OPEN

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk

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

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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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 diseases (CVD); 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 cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of 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 (CQs), interpret the evidence, and craft recommendations. In response to the 2011 report from the Institute of Medicine on the development of trustworthy clinical guidelines,[1] the NHLBI Advisory Council 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 Work Group/Work Groups 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 NHLBI Advisory Council, 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 because 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 CQs on 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/Work Group Reports include more detailed information about the evidence statements that serve 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 Classification 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.

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

Table 1. Applying Classification of Recommendation and Level of Evidence

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

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.

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 1. None of the ACC/AHA expert reviewers had relevant RWI (Appendix 2). See Appendix 3 for a list of abbreviations used in the guideline.

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, and the AHA Science Advisory and Coordinating Committee. In addition, ACC/AHA sought endorsement from other stakeholders, including professional organizations. It is the hope of the writing panels, stakeholders, professional organizations, NHLBI, and Task Force that the guidelines will garner the widest possible readership for the benefit of patients, providers, and the public health.

These guidelines are meant 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 (ASCVD) events.

See Tables 2 and 3 for an explanation of the NHLBI recommendation grading methodology.

Table 2. 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 there is 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 Work Group 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 Work Group 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 Work Group 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 (eg, strong recommendation when the evidence quality is moderate, such as smoking cessation to reduce cardiovascular disease 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 Work Group.

†Net benefit is defined as benefits minus risks/harms of the service/intervention.

ECG indicates electrocardiogram; MI, myocardial infarction; and NHLBI, National Heart, Lung, and Blood Institute.

Table 3. NHLBI Quality Rating of the Strength of Evidence

Type of Evidence	Quality Rating*
• Well-designed, well-executed† RCT that adequately represent populations to which the results are applied and directly assess effects on health outcomes. • Meta-analyses of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect.	High
• RCT 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‖. • Meta-analyses 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
• RCT 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 (eg, case series, case reports). • Physiological studies in humans. • Meta-analyses 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.	Low

*In some cases, other evidence, such as large all-or-none case series (eg, 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 Work Group and clearly justified.

†"Well-designed, well-executed" refers to studies that directly address the question; use adequate randomization, blinding, and allocation concealment; are adequately powered; use intention-to-treat 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 that are not prespecified for the primary outcomes, low follow-up rates, and 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 (eg, quasi-experimental study design).

‖Observational studies include prospective and retrospective cohort, case-control, and cross-sectional studies.

NHLBI indicates National Heart, Lung, and Blood Institute; and RCT, randomized controlled trials.

1. Introduction

1.1. Organization of the Work Group

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

1.2. Document Review and Approval

A formal peer review process, which included 12 expert reviewers and representatives of federal agencies, was initially completed under the auspices of the NHLBI. 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. The ACC and AHA Reviewers' RWI information is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and AHA and endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease.

1.3. Charge to the Work Group

The Work Group was 1 of 3 work groups appointed by the NHLBI to develop its own recommendations and provide cross-cutting input to 3 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 ASCVD events and to develop an approach for quantitative risk assessment that could be used in practice and used or adapted by the risk factor panels (blood cholesterol, hypertension, and obesity) in their guidelines and algorithms. Specifically, the Work Group was charged with 2 tasks:

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

1.4. Methodology and Evidence Review

This guideline is based on the Full Work Group Report supplement, which is provided as a supplement to the guideline. The Full Work Group Report supplement contains background and additional material related to content, methodology, evidence synthesis, rationale, and references and is supported by the NHLBI Systematic Evidence Review, which can be found at (http://www.nhlbi.nih.gov/guidelines/cvd_adult/risk_assessment/). These documents also describe the process for the development of novel, comprehensive multivariable risk equations for the prediction of 10-year risk of development of ASCVD in non-Hispanic African-American and non-Hispanic white men and women from 40 to 79 years of age. These equations were developed from several long-standing population-based cohort studies funded by the NHLBI. Ten-year risk was defined as the risk of developing a first ASCVD event, defined as nonfatal myocardial infarction 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.

In addition, through evaluation of evidence developed by systematic reviews of the literature, the Work Group addressed the following 2 CQs:

CQ1. "What is the evidence with regard to reclassification or contribution to risk assessment when high-sensitivity C-reactive protein (hs-CRP), apolipoprotein B (ApoB), glomerular filtration rate, microalbuminuria, family history, cardiorespiratory fitness, ankle-brachial index (ABI), carotid intima-media thickness (CIMT), or coronary artery calcium (CAC) score is considered in addition to the variables that are in the traditional risk scores?"

CQ2. "Are models constructed to assess the long-term (≥15 years or lifetime) risk of a first cardiovascular disease (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 in combination?"

The evidence and recommendations in the guideline focus on the large proportion of the adult population without clinical signs or symptoms of ASCVD who merit evaluation for the primary prevention of ASCVD. They do not apply to those with clinically manifest ASCVD, who require secondary prevention approaches, or to highly-selected patient subgroups, such as those with symptoms suggestive of CVD, who require diagnostic strategies rather than risk assessment. 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 (eg, patients with familial hypercholesterolemia).

2. Risk Assessment: Recommendations

See Table 4 for a summary of the recommendations for risk assessment.

3. Approach to Risk Assessment

In addressing its charge, the Work Group recognized the need for a risk assessment approach that was based on the types of data that primary care providers could easily collect and that could be implemented in routine clinical practice. After deliberation, the Work Group endorsed the existing and widely used paradigm of matching the intensity of preventive efforts with the individual's absolute risk.[23,24] The Work Group acknowledges that none of the risk assessment tools or novel risk markers examined in the present document have been formally evaluated in randomized controlled trials of screening strategies with clinical events as outcomes. Nevertheless, this approach balances an understanding of an individual's absolute risk of CVD and potential treatment benefits against the potential absolute risks for harm from therapy. With the use of this framework, treatment can be targeted to those most likely to benefit without undue risk of harm, in the context of a "risk discussion." A risk discussion could include the assessment of the patient's risk of ASCVD, as well as potential benefits, negative aspects, risks, and patient preferences with regard to initiation of relevant preventive therapies.

By its nature, such an approach requires a platform for reliable quantitative estimation of absolute risk based on data from representative population samples. It is important to note that risk estimation is based on group averages, which are then applied to individual patients in practice. This process is admittedly imperfect; no one has 10% or 20% 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. The 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 numerous and complex inclusion and exclusion criteria for a potentially large number of pertinent trials. 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.

Given the modification and adoption of the Framingham 10-year risk score for CHD risk assessment by the Third Report of the National Cholesterol Education Program Expert Work Group on Diagnosis, Evaluation, and Treatment of High

Table 4. Summary of Recommendations for Risk Assessment

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Assessment of 10-Year Risk of a First Hard ASCVD Event				
1. The race- and sex-specific Pooled Cohort Equations* to predict 10-year risk of a first hard ASCVD event should be used in non-Hispanic African Americans and non-Hispanic whites, 40–79 years of age.	B (Moderate)	N/A	I	B[4–8]
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.	E (Expert Opinion)	N/A	IIb	C
CQ1: Use of Newer Risk Markers After Quantitative Risk Assessment				
1. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of ≥1 of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.	E (Expert Opinion)	Appendix 4	IIb†	B[9–17]
2. Routine measurement of CIMT is not recommended in clinical practice for risk assessment for a first ASCVD event.	N (No recommendation for or against)	Appendix 4	III: No Benefit†	B[12,16,18]
3. The contribution of ApoB, CKD, albuminuria, and cardiorespiratory fitness to risk assessment for a first ASCVD event is uncertain at present.	N (No recommendation for or against)	Appendix 4	—	—
CQ2: Long-Term Risk Assessment				
1. It is reasonable to assess traditional ASCVD risk factors‡ every 4–6 years in adults 20–79 years of age who are free from ASCVD and to estimate 10-year ASCVD risk every 4–6 years in adults 40–79 years of age who are free from ASCVD.	B (Moderate)	Appendix 5 CQ2/ES7	IIa	B[19,20]
2. Assessment of 30-year or lifetime ASCVD risk on the basis of traditional risk factors‡ may be considered in adults 20–59 years of age who are free from ASCVD and are not at high short-term risk.	C (Weak)	Appendix 5 CQ2/ES2, CQ2/ES3, CQ2/ES4, CQ2/ES5, CQ2/ES6	IIb	C[20–22]

A downloadable spreadsheet enabling estimation of 10-year and lifetime risk of ASCVD and a Web-based calculator is available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx.

*Derived from the ARIC (Atherosclerosis Risk in Communities) study,[8] Cardiovascular Health Study,[5] CARDIA (Coronary Artery Risk Development in Young Adults) study,[7] and Framingham original and offspring cohorts.[4,6]

†Based on new evidence reviewed during ACC/AHA update of evidence.

‡Age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current smoking.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CKD, chronic kidney disease; COR, Class of Recommendation; CQ, critical question, ES, evidence statement; hs-CRP, high-sensitivity C-reactive protein; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; and —, not applicable.

Blood Cholesterol in Adults (Adult Treatment Panel III)[24] and the uptake of this algorithm by practice sites across the United States, the Work Group began by discussing the value of retaining this algorithm. In collaboration with other NHLBI panels, the Work Group decided not to use this algorithm in its 2013 recommendations because of the algorithm's derivation in an exclusively white sample population and the limited scope of the outcome (in determining CHD alone). Rather, the Work Group derived risk equations from community-based cohorts that are broadly representative of the US population of whites and African Americans, and the Work Group focused on estimation of first hard ASCVD events (defined as first occurrence of nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke) as the outcome of interest because they were deemed to be of greater relevance to both patients and providers. The focus on hard ASCVD, rather than CHD alone, is also consistent with evidence reviewed in a statement from the AHA and American Stroke Association calling for the inclusion of ischemic stroke in the outcome of interest for CVD risk assessment.[25]

Numerous multivariable risk scores and equations have been derived and published (Appendix 6; for more details, see the Full Work Group Report supplement). As part of its deliberations, the Work Group considered previously published risk scores with validation in NHLBI cohort data as one possible approach. However, several persistent concerns with existing risk equations were identified, including nonrepresentative or historically dated populations, limited ethnic diversity, narrowly defined endpoints, endpoints influenced by provider preferences (eg, elective revascularizations), and endpoints with poor reliability (eg, angina and heart failure). Given the inherent limitations of existing scores, the Work Group judged that a new risk score was needed to address some of the deficiencies of existing scores—for example, the need for a population sample that approaches, to the degree possible, the ideal sample for algorithm development and closely represents the US population.

Data are sparse on the use and impact of absolute risk scores in clinical practice in primary-prevention settings.[26]

Two systematic reviews, based on few studies, support the conclusion that risk assessment, combined with counseling, is associated with favorable but modest changes in patient knowledge and intention to change and in provider prescribing behavior and risk factor control.[27,28] No data are available on hard event outcomes. The Work Group specifically calls for research in this area (Section 8).

The Work Group notes that the "2009 ACCF/AHA Performance Measures for the Primary Prevention of Cardiovascular Disease in Adults" specifically recommended use of global CVD risk estimation in clinical practice.[29] Likewise, the US Preventive Services Task Force recommendations for aspirin,[30] the NHLBI Adult Treatment Panel III recommendations,[24] and European[31] and Canadian[32,33] guidelines for primary prevention of CVD, among others, have all recommended the use of absolute risk assessment for decision making about the intensity of lifestyle and pharmacological preventive interventions. Risk scores have been implemented in practice through paper scoring sheets and, increasingly, through Web sites and downloadable applications. The electronic medical record can be adapted to estimate absolute risks automatically by using patient data and published equations, and it is anticipated that risk estimation with this technology will become a mainstream application of the current and future risk algorithms.

4. Development of New Pooled Cohort ASCVD Risk Equations

Having made the decision to develop new equations to estimate the 10-year risk of developing a first ASCVD event, the Work Group used the best available data from community-based cohorts of adults, with adjudicated endpoints for CHD death, nonfatal myocardial infarction, and fatal or nonfatal stroke. Cohorts that included African-American or white participants with at least 12 years of follow-up were included. Data from other racial/ethnic groups were insufficient, precluding their inclusion in the final analyses. The final pooled cohorts included participants from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies, including the ARIC (Atherosclerosis Risk in Communities) study,[8] the Cardiovascular Health Study,[5] and the CARDIA (Coronary Artery Risk Development in Young Adults) study,[7] combined with applicable data from the Framingham Original and Offspring Study cohorts.[4,6]

The Work Group used state-of-the-art statistical methods to derive and internally validate the Pooled Cohort Equations, which provide sex- and race-specific estimates of the 10-year risk of ASCVD for African-American and white men and women 40 to 79 years of age. The variables that statistically merit inclusion in the risk assessment equations are age, total cholesterol, high-density lipoprotein cholesterol, systolic BP (including treated or untreated status), diabetes mellitus (diabetes), and current smoking status.

An expanded description of the derivation and validation of the Pooled Cohort Equations, as well as the means for implementing them in clinical practice, is provided in Appendix 7. Additional details are provided in the Full Work Group Report supplement. A specific clinical vignette is also provided as an example in Appendix 7. In the clinical vignette, the 10-year risk is calculated for a patient 55 years of age who is a nonsmoker without diabetes, and with total cholesterol level of 213 mg/dL, high-density lipoprotein cholesterol level of 50 mg/dL, and untreated systolic BP of 120 mm Hg. With these values used in the Pooled Cohort Equations, the predicted 10-year ASCVD risks are 2.1% for white women, 3.0% for African-American women, 5.3% for white men, and 6.1% for African-American men.

Numerous other potential risk markers were considered for inclusion in the Pooled Cohort Equations: for many, no additional utility was demonstrated when they were included; for others, data are insufficient at the present time to determine their additional value. The equations were also assessed in external validation studies with data from other available cohorts. Other than the Framingham CHD risk score (and its derivative ATP III risk assessment profile) and the European SCORE (System for Cardiac Operative Risk Evaluation) algorithm for CVD death, these equations have been subjected to more rigorous validation than other currently available equations, and they are the only risk assessment equations that include significant numbers of African Americans and that focus on estimation of 10-year risk of the clinically relevant endpoint of ASCVD. The Work Group specifically calls for further research to develop similar equations applicable to other ethnic groups, to validate the utility of the Pooled Cohort Equations in diverse primary-prevention settings, and to assess the potential benefit of novel risk markers when added to these equations, so that the equations maybe modified or expanded over time as new data become available.

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

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

NHLBI 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.

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

A Web-based application enabling estimation of 10-year and lifetime risk of ASCVD is available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx.

5. Implications for Risk Assessment

A range of estimated 10-year risk of a first hard ASCVD event is illustrated in the Full Work Group Report supplement (Tables 8 through 11), across a broad range of risk factor burdens for

*Ten-year risk was defined as the risk of developing a first ASCVD event, defined as nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke, over a 10-year period among people free from ASCVD at the beginning of the period.

selected combinations of the risk factors in sex–race groups (African-American and white women and men). The estimated risks are specific to defined combinations of the risk factors and demonstrate how they vary over a broad spectrum of potential profiles. Risk factor levels that are more adverse than those shown in these tables should always be associated with a higher estimated risk. For example, if a given risk factor combination indicates an estimated 10-year risk of hard ASCVD of 8%, but a patient has a higher level of systolic BP or total cholesterol, or a lower level of high-density lipoprotein cholesterol, than shown for that table cell, then the estimated risk would be ≥8%. Because the estimated probabilities can become unstable when approaching the limits of the sample data, the risk probabilities are truncated at 1% and 30%. The proportions of the US adult population, 40 to 79 years of age, in selected strata of estimated 10-year risk of hard ASCVD events, are shown overall and by sex and race/ethnicity in Table 5. When compared with non-Hispanic whites, estimated 10-year risk of ASCVD is generally lower in Hispanic-American and Asian-American populations and higher in American-Indian populations;[34,35] hence, the lack of race/ethnicity-specific risk algorithms is an important gap in our efforts to understand and prevent ASCVD in these populations. Although the development of algorithms specific to these racial/ethnic groups is encouraged, in the interim, providers may consider using the equations for non-Hispanic whites for these patients. When doing so, the estimated risks may be overestimates, especially for Hispanic and Asian Americans.

6. CQs and Systematic Evidence Review

6.1. Critical Question 1

"What is the evidence with regard to reclassification or contribution to risk assessment when hs-CRP, ApoB, glomerular filtration rate, microalbuminuria, family history, cardiorespiratory fitness, ABI, CAC, or CIMT is considered in addition to the variables that are in the traditional risk scores?"

The concept of matching the intensity of risk factor management to the estimated risk of CVD has been well established since the 27th Bethesda Conference in 1996.[23] As a consequence, widespread attention has focused on the accuracy and reliability of risk assessment. Claims that a minority of the risk of 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 disproved.[36,37] 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 that might further enhance risk assessment.

CQ1 was developed to address whether newer risk markers have been identified that actually improve risk assessment enough to warrant routine measurement in clinical practice. This question applies 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 CVD.

CQ1 was addressed through 2 independent approaches. First, in the process of developing the Pooled Cohort Equations, the additional risk markers listed in CQ1 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. A review of meta-analyses and systematic reviews published before September 19, 2013, was conducted in 2 stages. In the first stage, meta-analyses and systematic reviews published before April 2011 were identified and reviewed. In a second stage, conducted to update the evidence base before publication, additional meta-analyses and systematic reviews published before September 19, 2013, were identified and reviewed against 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.[38]

Members of the Work Group proposed an initial list of novel risk markers for inclusion in CQ1, which was then prioritized during several rounds of discussion. 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. In these deliberations, the Work Group considered availability, cost, assay reliability, and risks of the test or downstream testing. The final list of new risk markers to be evaluated included several blood and urine biomarkers (hs-CRP, ApoB, creatinine [or estimated glomerular filtration rate], and microalbuminuria), several measures of subclinical cardiovascular disease (CAC, CIMT, and ABI), family history, and cardiorespiratory fitness. Other novel potential screening tools maybe the subject of future guideline updates. Guidance published by Hlatky et al[39] was considered during discussion of the utility of incorporating these new risk factors into routine risk assessment. Special attention was given to the additional value these markers contributed to risk assessment in terms of discrimination, calibration, reclassification, and cost-effectiveness, in the context of any potential harm.

6.1.1. Summary of Systematic Reviews and Meta-Analyses for CQ1

Thirteen systematic review articles or meta-analyses met the inclusion/exclusion criteria.[9–18,40–42] Publication dates ranged from 2008 to 2013. The Work Group reviewed the 13 systematic reviews and meta-analyses and created a table to list their key findings (Appendix 4). None of these markers has been evaluated as a screening test in randomized controlled trials with clinical events as outcomes. On the basis of current (limited) evidence, it is the opinion of the Work Group that among the novel risk markers, assessments of family history of premature CVD, as well as measurement of hs-CRP, CAC, and ABI, show some promise for clinical utility. Table 6 provides expert opinion on thresholds of these measures that may be considered for clinical decision making.

The Work Group notes that the review by Peters et al[16] provides evidence to support the contention that measuring CAC is

Table 5. Distribution of Estimated 10-Year Risk of a First Hard ASCVD Event in the CVD-Free, Nonpregnant US Population, 40 to 79 Years of Age, by Sex and Race/Ethnicity*

	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							
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

*Data derived by applying the Pooled Cohort Equations to the National Health and Nutrition Examinations Surveys, 2007–2010 (*N*=5367, weighted to 100 542 000 US population).

ASCVD indicates atherosclerotic cardiovascular disease; and CVD, cardiovascular disease.

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 for CAC testing.[43] However, the Work Group notes that the outcomes in the studies reviewed by Peters et al[16] and by Greenland et al[43] were CHD outcomes, not hard ASCVD events that included stroke; hence, uncertainty remains about the contribution of CAC assessment to estimation of 10-year risk of first hard ASCVD events after formal risk assessment with the new Pooled Cohort Equations. Furthermore,

Table 6. Expert Opinion Thresholds for Use of Optional Screening Tests When Risk-Based Decisions About Initiation of Pharmacological Therapy Are Uncertain After Quantitative Risk Assessment

Measure	Support Revising Risk Assessment Upward	Do Not Support Revising Risk Assessment
Family history of premature CVD	Male <55 years of age Female <65 years of age (first-degree relative)	Occurrences at older ages only (if any)
hs-CRP	≥2 mg/L	<2 mg/L
CAC score	≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity*	<300 Agatston units and <75th percentile for age, sex, and ethnicity*
ABI	<0.9	≥0.9

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

ABI indicates ankle-brachial index; CAC, coronary artery calcium; CVD, cardiovascular disease; and hs-CRP, high-sensitivity C-reactive protein.

issues of cost and radiation exposure related to measuring CAC were discussed, resulting in some uncertainty about potential risks of more widespread screening, which resulted in a decision in the present guideline to make assessment of CAC an ACC/AHA COR IIb recommendation among individuals for whom a risk-based treatment decision is uncertain after formal risk estimation. The Work Group notes that this ACC/AHA COR IIb recommendation is consistent with the recommendations in the 2010 ACCF/AHA guideline[43] 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 of a first hard ASCVD event) adopted by the "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults"[44] for recommending initiation of statin therapy for ASCVD risk reduction.

Furthermore, it was noted that measurement of ApoB, albuminuria, glomerular filtration rate, or cardiorespiratory fitness is of uncertain value. Finally, the Work Group judged that the evidence provided by Den Ruijter et al,[18] reviewed during the ACC/AHA update period, in combination with the concerns about measurement quality, provided sufficient rationale to recommend against measuring CIMT in routine clinical practice for risk assessment for a first ASCVD event. If any of the 9 markers considered in the present report is 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.

6.1.2. Recommendations for CQ1: 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.

NHLBI 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.

NHLBI Grade: N (No recommendation for or against); ACC/AHA COR III: No Benefit†, LOE: B

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

NHLBI Grade: N (No recommendation for or against)

6.2. Critical Question 2

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

Younger men (typically <50 years of age) and most women have low (eg, <5% or <10%) predicted 10-year risks of CHD and more broad CVD outcomes, even in the presence of significant risk factor burden.[45,46] However, extensive epidemiological, pathological, and basic science data indicate that the development of atherosclerosis, the precursor of ASCVD, occurs over decades and is related to long-term and cumulative exposure to causal, modifiable risk factors. Thus, a life-course perspective on risk assessment and prevention must be taken, especially among younger individuals. The primary value of risk factor measurement and quantitative long-term risk estimation in younger adults is 2-fold: first, to identify risk in individuals with extreme values of risk factors (eg, familial hypercholesterolemia); and second, to provide risk information and context for the potential benefits of lifestyle modification. When posing CQ2, 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 and clinical decision making. Rather, longer-term risk estimates, if found to be useful, could provide adjunctive information for risk communication.

CQ2 was developed to assess the utility of long-term and lifetime risk assessment as an adjunct to short-term (10-year) risk assessment. It was recognized that there is little "disconnect" with regard to approaches to prevention when the 10-year risk estimate is high (eg, >10% predicted 10-year risk); such patients merit intensive prevention efforts and should be considered for drug therapy to reduce or modify adverse levels of causal risk factors. CQ2 was selected for evaluation to determine whether quantitative or semiquantitative 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 is unclear what the long-term predicted and observed risks for CHD and CVD are among individuals who are at low predicted 10-year risk. CQ2 was designed to identify studies that assessed both short- and long-term risk, focusing in particular 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 discussions with patients and guiding therapeutic lifestyle counseling and other aspects of care.

6.2.1. Summary of Evidence for CQ2

Ten studies that met inclusion/exclusion criteria were identified by the systematic review performed in April 2011 and were examined.[19–22,47–52] Publication dates ranged from 1999 to 2009. All of the studies were observational. On the basis of these studies, 7 evidence statements were adopted (Appendix 5).

Multiple sources provided consistent evidence for 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 of ASCVD events. In addition, most of these risk factors are both causal and modifiable, which indicates their central clinical importance for ASCVD prevention efforts. Given the additional evidence suggesting improved risk prediction with updated clinical covariates, the Work Group makes the following recommendations.

6.2.2. 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 years of age who are free from ASCVD and to estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years of age who are free from ASCVD.

NHLBI 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.

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

A Web-based application enabling estimation of 10-year and lifetime risk of ASCVD is available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx.

Evidence was not found on the utility of lifetime risk assessment for guiding pharmacological therapy decisions, and the Work Group 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 years as the starting point for long-term risk assessment, despite a threshold of age 40 years for short-term 10-year ASCVD risk assessment.

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

‡Age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current smoking.

7. Implementation Considerations for Risk Assessment

A suggested approach for incorporating these recommendations into clinical practice is shown in Figure 1. For patients 20 to 79 years of age who are free from clinical ASCVD, the first step is to assess ASCVD risk factors. Although it is reasonable to assess ASCVD risk factors in individuals younger or older than this age range, limitations of available data prevented the development of robust risk assessment algorithms in those populations. Hence, for patients outside this age range, providers should refer to applicable clinical practice guidelines (ie, pediatric[53] and adult primary prevention guidelines.[44,54,56] 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 years, formal estimation of the absolute 10-year risk of ASCVD is recommended.[20,21] Long-term or lifetime risk estimation is recommended for all persons who are between 20 and 39 years of age and for those between 40 and 59 years of age who are determined to be at low 10-year risk (<7.5%). As shown in Figure 1, all patients should receive applicable risk information and appropriate lifestyle counseling. The 10-year risk estimates provided by the new Pooled Cohort Equations differ from those generated by the Adult Treatment Panel III algorithm in several respects,[24] as discussed in detail in the Full Work Group Report supplement. To summarize, on the basis of the risk estimation algorithm recommended by Adult Treatment Panel III, approximately 31.9% of the ASCVD-free, nonpregnant US population between 40 and 79 years of age have a 10-year risk of a first hard CHD event of at least 10% or have diabetes. On the basis of the new Pooled Cohort Equations described here, approximately 32.9% have a 10-year risk of a first hard ASCVD of at least 7.5%. The outcomes and thresholds of these 2 approaches are different, but the overlap of these 2 means of defining high-risk groups is substantial, at roughly 75%. Nonetheless, these important differences make simple linear conversions imprecise. We recommend that healthcare organizations convert to these new Pooled Cohort Equations as soon as practical (Appendix 7). A Web-based application enabling estimation of 10-year and lifetime risk of ASCVD is available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx.

8. Evidence Gaps and Future Research Needs

The Work Group strongly recommends continued research to fill gaps in knowledge about short- and long-term ASCVD risk assessment and outcomes in all racial/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

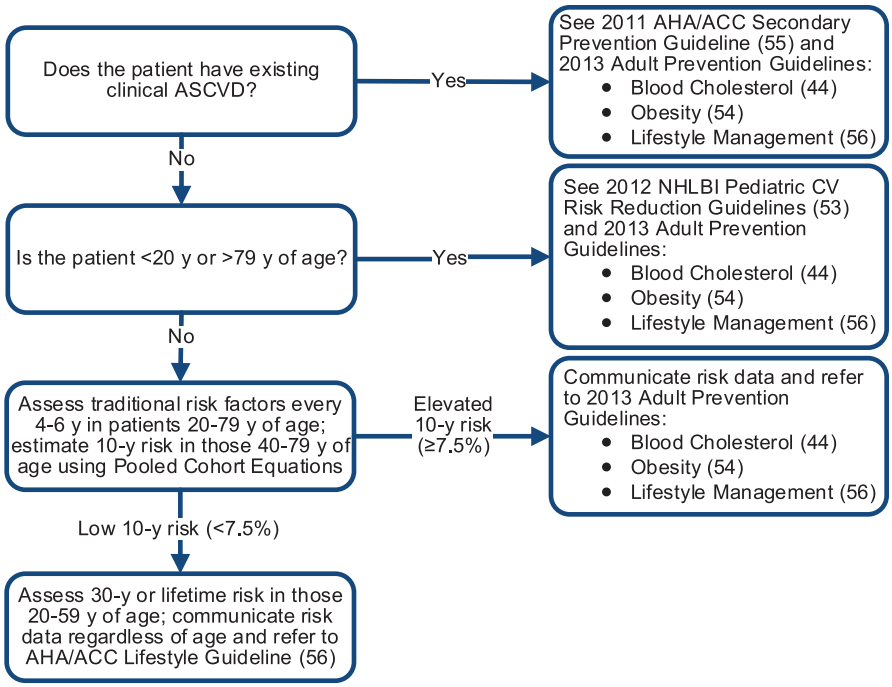

Figure 1. Implementation of Risk Assessment Work Group Recommendations. ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; and NHLBI, National Heart, Lung, and Blood Institute.

conveyed by short- and long-term risk assessment, and utility of novel risk markers in short- and long-term risk assessment.

9. Conclusions

The Work Group's approach to risk assessment represents a step forward in ASCVD prevention that is large enough to justify the challenges inherent in implementing a new approach, rather than staying with the CHD risk assessment approach recommended previously. The final recommendations are summarized in Table 4 and Figure 1. Two major advantages of this approach are the ability to estimate risk for a broader-based ASCVD outcome that is more relevant to additional segments of the population, including women and African Americans, and the ability to provide risk estimates specific to African Americans. Promotion of lifetime risk estimation may represent an additional step forward in supporting lifestyle behavior change counseling efforts. Periodic updates of the guidelines should address numerous issues related to risk assessment.

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KEY WORDS: AHA Scientific Statements ■ cardiovascular disease ■ cholesterol ■ primary prevention ■ biomarkers ■ risk assessment ■ risk reduction behavior

Appendix 1. 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 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: • Merck 2013: None	2008–2012: 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 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Glen Bennett, Ex-Officio	NHLBI—Coordinator	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Sean Coady, Ex-Officio	NHLBI—Statistician	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Ralph B. D'Agostino, Sr	Boston University—Professor of Mathematics and Statistics; Mathematics and Statistics Department—Chair	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None

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Appendix 1. Continued

Work Group Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Raymond Gibbons	Nuclear Cardiology Laboratory Mayo Clinic—Professor of Medicine and Co-Director	2008–2012: None 2013: • AstraZeneca • Lantheus Medical Imaging	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: 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 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Daniel T. Lackland	Medical University of South Carolina—Professor of Epidemiology and Medicine	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Daniel Levy, Ex-Officio	NHLBI—Framingham Heart Study, Director	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: • BG Medicine 2013: None	2008–2012: None 2013: None
Christopher J. O'Donnell, Ex-Officio	NHLBI—Associate Director and Senior Investigator	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Jennifer G. 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

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Appendix 1. Continued

Work Group Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
J. Sanford Schwartz	University of Pennsylvania—Leon Hess Professor of Internal Medicine, Health Management and Economics	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Susan T. Shero, Ex-Officio	NHLBI—Public Health Advisor	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Sidney C. Smith, Jr	University of North Carolina—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Paul Sorlie, Ex-Officio	NHLBI—Chief of Division of Epidemiology and Clinical Applications	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Neil J. Stone	Northwestern Memorial Hospital—Bonow Professor of Medicine, Feinberg School of Medicine, Northwestern University	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Peter W. F. Wilson	Atlanta VA Medical Center; Emory Clinical Cardiovascular Research Institute—Professor of Medicine	2008–2012: • Merck • XZK 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: • Merck • LipoScience 2013: None	2008–2012: None 2013: None

This table reflects the relevant healthcare-related relationships of authors with industry and other entities 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 conference calls of the Expert Work Group during the document development process. Authors with relevant relationships during the document development process recused themselves from voting on recommendations relevant to their relationships. In the spirit of full transparency, the ACC and AHA asked Expert Work Group 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.

ACC indicates American College of Cardiology; AHA, American Heart Association; and NHLBI, National Heart, Lung, and Blood Institute.

Appendix 2. Expert Reviewer Relationships With Industry and Other Entities—2013 ACC/AHA Guideline on Assessment of Cardiovascular Risk

Reviewer	Employment	Representing	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Ezra A. Amsterdam	University of California (Davis) Medical Center, Division of Cardiology—Professor	ACC/AHA	None	None	None	None	None
Ralph G. Brindis	University of California, San Francisco—Department of Medicine & the Phillip R. Lee Institute for Health Policy Studies—Clinical Professor of Medicine	ACC/AHA Task Force on Practice Guidelines	None	None	None	None	None
Frederick A. Masoudi	University of Colorado, Anschutz Medical Campus—Professor of Medicine (Cardiology)	ACC/AHA	None	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were self-disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. To review the NHLBI and ACC/AHA's current comprehensive policies for managing relationships with industry and other entities, 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.

ACC indicates American College of Cardiology; and AHA, American Heart Association.

Appendix 3. Abbreviations

ABI = ankle-brachial index
ApoB = apolipoprotein B
ASCVD = atherosclerotic cardiovascular disease
BP = blood pressure
CAC = coronary artery calcium
CHD = coronary heart disease
CIMT = carotid intima-media thickness
COR = Class of Recommendation
CQ = critical question
CVD = cardiovascular disease
hs-CRP = high-sensitivity C-reactive protein
LOE = Level of Evidence
NHLBI = National Heart, Lung, and Blood Institute
RWI = relationships of authors with industry and other entities

Appendix 4. Evidence Statements for CQ1

Evidence Statement Number	Author/Group	Factor	Evidence Statement/Conclusion
1	USPSTF[9]	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 its use resulted 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[12]	hs-CRP, CAC, CIMT, ABI	With regard 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 9 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 the present document are needed. CAC was associated with CHD and with some reclassification, but the size and value of this reclassification are uncertain. The document provides little evidence with regard to 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 the present document are needed. CIMT was associated with CHD, but the document provides little evidence for 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 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 the size and value of this reclassification are uncertain. Evidence suggests some improvement in discrimination, but the document provides little evidence with regard to 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[13]	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 of CVD. This analysis did not directly assess value in risk prediction. No additional evidence was provided for discrimination, calibration, reclassification, or cost-effectiveness.
4	Schnell-Inderst et al, 2010[17]	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 (generic) statins of at least moderate efficacy.
5	Emerging Risk Factors Collaboration[40]	ApoB	This article provided evidence of rough equivalence of associations of CVD with non–HDL-C and ApoB after multivariable adjustment (including HDL-C). See Figure 1 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.

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Appendix 4. Continued

Evidence Statement Number	Author/Group	Factor	Evidence Statement/Conclusion
6	Sniderman et al, 2011[42]	ApoB	ApoB was more strongly related to risk of 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 maymean that ApoB is more strongly related to risk than is total cholesterol. This article did not address directly the value of adding ApoB to a model with traditional risk factors. No information was presented for 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 about the validity of the evidence.
7	Kodama et al, 2009[41]	Cardiorespiratory fitness	Better cardiorespiratory fitness was associated with lower risk of all-cause mortality and CHD/CVD. According to 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[11]	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[10]	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 article 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 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 age 55 years in men and before age 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[15]	ABI	This article is an updated review of the utility of assessing ABI for the USPSTF. "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 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.

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Appendix 4. Continued

Evidence Statement Number	Author/Group	Factor	Evidence Statement/Conclusion
11.	Peters et al, 2012[16]	CIMT, CAC	This article is a systematic review of the literature on 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." With regard to 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 1,574 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 article provides some evidence to consider assessing CIMT; however, this conclusion was not supported by the article by Den Ruijter et al described below.[18] With regard to CAC: "The c-statistic increased from 0.04 to 0.13 when CAC was added to 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 article 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 estimation of 10-year risk of hard ASCVD after formal risk assessment.
12.	Kashani et al, 2013[14]	Family history	This article 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 articles. No evidence on discrimination, calibration, net reclassification index, or cost-effectiveness was provided.
13.	Den Ruijter et al, 2012[18]	CIMT	This article 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 MIs or strokes occurred." "We first refitted the risk factors of the FRS and then extended the model with common CIMT measurements to estimate the absolute 10-year risks to develop a first-time MI 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 FRS was associated with small improvement in 10-year risk prediction of first-time MI or stroke, but this improvement is unlikely to be of clinical importance." The Work Group judged this article to provide the strongest evidence available on 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.

ABI indicates ankle-brachial index; ApoB, apolipoprotein B; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CI, confidence interval; CIMT, carotid intima-media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; FMD, flow-mediated dilation; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IDI, integrative discrimination index; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; NRI, net reclassification index; PAD, peripheral artery disease; MI, myocardial infarction; and USPSTF, US Preventive Services Task Force.

Appendix 5. Evidence Statements for CQ2

Evidence Statement Number	Evidence Statement	References
1.	We found no evidence assessing variations in long-term or lifetime risk of CVD outcomes among persons at low or intermediate short-term risk in racial/ethnic groups other than non-Hispanic whites in the United States and Europe. *Strength of Evidence: None*	—
2.	ASCVD 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 of ASCVD. *Strength of Evidence:* Low (for diabetes and metabolic syndrome) to Moderate (for BMI, cholesterol, systolic BP, and smoking).	20,21,47,48,51,52
3.	Multivariable short-term (10-year) CHD risk prediction models underestimate absolute lifetime risk of CHD but maystratify relative lifetime risk of CHD in women and older men.* *Strength of Evidence: Low* *CHD is defined as all manifestations of CHD, or as CHD death/nonfatal MI.	22
4.	Long-term (30-year) risk equations based on traditional ASCVD risk factors* provide more accurate prediction of long-term ASCVD† risk than do extrapolations of short-term (10-year) risk equations among individuals 20–59 years of age who are free from ASCVD. *Strength of Evidence: Low* *Age, sex, total cholesterol, HDL-C, systolic BP, use of antihypertensive therapy, diabetes, and current smoking. †CHD death, nonfatal MI, or fatal/nonfatal stroke; or all ASCVD.	20
5.	The presence and severity of selected traditional ASCVD risk factors* stratify absolute levels of lifetime risk of ASCVD† among non-Hispanic white adults 45–50 years of age who are free of ASCVD and not at high short-term risk. *Strength of Evidence: Low* *Risk factors were considered in 5 mutually exclusive strata encompassing the full spectrum of risk levels, as follows: 1) ≥2 major risk factors (defined as total cholesterol ≥240 mg/dL or treated, systolic BP ≥160 or diastolic BP ≥100 mm Hg or treated, or diabetes, or current smoking) and lifetime risk of ASCVD >50%; 2) only 1 major risk factor and lifetime risk of ASCVD 39%–50%; 3) ≥1 elevated risk factor (defined as untreated total cholesterol 200 to 239 mg/dL, or untreated systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg, and no diabetes and no current smoking) and lifetime risk of ASCVD 39%–46%; 4) ≥1 risk factor at nonoptimal levels (untreated total cholesterol 180–199 mg/dL, or untreated systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg, and no diabetes and no current smoking) and lifetime risk of ASCVD 27%–36%; and 5) all optimal levels of risk factors (defined as untreated total cholesterol <180 mg/dL, and untreated BP <120/<80 mm Hg, and no diabetes, and no current smoking) and lifetime risk of ASCVD <10%. †CHD death, MI, coronary insufficiency, angina, fatal/nonfatal atherothrombotic stroke, claudication, other CVD death.	21
6.	Long-term (≥15 years) risk prediction models based on selected traditional ASCVD risk factors* predict CHD death with good discrimination and calibration, and better in women than men, in US non-Hispanic white populations. *Strength of Evidence: Low* *Age, sex, total cholesterol, systolic BP, diabetes, and smoking.	50
7.	Measuring and updating ASCVD risk factors every 4–6 years improves short- and long-term risk prediction. *Strength of Evidence: Moderate*	19,20

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CQ, critical question; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and —, none.

Appendix 6. Characteristics of Previously Published Risk Scores and Current Pooled Cohort Equations (Including Data Sources, Covariates, and Outcomes)

Risk Score				Risk Factors/Covariates Included																CVD 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[57]	Framingham MA, USA	EAF, EAM	1998	x	x	x	x	x		x		x		x						x	x	x	x				
ATP III[24]	Framingham MA, USA	EAF, EAM	2001	x	x	x		x		x	x			x									x	x				
Framingham Global[58]	Framingham MA, USA	EAF, EAM	2008	x	x	x		x		x	x	x		x									x	x	x	x	x	
PRO-CAM[59]	Muenster, Germany	EM	2002	x			x	x		x		x		x	x								x	x				
QRISK[60]	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		x
Reynolds Men[61]	Phys Health Study USA	EAF	2008	x		x		x	x	x				x	x				x				x	x	x	x		
Reynolds Women[62]	Women's Health Study USA	EAM	2007	x		x		x	x	x			x	x	x				x				x	x	x	x		
EURO-SCORE[63]	12 cohorts Europe	EF, EM	2003	x	x	x		x		x				x				x						x		x		
Pooled Cohort (current)	CARDIA, Framingham, 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; ARIC, Atherosclerosis Risk in Communities study; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults study; CHD, coronary heart disease; Chol, cholesterol; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CVD, cardiovascular disease; EAF, European-American females; EAM, European-American males; EF, European females; EM, European males; EURO-SCORE, European System for Cardiac Operative Risk Evaluation; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; Hx, history; LDL, low-density lipoprotein; Revasc, revascularization; Rx, medication; and TIA, transient ischemic attack.

Appendix 7. Development and Steps for Implementation of the ASCVD Pooled Cohort Risk Equations

Prior experience with the development of the Framingham Heart Study 10-year *CHD* risk prediction equations[24,57] and the more recent Framingham 10-year *general CVD* risk prediction equations,[58] was used as a basis for developing the new Pooled Cohort Risk Equations. To expand the utility and generalizability of the new equations, extensive data were used from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies, including the ARIC (Atherosclerosis Risk in Communities) study,[8] Cardiovascular Health Study,[5] and the CARDIA (Coronary Artery Risk Development in Young Adults) study,[7] combined with applicable data from the Framingham Original and Offspring Study cohorts.[4,6]

A total of 11 240 white women (who experienced 902 hard ASCVD events), 9098 white men (1259 hard ASCVD events), 2641 African-American women (290 hard ASCVD events), and 1647 African-American men (238 hard ASCVD events) who met the following criteria were included: 40 to 79 years of age, apparently healthy, and free of a previous history of nonfatal myocardial infarction (recognized or unrecognized), stroke, heart failure, percutaneous coronary intervention, coronary artery bypass surgery, or atrial fibrillation. Data from the included participants were used to develop sex- and race-specific equations to predict 10-year risk of a first hard ASCVD event. Because of 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 as an outcome. Because of known substantial geographic variation in use (Dartmouth Atlas of Healthcare, http://www.dartmouthatlas.org/), self-selection, and physician recommendation biases,[64] coronary revascularization was also not included as an endpoint.

The Pooled Cohort Equations for estimating ASCVD were developed from sex- and race-specific proportional-hazards models that included the covariates of age, treated or untreated systolic BP level, total cholesterol and high-density lipoprotein cholesterol levels, current smoking status (yes/no), and history of diabetes (yes/no). 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 the Full Work Group Report Data supplement, as are details of the methods used to derive, evaluate, and validate (internally and externally) the resulting risk equations and their potential limitations. In summary, discrimination and calibration of the models were very good. *C*-statistics ranged from a low of 0.713 (African-American men) to a high of 0.818 (African-American women). Calibration chi-square statistics ranged from a low of 4.86 (non-Hispanic white men) to a high of 7.25 (African-American women). The coefficients for the equations for calculating an estimate of an individual's 10-year risk of a first hard ASCVD event are provided in Table A, along with examples based on a specific risk profile for each race–sex group. The step-by-step process for estimating the risk in the specific examples of Table A is provided in Table B. These 2 tables are intended to enable programmers to integrate these equations into electronic health records.

The Work Group also considered the inclusion of additional and novel risk markers in the risk equations. On the basis of the availability of data across cohorts at applicable examination cycles, additional risk markers were evaluated for potential inclusion if they improved model performance within the framework of Hlatky et al.[39] The additional risk markers that were evaluated included diastolic BP, family history of ASCVD, moderate or severe chronic kidney disease (defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2),[65] and body mass index (continuous or categorical). None of these variables significantly improved discrimination for 10-year hard ASCVD risk prediction when added to the final base models. Other risk markers (hs-CRP, ApoB, microalbuminuria, cardiorespiratory fitness, CAC score, CIMT, and ABI) could not be evaluated in creating this new model because of absence of data or lack of inclusion in the appropriate examination cycle of 1 or more of the studies. Therefore, these and the other risk markers were addressed in CQ1 as potential adjuncts to quantitative risk estimation.

Further research using state-of-the art statistical techniques (including net reclassification improvement and integrative discrimination index[66]) is needed to examine the utility of novel biomarkers when added to these 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.

Table A. Equation Parameters of the Pooled Cohort Equations for Estimation of 10-Year Risk of 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 of 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 of Hard ASCVD	N/A	N/A	5.3%	N/A	N/A	6.1%

*Defined as first occurrence of nonfatal myocardial infarction 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 (eg, this example used untreated systolic BP, not treated systolic BP).

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

Table B. Estimating an Individual's 10-Year Risk of Incident Hard ASCVD

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 Ln transformed. Interactions between age and lipids or age and systolic BP use the natural log of each variable (eg, 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:

$1 - S_{10}^{(\text{IndX'B}-\textit{Mean}X'\text{B})}$

Using white men as an example:

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

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.