staff, with input from NHLBI, 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, and constructed and used templates with lists of data elements pertinent to the established I/E criteria to support abstraction

- Constructed detailed evidence tables, which organized the 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 the Question

The expert panels and work groups:

- Used summary tables to develop evidence statements for each Question. The quality of evidence for each evidence statement was graded as high, moderate, or low based on scientific methodology, scientific strength, and consistency of results. Used the graded

evidence statements to write clinical recommendations and graded the strength of each recommendation

- Performed GuideLine Implementability Appraisals (GLIAs), planned and coordinated by the NHLBI Implementation Work Group, to identify and address barriers to guideline implementation

- Drafted a report that underwent external review by representatives of Federal agencies, and a group of experts selected by the NHLBI.

System for Grading the Body of Evidence and Strength of Recommendations

The 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 for quality as high, moderate, or low. Recommendations were graded as Strong Recommendation (grade A), Moderate Recommendation (grade B), Weak Recommendation (grade C), Recommendation Against (grade D), Expert Opinion (grade E), or No Recommendation for or Against (grade N). The grades provide guidance to primary care physicians and other stakeholders on how much support the evidence provided for the evidence statement. 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 for bias, consistency, directness, and precision—were used to grade the strength of evidence.

Critical Question–Based Approach

The body of this report is organized by critical question. For each question, the Risk Assessment Work Group:

- Provides the rationale for its selection and describes the methods
- Summarizes the body of evidence and presents evidence statements that include a rating for quality; a narrative summary supports each evidence statement
- Accompanies recommendations and recommendation strength with a summary of how the recommendation derives from the evidence and discusses issues taken into consideration by the expert panel in formulating the recommendation

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 Risk Assessment Work Group (Work Group) was one of 3 work groups appointed by the National Heart, Lung, and Blood Institute (NHLBI) to develop its own recommendations and provide crosscutting input to 3 expert panels for updating guidelines on blood cholesterol, blood pressure (BP), and overweight/obesity. The Work Group 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 risk factor update panels (cholesterol, hypertension, obesity) in their guidelines and algorithms. Specifically, the Work Group was charged with 2 tasks:

To develop or recommend an approach to quantitative risk assessment that could be used to guide care

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 Work Group 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),(8) and the uptake of this algorithm by practice sites across the United States, the Work Group began its work by discussing the value of retaining this algorithm. With guidance from the guideline executive committee, the Work Group 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 risk assessment.(9)

The recommendations in this report focus on the large proportion of the population without clinical signs or symptoms of ASCVD, as these individuals may particularly benefit from primary prevention strategies. They do not apply to highly selected patient subgroups, such as those with symptoms suggestive of cardiovascular disease, who require diagnostic strategies rather than risk assessment in asymptomatic adults. Furthermore, these recommendations were not developed for use in specific subgroups of asymptomatic individuals at unusually high risk, such as those with genetically determined extreme values of traditional risk factors (e.g., patients with familial hypercholesterolemia).

CONSIDERATIONS IN DEVELOPING THE APPROACH TO RISK ASSESSMENT

The Work Group sought a simple, unifying approach to clinical decision-making that would not force clinicians to check an individual patient's profile against the I/E criteria for each randomized clinical trial (RCT) in the area of CVD prevention. After deliberation, the Work Group endorsed the existing and widely employed paradigm of matching the individual's absolute risk with the intensity of preventive efforts.(8,10) The Work Group 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 Work Group 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. This process is admittedly 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 decision making 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 use of absolute risk scores in clinical practice in primary prevention settings. (11-13) Two systematic reviews,(11-13) 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. No data are available on hard event outcomes. As noted below, the Work Group specifically calls for research in this area. The Work Group notes that the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Performance Measures for the Primary Prevention of CVD(14) have specifically recommended use of global risk estimation in clinical practice. Likewise, the USPSTF recommendations for aspirin,(15) ATP III panel recommendations,(8) and European(16) and Canadian(17,18) guidelines for primary prevention of CVD, among others, have all recommended use of absolute risk assessment for decision-

making 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.

METHODS FOR MODELING RISK AND DEVELOPING ALGORITHMS

Framingham Heart Study–based risk prediction equations have been used extensively in scientific publications, international and U.S. prevention guidelines, and on the NHLBI Web site's ATP III risk calculator (http://cvdrisk.nhlbi.nih.gov/calculator.asp).(8) Use of these risk 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 narrow 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 panel considered diabetes mellitus (hereinafter referred to as "diabetes") to be a CHD risk equivalent and did not include diabetes in its multivariable risk equations.(8) A large meta-analysis failed to support the hypothesis that diabetes is a CHD risk equivalent,(19) and it is judged that appropriate ASCVD risk estimates consider inclusion of diabetes as an independent predictor variable in this setting.

Numerous other risk scores/equations for ASCVD risk estimation have been derived and published (**table 1**).(8,20-26)

Table 1. Characteristics of previously published risk scores and current Pooled Cohort Equations, including data sources, covariates, and outcomes

Risk Score				Risk Factors/Covariates Included														Cardiovascular Disease Events								
																					Hard CVD including cardiac failure							
																					Hard ASCVD							
																					Hard CHD							
																			Total CHD								
																		Total CHD including revascularization								
Study Group	Study and Region	Data Source	Publication Year	Age	Sex	Total Chol	LDL-Chol	HDL-Chol	CRP	Systolic BP	BP Rx	Diabetes	HbA1c*	Smoking	Family Hx CVD†	Body Mass Index	Social	Region	Coronary Revasc	Angina Pectoris	Unstable Angina	Myocardial Infarct	CHD Death	Stroke	Stroke Death	Cardiac Failure	TIA
Framingham CHD(26)	Framingham MA, USA	EAF, EAM	1998	x	x	x	x	X		x		x		x						x	x	X	x				
ATP III(8)	Framingham MA, USA	EAF, EAM	2001	x	x	x		X		x	x			x								X	x				
Framingham Global(22)	Framingham MA, USA	EAF, EAM	2008	x	x	x		X		x	x	x		x								X	x	x	x	x	
PROCAM(20)	Muenster, Germany	EM	2002	x			x	X		x		x		x	x							X	x				
QRISK(23)	QRESEARCH, United Kingdom	EF, EM	2007	x	x	x		X		x	x			x	x	x	x‡	x	x	x	x	X	x	x	x		x
Reynolds Men(25)	Phys Health Study USA	EAF	2008	x		x		X	x	x				x	x				x			X	x	x	x		
Reynolds Women(24)	Women's Health Study USA	EAM	2007	x		x		X	x	x			x	x	x				x			X	x	x	x		

Risk Score				Risk Factors/Covariates Included														Cardiovascular Disease Events								
																					Hard CVD including cardiac failure					
																					Hard ASCVD					
																					Hard CHD					
																			Total CHD							
																		Total CHD including revascularization								
Study Group	Study and Region	Data Source	Pub-lication Year	Age	Sex	Total Chol	LDL-Chol	HDL-Chol	CRP	Systolic BP	BP Rx	Dia-betes	HbA1c*	Smok-ing	Family Hx CVD†	Body Mass Index	Social	Region	Coron-ary Revasc	Angina Pectoris	Unsta-ble Angina	Myo-cardial Infarct	CHD Death	Stroke	Stroke Death	Car-diac Failure	TIA
EURO-SCORE(21)	12 cohorts Europe	EF, EM	2003	x	x	x		X		x				x				x					x		x		
Pooled Cohort (current)	CARDIA, Framing-ham, ARIC, CHS,USA	EAF, EAM AAF, AAM		x	x	x		X		x	x	x		x								X	x	x	x		

* Only among those with diabetes

† Definitions of a positive family history vary

‡ Measure of social deprivation

AAF indicates African American females; AAM, African American males; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; Chol, cholesterol; CHD, coronary heart disease; 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; Revasc, revascularization; and TIA, transient ischemic attack.

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

1. 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. (20,21,23-25)

2. Most scores had been derived in exclusively or overwhelmingly White samples, without adequate representation of or sufficient events in non-White groups.(8,20-26) The Work Group 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 follow up of Hispanic and Asian American samples, and calls for further research in these and other groups.

3. Many scores used end points that the Work Group 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;(21) or CHD events only without other types of ASCVD;(8,20,26) or composite end points, including CVD events that are less severe or difficult to diagnose reliably (angina or transient ischemic attack)(23,26) or that are subject to significant variability depending on practice patterns (e.g., revascularization).(23-25)

4. 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 contemporary patients.(8,22,26)

5. 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 the NHLBI cohorts (as described below) and some end points were not collected or were defined differently than in the original scores.

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

The Work Group created a new risk assessment algorithm using pooled cohort data from a number of longitudinal NHLBI-funded community-based epidemiological cohort studies. 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 POOLED COHORT EQUATIONS FOR ASSESSING ASCVD RISK

The Work Group desired to build upon experience with prior Framingham 10-year *CHD* risk prediction equations(8,26-28) and the more recent Framingham 10-year *general CVD* risk prediction equations,(22) while also expanding the utility and generalizability of new equations. Therefore, the Work Group elected to capitalize on the extensive data from several large NHLBI-sponsored longitudinal community-based epidemiologic cohort studies to derive a more geographically and racially diverse database. Specifically, baseline data from the Atherosclerosis Risk in Communities (ARIC) study(29) 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 Framingham Original and Offspring cohort data.

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, congestive 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. Ten-year risk was defined as the risk of

developing a first ASCVD event, defined as nonfatal myocardial infarction (MI) or coronary heart disease (CHD) death, or fatal or nonfatal stroke, over a 10-year period among people free from ASCVD at the beginning of the period. 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, and 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 **table 2.** Interactions with age were tested for each risk factor and were 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)

Table 2. Baseline characteristics (unadjusted) of the risk estimation population by study cohort, sex, and race (age criterion 40 to 79)

	African American						White							
	ARIC		CARDIA		CHS		ARIC		CARDIA		CHS		Fram	
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
Women	*n*=2,137		*n*=110		*n*=394		*n*=5,508		*n*=131		*n*=2,131		*n*=3,470	
Age Range	(44–66)		(40–45)		(65–79)		(44–65)		(40–42)		(65–79)		(40–74)	
Age (yrs)	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 Cholesterol (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 Cholesterol (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 (%)	17.1%		6.4%		22.3%		6.1%		1.5%		9.9%		4.7%	
10 yr KM ASCVD Rate	7.2%		0.9%		23.0%		3.6%		0.0%		18.0%		3.8%	
Men	*n*=1,364		*n*=64		*n*=219		*n*=4,692		*n*=103		*n*=1,308		*n*=2,995	
Age Range	(44–66)		(40–45)		(65–79)		(44–65)		(40–42)		(65–79)		(40–74)	
Age (yrs)	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 Cholesterol (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 Cholesterol (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

	African American						White							
	ARIC		CARDIA		CHS		ARIC		CARDIA		CHS		Fram	
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
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 (%)	15.0%		3.1%		25.6%		7.8%		2.9%		15.4%		7.7%	
10 yr KM ASCVD Rate	11.1%		4.7%		24.9%		9.0%		1.0%		28.5%		9.5%	

SD: Standard deviation

SBP: Systolic Blood Pressure

KM: Kaplan-Meier

In developing the new Pooled Cohort Equations 10-year ASCVD risk model, the Work Group also addressed the critical question regarding the value of novel risk factors in risk assessment (Question 1). 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 3. Considerations for evaluating new risk factors when assessing clinical utility for risk assessment

1. Association: Has a statistically significant prospective association been demonstrated with the end point of interest for the new marker alone and after adjustment for traditional risk factors?
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, defined as agreement between the predicted and observed rates of end points?
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 (or score) is added.
6. Improvement in clinical outcomes: Does use of the new risk factor result in changes in clinical decision-making that result in 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?

Derived from Hlatky 2009(41)

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 (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 Work Group 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 Question 1. That evidence is reviewed below. Further research using state-of-the art statistical techniques (including net reclassification improvement and integrative discrimination index(37,38)) will be needed to examine the utility of novel biomarkers when added to the new Pooled Cohort Equations in different populations and patient subgroups. Randomized clinical trials 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 a first hard ASCVD are provided in **table 4**, and an example based on a specific risk profile is shown in **table 5**. As can be seen from the *C*-statistics (**table 6**), 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 follow up interval in these population samples.

Table 4. Equation Parameters of the Pooled Cohort Equations for Estimation of 10-Year Risk for Hard ASCVD* and Specific Examples for Each Race and Sex Group

	White			African American		
	Coefficient	**Individual Example Value**	**Coefficient × Value†**	**Coefficient**	**Individual Example Value**	**Coefficient × Value†**
Women (Example: 55 years of age with total cholesterol 213 mg/dL, HDL–C 50 mg/dL, untreated systolic BP 120 mm Hg, nonsmoker, and without diabetes)						
Ln Age (y)	–29.799	4.01	–119.41	17.114	4.01	68.58
Ln Age, Squared	4.884	16.06	78.44	N/A	N/A	N/A
Ln Total Cholesterol (mg/dL)	13.540	5.36	72.59	0.940	5.36	5.04
Ln Age×Ln Total Cholesterol	–3.114	21.48	–66.91	N/A	N/A	N/A
Ln HDL–C (mg/dL)	–13.578	3.91	–53.12	–18.920	3.91	–74.01
Ln Age×Ln HDL–C	3.149	15.68	49.37	4.475	15.68	70.15
Ln Treated Systolic BP (mm Hg)	2.019	–	–	29.291	–	–
Ln Age×Ln Treated Systolic BP	N/A	N/A	N/A	–6.432	–	–
Ln Untreated Systolic BP (mm Hg)	1.957	4.79	9.37	27.820	4.79	133.19
Ln Age×Ln Untreated Systolic BP	N/A	N/A	N/A	–6.087	19.19	–116.79
Current Smoker (1=Yes, 0=No)	7.574	0	0	0.691	0	0

Ln Age×Current Smoker	–1.665	0	0	N/A	N/A	N/A
Diabetes (1=Yes, 0=No)	0.661	0	0	0.874	0	0
Individual Sum			–29.67			86.16
Mean (Coefficient× Value)	N/A	N/A	–29.18	N/A	N/A	86.61
Baseline Survival	N/A	N/A	0.9665	N/A	N/A	0.9533
Estimated 10-Y Risk for hard ASCVD	N/A	N/A	2.1%	N/A	N/A	3.0%
Men (Example: 55 years of age with total cholesterol 213 mg/dL, HDL–C 50 mg/dL, untreated systolic BP 120 mm Hg, nonsmoker, and without diabetes)						
Ln Age (y)	12.344	4.01	49.47	2.469	4.01	9.89
Ln Total Cholesterol (mg/dL)	11.853	5.36	63.55	0.302	5.36	1.62
Ln Age×Ln Total Cholesterol	–2.664	21.48	–57.24	N/A	N/A	N/A
Ln HDL–C (mg/dL)	–7.990	3.91	–31.26	–0.307	3.91	–1.20
Ln Age×Ln HDL–C	1.769	15.68	27.73	N/A	N/A	N/A
Ln Treated Systolic BP (mm Hg)	1.797	–	–	1.916	–	–
Ln Untreated Systolic BP (mm Hg)	1.764	4.79	8.45	1.809	4.79	8.66
Current Smoker (1=Yes, 0=No)	7.837	0	0	0.549	0	0
Ln Age×Current Smoker	–1.795	0	0	N/A	N/A	N/A
Diabetes (1=Yes, 0=No)	0.658	0	0	0.645	0	0
Individual Sum			60.69			18.97
Mean (Coefficient× Value)	N/A	N/A	61.18	N/A	N/A	19.54

Baseline Survival	N/A	N/A	0.9144	N/A	N/A	0.8954
Estimated 10-Y Risk for hard ASCVD	N/A	N/A	5.3%	N/A	N/A	6.1%

*Defined as first occurrence of nonfatal MI or CHD death, or fatal or nonfatal stroke.
†Coefficient×Value: For age, lipids, and BP, defined as the natural log of the value multiplied by the parameter estimate. When an age interaction is present with lipids or BP, the natural log of age is multiplied by the natural log of the lipid or BP, and the result is multiplied by the parameter estimate. "N/A" indicates that that specific covariate was not included in the model for that sex-race group; "–" indicates that this value was not included in the example (e.g., this example used untreated systolic BP, not treated systolic BP).

ASCVD indicates atherosclerotic cardiovascular disease; BP indicates blood pressure; CHD, congestive heart disease; HDL–C, high-density lipoprotein cholesterol; Ln, natural logarithm; MI, myocardial infarction; and N/A, not included.

Table 5. Estimating an Individuals's 10-Year Risk for a First Hard ASCVD Event

The hypothetical profile provided in Table 5 (the "Individual Example Value" column) is identical for each race and sex group and is based on the overall sample mean. The profile assumes an individual 55 years of age (for which the Ln[Age]=4.01), with a total cholesterol of 213 mg/dL, HDL–C of 50 mg/dL, and an untreated systolic BP of 120 mm Hg. This individual is not a current smoker and does not have diabetes. For the equations, the values for age, lipids, and systolic BP are log transformed. Interactions between age and lipids or age and systolic BP use the natural log of each variable (e.g., Ln[Age]×Ln[Total Cholesterol]).

Calculation of the 10-year risk estimate for hard ASCVD can best be described as a series of steps. The natural log of age, total cholesterol, HDL–C, and systolic BP are first calculated with systolic BP being either a treated or untreated value. Any appropriate interaction terms are then calculated. These values are then multiplied by the coefficients from the equation ("Coefficient" column of Table A) for the specific race-sex group of the individual. 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 individual. For the profile shown in Table A, this value is shown as "Individual Sum" for each race and sex group.

The estimated 10-year risk of a first hard ASCVD event is formally calculated as 1 minus the survival rate at 10 years ("Baseline Survival" in Table A), 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% probability of a first hard ASCVD event within 10 years.

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; HDL–C, high-density lipoprotein cholesterol; and Ln, natural logarithm.

Internal Validation

The Work Group evaluated the internal consistency of the discrimination and calibration performance measures using a 10x10 cross-validation technique. 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 (**table 6**). 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 6. Summary of internal validation of risk prediction of hard ASCVD and the components of ASCVD within 10 years using a 10x10 cross-validation

	Women						Men					
	Original	**Mean**	**Std**	**P5**	**Median**	**P95**	**Original**	**Mean**	**Std**	**P5**	**Median**	**P95**
White												
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
African American												
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

Note: P5 and P95 represent the 5th and 95th percentiles, respectively.

* Calibration slope: Beta coefficient from a proportional hazards model using the linear predictor as the sole independent variable.

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, most recent examination cycles from ARIC and Framingham for which 10 years of follow up 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 follow up. 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 follow up 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 follow-up time through the baseline survival rate (S_{10} in the equation). Based on the algorithm development dataset, a 6-year rate was used for MESA, while 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 atherosclerotic CVD 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 (**table 7**).

Table 7. 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

	Women				Men			
	Algorithm Derivation Cohort	Validation Cohorts			Algorithm Derivation Cohort	Validation Cohorts		
		Contemporary (4)	MESA (5)	REGARDS (6)		Contemporary (4)	MESA (5)	REGARDS (6)
White								
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
African American								
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

	Women				Men			
	Algorithm Derivation Cohort	Validation Cohorts			Algorithm Derivation Cohort	Validation Cohorts		
		Contemporary (4)	MESA (5)	REGARDS (6)		Contemporary (4)	MESA (5)	REGARDS (6)
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 follow up window

(2) Observed number of events after Kaplan-Meier adjustment through follow up 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).

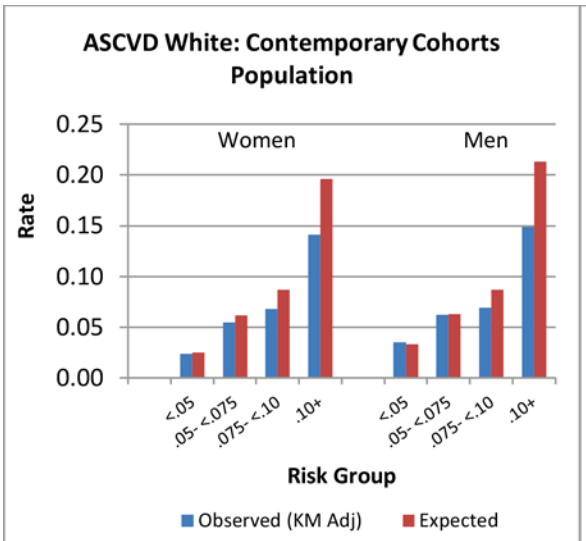
(5) Based on 6-year prediction

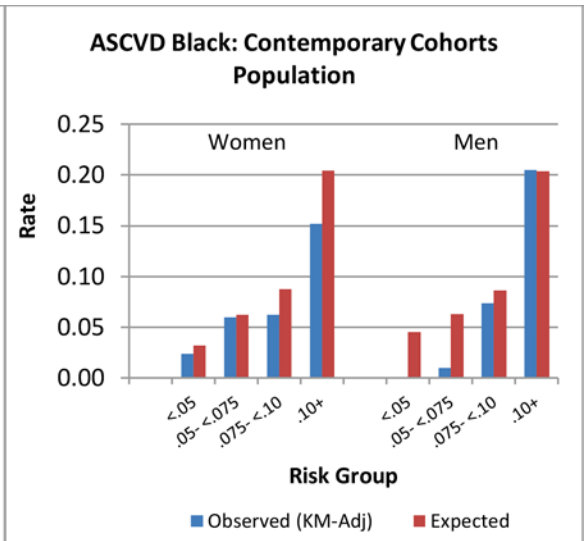
(6) Based on 4-year prediction

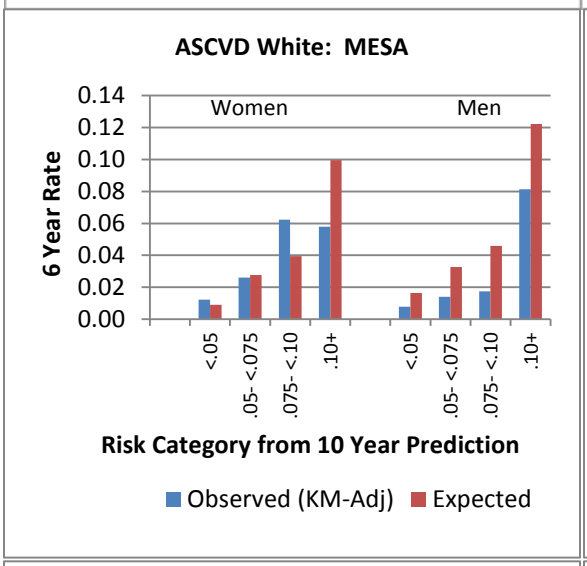
When considering overall event rates in the validation cohorts (**table 7**), overprediction of events was noted and was more pronounced for MESA. Calibration chi-squared statistics were above the threshold of 20 for 5 of the 12 race, sex, and cohort specific validation groups.

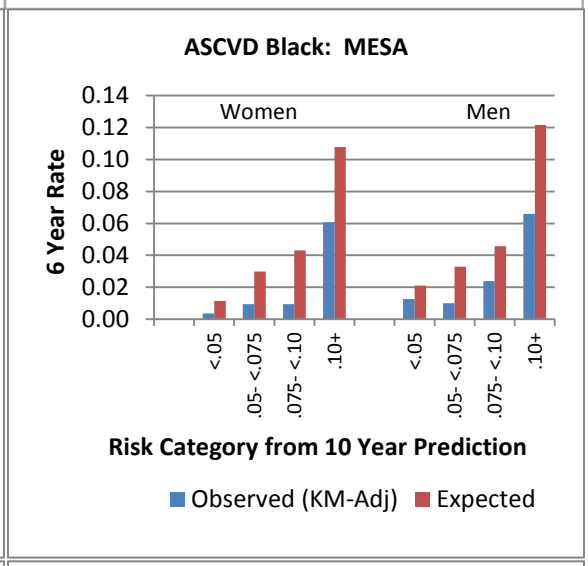
Calibration charts for each race-sex group in each validation cohort are shown in **figure 1** for the ASCVD end point. As opposed to traditional charts that show observed and predicted events in deciles, these calibration charts use clinically meaningful cutpoints in specific 10-year predicted risk categories (<.05, .05–<.075, .075–<.10, .10+) to illustrate prediction and also to help avoid categories with just a few events. Participants in MESA and REGARDS were first classified based on their predicted 10-year risk estimate; however, observed and predicted events were based on the available follow-up window (6 years in MESA and 4 years in REGARDS). In other words, a 10-year predicted risk estimate was used in MESA and REGARDS solely for the purpose of classifying participants into the risk categories, but the number of expected events was calculated from the adjusted 6-year (MESA) or 4-year (REGARDS) risk equations and compared with the observed events during that time interval. Overestimation of risk was more pronounced in MESA than in the other validation cohorts.

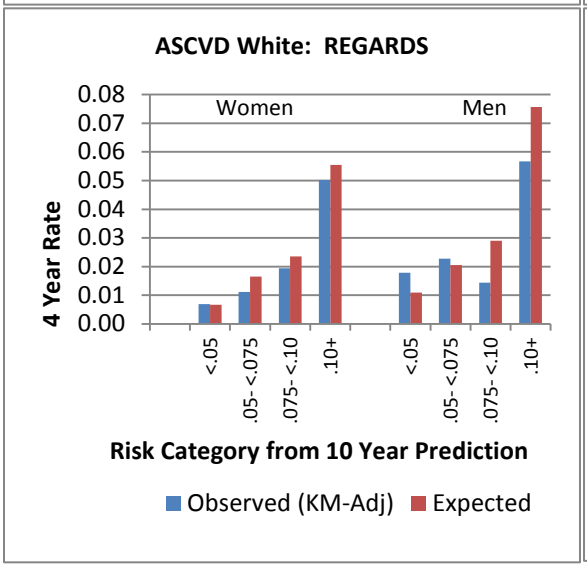
Figure 1. Kaplan-Meier Observed Event Rate and Predicted Event Rate for the ASCVD Outcome in the External Validation Samples From the Most Contemporary Cohort Studies Dataset, MESA, and REGARDS, by Race, Sex, and Selected Predicted Risk Groupings.

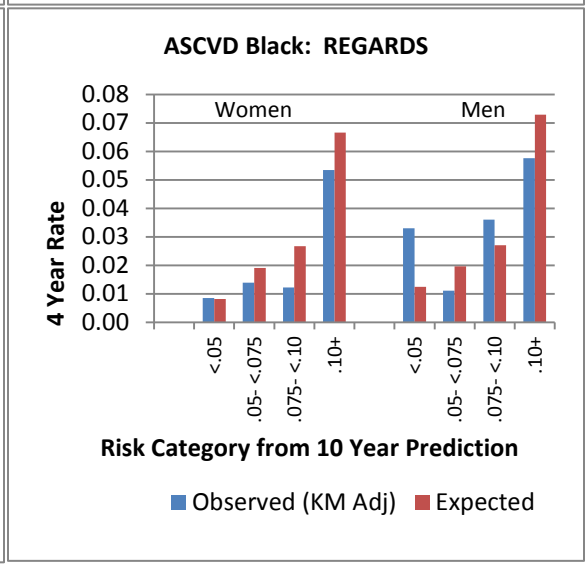

ASCVD White: Contemporary Cohorts Population
Rate
0.25
0.20
0.15
0.10
0.05
0.00
Women
Men
<.05
.05- <.075
.075- <.10
.10+
Risk Group
Observed (KM Adj)
Expected


ASCVD Black: Contemporary Cohorts Population
Rate
0.25
0.20
0.15
0.10
0.05
0.00
Women
Men
<.05
.05- <.075
.075- <.10
.10+
Risk Group
Observed (KM-Adj)
Expected


ASCVD White: MESA
6 Year Rate
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Women
Men
<.05
.05- <.075
.075- <.10
.10+
Risk Category from 10 Year Prediction
Observed (KM-Adj)
Expected


ASCVD Black: MESA
6 Year Rate
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Women
Men
<.05
.05- <.075
.075- <.10
.10+
Risk Category from 10 Year Prediction
Observed (KM-Adj)
Expected


ASCVD White: REGARDS
4 Year Rate
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Women
Men
<.05
.05- <.075
.075- <.10
.10+
Risk Category from 10 Year Prediction
Observed (KM-Adj)
Expected


ASCVD Black: REGARDS
4 Year Rate
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Women
Men
<.05
.05- <.075
.075- <.10
.10+
Risk Category from 10 Year Prediction
Observed (KM Adj)
Expected

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 the MESA baseline examination, more than 15 percent of that cohort was already 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 statins, blood pressure lowering therapy, aspirin, or elective revascularizations during follow up in any of the validation cohorts, and this issue may be important. For example, in MESA, by the second exam, following a mean follow-up period of 1.6 years, 10% of participants who were not on lipid-lowering medications at baseline had started such a medication, and initiation was greater in those at higher Framingham risk and in those with greater coronary artery calcification. Similar results were seen for initiation of blood pressure lowering medications and aspirin (46). Whereas the purpose of the risk prediction equation is to estimate

risk in the absence of future treatment, initiation of statins, blood pressure lowering therapy, or aspirin, or provision of revascularization in higher risk cohort members during the follow up periods may have significantly reduced events rates, and therefore impaired performance of the prediction equation in the manner observed.

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 Pooled Cohort Equations 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 limitations with respect to incorporating novel risk markers. Finally, although the cohorts from which the current Pooled Cohort 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.(47) 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.(48) 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 8 to 11 illustrate the range of estimated 10-year risks for a first hard ASCVD event, using the Pooled Cohort Equations, 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 8. Predicted 10-year risk of a first hard ASCVD event by specific combinations of total cholesterol, HDL-cholesterol, systolic blood pressure, current smoking, and diabetes for non-Hispanic African American women

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160
40	160	65	<.01	<.01	<.01	<.01	0.013	0.027	<.01	<.01	0.010	0.011	0.026	0.054	<.01	<.01	0.012	0.013	0.031	0.064	<.01	0.010	0.023	0.026	0.061	0.124
		55	<.01	<.01	<.01	<.01	0.020	0.041	<.01	<.01	0.015	0.017	0.039	0.080	<.01	<.01	0.018	0.020	0.046	0.095	<.01	0.015	0.035	0.039	0.090	0.180
		45	<.01	<.01	0.012	0.014	0.032	0.065	<.01	0.010	0.024	0.027	0.062	0.126	0.005	0.012	0.028	0.032	0.074	0.149	<.01	0.025	0.056	0.063	0.142	0.275
	200	65	<.01	<.01	<.01	<.01	0.016	0.034	<.01	<.01	0.012	0.014	0.032	0.066	<.01	<.01	0.014	0.016	0.038	0.079	<.01	0.013	0.029	0.032	0.075	0.151
		55	<.01	<.01	<.01	0.010	0.024	0.050	<.01	<.01	0.018	0.020	0.047	0.097	<.01	0.010	0.022	0.024	0.057	0.115	<.01	0.019	0.043	0.048	0.110	0.217
		45	<.01	<.01	0.015	0.017	0.039	0.080	<.01	0.013	0.029	0.033	0.076	0.153	<.01	0.015	0.035	0.039	0.090	0.181	0.012	0.030	0.068	0.077	0.172	>.30
	240	65	<.01	<.01	<.01	<.01	0.019	0.040	<.01	<.01	0.014	0.016	0.038	0.078	<.01	<.01	0.017	0.019	0.045	0.093	<.01	0.015	0.034	0.038	0.088	0.177
		55	<.01	<.01	0.011	0.012	0.029	0.059	<.01	<.01	0.021	0.024	0.056	0.114	<.01	0.011	0.026	0.029	0.067	0.136	<.01	0.022	0.050	0.057	0.129	0.252
		45	<.01	<.01	0.017	0.020	0.046	0.094	<.01	0.015	0.034	0.039	0.089	0.179	<.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	<.01	<.01	0.018	0.017	0.032	0.055	<.01	0.019	0.035	0.034	0.062	0.106	0.011	0.023	0.041	0.040	0.074	0.126	0.022	0.045	0.081	0.078	0.143	0.235
		55	<.01	0.012	0.022	0.021	0.040	0.069	0.012	0.024	0.044	0.042	0.078	0.132	0.014	0.028	0.052	0.051	0.093	0.156	0.027	0.056	0.101	0.098	0.178	0.288
		45	<.01	0.016	0.029	0.028	0.053	0.090	0.015	0.031	0.058	0.056	0.103	0.171	0.018	0.038	0.069	0.067	0.122	0.202	0.036	0.074	0.132	0.128	0.229	>.30
	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	0.013	0.028	0.051	0.049	0.091	0.153	0.027	0.055	0.099	0.096	0.173	0.281
		55	<.01	0.015	0.027	0.026	0.049	0.084	0.014	0.029	0.054	0.052	0.096	0.160	0.017	0.035	0.064	0.062	0.114	0.189	0.034	0.069	0.124	0.120	0.214	>.30
		45	<.01	0.020	0.036	0.035	0.065	0.110	0.019	0.039	0.070	0.068	0.125	0.207	0.023	0.046	0.084	0.081	0.148	0.243	0.044	0.090	0.161	0.156	0.274	>.30
	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	0.016	0.033	0.060	0.058	0.107	0.178	0.032	0.064	0.116	0.113	0.202	>.30
		55	<.01	0.018	0.032	0.031	0.058	0.099	0.017	0.035	0.063	0.061	0.113	0.187	0.020	0.041	0.075	0.073	0.134	0.220	0.040	0.081	0.145	0.141	0.249	>.30
		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	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	0.019	0.032	0.049	0.042	0.065	0.095	0.037	0.062	0.095	0.081	0.125	0.180	0.044	0.074	0.113	0.097	0.148	0.212	0.086	0.142	0.213	0.184	0.274	>.30
		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	0.049	0.081	0.124	0.107	0.163	0.232	0.095	0.156	0.232	0.201	0.298	>.30

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	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	0.055	0.091	0.139	0.119	0.181	0.257	0.106	0.174	0.258	0.224	>.30	>.30
	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	0.054	0.090	0.137	0.118	0.180	0.255	0.105	0.172	0.256	0.222	>.30	>.30
		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	0.060	0.099	0.151	0.130	0.197	0.277	0.116	0.188	0.278	0.242	>.30	>.30
		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	0.067	0.111	0.168	0.145	0.219	>.30	0.130	0.210	>.30	0.268	>.30	>.30
	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	0.064	0.106	0.161	0.139	0.210	0.295	0.124	0.201	0.295	0.257	>.30	>.30
		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	0.071	0.117	0.176	0.152	0.229	>.30	0.136	0.219	>.30	0.280	>.30	>.30
		45	0.034	0.057	0.087	0.075	0.115	0.166	0.066	0.110	0.167	0.143	0.217	>.30	0.079	0.131	0.196	0.170	0.254	>.30	0.152	0.244	>.30	>.30	>.30	>.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	0.139	0.193	0.251	0.198	0.258	>.30	0.258	>.30	>.30	>.30	>.30	>.30
		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	0.137	0.190	0.248	0.195	0.254	>.30	0.255	>.30	>.30	>.30	>.30	>.30
		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	0.135	0.187	0.244	0.192	0.250	>.30	0.251	>.30	>.30	>.30	>.30	>.30
	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	0.169	0.232	0.300	0.238	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
		55	0.073	0.103	0.136	0.106	0.140	0.178	0.141	0.195	0.254	0.200	0.260	>.30	0.166	0.229	0.296	0.235	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
		45	0.072	0.101	0.134	0.104	0.138	0.175	0.138	0.191	0.250	0.196	0.256	>.30	0.163	0.225	0.292	0.231	0.299	>.30	0.300	>.30	>.30	>.30	>.30	>.30
	240	65	0.087	0.122	0.162	0.126	0.167	0.211	0.167	0.230	0.297	0.235	>.30	>.30	0.197	0.269	>.30	0.276	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
		55	0.086	0.121	0.160	0.124	0.164	0.208	0.164	0.226	0.293	0.232	>.30	>.30	0.194	0.265	>.30	0.272	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
		45	0.085	0.119	0.157	0.122	0.161	0.205	0.162	0.223	0.289	0.229	0.296	>.30	0.191	0.261	>.30	0.268	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30

Table 9. Predicted 10-year risk of a first hard ASCVD event by specific combinations of total cholesterol, HDL-cholesterol, systolic blood pressure, current smoking, and diabetes for non-Hispanic White women

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160
40	160	65	<.01	<.01	<.01	<.01	<.01	<.01	<.01	0.010	0.013	0.013	0.018	0.023	<.01	<.01	<.01	<.01	<.01	0.011	0.013	0.019	0.025	0.025	0.034	0.044
		55	<.01	<.01	<.01	<.01	<.01	<.01	<.01	0.013	0.018	0.018	0.025	0.032	<.01	<.01	<.01	<.01	0.011	0.015	0.018	0.026	0.035	0.035	0.047	0.061
		45	<.01	<.01	<.01	<.01	<.01	0.011	0.014	0.020	0.027	0.027	0.036	0.047	<.01	<.01	0.012	0.012	0.017	0.022	0.027	0.038	0.051	0.051	0.069	0.089
	200	65	<.01	<.01	<.01	<.01	<.01	0.009	0.011	0.015	0.021	0.021	0.028	0.036	<.01	<.01	0.010	0.010	0.013	0.017	0.021	0.029	0.040	0.039	0.053	0.069
		55	<.01	<.01	<.01	<.01	<.01	0.012	0.015	0.021	0.028	0.028	0.038	0.050	<.01	0.010	0.013	0.013	0.018	0.023	0.029	0.041	0.054	0.054	0.073	0.095
		45	<.01	<.01	<.01	0.010	0.010	0.018	0.022	0.031	0.042	0.042	0.057	0.073	0.010	0.015	0.020	0.020	0.027	0.035	0.042	0.059	0.080	0.079	0.107	0.137
	240	65	<.01	<.01	<.01	<.01	<.01	0.013	0.016	0.022	0.030	0.030	0.040	0.052	<.01	0.010	0.014	0.014	0.019	0.025	0.030	0.042	0.057	0.057	0.077	0.099
		55	<.01	<.01	0.010	0.010	0.010	0.018	0.022	0.031	0.041	0.041	0.055	0.072	0.010	0.014	0.019	0.019	0.026	0.034	0.041	0.058	0.078	0.078	0.105	0.135
		45	<.01	0.011	0.015	0.015	0.015	0.026	0.032	0.045	0.060	0.060	0.081	0.105	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	<.01	<.01	<.01	<.01	0.016	0.013	0.019	0.025	0.025	0.034	0.045	<.01	0.013	0.017	0.017	0.023	0.030	0.025	0.036	0.049	0.048	0.065	0.085
		55	<.01	<.01	0.011	0.011	0.011	0.019	0.016	0.023	0.031	0.031	0.042	0.055	0.011	0.016	0.021	0.021	0.028	0.037	0.031	0.044	0.060	0.059	0.080	0.104
		45	<.01	0.010	0.014	0.014	0.014	0.025	0.021	0.030	0.040	0.040	0.054	0.070	0.014	0.020	0.027	0.027	0.037	0.048	0.040	0.057	0.076	0.076	0.102	0.131
	200	65	<.01	<.01	0.012	0.012	0.012	0.021	0.018	0.025	0.034	0.034	0.046	0.060	0.012	0.017	0.023	0.023	0.031	0.041	0.034	0.049	0.065	0.065	0.088	0.113
		55	<.01	0.011	0.015	0.015	0.015	0.026	0.022	0.031	0.042	0.042	0.057	0.074	0.015	0.021	0.028	0.028	0.038	0.050	0.042	0.060	0.080	0.079	0.107	0.138
		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	0.019	0.027	0.036	0.036	0.049	0.064	0.054	0.076	0.102	0.101	0.135	0.174
	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	0.015	0.022	0.029	0.029	0.040	0.052	0.044	0.062	0.083	0.082	0.111	0.142
		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	0.019	0.027	0.036	0.036	0.049	0.064	0.054	0.076	0.101	0.101	0.135	0.173
		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	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	0.015	0.022	0.029	0.029	0.029	0.052	0.032	0.046	0.062	0.061	0.083	0.107	0.030	0.042	0.056	0.056	0.076	0.098	0.062	0.087	0.116	0.116	0.154	0.197
		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	0.033	0.047	0.063	0.063	0.084	0.109	0.069	0.097	0.129	0.129	0.171	0.218

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	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	0.038	0.054	0.072	0.071	0.096	0.124	0.079	0.111	0.147	0.146	0.194	0.246
	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	0.035	0.050	0.067	0.066	0.090	0.116	0.073	0.103	0.137	0.136	0.181	0.230
		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	0.039	0.056	0.075	0.074	0.100	0.129	0.082	0.115	0.152	0.152	0.201	0.255
		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	0.045	0.064	0.085	0.085	0.114	0.146	0.093	0.131	0.173	0.172	0.227	0.286
	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	0.040	0.057	0.077	0.076	0.103	0.132	0.084	0.118	0.156	0.156	0.206	0.261
		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	0.045	0.064	0.086	0.085	0.114	0.147	0.094	0.132	0.174	0.173	0.228	0.288
		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	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	0.054	0.076	0.102	0.101	0.101	0.174	0.088	0.123	0.162	0.161	0.214	0.270	0.102	0.142	0.188	0.187	0.246	>.30	0.163	0.224	0.290	0.289	>.30	>.30
		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	0.105	0.147	0.193	0.193	0.253	>.30	0.168	0.231	0.298	0.297	>.30	>.30
		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	0.109	0.152	0.200	0.200	0.262	>.30	0.174	0.239	>.30	>.30	>.30	>.30
	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	0.109	0.152	0.200	0.199	0.261	>.30	0.173	0.238	>.30	>.30	>.30	>.30
		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	0.112	0.157	0.206	0.205	0.269	>.30	0.178	0.245	>.30	>.30	>.30	>.30
		45	0.062	0.087	0.116	0.116	0.116	0.198	0.100	0.140	0.185	0.184	0.242	>.30	0.117	0.162	0.213	0.212	0.278	>.30	0.185	0.253	>.30	>.30	>.30	>.30
	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	0.115	0.160	0.210	0.209	0.274	>.30	0.182	0.250	>.30	>.30	>.30	>.30
		55	0.063	0.089	0.118	0.118	0.118	0.201	0.102	0.142	0.187	0.187	0.246	>.30	0.119	0.165	0.216	0.215	0.282	>.30	0.188	0.257	>.30	>.30	>.30	>.30
		45	0.066	0.092	0.123	0.122	0.122	0.208	0.106	0.148	0.194	0.193	0.254	>.30	0.123	0.171	0.224	0.223	0.291	>.30	0.195	0.266	>.30	>.30	>.30	>.30

Table 10. Predicted 10-year risk of a first hard ASCVD event by specific combinations of total cholesterol, HDL-cholesterol, systolic blood pressure, current smoking, and diabetes for non-Hispanic African American men

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	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	0.034	0.047	0.062	0.078	0.103	0.131	0.058	0.080	0.105	0.130	0.171	0.215
		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	0.036	0.050	0.066	0.082	0.109	0.138	0.062	0.085	0.111	0.138	0.181	0.227
		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	0.039	0.054	0.071	0.089	0.117	0.149	0.067	0.092	0.119	0.148	0.194	0.243
	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	0.037	0.050	0.066	0.083	0.110	0.139	0.062	0.086	0.112	0.139	0.182	0.229
		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	0.039	0.054	0.070	0.088	0.116	0.147	0.066	0.091	0.118	0.147	0.192	0.241
		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	0.042	0.058	0.076	0.094	0.125	0.158	0.071	0.098	0.127	0.158	0.206	0.258
	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	0.039	0.053	0.070	0.087	0.115	0.146	0.066	0.090	0.118	0.146	0.191	0.240
		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	0.041	0.056	0.074	0.092	0.122	0.155	0.070	0.096	0.125	0.155	0.202	0.253
		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	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	0.031	0.043	0.057	0.071	0.094	0.120	0.053	0.073	0.096	0.119	0.157	0.198	0.059	0.080	0.105	0.131	0.172	0.216	0.099	0.135	0.175	0.215	0.278	>.30
		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	0.062	0.085	0.111	0.138	0.181	0.228	0.105	0.143	0.185	0.227	0.293	>.30
		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	0.067	0.092	0.120	0.149	0.194	0.244	0.113	0.154	0.198	0.243	>.30	>.30
	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	0.062	0.086	0.112	0.139	0.182	0.229	0.106	0.144	0.186	0.228	0.294	>.30
		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	0.066	0.091	0.119	0.147	0.193	0.242	0.112	0.152	0.196	0.241	>.30	>.30
		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	0.071	0.098	0.127	0.158	0.206	0.258	0.120	0.163	0.210	0.258	>.30	>.30
	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	0.066	0.090	0.118	0.146	0.192	0.240	0.111	0.151	0.195	0.240	>.30	>.30
		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	0.070	0.096	0.125	0.155	0.202	0.253	0.118	0.160	0.206	0.253	>.30	>.30
		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	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	0.048	0.067	0.087	0.109	0.143	0.181	0.082	0.113	0.146	0.181	0.235	0.293	0.090	0.123	0.160	0.197	0.256	>.30	0.151	0.204	0.260	>.30	>.30	>.30
		55	0.051	0.071	0.092	0.115	0.152	0.192	0.087	0.119	0.155	0.191	0.248	>.30	0.096	0.131	0.169	0.208	0.269	>.30	0.160	0.215	0.274	>.30	>.30	>.30

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	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	0.103	0.140	0.181	0.223	0.288	>.30	0.172	0.230	0.292	>.30	>.30	>.30
	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	0.096	0.131	0.170	0.209	0.271	>.30	0.161	0.216	0.275	>.30	>.30	>.30
		55	0.055	0.076	0.099	0.123	0.162	0.203	0.093	0.127	0.165	0.203	0.263	>.30	0.102	0.139	0.180	0.221	0.285	>.30	0.170	0.228	0.290	>.30	>.30	>.30
		45	0.059	0.081	0.106	0.132	0.173	0.218	0.100	0.137	0.176	0.217	0.281	>.30	0.110	0.149	0.192	0.237	>.30	>.30	0.182	0.244	>.30	>.30	>.30	>.30
	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	0.101	0.138	0.178	0.220	0.284	>.30	0.169	0.227	0.288	>.30	>.30	>.30
		55	0.058	0.080	0.104	0.129	0.170	0.214	0.098	0.134	0.173	0.213	0.276	>.30	0.108	0.146	0.189	0.232	0.299	>.30	0.179	0.240	>.30	>.30	>.30	>.30
		45	0.062	0.086	0.112	0.139	0.182	0.229	0.106	0.144	0.185	0.228	0.294	>.30	0.116	0.157	0.202	0.248	>.30	>.30	0.192	0.256	>.30	>.30	>.30	>.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	0.129	0.175	0.225	0.275	>.30	>.30	0.213	0.284	>.30	>.30	>.30	>.30
		55	0.074	0.102	0.132	0.164	0.214	0.267	0.125	0.170	0.218	0.267	>.30	>.30	0.137	0.185	0.237	0.290	>.30	>.30	0.225	0.299	>.30	>.30	>.30	>.30
		45	0.080	0.110	0.142	0.176	0.229	0.285	0.135	0.182	0.233	0.285	>.30	>.30	0.147	0.198	0.253	>.30	>.30	>.30	0.241	>.30	>.30	>.30	>.30	>.30
	200	65	0.075	0.102	0.133	0.165	0.215	0.269	0.126	0.171	0.219	0.268	>.30	>.30	0.138	0.186	0.238	0.291	>.30	>.30	0.226	0.300	>.30	>.30	>.30	>.30
		55	0.079	0.109	0.141	0.175	0.227	0.283	0.133	0.180	0.231	0.283	>.30	>.30	0.146	0.197	0.251	>.30	>.30	>.30	0.239	>.30	>.30	>.30	>.30	>.30
		45	0.085	0.117	0.151	0.187	0.243	>.30	0.143	0.193	0.247	>.30	>.30	>.30	0.156	0.211	0.269	>.30	>.30	>.30	0.255	>.30	>.30	>.30	>.30	>.30
	240	65	0.079	0.108	0.140	0.174	0.226	0.282	0.133	0.179	0.230	0.281	>.30	>.30	0.145	0.196	0.250	>.30	>.30	>.30	0.237	>.30	>.30	>.30	>.30	>.30
		55	0.084	0.114	0.148	0.183	0.238	0.297	0.140	0.190	0.243	0.296	>.30	>.30	0.153	0.207	0.264	>.30	>.30	>.30	0.250	>.30	>.30	>.30	>.30	>.30
		45	0.090	0.123	0.159	0.197	0.255	>.30	0.151	0.203	0.259	>.30	>.30	>.30	0.165	0.221	0.281	>.30	>.30	>.30	0.267	>.30	>.30	>.30	>.30	>.30

Table 11. Predicted 10-year risk of a first hard ASCVD event by specific combinations of total cholesterol, HDL-cholesterol, systolic blood pressure, current smoking, and diabetes for non-Hispanic White men

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160
40	160	65	<.01	<.01	<.01	<.01	<.01	0.011	0.013	0.018	0.024	0.022	0.028	0.036	<.01	0.011	0.014	0.012	0.016	0.021	0.026	0.035	0.046	0.041	0.054	0.068
		55	<.01	<.01	0.010	<.01	0.011	0.014	0.018	0.025	0.032	0.029	0.038	0.048	0.010	0.014	0.019	0.017	0.022	0.028	0.034	0.047	0.061	0.055	0.072	0.090
		45	<.01	0.011	0.014	0.012	0.016	0.021	0.026	0.035	0.046	0.041	0.054	0.068	0.015	0.020	0.027	0.024	0.031	0.040	0.049	0.067	0.087	0.078	0.102	0.128
	200	65	<.01	<.01	0.011	0.010	0.013	0.017	0.021	0.029	0.038	0.034	0.044	0.056	0.012	0.017	0.022	0.019	0.026	0.032	0.040	0.055	0.071	0.064	0.083	0.105
		55	<.01	0.012	0.015	0.014	0.018	0.023	0.028	0.038	0.050	0.045	0.059	0.074	0.016	0.022	0.029	0.026	0.034	0.043	0.053	0.073	0.095	0.085	0.110	0.138
		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	0.023	0.032	0.042	0.037	0.049	0.062	0.076	0.104	0.134	0.120	0.155	0.193
	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	0.017	0.024	0.031	0.028	0.037	0.046	0.057	0.078	0.102	0.091	0.118	0.148
		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	0.023	0.032	0.042	0.037	0.049	0.062	0.076	0.104	0.134	0.120	0.156	0.193
		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	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	0.015	0.020	0.027	0.024	0.031	0.040	0.033	0.046	0.059	0.053	0.069	0.087	0.028	0.039	0.051	0.046	0.060	0.075	0.063	0.086	0.111	0.100	0.130	0.162
		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	0.035	0.048	0.063	0.056	0.073	0.092	0.078	0.105	0.136	0.122	0.158	0.197
		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	0.046	0.063	0.081	0.073	0.095	0.119	0.100	0.136	0.174	0.157	0.202	0.249
	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	0.039	0.053	0.069	0.062	0.081	0.102	0.086	0.116	0.150	0.135	0.174	0.216
		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	0.048	0.066	0.085	0.076	0.100	0.125	0.105	0.142	0.182	0.164	0.211	0.260
		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	0.062	0.085	0.110	0.099	0.128	0.160	0.135	0.182	0.232	0.210	0.267	>.30
	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	0.050	0.069	0.089	0.080	0.104	0.130	0.110	0.148	0.190	0.172	0.220	0.271
		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	0.062	0.084	0.109	0.098	0.127	0.159	0.134	0.181	0.230	0.208	0.265	>.30
		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	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	0.043	0.059	0.076	0.069	0.089	0.112	0.069	0.094	0.121	0.109	0.141	0.176	0.081	0.110	0.142	0.128	0.165	0.205	0.129	0.173	0.221	0.200	0.255	>.30
		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	0.094	0.127	0.163	0.147	0.189	0.234	0.148	0.199	0.252	0.228	0.290	>.30

			Diabetes (No)												Diabetes (Yes)											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
Age	Total Chol	HDL Chol	Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
			100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	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	0.112	0.151	0.194	0.175	0.224	0.275	0.176	0.234	0.296	0.269	>.30	>.30
	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	0.099	0.135	0.173	0.156	0.200	0.247	0.157	0.210	0.266	0.241	>.30	>.30
		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	0.115	0.155	0.198	0.178	0.228	0.281	0.180	0.239	>.30	0.274	>.30	>.30
		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	0.137	0.183	0.233	0.211	0.269	>.30	0.213	0.281	>.30	>.30	>.30	>.30
	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	0.117	0.158	0.202	0.182	0.233	0.286	0.183	0.244	>.30	0.279	>.30	>.30
		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	0.135	0.181	0.230	0.208	0.265	>.30	0.210	0.277	>.30	>.30	>.30	>.30
		45	0.086	0.117	0.151	0.136	0.175	0.217	0.137	0.184	0.234	0.212	0.269	>.30	0.160	0.214	0.271	0.246	>.30	>.30	0.247	>.30	>.30	>.30	>.30	>.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	0.190	0.253	>.30	0.289	>.30	>.30	0.229	>.30	>.30	>.30	>.30	>.30
		55	0.113	0.153	0.196	0.177	0.226	0.278	0.138	0.185	0.236	0.213	0.271	>.30	0.207	0.274	>.30	>.30	>.30	>.30	0.249	>.30	>.30	>.30	>.30	>.30
		45	0.127	0.170	0.217	0.197	0.251	>.30	0.154	0.206	0.261	0.237	0.300	>.30	0.230	>.30	>.30	>.30	>.30	>.30	0.276	>.30	>.30	>.30	>.30	>.30
	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	0.212	0.280	>.30	>.30	>.30	>.30	0.254	>.30	>.30	>.30	>.30	>.30
		55	0.127	0.170	0.217	0.197	0.251	>.30	0.154	0.206	0.261	0.237	0.300	>.30	0.230	>.30	>.30	>.30	>.30	>.30	0.276	>.30	>.30	>.30	>.30	>.30
		45	0.142	0.190	0.241	0.218	0.278	>.30	0.172	0.229	0.289	0.262	>.30	>.30	0.255	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30
	240	65	0.127	0.171	0.218	0.197	0.251	>.30	0.154	0.206	0.262	0.237	0.300	>.30	0.231	>.30	>.30	>.30	>.30	>.30	0.277	>.30	>.30	>.30	>.30	>.30
		55	0.139	0.186	0.237	0.214	0.273	>.30	0.168	0.225	0.284	0.258	>.30	>.30	0.251	>.30	>.30	>.30	>.30	>.30	0.300	>.30	>.30	>.30	>.30	>.30
		45	0.155	0.207	0.263	0.238	>.30	>.30	0.188	0.249	>.30	0.285	>.30	>.30	0.277	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30	>.30

The estimated risk probabilities shown are specific to defined combinations of the 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-C, 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 Pooled Cohort 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 non-White and non-African American ethnic 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).

Table 14 displays 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(8) for hard CHD (coronary death or nonfatal MI) as the end point, compared with use of the new Pooled Cohort Equations for 10-year risk assessment 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 Pooled Cohort 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.(8) In the new Pooled Cohort Equations, individuals with diabetes may have a risk estimate of less than 10 percent.

Table 12. Distribution of Estimated 10-year risk for a first hard ASCVD event in the CVD-free, non-pregnant 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)

	Predicted 10-Year Risk of Hard ASCVD Event						
	<2.5%	**2.5%–4.9%**	**5.0%–7.4%**	**7.5%–9.9%**	**10.0%–14.9%**	**15.0%–19.9%**	**≥20.0%**
Total							
% (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)
n	33,534,000	21,151,000	12,766,000	7,470,000	8,940,000	6,380,000	10,300,000
Sex							
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)
n	8,386,000	10,950,000	7,511,000	4,847,000	5,849,000	4,248,000	6,388,000
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)
n	25,148,000	10,200,000	5,256,000	2,622,000	3,091,000	2,131,000	3,912,000
Race/Ethnicity							
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)
n	6,467,000	8,016,000	5,616,000	3,584,000	4,189,000	3,112,000	4,870,000
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)
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)
n	60,000	1,008,000	866,000	495,000	731,000	466,000	583,000
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)
n	1,921,000	985,000	572,000	339,000	496,000	300,000	645,000
Hispanic							

	Predicted 10-Year Risk of Hard ASCVD Event						
	<2.5%	**2.5%–4.9%**	**5.0%–7.4%**	**7.5%–9.9%**	**10.0%–14.9%**	**15.0%–19.9%**	**≥20.0%**
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)
n	1,303,000	1,200,000	718,000	574,000	619,000	339,000	683,000
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)
n	3,293,000	803,000	418,000	248,000	273,000	164,000	347,000
Others							
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)
n	555,000	726,000	310,000	193,000	309,000	330,000	251,000
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)
n	1,757,000	548,000	128,000	49,000	188,000	71,000	195,000

Table 13. Distribution of 10-year risk for a first hard ASCVD event in the non-pregnant 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)

	10-Year Hard ASCVD Risk Estimate						
	<2.5%	2.5–4.9%	5.0–7.4%	7.5–9.9%	10.0–14.9%	15.0–19.9%	**≥20.0%**
	% (*n*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)
Age 40–50 (*n*=1,684, weighted to 37,263,000 U.S population)							
Total	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	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	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)
Age 50–60 (*n*=1,435, weighted to 32,569,000 U.S. population)							
Total	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	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	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)
Age 60–70 (*n*=1,375, weighted to 19,927,000 U.S. population)							
Total	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	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	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)
Age 70–79 (*n*=873, weighted to 10,782,000 U.S. population)							
Total	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	0	0	0	0.1 (5,000)	6.5 (291,000)	10.1 (449,000)	83.3 (3,710,000)
Women	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)

Table 14. Distribution of 10-year risk for a first hard CHD event (per ATP III risk equation) vs. 10-year risk for a first hard ASCVD event (per Pooled Cohort Equations) in the ASCVD-free, non-pregnant U.S. population ages 40 to 79 (NHANES 2007–2010)

10-Year Risk for Hard CHD (ATP III) (8)	10-Year Risk for Hard ASCVD (Pooled Cohort Equations)				
	<5%	5.0–7.4%	7.5–9.9%	≥10.0%	
	% of total *N* (*N*)	% of total *N* (*N*)	% of total *N* (*N*)	% of total *N* (*N*)	
All					
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)	
Men					
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)	

10-Year Risk for Hard CHD (ATP III) (8)	10-Year Risk for Hard ASCVD (Pooled Cohort Equations)				
	<5%	**5.0–7.4%**	**7.5–9.9%**	**≥10.0%**	
	% of total *N* (*N*)	**% of total *N* (*N*)**	**% of total *N* (*N*)**	**% of total *N* (*N*)**	
Women					
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)	

Recommendations for Assessment of 10-Year Risk for a First Hard ASCVD Event

Recommendation 1.
The race- and sex-specific Pooled Cohort Equation*s to predict 10-year risk for a first hard ASCVD event should be used in non-Hispanic African Americans and non-Hispanic Whites, 40 to 79 years of age.

(Grade B, Moderate); ACC/AHA COR I, LOE B

Recommendation 2.
Use of the sex-specific Pooled Cohort Equations for non-Hispanic whites may be considered for estimation of risk in patients from populations other than African Americans and non-Hispanic Whites.

(Grade E, Expert Opinion); ACC/AHA COR IIb, LOE C

*Derived from the ARIC (Atherosclerosis Risk in Communities) study, Cardiovascular Health Study, CARDIA (Coronary Artery Risk Development in Young Adults) study, and Framingham original and offspring cohorts.

CRITICAL QUESTIONS AND SYSTEMATIC EVIDENCE REVIEWS

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?"

The Work Group applied the PICOTSS paradigm to ensure that the question and the I/E criteria were well stated with regard to the seven PICOTSS dimensions. Following are the high-level elements of Question 1 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, 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 1 year

- **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.

Selection of the I/E Criteria

In addition to using the PICOTSS analysis to refine the question, the Work Group 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, *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.

Rationale for Selecting This Question 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 cardiovascular disease has been well established since at least the 27th Bethesda Conference in 1996.(10) As a consequence, great attention has been placed on the accuracy and reliability of risk assessment. Claims that only a minority of the risk for CVD can be explained by the major traditional risk factors, or that most patients presenting with CHD have no elevated traditional risk factors, have been disproven.(49,50) Nonetheless, the desire to improve existing quantitative risk estimation tools has helped to stimulate and maintain interest in the search for new risk markers for CVD which might further enhance risk assessment. Recently, a general ASCVD 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.(22) 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 question 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 question is meant to apply to risk assessment in the general population, that is, the typical asymptomatic adult in routine clinical practice. This question does not address other highly selected patient subgroups, such as those with symptoms suggestive of cardiovascular disease.

Members of the Work Group proposed new risk markers of potential interest, and the initial list was prioritized based on several rounds of discussion within the Work Group and with the guidelines executive committee. In selecting the final list, the Work Group 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 Work Group included several blood and urine biomarkers (hs-CRP, ApoB, creatinine [or estimated GFR], and microalbuminuria), several measures of subclinical cardiovascular disease (CAC, CIMT, and ABI), family history, and cardiorespiratory fitness. When considering the utility of incorporating these new risk factors into routine risk assessment, the Work Group was guided by the considerations published by Hlatky 2009(41) shown in **table 3**.

The Work Group addressed this question using two independent approaches. First, the work group developed a new risk prediction model (described above) for hard ASCVD using data from pooled cohorts (Framingham Heart Study, Framingham Offspring Study, ARIC, CHS, and CARDIA). 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 follow up. Second, a review of meta-analyses and systematic reviews published before September 19, 2013 was conducted in two stages. In the first stage, meta-analyses and systematic reviews published before April, 2011 were identified and reviewed. In a second stage conducted after transition to the ACC/AHA process in order to update the evidence base before publication, additional meta-analyses and systematic reviews

published before September 19, 2013 were identified and reviewed using the same criteria applied in the first stage. 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 we relied on a mature body of evidence. (51)

Methods for Question 1

The Work Group 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 Question 1 criteria. Formal evidence and summary tables were not constructed. Rather, the work group developed the "Systematic Review Evidence Conclusion" document shown in **table B-3** for this purpose.

Evidence Summaries

Summary Table for the Question

Thirteen systematic review articles met the I/E criteria. Publication dates ranged from 2008 to 2013. Two of the articles were products of the Emerging Risk Factor Coalition Study and three were by the USPSTF.

Summary of Systematic Reviews and Meta-Analyses for Question 1

Formal evidence and summary tables were not generated for this question. The work group reviewed the thirteen 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. None of these markers have been evaluated as screening tests in RCTs.

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.(52) 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.(52)*

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.(53) The authors concluded the following:

> *The current evidence does not support the routine use of any of the 9 risk factors for further risk stratification of intermediate-risk persons.(53)*

This report was based on the same evidence reviewed in more detail by the Buckley et al., 2009, paper(52) 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.(54) 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.(54)*

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.(55) This review was rated by the methodology staff as Fair-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. (55)

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(56) 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 Work Group concluded that this evidence 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(56) 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. (55) 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 Work group recommends that if, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of hs-CRP may be considered to inform treatment decision making. The Work Group encourages additional research on this risk marker, including

attention to the considerations elaborated by Hlatky 2009(41) in studies evaluating addition of hs-CRP to the new Pooled Cohort Equations in the context of updated prevention guideline recommendations and in representative populations, and when updating pertinent systematic reviews.

ApoB

The Work Group 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 cholesterol, or LDL cholesterol in risk assessment, rather than as an additional variable to be incorporated along with traditional lipid measurements in risk assessment. The Work Group did not need to evaluate the potential additional value of non-HDL cholesterol to risk assessment because non-HDL cholesterol 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 cholesterol, or non-HDL and HDL cholesterol. The only way that HDL cholesterol can differ between two individuals with the same level of total cholesterol is if non-HDL cholesterol 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. (57) This meta-analysis was rated by the methodology staff as Fair quality evidence. The authors concluded that the associations of cardiovascular disease with non-HDL cholesterol and ApoB were roughly equivalent after full adjustment (including HDL-C). By inference, the Work Group 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 cardiovascular disease than either LDL-C or non-HDL cholesterol.(58) 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 cardiovascular disease than was either non-HDL cholesterol or LDL cholesterol in substitution models. By inference, the Work Group 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 Work Group to be incomplete, leaving substantial potential for residual confounding.

The Work Group 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. This review did not provide the Work Group with sufficient evidence to make a recommendation about the potential value of assessing ApoB in routine cardiovascular disease risk assessment in clinical practice. The Work Group 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 Pooled Cohort Equations in the context of updated prevention guideline recommendations and in representative populations, and when updating pertinent systematic reviews.

CKD

The Work Group was able to examine moderate 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) 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 (GFR<60 vs. >=60) did not significantly improve model discrimination. The Work Group 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 focused on persons free from ASCVD. This review did not provide the Work Group with sufficient evidence to make a recommendation about assessing CKD or GFR in routine cardiovascular disease risk assessment in clinical practice. The Work Group 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 Pooled Cohort Equations in the context of updated prevention guideline recommendations and in representative populations, and when producing pertinent systematic reviews.

Microalbuminuria

The Work Group 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; hence, this review did not provide the Work Group with any evidence with which to make a recommendation about assessing microalbuminuria in routine

cardiovascular disease risk assessment in clinical practice. The Work Group 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 Work Group encourages additional research on this marker, including attention to the considerations elaborated by Hlatky 2009, (41) in studies evaluating addition of albuminuria to the new Pooled Cohort Equations in the context of updated prevention guideline recommendations and in representative populations, and when updating pertinent systematic reviews.

Family history of premature cardiovascular disease

The Work Group was able to examine family history of premature cardiovascular disease 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.

Two systematic reviews were found addressing family history. Empana, et al. published a algorithm to predict risk of CHD based on pooled data from 4 French cohorts and found that family history was associated with risk of CHD, but did not improve model discrimination. (59) No evidence related to calibration, reclassification, or cost-effectiveness was provided. Kashani, et al. (60) published an integrative literature review on the contribution of assessing family history to risk appraisal, and concluded that family history is an independent contributor to risk

appraisal; however, Kashani did not provide any evidence regarding improvements in model discrimination, calibration, reclassification, or cost effectiveness. (60)

The Work group concluded that assessing family history of multiple medical conditions remains a best practice in clinical medicine, and recommends that if, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of family history may be considered to inform treatment decision making. The Work Group encourages additional research on this characteristic, including attention to the considerations elaborated by Hlatky 2009, (41) in studies evaluating addition of family history to the new Pooled Cohort Equations in the context of updated prevention guideline recommendations and in representative populations, and when producing pertinent systematic reviews.

Cardiorespiratory fitness

The Work Group 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. We found one pertinent systematic review by Kodama et al., 2009. (61) 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 Work Group encourages additional research on this marker, including attention to the considerations elaborated by Hlatky 2009, (41) in studies evaluating addition of cardiorespiratory fitness to the

new Pooled Cohort Equations in the context of updated prevention guideline recommendations and in representative populations, and when producing pertinent systematic reviews.

ABI

We were 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 Work Group 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, (62) 16 population cohort studies were included. During 480,325 person-years of follow up 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 (< or =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, 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. (62)

The USPSTF performed systematic reviews of nine risk markers, including ABI.(53) 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. This review was updated in 2013 with similar conclusions. (63)

The Work Group 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). The Work Group recommends that if, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of ABI may be considered to inform treatment decision making. The Work Group encourages additional research on this characteristic, including attention to the considerations elaborated by Hlatky 2009. (41)

CAC

The Work Group 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. (53) In this review of papers published before 2009, CAC was associated with CHD risk and with some reclassification, but it was uncertain how much and how valuable this reclassification is. The document provides little evidence about discrimination, calibration, and cost-effectiveness. Peters, et al., published a systematic review of the contribution of measuring CAC to risk assessment. (64) This paper provides evidence to support the conclusion that assessing CAC is

likely to be a useful approach to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment. However, CHD outcomes (not ASCVD outcomes) were examined in the studies included in the review. The Work Group discussed the uncertainty of the contribution of assessing CAC to estimating 10-year risk of hard ASCVD (including stroke) after formal quantitative risk assessment with the new equations.The Work Group also was concerned about cost and radiation exposure, (65,66) and relatively limited information was available on how incidental findings from CAC testing are actually handled in routine clinical practice.(67-69) The Work Group recommends that if, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of CAC may be considered to inform treatment decision making. The Work Group encourages additional research on this characteristic, including attention to the considerations elaborated by Hlatky 2009. (41)

CIMT by Ultrasound

The Work Group 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 Work Group examined the USPSTF systematic reviews of nine risk markers, one of which was CIMT. (53) 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. Peters, et al., reviewed the contribution of measuring CIMT, (64) and found that CIMT improved risk assessment, based on measures of reclassification in 2 of 3 studies reviewed. The Work group judged these improvements to be modest, with reported net reclassification indices of 7.1% and 11.6%. Den Ruijter, et al., published an individual level meta-analysis of 14 population-based cohorts combining data on 45,828 participants with 4007 first heart attacks or strokes and found no meaningful contribution of CIMT to risk assessment with respect to

measures of discrimination or calibration. (70) The Work Group also has concerns about measurement of CIMT. Specifically, standardization of CIMT measurement from laboratory to laboratory is a major challenge. (71) The Work Group judged that the evidence provided in the Den Ruijter manuscript in combination with the concerns about measurement quality provides sufficient rationale to recommend against measuring CIMT in routine clinical practice for risk assessment for a first ASCVD event.

Recommendations About Assessing Novel Risk Markers in Routine Practice

These recommendations should be interpreted in the context of the limitation that resources were not available to support de novo systematic reviews of these nine factors. Hence, individual original scientific reports were not evaluated; however, the reliance on published meta-analyses and systematic reviews 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 we relied on a mature body of evidence. (51) At present, no valid approaches exist to quantitatively incorporate information about these markers into ASCVD risk assessment using the equations recommended in this document. For all of the markers examined in this document, with the possible exception of CIMT, additional research is needed, including updated systematic reviews addressing discrimination, calibration, reclassification, cost, and measurement (standardization) issues in the context of the new Pooled Cohort Equations in representative populations. Although we were not able to examine the potential contributions of several of these markers to risk assessment in our algorithm development process, we were able to evaluate hs-CRP and family history of CHD using a subset (those with hs-CRP and data on parental history of MI

before age 55) of the contemporary cohorts external validation database described above. These results provided additional information to guide our recommendations. The contemporary cohort database, restricted to participants not on lipid-lowering medications, was used to fit a model incorporating all of the variables in the new Pooled Cohort Equations, allowing the best fits of the coefficients. The resulting *C*-statistics ranged from 0.694 (White men) to 0.728 (White women). When elevated hs-CRP (>/= 2.0 mg/L) and family history were added to the models as categorical variables, the change in *C*-statistics ranged from –0.001 (worsening in African American women) to 0.007 (White men). Calibration chi-squared results were consistently less than 20 for all models and increased (indicating slightly worse fit) when hs-CRP and family history were added for all four race-sex groups. Categorical net reclassification indices (using thresholds of 5% and 7.5% for 10-year risk for a first ASCVD event) ranged from –0.013 (African American women) to 0.050 (White men); when restricted to an intermediate risk group defined as ASCVD risk of 5.0 to 7.49 percent, net reclassification indices ranged from –0.005 (African American women) to 0.246 (White men), indicating potential improvement in discrimination among Whites, but not among African Americans, however, the number of African Americans meeting the inclusion criteria was low (1,212 women, 653 men).

The Work Group recognizes that clinicians and patients might appreciate expert guidance regarding the potential value of these measures in risk assessment. These measures are more likely to be helpful in individuals who are sufficiently close to pharmacologic treatment initiation thresholds identified by one of the guideline panels that a treatment decision may be altered with additional information. On the basis of current evidence, it is the opinion of the Work Group that assessments of family history of premature cardiovascular disease, hs-CRP, CAC, and ABI show the greatest promise for clinical utility among the novel risk markers. A family history of

premature cardiovascular disease is relatively easy to obtain. A positive history, namely a first-degree relative with cardiovascular disease before age 55 for a male or age 65 for a female, might support initiation of pharmacologic therapy, and a negative history might support not initiating pharmacologic therapy. Assays for hs-CRP are widely available and reasonably affordable. An elevated value (≥2.0 mg/L) might likewise support initiation of treatment, while a normal value might support not initiating treatment. The Work Group notes that the review by Peters, et al. (64) provides evidence to support the contention that assessing CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment. Furthermore, the Work Group recognizes that the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults made recommendations regarding CAC testing.(72) However, we note that the outcomes in the studies reviewed by Peters , et al.(64), and by Greenland , et al.(72) were CHD outcomes, not hard ASCVD events that included stroke; hence, uncertainty remains regarding the contribution of assessing CAC to estimating 10-year risk of first hard ASCVD events after formal risk assessment using the new Pooled Cohort Equations. Furthermore, issues of cost and radiation exposure related to measuring CAC were discussed resulting in some uncertainty regarding potential risks of more widespread screening, which resulted in a decision in the current guideline to make assessment of CAC a Class IIb recommendation among individuals for whom a risk-based treatment decision is uncertain after formal risk estimation. The Work Group notes that this Class IIb recommendation is consistent with the recommendations in the 2010 ACCF/AHA guideline(72) for patients with a 10-year CHD risk of <10%, as well as for many other patients, because of the lower risk threshold (7.5% 10-year risk for a first hard ASCVD event) adopted by the current “2013 ACC/AHA Guideline on the Treatment of Blood

Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" for recommending initiation of statin therapy for ASCVD risk reduction (72,73). CAC is increasingly available and affordable and more easily standardized than CIMT. The presence of significant CAC (e.g., ≥ 300 Agatston units) might support initiation of treatment, whereas the absence of significant CAC might support not initiating treatment. Finally, ABI can be assessed easily in routine practice. An abnormal ABI (<0.9), indicative of lower extremity arterial disease, might support initiation of treatment, whereas a normal ABI might support not initiating therapy. **Table 15** provides expert opinion regarding thresholds that might be useful for clinical decision-making. On the basis of current evidence, it is the opinion of the work group that measuring ApoB, albuminuria, GFR, cardiorespiratory fitness, or CIMT is less likely to be useful, and the evidence is sufficiently strong to recommend against use of CIMT in this setting. If any of these nine markers are assessed in selected patients, the use of the information to guide treatment decisions will require sound clinician judgment and should be based on shared decision-making. In this process, it is important to recognize that the quantitative risk estimate provided by the algorithm recommended above (or any other such risk estimation equation) represents an average risk estimate for patients with the specified values for the measures included in the model. Some patients will have actual risk higher than the estimate, and others will have actual risk lower than the estimate. Therefore, while the goal is to "individualize" therapy based on the level of individual risk, risk scores are simply our best estimate of the individual's risk as a guide to treatment decisions.

Table 15. Expert opinion thresholds for use of optional screening tests when risk-based decisions regarding initiation of pharmacologic therapy are uncertain following quantitative risk assessment

Measure	Support Initiating Medical Therapy	Do Not Support Initiating Medical Therapy
Family history of premature CHD	Male <55 years old Female <65 years old (1st degree relative)	Occurrences at older ages only (if any)
hs-CRP	>/=2.0 mg/L	<2.0 mg/L
CAC score	>/=300 Agatston units or >/=75 percentile for age, sex, and ethnicity*	<300 Agatston units and <75 percentile for age, sex, and ethnicity*
ABI	<0.9	>/=0.9

* NOTE: For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.

Recommendations for CQ 1 regarding use of newer risk markers after quantitative risk assessment

Recommendation 1. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.

(Grade E, Expert Opinion); ACC/AHA COR IIb, LOE B*

*Based on new evidence reviewed during ACC/AHA update of the evidence

Recommendation 2. Routine measurement of CIMT is not recommended in clinical practice for risk assessment for a first ASCVD event.

(Grade N, No Recommendation For or Against); ACC/AHA Class III: No Benefit, LOE B*

*Based on new evidence reviewed during ACC/AHA update of the evidence

Recommendation 3. The contribution of ApoB, CKD, albuminuria, and cardiorespiratory fitness to risk assessment for a first ASCVD event is uncertain at present.

(Grade N, No Recommendation For or Against)

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?"

As described in appendix B, the draft version of Question 2, including I/E criteria, had an initial phrasing that was revised by the Work Group after additional discussion and deliberation and application of the PICOTSS framework. The work group applied the PICOTSS paradigm to ensure that the question and the I/E criteria were well stated with regard to the seven PICOTSS dimensions. Following are the high-level elements of Question 2 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 follow up 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.

Selection of the I/E Criteria

In addition to using the PICOTSS analysis to refine the question, the Work Group 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.

Rationale for Selecting This Question 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. (10) 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(8,15-18) 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 panel(8) operationalized this concept by employing a modified version of the FRS to predict 10-year absolute risk for development of coronary death or nonfatal myocardial infarction, 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) (5) 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 (typically <50 years of age) and most women have low (e.g., <5% or <10%) predicted 10-year risks for CHD, and more broad CVD outcomes, despite the presence of significant risk factor burden. (74-78) 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 lifecourse 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 (10) and ATP III (8) 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 question, the Work Group 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 Work Group developed this question to assess the utility of long-term and lifetime risk assessment as an adjunct to short-term (10-year) risk assessment. The Work Group 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 Work Group selected this question 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 question 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.

Methods for Critical Question 2

All the Question 2 articles were original research publications and did not include systematic reviews or meta-analyses because none was 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.

Evidence Summaries

Summary Table for the Question

Table B-6 shows the Risk Assessment Question 2 Summary Table.

Summary Text for the Question

Ten articles met the Question 2 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. Follow up 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.

Evidence Statements for Critical Question 2

The following evidence statements are derived solely from studies that met I/E criteria for this question 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 Work Group to be more or less relevant to the question. Because of the nature of this question, 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 question.

Evidence Statement 1

We found 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.

Evidence Statement 2

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 Question 2 and do not reflect the totality of the available evidence regarding risk factors 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 follow up in 16,608 participants of the Chicago Heart Association Detection Project in Industry (CHA Study) ages 40 to 59 at baseline. (79) 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' follow up. 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' follow up. (79) Data from the FHS indicate that diabetes is associated with the highest lifetime risk for any single CVD risk factor. Remaining lifetime risks for atherosclerotic CVD 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. (80) Clear differences were seen between cumulative risks for atherosclerotic CVD 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). (81)

Body mass index or categorical obesity is not associated independently with short-term CVD risk, but is generally associated with long-term/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 follow up associated with higher baseline BMI among middle-aged men in the CHA Study. (79) For women, the independent risks associated with higher baseline BMI were similar across 0 to 10, 10 to 20, and greater than 20 years' follow up, but they became significant only with CVD deaths occurring after greater than 20 years' follow up. In a similar analysis of 14,403 men ages 40 to 49 by Håheim et al., 2007, (82) baseline BMI was not significantly associated with fatal CHD events occurring before 15 years of follow up 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 follow up 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 atherosclerotic CVD events, even after considering competing outcomes of non-CVD death. (80,83)

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 follow up intervals.

(79,82,84) Pencina et al., 2009,(83) and Lloyd-Jones et al., 2006 (80) 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, systolic blood pressure is associated with short-term, long-term and lifetime CVD risk (strength of evidence: Moderate). The association of baseline systolic blood pressure with ASCVD events remains significant during all follow up intervals, (79,82,84) and in the context of 30-year competing risks for CVD as well as lifetime risk for CVD in men and women. (80,83)

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 follow up intervals. (79,82,85) 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. (83) Remaining lifetime risks for atherosclerotic CVD were similar for smokers and nonsmokers among men and women ages 50 through 95. However, smokers had CVD events at substantially younger ages and had substantially shorter median survival compared with nonsmokers, who survived longer and had their CVD events much later in life. (80)

The above studies generally considered the individual associations of risk factors across different time intervals of follow up, 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.

Evidence Statement 3

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 (86) examined the ability of the FRS, (26) 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 Work Group 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 that they may not adequately

represent the full spectrum of risk information regarding CHD. Likewise, the Work Group 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. (86)

Evidence Statement 4

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. (83) 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 ASCVD 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. (83)

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.

Evidence Statement 5

The presence and severity of traditional ASCVD 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 ASCVD 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. (80) The data allowed for comparisons of short- and long-term risks by aggregate risk factor burden. In this 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 of approximately 10 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 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 average 10-year ASCVD risk 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 less than 5 percent and lifetime risk for ASCVD of less than 10 percent. (80)

The Work Group reviewed another study that was not included in the 10 manuscripts for the evidence base for this question 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, (77) 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. (22) 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: those with low 10-year (<10 percent)/low lifetime (<39 percent) predicted risk, those with low 10-year (<10 percent)/high lifetime (≥39 percent) predicted risk, and 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. (77) 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.

Evidence Statement 6

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, systolic blood pressure, 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' follow up in the Framingham Heart Study and NHANES I and NHANES II mortality follow up cohorts. (87) 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 overpredict 15-year risk for men somewhat. (87)

Evidence Statement 7

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.(88) 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 follow up 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 of risk factor values every 6 years led to the best predictive utilities. (88)

In the aforementioned Pencina 2009 study (83) from Framingham that generated 30-year risk competing risk prediction models for hard ASCVD 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 hazards ratios associated with 30-year ASCVD events were similar whether baseline or time-dependent covariates were used. However, the association for smoking was stronger and for BMI weaker when 4-year risk factor updating was used. (83)

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.

Recommendations for CQ2: Long-Term Risk Assessment

Recommendation 1.

It is reasonable to assess traditional ASCVD risk factors† every 4 to 6 years in adults 20 to 79 year of age who are free from ASCVD and estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years without ASCVD.

(Grade B, Moderate); ACC/AHA COR IIa, LOE B

Recommendation 2.
Assessment of 30-year or lifetime ASCVD risk on the basis of traditional risk factors† may be considered in adults 20 to 59 years of age who are free from ASCVD and are not at high short-term risk.

(Grade C, Weak); ACC/AHA COR IIb, LOE C

†Age, sex, total and HDL-cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current smoking.

After synthesizing the data from the 10 included studies and the approved evidence statements, the Work Group judged that there was consistent evidence from multiple sources regarding the associations of traditional risk factors with events occurring during both short-term and long-term follow up. The important associations are best represented and understood in the context of multivariable risk equations that reliably predict absolute risk for ASCVD events. In addition, most of these risk factors are both causal and modifiable, indicating their central clinical importance for ASCVD prevention efforts. Given the additional evidence suggesting improved risk prediction using updated clinical covariates, the Work Group endorsed this recommendation to assess risk factor levels every 4 to 6 years and to incorporate the information into global ASCVD risk prediction equations to quantify short-term ASCVD risk. The data from the included studies were derived from individuals between the ages of 20 and 79, with the majority being between the ages of 40 and 74. For individuals at older ages (≥80 years), or those with limited life expectancy, where risk factor associations are weaker or irrelevant, competing risks and associated comorbidities are likely to be more prevalent and potential benefits of ASCVD prevention strategies are unknown or likely to be low. For these individuals, the Work Group recognizes that individual clinical considerations should dictate the intensity of risk assessment

and prevention efforts. The Work Group also recognizes that risk factor measurement for younger adults (i.e., 20 to 39 years old) is most useful for identifying two groups: the smaller group of individuals with extreme risk factor levels who might be candidates for pharmacologic interventions and the larger group of individuals with less extreme adverse risk factor levels in whom early initiation of intensive lifestyle interventions may be particularly important.

The Work Group judged that the studies that addressed this question had revealed a number of important issues. First, long-term and lifetime risks for ASCVD are dramatically elevated for large segments of the population, even when risk factor levels are only mildly elevated from a current clinical perspective. For individuals with markedly elevated risk factors in younger and middle age, the majority will experience an ASCVD event during their lifespan and have a high risk for death, and especially premature death, from ASCVD. The prevalence of abnormal risk factors and the burden of predicted long-term risk combine to create an important potential for prevention efforts in the short and long terms.

Second, it was evident that 10-year ASCVD risk equations do not adequately predict, or even stratify, long-term or remaining lifetime risks for development of ASCVD. The Work Group found no reliable means for extrapolating 10-year risk assessment to represent longer term risks appropriately.

This recommendation is limited by lack of data pertinent to ethnic groups other than non-Hispanic Whites. Furthermore, compared with the use of 10-year ASCVD risk assessment, clinicians have much less experience applying long-term risk estimates in clinical settings. Nonetheless, the evidence reviewed provides face validity for the concept that additional benefit may be gained from estimating 30-year and/or lifetime ASCVD risks with regard to

understanding and communicating the full picture of ASCVD risk across the lifespan to patients, and there is little expected harm from doing so. The Work Group did not determine thresholds for unacceptably high long-term or lifetime risk that could be used for clinical recommendations regarding drug treatment thresholds. The Work Group did not find evidence about the utility of lifetime risk assessment for guiding pharmacologic therapy decisions, and judged that long-term and lifetime risk information may be used more appropriately at this time to motivate therapeutic lifestyle change in younger individuals. This perspective influenced the choice of age 20 as the starting point for long-term risk assessment despite a threshold of age 40 for short-term 10-year ASCVD risk assessment. Based on the current evidence, the short-term risk for ASCVD is quite low in the vast majority of adults younger than age 40, and the ability to estimate short-term (10-year) risk with precision is limited by lack of data in younger adults. Hence, long-term risk assessment is recommended for adults ages 20 to 39 who are free from ASCVD and adults ages 40 to 59 who are free from ASCVD and are not at high short-term risk. **Table 16** presents the prevalence of U.S. adults ages 40 to 79 according to their 10-year and lifetime predicted risks. This population is stratified into three groups: (1) those with low (<7.5 percent) estimated 10-year risk for ASCVD and relatively low, though not necessarily optimal, estimated lifetime risk for ASCVD (as indicated by nonelevated levels of traditional risk factors, corresponding to estimated lifetime risks for ASCVD of <39 percent according to Framingham data (80) (see Evidence Statement 5); (2) those with low (<7.5 percent) 10-year but high estimated lifetime risk for ASCVD (as indicated by presence of one or more elevated traditional risk factors, corresponding to lifetime risk estimates of ≥39 percent according to Framingham data (80)); and (3) those with high (≥7.5 percent) estimated 10-year risk for ASCVD.

Table 16. Distribution of estimates of 10-year and lifetime risk for a first hard ASCVD event in the non-pregnant U.S. population ages 40 to 79 years (NHANES 2007–2010) (*N*=5,367, weighted to 100,542,000 U.S. population)

	Estimated Risk for ASCVD		
	Low 10-Year/Low Lifetime*	**Low 10-Year/High Lifetime†**	**High 10-Year‡**
Total	14.8 (1,4821,000)	52.3 (52,630,000)	32.9 (33,090,000)
Sex			
Men	13.3 (6,400,000)	42.4 (20,447,000)	44.3 (21,334,000)
Women	16.1 (8,422,000)	61.5 (32,183,000)	22.5 (11,757,000)

*10-year estimated risk <7.5%, and no traditional risk factor elevated (no current smoking, no diabetes, and untreated total cholesterol <200 mg/dL and untreated blood pressure <140 mmHg for systolic and <90 mmHg for diastolic). (80)

†10-year estimated risk <7.5%, but one or more traditional risk factors elevated (current smoking, or diabetes, or total cholesterol ≥200 mg/dL or blood pressure ≥140 mmHg for systolic or ≥90 mmHg for diastolic, or receiving treatment for high cholesterol or high blood pressure), corresponding to lifetime risk estimates of ≥39% according to Framingham data. (80)

‡10-year estimated risk ≥7.5%.

Long-term and lifetime risk estimation may be less valuable for individuals who are found to be at high short-term (10-year) risk based on multivariable equations in whom decisions regarding prevention efforts may be clear. However, an understanding of long-term risk may provide a means for encouraging adherence to lifestyle or pharmacologic therapies, especially for patients who might have difficulty understanding the importance of their short-term risk. Likewise, for individuals at older ages, or those with limited life expectancy, the Work Group recognizes that individual clinical considerations should dictate the intensity of risk assessment and prevention efforts.

For the purposes of **table 16**, the Work Group adopted as an example the threshold of equal to or greater than 7.5 percent estimated 10-year risk for hard ASCVD to indicate “high risk” status in the short term, using the perspective used by Rose, 1991, 1992, to describe “high risk” and

"population" approaches to prevention. (89,90) Rose used the language of the "high risk" approach to describe the process of identifying individuals with a risk factor level above a given threshold, in whom individualized clinical approaches to prevention, whether pharmacologic or behavioral, would be appropriate. For this example, the Work Group selected the threshold of ≥7.5 percent estimated 10-year risk for hard ASCVD as one supported by the evidence that statin therapy is effective and cost-effective for preventing ASCVD in study populations with at least this level of risk. This evidence is reviewed in detail in the report from the Adult Treatment Panel IV (ATP IV).

EVIDENCE GAPS AND FUTURE RESEARCH NEEDS

The Work Group 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

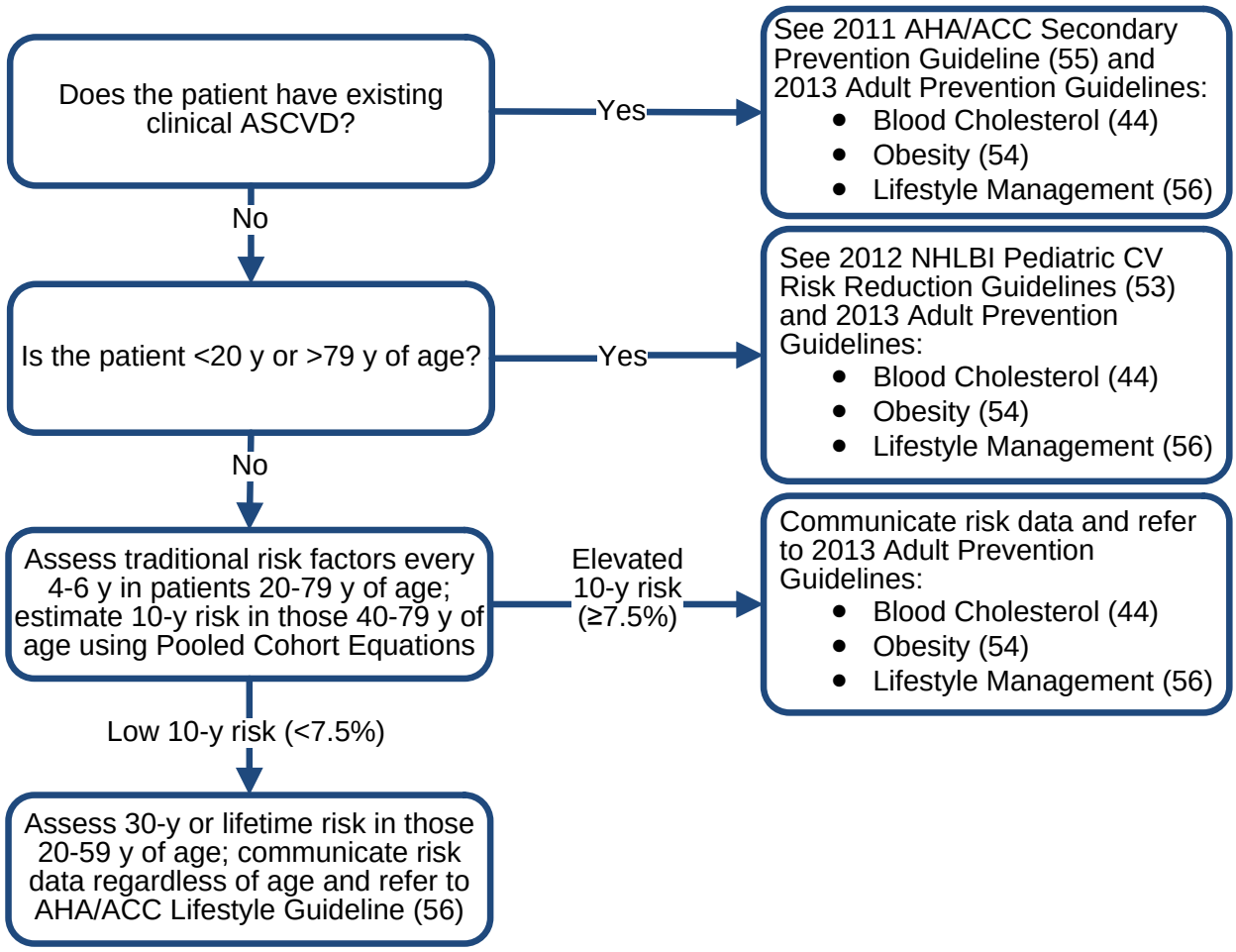
- Short- and long-term risk in diverse groups
- Optimal communication of ASCVD risk information
- Utility of short-and long-term risk assessment for motivating behavioral change and adherence to therapy
- Utility of short-and long-term risk assessment for influencing risk factor levels and clinical outcomes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

- Utility of novel risk markers in short- and long-term risk assessment

CONSIDERATIONS FOR IMPLEMENTATION

This approach to risk assessment was developed to support the risk factor–specific updates for blood cholesterol, blood pressure, and obesity, according to the discretion of those update panels. A suggested approach for incorporating these recommendations into clinical practice is shown in **figure 2.** For patients ages 20 through 79 who are free from clinical ASCVD, the first step is to assess ASCVD risk factors. Whereas it is reasonable to assess ASCVD risk factors in younger and older individuals, limitations in available data prevented the development of robust risk assessment algorithms in these populations. Hence, for patients outside this age range, providers should refer to applicable clinical practice guidelines (i.e., pediatric (91) and adult Primary Prevention Guidelines (73,92)). Risk assessment should be repeated every 4 to 6 years in persons who are found to be at low 10-year risk (<7.5%). Beginning at age 40, formal quantitative estimation of the 10-year risk for a first hard ASCVD event is recommended. Long-term or lifetime risk estimate is recommended for all persons who are between the ages of 20 through 39 years and for those between the ages of 40 through 59 years who are determined to be at low 10-year risk (<7.5%). These data may best be used in the context of a "risk conversation" with the patient that reviews the absolute risk for ASCVD events, origins of the patient's risk, consequences of ASCVD events, and potential benefits and harms of lifestyle modification or drug therapy, if appropriate. As shown in Figure 2, all patients should receive applicable risk information and appropriate lifestyle counseling.

Figure 2. Implementation of Risk Assessment Work Group Recommendations



ACC indicates American College of Cardiology; AHA, American Heart Association; and ASCVD, atherosclerotic cardiovascular disease.

The Work Group recommends that electronic health record vendors incorporate these risk algorithms directly into their products to support meaningful use.

Risk estimates provided by the new Pooled Cohort Equations differ from those generated by the ATP III algorithm in several respects, as discussed previously (**table 14**). These differences in ASCVD outcomes and model coefficients make simple linear conversions imprecise. For example, from **table 14**, it is clear that using a treatment threshold of 10 percent 10-year CHD risk or diabetes based on the ATP III risk algorithm would result in a different population

eligible for treatment than using a 7.5 percent 10-year ASCVD risk threshold based on the Pooled Cohort Equations. Despite the observation that similar proportions of the middle-aged population would be eligible for treatment (31.9 percent and 32.9 percent, respectively), only 25 percent of the overall population would be eligible for treatment based on both thresholds. In collaboration with the ACC/AHA Blood Cholesterol Guideline panel, and following their recommendations, we developed **table 17** to provide additional insight into this issue. Using the recommendations of ATP III, 32.3 to 42.8 percent of ASCVD-free adults aged 40 through 79 might qualify for treatment. Using the recommendations of ACC/AHA Blood Cholesterol Guideline, 51.0 to 66.4 percent might qualify for a risk discussion as recommended by the panel. Based on these important differences, we recommend that health care organizations convert to the Pooled Cohort Equations for risk assessment as soon as practical.

Table 17. Distribution of individuals recommended for treatment and optional treatment in the ASCVD-free, non-pregnant U.S. population ages 40 to 79 (NHANES 2007–2010)

	Percentage (*N*) of ASCVD-free, non-pregnant U.S. population ages 40 to 79 (NHANES 2007–2010)					
	Treatment Recommended*			**Optional Treatment***		
10-Year Risk for Hard CHD (ATP III) (8)	>20% or DM	LDL cholesterol ≥190 mg/dL	Subtotal	10–20% and LDL cholesterol ≥130 mg/dL	<10.0% and LDL cholesterol ≥160 mg/dL	Subtotal
Total	29.5 (16,815,000)	2.8 (1,578,000)	32.3 (18,393,000)	5.1 (2,894,000)	5.4 (3,078,000)	10.5 (5,972,000)
Sex						
Men	38.2 (10,896,000)	2.2 (614,000)	40.3 (11,510,000)	8.5 (2,417,000)	3.1 (873,000)	11.6 (3,289,000)
Women	20.8 (5,919,000)	3.4 (963,000)	24.1 (6,883,000)	1.7 (477,000)	7.7 (2,206,000)	9.4 (2,683,000)
	Treatment Recommended*					**Optional Treatment***
10-Year Risk for Hard ASCVD (Pooled Cohort Equations)	LDL cholesterol ≥190 mg/dL	DM and age ≥40	≥7.5%	Subtotal		5–7.4%
Total	2.5 (1,837,000)	16.1 (11,926,000)	32.4 (24,099,000)	51.0 (37,862,000)		15.4 (11,446,000)
Sex						
Men	2.1 (800,000)	16.1 (6,274,000)	41.1 (16,013,000)	59.3 (23,087,000)		17.6 (6,858,000)
Women	2.9 (1,037,000)	16.0 (5,652,000)	22.9 (8,086,000)	41.8 (14,775,000)		13.0 (4,587,000)

Abbreviations: ASCVD=atherosclerotic cardiovascular disease, CHD=coronary heart disease, CVD=cardiovascular disease, DM=diabetes mellitus, LDL=low density lipoprotein

*Categories are mutually exclusive and assigned in order shown from left to right.

The Work Group judged that this new approach to risk assessment represents a step forward in ASCVD prevention that is large enough to warrant the challenges inherent in implementing a new approach, rather than continuing with the CHD risk assessment approach recommended in ATP III. The ability to estimate risk for a broadly based ASCVD outcome that is more relevant to contemporary populations, including especially women and African Americans, and the ability to provide risk estimates specific to African Americans are the two major advances of this approach. Promotion of lifetime risk estimation may represent an additional step forward in supporting lifestyle behavior change counseling efforts. Further research regarding the merit of these approaches to risk assessment is clearly warranted, and specific recommendations regarding topics of interest are provided above. The process of periodically updating the guidelines is expected to address issues related to risk assessment in future reports. For example, specific equations may be needed for other ethnic groups, and future research may support the incorporation of additional risk factors or measures of subclinical disease into newer risk estimation algorithms.

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
CAC	Coronary artery calcium
CHD	Coronary heart disease
CHF	Congestive heart failure
CIMT	Carotid artery intima-medial thickness
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FRS	Framingham Risk Score
GFR	Glomerular filtration rate
GLIA	GuideLine Implementability Appraisal
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
IDI	Integrated discrimination improvement index
I/E	Inclusion and exclusion
IOM	Institute of Medicine
LDL-C	Low-density lipoprotein cholesterol
MA	Meta-analysis/Meta-analyses
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 clinical trial
SBP	Systolic blood pressure
SR	Systematic Review
USPSTF	United States Preventive Services Task Force

APPENDIX A. DETAILED METHODS APPLYING TO ALL CRITICAL QUESTIONS

Description of How 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 the NHLBI Web site for several weeks and also was distributed to a guidelines leadership group that had given advice to the 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 the NHLBI conflict of interest disclosures and a copy of their curriculum vitae. The NHLBI 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 the NHLBI to select panel members from the list of nominees.

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 blood pressure, high blood cholesterol, obesity) as well as in specific disciplines, including 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 include, as voting ex officio members, senior scientific staff from NHLBI and other NIH Institutes who are recognized experts in the topics under consideration.

Description of How 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, which is primary care providers.

Proposed questions and topic areas were collected from panel members over a period of several months. The number of critical questions was scoped, and questions were prioritized based on clinical importance. After group discussion, panel members ranked priority critical questions through a combination of collaborative dialogue and voting. The rationale for each priority critical question is addressed in the sections on Critical Questions 1 and 2.

With support from the methodologist and systematic review team, priority critical questions were formulated. I/E criteria were defined and formatted using the PICOTSS framework. PICOTSS is a framework for a structured research question and includes the following components in the statement of the critical question 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 critical question. They 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 critical questions and criteria were submitted to the literature search team for search strategy development.

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 the NHLBI guidelines initiative.

The central repository consisted of 1.9 million citations and 71,000 full text articles related to cardiovascular disease risk reduction. Citations were acquired from PubMed, Embase, Cinahl, Cochrane, PsycInfo, Wilson Science, and Biological Abstracts databases. 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 critical question, 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. Data elements that were frequently extracted and used were study size and intervention follow up 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 to 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 critical question's Include List to ensure completeness of the search strategy.

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 critical question. I/E criteria address the parameters in the PICOTSS framework and determine what types of studies are eligible and appropriate to answer the critical question. Additional criteria, such as sample size restrictions, were included by the panel to fit the context of the critical question.

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 the publication for full text review or voted to exclude it. 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 where appropriate. For example, if criteria were not specific enough to be clearly applied to include or exclude a citation, guidance was sought to more explicitly word criteria.

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 where 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) 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, they asked the methodologist for advice. If a decision was not reached after consultation with the methodologist, the panel was consulted. 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, which are posted and available for viewing on the VCW, all citations screened for a critical question are maintained in the VCW with their reviewer voting status and all collected comments.

Description of Methods for Quality Assessment of Individual Studies

Articles meeting the criteria after the three-phase review literature review process were then rated for quality. Separate quality rating tools were used for each study design.

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 developed based on quality assessment methods, concepts, and other tools developed by researchers in Evidence-Based Practice Centers, The Cochrane Collaborative, the USPSTF, the National Health Service Centre for Reviews and Dissemination, consulting epidemiologists, and others working in evidence-based medicine, with adaptations by methodology and NHLBI staff for this project.

These tools were designed to assist reviewers to focus on concepts 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 to evaluate potential flaws in study methods or implementation, including sources of bias (e.g., patient selection, performance, attrition, 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 on the tool. For each item where "no" was checked, reviewers were instructed to consider the potential risk for bias that may 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, also developed by the methodology team and NHLBI. The guidance documents were specific to each tool and provided detailed descriptions and examples of application of the items, as well as justifications for item inclusion. For some items, examples were provided to clarify the intent of the question and the appropriate rater response.

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 for bias in the study due to flaws in study design or implementation.

In general terms, a Good study has the least risk for 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 for bias. Studies rated Poor were excluded from the body of evidence to be considered for each critical question. The only exception allowed for this general policy of excluding Poor studies was if no other evidence was available. In this case, 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 critical question.

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. 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.

The before-after and case series studies quality assessment tools were applied only to the obesity panel's Critical Question 5, which addresses bariatric surgery interventions. This critical question included those types of study designs due to the different types of issues addressed for this surgical intervention. As a result, a formal training program for use of these quality assessment tools was not conducted. The training efforts were more individual and focused on reviewing the tool and guidance document with staff working on quality assessment for this critical question.

Quality Assessment Process

For all studies, except for systematic reviews and meta-analyses, each article that met the critical question's inclusion criteria was rated for quality, using the appropriate tool, by two reviewers independently. If the ratings differed, the reviewers discussed the article in an effort to reach consensus. If 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, 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 reported to the panel members. However, the final decision on quality ratings was made by the methodology team, and not by panel members, to enhance the objectivity of the quality rating process.

Quality Assessment Tool for Controlled Intervention Studies

The quality assessment tool for controlled intervention was developed by the methodology team and NHLBI based in part on criteria from AHRQ's 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 intention-to-treat analysis (i.e., analysis of all randomized patients even if some were lost to follow up), adequacy of blinding, the overall percentage of subjects lost to follow up, the differential rates of loss to follow up between the intervention and control groups, and other factors.

Quality Assessment Tool for Systematic Reviews and Meta-Analyses

The quality assessment tool for systematic reviews and meta-analyses 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.

Quality Assessment Tool for Cohort and Cross-Sectional Studies

The quality assessment tool for cohort and cross-sectional studies 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 follow up; study analysis and power; and other factors.

Quality Assessment Tool for Case-Control Studies

The quality assessment tool for case-control studies 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.

Quality Assessment Tool for Before-After Studies

The quality assessment tool for before-after (pre-post) studies was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-Based Practice Centers, papers addressing quality assessment of similar studies, 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 intervention and outcome variables; adequacy of blinding; statistical methods; and other factors.

Quality Assessment Tool for Case Series Studies

The quality assessment tool for case series studies was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-Based Practice Centers, papers addressing quality assessment of similar studies, and other factors.

This tool includes nine 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 intervention and outcome variables; statistical methods; and other factors.

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 critical question. The evidence table template included data elements relevant to the critical question, 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.

Development of Evidence Tables and Summary Tables

Evidence Tables

For each critical question, methodologists worked with the expert panel/work group members to identify the key data elements needed to answer the question. Using the PICOTSS criteria as the foundation, expert panel/work group members determined what information was needed from each study to be able to understand the design, sample, and baseline characteristics and 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/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 critical question.

Only studies rated Good and Fair were included in the evidence tables.

Templates varied by each individual critical question 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 follow up, run-in, wash-out, intervention *N*s
- Baseline population characteristics: demographics, biomarkers, other measures relevant to the outcomes
- Results: outcomes of interest for the critical question with between group *p* values or confidence intervals for risk ratios, adverse events, attrition, adherence

Studies are presented in alphabetical order by the study name (if none, the first author's last name). 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.

Summary Tables

To enable a more targeted focus on the specific aspects of a critical question, 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 presented 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 critical question being addressed but generally provided 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, adherence

Each expert panel/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.

Development of Evidence Statements, Recommendations, and 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 physicians 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 expert panels with overarching guidance on how to grade the level of evidence (High, Moderate, Low) and the panels used this guidance to grade each evidence statement. This guidance is documented in the following section.

Expert panel members having 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 a panel chair asking each member to signify his or her vote. NHLBI project staff and contractors did not vote.

Once evidence statements were finalized, attention turned to recommendations. Recommendations were developed using a similar process to evidence statements. Voting could be open so that differing viewpoints could be identified easily and further discussion and revisions facilitated to address areas of disagreement (e.g., by crafting language or dividing an evidence statement into more than one statement). Voting could be by confidential ballot if the group chose.

For both evidence statements and recommendations, a record of the vote count (for, against, recusal) was made without attribution. The ideal was 100 percent consensus, but a 2/3 majority was considered acceptable. For approval of a recommendation rated E (Expert Opinion) at least 75 percent of the expert panel members had to vote "yes."

Description of Methods for Grading the Body of Evidence

The NHBLI Adult Cardiovascular Disease Guidelines Project applied related but distinct processes for grading the bodies of evidence for critical questions, for bodies of evidence for different outcomes included within critical questions, and for the subsequent strength of recommendations developed from those bodies of evidence. Each of these processes is described in turn below.

Grading the Body of Evidence

In developing the system for grading the body of evidence, the NHLBI reviewed a number of systems, including GRADE (Grading of Recommendations Assessment, Development, and Evaluation), USPSTF, 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 the NHLBI 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 panels and work groups 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 critical question. The first process was to conduct a de novo literature search and literature review for all of the individual studies that met a critical question's I/E criteria. This was used for most of the critical questions. The second process 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 critical questions across expert panels and work groups. Additional information on the use of systematic reviews and meta-analyses is provided below.

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 physicians 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 following types of evidence 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:

Type of Evidence	Strength of Evidence Grade
• Well-designed, well-executed randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes • Meta-analyses of such studies • *Our confidence is high that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.*	**High**

• RCTs with minor limitations affecting 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 • *Our confidence is moderate that the evidence reflects the true effect. Further research may change our 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 affecting confidence in, or applicability of, the results • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports) • Physiological studies in humans • Meta-analyses of such studies • *Our confidence is low that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.*	**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 to the expert panels and work groups provided guidance on assessing the body of evidence for each outcome or summary table of interest using four domains: (1) risk for 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 the NHLBI Evidence Quality Grading System shown above. The four domains are explained in more detail below:

Risk for Bias

Risk for 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 for bias and internal validity are similar concepts that are inversely correlated. A study with a low risk for bias has high internal validity and is more likely to provide correct results than one with high risk for bias and low internal validity. At the individual study level, risk for bias is determined by rating the quality of each individual study using standard rating instruments, such as the NHLBI study quality rating tools presented and discussed in the previous section of this report. Overall risk for 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 for bias was low, it increased the strength of evidence rating for the strength of the overall body of evidence. If the risk for bias was high, it decreased the strength of evidence rating.

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 effect sizes that are in different directions, a broad range of effect sizes, nonoverlapping confidence intervals, or 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 the NHLBI project, consistent with the Evidence-Based Practice Centers approach, 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.

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 versus 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, the evidence is direct and strengthened. If they are different, the evidence is indirect and weakened.

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 as 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 body mass index 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.

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 SRs or MA of randomized controlled trials are generally considered to be among the

highest forms of evidence. As a result, SRs or MA could be used to inform guideline development in the NHLBI CVD adult guidelines project if certain criteria were net. Guidance on using existing SRs has been published by AHRQ and helped to inform the development of the NHLBI criteria: www.effectivehealth care.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=329.

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

In general, for this project:

- Eligibility of SRs and MA was determined by the methodologists, consulting with panels/workgroups as needed.

- Data were not abstracted from SRs or MA, so they were not included in evidence tables. However, if an SR or MA was used to make a recommendation, a summary of the evidence was provided in the text, information from the SR or MA was included in a summary table or appendix, and the citation was included in the reference list.

- SRs or MA were rated using the quality assessment tool for this project. SRs or MA were used to develop recommendations if they were rated Good or Fair or were comprehensive reviews commissioned by the Federal government. SRs or MA rated as Poor were used only

when there were no eligible Good or Fair publications; this occurred for the obesity panel's Critical Question 2.

- If an existing SR or MA was used to develop recommendations:
  - Multiple eligible SRs and MA addressing the same topic were identified through a systematic search to minimize bias. The SRs or MA used were summarized in text, table, or 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 [SRs/MA rated Good only], Moderate, or Low rating based on number, type, and quality of the studies in the MA or SR.
  - Recommendation strength took into account whatever evidence was available in the SRs or MA used to make the recommendation, including issues such as strength of the evidence, applicability of the evidence, and consistency of the evidence. Any level of recommendation could be made, as long as it was supported by the evidence being used to make the recommendation: Grade A (Strong) [a strong recommendation could be given only if the SRs/MA used to make the recommendation were rated as Good], B (Moderate), C (Weak), (D) Against, (E) Expert Opinion, and (N) No Recommendation.

Three criteria were used to determine when SRs or MA could be used.

Situation 1

When an SR or MA addressed a topic relevant to the NHLBI CVD guidelines that was *not covered* by an existing critical question (e.g., effects of physical activity on CVD risk):

1. In order for an SR or MA to be examined for relevance to the topic of interest, the topic needed to be prespecified in the form of a critical question using the PICOTSS structure. If only portion(s) of an SR were relevant, those relevant portions that were reported separately could be used. For example, in HHS' systematic review on physical activity, *Physical Activity Guidelines Advisory Committee Report, 2008*, (93) the effects of physical activity on CVD were relevant and were used to make recommendations because they were reported in a separate chapter. However, the effects of physical activity on mental health would not be relevant and therefore were not used in crafting recommendations.

2. SRs or MA could be used if they were recent, in other words published within 3 years of the end date of the NHLBI systematic review publication window (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 recommendations. If the end date of the SR or MA 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 of the SR or MA. 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 SR or MA and extend to no later than December 31, 2009.

Situation 2

If the NHLBI literature review identified an existing SR or MA that could possibly *replace* NHLBI's review of a critical question or subquestion:

- The SR or MA was examined for consistency between the studies included in the SR or MA and the critical question I/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 NHLBI project's search date window, as long as a truly systematic approach was used.

- SRs or MA 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 SR or MA 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 of the SR or MA. 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 SR or MA and extend to no later than December 31, 2009.

Situation 3

If the NHLBI literature review identified an existing SR or MA that addressed the same or a similar critical question or subquestion as one undergoing NHLBI review:

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

APPENDIX B. QUESTION-SPECIFIC METHODS

Search Strategy Overview

The following sections describe specific results of the search strategies for each risk assessment critical question.

Risk Assessment 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?

Risk Assessment Question 1 Search Strategy Results and PRISMA Diagram

Risk Assessment Question 1 was initially intended to be a de novo systematic review of original studies plus systematic reviews and meta-analyses. In 2011, the question was de-scoped and restricted to SR/MA only. The initial search included the following bibliographic databases. On April 27, 2011, a supplemental search from PubMed was executed that sought exclusively SR/MA. The search strategy presented above is the final strategy, which queries for SR/MA.

1. PubMed from January 1998 to December 2009, later extended to April 2011

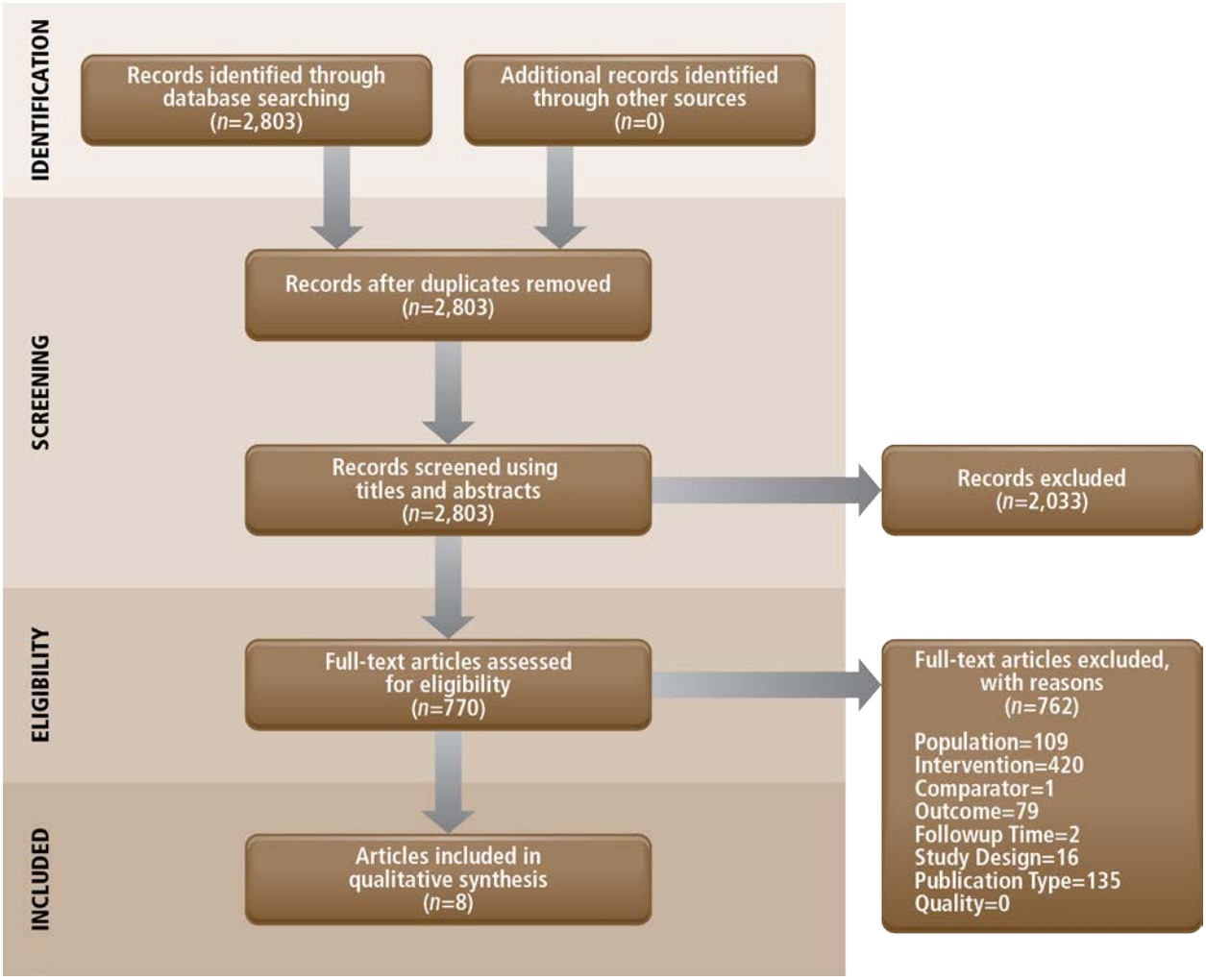
2. CINAHL from January 1998 to July 2008
3. Embase from January 1998 to July 2008
4. PsycINFO from January 1998 to July 2008
5. EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008
6. Biological Abstracts from January 2004 to July 2008
7. Wilson Social Sciences Abstracts from 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 2,803 citations; this number includes the search for original studies and SR/MA sought from the initial search plus results from the supplemental search that was restricted to SR/MA.

The titles and abstracts of these 2,803 publications were screened against the I/E criteria independently 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 SR/MA were quality rated using the NHLBI Quality Assessment Tool for Systematic Reviews and Meta-Analyses; two were rated as Good and six were rated as Fair. Thus, eight SR/MA were eligible for inclusion in the Question 1 evidence base. Six of the eight SR/MA were published after December 2009 and captured by the supplemental search.

Additional supplemental literature searches were conducted to find publications up to September 19, 2013. The initial search strategy was re-done and run in seven databases with small modifications in the different databases resulting in 678 additional references. Pubmed. Embase, CINAHL, Cochrane Database of Systematic Reviews, were searched from 2008-September 2013. Biosis (Biological Abstracts), PsycInfo, Wilson Social Sciences Abstracts were searched from July 2008-September 2013. Although a search had been run previously in Pubmed up to April 2011, Pubmed was searched again from 2008 – September 2013. Searches were limited primarily to systematic reviews and meta-analyses.

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



Risk Assessment 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?

Risk Assessment Question 2 Search Strategy Results and PRISMA Diagram

The following databases were searched for prospective or retrospective cohort studies, RCTs, and systematic reviews to answer Question 2:

1. PubMed from January 1998 to December 2009
2. CINAHL from January 1998 to July 2008
3. EMBASE from January 1998 to July 2008
4. PsycInfo from January 1998 to July 2008
5. EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008
6. Biological Abstracts from January 2004 to July 2008
7. 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.

The titles and abstracts of these 2,348 publications were screened against the I/E criteria independently 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 the NHLBI Quality Assessment Tool for Cohort or Cross-Sectional Studies; 8 were rated as Good and 2 were rated as Fair. Thus, 10 publications were eligible for inclusion in the Question 2 Evidence Base.

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

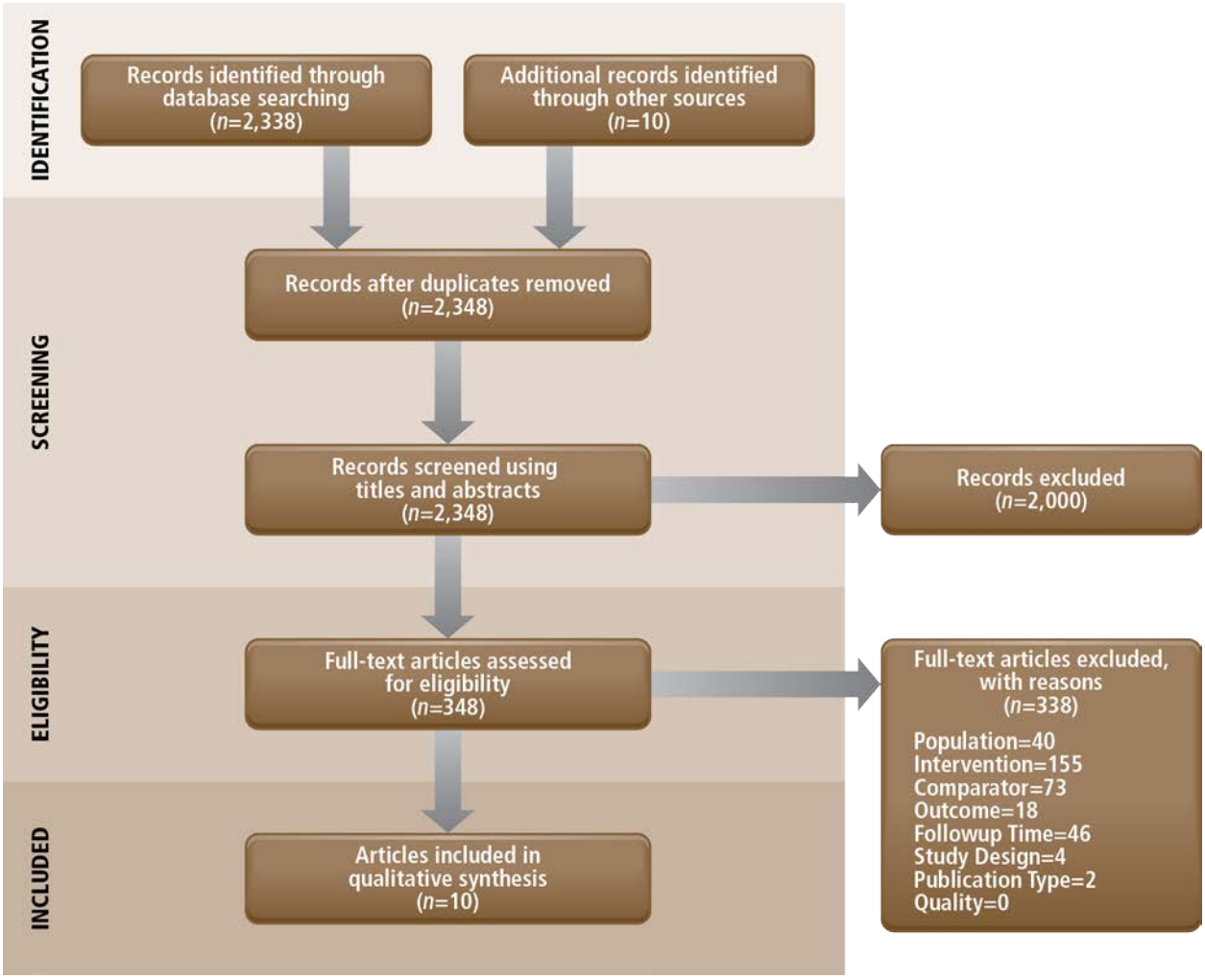


Table B–1. Risk Assessment Work Group Question 1 PICOTSS

PICOTSS	From Inclusion/Exclusion Criteria	Notes
Population	INCLUDE: a. Adults older than or equal to age 18 b. Primary prevention populations: No clinical manifestation of CVD. EXCLUDE c. Studies of children d. Studies of animals	
Intervention/ Exposure	All of the following: a. One or more of the following: measured or calculated total cholesterol, non-HDL, LDL-C, or ApoB b. Measured HDL-C c. Traditional risk factors included in assessment—smoking, diabetes, BP level or hypertension, age, sex d. 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	**Outcomes/Events** Studies must report one or more of the following outcomes: a. CVD mortality b. Fatal or nonfatal MI c. Fatal or nonfatal stroke d. Hospitalization for or death from arrhythmia e. Hospitalization for or death from CHF f. Composite CVD outcomes that include any of the above outcomes	
Timing	>1 year	
Setting	a. Any geographic location—single or multicenter b. Any clinical, diagnostic, or research setting	
Study Design	Systematic reviews, prospective or retrospective cohort studies	

Abbreviations: 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 Question 1 Inclusion/Exclusion Criteria

1. Population

a. Adults older than or equal to 18
   i. Primary prevention populations: No clinical CVD.

2. Intervention—Diagnosis or Assessment or Therapy

All of the following:

a. One or more of the following: measured or calculated total cholesterol, non-HDL, LDL-C, or ApoB
b. Measured HDL-C
c. Traditional risk factors included in assessment—smoking, diabetes, BP level or hypertension, age, sex
d. Data include at least one of the following: family history, hs-CRP, ApoB, microalbuminuria, GFR, cardiorespiratory fitness, CAC, CIMT, or ABI.

3. Outcomes/Events

All major initial CVD events, specifically any or all of the following:

a. Fatal or nonfatal MI
b. Stroke
c. CVD death (including CHD and stroke death)
d. Congestive heart failure (hospitalized CHF or fatal CHF)

4. Setting

a. Any geographic location—single or multicenter
b. Any clinical, diagnostic, or research setting

5. Study Design

a. Systematic reviews, prospective or retrospective cohort studies
b. Sample size: no restrictions
c. Exclusions: follow up less than 12 months; case series; case reports

6. Measures of Association

Examples

a. Relative risk
b. Hazards ratio
c. Odds ratio
d. AUC/C statistic
e. Reclassification
f. Measures of model fit (e.g., R^2, pseudo-R^2, AIC, BIC, LR or Wald chi^2)

7. Follow up Interval

a. More than 1 year

8. Language

a. Full text must be available in English
b. Exclusions: studies for which abstract only is available in English

9. Publication

a. Published studies

b. Exclusions

i. Unpublished literature

ii. Theses

iii. Studies published only as abstracts

iv. Letters, unless sufficient data on the population, intervention and results are presented and adequate information is available for quality assessment

v. Commentaries and opinion pieces

vi. Nonsystematic reviews

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

Abbreviations: 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 Question 1 Systematic Reviews Evidence Conclusions

#	Author/Group	Factor	Evidence Statement/Conclusion
1	Buckley et al., 2009 (52)	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 (53)	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 Work Group 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 Work Group also is concerned about radiation and incidental findings. The Work Group 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 Work Group also has concerns about measurement issues. Standardization of CIMT measurement is a major challenge. The Work Group recognizes that more recent individual study results have been published. Updated systematic

#	Author/Group	Factor	Evidence Statement/Conclusion
			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 Work Group 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.
3	Emerging Risk Factors Collaboration (54)	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 (55)	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 (57)	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 2 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 (58)	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

#	Author/Group	Factor	Evidence Statement/Conclusion
			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 Work Group members concerned regarding the validity of the evidence.
7	Kodama et al., 2009 (61)	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 (62)	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.
9	Empana, et al, 2011 (59)	Family history of CHD	"In separate models adjusted for age, gender, and study cohort, a family history of CHD, BMI, and waist circumference were all predictors of CHD. When traditional risk factors were controlled for, family history of CHD ($p<0.001$) and BMI ($p=0.03$) but not waist circumference ($p=0.42$) remained associated with CHD. However, the addition of family history of CHD or BMI to the traditional risk factors model did not improve the discrimination of the model (not shown)." This paper developed a CHD risk prediction algorithm based on 4 French population studies, and evaluated, among other factors, the contribution of family history to traditional risk factors. Family history of CHD was defined as the self-report of a myocardial infarction (MI) in first degree relatives (parents and siblings) in the D.E.S.I.R. and SU.VI.MAX. studies, as a history of MI before 55 years in men and before 65 years in women in parents, siblings, and grandparents in the PRIME study, and as a death due to MI in first degree relatives in the Three City study. No evidence on calibration, net reclassification index, or cost-effectiveness was provided.
10	Moyer et al. 2013 (63)	ABI	This paper is an updated review of the utility of assessing ABI for the USPSTF.

#	Author/Group	Factor	Evidence Statement/Conclusion
			"The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for PAD and CVD risk assessment with the ABI in adults. (I statement)" "The USPSTF found no evidence that screening for and treatment of PAD in asymptomatic patients leads to clinically important benefits. It also reviewed the potential benefits of adding the ABI to the Framingham Risk Score (FRS) and found evidence that this results in some patient risk reclassification; however, how often the reclassification is appropriate or whether it results in improved clinical outcomes is not known." The Work Group notes that this review provides some evidence that assessing ABI may improve risk assessment; however, no evidence was found by the USPSTF reviewers pertinent to the question of whether measuring ABI leads to better patient outcomes.
11.	Peters et al. 2012 (64)	CIMT, CAC	This paper is a systematic review of the literature regarding the contribution to risk assessment of imaging for subclinical atherosclerosis. "Published evidence on the added value of atherosclerosis imaging varies across the different markers, with limited evidence for FMD and considerable evidence for CIMT, carotid plaque and CAC. The added predictive value of additional screening may be primarily found in asymptomatic individuals at intermediate cardiovascular risk. Additional research in asymptomatic individuals is needed to quantify the cost effectiveness and impact of imaging for subclinical atherosclerosis on cardiovascular risk factor management and patient outcomes." Regarding CIMT: "The c-statistic of the prediction models without CIMT increased from 0.00 to 0.03 when CIMT was added. In the Atherosclerosis Risk In Communities (ARIC) study, addition of CIMT to the prediction model resulted in an NRI overall of 7.1% (95% CI 2.2% to 10.6%) and an IDI of 0.007 (95% CI 0.004 to 0.010). The NRI intermediate was 16.7% (95% CI 9.3% to 22.4%). In contrast, 10 year results from the Carotid Atherosclerosis Progression Study showed that addition of CIMT to the prediction model resulted in an IDI of 0.04% and NRI overall of -1.41%. Analysis of 1574 participants from the Firefighters and Their Endothelium study showed an NRI overall of 11.6% (p=0.044) and an NRI intermediate of 18.0% (p=0.034)." The Work Group notes that this paper provides some evidence to consider assessing CIMT; however, this conclusion was not supported by the Den Ruijter article described below. Regarding CAC: "The c-statistic increased from 0.04 to 0.13 when CAC was added to

#	Author/Group	Factor	Evidence Statement/Conclusion
			the model. Four recently published studies also reported results on the NRI and/or the IDI. One of these studies comprised a subgroup analysis of an earlier publication in the total population in individuals without indications for statin therapy. Analyses of the MESA study showed that addition of CAC to the conventional prediction model resulted in an NRI overall of 25% (95% CI 16% to 34%) and an NRI intermediate of 55% (95% CI 41% to 69%). The IDI in the MESA study was 0.026. Results were similar in the Rotterdam study. Addition of CAC to the prediction model led to an NRI overall of 14% ($p<0.01$) which was mainly driven by correctly reclassifying those at intermediate risk according to the traditional prediction model. Results from the Heinz Nixdorf Recall study also showed large NRIs when CAC was added to the Framingham Risk Score. Using different thresholds to define the intermediate risk category (10-20% or 6-20%), the NRI overall was 22% and 20%, respectively. The NRI intermediate was 22% for intermediate risk thresholds of 10-20% and 31% for intermediate risk thresholds of 6-20%. In addition, the IDI was 0.0152 when the prediction models with and without CAC were compared. The NRI overall was 25.1% and the IDI was 0.0167 in individuals from the Heinz Nixdorf Recall study without indications for statin therapy." The Work Group notes that this paper provides evidence to support the conclusion that assessing CAC is likely to be the most useful approach to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment. Furthermore, we note that the outcomes in the studies reviewed above were CHD, not ASCVD. The Work Group discussed concerns about cost, radiation exposure and the uncertainty of the contribution of assessing CAC to estimating 10-year risk of hard ASCVD after formal risk assessment.
12.	Kashani et al, 2013 (60)	Family history	This paper is an integrative literature review on the contribution of assessing family history to risk appraisal. "The evidence demonstrates that family history is an independent contributor to risk appraisal and unequivocally supports its incorporation to improve accuracy in global CVD risk estimation." The Work Group notes that a variety of endpoints, clinical and subclinical, were included in the reviewed papers. No evidence on discrimination, calibration, net reclassification index, or cost-effectiveness was provided.
13.	Den Ruijter et al, 2012	CIMT	This paper is an individual level meta-analysis of "14 population-based cohorts contributing data for 45 828 individuals. During a median follow-up of 11 years, 4007 first-time myocardial infarctions or strokes occurred." "We first refitted the risk factors of the Framingham Risk Score and then extended the model with common CIMT measurements to estimate the absolute 10-year risks to develop a first-time myocardial

#	Author/Group	Factor	Evidence Statement/Conclusion
			infarction or stroke in both models. The C statistic of both models was similar (0.757; 95% CI, 0.749-0.764; and 0.759; 95% CI, 0.752-0.766). The net reclassification improvement with the addition of common CIMT was small (0.8%; 95% CI, 0.1%-1.6%). In those at intermediate risk, the net reclassification improvement was 3.6% in all individuals (95% CI, 2.7%-4.6%) and no differences between men and women." "The addition of common CIMT measurements to the Framingham Risk Score was associated with small improvement in 10-year risk prediction of first-time myocardial infarction or stroke, but this improvement is unlikely to be of clinical importance." The Work Group judged this paper to provide the strongest evidence available regarding the potential value of CIMT to risk assessment. The Work Group also has concerns about measurement issues. Standardization of CIMT measurement is a major challenge.

Abbreviations: 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

Table B–4. Risk Assessment Work Group 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: a. Studies with individuals at high risk (>=20%) or with CHD risk equivalents unless the studies stratify the risk levels b. Studies of children c. Studies of animals	
Intervention/Exposure	INCLUDE: a. 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 b. Minimum set of risk factors to be considered in the model are age, sex, smoking measure, and either blood pressure measure or hypertension variable EXCLUDE: c. Exclude any model that does not include these four risk factors: age, sex, smoking measure, blood pressure measure or hypertension variable	This is an assessment intervention, not a therapeutic intervention.
Comparator	INCLUDE: a. Long-term risk (>= 15 years, or lifetime) assessed by a risk factor counting method, stratification method, or multivariable risk score or equation. b. Minimum set of risk factors to be considered in the model are age, sex, smoking measure, and either blood pressure measure or hypertension variable EXCLUDE: c. Exclude any model that does not include these four risk factors: age, sex, smoking measure, blood pressure measure or hypertension variable	

PICOTSS	From Inclusion/ Exclusion Criteria	Notes
Outcomes	Studies have to report one or more of the following outcomes: a. CVD mortality b. Fatal or nonfatal MI c. Fatal or nonfatal stroke d. Hospitalization for or death from arrhythmia e. Hospitalization for or death from CHF f. Composite CVD outcomes that include any of the above outcomes	Exclusions: None
Timing	Minimum average follow up: 15 years	
Setting	Any geographic location—single or multicenter	
Study design Prospective or retrospective cohort studies	RCTs or systematic reviews; appropriate statistical significance reporting.	

Abbreviations: ATP III=Adult Treatment Panel III, CHD=coronary heart disease, CHF=congestive heart failure, CVD=cardiovascular disease, MI=myocardial infarction

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

1. Population

a. 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)

b. With or without risk factors or comorbid conditions (excluding CHD risk equivalents, but including individuals with diabetes)

2. Intervention—Diagnosis or Assessment or Therapy

a. 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

b. Longer-term risk (>10 years, or lifetime) assessed by risk factor counting/stratification method or multivariable score or equation

3. Outcomes/Events

All CVD events, including any or all of the following:

a. CVD death (including CHD and stroke deaths)

b. Fatal or nonfatal MI

c. Fatal or nonfatal stroke

d. Hospitalized CHF

d. Peripheral vascular disease (defined as abdominal aortic aneurysm repair, surgical revascularization of upper/lower extremity, or amputation)

f. Total mortality

4. Setting

a. Any geographic location—single or multicenter

b. Any clinical, diagnostic, or research setting

5. Study Design

a. Prospective or retrospective cohort studies, RCTs or systematic reviews with or without a comparison group

b. Sample size: No restrictions

c. Exclusions: case reports

6. Measures of Association

Comparison (qualitative or quantitative) of short-term and long-term risk estimates

7. Follow up Interval

N/A

8. Language

a. Full text must be available in English

b. Exclusions: studies for which the abstract only is available in English, and not the full text

9. Publication

a. Published studies

b. Exclusions

i. Unpublished data

ii. Theses

iii. Studies published only as abstracts

iv. Letters, unless sufficient data on the population, intervention and results are presented, and adequate information is available for quality assessment

Abbreviations: 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 Question 2 Summary Table

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?

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
The Framingham Heart Study (FHS) (87) 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	*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 follow up study 1971 NHANES II mortality follow up 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:

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
the Framingham Study can rank individual risk as well as predict absolute risk for death in the new cohorts. See p. 5 in evidence table				– 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 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 follow up 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 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

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				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. • 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 (86) Good To investigate	*N*: 6,216 25 years max	1. Stratification by age- and sex-specific tertiles of Framingham risk score	Subjects examined between 1971 and 1976 Aged 40 to 94,	• 10-year risk score: Categorical values of age, total cholesterol, high-density lipoprotein cholesterol, blood pressure, smoking, and diabetes. • For women at all ages, the 10-year risk score appeared to

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
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		(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 FRS at specific ages. CHD events included angina pectoris, coronary insufficiency, myocardial infarction, and	without CHD	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 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.

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
		death due to CHD.		
The Framingham Heart Study (88) 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 follow up. End point was the first occurrence of	Study began 1948 Subjects with no CHD Ages 28 to 62 44.8% male	Candidate risk factors: age, current smoking, systolic blood pressure, 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.

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
		CHD, defined as MI, angina pectoris, coronary insufficiency, or CHD death		
The Framingham Heart Study (80) 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 Follow up 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 follow up 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 blood pressure 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 shown in figure 1, indicating that low HDL cholesterol and obesity were equivalent to major risk factors.

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				• Lifetime risk for ASCVD was similar for smokers and nonsmokers. • Among men free of ASCVD at age 50, lifetime risk to 95 years of age 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 blood pressure 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 (83) 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	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 ($p = 0.04$); 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

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
		of hard CHD events, such as coronary death, MI, stroke (fatal and nonfatal)		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 = 0.894; internally validated χ^2=3.98; p = 0.913) (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: – 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 = 0.04) but lost its entire impact (hazard ratio=0.99; p = 0.82) 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

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				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 (94) 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	*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	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 follow up, 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 follow up time was extended: – During the 5-year the age-adjusted hazard ratio was 1.86. – During the 23-year follow up, the age-adjusted hazard ratio was 1.24. – Adjustment for smoking, systolic blood pressure, 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
was independent of other cardiovascular risk factors, such as BP, smoking, diabetes, obesity, and serum cholesterol. See p. 16 in evidence table		of chronic headache with the risk for stroke was analyzed for 1, 5, and a maximum of 23 years of follow up 4. **Primary Outcome**: Predictive value of chronic unspecified headache for stroke		
The Seven Countries Study (84) Good To study the time-related association of a single measurement of coronary risk factors with CHD deaths occurring during a very long follow up period in a population sample of middle-aged men. See p. 20 in	*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 follow up, as a function of baseline risk factor measurements 3. Seven results	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 follow up, 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 follow up, suggesting relatively regular and constant association of risk factors with events during the whole follow up 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 follow

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
evidence table		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		up point. • The curve for cigarette smoking increased during the 35 years of follow up 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 (81) Fair To compare MetS with the FRS as predictors of CHD,	*N*: 5,128 21.3 years mean follow up	1. Cox proportional hazard model assessed the adjusted relative risks. 2. ROC curves and their	Study began 1978. Men ages 40 to 59 years with no history of ASCVD (CHD or stroke) or DM2	Candidate risk factors: Age, current cigarette smoker, inactive, manual social class, non-drinker, heavy drinker, BMI, SBP, DBP, triglyceride, HDL-C, cholesterol, glucose, hypertension, MetS and its components (high triglyceride, 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:

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
stroke, and type 2 diabetes in middle-aged men. (See p. 1 in evidence table)		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		– CHD (RR, 1.64; 95% confidence interval [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 follow up. • 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). • 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' follow up. • 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	*N*:	1. Cox	Study began 1972	Candidate risk factors: Age, total cholesterol, SBP, DBP, glucose,

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
(82) Good To examine the predictive role of BMI and other CHD risk factors at pre-specified periods of follow up using a test for trend. See p. 18 in evidence table	14,403 21 years mean follow up	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	Men, ages 40 to 49, no CHD	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 follow up 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 follow up. • A U-shaped relationship was observed during the first 10 years. During the subsequent 10 years of follow up, 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, systolic blood pressure, and cigarette smoking remained significant predictors of fatal CHD, but not BMI. • Relation between risk factors and risk for fatal CHD by pre-specified periods of follow up: age, cigarette smoking, serum cholesterol, and SBP were significant predictors of CHD during all four periods of follow up, 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 follow up, but not subsequently (*p* for trend = .03) • Increasing BMI was predictive of increased risk in the Cox analyses only after 15 years of follow up (*p* for trend = .002). • Moderate risk increase from the second quintile of BMI during the second 10-year period of follow up. An elevation in BMI of one unit (kg/m^2) was associated with a multivariate relative risk for fatal CHD

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
				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 follow up, 0.99 (95% CI 0.93–1.06) during the 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 (79) 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 follow up periods—0 to 10, 10 to 20, and >20 years follow up periods See p. 2 in evidence table	*N*: 16,608 33 years mean follow up	1. Cox proportional hazards models constructed for each follow up 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 follow up intervals 4. **Primary Outcome:** Strength of the association	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 follow up for both men and women for CVD, coronary heart disease, and non-CVD mortality. • Rates for CVD and CHD death were low for women in the initial decade of follow up. • SBP, total cholesterol, current smoking, and diabetes were independently associated with CVD death during nearly all follow up intervals in men and women: • The HR for CVD death associated with SBP differed significantly across follow up periods and decreased in later follow up periods in both men and women. • The HR for total cholesterol did not differ across follow up periods. – There were gender differences for other risk factors in association with CVD death: • In men, the HR for diabetes remained consistent across the follow up periods. • In women, the HR for diabetes showed a decrease in strength across the distinct follow up periods. • Sex differences for smoking showed a similar pattern. • For BMI in men, the HR increased across the follow up periods but not in women. • The association of baseline major and minor electrocardiographic abnormalities with CVD death in men was strong in the initial follow up period, with marked attenuation in the subsequent follow up

Study/Grade/ Objective	Sample/ Duration	Analysis/Primary Outcome	Sample Characteristics/ Inclusion Criteria	Results
		between traditional risk factors and CVD death		periods. • In women, there was no consistent association. – Results were similar for CHD death as the end point.

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 Surveys, ROC=receiver operator characteristic, SBP=systolic blood pressure

APPENDIX C. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)– 2013 ACC/AHA GUIDELINE ON ASSESSMENT OF CARDIOVASCULAR RISK

Work Group Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/Principal	Personal Research	Expert Witness
David C. Goff, Jr *Co-Chair*	Colorado School of Public Health—Dean	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** • Merck	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Donald M. Lloyd-Jones *Co-Chair*	Northwestern University Feinberg School of Medicine—Senior Associate Dean; Chair and Professor of Preventive Medicine; Professor of Medicine (Cardiology)	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Glen Bennett *Ex-Officio*	NHLBI—Coordinator	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013:	**2013:**	**2013:**	**2013:**	**2013:**

		None	None	None	None	None
Sean Coady *Ex-Officio*	NHLBI—Statistician	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Ralph B. D'Agostino	Boston University—Professor of Mathematics and Statistics; Mathematics and Statistics Department—Chair	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Raymond Gibbons	Nuclear Cardiology Laboratory Mayo Clinic—Professor of Medicine and Co-Director	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: • AstraZeneca • Lantheus Medical Imaging	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Philip Greenland	Northwestern University Feinberg School of Medicine—Senior Associate Dean for Clinical and Translational Research; Harry W. Dingman Professor of Medicine	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Daniel T. Lackland	Medical University of South Carolina—Professor of Epidemiology and Medicine	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Daniel Levy *Ex-Officio*	NHLBI—Framingham Heart Study, Director	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** • BG Medicine	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Christopher O'Donnell *Ex-Officio*	NHLBI—Associate Director and Senior Investigator	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None

Jennifer Robinson	University of Iowa—Professor of Epidemiology and Medicine; Director, Prevention Intervention Center	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** • Aegerion • Amarin* • Amgen* • AstraZeneca* • Daiichi-Sankyo* • Esperion • Genentech/Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/Regeneron*	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** • Amarin* • Amgen* • AstraZeneca* • Daiichi-Sankyo* • Genentech/Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/Regeneron*	**2013:** None
J. Sanford Schwartz	University of Pennsylvania—Leon Hess Professor of Internal Medicine, Health Management and Economics	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Susan T. Shero *Ex-Officio*	NHLBI—Public Health Advisor	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Sidney C. Smith, Jr	University of North Carolina—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None

Paul Sorlie *Ex-Officio*	NHLBI—Chief of Division of Epidemiology and Clinical Applications	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Neil J. Stone	Northwestern Memorial Hospital—Bonow Professor of Medicine, Feinberg School of Medicine, Northwestern University	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Peter W.F. Wilson	Atlanta VA Medical Center, Emory Clinical Cardiovascular Research Institute—Professor of Medicine	**2008-2012:** • Merck • XZK	**2008-2012:** None	**2008-2012:** None	**2008-2012:** • Merck • LipoScience	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None

This table reflects the relevant healthcare-related relationships of authors with industry and other entities (RWI) provided by the panels during the document development process (2008-2012). Both compensated and uncompensated relationships are reported. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the expert panel during the document development process. Authors with relevant relationships during the document development process recused themselves from voting on recommendations relevant to their RWI. In the spirit of full transparency, the ACC and AHA asked expert panel members to provide updates and approve the final version of this table which includes current relevant relationships (2013).

To review the NHLBI and ACC/AHA's current comprehensive policies for managing RWI, please refer to http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm and http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

Per ACC/AHA policy:
A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

*Significant relationship.
NHLBI indicates National Heart, Lung, and Blood Institute.

REFERENCES

1. Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
2. Gibbons GH, Harold JG, Jessup M, et al. The next steps in developing clinical practice guidelines for prevention. J Am Coll Cardiol. 2013;62:1399–400.
3. Gibbons GH, Shurin SB, Mensah GA, et al. Refocusing the agenda on cardiovascular guidelines: an announcement from the National Heart, Lung, and Blood Institute. J Am Coll Cardiol. 2013;62:1396–8.
4. National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. NIH Publication No. 02-5215. Bethesda, MD: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health; 2002.
5. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-1252.
6. National Heart L, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Institutes of Health; 1998.
7. (U.S.) IoM. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
8. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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;106:3143–421.
9. Lackland DT, Elkind MSV, D'Agostino R Sr, 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;43:1998–2027.
10. 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;27:957–1047.
11. Sheridan SL, Crespo E. Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? A systematic review of the literature. BMC Health Serv Res. 2008;8:60.
12. Sheridan SL, Viera AJ, Krantz MJ, et al. The effect of giving global coronary risk information to adults: a systematic review. Arch Intern Med. 2010;170:230–9.
13. Shillinglaw B, Viera AJ, Edwards T, et al. 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. Redberg RF, Benjamin EJ, Bittner V, et al. AHA/ACCF [corrected] 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). Circulation. 2009;120:1296–336.
15. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150:396–404.
16. Perk J, De Backer G, Gohlke H, 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;33:1635–701.
17. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29:151–67.
18. Genest J, McPherson R, Frohlich J, 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;25:567–79.

19. Bulugahapitiya U, Siyambalapitiya S, Sithole J, et al. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26:142-8.
20. 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;105:310–5.
21. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003.
22. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation. 2008;117:743–753.
23. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007;335:136.
24. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007;297:611–9.
25. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation. 2008;118:2243–2251, 4p following 2251.
26. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–47.
27. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. Am Heart J. 1991;121:293-8.
28. D'Agostino RB, Sr., Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286:180-7.
29. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129:687–702.
30. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991;1:263–76.
31. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41:1105–16.
32. Rose KM, Foraker RE, Heiss G, et al. Neighborhood socioeconomic and racial disparities in angiography and coronary revascularization: the ARIC surveillance study. Ann Epidemiol. 2012;22:623-9.
33. Mumma BE, Baumann BM, Diercks DB, et al. Sex bias in cardiovascular testing: the contribution of patient preference. Ann Emerg Med. 2011;57:551-560 e4.
34. Takakuwa KM, Shofer FS, Limkakeng AT, Jr., et al. Preferences for cardiac tests and procedures may partially explain sex but not race disparities. Am J Emerg Med. 2008;26:545-50.
35. Epstein AM, Weissman JS, Schneider EC, et al. 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;41:1240-55.
36. Ibrahim SA, Whittle J, Bean-Mayberry B, et al. Racial/ethnic variations in physician recommendations for cardiac revascularization. Am J Public Health. 2003;93:1689-93.
37. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27:157–72; discussion 207–212.
38. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med. 2011;30:11-21.
39. Uno H, Cai T, Pencina MJ, et al. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Stat Med. 2011;30:1105-17.
40. D'Agostino RB, Nam BH. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan N, editor Handbook of Statistics. New York, NY: Elsevier; 2004:1-25.
41. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119:2408–16.
42. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
43. Hosmer DW, Lemeshow S. Applied Logistic Regression, Second Edition. New York, NY: John Wiley & Sons; 2000.

44. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156:871-81.
45. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135-43.
46. Nasir K, McClelland RL, Blumenthal RS, et al. Coronary artery calcium in relation to initiation and continuation of cardiovascular preventive medications: The Multi-Ethnic Study of Atherosclerosis (MESA). Circ Cardiovasc Qual Outcomes. 2010;3:228-35.
47. Rosamond WD, Chambless LE, Heiss G, 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;125:1848-57.
48. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362:2155-65.
49. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003;290:891–7.
50. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. Arch Intern Med. 2001;161:2657–60.
51. Ioannidis JPA, Panagiotou OA. Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. JAMA. 2011;305:2200–10.
52. Buckley DI, Fu R, Freeman M, et al. 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;151:483–95.
53. Helfand M, Buckley DI, Freeman M, 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;151:496–507.
54. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132–40.
55. Schnell-Inderst P, Schwarzer R, Göhler A, 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;26:30–9.
56. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207.
57. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302:1993–2000.
58. Sniderman AD, Williams K, Contois JH, 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;4:337–45.
59. Empana JP, Tafflet M, Escolano S, et al. Predicting CHD risk in France: a pooled analysis of the D.E.S.I.R., Three City, PRIME, and SU.VI.MAX studies. Eur J Cardiovasc Prev Rehabil. 2011;18:175–85.
60. Kashani M, Eliasson A, Vernalis M, et al. Improving assessment of cardiovascular disease risk by using family history: an integrative literature review. J Cardiovasc Nurs. 2013;28:E18–27.
61. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301:2024–35.
62. Ankle Brachial Index Collaboration, Fowkes FGR, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208.
63. Moyer VA, U.S. Preventive Services Task Force. Screening for peripheral artery disease and cardiovascular disease risk assessment with the ankle-brachial index in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;159:342–8.
64. Peters SAE, den Ruijter HM, Bots ML, et al. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. 2012;98:177–84.
65. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? J Am Coll Cardiol. 2012;59:553-65.
66. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med. 2009;169:1188-94.

67. Burt JR, Iribarren C, Fair JM, et al. Incidental findings on cardiac multidetector row computed tomography among healthy older adults: prevalence and clinical correlates. Arch Intern Med. 2008;168:756-61.
68. Iribarren C, Hlatky MA, Chandra M, et al. Incidental pulmonary nodules on cardiac computed tomography: prognosis and use. Am J Med. 2008;121:989-96.
69. Killeen RP, Cury RC, McErlean A, et al. Noncardiac findings on cardiac CT. Part II: spectrum of imaging findings. J Cardiovasc Comput Tomogr. 2009;3:361-71.
70. Den Ruijter HM, Peters SAE, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012;308:796–803.
71. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21:93-111; quiz 189-90.
72. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56:e50–103.
73. Stone N, Robinson J, AH L, 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. J Am Coll Cardiol. 2013.
74. Berry JD, Lloyd-Jones DM, Garside DB, et al. Framingham risk score and prediction of coronary heart disease death in young men. Am Heart J. 2007;154:80-6.
75. Cavanaugh-Hussey MW, Berry JD, Lloyd-Jones DM. Who exceeds ATP-III risk thresholds? Systematic examination of the effect of varying age and risk factor levels in the ATP-III risk assessment tool. Prev Med. 2008;47:619–23.
76. 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;43:1791-6.
77. Marma AK, Berry JD, Ning H, et al. 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. Circulation Cardiovascular quality and outcomes. 2010;3:8-14.
78. Marma AK, Lloyd-Jones DM. Systematic examination of the updated Framingham Heart Study general cardiovascular risk profile. Circulation. 2009;120:384–90.
79. Berry JD, Dyer A, Carnethon M, et al. 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;101:89–94.
80. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113:791–8.
81. Wannamethee SG, Shaper AG, Lennon L, et al. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med. 2005;165:2644–50.
82. Håheim LL, Tonstad S, Hjermann I, et al. 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;35:4–10.
83. Pencina MJ, D'Agostino RB Sr, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation. 2009;119:3078–84.
84. Menotti A, Lanti M. Coronary risk factors predicting early and late coronary deaths. Heart. 2003;89:19–24.
85. Menotti A, Lanti M, Puddu PE, et al. First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study. Italian heart journal : official journal of the Italian Federation of Cardiology. 2000;1:394-9.
86. Lloyd-Jones DM, Wilson PWF, Larson MG, et al. Framingham Risk Score and prediction of lifetime risk for coronary heart disease. Am J Cardiol. 2004;94:20–4.
87. Liao Y, McGee DL, Cooper RS, et al. How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts. Am Heart J. 1999;137:837–45.
88. Karp I, Abrahamowicz M, Bartlett G, et al. Updated risk factor values and the ability of the multivariable risk score to predict coronary heart disease. Am J Epidemiol. 2004;160:707–16.
89. Rose G. Environmental health: problems and prospects. J Roy Coll Phys Lond. 1991;25:48-52.
90. Rose G. The Strategy of Preventive Medicine. Oxford: Oxford University Press; 1992.

91. HEALTH EPOIGFC, CHILDREN RRI, ADOLESCENTS. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011;128:S213-S256.
92. MD J, DH R, CM A, 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. J Am Coll Cardiol 2013.
93. Services UDoHaH. 2008 Physical Activity Guidelines for Americans. Washington, DC; 2008.
94. Jousilahti P, Tuomilehto J, Rastenyte D, et al. Headache and the risk of stroke: a prospective observational cohort study among 35,056 Finnish men and women. Arch Intern Med. 2003;163:1058–62.