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Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: A Systematic Evidence Report for the U.S. Preventive Services Task Force

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Structured Abstract

Importance: Cardiovascular risk assessment employs traditional risk factors to identify individuals who may benefit from primary prevention therapies. Incorporating nontraditional risk factors may improve traditional multivariate risk assessment.

Objective: To systematically review evidence for the use of nontraditional risk factors—ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP), and coronary artery calcium (CAC)—in asymptomatic adults without known cardiovascular disease (CVD). Five key questions address: clinical impact of nontraditional risk factor assessment versus traditional risk factor assessment with Framingham Risk Score (FRS) or Pooled Cohort Equations (PCE) (KQ1), performance of nontraditional risk factor assessment added to the FRS or PCE (KQ2), harms of nontraditional risk factor assessment (KQ3), and benefits (KQ4) and harms (KQ5) of nontraditional risk factor-guided therapy. The United States Preventive Services Task Force (USPSTF) will use this review to update prior recommendations on the use of nontraditional risk factors and the use of CVD risk assessment with the ABI.

Data Sources: MEDLINE, PubMed, and Cochrane Collaboration Registry of Controlled Trials through May 22, 2017, to update existing systematic reviews supporting the previous USPSTF recommendations.

Study Selection: We screened 22,707 abstracts and 483 full-text articles against *a priori* inclusion criteria. For KQ1 and KQ4 we limited studies to trials reporting patient health outcomes. For KQ2 we included risk prediction studies comparing a base model with traditional risk factors (the FRS or PCE) to extended models also including one of the three nontraditional risk factors (ABI, hsCRP, CAC) predicting CHD or CVD outcomes. For KQ3 and KQ5 we broadly included any study design examining harms of nontraditional risk assessment or nontraditional risk factor-guided therapy. All KQs were limited to studies of asymptomatic populations that were conducted in developed nations and published in the English language.

Data Extraction and Synthesis: Two investigators independently and critically appraised each article that met inclusion criteria using USPSTF's design-specific criteria, supplemented by the Checklist for Critical Appraisal and Data Extraction for Systematic Review of Prediction Modelling Studies (CHARMS) for risk prediction studies. Poor-quality studies were excluded. Data from fair- and good-quality trials were abstracted into standardized evidence tools in DistillerSR, with all data double-checked by a second reviewer for accuracy. Due to the limited number of included studies and/or clinical heterogeneity of included studies, we did not conduct meta-analyses. We graded the strength of the overall body of evidence for each KQ.

Main Outcomes and Measures: For KQ1 and KQ4, outcomes included fatal and nonfatal CVD events (e.g., myocardial infarction [MI], cerebrovascular accident [CVA]) and all-cause mortality. For KQ2, outcomes included any measure of calibration (e.g., calibration plot, Hosmer-Lemeshow test) or overall performance (e.g., likelihood ratio tests, R^2), discrimination (e.g., c-statistic/area under the curve [AUC]), or reclassification (e.g., net reclassification index [NRI]). For KQ3, outcomes comprised any harms, including radiation exposure due to CT imaging for CAC and downstream health care utilization. For KQ5, outcomes included any

serious adverse event as defined by the included study.

Results: We included a total of 43 unique studies reported in 54 publications (some studies were included for multiple KQs): 1 study for KQ1, 33 studies for KQ2, 8 studies for KQ3, 4 studies for KQ4, and 3 studies for KQ5.

KQ1. One fair-quality RCT (n=2,137), primarily designed to assess the impact of CAC on CVD risk factors and downstream testing, reported health outcomes and found no statistically significant differences in CVD events between CAC score and control groups at 4 years. This study was not adequately powered for CVD outcomes.

KQ2. Ten studies (n=81,590) evaluated ABI, 25 studies (n=269,449) evaluated hsCRP, and 19 studies (n=69,720) evaluated CAC. Only four studies evaluated nontraditional risk factors in addition to the PCE; the rest used a base model of FRS. Overall, limited data suggest all three nontraditional risk factors can improve calibration, but the clinical impact of this change in calibration is uncertain due to the lack of reporting of preferred measures. We have more data to inform the change in discrimination and risk reclassification when adding ABI, hsCRP, or CAC to traditional cardiovascular risk assessment.

ABI. One large, individual-participant data (IPD) meta-analysis including 18 different cohorts demonstrated that ABI can improve discrimination and reclassification in women to predict hard CHD events when added to a published coefficient FRS model, with a c-statistic change of 0.112 and net reclassification index (NRI) of 0.096. This incremental improvement for women is most likely due to poorer discrimination of the base model in women, compared to men.

hsCRP. Results for hsCRP are mixed. Studies using published coefficients for FRS demonstrate that hsCRP can improve discrimination, but results are inconsistent. One large IPD meta-analysis, a model development study that included 38 different cohorts, demonstrated that hsCRP only had very small improvement on discrimination. Results for reclassification were similar and best evidence suggests an overall NRI of less than 0.02.

CAC. Based on a smaller body of evidence, CAC consistently appears to improve discrimination and reclassification in both published coefficient and model development studies; NRIs ranged from 0.084 to 0.35.

KQ3. No studies address the harms of ABI or hsCRP. Four studies (n=11,473) demonstrated that radiation exposure from CT imaging for CAC is low. Two studies (n=1,619) found no evidence for adverse psychological health outcomes for screening CAC. Two studies (n=11,364) found no evidence that CAC paradoxically increases CVD events. Three studies (n=13,204) found mixed results for CAC on downstream health care utilization. Best evidence suggests no overall increase in cardiac imaging or revascularization; however, this RCT may have limited applicability to real-world practice. One large retrospective study using Medicare claims data found an association for higher utilization compared to hsCRP or lipid screening.

KQ4. No trials directly compared treatment guided by nontraditional risk factors when added to traditional cardiovascular risk assessment; however, we included studies in which preventive

therapies were guided by the use of nontraditional risk factors. Two RCTs (n=4,626) found no benefit for ABI-guided low-dose aspirin on CVD outcomes or all-cause mortality at approximately 7 to 8 years of followup. One RCT (n=17,802) found a benefit for hsCRP-guided, high-intensity statin on CVD outcomes and all-cause mortality at 1.9 years of followup. One RCT (n=1,005) found no benefit for CAC-guided moderate-intensity statin at approximately 4 years, but the study was inadequately powered to detect a benefit for CVD outcomes.

KQ5. Low-dose aspirin in the two RCTs (n=4,626) included for KQ4 did not result in increased major bleeding events. High-intensity statin in one RCT (n=17,802) included in KQ4 was associated with an increase in incident diabetes but not with other serious adverse events.

Conclusions and Relevance: There is no direct evidence from adequately powered clinical impact trials comparing traditional cardiovascular risk assessment to risk assessment using nontraditional risk factors on patient health outcomes. The best available indirect evidence is mainly limited to studies evaluating the incremental value on discrimination and risk reclassification when adding ABI, hsCRP, or CAC to the FRS. We have much less evidence on the addition of these nontraditional risk factors to the PCE (compared to the FRS) and much less evidence to inform how these nontraditional risk factors improve calibration of traditional cardiovascular risk assessment. Therefore, the value of nontraditional risk factors to correct the over- or under-prediction of traditional risk assessment goes unanswered. Overall, ABI may improve discrimination and reclassification in women when the base model performs poorly, and CAC can moderately improve discrimination and reclassification with an unclear effect on downstream health care utilization. One large RCT shows that high-intensity statin therapy in individuals with elevated hsCRP and normal lipid levels can reduce CVD morbidity and mortality, but it is unclear if these benefits would not also be applicable to individuals with normal hsCRP. Treatment guided by nontraditional risk factors has not been evaluated against treatment guided by traditional multivariate cardiovascular risk assessment.

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Chapter 1. Introduction

Condition Definition

Cardiovascular disease (CVD) is a broad term encompassing diseases of the heart, vascular diseases of the brain, and diseases of blood vessels.[1, 2] It generally refers to atherosclerosis, including but not limited to coronary heart disease (CHD; also called ischemic heart disease), cerebrovascular disease, and peripheral artery disease (PAD). CVD can also include other diseases in the heart or vascular system, such as heart failure, atrial fibrillation, congenital heart disease, cardiomyopathies, and rheumatic heart disease; these conditions are not addressed in this report.

Prevalence and Burden of Cardiovascular Disease

CVD is the leading cause of death in the United States for both men and women, accounting for about one in three deaths.[3] Although CVD mortality is decreasing over time in the United States, it remains a significant cause of morbidity and mortality. Despite a nearly 7 percent reduction in the number of CVD deaths per year between 2004 and 2014, an estimated 580,000 Americans have a first myocardial infarction (MI) each year and about 610,000 experience a first cerebrovascular accident (CVA).[3]

The burden of CVD varies by age, sex, and race/ethnicity. The prevalence of CVD increases dramatically with age. According to the most recent data from the Centers for Disease Control and Prevention (2006-2010), the prevalence of CHD among adults ages 65 or older was 19.8 percent, which was almost triple that of those ages 45 to 64 years (7.1%).[4] Similarly, the CVA prevalence of 8.3 percent among those age 65 years or older was almost triple that of those ages 45 to 64 years (2.9%).[5] Before age 75 years, men experience higher rates of CHD events as a proportion of cardiovascular events than women do, whereas women experience more CVA.[6] Men tend to experience CHD events earlier in life. For example, the mean age of first MI is 65.3 years for men and 71.8 years for women.[3] In addition to age and sex differences, certain racial/ethnic groups experience an increased burden of CVD. From 2006 to 2010, American Indians/Alaska Natives had the highest prevalence of both CHD and CVA (11.6% and 5.9%, respectively), followed by African Americans (6.5% and 3.9%), Latinos (6.1% and 2.5%), Whites (5.8% and 2.4%), and Asians/Native Hawaiians/other Pacific Islanders (3.9% and 1.5%).[4, 5]

Cardiovascular Disease Risk Assessment

CVD risk assessment integrates information about multiple risk factors with the aim of tailoring preventive treatment to maximize the potential benefit for the patient.[7, 8] Risk assessment also offers a platform for discussion between provider and patient, which may improve patients' perception of risk and motivate initiation and adherence to medical or lifestyle therapy, as well as physician adherence to best clinical practices.[7, 9-12]

In past decades, there has been a proliferation of CVD risk-assessment models, which are sometimes interchangeably referred to as equations, tools, calculators, algorithms, and scores. A 2016 systematic review of prediction models for CVD risk in the general population found 125 articles describing the development of 363 different models, only one-third of which (132 models) were externally validated.[13] Several models have been externally validated, are publicly available as calculators or tools, and have been endorsed by clinical practice guidelines (**Table 1**). These risk assessment tools vary across several important dimensions. The biggest differences among models are the predicted outcomes, which may be CHD-specific or also include CVA. Additionally, there is variation in the severity of outcomes included (soft, hard, or fatal only). Risk assessment tools also vary in the included risk factors. The basic risk factors include measures of age, sex, blood pressure, total cholesterol and HDL-C, and smoking; some include diabetes (with or without hemoglobin A1c). Family history of premature CHD is included in selected tools but not those broadly recommended in the United States. Recent risk assessment tools have incorporated race/ethnicity. Last, risk assessment tools were developed in different derivation cohorts and have varying degrees of external validation. Notable limitations of these models may include nonrepresentative or historically dated populations, limited ethnic diversity in derivation and validation cohorts, and outcome endpoints with poor reliability.[7, 14, 15]

The first widely used CVD risk prediction tool was the Framingham Risk Score (FRS), which was derived from the Framingham Heart Study and includes the "traditional" risk factors of: age, sex, total and high-density lipoprotein cholesterol [HDL-C], blood pressure, smoking, and diabetes. Externally validated Framingham-based models include those by Anderson, Wilson, D'Agostino, and the Adult Treatment Panel (ATP III).[16-21] These models generally include the same risk factors (left ventricular hypertrophy as determined by electrocardiography was included in one older model but subsequently dropped[16, 17]) but predict somewhat different composite CHD or CVD outcomes. Of note, the ATP III model was not intended for use in individuals with diabetes, which was considered a CHD risk equivalent.[22] In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Assessment of Cardiovascular Risk released the Pooled Cohort Equations (PCE). The PCE is based on four population-based cohort studies and includes the same risk factors as the FRS, but inclusion of multi-ethnic populations in the derivation cohorts also enabled race- and sex-specific equations for African Americans and Whites. Included risk factors were selected based on their ability to improve the model and were not selected *a priori* to be the same as the FRS.[7] The PCE predicts hard CVD outcomes (MI, CVA, CHD, or CVD mortality) and includes diabetes as a risk factor.[7] U.S. population estimates of the distribution of 10-year CVD risk from the PCE using 2001-2010 NHANES data show that the vast majority of Americans aged 40 to 49 years have an estimated 10-year CVD risk of 10 percent or less (94% of women and 88% of men). For ages 50 to 59 years, 86 percent of women and 62 percent of men have estimated 10-year risk of 10 percent or less; at ages 60 to 69, 58 percent of women and 20 percent of men have estimated 10-year risk at this level.[23]

However, external validation studies of various risk assessment tools show that models can over- or under-predict risk and no model has "perfect" calibration or discrimination. In fact, there are tradeoffs between these two performance characteristics and a model cannot be perfect in both.[24] The clinical importance of miscalibration (both over- and under-prediction) will depend on whether it is occurring above or below accepted treatment thresholds. Direct comparison across

models is complicated due to the differences in outcomes predicted, definitions of risk categories, and the availability of external validation cohorts with sufficient years of followup and robust outcome surveillance; additionally, there may be various degrees of heterogeneity in population risk across derivation and validation cohorts.

A recent systematic review identified three trials comparing the use of CVD risk scores versus no use of risk scores or usual care and found that CVD risk scoring had little to no effect on CVD outcomes.[25] This review found a larger body of evidence suggesting that CVD risk scoring is associated with small reductions in total cholesterol, systolic blood pressure, and CVD risk scores, and that CVD risk scoring is associated with new or intensified lipid or antihypertensive medication management. However, the quality of evidence for all outcomes was characterized as low, with study limitations including limited power, various sources of study bias, and heterogeneity. Therefore, the true benefit of implementing CVD risk assessment tools on patient outcomes is uncertain. Furthermore, the comparative benefit of using different tools has never been evaluated in a trial assessing the impact of using one versus another model on CVD outcomes. This type of trial may never be done due to the large sample and long followup needed to detect differences in CVD event rates.[26]

Use of Nontraditional Risk Factors to Improve Risk Prediction

Given that current risk assessment tools can under- or overestimate CVD risk, it follows that nontraditional risk markers or factors may be helpful in improving the calibration in addition to the discrimination and risk reclassification of currently used risk assessment tools. Over 100 nontraditional risk markers have been proposed as candidates to improve CVD risk assessment; the most commonly investigated are markers of inflammation and atherosclerotic burden.[27] Our review focuses on three of the most promising nontraditional risk factors: ankle-brachial index (ABI), high sensitivity C-reactive protein (hsCRP), and coronary artery calcium (CAC) score (**Table 2**).

In developing the PCE, the ACC/AHA examined a number of promising nontraditional risk factors but did not include them because either: 1) there was no significant improvement in discrimination when included in the model (diastolic blood pressure, family history of CVD, moderate or severe kidney disease [defined as eGFR <60 mL/min/1.73 m^2], and BMI) or 2) data were unavailable in the model development cohorts (hsCRP, apolipoprotein [apoB], microalbuminuria, cardiorespiratory fitness, CAC, carotid intima-media thickness [CIMT], and ABI). Based on expert opinion, the ACC/AHA guidelines did recommend that family history, hsCRP, CAC, and ABI be considered if risk-based treatment was uncertain after using the PCE. Per experts, family history did not improve discrimination but was free and easy to assess; while CAC appeared to be the most promising nontraditional risk factor, there was not enough data or followup to include it in the PCE (D. Lloyd-Jones, personal communication, 2015). The ACC/AHA guidelines recommended against using CIMT.

Likewise, several nontraditional risk factors were considered in alternate models of CHD or CVD risk prediction but not included in the final model of other recommended risk assessment tools.[28] Currently only one U.S.-based tool, the Reynolds Risk Score (RRS), incorporates nontraditional risk factors (i.e., hsCRP, family history, and A1c if diabetes is present).

Treatment Approaches Based on Risk

Risk assessment-guided therapy for the primary prevention of CVD includes statins, aspirin, and intensive lifestyle counseling.[7, 29-32] In the United States, recommendations for initiation of antihypertensive medications are not based on multivariate risk assessment.

Both the USPSTF and ACC/AHA have 10-year, risk-based recommendations for the use of statins, based on the PCE.[33, 34] The USPSTF has a B recommendation for a low- to moderate-dose statin to prevent CVD events in adults ages 40 to 75 years with no history of CVD, one or more CVD risk factors, and a calculated 10-year CVD event risk of 10 percent or greater; there is a C recommendation to individualize the decision (shared decisionmaking) for those at 7.5 to 10 percent risk.[19, 33] The ACC/AHA has a recommendation for moderate- to high-intensity statin treatment in adults 40 to 75 years of age with LDL-C 70 to 180 mg/dL, without diabetes or CVD, and with an estimated 10-year risk of 7.5 percent of higher (class of recommendation: I, level of evidence: A); there is also a recommendation for moderate-intensity statin treatment when 10-year risk is 5 percent to less than 7.5 percent (class of recommendation: IIa, level of evidence: B). This recommendation represents a lower treatment threshold than in previous guidelines.[19] The lowered threshold for discussion or initiation of statin therapy has reinforced concern about calibration of the PCE.[34, 35] Recent U.K. guidelines similarly lowered the threshold for statin therapy to a 10 percent or greater 10-year risk for CVD as assessed with the QRISK2 tool.[36] All of these recommendations explicitly indicate an informed clinician-patient discussion of benefits and harms prior to initiation of statin therapy.

In 2016, the USPSTF made a B recommendation for initiating low-dose aspirin for the primary prevention of CVD (and colorectal cancer) in adults ages 50 to 59 years who have a 10 percent or greater 10-year CVD risk, and a C recommendation to individualize the decision in adults ages 60 to 69 years with a 10 percent or greater 10-year CVD risk.[37]

Intensive lifestyle counseling to promote a healthful diet and regular physical activity is recommended for people at elevated risk for CVD. In 2014, the USPSTF made a B recommendation to offer or refer adults who are overweight or obese and have additional CVD risk factors (i.e., hypertension, dyslipidemia, impaired fasting glucose, or the metabolic syndrome) to intensive behavioral counseling interventions to promote a healthful diet and physical activity.[38] This recommendation also includes people identified as high risk based on CVD risk assessment.

In the United States, recommendations for initiation of antihypertensive medications are not currently based on estimated 10-year CVD risk.[29, 39] Thresholds for initiation of blood pressure medication were raised in the most recent U.S. guidelines for patients at least 60 years old (from ≥140/90 mm Hg to ≥150/90 mm Hg) and adults with diabetes or chronic kidney disease (from ≥130/80 mm Hg to ≥140/90 mm Hg).[40] U.K. blood pressure guidelines, however, recommend initiation of antihypertensive drugs to patients with a 10-year CVD risk of at least 20 percent when clinic blood pressure is higher than 140/90 mm Hg and elevated blood pressure is confirmed by ambulatory or home blood pressure monitoring.[41]

Current Recommendations and Clinical Practice in the United States

CVD risk assessment, whether with traditional or nontraditional risk factors, intersects numerous current USPSTF recommendations (**Appendix A**). USPSTF recommendations exist for each of the traditional modifiable Framingham risk factors (cholesterol, blood pressure, diabetes, and smoking) as well as some nontraditional risk factors (ABI) and screening modalities related to nontraditional risk factors (carotid intima-media thickness, electrocardiography). Several recommendations provide discussions of risk assessment in the top-line recommendation or clinical considerations, including: screening for abnormal blood glucose and diabetes, PAD screening, CHD screening with electrocardiography, healthful diet and physical activity counseling, carotid artery stenosis screening, aspirin use to prevent CVD and colorectal cancer, and statin use for the primary prevention of CVD.

A wide range of CVD and CHD risk assessment models are recommended by international guideline bodies (**Table 1**). Some recommended models include nontraditional risk factors. Although the ACC/AHA did not formally include nontraditional risk factors, they did recommend considering family history, hsCRP, CAC, and ABI if risk-based treatment was still uncertain after a quantitative risk assessment was performed using the PCE. The Canadian Cardiovascular Society added family history to the Framingham global CVD risk tool.[22] QRISK2, the risk tool recommended by NICE, includes chronic kidney disease, atrial fibrillation, and a measure of social deprivation.[36] ASSIGN, the risk score recommended by the Scottish Intercollegiate Guideline Network (SIGN), also includes a measure of social deprivation.[42]

Despite recommendations for periodic risk assessment, a recent survey of U.S. physicians found that only 41 percent use cardiovascular risk assessment in practice even though awareness of available tools is high.[43] The most commonly cited reason for not performing risk assessment is that it is too time consuming. Even when risk assessment is conducted, results are communicated to patients less than half the time, limiting its potential impact to motivate behavior change or adherence to therapy.[43] A 2012 survey of European physicians found that over 90 percent of them felt that risk assessment tools miss important risk factors and over one-third felt that these tools overestimate risk.[44] The uptake of cardiovascular risk assessment using nontraditional risk factors is largely unknown and likely varies across practice settings.

Previous USPSTF Recommendation

In 2009, the USPSTF concluded that the evidence was insufficient to assess the benefits and harms of using nontraditional risk factors studied to screen asymptomatic men and women with no history of CHD to prevent CHD events (I Statement).[45] The nontraditional risk factors included in this previous recommendation were: hsCRP, ABI, leukocyte count, fasting blood glucose level, periodontal disease, CIMT, CAC score on electron beam computed tomography [EBCT], homocysteine level, and Lp(a) level. In 2013, the USPSTF again concluded that there

was insufficient evidence to assess the balance of benefits and harms of screening for PAD and CVD risk assessment with the ABI in adults (I statement).[46]

Chapter 2. Methods

Scope and Purpose

This systematic review examined the evidence for using nontraditional risk factors—ABI, hsCRP, and CAC—in cardiovascular risk assessment. For the purposes of this review, we use the terms "risk assessment" and "risk prediction" as synonyms. Our review focuses specifically on these three risk factors, and was informed by a scan of existing literature and guidelines, consultation with experts in the field, consultation with the USPSTF, and a period of public comments. These three nontraditional risk factors satisfied our *a priori* criteria for relevance; that is, a novel risk factor should:

1. Be easily and reliably measured (i.e., laboratory, radiographic, or clinical measurement should have accepted population reference values).
2. Have established predictive ability beyond traditional risk factor assessment (i.e., independently associated with CHD or CVD risk using measures of risk association including hazard ratios, rate ratios, or odds ratios).
3. Have data to describe the prevalence and distribution of nontraditional risk factor status by traditionally identified risk groups (i.e., adequate variation in the distribution of abnormal and normal values).

The USPSTF will use this review to update its 2009 recommendation statement on screening for coronary heart disease with nontraditional risk factors[45] and its 2013 recommendation on CVD risk assessment with the ABI.[46]

Key Questions and Analytic Framework

In consultation with members of the USPSTF, we developed an analytic framework (**Figure 1**) and five Key Questions (KQs) to guide our review.

1. Compared with the Pooled Cohort Equations or Framingham risk factors alone, does risk assessment of asymptomatic adults using nontraditional risk factors—followed by treatment specific to risk level—lead to reduced incidence of cardiovascular events (e.g., myocardial infarction, cerebrovascular accident) and/or mortality?
2. Does use of nontraditional risk factors in addition to traditional risk factors to predict cardiovascular disease risk improve measures of calibration, discrimination, and risk reclassification?
3. What are the harms of nontraditional risk factor assessment?
4. Does treatment guided by nontraditional risk factors, in addition to traditional risk factors, lead to reduced incidence of cardiovascular events (e.g., myocardial infarction, cerebrovascular accident) and/or mortality?
5. What are the harms of treatment guided by nontraditional risk factors?

Data Sources and Searches

We conducted a search to identify literature published since a set of previous reviews for the USPSTF through May 22, 2017. We worked with a research librarian to develop our search strategy, which included the following databases: MEDLINE, PubMed (published-supplied records only) and the Cochrane Central Register of Controlled Trials (**Appendix B**). For hsCRP, we bridged from the previous USPSTF review by Buckley and colleagues[47] and searched from 2007; for CAC, we bridged from the previous review by Helfand and colleagues[48] and searched from 2008. For ABI, we bridged from the review by Lin and colleagues[49] and search from 2012. We evaluated all previously included studies from the prior reviews for the USPSTF as well as reference lists of other systematic reviews and meta-analyses to identify additional studies not identified in our literature searches. We also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for relevant ongoing trials (Appendix B). We managed all literature search results using EndNote™ version 7.3.1 (Thomson Reuters, New York, NY).

Study Selection

One investigator independently prescreened titles and abstracts of a subset of studies that were electronically identified as having keywords pertaining to an excluded setting, population, or condition in the abstract or keyword fields of EndNote (**Appendix B Table 1**); abstracts deemed potentially relevant during single review were advanced for dual review. Of the 22,707 total citations screened, 8,013 were prescreened by a single reviewer; of these, 265 were identified as potentially relevant and moved forward for dual review. Two investigators independently reviewed 483 full-text articles against prespecified inclusion criteria (**Appendix B Table 2**).

Our review focuses on the benefit and harm of adding ABI, hsCRP, or CAC to the current standard of practice of CVD or CHD risk prediction using traditional risk factors (i.e., the PCE or the FRS). Specifically, eligible base models had to include age, sex, systolic blood pressure, antihypertensive medication use, total cholesterol, HDL, and current smoking status. Models were eligible with or without the inclusion of race/ethnicity and diabetes as these predictors are included in some but not all eligible base models.[7, 18-20] Studies with additional variables (e.g., measures of kidney function, family history, left ventricular hypertrophy) in their base models were excluded, as this would preclude us from isolating the effect of the nontraditional risk factor of interest. If we could not isolate the effect of newly added risk factors, we excluded extended models comprising multiple nontraditional risk factors. Thus, the Reynolds Risk Score, which includes hsCRP, family history, and HbA1c for individuals with diabetes (in the model for women but not men)[15, 50] was not evaluated in this review; information about its performance in external validation studies is described in the Discussion.

We included studies or cohorts of adults without known CVD in developed countries as defined using the Human Development Index by the United Nations Development Program. For KQ1, we included randomized or controlled clinical trials comparing traditional risk assessment to risk assessment including nontraditional risk factors that reported patient health outcomes. For KQ4, we included randomized or controlled clinical trials of treatment guided by nontraditional risk

factor assessment in addition to traditional risk assessment versus no treatment or usual care that reported patient health outcomes. Patient health outcomes were defined as CVD events (e.g., MI, CVA) and/or mortality (e.g., CVD-specific or all-cause). For KQ2, we included individual participant data (IPD) meta-analyses, trials, or well-designed prospective cohort studies evaluating risk prediction in models with traditional risk factors (base model) compared to models additionally including ABI, hsCRP, or CAC (extended model). We included any measure of calibration, discrimination, or reclassification as risk assessment performance measures. For KQ3 and 5, studies examining the harms of risk assessment (or treatment guided by risk assessment), we included trials, prospective and retrospective cohort studies, and well-designed case-control studies examining harms. We defined harms as any serious adverse event (i.e., unexpected or unwanted medical attention) resulting from risk factor assessment itself or aggressive risk factor modification resulting from risk assessment. For CAC assessment, we also included radiation exposure from CT as a potential harm (i.e., studies included for other questions that reported radiation exposure or studies with the explicit aim to measures/evaluate radiation exposure). All KQs restricted inclusion to good- or fair-quality studies published in English.

Quality Assessment and Data Abstraction

Two reviewers independently and critically appraised articles meeting inclusion criteria. For trials and cohort studies, we used the USPSTF's design-specific quality criteria and items from the Newcastle-Ottawa Scale.[51, 52] For risk prediction studies, we adapted and tailored items from the Checklist for Critical Appraisal and Data Extraction for Systematic Review of Prediction Modelling Studies (CHARMS),[53] and selected domains pertaining to IPD meta-analyses (if applicable)[54] (**Appendix B Table 3**). We rated articles as good, fair, or poor quality. In general, a good-quality study met all criteria. A fair-quality study did not meet, or it was unclear whether it met, at least one criterion but had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. Two studies, both for KQ2, were excluded for poor quality.[55, 56] Both had multiple limitations, including nonrepresentative sampling of patients, self-reported outcomes, limited duration of followup, and/or very small number CVD events. We excluded poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, in consultation with a third independent reviewer.

One reviewer abstracted key elements of included studies using standardized evidence tables in DistillerSR (Evidence Partners, Ottawa, Canada). A second reviewer checked the data for accuracy. For each study, we abstracted general characteristics of the study (e.g., author, year, recruitment, study design, length of followup), clinical and demographic characteristics of the included population (e.g., age, race/ethnicity, means or proportions of traditional cardiovascular risk factors), characteristics of the base model (e.g., published coefficient vs model development, recalibration, outcome predicted by the model), treatment details (if applicable [KQ4]), and outcomes (e.g., CVD outcomes, mortality, risk prediction performance). The performance of risk prediction models, or the comparative performance of one model to another, can be described using a few key dimensions:[57-59]

- Calibration: Agreement between observed and predicted outcomes
- Discrimination: Ability to distinguish between individuals who will and will not have an event
- Reclassification: Ability to (correctly) reassign people into clinically meaningful risk strata

We abstracted any of these performance measures reported by the included studies. Descriptions of specific measures are provided in **Table 3**; additional measures to describe test performance exist, such as the Greenwood-Nam-D'Agostino calibration approach,[60] but we only describe those reported in included studies. Studies reporting measures of association (e.g., hazard ratios) between ABI, hsCRP, or CAC and cardiovascular outcomes that did not also report one of the three risk prediction outcomes above were excluded.

For calibration, we preferred graphical representations because they are more intuitive and can indicate the direction of miscalibration. When reported, we extracted information on the total number of observed (O) and expected (E) events; the O:E ratio is a proxy for overall model calibration (i.e., strongly related to the calibration in the large measure) and can be compared across studies. However, both calibration plots and O:E ratio are rarely reported. The Hosmer-Lemeshow test was the most commonly reported measure of calibration. Several measures, including R^2 and the Brier score, are considered "overall performance measures" in that they are integrated measures of calibration and discrimination;[57, 59] we report these with calibration. We used the c-statistic (and change in the c-statistic) as our primary measures of discrimination. Although we recognize the difference between the area under the curve (AUC) and the c-statistic (Harrell's C), we summarize these together. We used the net reclassification index (NRI) as our primary measure of reclassification, and report event and nonevent NRI separately where possible. IDI was included in the Appendix (**Appendix E**) but not discussed in detail due to the very sparse reporting of this measure.

Data Synthesis and Analysis

Our analyses were organized by KQ. We address the clinical value of risk assessment hierarchically, meaning—does measurement of the nontraditional risk factor:

1. Demonstrate a clinical benefit on CVD or mortality outcomes to those reclassified using nontraditional risk factors (KQ1)?
2. Improve discrimination or calibration (KQ2)?
3. Correctly reclassify those with a predicted intermediate risk into higher or lower risk, or demonstrate the ability to correctly reclassify those whose risk has been over- or underestimated into a more accurate risk group (e.g., from a high-risk to lower-risk group) (KQ2)? or
4. Result in any serious harm (KQ3)?

We also summarized the evidence on the effectiveness (KQ4) and harms (KQ5) of various preventive treatments guided by the addition of nontraditional risk factors to traditional risk factor assessment.

For KQ2, we stratified our analyses based on a few important dimensions of heterogeneity: 1) choice of the FRS[18-20] or the PCE[7] as the base model; 2) prediction of CVD vs CHD outcomes; and 3) type of model design. In addition, studies used different CVD and CHD outcomes or events. The most severe of these outcomes (i.e., fatal or nonfatal MI or CVA) are commonly referred to as hard outcomes. Other studies include events of differing degrees of severity (e.g., angina, transient ischemic attack [TIA], claudication), and utilization outcomes (e.g., revascularization); these are commonly referred to as soft outcomes. Risk prediction studies evaluating the PCE as a base model used CVD outcomes; however, studies evaluating the FRS as a base model used both CHD and CVD outcomes, with varying events or endpoints included in these outcomes (**Table 4**).

We prioritize analyses using the PCE base model with hard CVD outcomes, and the FRS base model with hard CHD outcomes. While we included models predicting fatal outcomes only, we do not discuss these results, unless it was the only outcome reported/predicted.

Risk prediction studies evaluating the added prognostic value of ABI, hsCRP, or CAC were either pragmatic in design (i.e., preserved the coefficients from the published model) or model development studies. Studies that used the original published coefficients of the FRS[18-20] or the PCE[7] were considered preferable to model development studies on the basis that these studies are the most applicable to current practice; in these studies, nontraditional risk factors of interest were added to publicly available, externally validated models used in clinical practice. We refer to models with this design as published coefficient models. This term is used to designate the specific application of an externally validated model in which the original coefficients are preserved (with or without updating to a local population). We use the term external validation more broadly to refer to the generalizability or transportability of a clinical prediction model to other "plausibly related" populations;[61] both the FRS and PCE as base models are externally validated. However, because the minority of included studies preserved the original published coefficients, we also discuss studies that included the same predictor variables in the FRS or PCE, but with locally developed coefficients from newly fitted models (e.g., full recalibration, *de novo* model development). We refer to models with this design as model development studies. Although such model development studies are less clinically relevant, they do serve the explanatory purpose of evaluating more generally whether an added nontraditional risk factor improves model performance. In this report, the terms FRS and PCE will refer to published coefficient models, and the terms "FRS variables" and "PCE variables" will be used to refer to model development studies.

In addition to these dimensions of heterogeneity (i.e., choice of base model, corresponding CVD or CHD outcomes, and type of model design), we *a priori* looked at other characteristics that might explain differences in findings across studies, including:

- Updating the model to the local/studied population (i.e., "recalibration" among published coefficient models). We considered such studies to more conservatively estimate the incremental value of ABI, hsCRP, or CAC.[62]
- Continuous versus dichotomized or categorized predictors. Treatment of continuous risk predictors as dichotomous or categorical variables results in loss of statistical power and compromises predictive performance.[63]

- Number of events or events per variable (EPV) (stratification with 100 event cut-off).[64]
- Length of followup/time horizon (i.e., longer followup preferred).
- Definition of low-, intermediate-, and high-risk strata (for risk reclassification).
- Sex (where subgroup analyses allow).
- Presence of diabetes (where subgroup analyses allow).
- Race/ethnicity (where subgroup analyses allow).

Often, we identified multiple publications for model development analyses for any given outcome from the same cohort. In these instances, we preferred analyses with the larger sample size (n) and/or the longest followup (largest number of events). For bodies of evidence where IPD meta-analyses were included,[65, 66] we used the IPD meta-analyses as the central piece of evidence and only analyzed separate studies from those included cohorts if different (and preferable) base models, outcomes, types of model design, or performance measures were reported in separate publications.

We did not quantitatively synthesize information because of the limited number of studies for most key questions as well as the clinical and methodological heterogeneity of included studies for KQ2 (i.e., differences in types of model design, populations, base models, CHD or CVD outcomes, definition of risk strata, and performance or statistical measures reported). If the change in discrimination between base and extended models was not reported (and it rarely was), we calculated a crude change by subtracting the base model discrimination from that of the extended model. However, confidence intervals for these differences could not be calculated.

As there is no guidance in existing literature about how to characterize the magnitude or clinical meaning of changes in discrimination (KQ2),[67] we used the following definitions for practical reasons. For changes in the c-statistic, the term "large" is used to denote changes of 0.1 or greater, "moderate" for changes of 0.05-0.1, "small" for 0.025-0.05, and "very small" for changes less than 0.025. C-statistics range from 0.5 to 1.0; the 0.1 cutpoint for "large" was set because it represents 20 percent of the possible range. A change in c-statistic of 0.025 approximates a 5 percent higher sensitivity when specificity is 50 percent.[68]

When a reclassification table for an entire study population was available, we calculated the event NRI, nonevent NRI, and bias-corrected NRI for the immediate-risk group (NRI_{INT}), if not reported.[69, 70] We abstracted uncorrected NRI_{INT} if a reclassification table was not provided; however, uncorrected NRI_{INT} can overestimate the reclassification effect.[71] Details of the calculations for NRIs and confidence intervals are included in **Appendix B**.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center approach,[72] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[73] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or

selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there is insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual studies and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body of evidence limitations field highlights important restrictions in answering the overall KQ.

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" suggests moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from June 11 to July 8, 2015. The draft version of this report was reviewed by six invited experts and two USPSTF Federal Partners. Experts were selected based on their expertise on fundamental methodologic and content aspects of the review (i.e., risk prediction, cardiovascular epidemiology, ABI, hsCRP, and CAC) and were selected to obtain diverse informed perspectives, including developers of included risk prediction models, researchers who have validated risk prediction models, guideline developers, trialists, specialists in cardiovascular imaging, and practicing clinicians. All expert comments were considered, and selected comments from experts were used to clarify and extend the synthesis of evidence to ensure accuracy and address scientifically relevant concerns. All comments were shared with members of the USPSTF and the Agency for Healthcare Research and Quality (AHRQ). Additionally, a draft of the full report was posted on the USPSTF Web site from January 16, 2018 to February 12, 2018. Based on the public comments received, we made a few minor revisions to the evidence report, including addition of background information about the distribution of 10-year CVD risk in the U.S. and additional clarification about included and discussed studies and analyses.

USPSTF Involvement

This systematic review was funded by AHRQ under contract to support the USPSTF. We consulted with USPSTF liaisons at key points in the review including the development of the research plan (i.e., KQs, analytic framework, and inclusion and exclusion criteria) and the finalization of the systematic review. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the review, and assisted with public comment on the research plan and draft review. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the systematic review.

Chapter 3. Results

Overview of Included Trials and Cohorts

Our literature search yielded 22,707 unique citations. From these, we provisionally accepted 483 articles for review based on titles and abstracts (**Appendix B Figure 1**). After reviewing the full-text articles and performing critical appraisal, we included a total of 43 studies that reported results in 54 publications (some studies were included for multiple questions). We found 1 study (1 article) for KQ1,[11] 33 studies (43 articles) for KQ2,[65, 66, 74-114] 8 studies (8 articles) for KQ3,[11, 88, 89, 115-119] 4 studies (5 articles) for KQ4,[120-124] and 3 studies (3 articles) for KQ5.[120, 122, 123] **Appendix C** contains a full list of included studies. For the 483 articles that we reviewed in full, the most common reasons for exclusion were study aim, outcomes, study design, and eligibility of the base prediction model (KQ2). **Appendix D** contains a list of all excluded full-text articles and their reasons for exclusion.

Table 5 is an overview of all included trials and cohorts, and the key questions each trial or cohort addresses. In total, our review includes studies representing 38 unique trials or cohorts. We describe the included populations separately for each respective KQ, and for KQ2, describe populations included in ABI, hsCRP, and CAC studies separately.

KQ1. Compared With the PCE or FRS Alone, Does Risk Assessment of Asymptomatic Adults Using Nontraditional Risk Factors—Followed by Treatment Specific to Risk Level—Lead to Reduced Incidence of Cardiovascular Events and/or Mortality?

We included only one study that examined the effectiveness of nontraditional risk factor assessment on patient health outcomes.[11] This fair-quality randomized controlled trial (RCT) (n=2,137) was primarily designed to assess the impact of CAC screening on CVD risk factors and downstream testing, but it also reported health outcomes and therefore is included for this key question. The Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research (EISNER) trial, conducted in the United States, randomized volunteers to undergo CT scanning for CAC scoring in addition to the FRS versus no CT before risk factor counseling (**Table 6**). The primary outcome was a change in CVD risk factors and Framingham Risk Score at 4 years. Participants were middle-aged adults with CVD risk factors but no known CVD or symptoms (**Table 7**). This study found no statistically significant difference in MI, mortality, or combined MI and mortality at 4 years between the two groups (**Table 8**). The trial was well conducted but did not have adequate sample size and length of followup to detect differences in patient health outcomes. This study is discussed with respect to downstream testing and radiation dose in KQ3, and to adherence to risk factor modification in the Discussion section.

KQ2. Does Use of Nontraditional Risk Factors in Addition to Traditional Risk Factors to Predict CVD Risk Improve Measures of Calibration, Discrimination, and Risk Reclassification?

Summary

We included 33 studies reported in 43 articles that evaluated ABI, hsCRP, and/or CAC in addition to traditional cardiovascular risk assessment using one or more measures of calibration, discrimination, and/or risk reclassification. Ten studies (including 1 large IPD meta-analysis) evaluated ABI, 25 studies (including 1 large IPD meta-analysis) evaluated hsCRP, and 19 studies evaluated CAC (**Table 9**). This body of evidence answers two related yet distinct questions: 1) studies using the published coefficients answer "what is the added predictive value of assessing ABI, hsCRP, or CAC after using a traditional risk assessment tool like the FRS (recommended by ATP III) or the PCE (recommended by the ACC/AHA)?" and 2) model development studies answer "what is the incremental predictive value of adding a nontraditional risk factor to traditional CVD risk factors when developing a risk prediction tool?" Only four studies evaluated ABI, hsCRP, and/or CAC in addition to the PCE;[89, 90, 111, 112] most used a base model of the FRS. The vast majority of the included studies are model development studies (as opposed to studies using published coefficients) without external validation.

Overall, while good measures of calibration are not well reported in this body of literature, it appears that all three nontraditional risk factors can improve calibration of CHD or CVD risk prediction when added to the FRS or PCE; the magnitude and clinical impact of this improvement is not certain. Calibration plots and O:E ratio are preferable because of their ease of interpretation and ability to indicate direction of miscalibration, but are rarely reported.

Discrimination and reclassification are commonly reported. The improvement in discrimination, in large part, is dependent on the underlying performance of the base model, such that if the FRS or PCE has poor discrimination, the improvement in discrimination by adding ABI, hsCRP, and/or CAC is larger. Two included studies recalibrated the FRS or PCE to the analyzed population;[90, 91] because this will improve the base model discrimination, estimates of improvement in with the addition of a nontraditional risk factor will be conservative (i.e., underestimate the change in discrimination with the addition of a nontraditional risk factor to a non-recalibrated based model). Changes in discrimination were most often less than 0.025 for ABI and hsCRP, and it is difficult to interpret the clinical impact of very small or small improvements in AUC or c-statistic. Measures of reclassification may be more clinically intuitive, but there are limitations in its interpretation; the most common measure of reclassification reported in this literature is the total NRI. Total NRI is the sum of event and nonevent NRI and is not weighted by the prevalence of events and nonevents. Because nonevents are substantially more common, the total NRI may overstate the improvement in reclassification.

ABI

Based on one large IPD meta-analysis by the ABI Collaboration that includes 18 different cohorts, ABI can lead to potentially meaningful improvements in discrimination (c-statistic change >0.1) and reclassification (NRI >0.09) in women to predict hard CHD events when added to the FRS using published coefficients. The incremental improvement in c-statistic and NRI for women is most likely due to the poorer discrimination of the base model in women, compared to men; in other words, ABI is not inherently superior in women than in men, but is compensating for the poorer performance of the FRS in women than in men. Examination of separate components of the NRI (event and nonevent NRI) suggests that improvement in reclassification comes from women who had events being appropriately reclassified as having a higher risk; in contrast, women who did not have a cardiovascular event (which is the majority of the population) were inappropriately reclassified as having a higher risk (i.e., a negative nonevent NRI). In the model development analyses conducted by the ABI Collaboration, the discrimination for the base model was higher in women compared to men (the opposite of what was observed using published coefficients), and subsequently, the improvement in discrimination and reclassification (observed using published coefficients) was not observed (i.e., no statistically significant change in discrimination or NRI). Based on this IPD meta-analysis, ABI appears to be most promising for women at intermediate risk (10-19% 10-year risk for hard CHD outcomes) with an NRI of 0.288 (95% CI, 0.064 to 0.513). However, the ABI Collaboration analyses were restricted to Whites only.

hsCRP

Results for hsCRP are less consistent, and while hsCRP can improve discrimination and risk reclassification, the improvements are small at best. Studies using published coefficients for the FRS demonstrate that hsCRP can improve discrimination, but results are not consistent, and the higher estimates of improvement in discrimination, which are small (0.03), likely represent an upper bound of improvement. Based on one large IPD meta-analysis, a model development study, by the Emerging Risk Factors Collaboration that included 38 different cohorts, hsCRP had a very small improvement on discrimination to predict hard CHD (0.005) or CVD (0.004) events. Correspondingly, the improvement in NRI is 0.015 (95% CI, 0.008 to 0.023). Sex-stratified analyses suggest that improvement in discrimination and reclassification may be better for men than women.

CAC

CAC has the smallest body of evidence, owing to the smaller sample sizes of included cohorts; no IPD meta-analysis presents results for the incremental predictive value of CAC. Nonetheless, CAC consistently appears to result in at least small, and often larger, improvements in discrimination in studies evaluating hard outcomes in all participants using published coefficients (0.02 to 0.102) and model development studies (0.02 to 0.05). Five studies report improvement in discrimination and reclassification from adding CAC to the PCE or models with PCE variables: three published coefficient studies evaluating just two cohorts and two model development studies. Categorical NRI from model development studies in all participants ranged from 0.14 to 0.319 (continuous NRI ranged from 0.20 to 0.28); evaluation of separate

components of the NRI shows that improvements in NRI are consistently driven by event NRIs much larger than nonevent NRIs, which were commonly negative (when reported), and sometimes statistically significant. A limited number of studies report sex-stratified analyses; however, without IPD meta-analyses, it is unclear if there are any consistent sex differences in discrimination or reclassification. The bias-corrected NRI_{INT} was not consistently reported or calculable. Based on limited data, the bias-corrected NRI_{INT} is not consistently greater than the NRI for all participants.

Direct Comparisons of ABI, hsCRP, and CAC

Nine studies evaluate more than one nontraditional risk factor and therefore allow for more direct comparison across ABI, hsCRP, and CAC (**Table 10**). Overall, CAC appears to be the most promising nontraditional risk factor to add to traditional cardiovascular risk factor assessment. Only two studies using published coefficients evaluated multiple nontraditional risk factors; one evaluated both the PCE and FRS. This study, using the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, found no improvement in discrimination or reclassification for ABI and hsCRP, but the study was limited to lower-risk people because participants taking a statin were excluded from the analyses. However, in this study, CAC did improve both discrimination and reclassification. The other published coefficient analysis using the Heinz Nixdorf Recall cohort evaluated both ABI and CAC added to the FRS and similarly found greater improvement for CAC than ABI. Six model development studies evaluated more than one nontraditional risk factor in addition to the FRS to predict hard CHD or soft CVD events. Five of these six studies included CAC and found statistically significant improvements in discrimination and reclassification; these improvements were greater than effects seen for either ABI and/or hsCRP.

Detailed Results for ABI

Description of Cohorts

We included 10 unique studies, including one IPD meta-analysis that examined whether ABI added to traditional CVD risk assessment could improve calibration, discrimination, or risk reclassification (**Tables 11** and **12**).[66, 79-82, 90, 91, 95] These 10 studies include data from 22 different cohorts (**Table 11**). The included IPD meta-analysis[66] is an updated analysis from the ABI Collaboration's prior analyses in 2008.[125] This IPD meta-analysis includes 18 of the 22 cohorts (Heinz Nixdorf Recall, MESA, Nijmegen Biomedical Study, and REGICOR populations are not included).

In total, 12 models were evaluated (**Table 13**). Four studies evaluated five different models employing published coefficients of the PCE or FRS.[66, 90, 91, 114] Seven model development studies used FRS variables.[66, 75, 79-82, 95] Generally, the intended outcome of interest for the FRS is CHD hard outcomes (e.g., ATP III) or soft CVD outcomes (e.g., D'Agostino 2008), and for the PCE, CVD hard outcomes. Two cohorts (Nijmegen and REGICOR) report soft, as opposed to hard, CVD outcomes.[91, 95] One analysis of the MESA cohort focusing exclusively on intermediate-risk people also reported only soft CHD and CVD outcomes.[75]

In general, study cohorts were sufficiently large (adequate number of outcome events accrued)

and representative of the general population for whom CVD risk assessment would be applicable. Analyzed cohorts range from approximately 1,000 to 11,000 people; the ABI Collaboration IPD meta-analysis includes over 44,000 individuals. Studies have a median of at least 5 years of followup, except the Nijmegen Biomedical Study (n=1,242), which has both short followup (3.8 years) and fewer than 100 outcome events observed.[95] Cohorts include a mix of men and women, with a mean age ranging from 53.7 to 73.5 years. The ARIC cohort analysis excluded individuals with known diabetes.[79] Only MESA, ARIC, and the Health, Aging, and Body Composition Study (Health ABC), all conducted in the United States, reported any racial/ethnic diversity.[79, 81, 90] All of the cohorts except Nijmegen and ARIC included diabetes as a variable in the risk prediction model.[95] Only MESA and ARIC included race/ethnicity as a variable in the risk prediction model.[79, 90] In the most recent analyses from the MESA cohort, people already taking statins (approximately a quarter of the population) were removed from the analysis.[90]

Most studies reported excluding or are assumed to have excluded people with missing data (e.g., for ABI or other CVD risk factors). Five studies handled ABI as a categorical variable in the model, four studies handled ABI continuously, and one study evaluated ABI both categorically and continuously. When ABI was handled categorically, a threshold of ≤0.9 was considered abnormal. Treatment of continuous risk predictors as dichotomous or categorical variables results in loss of statistical power. However, because ABI has a well-established cut-point in clinical practice, treating it as a categorical variable is a pragmatic approach; preserving the continuous form (including more complex nonlinear relations) addresses a more explanatory question.[126]

Most studies were fair quality. Limitations of included studies are described above. Fair-quality, as opposed to good-quality, studies had less than 10 years of followup to predict 10-year CHD or CVD risk, had fewer than 20 outcome events per variable, did not report any calibration or goodness-of-fit measures, and/or did not report confidence intervals or statistical significance of changes in measures of discrimination or risk reclassification; additionally, published coefficient models did not conduct recalibration. The IPD meta-analysis by the ABI Collaboration was a well-conducted analysis and represents the best evidence to address this key question; however, it was rated as fair quality because many of the cohorts had less than 10 years of followup and the model was not recalibrated to the population analyzed which may result in overly optimistic results.

Model Performance (Calibration, Discrimination, Risk Reclassification)

For model performance, we will first discuss results of calibration, then discrimination, and finally risk reclassification. Of the 10 studies (22 cohorts) included, 5 articles (20 cohorts) reported some measure of calibration, all articles and cohorts reported discrimination, and 9 articles (22 cohorts) reported risk reclassification (**Table 9**). To guide the reader, each section is formatted similarly with a discussion of results from models using the published coefficients first, then model development studies. Because this body of evidence includes a single, large IPD meta-analysis from the ABI Collaboration, which includes 18 different cohorts, we discuss findings from the ABI Collaboration as the central piece of evidence, and discuss other studies of individual cohorts in relation to the ABI Collaboration findings if these studies provide

additional insight.

Calibration

In general, we have very limited information to assess the change in calibration from the addition of ABI to a base model consisting of the FRS or PCE, or a model using similar traditional risk factors (**Table 14**). None of the included studies reported graphical measures of calibration. Five of the 10 studies reported the Hosmer-Lemeshow test or measures of overall performance, which are integrated measures of both calibration and discrimination.[66, 95] None of the included studies reported the O:E ratio or provided sufficient data for us to calculate the change in O:E ratio. From limited reported data on calibration, it appears ABI can improve upon the calibration of the FRS. The only study using the PCE as the base model did not report on calibration.[90]

Published coefficient models. The ABI Collaboration, which used published coefficients, reported the overall performance measures of R^2, Akaike information criterion (AIC), and Bayes information criterion (BIC). All three measures suggest that the ABI can improve the overall performance of the FRS in both men and women (**Table 14**). Reductions in AIC greater than 10 indicate important differences in model fit;[84] however, the clinical importance of these changes is uncertain. The REGICOR study, not included in the ABI Collaboration, which also used published coefficients of the FRS, only reported the AIC and found improvements in all participants (sex-specific analyses not reported) to predict both soft CHD and CVD outcomes, in contrast to hard CHD outcomes in the ABI Collaboration.

Model development. Three model development studies, one cohort of which was not included in the ABI Collaboration, reported some measure of calibration or overall performance. The Nijmegen Biomedical Study, not included in the ABI Collaboration, had a total of only 71 soft CVD events over an average of 3.8 years.[95] While the Hosmer-Lemeshow test suggests a decrement in calibration by adding the ABI to FRS variables in women, this is likely a result of sparse data bias.[127] In addition, the R^2 statistic for this same comparison in women suggests an improvement in calibration and discrimination with the addition of ABI to a base model including FRS variables. Overall, the BIC and Hosmer-Lemeshow test in the Health ABC study do not suggest an improvement with the addition of ABI to an FRS base model to predict hard CHD outcomes. The Rotterdam study conducted sex-specific analyses and demonstrated that while the addition of ABI to a base model of FRS variables improved the overall model performance for predicting hard CHD outcomes, as measured by the likelihood ratio test, this appears to be true for men but not women. Since this is an integrated measure, we cannot determine whether calibration, discrimination, or both are improved in the absence of other measures, which are not reported.

Discrimination

All of the included studies reported measures of discrimination (i.e., AUC, c-statistic) by adding ABI to traditional cardiovascular risk assessment (**Table 15**). Only one study evaluated the addition of ABI to the PCE and this study did not show improved discrimination;[90] however, this cohort excluded people already taking statins, and over 80 percent of the population had 10-year hard CVD risk of 7.5 percent or less. Additionally, this analysis recalibrated the PCE to the

MESA population which would render a conservative estimate of change in discrimination in the extended model. The IPD meta-analysis by the ABI Collaboration demonstrated that improvement in discrimination with the addition of ABI was higher for women than for men. This difference between men and women is likely due to the poorer performance of the FRS in women compared to men. Studies in cohorts not represented in the IPD meta-analyses mostly do not present sex-stratified analyses. In the one study not included in the ABI Collaboration that reported sex-stratified analyses, the Nijmegen Biomedical cohort, findings of improvement in discrimination for women were not statistically significant, likely owing to lack of power.

Published coefficient models. The ABI Collaboration, which used published coefficients for the FRS, presented only sex-stratified analyses, and the base model discrimination was lower in women (0.578) than in men (0.672).[66] This study demonstrated a large improvement in discrimination with the addition of ABI in women (but not men) to predict hard CHD outcomes (0.112); although statistical significance is not reported, the 95% CI of the base model does not include the point estimate of the extended model (however, 95% CI of base and extended models do overlap). MESA, REGICOR, and Heinz Nixdorf Recall did not report discrimination separately for men and women; the overall change in discrimination in these three studies was very small (-0.006 to 0.01), with borderline or no statistical significance.[90, 91, 114] One study, conducted in the MESA cohort, reported a base model discrimination of 0.74 for both the PCE and FRS. This study demonstrated a very small improvement in discrimination with the addition of ABI to the FRS to predict hard CHD outcomes (0.010, p=0.042); in contrast, results were not statistically significant with the addition of ABI to the PCE to predict hard CVD outcomes (0.010, p=0.55). In one study, REGICOR, the base model discrimination for the FRS was good (0.787 for soft CVD, 0.795 for soft CHD), such that there was only very small improvement in discrimination with the addition of ABI to predict soft CVD (0.008, p=0.049) but not soft CHD outcomes.

Model development. The ABI Collaboration also conducted model development analyses. For these sex-stratified analyses, the discrimination for the base model was higher than analyses using published coefficients, and higher in women (0.788) than in men (0.683). In these analyses, the incremental benefit of adding ABI to FRS variables to predict hard CHD outcomes is very small (0.003 for women and 0.007 for men); although statistical significance is not reported, the 95% CI of the base model includes the point estimates for the extended models. Results from individual model development studies of cohorts included in the ABI Collaboration (ARIC, EAS, Rotterdam, and Health ABC) were consistent with the ABI Collaboration's findings of very small to small improvements in discrimination.[79-82] The Nijmegen Biomedical Study, not included in the ABI Collaboration, had both limited followup and a limited number of soft CVD events.[95] Sex-stratified analyses showed lower base model discrimination in women (0.691) than in men (0.748). This study reported a small but not statistically significant improvement in discrimination in women (0.036, p=0.26) but not men (data NR). An analysis of the MESA cohort, also not included in the ABI Collaboration and restricted to intermediate-risk people (5-20% 10-year risk of soft CVD outcomes), found a small improvement (0.027, p=0.01).

Risk Reclassification

All but one of the included studies reported NRI plus or minus IDI (**Table 16; Appendix E**

Table 1). Studies used different definitions of low, intermediate, and high CHD or CVD risk categories and one study reported a continuous NRI.[114] Overall, and based primarily on the ABI Collaboration IPD meta-analysis, the addition of the ABI to the FRS can improve reclassification; NRI are at best less than 0.1 and are usually much smaller and often nonsignificant. Consistent with findings on changes in discrimination, the effect of ABI on reclassification appears to be larger for women than men. However, the nonevent NRI in women was negative, suggesting incorrect upward reclassification of risk in women who did not have a CHD event. Considering that the vast majority of women did not have events (92.9%), the overall NRI measure may overstate the improvement in reclassification.[67] Based on data from a single cohort (MESA) using a PCE base model, ABI does not appear to result in statistically significant change in reclassification to detect hard CVD outcomes in people not already taking statins. Four studies, including the ABI Collaboration, allow for bias-corrected calculation of NRI for the intermediate-risk group. The most promising results appear to be for adding ABI in women at intermediate risk for developing hard CHD events (10-19% over 10 years).

Published coefficient models. The ABI Collaboration, using published coefficients for the FRS, demonstrated an improvement in reclassification with the addition of ABI in women to predict hard CHD outcomes, but not in men as confidence intervals included 0. The ABI Collaboration used 10-year risk thresholds of <10 percent for low, 10-19 percent for intermediate, and ≥20 percent for high risk of hard CHD outcomes. NRI for ABI in addition to the FRS in women was 0.096 (95% CI, 0.061 to 0.164), and the bias-corrected NRI_{INT} in women was 0.288 (95% CI, 0.064 to 0.513). The overall NRI is largely driven by reclassification upward of those having events (event NRI: 0.145 [95% CI, 0.101 to 0.189]), but this represents the minority of the population as only 7.1 percent of women experienced a hard CHD event. Of note, the nonevent NRI was negative and statistically significant (-0.051 [95% CI, -0.059 to -0.043]). MESA, REGICOR, and Heinz Nixdorf Recall, not included in the ABI Collaboration, did not report sex-stratified analyses. MESA, employing published coefficients, found no change in NRI when ABI was added to the FRS in analyses employing the same risk categories as the ABI Collaboration, and no change in NRI when ABI was added to the PCE in analyses using a threshold of ≥7.5% 10-year risk for hard CVD outcomes. REGICOR, using published coefficients for the FRS, employed categories of low (<5%), intermediate (5-10%), and high (≥10%) 10-year risk for either soft CHD or CVD outcomes. NRI for soft CVD outcomes was 0.029 (95% CI, 0.014 to 0.045) in all people and the bias-corrected NRI_{INT} was 0.061 (95% CI, 0.024 to 0.098); NRI for soft CHD outcomes was not statistically significant. REGICOR also reported IDI as a measure of reclassification for adding ABI; the magnitude and statistical significance of improvement was generally consistent with findings using NRI (**Appendix E Table 1**). Analyses of the Heinz Nixdorf Recall cohort using a published coefficient FRS base model found a statistically significant improvement in NRI when ABI was added to the model; however, a continuous NRI was reported, which is not comparable in scale to categorical NRIs reported in other studies (0.190 [95% CI, 0.102 to 0.278]).[114] Subgroup analyses by risk group showed statistically significant NRI only in the intermediate (10-20% 10-year risk) and high (>20% 10-year risk) risk groups.

Model development. The ABI Collaboration also conducted model development analyses; in these analyses, adding ABI to FRS variables did not improve risk reclassification in men or women. We were not able to calculate bias-corrected NRI_{INT}; however, uncorrected NRI_{INT} were

not statistically significant. Results from individual model development studies of cohorts included in the ABI Collaboration (ARIC, Rotterdam, and Health ABC) did not report sex-stratified analyses and found no statistically significant risk reclassification with the addition of ABI to FRS variables to predict hard CHD or CVD outcomes. The Nijmegen Biomedical Study found an improvement in reclassification (NRI 0.159, p=0.056) for women but not men for soft (and not hard) CVD outcomes. This study was not included in the ABI Collaboration but used similar risk categories; followup and number of events were limited. The Nijmegen Biomedical Study also reported IDI as a measure of reclassification; the IDI for addition of ABI to FRS variables in women was not statistically significant (**Appendix E Table 1**). An analysis of the MESA cohort, also not included in the ABI Collaboration, demonstrated an improvement in reclassification with ABI for intermediate-risk people (5-20% 10-year risk of soft CVD outcomes). However, this study did not report bias-corrected NRI_{INT} (and data were not sufficient to calculate) nor statistical significance.

Detailed Results for hsCRP

Description of Cohorts

We included 25 unique studies, including one IPD meta-analysis, that examined whether hsCRP added to traditional CVD risk assessment could improve calibration, discrimination, or risk reclassification (**Tables 17** and **18**).[65, 75, 76, 78, 81-85, 87, 90, 92, 96-100, 102-105, 107-110] These 26 studies include data from 49 different cohorts, and the included IPD meta-analysis[65] includes 38 of the 49 cohorts (**Table 17**). The 11 cohorts not represented in the IPD meta-analysis are: the British Regional Heart Study,[102] EISNER,[99] the Framingham Heart Study (original cohort),[85] Health ABC,[81] Heinz Nixdorf Recall,[103] Inter99,[92] MONItoring of trends and determinants in Cardiovascular disease (MONICA) Copenhagen,[96] the Northwick Park Heart Study,[78] the Scottish Health Survey,[105] the Study of Health in Pomerania,[100] and the Singapore Chinese Health Study.[109]

In total, 28 models were evaluated (**Table 19**). Six studies evaluated seven models using published coefficients for the PCE or FRS. Twenty studies reported the results of 21 newly developed models based on FRS variables; 2 of these models additionally included race/ethnicity as a predictor.[75, 110] Fifteen models predicted CVD outcomes, and 13 predicted CHD. Seventeen models predicted hard outcomes (CVD or CHD), 10 models predicted soft outcomes (CVD or CHD), and 1 model predicted fatal CVD outcomes only.

In general, study cohorts were sufficiently large, with an adequate number of outcome events accrued and reflective of the general population for whom CVD risk assessment would be applicable. Analyzed cohorts ranged from approximately 1,000 to nearly 27,000 participants; the Emerging Risk Factors Collaboration IPD meta-analysis included 166,596 individuals. Most populations were from prospective, population-based cohort studies, including one case-cohort analysis[110] and three nested case-control analyses.[87, 104, 109] Additionally, five populations consisted of randomized control trial participants; these trials evaluated CAC screening (an included study for KQ1),[99] lifestyle modification for CVD risk reduction,[92] statins,[98, 108] and aspirin.[83] The cohort from the EISNER RCT, with just 4.1 years of followup, modeled a predicted time horizon of 4 years, though only 35 events accrued.[99] Otherwise, cohorts reported

about 100 events at minimum and the Emerging Risk Factors Collaboration IPD meta-analysis reported 13,568 hard CVD events and 8,816 hard CHD events.[65]

Of the 25 studies, 4 were analyses of men only,[78, 84, 98, 102] and 2 were exclusively in women.[83, 97] Mean ages ranged from 45.5 to 75.4 years. Three studies excluded participants with diabetes;[75, 83, 109] diabetes status was not included as a variable in the respective risk prediction models, nor was it in the Reykjavik case-control analysis, where a very small proportion of participants had diabetes (2.3%).[87] The proportion of participants with diabetes in other studies ranged from 1.9 to 13.3 percent, where reported, and diabetes was included as a predictor in these models. MESA, ARIC, and Health ABC, all conducted in the United States, reported racial/ethnic diversity, of which analyses for MESA and ARIC included race/ethnicity as a variable in their risk prediction model.[75, 81, 90, 110] The analysis by Salim and colleagues[109] was conducted in a cohort of exclusively Chinese adults in Singapore. Three studies excluded participants taking statins at baseline,[90, 104, 108] and where reported, statin use ranged from 3 to 14 percent in other studies. Use of antihypertensive agents was relatively common in studies reporting it, generally about 12 to 32 percent. Aspirin use was reported in only Health ABC, a study of adults age 70 or older, which reported that 18.8 percent of this primary prevention population was taking the drug.

Mean baseline Framingham Risk Scores were sparsely reported, and the distribution of risk among low-, intermediate-, and high-risk classifications varied widely between studies. Comparisons of baseline risk across cohorts are limited by different predicted outcomes and variable followup time, but generally suggest heterogeneity. For example, 6.2 percent of the MESA cohort experienced a hard CVD event over 10 years of followup,[90] whereas the hard CVD event rate was nearly twice as high in the British Regional Heart Study of exclusively men (13.9% over 9 years of followup).[102]

Ten of 26 studies explicitly indicated that a high-sensitivity CRP assay was used; however, others reported low limits of detection consistent with hsCRP. Where reported, the threshold defining an elevated hsCRP was 3.0 mg/L, and in one case it was 2.0 mg/L.[87] In studies reporting the proportion of participants with an elevated hsCRP, about 22 to 52 percent of participants met the studies' respective definitions. Mean hsCRP levels ranged from 1.69 to 5.0 mg/L, and median hsCRP levels ranged from 0.9 to 2.3 mg/L. Most studies excluded or are assumed to have excluded people with missing data for hsCRP or traditional cardiovascular risk factors; two analyses, both from the Rotterdam cohort, used imputation.[76, 82] HsCRP was most commonly log-transformed when included in risk prediction models, owing to its frequently skewed distribution. When entered categorically in risk prediction models—as it was in five studies—thresholds were typically defined as: less than 1 mg/L, 1 to 3 mg/L, and greater than 3 mg/L. Treatment of continuous risk predictors as dichotomous or categorical variables results in loss of statistical power and compromises predictive performance.[63] However, the threshold of 2 mg/L has been used in a large randomized trial of statin therapy in participants with elevated hsCRP but normal LDL levels;[120] thus, use of a categorical form may address a more explanatory question, although most included risk prediction studies used a threshold of 3 mg/L when categorical analyses were used.

Most studies were fair quality. Limitations of studies are described above. Fair-quality as

opposed to good-quality studies had followup time equivalent to the time horizon predicted by the model, had fewer than 20 outcome events per variable, did not report any calibration or goodness-of-fit measures, and/or did not report confidence intervals or statistical significance of changes in measures of discrimination or risk reclassification; additionally, published coefficient models did not conduct any recalibration. Just two studies evaluating hsCRP had these characteristics and were therefore assessed as good quality.[81, 96] The Emerging Risk Factors Collaboration IPD meta-analysis was a well-conducted model development study and represents the best evidence to address this key question; however, it was deemed fair quality because calibration, a key domain of model performance, was not reported.[65] Additionally, many of the included cohorts had less than 10-year followup (although reclassification analyses were limited to studies reporting this duration). The Emerging Risk Factors Collaboration model has limited applicability because it is not publicly available as a calculator for clinical practice.

Model Performance (Calibration, Discrimination, Risk Reclassification)

For model performance, we will first discuss results of calibration, then discrimination, and finally risk reclassification. Of the 25 studies (49 cohorts) included, 9 articles (10 cohorts) reported some measure of calibration, all articles and cohorts reported discrimination, and 15 articles (33 cohorts) reported risk reclassification. To guide the reader, each section is formatted similarly, with a discussion of results from models using the published coefficients first, then model development studies. Because this body of evidence includes a single, large IPD meta-analysis by the Emerging Risk Factors Collaboration, which comprises 38 different cohorts, we discuss findings from the Emerging Risk Factors Collaboration as the central piece of evidence and discuss other studies of individual cohorts in relation to these IPD meta-analyses findings if these studies provide additional information/insight.

Calibration

Limited evidence from three published coefficient models, each reporting different measures, suggests that the addition of hsCRP to traditional cardiovascular risk factors can improve calibration (**Table 20**). However, calibration plots and O:E ratios are not available for these studies. More evidence is available for model development studies, although better calibration would be expected in these models because measures are evaluated in the same population from which the model was derived. Calibration plots are available for a small subset of model development studies and show that the addition of hsCRP can improve model fit in some risk groups, but may worsen it in others. Based on the included studies and limited reporting around calibration, we cannot determine when hsCRP improves calibration in some risk groups but not others. Various measures generally show improvement when models are extended to include hsCRP, with some exceptions. The Health ABC cohort of older adults showed a decrement in most measures of model fit with the addition of hsCRP to the model. Calibration measures are not reported in the Emerging Risk Factors Collaboration IPD meta-analysis. No studies evaluating the extension of hsCRP to a PCE base model, or a model including race/ethnicity, reported any measure of calibration.

Published coefficient models. Three published coefficient models reported measures of calibration or overall performance (**Table 20**).[84, 96, 104] Overall performance measures suggested

smaller (i.e., improved) differences between observed and predicted outcomes when hsCRP was added to the model, but these measures capture both calibration and discrimination.

The Hosmer-Lemeshow test, which addresses calibration more directly, was reported in just one published coefficient analysis. In this nested-case control analysis of the EPIC-Norfolk study, calibration appeared to improve with the addition of hsCRP to the model (as evaluated by an increase in p-value, and decrease in test value), when assessed in the subset of intermediate-risk participants, but the addition of hsCRP resulted in poorer fit when assessed in all analyzed participants. However, the base model itself signaled poor fit (p=0.02); the p-value for the extended model was 0.009. Results of the Hosmer-Lemeshow test are sensitive to how populations are grouped for analysis, so comparison of overall results to those of the intermediate-risk subset should be interpreted with caution. Additionally, the higher p-value in the intermediate group could occur because of a smaller sample, so it is not possible to determine whether apparent improvement is consistent with the whole cohort.

Model development studies. Two model development studies, reporting results from three cohorts, presented calibration plots, and one reported the O:E ratio (**Table 20**).[78, 83] Shah and colleagues[78] reported calibration plots and the O:E ratio by quintile of risk for their analyses of the Northwick Park Heart Study II (NPHSII) and the Edinburgh Artery Study (EAS), that had 162 and 147 events, respectively. For NPHSII, the addition of hsCRP to Framingham variables worsened the O:E ratio (i.e., moved away from 1) for the lower three quintiles of risk, and improved (i.e., got closer to 1) for the higher two quintiles of risk. Results showed a similar pattern for the EAS analysis, but the O:E ratio improved for only the highest-risk quintile, and in this group the base model was already well calibrated. For both base and extended models, there was not a consistent trend of over- or underprediction across the two studies; overprediction occurred in the middle-risk quintiles in NPHSII and in the lowest-risk quintile in EAS. However, the small number of events in these studies substantially limits the reliability of such an assessment, particularly in low-risk strata in which very few events occur. For most risk quintiles, base models were reasonably well calibrated, which is consistent with this being a model development study in which model performance is being evaluated in the same population from which it was derived.

A calibration plot is also reported for the Women's Health Study (WHS) model development study that shows predicted and observed risks for 2-percentage-point increments in predicted 10-year risk of soft CVD outcomes; O:E ratios are not reported.[83] Visual inspection of the calibration plots shows that predicted and observed risk is reasonably concordant for low- and high-risk levels but less concordant for intermediate-risk women (12 to 18%), with predicted risk being higher than observed risk. Within this intermediate-risk group, the addition of hsCRP to the WHS model had little impact for the 12- to 13-percent risk increment, markedly improved calibration in the 14- to 15-percent risk increment, and worsened in calibration in the 16- to 17-percent risk increment. In the WHS analysis, the Hosmer-Lemeshow test, R^2, and Brier score all showed improvement in model fit when hsCRP was added to base models.

In most studies, overall performance measures generally suggested improvement when hsCRP was added to models.[78, 81-83, 108] The calibration-specific Hosmer-Lemeshow test suggested that the addition of hsCRP to the base model of traditional cardiovascular disease risk factors

worsened model fit in the Health ABC study; the AIC and BIC measures of overall performance were consistent with this finding.[81] Of note, multivariate-adjusted associations of hsCRP with soft CHD events were not statistically significant in this study. The Health ABC cohort is an intermediate- to high-risk cohort, with a mean FRS of 16.6 percent and average age of over 73. Hosmer-Lemeshow test results in other studies were mixed. In analyses by Shah and colleagues,[78] the Hosmer-Lemeshow test showed no change in the EAS with the addition of hsCRP to the base model and a small improvement in the NPHSII.

Discrimination

All of the included studies reported change in discrimination (i.e., AUC or c-statistic) by adding hsCRP to traditional cardiovascular risk assessment (**Table 21**). The discrimination of base models using traditional cardiovascular risk factors ranged widely in both published coefficient models and model development studies, from 0.58 to 0.898 collectively. The addition of hsCRP to published coefficient models showed mixed results, ranging from no change in discrimination in recalibrated models evaluating the PCE and FRS to small improvement in discrimination (0.03), although higher estimates likely represent an upper bound owing to study design limitations. For model development studies, the most expansive evidence comes from the Emerging Risk Factors Collaboration IPD meta-analysis, which found very small but statistically significant improvement in discrimination for hard CVD (0.0039) and for hard CHD (0.0051); interaction testing in exploratory analyses provides some evidence that men achieve a greater predictive improvement than women, but these changes are nonetheless very small. Evidence from the nine model-development studies of cohorts not included in the IPD meta-analysis were also inconsistent, although comparisons are limited by sparse reporting of statistical significance and confidence intervals. At best, improvement in discrimination from the addition of hsCRP to traditional cardiovascular risk assessment is small and more likely to occur in the context of a poorly discriminating base model, but the clinical meaning of these small changes in discrimination is unknown.

Published coefficient models. The one published coefficient model evaluating the addition of hsCRP to the PCE had a base model discrimination of 0.74.[90] Base model discrimination in published coefficient models for the FRS ranged from 0.59 to 0.777.[105] The one published coefficient model evaluating the addition of hsCRP to the PCE in the multiethnic MESA cohort showed no change in discrimination when hsCRP was added; this model was recalibrated to the local population.[90] Similarly, when hsCRP was added to a recalibrated FRS base model in the MESA population, no change in discrimination was detected. Of note, participants taking statins were excluded in this analysis; therefore, about 95 percent of the population was at low risk, defined as 10-year CHD risk of 10 percent or less. In other studies using a published coefficient FRS as a base model, the change in c-statistic showed mixed results. The largest improvements occurred in the EPIC-Norfolk case-control analysis (0.03 [95% CI, 0.01 to 0.05])[104] and MONICA-Augsburg (0.027, p=0.0077).[84] Because of study design considerations, these could be considered upper bounds of change in discrimination. The case-control design of the EPIC-Norfolk analysis likely reduced the base model c-statistics (because of reduced variation from the process and matching for sex and age), and thus likely overstated the change from the addition of hsCRP to the model.[128] The MONICA-Augsburg analysis entered the FRS categorically instead of continuously in prediction models, which will underestimate the

prognostic value of the FRS and overestimate the value of hsCRP. [63]

The MONICA-Copenhagen analysis showed a very small but statistically significant improvement in discrimination of 0.012 (p=0.037) in men, but improvement was not statistically significant in women (0.007, p=0.262).[96] An analysis of only women from the Framingham Offspring Study showed similar results.[97] An analysis from the Scottish Health Survey showed that the addition of hsCRP to published coefficient FRS base models resulted in very small improvements in discrimination for all outcomes evaluated, ranging from 0.002 to 0.004, but neither statistical significance nor confidence intervals were reported. Two studies reported discrimination for intermediate-risk subgroups, both defined by 10-year CHD risk of 10 to 20 percent.[97, 104] In both studies, the statistical significance of results in intermediate-risk groups were concordant with that of the overall population in the study (i.e., significant for EPIC-Norfolk in the context of a poorly discriminating base model and not significant in women from the Framingham Offspring cohort), but showed a markedly larger change in c-statistic.

Model development studies. Similar to published coefficient models, base model discrimination in model development studies showed a wide range. In the Emerging Risk Factors Collaboration IPD meta-analysis, which involved 166,596 participants and 13,568 hard CVD events, base model discrimination was 0.714.[65] In other model development studies, discrimination ranged from 0.58 to 0.863 in models predicting hard CHD or hard CVD.

In the Emerging Risk Factors Collaboration IPD meta-analysis models, the addition of hsCRP to the base model increased discrimination by 0.0039 (95% CI, 0.0028 to 0.0050) for hard CVD and by 0.0051 (95% CI, 0.0035 to 0.0066) for hard CHD. Exploratory subgroup analyses suggest effect modification by sex, where the improvement in discrimination of hsCRP is greater in men than women. This analysis showed a very small, statistically significant improvement in men and no change in women; the p-value for heterogeneity was less than 0.001. Analyses by diabetes status suggested no effect modification, and analyses by 10-year risk for CVD suggested that the intermediate-risk group (defined as 10-20% 10-year risk) may have a larger change in the c-statistic when compared with the low-risk group (less than 10% 10-year risk), but confidence intervals overlapped.

Of the 11 cohorts not represented in the Emerging Risk Factors Collaboration IPD meta-analysis, 9 were model development studies.[78, 81, 85, 92, 99, 100, 102, 103, 109] Changes in discrimination in these studies ranged from -0.008 for a model predicting hard CHD in the Health ABC study of older adults[81] to 0.04 for hard CHD in the Northwick Park Heart Study, which exclusively recruited men.[78] Statistical significance or confidence intervals were rarely reported; when they were, no improvements in discrimination were statistically significant. Concordant with findings from the IPD meta-analysis, a nested case-control study from the Singapore Chinese Health Study suggested that the improvement in discrimination from the addition of hsCRP to risk prediction models was larger in men (but still very small) than women (0.01 vs 0.002); however, confidence intervals for change in c-statistic were not reported.[109] The base model had poorer initial discrimination in men than women (0.679 vs 0.778), allowing for more opportunity for improvement. Yeboah and colleagues[75] evaluated a subset of intermediate-risk participants from MESA (defined as those between 5 and 20% 10-year CHD risk) and found a very small, statistically significant improvement in discrimination for both soft CVD and soft CHD

outcomes (0.017; p=0.03); base model discrimination was 0.623.

Risk Reclassification

Fifteen of 25 studies evaluated reclassification from hsCRP when added to traditional cardiovascular risk factors, encompassing data from 33 cohorts (22 of which were represented in the Emerging Risk Factors Collaboration IPD meta-analysis) (**Table 22**). One study addressed the addition of hsCRP to a recalibrated PCE, which used a risk threshold of 7.5 percent or greater 10-year risk for hard CVD; this study showed no statistically significant reclassification. In FRS-based models, low risk was typically defined as less than 10 percent 10-year risk for a CVD or CHD event, although was sometimes defined as less than 6 percent. Intermediate risk was generally defined as 10 to 15 percent, or 10 to 20 percent 10-year risk, although it sometimes had a lower bound of 6 percent. High risk was usually defined as greater than 20 percent 10-year risk, and sometimes greater than 15 percent. The one PCE-based analysis used a risk threshold of 7.5 percent or greater 1-year risk for a hard CVD event. Findings for NRI were somewhat inconsistent. The Emerging Risk Factors Collaboration IPD meta-analysis represents the most expansive evidence and showed an NRI no greater than 0.02. The IPD meta-analysis and several smaller studies suggest that improvement in risk reclassification occurs in men but not women, and is driven by improvement in those having events being reclassified to higher-risk categories. When a bias-corrected NRI_{INT} could be calculated, NRI_{INT} were usually slightly higher than the NRI for overall population, and statistical significance was sometimes maintained.

Published coefficient models. Three published coefficient studies evaluating four models offer inconsistent evidence about the added value of hsCRP to improve reclassification of risk compared to the FRS or PCE. The published coefficient analyses of recalibrated PCE and FRS models by Yeboah and colleagues[90] showed no statistically significant improvement in NRI for either model (PCE: 0.024 [95% CI, -0.015 to 0.067], FRS: 0.003 [95% CI, -0.028 to 0.026]). We calculated a bias-corrected NRI_{INT} for the FRS intermediate-risk group, which similarly showed no significant improvement. Similar to findings for discrimination outcomes in MONICA-Copenhagen, men achieved a statistically significant improvement in continuous NRI, whereas women did not (men: 0.308 [95% CI, 0.081 to 0.534]; women: -0.083 [95% CI, -0.354 to 0.189]).[96] Continuous NRI should not be directly compared to NRI using defined risk strata. The case-control analysis of the EPIC-Norfolk study suggests that hsCRP can reclassify individuals (NRI 0.120) but did not report statistical significance or confidence intervals.[104] IDI was reported only in the MONICA-Copenhagen analysis, and the sex-specific findings of improvement in men but not women were consistent (**Appendix E Table 2**).

While two studies using published coefficients report NRI for individuals at intermediate risk for CHD or CVD events, one study did not allow for calculation of a bias-corrected NRI_{INT} (and did not report statistical significance),[104] and the other study found nonstatistically significant results. However, this study had only 27 hard CHD events in the intermediate-risk group.[90]

Model development. The Emerging Risk Factors Collaboration IPD meta-analysis calculated NRI in 22 of 38 included cohorts that had 10 or more years of followup and that reported data for both fatal and nonfatal CVD events.[65] The overall NRI was 0.0152 (95% CI, 0.0078 to 0.0227) and was driven by improvement in event NRI (0.0146 [95% CI, 0.0073 to 0.0219]). Sex-specific

analyses were conducted in 15 studies that included both men and women, and provide some confirmatory evidence for the MONICA-Copenhagen published coefficient study showing that the benefit in risk reclassification from the addition of hsCRP accrues in men but not in women. In the IPD meta-analysis, the NRI for men was 0.0124 (95% CI, -0.0020 to 0.0269) and for women was 0.0036 (95% CI, -0.0070 to 0.0142); neither result was statistically significant and subgroup analyses were exploratory (no formal interaction testing was reported).

Additional reclassification data are available from nine model development studies in cohorts not analyzed in the Emerging Risk Factors Collaboration analyses of NRI (cohorts included in IPD MA analyses of reclassification are a subset of included cohorts, restricted to those with greater than 10 years of followup and recording both fatal and nonfatal events).[75, 78, 92, 98, 100, 102, 103, 107, 109] Overall, these studies had mixed findings. The smallest NRI of 0.010 (95% CI, 0.002 to 0.018) was from a two-category analysis with a risk threshold of 20 percent or greater, reported in a primary prevention subgroup of exclusively men from a statin RCT.[98] The largest reclassification, NRI 0.1177 (95% CI, 0.030 to 0.205), was seen in an analysis of the Framingham Offspring cohort of which 82.5 percent of the population were low risk (defined as less than 6% 10-year risk).[107] The Health ABC cohort of older adults evaluated the additional predictive value of hsCRP added to traditional risk factors, but reclassification was not reported because hsCRP was not statistically significantly associated with soft CHD events after adjustment for traditional cardiovascular risk factors.[81] The case-control analysis from the Singapore Chinese Health Study is concordant with findings from the Emerging Risk Factors Collaboration IPD meta-analysis in that event NRI was substantially larger than nonevent NRI, and that reclassification improved significantly in men, but not women.[109] One study, NHPSII, had a statistically significant negative nonevent NRI (-0.008 [95% CI, -0.014 to -0.001), meaning that more participants not having events were reclassified inappropriately upward; this analysis is based on a 10-year risk threshold of 15 percent.[78] We explored whether results varied by predicted outcome, definitions of risk strata, or case mix. These variables did not appear to explain differences in across studies; however, such comparisons are limited by several concurrent sources of heterogeneity. Four model development studies reported IDI (**Appendix E Table 2**). The IDI was statistically significant in 2 of 4 studies, and where significant, was no greater than 0.02.

NRI_{INT} is available in six model development studies, including the Emerging Risk Factors Collaboration IPD meta-analysis. In the IPD meta-analysis, a bias-corrected NRI_{INT} was slightly larger than for the overall population and retained statistical significance: NRI_{INT} 0.027 (95% CI, 0.007 to 0.047) and NRI 0.0152 (95% CI, 0.0078 to 0.0227).[65] Other model development studies where a bias correction could be performed showed larger NRI_{INT} than in the Emerging Risk Factors Collaboration IPD meta-analysis, and larger reclassification when evaluated to the overall population in each respective study: NRI_{INT} for hard events ranged from 0.076 to 0.130.[78, 102, 107] Statistical significance was only maintained in some studies, likely due to greatly reduced power when evaluating a smaller subset of participants. The NRI_{INT} in the Rotterdam study could not be bias-corrected based on reported information.

Detailed Results for CAC

Description of Cohorts

We included 19 unique studies that examined whether CAC added to traditional CVD risk assessment could improve calibration, discrimination, or risk reclassification (**Table 23**). These studies include data from 10 different cohorts. In total, 24 different models were evaluated (**Table 24**). Six studies evaluated eight different models using published coefficients for the PCE or FRS. Thirteen studies reported the results of newly developed models based on FRS variables (three studies using the MESA cohort evaluated models which included race/ethnicity as a predictor[77, 101, 113]), and two studies reported the results of newly developed models based on PCE variables. Ten models predicted CVD outcomes and 17 predicted CHD. Sixteen models predicted hard outcomes (CVD or CHD), 7 models predicted soft outcomes (CVD or CHD), and 1 model predicted only fatal CVD outcomes.

Study cohorts were generally smaller than those contributing to the ABI and hsCRP evidence base, and no IPD meta-analysis was available. Analyzed cohorts ranged from 946 to 7,772 participants. Seven of the cohorts represented were prospective population-based cohorts (MESA, Heinz-Nixdorf Recall, Framingham Offspring Study, Framingham 3rd Generation, Dallas Heart Study, Rotterdam, South Bay Heart Watch), and the other three were derived from randomized control trial participants (EISNER) or selective samples of asymptomatic people getting a CAC scan (Houston Methodist DeBakey Heart and Vascular Center, Cardiac Research Database). With the exception of analyses from the MESA cohort,[90, 113] Heinz Nixdorf Recall,[114] and a pooled analysis of five cohorts of low-risk women,[111] all studies had less than 10 years of followup. With the exception of the MESA, Rotterdam, and Heinz Nixdorf Recall cohorts, studies had fewer than 100 hard CHD or CVD events. The studies using a cohort from the EISNER RCT had a very limited number of events (35 soft CVD events and 47 soft CVD events [EISNER RCT supplemented by a Cardiac Research Database]). Studies included a mix of both men and women, with a mean age ranging from 50 to 69.5 years. Only two cohorts (South Bay Heart Watch, MESA) reported including any non-White participants. Two studies (South Bay Heart Watch,[86] MESA[77]) explicitly excluded participants with diabetes. One study using the MESA cohort included only participants with diabetes.[94] All but three of the models included diabetes as a variable in the risk prediction model, if individuals with diabetes were included in the cohorts.[74, 101, 106] In one analysis from the MESA cohort, people already taking statins (approximately a quarter of the population) were removed from the analysis; therefore, about 81 percent of the included participants had a less than 7.5 percent 10-year risk for a hard CVD event.[90] Otherwise, when reported, cohorts typically included a more even distribution of CHD/CVD risk, but notably, a 2016 analysis by Kavousi and colleagues pooled low-risk women from 5 population-based cohorts.[111] Differences in definitions of risk strata and type of CHD or CVD event being predicted limits direct comparison across studies and cohorts.

We did not include studies in which the CAC score was derived from CT angiography. In the included studies, there was some variation in how CAC scores were obtained. Studies either used electron beam or multidetector CT (EBCT or multidetector computer tomography [MDCT]) with varying protocols. In some instances in which EBCT is used, the protocol specified electrocardiograph (ECG)-gated EBCT. Estimated radiation exposure from CT imaging is

discussed in the harms of screening section (KQ3). A CAC score (also referred to as Agatston score) is calculated based on a person's age, sex, and sum of coronary artery calcification (density x volume) seen. The CAC score is often interpreted categorically; for example: no coronary calcification (score of 0), mild (<100), moderate (≥100 to 399), severe (≥400 to 999), and extensive (≥1000) coronary calcification. When reported in the included studies, thresholds defining an elevated CAC score varied widely from the presence of any CAC (>0) to thresholds of above 100, and more commonly above 300 or 400. In the convenience sample (as opposed to population-based) cohort, the prevalence of abnormal CAC scores was higher. For example, the prevalence of a CAC score of greater than 400 was approximately 25 percent in the Houston Methodist DeBakey Heart & Vascular Center cohort, as compared to approximately 10 percent or less in the Heinz Nixdorf Recall, Framingham Offspring, and MESA cohorts.

Most studies excluded or are assumed to have excluded people with missing data for CAC or traditional cardiovascular risk factors; some analyses using the Rotterdam and MESA plus Heinz Nixdorf Recall cohorts used imputation.[76, 82, 89, 94] CAC was most commonly log-transformed when included in risk prediction models. In four instances, CAC was entered categorically in risk prediction models with a varying number of strata used, with different definitions.

All the studies were assessed as fair quality. Limitations of studies are described above. Fair-quality as opposed to good-quality studies did not conduct any recalibration in the setting of using published coefficients for PCE or FRS models, had followup time equivalent to the time horizon predicted, had fewer than 20 outcome events per variable, did not report any calibration or goodness-of-fit measures, and/or did not report confidence intervals or statistical significance of changes in measures of discrimination or risk reclassification.

Model Performance (Calibration, Discrimination, Risk Reclassification)

For model performance, we will first discuss results of calibration, then discrimination, and finally risk reclassification. Of the 19 studies (10 cohorts) included, 8 articles (4 cohorts) reported some measure of calibration, all articles and cohorts reported discrimination, and 15 articles (9 cohorts) reported risk reclassification. To guide the reader, each section is formatted similarly with a discussion of results from models using the published coefficients first, then model development studies.

Calibration

Limited evidence from four cohorts and primarily model development studies suggests that the addition of CAC to the FRS can improve calibration; however, the magnitude and clinical significance of this improvement are not certain (**Table 25**). Calibration plots and O:E ratios are not available.

Published coefficient models. One published coefficient analysis using the PCE as a base model reported the Hosmer-Lemeshow test and the overall performance measure of the BIC for sex and race/ethnicity subgroups.[112] The Hosmer-Lemeshow test showed no evidence of miscalibration in the extended model for all subgroups except women; the publication does not report calibration for the base model. The overall performance measure of the BIC, which captures both

calibration and discrimination, suggested improvement, which was characterized as "very strong" for all groups except Asians.

Model development studies. No studies reported calibration plots or O:E ratio. Only one model development study, using the Rotterdam cohort, reported calibration or overall performance measures for the addition of CAC to PCE variables.[89] Overall performance measures (i.e., AIC, likelihood ratio χ^2 and global χ^2) consistently showed improvement in performance with the addition of CAC to base models.[76, 82, 89, 93] However, because of the integrated nature of these measures, we are unable to draw conclusions about whether calibration, discrimination, or both improved due to the addition of CAC. The one study evaluating a base model of PCE variables found no evidence of miscalibration in the base model based on the Hosmer-Lemeshow test and an improvement in calibration with the addition of CAC; however, this study predicted fatal CVD outcomes as opposed to hard CVD outcomes (**Table 25**).[89] There were fewer than 100 fatal CVD outcomes in this analysis. Three studies, two using the Heinz Nixdorf Recall cohort and one using MESA, only report the Hosmer-Lemeshow test (**Table 25**).[74, 77, 103] Two of the three models suggest improvement in calibration with the addition of CAC to the base model; however, the Hosmer-Lemeshow test is not a sensitive test.

Discrimination

All of the included studies reported the improvement in discrimination, as measured by a change in AUC or c-statistic, by adding CAC to traditional cardiovascular risk assessment (**Table 26**). The discrimination of base models using traditional cardiovascular risk factors ranged widely in both published coefficient models and model development studies, from 0.63 to 0.80 in all participants. The addition of CAC to published coefficient models and model development studies consistently resulted in at least small and sometimes large improvements in discrimination. Four studies evaluated the addition of CAC to the PCE. One of these studies, using the MESA cohort, also evaluated the FRS and findings suggest that improvement in discrimination was higher for CAC in addition to the FRS (0.04) than to the PCE (0.02).

Published coefficient models. Two published coefficient analyses, both using the MESA cohort, evaluated a PCE base model. One is an analysis by Yeboah and colleagues,[90] which excluded people already taking statins and therefore represents a population at lower risk for CVD; the other analysis by Fudim and colleagues[112] explored the addition of CAC in sex and racial/ethnic subpopulations, and, as such, results are exclusively reported by subpopulation. The base model discrimination of the PCE to predict hard CVD events in the analysis by Yeboah and colleagues was 0.74; the addition of CAC resulted in an improvement of 0.02 (p=0.04).[90] However, as this was a model that recalibrated the PCE to the MESA population, estimates of improvement in discrimination may be conservative. The analysis by Fudim and colleagues showed a PCE base model discrimination of 0.705 in men and 0.766 in women; c-statistics varied across racial and ethnic groups, with the poorest performance in African Americans (0.707) and the best performance in Latinos (0.800). Improvements in discrimination were very small to small in all subpopulations but were statistically significant only in men, who were the group with the poorest base model performance (improvement of 0.025, p=0.047); neither confidence intervals nor statistical significance are reported. Subgroup analyses by race/ethnicity may not be adequately powered to detect statistically significant differences (i.e., smaller n's and number of

events for African Americans, Latinos, and Asians/Chinese). The MESA analysis by Yeboah and colleagues also evaluates the addition of CAC to a published coefficient FRS base model to predict hard CHD events; base model discrimination was also 0.74 and the addition of CAC resulted in an improvement of 0.04 (p=0.001). In other studies using the FRS to predict hard CHD, the base model discrimination ranged from 0.63 to 0.757.[74, 86, 106, 114] In these studies, the addition of CAC resulted in an improvement in discrimination of 0.038 to 0.102; however, results in the analysis of EISNER combined with the Cardiac Research Database were not statistically significant due to the limited number of events.[106] Presumably due to the low number of hard CHD events in this cohort, this study also conducted analyses with soft CHD and soft CVD outcomes, in which similar improvements in discrimination were statistically significant. In one study using the Heinz Nixdorf Recall cohort, sex-stratified analyses suggest a greater improvement in discrimination using CAC in addition to the FRS, for men (compared to women), owing to the poorer performance of the base model in men (compared to women).[74]

Model development studies. Two model development studies evaluated the addition of CAC to PCE variables. One study was a pooled analysis of low-risk (<7.5%) women in five population-based cohorts which had a base model discrimination of 0.73 (95% CI, 0.69 to 0.77) and a very small to small improvement in discrimination with the addition of CAC (0.02 [95% CI, 0.0 to 0.05]).[111] The other model development study, using the Rotterdam cohort, evaluated the addition of CAC to PCE variables used fatal (as opposed to hard) CVD events.[89] This study's base model discrimination was 0.78 (95% CI, 0.73 to 0.83) and with the addition of CAC was 0.81 (95% CI, 0.76 to 0.86), with overlapping 95% CI in which the CI of the base model includes the point estimate of discrimination of the extended model with CAC (p-value not reported).

The remaining 12 model development studies used FRS variables in their base model; the pooled analysis of low-risk women by Kavousi and colleagues evaluated the addition of CAC to FRS variables as well as PCE variables. The discrimination in five studies using a base model of FRS variables to predict hard CHD events in all participants ranged from 0.712 to 0.79.[74, 76, 82, 88, 103, 111] In these studies, CAC led to small statistically significant improvements in discrimination (0.04 to 0.05). Only one study, which used the Rotterdam cohort, conducted sex-stratified analyses, and found similar improvements in discrimination in both men and women.[82] One study that used MESA included only participants with diabetes; while the base model discrimination may be lower (difficult to compare across studies as confidence intervals were not reported), improvement in discrimination using CAC was similar in magnitude.[94] Three additional studies using a model of FRS variables to predict soft CHD events generally found similar improvements in discrimination with CAC in all participants.[77, 93, 101] The lower base model performance of FRS variables in the Houston Methodist DeBakey Heart and Vascular Center cohort, may have something to do with the more selected (higher risk) population studied. One of these studies, using MESA, conducted sensitivity analyses with and without those with diabetes (as their base model did not include diabetes as a risk factor); both these analyses yielded similar results.[101] One additional study, using MESA, included only intermediate-risk people, defined as 2.0 to 15.4 percent 7.5-year risk of having a soft CHD event; this study found the base model discrimination was 0.623, and the improvement in discrimination with CAC was 0.161 (p<0.001).[75] Last, results from one study, using the EISNER RCT, only reported discrimination using soft CVD events and generally found concordant results.[99]

Risk Reclassification

Most of the included studies (k=15) reported risk reclassification using NRI with or without IDI (**Table 27**). Although population risk, outcomes predicted, and definitions of risk strata vary across studies, CAC added to traditional cardiovascular risk factors consistently improves risk reclassification as measured by the total NRI. Four studies evaluated the addition of CAC to the PCE, and these studies demonstrate that CAC can improve risk reclassification, albeit with some study limitations. CAC appears to improve reclassification across a spectrum of risk and in both men and women. Improvements in the total NRI were consistently driven by event NRIs much larger than nonevent NRIs, yet nonevents were considerably more common (less than about 8% of participants in each included study had a hard event) and the total NRI is not weighted by event prevalence. It was not uncommon in the CAC literature for nonevent NRIs to be negative (sometimes statistically significant), indicating than on net, more participants were inappropriately reclassified upward.

Published coefficient models. Three studies of two cohorts using published coefficients reported measures of risk reclassification. Analyses of a PCE base model were restricted to just one cohort, MESA.[90] Again, the MESA analysis by Yeboah and colleagues excluded people already taking statins, and therefore represents a population at lower risk for CVD. For the PCE analysis, the study defined low risk as having less than 7.5 percent 10-year risk of a hard CVD event, and high risk as 7.5 percent or greater risk. This study found an NRI of 0.119 (95% CI, 0.08 to 0.256), with a greater proportion of those having a CVD event (vs. not having an event) reclassified to higher-risk categories with the addition of CAC to the PCE; the nonevent NRI was negative but not statistically significant (-0.059 [95% CI, -0.075 to 0.03]). The MESA analysis by Fudim and colleagues[112] reported statistically significant NRI for both men and women (0.080 and 0.095, respectively), but event and nonevent NRI were not reported and could not be calculated; the risk threshold was 5.25 percent 7-year risk which corresponds to 7.5 percent 10-year risk. Subgroup analyses by race/ethnicity showed that the NRI was statistically significant only for Whites (0.111), which was also the largest group in the study; other NRIs ranged from -0.121 (p=0.11) for Asians to 0.111 (p=0.082) for African Americans. Again, subgroup analyses by race/ethnicity had limited samples and number of events. For the FRS analysis by Yeboah and colleagues,[90] the study defined low risk as less than 10 percent 10-year risk of a hard CHD event, intermediate risk as 10 to 20 percent risk, and high risk as greater than 20 percent risk. This study found an NRI 0.084 (95% CI, 0.024 to 0.196), again with a greater proportion of those having a CVD event reclassified, with the addition of CAC to the FRS; again, the nonevent NRI was negative but not statistically significant. The bias-corrected NRI_{INT} was lower and not statistically significant. An analysis of the Heinz Nixdorf Recall cohort showed a statistically significant NRI for all analyzed participants, as well as for participants defined as low risk (<10%) and intermediate risk (10-20%); however, continuous NRIs are reported and are not comparable in scale to the categorical NRIs reported above.[114] Event and nonevent NRIs were not reported and the intermediate-risk NRI was not bias-corrected and could not be calculated.

Model development studies. Two model development studies evaluated the addition of CAC to PCE variables.[89, 111] An analysis by Kavousi and colleagues pooled low-risk women (<7.5% 10-year risk) from five population-based cohorts and found a statistically significant continuous NRI of 0.20 (95% CI, 0.09 to 0.31); event and nonevent NRIs were not reported and could not be

calculated. The other study in the Rotterdam cohort evaluated fatal (as opposed to hard) CVD events, and because there are no accepted risk categories for fatal events, this study used continuous NRI. This study found an NRI 0.55 (95% CI 0.33 to 0.76), with a greater proportion of those having a fatal event (vs. not having an event) reclassified with the addition of CAC to PCE variables. This NRI should not be directly compared to NRI using categorical risk strata. The IDI is also reported but not discussed further (**Appendix E Table 3**).

The remaining 11 model development studies used FRS variables in their base model; the pooled analysis by Kavousi and colleagues evaluated the addition of CAC to both FRS variables and PCE variables.[111] Six studies included analyses using FRS variables to predict hard CHD events for all participants.[74, 76, 82, 88, 103] With the exception of the analysis by Hoffmann and colleagues, which predicted 5-year risk and used four instead of three risk categories, these studies used similar risk categorizations, with low risk defined as less than 10 percent 10-year risk of a hard CHD event, intermediate risk as 10 to 20 percent risk, and high risk as greater than 20 percent risk. In these studies, categorical NRI ranged from 0.14 to 0.319 and one study reported a continuous NRI of 0.28. For those studies reporting or allowing for calculation of event and nonevent NRI, a greater proportion of those having a hard CHD event (versus not having an event) were reclassified with the addition of CAC to FRS variables. In half of these studies, the nonevent NRI was negative and was statistically significant in two studies;[82, 88] it was also negative and statistically significant in one study reporting soft CHD outcomes.[113] The IDI, reported in two of these studies, was congruent with findings using NRI as a measure of reclassification (**Appendix E Table 3**).[74, 103] One study, which used the Rotterdam cohort, conducted sex-stratified analyses and found greater reclassification in men than women.[82] Bias-corrected NRI_{INT} was calculated for three of these studies.[74, 82, 88] One of these studies, which used the Framingham Offspring cohort, found slightly greater reclassification for the intermediate-risk group as compared to all participants.[88] The other two studies found a similar magnitude in NRI in the intermediate-risk group as compared to all participants.[74, 82] The reasons for the differences in findings among these three studies comparing intermediate versus all-risk participants is not clear.

Three additional studies using FRS variables to predict soft CHD events generally found similar improvements in reclassification with CAC in all participants.[77, 93, 113] These studies use different categorization of risk (different from one another and different from studies predicting hard CHD events); nonetheless, NRI and IDI results in these two studies are similar to findings using hard CHD events. One of these studies, which used MESA, conducted sensitivity analyses with and without individuals with diabetes (as their base model did not include diabetes as a risk factor); this analysis yielded similar results.[77] In two of these studies, both which used MESA and in which we could calculate a bias-corrected NRI_{INT}, the NRI_{INT} was smaller than the NRI for all participants.[77, 113] One additional study that used MESA included only intermediate-risk people, but a bias-corrected NRI_{INT} could not be calculated.[75] Last, results from one study that used the EISNER RCT included soft CVD events as an outcome, presumably to increase power; reclassification results were generally concordant to other studies using hard CHD or CVD events, and results for bias-corrected NRI_{INT} were no longer statistically significant.[99]

KQ3. What Are the Harms of Nontraditional Risk Factor Assessment?

Summary

We included eight studies that evaluated the harms of nontraditional risk factor assessment, all of which focused on harms of CAC;[11, 88, 89, 115-119] we found no studies evaluating potential harms of ABI or hsCRP. Four studies reported radiation exposure for CT imaging to obtain CAC (**Table 28**), and five studies reported other potential adverse events from CAC (i.e., psychological outcomes, adverse cardiovascular events, and health care utilization) (**Tables 29-31**). We did not find any studies that met our inclusion criteria that reported incidental findings (or subsequent testing/procedures from incidental finding) on CT imaging to obtain CAC. Overall, the radiation exposure or effective radiation dose per CT exam is low, ≤2 mSv. Based on two studies, risk assessment with CAC does not appear to cause any short-term (up to 1 year) mental distress. Based on two additional studies, risk assessment with CAC did not appear to paradoxically increase CVD events. Studies evaluating the impact of CAC on downstream health-care utilization have mixed findings. Two studies suggest CAC for CVD risk assessment is not associated with increased testing from 6 months up to 4 years. One large study using administrative Medicare claims data suggest that CAC in asymptomatic people was associated with increased use of cardiac tests and procedures compared to people receiving hsCRP or lipid screening. It is unclear whether the increase in testing or procedures among those receiving a CAC score represents a true harm because there was a trend (not statistically significant) for improved MI, CVA, and mortality outcomes at a median of 3 years of followup in people who had a CAC screen versus those who had hsCRP testing; there was but no difference in clinical outcomes between people who received CAC versus lipid screening alone.

Detailed Results

Description of Studies

Four studies reported radiation exposure for CT imaging to obtain CAC,[11, 88, 89, 115] three of which were included studies for KQs 1 and 2 (**Table 28**). These studies report the radiation exposure or effective radiation dose range from obtaining CAC in three population-based cohorts (Rotterdam, Framingham Offspring, MESA) and the EISNER RCT. Two articles that reported ranges of radiation exposure or effective radiation dose from CAC using nonsystematic literature reviews were not included but are summarized in the discussion.[129, 130] There was some variation in how CAC scores were obtained across included studies. These four studies each had multiple sites with varying protocols across sites. Studies used electron beam or multidetector CT (EBCT or MDCT) scanners. Only the MESA study explicitly mentioned ECG-triggered or gated acquisition of images using EBCT and reported how the effective radiation dose was calculated. Only two studies explicitly state that they calculated the effective radiation dose,[88, 115] while the other two studies did not specify "effective" radiation dose[11, 89] and generically refer to an estimated radiation dose. The effective dose specifically refers to the tissue-weighted sum of equivalent doses.

Five studies reported other potential adverse events from CAC, including: mental distress, adverse cardiovascular events, and health care utilization (**Tables 29-31**). One of these studies was the EISNER RCT included for KQ1.[11] Two studies reported measures of mental distress from CAC obtained for CVD risk assessment.[118, 119] One of these studies (n=1,169) was a subsample selected from two centers participating in DanRisk, a population-based cohort in Denmark to study CAC progression and the incidence of CVD events.[118] Participants were men and women ages 50 or 60 years. Approximately 10 percent of responders were on lipid-lowering medications, 20 percent were on antihypertensive medications, and 25 percent were current smokers. About 8 percent of responders reported taking some type of medication for depression, anxiety, or other mental health condition. The other study (n=450) was a U.S.-based RCT of CAC as a motivational factor in intensive CVD screening versus usual care among people in active military duty.[119] Participants were ages 39 to 45 years, mostly men, and about 22 percent were African American. Approximately 4 percent of participants were taking statins, 6 percent were taking antihypertensive medications, and 8 percent were current smokers. About 5 percent of participants reported taking antidepressant medication. Both studies used validated scales to measure depression; the RCT also measured anxiety and overall mental health functioning. The observational study reported depression scores before and 6 months after CAC screening in 539 of 591 people offered a depression questionnaire. The RCT reported depression, anxiety, and mental health functioning scores between groups who did and did not receive CAC information in 406 of the 450 participants at 1 year of followup.

Three studies reported adverse cardiovascular outcomes and/or health care utilization associated with CAC.[11, 116, 117] Again, one of these studies was the EISNER RCT included for KQ1.[11] Two observational studies used claims data geographically representative of the entire United States.[116, 117] One study by Chi and colleagues used a research database and identified participants ages 18 to 64 years old who received CAC (n=2,679), and downstream utilization was analyzed for non-high-risk people (n=2,139), defined as those people without known diabetes or CVD in the 12 months preceding CAC. A comparator group (n=867) comprised people whose physicians requested CAC but were denied because the procedure was not covered by their health plan benefits. Subsequent cardiac imaging, revascularization, and cardiovascular medications were assessed in the 6 months following CAC. This study also assessed CVD events, with a median followup of about 22 months for the group that received CAC and about 17 months for the group that did not receive CAC. The other observational study by Shreibati and colleagues used Medicare data and identified asymptomatic participants who received CAC (n=4,184), and assessed downstream utilization and clinical outcomes after CAC. Two reference groups were used for comparison: one propensity-matched group that received hsCRP (n=261,356) and one that received lipid screening (n=118,093). Subsequent cardiac imaging, revascularization, and hospitalization were assessed in the180 days following CAC, as well as clinical CVD outcomes, mortality, and cost (not reported here) in the 3 years following CAC. In addition to limitations of using claims data, both studies have limitations in their assembly of comparator groups, although the study by Shreibati and colleagues state they used propensity scores to help match controls. The EISNER trial randomized middle-aged volunteers from a single medical center who had CVD risk factors but no known CVD to receive CAC or not. Subsequent cardiac imaging, revascularization, cardiovascular medications, and cost (not reported here) were assessed in the 4 years following randomization.

Radiation Dose

The radiation exposure reported ranged from an effective dose of 0.74 to 1.26 mSv in the MESA and Framingham Offspring cohorts[88, 115] to radiation dose (did not specify effective dose) of ≤2.1 mSv in the Rotterdam and EISNER cohorts (**Table 28**).[11, 89] The radiation exposure was not reported separately for EBCT versus MDCT.

Psychological Outcomes

Neither of the two included studies suggested any adverse mental health effects from CAC (**Table 29**). The observational study found a statistically significant improvement in depression, as measured by the Major Depression Inventory (MDI), from before CAC to 6 months after CAC. The clinical meaningfulness of this small change (-1.4, p<0.0001) on a scale of 0 to 50 is not clear. A score of 0 to 20 on the MDI indicates no depression; the mean before-and-after scores in this cohort were 5.3 and 3.9, respectively.[118] The RCT found no statistically significant difference in depression or anxiety (as measured by PRIME-MD) or overall mental health functioning (as measured by the SF-36) at 1 year followup between the group that received CAC scores versus the group which did not.[119] Changes in these measures were small, and baseline scores in depression, anxiety, and overall mental health functioning were not reported.

Cardiovascular Outcomes

Neither of the two included studies suggested any paradoxical increase in adverse CVD events (**Table 30**). Both studies used administrative data. One study by Chi and colleagues found no difference in MI, CVA, or hospital admission for unstable angina in the 22 months for the group that received CAC versus 17 months for the group that did not receive CAC.[116] The other study by Shreibati and colleagues found no statistically significant difference in MI, CVA, or all-cause mortality up to a median of 3 years between those who received CAC versus those who received hsCRP or lipid screening.[117] This study observed a trend, but not statistically significant, for fewer MI events in the group that received CAC versus that which received hsCRP.

Health Care Utilization

Three studies that reported health care utilization following CAC had mixed findings (**Table 31**). The EISNER RCT found no statistically significant increase in cardiac imaging or revascularization at up to 4 years after CAC screening compared to those who did not receive CAC screening.[11] People who were randomized to CAC screening had a trend for increased nuclear stress testing (12.9%) compared to those who did not (10.0%), but this increase was not statistically significant (p=0.06). Two studies using administrative data evaluated downstream health care utilization following CAC. One study found no difference in cardiac imaging or revascularization in people without known diabetes or CVD who received CAC versus those who were denied CAC.[116] However, one study using Medicare claims data found greater number of subsequent cardiac imaging tests and revascularization in asymptomatic people who received CAC compared to people receiving hsCRP or lipid screening.[117] While the EISNER RCT had a superior study design, the findings may be less applicable to clinical practice. On the other hand, whilst the administrative data reflects clinical practice, the limitations of administrative data and

the assembly of control groups limit our confidence as to how much, if any, increase in downstream testing may occur following CAC in asymptomatic adults for CVD risk prediction.

KQ4. Does Treatment Guided by Nontraditional Risk Factors, in Addition to Traditional Risk Factors, Lead to Reduced Incidence of Cardiovascular Events and/or Mortality?

Summary

We did not identify any trials examining nontraditional risk factor assessment in addition to the FRS or PCE to guide treatment and reduce cardiovascular events. We included four RCTs that evaluated whether pharmacologic treatment guided by nontraditional risk factor assessment alone (i.e., ABI, hsCRP, or CAC) lead to reduced CVD events and/or mortality.[120-124] Two of these trials evaluated aspirin therapy in individuals with an abnormal ABI, one trial evaluated statin therapy in people with an abnormal hsCRP, and one trial evaluated statins in individuals with an abnormal CAC. Two good-quality trials (AAA and POPADAD) in asymptomatic adults (including one trial exclusively in participants with diabetes) with an abnormal ABI did not find any statistically significant benefit for low-dose aspirin (aspirin 100 mg daily) on reducing CVD outcomes or all-cause mortality compared to placebo after approximately 7 to 8 years of followup. One fair-quality trial (St. Francis Heart Study) in asymptomatic people with LDL <175 mg/dL and CAC at the 80th percentile or greater for age and gender did not find any statistically significant benefit for moderate-intensity statin therapy (atorvastatin 20 mg daily) on reducing CVD outcomes compared to placebo after about 4 years of followup. However, this study had a lower than expected number of events and was terminated early. One good-quality trial, JUPITER, in asymptomatic people with LDL <130 mg/dL and hsCRP of 2.0 or greater mg/L found a rather large relative reduction in CVD events for high-intensity statin therapy (rosuvastatin 20 mg daily) compared to placebo (HR 0.56 [95% CI, 0.46 to 0.69]) at approximately 2 years (terminated early); however, absolute benefits were small.

Detailed Results

Description of Studies

Two RCTs, Aspirin for Asymptomatic Atherosclerosis (AAA) (n=3,350) and Prevention of Progression of Arterial Disease and Diabetes (POPADAD) (n=1,276) evaluated the benefit of low-dose aspirin in asymptomatic people with abnormal ABI (**Tables 32** and **33**).[122, 123] Both trials were conducted in Scotland, with a mean age of participants of about 60 to 62 years. The AAA trial included a predominance of women (71.5%). The POPADAD trial was exclusively in people with known diabetes, approximately one-third of whom were treated with insulin. Only 2.6 percent of people in the AAA trial had diabetes. Approximately one-third of the participants in both trials were identified as current smokers. At baseline 4.2 percent of participants were taking a statin (25% at 5 years) in the AAA trial. The POPADAD trial did not report the proportion taking a statin. Neither trial used the conventional 0.90 threshold for an abnormal ABI; the AAA trial defined an abnormal ABI as ≤0.95, and the POPADAD trial defined an

abnormal ABI as ≤0.99. Both trials randomized participants to take aspirin 100 mg daily or placebo; the POPADAD trial used a factorial design to also evaluate a combination antioxidant capsule (data not discussed). There was no evidence of an interaction between aspirin and the antioxidants. Both trials defined a composite CVD outcome (i.e., MI, CVA, revascularization or amputation for critical ischemia) as their primary endpoint, and were powered to detect a difference in this outcome. Average followup was 8.2 years for the AAA trial (terminated early due to futility) and 6.7 years for the POPADAD trial. Both of these trials were good-quality RCTs with good baseline comparability, intention to treat analyses, and minimal loss to followup, and were powered for composite CVD outcomes.

One RCT, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (n=17,802), evaluated the benefit of rosuvastatin 20 mg daily in persons with an elevated hsCRP but normal LDL (**Tables 32** and **33**).[120] This trial was conducted across 26 countries. The median age of participants was 66 years old, approximately 38 percent of whom were women and approximately 25 percent of whom were African American or Latino. Participants had to have an LDL <130 mg/dL. People with known diabetes were excluded from the trial. Approximately 16 percent were current smokers and approximately 17 percent of participants were taking aspirin. An abnormal hsCRP was defined as ≥2.0 mg/L (as opposed to 3.0 mg/L which was most often employed in included KQ2 studies); the median hsCRP of participants was 4.2 mg/L. Half of trial participants had an FRS of 10 percent or less. The primary endpoint was a composite CVD outcome that included MI, CVA, hospitalization for unstable angina, and/or revascularization. This was a good-quality trial but terminated early because the stopping boundary was crossed at the first efficacy evaluation; thus, the trial had a median 1.9 years of followup.

One RCT, the St. Francis Heart Study (n=1,005), evaluated the benefit of atorvastatin 20 mg daily in individuals with elevated CAC (**Tables 32** and **33**).[121] This trial was conducted in the United States. The mean age was 59 years old, and approximately 26 percent of participants were women. Participants had to have an LDL <175 mg/dL. Approximately 9 percent of participants had diabetes and 13 percent were current smokers. All participants were given low-dose aspirin as part of the trial. The mean hsCRP in participants was lower in this trial (about 2 mg/L) as compared to the JUPITER trial (about 4 mg/L). An abnormal CAC was defined as above the 80th percentile for age and sex. This trial also evaluated vitamin C and E (data not discussed). The primary endpoint was a composite CVD outcome that included MI, CVA, and revascularization. This study did not report on adverse effects of atorvastatin. This was a fair-quality trial in that it was not powered for composite CVD outcomes due to a lower than expected event rate. Trial investigators terminated the study early, with mean 4.3 years of followup.

Cardiovascular Outcomes

AAA and POPADAD found no difference between low-dose aspirin and placebo in composite CVD outcomes (**Tables 34** and **35**). The AAA trial reported 10.8 percent CVD events in the aspirin and 10.5 percent events in the placebo group, with an adjusted HR of 1.0 (95% CI, 0.81 to 1.23) at 8.2 years of followup. The POPADAD trial reported 18.2 percent CVD events in the aspirin and 18.3 percent events in the placebo group (HR 0.98 [95% CI, 0.76 to 1.26]) at 6.7

years of followup. Both trials reported age- and sex-stratified analyses, again with no differences between randomized groups (**Tables 36** and **37**). Both trials also found no difference in all-cause mortality.

JUPITER found a benefit for hsCRP-guided, high-intensity statin therapy (**Tables 34** and **35**). This trial reported 1.6 percent CVD events in the rosuvastatin group compared to 2.8 percent events in the placebo group (HR 0.56 [95% CI, 0.46 to 0.69]) at 1.9 years of followup. Benefits were statistically significant for both MI and CVA outcomes individually. Benefits were statistically significant for both men and women, as well as for people with a baseline FRS of ≤10 percent and >10 percent 10-year risk, in *a priori* specified analyses (i.e., there was no suggestion of effect modification based on interaction testing) (**Table 37**). This trial also found a statistically significant difference in all-cause mortality, with 2.2 percent deaths in the rosuvastatin group versus 2.8 percent deaths in the placebo group (HR 0.80 [95% CI 0.67 to 0.97]).

The St. Francis Heart Study found no statistically significant benefit for CAC-guided moderate-intensity statin therapy but was not adequately powered (**Tables 34** and **35**).[121] This trial reported 6.9 percent CVD events in the atorvastatin group compared to 9.9 percent events in the placebo group (RR 0.70 [95% CI 0.44 to 1.10]) at 4.3 years of followup. Among participants with baseline CAC greater than 400, there was a statistically significant reduction in CVD events in the atorvastatin group compared to the placebo group (8.7% with events versus 15.0%; p=0.046); it is not clear whether this was a prespecified subgroup analysis and interaction testing is not reported.

KQ5. What Are the Harms of Treatment Guided by Nontraditional Risk Factors?

Summary

Three of the four included RCTs for KQ4 reported harms of treatment (i.e., aspirin or statin) guided by nontraditional risk factor assessment.[120, 122, 123] We found no other studies evaluating harms meeting our inclusion criteria. Neither aspirin trial (AAA and POPADAD) found evidence of increased major bleeding (including hemorrhagic CVA) for low-dose aspirin compared to placebo after approximately 7 to 8 years of followup. The JUPITER trial did find evidence of an increased incidence of diabetes in the high-intensity statin therapy group (3.0 percent) compared to placebo (2.4 percent), p=0.01 after approximately 2 years; however, it did not find evidence of increases in other serious adverse effects (including hemorrhagic CVA) or myopathic events for high-intensity statin therapy compared to placebo.

Detailed Results

Description of Studies

Please refer to the KQ4 section (**Tables 32** and **33**).

Harms

AAA and POPADAD found no statistically significant difference between low-dose aspirin and placebo group in major bleeding events (**Table 38**). Overall the number of adverse events was low. The AAA trial reported 2.0 percent major bleeding events (e.g., major GI bleeding, hemorrhagic CVA, and intracranial bleeding) in the aspirin and 1.2 percent events in the placebo group (HR 1.71 [95% CI, 0.99 to 2.97]) at 8.2 years of followup. The POPADAD trial reported only on fatal hemorrhagic CVA. Event rates were low, with no statistically significant difference between the aspirin and placebo groups.

JUPITER found a statistically significant increase in physician-diagnosed diabetes, but not in other serious adverse events, in the rosuvastatin group compared to the placebo group (**Table 38**). This trial reported 3.0 percent incident diabetes in the rosuvastatin group compared to 2.4 percent in the placebo group (RR 1.25 [95% CI, 1.04 to 1.50]) at 1.9 years of followup. However, there was no difference in a composite outcome of serious adverse events between the rosuvastatin group (15.2 percent) versus the placebo group (15.5 percent) (RR 0.98 [95% CI, 0.91 to 1.06]) and no difference in hemorrhagic CVA between the two groups, but this outcome was rare (0.1%).

Chapter 4. Discussion

Summary of Evidence

A large body of evidence has accrued since the previous USPSTF insufficient evidence statements for nontraditional risk factors in CHD risk assessment in 2009 and for ABI in CVD risk assessment in 2013 (**Tables 39** and **40**). However, we still lack direct evidence from adequately powered trials evaluating the impact of CVD risk assessment with or without the addition of nontraditional risk factors on patient health outcomes. While comparative trials evaluating the incremental value of nontraditional risk factor assessment to traditional cardiovascular risk assessment on patient health outcomes may never be conducted, there are two trials currently in progress that will help us understand the role of ABI and CAC screening in people without known CVD: the Danish Cardiovascular Screening Trial (DANCAVAS) and the Risk or Benefit IN Screening for Cardiovascular disease (ROBINSCA) trial (**Appendix F**). DANCAVAS is a large screening RCT (n~40,000) in older adults evaluating ABI and CAC to screen for vascular disease.[131] DANCAVAS began in 2014 and has primary outcomes including CVD morbidity and mortality at 10 years; however, interim analyses are planned for 2018. ROBINSCA is a similarly large RCT (n~40,000) in asymptomatic adults (ages 45 to 74 years old) in the Netherlands evaluating CVD risk assessment using SCORE versus CAC screening versus a control group.[132] The primary outcome of this trial is fatal or nonfatal CHD at 5 years, with results expected in 2019. The recently published Viborg Vascular (VIVA) population-based screening trial for AAA, PAD, and hypertension does not address the additive value of ABI to traditional CVD risk assessment and does not allow for the assessment of benefit of ABI separate from the other two screening interventions.[133] Short of having trial data on health outcomes, we should consider the incremental improvement of nontraditional risk factor assessment with the ABI, hsCRP, and CAC on the calibration, discrimination, and risk reclassification of traditional cardiovascular risk assessment.

Predictive Performance of ABI, hsCRP and CAC

Unfortunately, risk prediction studies to date offer limited information about how ABI, hsCRP, or CAC can improve the calibration—agreement between predicted and observed events—of PCE or FRS risk assessment, due to sparse and inconsistent reporting of various measures (**Table 39**). The sparse reporting of calibration measures is not surprising and is consistent with the findings of other systematic reviews,[13] as historically, the performance of risk prediction models has focused on discrimination.[134] While limited reporting of measures of calibration suggests that all three nontraditional risk factors can improve model fit, the lack of reporting on calibration plots and O:E ratios, as well as the overall inconsistent reporting of calibration measures, severely limits our ability to understand the clinical meaning of these improvements in calibration. Given that current risk assessment tools can both under- and overestimate CVD risk, it is crucial to understand the impact of these risk factors on calibration as much as their impact on discrimination and risk reclassification. In addition, because the c-statistic or AUC is a rank order statistic, a model can discriminate well but still systematically under- or overestimate risk.[57] Overall performance measures such as likelihood statistics, AIC, BIC, and R^2 were reported more commonly than measures directly assessing calibration; however, since these measures capture both discrimination and calibration, improvements in these measures could indicate improvements to one or both aspects of model performance. Because we found that nontraditional risk factors can improve discrimination, the interpretation of improvements in overall performance measures on calibration is unclear.

Fortunately, we have more complete data to inform the impact of nontraditional risk factors on discrimination and risk reclassification when added to traditional risk factor assessment. Very few risk prediction studies in this review evaluated base models using published coefficients of existing models, therefore do not answer the pragmatic question for clinicians on whether to add ABI, hsCRP or CAC to their existing cardiovascular risk assessment using publicly available tools like the PCE or ATP III's risk calculator. Overall, we found only four studies that evaluated the PCE as a base model; therefore, we cannot make any definitive conclusions about the value of ABI, hsCRP, or CAC to the PCE, and in particular about the ability of these nontraditional risk factors to improve the performance of the PCE. Almost the entirety of the evidence is focused on an FRS base model. The IPD meta-analysis by the ABI Collaboration demonstrated the improvement in both discrimination and risk reclassification after adding ABI to the FRS using published coefficients. This improvement was most promising for women and women at intermediate-risk; however, this is likely due to the poor base model performance. When investigators developed new models for women, which corrected the poor calibration and discrimination of the base model, improvements in discrimination and reclassification for ABI were no longer statistically significant. Findings from other studies were generally concordant with findings from the IPD meta-analysis. Findings for hsCRP were less consistent compared to ABI or CAC. Limited studies with methodological limitations suggest that at best, the addition of hsCRP to the FRS results in small improvements in discrimination and reclassification. The IPD meta-analysis by the Emerging Risk Factors Collaboration demonstrated statistically significant improvements in the c-statistic of only 0.0039 and NRI of only 0.0152 when hsCRP was added to the FRS, but this was a model development study. These improvements appear to accrue more for men than women. Sex differences observed in the ABI evidence base can be explained by

performance of base models rather than biologic plausibility that the ABI performs differently in men and women; this is likely the case for sex differences in hsCRP as well, although more limited reporting about sex-specific base model performance prevents definitive conclusions. CAC appears to be the most promising nontraditional risk factor; however, this interpretation is based on a much smaller body of evidence compared to ABI or hsCRP. CAC, when added to the FRS, consistently resulted in improvements in discrimination and reclassification in studies using published coefficients and model development studies.

When we could evaluate event and nonevent NRI separately, the improvement in NRI for ABI and CAC appeared to be driven by the event (as opposed to nonevent) NRI, meaning the upward classification of individuals who had a cardiovascular event. Because the prevalence of nonevents is substantially greater than that of events, the total NRI may overstate the magnitude of improvement as the event and nonevent NRI are weighted equally. In addition, a negative nonevent NRI (i.e., erroneous classification of individuals without events into a higher-risk category) may lead to harms due to overtreatment or overutilization.[67] For both ABI and CAC there was evidence of negative nonevent NRIs. In the ABI Collaboration IPD meta-analysis, the nonevent NRI was negative and statistically significant for women (for whom benefits were most promising), and similarly across the CAC evidence base, the nonevent NRI was negative (and sometimes statistically significant).

Experts have advocated for the separate consideration of NRI in the intermediate-risk group, as these are the individuals for whom the initiation of preventive therapies may be less certain. In instances where the bias-corrected NRI_{INT} was reported or could be calculated, it was not consistently greater than the NRI observed for all individuals (all risk strata). The most commonly used risk strata for the FRS base model was low (<10%), intermediate (10-19 or 20%), and high (>20%). These risk strata may no longer be as relevant for clinical decisionmaking because current practice has lowered the threshold to initiate preventive therapies, for example, with statins (USPSTF at 10% or greater, ACC/AHA at 7.5% or greater).

Clinical Importance of Improvements in Discrimination and Risk Reclassification

Measures of discrimination (AUC, c-statistic) and reclassification (NRI) are important to evaluate in the context of one another, in addition to measures of calibration. For cardiovascular risk prediction, small changes in risk that do not change clinical decisionmaking can result in changes in discrimination. Conversely, the c-statistic or AUC can be insensitive and new markers can improve reclassification with little change in discrimination.[134] Reclassification captures changes in risk categories or decision thresholds; however, the NRI only measures the difference between the base and extended models, without providing actual information about the performance of the models. Both the c-statistic/AUC and NRI lack consensus on how to interpret clinical meaningfulness. While the NRI may be more clinically helpful because it captures changes in risk categories, it is a combination of four proportions. Event NRI and nonevent NRI may be easier to interpret, as they are each a difference in proportion. For example, the event NRI is the net proportion of events assigned to a higher risk; that is, those with an event correctly reclassified into a higher-risk category minus those with an event who were incorrectly reclassified into a lower group. For cardiovascular risk assessment using three

categories (low, intermediate, and high risk), the NRI equally weights reclassification; for example, all upward movement in the low to intermediate risk is valued the same as low to high risk, and likewise, intermediate to high risk.[67] This is further complicated by the point made earlier: that the risk strata used to calculate the categorical NRI may no longer be relevant to clinical practice. For example, much of the reclassification evidence base uses three categories, whereas clinical decisions are based on a single threshold (of 7.5% or 10% 10-year risk), so the overall NRI will take into account movement between groups that is irrelevant for clinical decisionmaking (e.g., movement between 10-20% and >20% 10-year risk).

The bottom line is there is no consensus on a threshold for clinically meaningful changes in the c-statistic/AUC or NRI. However, we can state that there is moderate strength of evidence that the magnitude of improvement in discrimination and reclassification can be clinically important for ABI for populations in whom the FRS has poor discrimination, and for CAC, but not for hsCRP. These findings of potential benefit should be tempered by the observed misclassification of individuals (negative nonevent NRI) observed in both these instances and other potential harms, specifically for CAC (discussed below). Experts in CAC have argued that a CAC score of 0 may be helpful in reducing unnecessary care (subtractive medicine), as a CAC score of 0 portends a good prognosis in asymptomatic persons, and many asymptomatic persons have a CAC score of 0 (e.g., in the EISNER RCT 48% had a CAC score of 0).[135] An analysis of the MESA cohort by Nasir and colleagues showed that the distribution of CAC is heterogeneous across groups recommended, not recommended, or considered for statins as defined by the 2013 ACC/AHA cholesterol guidelines.[136] These recommendation groups are defined by a combination of risk equivalents (LDL of 190 mg/dL or greater or diabetes) or calculated 10-year PCE risk. In this analysis, 41 percent of those who would be recommended a statin based on LDL of 190 mg/dL or greater, diabetes, or 7.5 percent or greater 10-year risk have a CAC score of 0 and a 10-year risk of approximately 5%. While this analysis shows that a CAC score of 0 can appropriately downward reclassify a large proportion of individuals previously recommended a statin, the downward classification may be of nominal clinical importance because observed risk of 5% is still in the statin considered range. These results are not comparable to the analysis by Yeboah and colleagues[90] used in our evidence review because of the different definition of risk categories (i.e., the use of risk equivalents in one but not both analyses) and the use of a different reclassification strategy (PCE in addition to CAC versus a CAC score of 0). The MESA analysis by Yeboah and colleagues[90] shows that almost half of individuals with diabetes have calculated 10-year risk of less than 7.5 percent, whereas these individuals are automatically placed in the statin recommended group by ACC/AHA guidelines[33] and in the analysis by Nasir and colleagues.[136] Although this analysis underscores the potential of CAC to reclassify individuals across the risk spectrum, the body of evidence reviewed for this report suggests that on a population level, the majority of reclassification is for individuals moved to a higher category of risk (i.e., more persons are inappropriately being reclassified to a higher risk than appropriately being reclassified to a lower risk category).

The use of nontraditional risk factor measurement is primarily important for aiding in the decisions to initiate preventive cardiovascular therapies (i.e., aspirin and statin) by improving on existing cardiovascular risk assessment, for example, in persons for whom traditional risk prediction does not perform adequately. Currently, the USPSTF has recommendations to initiate preventive low-dose aspirin and statins based on a 10-year CVD risk of 10 percent or greater,

while the ACC/AHA advocates for initiating a discussion for statin initiation at a threshold of 7.5 percent using their PCE. We illustrate the impact of reclassification using current day thresholds based on reclassification tables from three selected included studies (**Table 41**). In this example, we show the absolute number of people and people-per-100 who are appropriately and inappropriately reclassified with ABI, hsCRP, or CAC using data from the MESA cohort[90] and the two IPD meta-analyses included in our review.[65, 66] These examples were selected because the studies reported reclassification tables and they represented the most applicable studies to current day practice in the United States. The MESA analysis used a published coefficient model and evaluated both the FRS and PCE, and the IPD meta-analyses represent the largest assembled populations for their respective analyses. For the FRS-based analyses, which used 3 risk strata, the top 2 risk strata (10-20% and >20%) were combined to conform to the current USPSTF recommendation to initiate preventive low-dose aspirin and statins based on a 10-year CVD risk of ≥10 percent. Among individuals having an event, appropriate reclassification is defined as reclassification above a treatment threshold (7.5 or 10%), and inappropriate reclassification is defined as reclassification below a treatment threshold. The converse definitions are used for individuals not having an event. In our example for the PCE, CAC has the greatest reclassification but does inappropriately reclassify individuals who did not have an event to above the 7.5 percent treatment threshold. In the example for the PCE, 76 people having CVD events were appropriately reclassified upward when CAC was added to risk assessment, and 19 people who had events were inappropriately reclassified downward who had a CVD event—a net improvement of 57 individuals among the 320 having events—about 18 per 100 people (reported event NRI of 0.178 [95% CI, 0.080-0.256]). However, in the primary prevention populations to which CVD risk assessment with the PCE or FRS applies, the majority of people will not experience a CVD event. With the addition of CAC to risk assessment, 202 people not having events are appropriately reclassified downward, but 496 people are inappropriately reclassified upward—on net, a worsening of reclassification of 294 individuals out of 4865 not having events—or about 6 per 100 people (reported nonevent NRI of -0.059 [95% CI, -0.075-0.030]). Therefore, the NRI of 0.119 [95% CI, 0.080-0.256) does not convey that for CAC, a sizeable proportion of individuals who are not having events will now be considered for treatment. The addition of the ABI to the FRS in women showed a similar pattern.

Some experts and advocates have argued that nontraditional risk factor assessment may also be helpful for individuals who choose not to initiate preventive therapy (e.g., aspirin or statin), although this has not been proven. One comprehensive systematic review addressed the effect of CAC screening on risk perception, adherence to medication, and behavioral therapies.[10] This review included 15 studies of varying study designs. While the findings were somewhat mixed across different studies and outcomes, in general this review found that CAC screening can increase adherence to lifestyle changes, increase use of preventive medications, influence physician-prescribing practices, and improve risk factor control from 6 months up to 6 years compared to no CAC screening. Only two of these studies evaluated traditional cardiovascular risk assessment versus CAC.[137, 138] Neither of these studies found that screening CAC was superior to traditional cardiovascular risk assessment on use of preventive medications or risk factor control (cholesterol).

Reynolds Risk Score

The Reynolds Risk Score (RRS), which includes hsCRP, family history, and HbA1c for individuals with diabetes (in the model for women but not men),[15, 50] was not evaluated in this review because the addition of multiple nontraditional risk factors precludes examination of the additional value of hsCRP alone. External validation studies of the RRS have shown moderate discrimination in the range of 0.72 to 0.756; these values are similar to those of hsCRP-extended models in our review such as the IPD MA, which reports an extended model discrimination of 0.7179.[65, 139, 140] These external validation studies are mixed with respect to findings for calibration. The external validation study in the MESA cohort showed an overprediction of 9 percent in men and an underprediction of 21 percent in women;[139] calibration plots from an external validation study in the Women's Health Initiative, however, showed O:E ratios very close to 1 for most of the spectrum of risk, and overprediction of only about 4 percent in persons with 15 percent 10-year risk (which is not clinically important as these persons are already above treatment thresholds of 7.5 or 10%).[140] Differences in findings for calibration could be due to differences in risk and case mix between validation and development cohorts and/or differences in ascertainment of CVD events across the different cohorts.[141] In our analyses evaluating the incremental value of hsCRP to improve risk prediction, calibration outcomes were reported in only about one-third of included studies (9 of 25 articles), and preferred measures of calibration such as graphical measures and O:E were rarely reported. From these limited data, we conclude that hsCRP could improve the calibration of risk prediction models, at least for individuals in some risk groups. Therefore, the evidence for calibration of the RRS shown in these external validation studies is consistent with our review's finding.

Harms of Nontraditional Risk Factors

While CAC is the most promising nontraditional risk factor to improve discrimination and reclassification, it does have potential harms. We have previously discussed the issue with erroneous upward reclassification for individuals without a cardiovascular event, which is not specific to CAC. In addition, CT imaging for CAC is associated with exposure to low-dose radiation and a potential for increased burden of testing/procedures. Our review found that the estimate of radiation exposure or effective radiation dose is low—0.4 to 2.1 mSv per exam. Given that the average amount of radiation exposure from background sources in the United States is about 3.0 mSv per year,[142] ionizing radiation from a single examination for CAC is low. Even low doses of ionizing radiation, however, may convey a small excess risk of cancer.[143, 144]

Literature reviews of radiation exposure or effective radiation dose from CT imaging for CAC confirm that the exposure to radiation is low, but observe a wider range of doses. One review found the effective dose in 20 studies ranged from 0.5 to 7.7 mSv (excluding CAC from CT angiography).[129] This review found that prospective ECG-triggering had lower radiation exposure than retrospective ECG gating. Another recent review of 20 MDCT imaging protocols for CAC found a median exposure of 2.3 mSv per exam and a range of 0.8 to 10.5 mSv per exam.[130] This review also modeled cancer risk using the risk models from the National Research Council's Biological Effects of Ionizing Radiation (BIER) VII committee. Based on a one-time

screen at age 40 years, using a median dose of 2.3 mSv, the estimated lifetime excess cancer risk of 9 (range 3 to 42) cancers per 100,000 men, and 28 (range 9 to 130) cancers per 100,000 women. This excess risk decreased as individuals aged. The greater risk in women was attributed to excess breast cancer risk and a 2-fold-higher lung cancer risk.

CAC may also increase downstream health care utilization. We found mixed findings on whether CAC increased subsequent cardiac imaging or procedures (including revascularization). In the EISNER RCT, CAC did not increase subsequent imaging or procedures; however, a large retrospective analysis of Medicare claims data found an association of greater cardiac imaging and revascularization compared to an hsCRP or lipid screening group. Even if CAC does increase downstream testing in certain practice settings, it is unclear if this is a net benefit or harm, as the analysis from the Medicare claims data also found a nonstatistically significant association of fewer CVD events in the CAC versus hsCRP screening groups. A very small body of evidence, clinical heterogeneity, and methodological limitations of retrospective analyses of claims data prevent any definitive conclusions.

None of our included studies examined the prevalence of incidental findings on CT imaging for CAC. One systematic review included seven studies of screening CAC that reported the prevalence of any incidental findings (majority pulmonary nodules), which ranged from 8 to 58.1 percent of scans, 2.8 to 41.5 percent for "significant" findings, defined as cases requiring followup and 0.07 to 1.2 percent for newly diagnosed cancer.[145] Again, it is unclear whether identification of incidental findings represents a net benefit or harm. We found no studies that addressed downstream utilization of medical testing or procedures secondary to incidental findings, and/or benefits/harms from detection of incidental findings.

Benefits and Harms of Nontraditional Risk Factor-Guided Therapy

We found no studies that evaluated the benefit of nontraditional risk factor assessment when added to traditional multivariate risk factor assessment. Nonetheless, we included four trials that evaluated ABI, hsCRP, and CAC-guided therapy in asymptomatic individuals without known CVD. JUPITER found a benefit in CVD morbidity and all-cause mortality for high-intensity statin therapy consisting of rosuvastatin 20 mg in people with an elevated hsCRP but normal LDL (less than 130 mg/dL) compared to a placebo group. At baseline, approximately half of the participants had a 10-year risk of 10 percent or less (as calculated by the FRS) and therefore would likely not have been treated with a statin. All trial participants had an hsCRP of 2.0 mg/L or greater and thus this trial provides no direct evidence comparing treatment in those with an elevated compared to a normal hsCRP. Exploratory subgroup analyses by baseline hsCRP showed an increased absolute risk of a cardiovascular event with higher hsCRP levels, but similar relative risk reductions with rosuvastatin across the range of hsCRP levels included in the study.[146] It is unclear whether the benefit seen in JUPITER is applicable to just those with an elevated hsCRP or if this benefit would be applicable to a broader, unselected population as studies have shown mixed results about whether the benefit of statins extends to both those with normal and elevated hsCRP. A post-hoc analysis of the AFCAPS/TexCAPS trial showed the strongest support for effect modification; among participants with LDL less than 149 mg/dL, low- or moderate-intensity statin (lovastatin 20 or 40 mg) was associated with a reduction in CHD events in those with baseline hsCRP of 1.6 mg/L or greater (RR 0.58 [95% CI, 0.34 to

0.98]), but not in those with hsCRP below this level (RR 1.08 [95% CI, 0.56 to 2.08]); the p-value in a test for interaction among statin treatment, CRP, and lipid level was 0.06.[147] This was the hypothesis-generating analysis for JUPITER, which restricted its inclusion to individuals with normal LDL and elevated hsCRP (≥2.0 mg/L). HOPE-3, which evaluated moderate-intensity statin therapy consisting of rosuvastatin 10 mg compared to placebo, showed largely overlapping confidence intervals for CVD outcomes in analyses stratified by a hsCRP threshold of 2.0 mg/L (HR 0.82 [95% CI 0.64 to 1.06] for hsCRP ≤2.0 versus 0.77 [95% CI, 0.60 to 0.98] for hsCRP >2.0; p for interaction=0.694).[148] The Heart Protection Study, which included a higher-risk population (existing CHD, occlusive disease, diabetes, or receiving antihypertensive therapy), similarly showed no evidence of effect modification for CVD events by CRP level, with an overall event rate ratio of 0.76 (95% CI, 0.72 to 0.81) for moderate-intensity statin therapy consisting of simvastatin 40 mg versus placebo.[149] The benefit observed in JUPITER may represent an upper bound as the trial was stopped early at 1.9 years of followup. This trial found an increase in diabetes incidence in the statin group compared to the placebo group, but no other serious adverse events. The nonstatistically significant results of the St. Francis trial which evaluate CAC-guided statin therapy should not be directly compared to JUPITER (i.e., lack of benefit for CAC-guided statin therapy and benefit for hsCRP-guided statin therapy), as the St. Francis trial evaluated moderate-intensity statin therapy (as opposed to high-intensity) and was not adequately powered to detect differences in CVD events.

Limitations of the Review

Our review has numerous limitations. First, we focused this review on the three most promising nontraditional risk factors: ABI, hsCRP, and CAC. We also restricted our inclusion to English language studies and studies in developed countries, although we do not believe this restriction biased our review findings. Given the large volume of studies included for KQ2, we made some explicit exclusions so as to focus on the most clinically relevant analyses, such as the exclusion of: CVA-specific outcomes, CAC derived from lung cancer screening, or CT angiography, studies in which the comparator was a single nontraditional risk factor alone, and analyses that did not allow us to isolate the contribution of individual nontraditional risk factors (i.e., studies using base models including other risk factors and studies comparing the FRS to the RRS). Additionally, studies were excluded if it could not be determined whether reclassification was appropriate (i.e., reclassification was reported without respect to events). Additionally, the predictive value of traditional risk factors such as total or HDL cholesterol was taken as given, but some literature suggests that these, too, might be very small to small when assessed in terms of the c-statistic.[65] We were conservative in our data synthesis across the body of evidence; that is, we did not quantitatively pool c-statistics/AUC or NRI and we did not make direct comparisons of finding across studies. Even though we stratified our discussion by base model (the FRS vs. PCE) and model type (published coefficients vs. model development), many of the studies had variations in included populations (e.g., inclusion of patients with diabetes, distribution of CVD risk), differences in analyses (e.g., model recalibration, time horizon), differences in outcomes predicted (e.g., hard vs. soft events), and definitions of risk strata that prohibited more definitive conclusions. We did, however, explore differences in nontraditional risk factor performance in those studies which examined more than one nontraditional risk factor.

Limitations of Included Studies and Future Research Needs

No studies have evaluated the clinical impact of cardiovascular risk assessment with or without nontraditional risk factors on patient health outcomes. Clinical impact studies should be a priority if any of these nontraditional risk factors are implemented on a targeted population level. Largely speaking, the proliferation of cardiovascular risk assessment literature, particularly model development studies without external validation, will not provide the much-needed clinical answers on nontraditional risk factor assessment. However, there are some exceptions. Given that traditional risk tools can overestimate CVD risk, it is crucial to understand the incremental value of promising nontraditional risk factors on calibration, as well as discrimination and reclassification. More consistent reporting of calibration plots will allow for better understanding of what individuals will benefit from improved calibration and O:E ratios will facilitate comparison of calibration across studies. To understand the true net benefit of reclassification, robust reporting of event and nonevent NRI, and reporting of integrated measures that weight the erroneous misclassification for nonevent proportionally, are important. More studies in diverse populations will aid in understanding whether there are population segments for whom traditional risk factor assessment may underperform to a greater degree and thereby achieve greater benefit from nontraditional risk factor assessment. External validation studies of extended models with nontraditional risk factors are needed. Apart from the ABI Collaboration IPD meta-analysis, none of the extended models has been externally validated.

Given that CAC appears to be the most promising nontraditional risk factor, an IPD meta-analysis for CAC (including longer followup of included cohorts) would be informative in furthering understanding of reclassification in subpopulations (e.g., intermediate-risk groups, those for whom traditional risk factor assessment typically underperforms), and vet what impact a CAC score of 0 has on appropriate downward classification of people at intermediate or high risk by traditional risk assessment. Well-designed prospective studies that are reflective of real-world practice are needed to evaluate the downstream effects of CAC on cardiac imaging and revascularization, as well as incidental findings, since these are common. These include studies that aid in determining whether the identification of incidental findings, and/or increased health care utilization, is a net benefit or net harm.

Conclusion

In the absence of true clinical impact studies reporting cardiovascular morbidity and/or mortality, we need to understand the incremental value of risk prediction with nontraditional risk factors, using calibration, discrimination and reclassification. Despite limitations in the reporting of these performance measures as well as limitations in the measures themselves, we can draw some conclusions. There remains scant information on the incremental value of nontraditional risk factors to help with the problem of miscalibration of traditional cardiovascular risk assessment. Evidence from one large IPD meta-analysis suggests that clinicians could use ABI in addition to the FRS to improve upon discrimination and reclassification in populations for whom the FRS model has poor discrimination. While CAC appears to be the most promising nontraditional risk

factor to improve discrimination and reclassification, it is based on a smaller body of evidence which lacks IPD meta-analyses. CAC may also result in additional downstream testing/procedures, and it is unclear whether these sequelae represent a net benefit or harm to individuals. One large RCT shows that high-intensity statin therapy in individuals with elevated hsCRP and normal lipid levels can reduce CVD morbidity and mortality, but it is unclear whether these benefits would not also be applicable to individuals with normal hsCRP. The use of hsCRP-guided therapy has not been evaluated against therapy guided by multivariate cardiovascular risk assessment.

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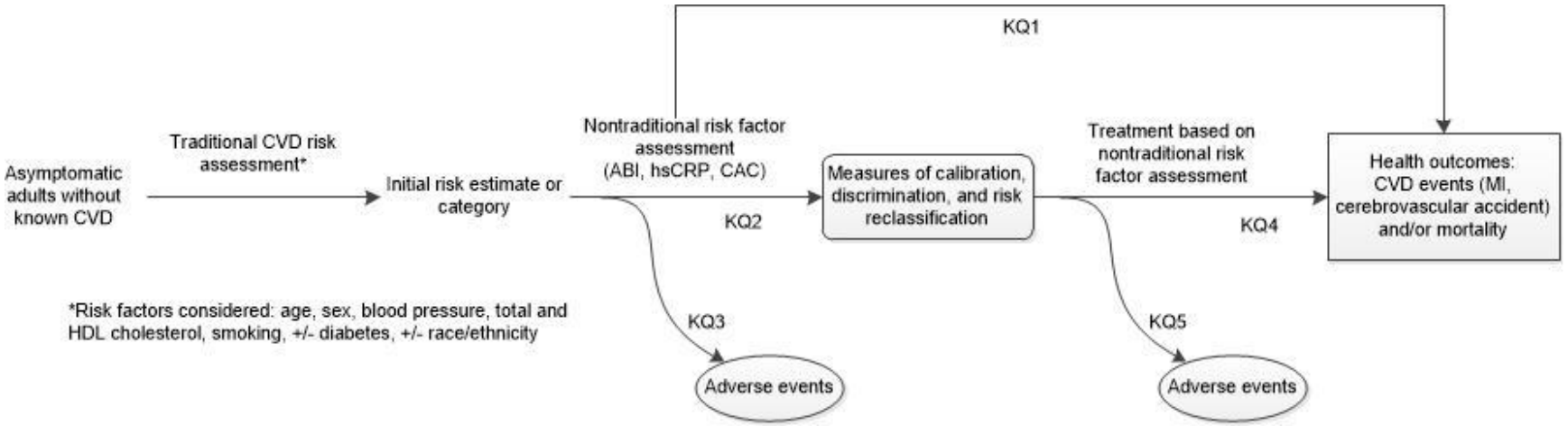
Figure 1. Analytic Framework



Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CVD = cardiovascular disease; hsCRP = high sensitivity C-reactive protein, KQ = key question; MI = myocardial infarction

Table 1. Characteristics of Available and Externally Validated Cardiovascular and Coronary Risk Assessment Models

Risk score Recommending body	Risk factors included in the model	Time horizon and outcome	Derivation cohort(s)
ACC/AHA Pooled Cohort Equation, 2013[21] ACC/AHA[7]	• Age • Sex • Race/ethnicity • Treated or untreated SBP • TC • HDL-C • Current smoking • Diabetes Other CVD RF evaluated but not included*	10-year risk First hard CVD event (nonfatal MI, CHD death, fatal or nonfatal stroke)	ARIC, CHS, CARDIA, Framingham/ Framingham Offspring
Framingham CVD, 2008[20] Canadian Cardiovascular Society[22]	• Age • Sex • TC • HDL-C • SBP • Antihypertensive medication use • Smoking • Diabetes • (Family history)†	10-year risk Any CVD event (coronary death, MI, coronary insufficiency, and angina, cerebrovascular events, peripheral artery disease [intermittent claudication], and CHF)	Framingham Heart Study
QRISK2, 2008[150] NICE[36]	• Age • Sex • Race/ethnicity • Smoking status • SBP • Ratio of TC/HDL-C • BMI • Family history of CHD in first degree relative <60 years • Townsend deprivation score • Treated HTN • Rheumatoid arthritis • Chronic kidney disease • Diabetes • Atrial fibrillation	10-year risk CVD event (angina, MI, stroke, TIA)	UK primary care database; 2/3 of participants randomly allocated to derivation dataset and 1/3 assigned to validation data set
Reynolds, men, 2008[50] N/A	• Age • SBP • Smoking • TC • HDL-C • hsCRP • Parental history of MI <60 years	10-year risk CVD event (CVD death, MI, stroke, coronary revascularization)	PHS
Reynolds, women, 2007[15] N/A	• Age • SBP • Smoking • TC • HDL-C • hsCRP • Parental history of MI <60 years • HbA1c if diabetic	10-year risk CVD events (CVD death, MI, stroke, coronary revascularization)	WHS; 2/3 of participants assigned to model derivation data set and 1/3 assigned to validation data set
ASSIGN, 2007[151] SIGN[42]	• TC • HDL-C • SBP • Smoking • Cigarettes per day • Family history • Diabetes • Index of social status/ deprivation	10-year risk CVD events (CVD death, hospitalization for CHD or cerebrovascular disease, revascularization)	SHHEC

Table 1. Characteristics of Available and Externally Validated Cardiovascular and Coronary Risk Assessment Models

Risk score Recommending body	Risk factors included in the model	Time horizon and outcome	Derivation cohort(s)
ARIC, 2003[28] N/A	• Sex • Race • Cigarette smoking • TC • HDL-C • SBP • Antihypertensive medication use • Diabetes Other CVD RF evaluated but not included‡	10-year risk CHD event (CHD death, MI, unrecognized MI defined by ECG readings, or coronary revascularization)	ARIC
SCORE, 2003[152] European Society of Cardiology[153]	• Age • Sex • Smoking • TC or TC/HDL ratio • SBP • Smoking • High- and low-risk regions of Europe	10-year risk Fatal CVD event (MI, stroke, aortic aneurysm)	Pooled data set of population-based and occupational cohort studies from 12 European countries
PROCAM, 2002[154] N/A	• Age • LDL-C • HDL-C • TG • Smoking • Diabetes • Family history of MI <60 years • SBP	10-year risk CHD event (sudden cardiac death, definite MI)	Prospective German cohort of men
ATP III modification of Wilson Framingham model, 2002§[19] ATP III[19]‖	• Age • Sex • TC • HDL-C • SBP • Treatment for HTN • Smoking	10-year risk Hard CHD (MI and CHD death)	Framingham Heart Study

* ACC/AHA recommends that if risk-based treatment is uncertain using this tool, then consider one or more of the following: family history, hsCRP, CAC score or ABI. Do not use CIMT for risk assessment. No recommendation for or against use of ApoB, CKD, microalbuminuria, and cardiorespiratory fitness.

† Canadian Cardiovascular Society recommends a modified version of the model that includes family history of premature CHD.[22]

‡ Other CVD RF explored: age, BMI, waist-hip ratio, sport activity index, forced expiratory volume, plasma fibrinogen, factor VII, factor VIII, von Willebrand factor, Lp(a), heart rate, Keys score, pack-years smoking, CIMT, fasting TG, ApoA, ApoB, albumin, white blood cell count, creatinine

§ There are additional Framingham-based risk assessment models with variations in outcomes predicted and risk factors included.[16-18, 155] In this table we have focused on models recommended by guideline bodies.[19, 20]

‖ Replaced by 2014 recommendations from the ACC/AHA[7]

Abbreviations: ACC: American College of Cardiology; AF: atrial fibrillation; AHA: American Heart Association; ApoA: apolipoprotein A; ApoB: apolipoprotein B; ARIC: Atherosclerosis Risk in Communities Study; ATP III: Adult Treatment Panel III; BMI: body mass index; BP: blood pressure; CARDIA: Coronary Artery Risk Development in Young Adults; CHD: coronary heart disease; CHF: congestive heart failure; CHS: Cardiovascular Health Study; CIMT: carotid intima-media thickness; CKD: chronic kidney disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; ECG: electrocardiogram; HbA1c: glycated hemoglobin; HDL-C: low-density lipoprotein cholesterol; HHP: Honolulu Heart Program; hsCRP: high-sensitivity c-reactive protein; HTN: hypertension; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein a; MESA: Multi-Ethnic Study of Atherosclerosis; MI: myocardial infarction; N/A: not applicable; NHLBI: National Heart, Lung, and Blood Institute; NICE: National Institute for Health and Care Excellence; PHS: Physician's Health Study; PR: Puerto Rico Heart Health Program; PROCAM: Prospective Cardiovascular Münster; REGARDS: Reasons for Geographic and Racial Differences in Stroke study; RF: risk factors; SBP: systolic blood pressure; SCORE: Systematic Coronary Risk Evaluation; SES: socioeconomic status; SHHEC: Scottish Heart Health Extended Cohort; SHS: Strong Heart Study; SIGN; Scottish Intercollegiate Guidelines Network; TC: total cholesterol; TG: triglycerides; TIA: transient ischemic attack; UK: United Kingdom; US: United States; WHI: Women's Health Initiative; WHS: Women's Health Study

Table 2. Description of Nontraditional Risk Factors Evaluated in This Review

Risk factor	Description
ABI	The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the brachial artery; an ABI of <0.9 is considered diagnostic for PAD.[156]
hsCRP	hsCRP is a serum protein involved in immune and inflammatory responses that can be readily measured in widely available lab tests.[47, 48] Several assays are available, including conventional, high-sensitivity, and cardiac hsCRP tests. High-sensitivity and cardiac hsCRP assays have a lower detection limit than conventional tests.[157] Cutoff values of >2 and >3 mg/L have been proposed to define elevated hsCRP for the purposes of CVD risk assessment.[48, 120]
CAC	Calcium content of the coronary arteries estimated from CT imaging using 1 of several scoring systems. Categories indicating elevated CAC vary across study, but are often compared with 0 CAC.[48]

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CT = computed tomography; hsCRP = high sensitivity C-reactive protein

Table 3. Examples of Types of Test Performance Measures for Comparing Risk Assessment or Prediction Models[59-61, 63, 64]

Purpose of outcome measure	Example measures of test performance	Description
Calibration	Calibration plot	Graphical assessment of calibration with predictions on the x-axis and outcome on the y-axis. Calibration in the large and calibration slope can be derived from calibration plots.
	O:E	The ratio of observed to expected events.
	Hosmer–Lemeshow χ^2	Calculated by summing differences between observed and predicted probabilities in each group (a group being some parsing of the population, e.g., by decile, risk strata); a significant p-value signals poor fit. The test is sensitive to how groups are constructed and is sensitive to sample size, often being nonsignificant for small N and significant for large N.[59] The Hosmer–Lemeshow χ^2 does not adjust for time-to-event, and several approaches have been developed to extend the test for survival data (but were not reported in included studies).[60]
Overall performance (captures both calibration and discrimination aspects)[57]	Akaike information criterion (AIC) and Bayes information criterion (BIC)	The AIC and BIC are measures used during model development to aid in inclusion or exclusion of predictors in a model. The AIC is a function of log likelihood that adds a penalty for each added predictor. The BIC is similar, although it imposes a greater penalty than the AIC for added variables. Lower values of both measures indicate better model fit. A change of >10 in the AIC has been proposed to indicate strong evidence for a difference in models.[84]
	Likelihood ratio χ^2	Likelihood ratio χ^2 is a global test of model fit and a function of the number of terms in the model. Higher values for the ratio, or difference between models, indicate better fit (as do lower absolute log-likelihood values).[83] A global χ^2 is generally the same as a likelihood χ^2 (twice the log likelihood ratio).
	Brier score	The Brier score computes the sum of squared differences between observed outcomes and fitted probability, where lower values indicate that predicted probabilities are closer to observed outcomes.[83]
	R^2	There are a number of ways to calculate an R^2 for a logistic regression.[59] Nagelkerke's generalized R^2, which is reported in included studies in this body of literature, is generally analogous to the percentage of variance explained in a linear model and is adjusted to a range of 0 to 1. Higher values indicate better fit.[83] The R^2 is more helpful than the Brier score because it can be compared across models/studies.
Discrimination	c-statistic or area under the curve (AUC); change in c-statistic or AUC	The probability that, for a randomly selected pair of individuals, one with disease and the other without, the person with disease will have the higher estimated disease probability according to the model.[83] The c-statistic can be conceptualized as the area under the ROC curve (plots sensitivity against 1−specificity); as a rank order statistic it is insensitive to systematic errors in calibration.[57] The Harrell's c-statistic is an extension of the AUC for survival analysis allowing for right-censored data and variable time to follow up.[158] The change in c-statistic or AUC can be insensitive in assessing the impact of adding new predictors to a model, and the impact of a new predictor on c-statistics is lower when other strong predictors are in the model.[134]
Risk reclassification	Net reclassification index or improvement (NRI)	The sum of differences in proportions of individuals moving up a risk category minus those moving down a risk category with a cardiovascular disease outcome, plus the proportion moving down a risk category minus those moving up a risk category without an outcome. The NRI can be considered separately as the sum of the event NRI (P[up|event] – P[down|event]) and nonevent NRI (P[down|nonevent] – P[up|nonevent]). The NRI is not weighted for the prevalence of events or nonevents; some experts have advocated against combining event and nonevent NRI[67] and others have commented that NRI is naturally weighted by event and nonevent

Table 3. Examples of Types of Test Performance Measures for Comparing Risk Assessment or Prediction Models[59-61, 63, 64]

Purpose of outcome measure	Example measures of test performance	Description
		categories serving as their own denominators.[159] The NRI is of limited value in comparing models with different risk categories.
	Integrated discrimination improvement (IDI)	Integrates the NRI over all possible cutoffs; equivalent to difference in discrimination slopes of the 2 models and to the difference in R^2.[57]

Table 4. Cardiovascular Risk Prediction Base Models and Types of Outcomes (Events) Used

Outcomes	Fatal only	Hard*	Soft
CVD	SCORE†	PCE	D'Agostino 2008[20]
CHD		ATP III	Wilson, 1998[18]

* Preferable analyses

† SCORE was not evaluated in this review

Abbreviations: ATP III = Adult Treatment Panel III; CHD = coronary heart disease; CVD = cardiovascular disease; PCE = Pooled Cohort Equations

Table 5. Evidence Landscape

KQ1	KQ2	KQ3	KQ4	KQ5	Cohort study	Author, Year	Nontraditional risk factor(s) evaluated
X		X			EISNER	Rozanski, 2011[11]	CAC
	X	X			Framingham Offspring + 3rd Generation	Hoffmann, 2016[88]	CAC
	X	X			Rotterdam	Bos, 2015[89]	CAC
	X				ABI Collaboration	Fowkes, 2014[66]	ABI
	X				ARIC	Murphy, 2012[79]	ABI
	X				ARIC	Folsom, 2006[110]	CRP
	X				British Regional Heart Study	Wannamethee, 2011[102]	CRP
	X				EAS	Price, 2007[80]	ABI
	X				EAS	Shah, 2009[78]	CRP
	X				EISNER	Rana, 2012[99]	CAC, CRP
	X				EISNER + Referred Participant Database	Wong, 2009[106]	CAC
	X				EPIC-Norfolk	Rana, 2009[104]	CRP
	X				ERFC IPD MA	Emerging Risk Factors Collaboration, 2012[65]	CRP
	X				Framingham + Framingham Offspring	Wilson, 2005[85]	CRP
	X				Framingham Offspring	Wilson, 2008[107]	CRP
	X				Framingham Offspring	Zhou, 2013[97]	CRP
	X				Health ABC	Rodondi, 2010[81]	ABI, CRP
	X				HNR	Geisel, 2017[114]	ABI, CAC
	X				HNR	Mohlenkamp, 2011[103]	CAC, CRP
	X				HNR	Erbel, 2010[74]	CAC
	X				Houston Methodist DeBakey Heart and Vascular Center	Chang, 2015[93]	CAC
	X				Inter99	Seven, 2015[92]	CRP
	X				MESA	Yeboah, 2016[90]	ABI, CAC, CRP
	X				MESA	Yeboah, 2012[75]	ABI, CAC, CRP
	X				MESA	Polak, 2017[113]	CAC
	X				MESA	Fudim, 2016[112]	CAC
	X				MESA	Polonsky, 2010[77]	CAC
	X				MESA	Malik, 2011[101]	CAC
	X				MESA and HNR	Yeboah, 2014[94]	CAC
	X				MONICA - Augsburg	Koenig, 2004[84]	CRP
	X				MONICA - Copenhagen	Lyngbaek, 2013[96]	CRP
	X				Nijmegen Biomedical Study	Holewijn, 2014[95]	ABI
	X				NPHS II	Shah, 2009[78]	CRP
	X				Pooled Analysis of 5 Cohorts‡ of Low Risk Women	Kavousi, 2016[111]	CAC
	X				PROSPER	Sattar, 2007[108]	CRP
	X				REGICOR	Velescu, 2015[91]	ABI
	X				Reykjavik	Danesh, 2004[87]	CRP
	X				Rotterdam	Kavousi, 2012[82]	ABI, CAC, CRP
	X				Rotterdam	Elias-Smale, 2010[76]	CAC, CRP
	X				Scottish Health Survey	Hamer, 2009[105]	CRP
	X				SHIP	Schneider, 2012[100]	CRP
	X				Singapore Chinese Health Study	Salim, 2016[109]	CRP
	X				South Bay Heart Watch	Greenland, 2004[86]	CAC
	X				WHS	Cook, 2006[83]	CRP
	X				WOSCOPS	Welsh, 2013[98]	CRP
		X			Active-duty Army personnel	O'Malley, 2003[119]	CAC
		X			DanRisk	Nielsen, 2012[118]	CAC
		X			HealthCore Integrated Research Database	Chi, 2014[116]	CAC
		X			Medicare	Shreibati, 2014[117]	CAC, CRP

Table 5. Evidence Landscape

KQ1	KQ2	KQ3	KQ4	KQ5	Cohort study	Author, Year	Nontraditional risk ractor(s) evaluated
		X			MESA	Messenger, 2016[115]	CAC
			X	X	AAA	Fowkes, 2010[122]	ABI
			X	X	JUPITER	Ridker, 2008[120]	CRP
			X		JUPITER	Mora, 2010[124]†	CRP
			X	X	POPADAD	Belch, 2008[123]	ABI
			X		St. Francis Heart Study	Arad, 2005[121]	CAC
1	***44****	***8***	***5***	***3***	***Number of total articles***		

* There are 44 cohorts reported in 43 articles. Shah, 2009, analyzes both EAS and NPHS cohorts.
† Sex-specific analyses
‡ Five pooled cohorts: DHS, FHS, HNR, MESA, and Rotterdam

Abbreviations: AAA = the Aspirin for Asymptomatic Atherosclerosis trial; ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities study; CAC = coronary artery calcium; CRP = C-reactive protein; DanRisk = the Danish Risk Score study; DHS = Dallas Heart Study; EAS = Edinburgh Artery Study; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC = Emerging Risk Factors Collaboration; FHS = Framingham Heart Study; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; IPD MA = individual participant data meta-analyses; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KQ = key question; MESA = Multi-Ethnic Study of Atherosclerosis; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; POPADAD = the Prevention of Progression of Arterial Disease and Diabetes trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry); SHIP = the Study of Health in Pomerania; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study

Table 6. Methodological and Intervention Characteristics of Included Screening Studies (KQs 1 and 3)

Author, Year Study name	Quality	Country	N	Recruitment setting and method	Followup	Intervention	Control	Primary outcome
Rozanski, 2011[11] EISNER	Fair	U.S.	2,137	Volunteers recruited from medical center	4 years	One individual risk factor counseling session with trained NP and CAC scan. Counseling session included review of CAC images, score and percentile; patients encouraged to share CAC scan report with their physician (report was not directly shared) CAC scanning performed with electron beam or multislice CT; imaging protocol involved single scan of ~30 to 40 slices of 3 or 2.5 mm thickness. Agatston method used to determine calcium score.	One individual risk factor counseling session with trained NP	4-year change in CAD risk factors and FRS

Abbreviations: CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FRS = Framingham Risk Score; mm = millimeter; NP = nurse practitioner

Table 7. Patient Characteristics of Included Screening Studies (KQs 1 and 3)

Author, Year Study name	Population description	Mean age, years	% Women	% by Race/ethnicity	% Smoking	% Diabetes	% High Cholesterol	% HTN	% Medications	% by CAC score categories*	FRS, %
Rozanski, 2011[11] EISNER	Middle-aged individuals with CAD risk factors, but no CVD history or symptoms	58.5	47.5	Caucasian: 77.0 African American: 5.0 Asian/PI: 10.5 Latino: 4.2	Past: 41.5 Current: 5.7	8.2	77.5	57.3	Aspirin: 12.8 BP: 32.2 Diabetes: 4.1 Statins: 23.5	0: 48.1 1-99: 30.5 100-399: 13.0 ≥400: 8.3	6 (2, 12)†

* For N=1,311

† Median (25th, 75th percentile) 10-year risk for CAD; patients with diabetes automatically assigned high risk of 20%, or higher if so calculated

Abbreviations: BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FRS = Framingham Risk Score; PI = Pacific Islander; HTN = hypertension

Table 8. Cardiovascular Events, Mortality, and Harms Outcomes in Included Screening Studies (KQs 1 and 3)

Author, Year Study name	Followup	Outcome	IG N	IG N (% or level)	CG N	CG N (% or level)	Between group difference; RR (95% CI)*; p
Rozanski, 2011[11] EISNER	4 years	Composite of all deaths and MI	1,256	27 (2.1)	584	6 (1.0)	2.09 (0.87 to 5.04); p=0.08
		All-cause death	1,256	17 (1.3)	584	4 (0.6)	1.98 (0.67 to 5.85); p=0.24
		Cardiac death	1,256	2 (0.2)	584	1 (0.2)	0.93 (0.08 to 10.24); p=1.00
		MI	1,256	10 (0.8)	584	2 (0.3)	2.32 (0.51 to 10.58); p=0.36
		Estimated radiation dose (mSv)	1,256	1 to 2	584	NA	NR

*****Calculated crude RR and CI; p-values are study-reported

Abbreviations: CG = control group; CI = confidence interval; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; IG = intervention group; MI = myocardial infarction; mSv = millisievert; RR = relative risk

Table 9. Study Counts for Key Question 2

Risk factor	For any KQ2 outcome	Calibration	Discrimination	Reclassification
ABI	10 articles 22 cohorts* 12 models	5 articles 20 cohorts* 5 models	10 articles 22 cohorts* 12 models	9 articles 22 cohorts* 10 models
CRP	25 articles† 49 cohorts‡ 28 models	9 articles† 10 cohorts 11 models	25 articles† 49 cohorts‡ 28 models	15 articles† 33 cohorts§ 17 models
CAC	19 articles 10 cohorts 24 models	8 articles 4 cohorts 8 models	18 articles 10 cohorts 23 models	15 articles 9 cohorts 18 models

*18 cohorts represented in 1 IPD MA

† 1 article, Shah 2009, reports 2 cohorts separately

‡ 38 cohorts represented in 1 IPD MA

§ 22 cohorts represented in 1 IPD MA (studies were included for reclassification analyses if they had >10 years of followup and reported both fatal and nonfatal CVD events)

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CRP = C-reactive protein; CVD = cardiovascular disease; IPD MA = individual participant data meta-analyses; KQ = key question

Table 10. Comparison of Predictive Ability of Nontraditional Risk Factors Across Selected Analyses Reporting More Than One Nontraditional Risk Factor (ABI, hsCRP, CAC)

	Cohort (Publication)	MESA (Yeboah, 2016)[90]	MESA (Yeboah, 2016)[90]	Heinz Nixdorf Recall (Geisel, 2017)[114]	MESA–Intermediate risk only# (Yeboah, 2012)[75]	Rotterdam** (Kavousi, 2012)[82]	Health ABC (Rodondi, 2010)[81]	Heinz Nixdorf Recall (Mohlenkamp, 2011)[103]	EISNER (Rana, 2012)[99]
	Model Type	Published coefficient	Published coefficient	Published coefficient	Model development	Model development	Model development	Model development	Model development
	Base Model	PCE	FRS	FRS	FRS variables	FRS variables	FRS variables	FRS variables	FRS variables
	Predicted Outcome	Hard CVD	Hard CHD	Hard CVD	Soft CVD	Hard CHD	Hard CHD	Hard CHD	Soft CVD
	Risk Thresholds (%)	≥7.5 <7.5 10 yr-risk	>20 10 to 20 <10 10-yr risk	>20 10 to 20 <10 10-yr risk	>21.1 3.4 to 21.1 <3.47 5-yr risk	>20 10 to 20 <10 10-yr risk	≥15 7.5 to <15 <7.5 7.5-yr risk	>20 10 to 20 <10 10-year risk	>8 2.4 to 8 <2.4 4-yr risk
	N analyzed; # events	5,185 320	5,185 194	3,108 223	1,330 132	3,029 to 5,933‡ 347	1,515 to 2,191†† 197	3,966 91	1,286 35
ABI	C-statistic (Δ*)	0.75 (Δ=0.01) p=0.55	0.75 (Δ=0.01) p=0.042	0.687 (Δ=-0.006) p=0.54	0.65 (Δ=0.027) p=0.01	NR (Δ=0.00†, [0.00 to 0.00]) p=NR	0.612 (Δ=0.012) p=NR; N=1,515		
	Event NRI Nonevent NRI *Total NRI* *(95% CI)*	0.013 0.004 *0.017* *(-0.031 to 0.058)*	0.041 -0.003 *0.039* *(-0.011 to 0.109)*	NR NR 0.190‡‡ (0.102 to 0.278)	0.041 0.027 *0.068* *(NR)*	NR NR *0.006* *(-0.018 to 0.029)*	NR NR *0.079* *(NR)*		
hsCRP	C-statistic (Δ*)	0.74 (Δ=0.0) p=0.25	0.74 (Δ=0.0) p=0.925		0.64 (Δ=0.017) p=0.03	NR (Δ=0.00† [-0.01 to 0.00]) p=NR	0.592 (Δ=-0.008) p=NR	0.732 (0.684 -0.780) (Δ=0.013) p=0.12	0.73 (0.65 - 0.82) (Δ=0.0) p=0.95
	Event NRI Nonevent NRI *Total NRI* *(95% CI)*	0.028 -0.005 *0.024* *(-0.015 to 0.067)*	0.005 -0.002 *0.003* *(-0.028 to 0.026)*		0.016 0.021 *0.037* *(NR)*	NR NR *0.020* *(-0.023 to 0.064)*	*NR*‖	NR NR *0.105* *p=0.026*	*NR*‖
CAC	C-statistic (Δ*)	0.76 (Δ=0.02) p=0.04	0.78 (Δ=0.04) p=0.001	0.731 (Δ=0.038) p=0.02	0.78 (Δ=0.161) p<0.001	NR (Δ=0.05†, [0.02 to 0.06])		0.763 (0.715 to 0.812) (Δ=0.044) p=0.0067	0.84 (0.78 to 091) (Δ=0.11) p=0.003
	Event NRI Nonevent NRI *Total NRI* *(95% CI)*	0.178 -0.059 *0.119* *(0.080 to 0.256)*	0.119 -0.034 *0.084* *(0.024 to 0.19)*	NR NR 0.551‡‡ (0.416 to 0.686)	0.106 0.360 *0.466* *(NR)*	0.235 -0.041 *0.193* *(0.125 to 0.262)*		NR NR *0.238* *p=0.0007*	0.286 0.060 *0.35* *(0.11 to 0.58)*

* Change in c-statistics calculated as extended model minus base model

† c-statistic is corrected for over-optimism by using 100 bootstrap repetitions

‡ The analyses for hsCRP (n=3,029) and CAC score (n=3,678) were performed in a smaller group.

§ In case of hsCRP, power was not enough to perform sex-specific analysis.

‖ NRI was not reported because hsCRP did not result in significant improvement in c-statistics

¶ Chose external validation dataset; model development was available

NRI is not bias-corrected.

** Not shown: Elias-Smale,2010[76] obtained similar results with a smaller cohort (n=2,028) from the Rotterdam Study: C-statistics – hsCRP: Δ*=0.0, p=0.31; CAC: Δ*=0.04 p<0.001; NRI – CAC: 0.14; hsCRP: NR, due to c-statistics not resulting in significant improvement.

†† c-statistics analyzed with completed data on all markers in Health ABC, n=1,515; NRI analyzed with complete data on ABI in Health ABC, n=1,985.

‡ ‡ Continuous NRI

Table 10. Comparison of Predictive Ability of Nontraditional Risk Factors Across Selected Analyses Reporting More Than One Nontraditional Risk Factor (ABI, hsCRP, CAC)

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FRS = Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; hsCRP = high-sensitivity C-reactive protein; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement; PCE = Pooled Cohort Equations

Table 11. A Comparison of Cohorts in the Included ABI Risk Prediction Studies With ABI Collaboration IPD Meta-Analysis

Cohort	2014 IPD MA[66]*	Individual publications
ARIC	n=10,467	Murphy, 2012[79]; n=11594
Belgian Physical Fitness	n=2,020	
CHS	n=3,877	
EAS	n=1,392	Price, 2007[80]; n=1007
Framingham Offspring	n=3,126	
Health ABC	n= 1,405	Rodondi, 2010[81]; n=2191
Health in Men	n=3,217	
Honolulu Heart Program		
HNR		Geisel, 2017[114]; n=3,108
Hoorn Study	n=557	
InCHIANTI	n=1,161	
Limburg PAOD	n=2,361	
Men Born in 1914	n=392	
MESA		Yeboah, 2016[90]; n=5185
MONICA Augsburg	n= 1,283	
Mr OS	n=4,167	
Nijmegen		Holewijn, 2014[95]; n=1367
REGICOR		Velescu, 2015[91]; n=5248
Rotterdam	n=5,549	Kavousi, 2012[82]; n=5933
San Diego	n=556	
San Luis Valley Diabetes	n=1,513	
Strong Heart		
Study of Osteoporotic Fractures	n=1,233	
Women's Health and Aging	n=476	
22 total cohorts; 4 not represented in IPD MA		

*The 2008 IPD MA from the ABI Collaboration additionally included the Honolulu Heart Program and Strong Heart Study, which were excluded in the 2014 updated due to restriction to White populations.[125]

Abbreviations: ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities study; CHS = Cardiovascular Health Study; EAS = Edinburgh Artery Study; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall = InCHIANTI = *Invecchiare in Chianti* (aging in the Chianti area); IPD MA = individual participant data meta-analyses; Limburg PAOD = the Limburg peripheral arterial occlusive disease study; MESA = Multi-Ethnic Study of Atherosclerosis; MONICA = MONItoring of trends and determinants in CArdiovascular disease; Mr OS = the Osteoporotic Fractures in Men study; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry)

Table 12. Study Design and Participant Characteristics of Included ABI Risk Prediction Studies (KQ 2)

Author, Year	Model type: Base model	Study name	Country	N	F/U, mean (yrs); range	Mean age	% Women	% White	% DM	% HTN (% treated)	% Chol meds*	% Current smoker	Mean ABI; (% Low ABI)¶¶¶
Yeboah, 2016[90]‖‖	Published coefficient: PCE	MESA	United States	5,185	10; NR	61.2	53.1	38	9.8	NR (32.5)	0	13.6	1.1§; (NR)
	Published coefficient: FRS	MESA	United States	5,185	10; NR	61.2	53.1	38	9.8	NR (32.5)	0	13.6	1.1§; (NR)
Geisel, 2017 [114]	Published coefficient: FRS	HNR	Germany	3,108	10.3; NR	59.2	52.9	NR	11.5	NR (31.6)	9.2	22.6	1.14; (3.7)
Velescu, 2015[91]	Published coefficient: FRS	REGICOR	Spain	5,248	5.9§; NR	53.7	54.5	NR	12.6	41.8 (NR)	NR	24.1	NR; (3.2)
Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration IPD MA†	Multi-national	44,752‡	NR; 5.0-19.6§	NR	45.5	100	NR	NR (NR)	NR	NR	NR; (NR)
	Model development: FRS variables	ABI Collaboration IPD MA†	Multi-national	44,752‡	NR; 5.0-19.6§	NR	45.5	100	NR	NR (NR)	NR	NR	NR; (NR)
Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study	Netherlands	1,242	3.8; 0.083-5.6	60.8	53.1	NR***	4.5	35 (21.6)	9.9	16.5	1.11; (1.3)
Yeboah, 2012[75]‖‖	Model development: FRS variables	MESA	United States	1,330‖‖‖	7.6§; 7.3-7.8 (IQR)	63.8	33.3	35.7	0	NR (38.2)	14.1	16.5	1.14§; (NR)
Kavousi, 2012[82]‖‖	Model development: FRS variables	Rotterdam	Netherlands	5,933	6.8§; 5.8-8.1 (IQR)	69.1	59.4	NR	12.9	NR (23.5)	10.2	17.5	1.1; (14)
Murphy, 2012[79]	Model development: FRS variables	ARIC	United States	11,594	14§; (Max 16)	53.8	56.4	75.8	0	33.4 (24.5)	2.1	25.7	1.15; (2.3¶)
Rodondi, 2010[81] ††	Model development: FRS variables	Health ABC	United States	2,191	8.2§; (Max 10.2)	73.5	55.3	58.9	13.3	46.1 (12.5§§)	10.5	10.1	NR; (12.2‡‡‡)
Price, 2007[80]	Model development: FRS variables	EAS	United Kingdom	1,007	NR; (Max 12)	69.4	51.7	NR	3.9	NR (NR)	NR	2.48**	1.02; (18.7)

* Percent with hyperlipidemia not reported in any included ABI study

† 18 included cohorts: ARIC, Belgian Physical Fitness Study, CHS, EAS, Framingham Offspring Study, Health ABC Study, Health In Men Study, Hoorn Study, InCHIANTI Study, Limburg PAOD Study, Men Born in 1914 Study, MONICA Augsburg Survey, Mr OS Study, Rotterdam Study, San Diego Study, San Luis Valley Diabetes Study, Study of Osteoporotic Fractures, Women's Health and Aging Study. Strong Heart Study and Honolulu Heart Program included in Fowkes, 2008, but not present study as non-Whites excluded from this analysis.

‡ 24,707 in development/internal validation dataset and 20,045 in external validation data set

§ Median

¶ Symptomatic PAD present in 3.7% of those with ABI <0.9 and 0.4% in those with ABI ≥0.9

** Mean pack-years

†† Also a study of CRP

Table 12. Study Design and Participant Characteristics of Included ABI Risk Prediction Studies (KQ 2)

§§ ACE inhibitors are the only anti-HTN drug class reported
‖‖ Also a study of CAC and CRP
*** "Most" Caucasian
††† FRS recalibrated to REGICOR population
‡‡‡ Calculated from denominator of 1702 in Table 6 (207/1702)
‖‖‖ Intermediate-risk population only, defined as >5% to <20% 10-yr CHD risk
¶¶¶ Threshold for low ABI was < or ≤0.9 where reported

Abbreviations: ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities study; CAC = coronary artery calcium; CHD = coronary heart disease; Chol = cholesterol; CRP = C-reactive protein; DM = diabetes mellitus; EAS = Edinburgh Artery Study; FRS=Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HTN = hypertension; InCHIANTI = *Invecchiare in Chianti* (aging in the Chianti area); IPD MA = individual participant data meta-analyses; IQR = interquartile range; Limburg PAOD = the Limburg peripheral arterial occlusive disease study; meds = medications; MESA = Multi-Ethnic Study of Atherosclerosis; MONICA = MONItoring of trends and determinants in CArdiovascular disease; Mr OS = the Osteoporotic Fractures in Men study; NR = not reported; PCE = Pooled Cohort Equations; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry); yr(s) = year(s)

Table 13. Base Models for Included ABI Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	TC: HDL ratio	DM	Predicted outcomes[llll]: N (%)	Handling of ABI in extended model
Yeboah, 2016[90]††	Published coefficient: PCE (Goff, 2014)‡‡	MESA	x	x	x	x	x	x	x	x		x	Hard CVD: 320 (6.2)	Continuous (ABI ≥1.4 excluded)
Yeboah, 2016[90]††	Published coefficient: FRS (D'Agostino, 2001)‡‡	MESA	x	x		x	x†		x	x		x	Hard CHD: 194 (3.7)	Continuous (ABI ≥1.4 excluded)
Geisel, 2017[114]	Published coefficient: FRS	HNR	x	x		x	x	x	x	x		x	Hard CVD: 223 (7.2)	Continuous (per-SD decrease) for discrimination analyses; Categorical: <0.9, ≥0.9 for reclassification analyses
Velescu, 2015[91]	Published coefficient: FRS (D'Agostino, 2001)§§	REGICOR	x	x		x	x†		x	x		x	Soft CVD: 175 (3.3) Soft CHD: 111 (2.1)	Categorical: ≤0.9, >0.9 (>1.39 excluded)
Fowkes, 2014[66]	Published coefficient: FRS (Wilson, 1998)	ABI Collaboration IPD MA	x	x		x	x†		x	x		x	Hard CHD: 2950 (6.6)§ Fatal CVD‡: 2704 (6.0)§	Categorical: ≤0.90, 0.91-1.10, 1.11-1.40, >1.40
Fowkes, 2014[66]	Model development: FRS variables	ABI Collaboration IPD MA	x	x		x	x†		x	x		x	Hard CHD: 2950 (6.6)§	Categorical: ≤0.90, 0.91-1.10, 1.11-1.40, >1.40
Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study	x	x		x	x				x		Soft CVD: 71 (5.7)	Categorical: ≤0.9, >0.9 (>1.4 excluded)
Yeboah, 2012[75]††	Model development: FRS variables	MESA	x	x	x	x	x	x	x	x			Soft CVD: 123 (9.2) Soft CHD: 94 (7.1)	Continuous
Kavousi, 2012[82]††	Model development: FRS variables	Rotterdam	x	x		x	x	x	x	x		x	Hard CHD: 347 (5.8)	Categorical: ≤0.9, >0.9 (>1.4 excluded)
Murphy, 2012[79]	Model development: FRS variables	ARIC	x	x	x	x	x	x		x¶			Hard CVD: 659 (5.7) Hard CHD: 403 (3.5)	Continuous#
Rodondi, 2010[81]**	Model development: FRS variables	Health ABC	x	x		x	x	x	x	x		x	Hard CHD: 197 (9.0) Soft CHD: 351 (16.0)	Categorical: ≤0.9, 0.91-1.00, 1.01-1.30, 1.31-1.40, >1.4

Table 13. Base Models for Included ABI Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	TC: HDL ratio	DM	Predicted outcomes‖‖: N (%)	Handling of ABI in extended model
Price, 2007[80]	Model development: FRS variables	EAS	x	x		x	x				x	x	Hard CVD: 137 (13.6) Soft CVD: 249 (24.7)	Continuous (ABI >1.5 excluded)

† BP categories as defined in JNC-V; includes DBP
‡ This outcome only reported for published coefficient model, not the newly developed model
§ For development and validation datasets
‖ Recalibration applies only to published coefficient models, not model development studies
¶ Also included LDL
# C-statistics measured with continuous ABI, but categorical ABI is reported for "2-step" risk assessment analysis which reports sensitivity, specificity, PPV, etc.
** Also a study of CRP
†† Also a study of CRP and CAC
‡‡ Recalibrated by including the PCE in the Cox model predicting Hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events
§§ Recalibrated by replacing Framingham means of risk factors and average event rate with those of Girona population (Marrugat, 2003).
‖‖ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; BP = blood pressure; CAC = coronary artery calcium; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; EAS = Edinburgh Artery Study; FRS=Framingham Risk Score; HDL = high-density lipoprotein; Health ABC = Health, Aging, and Body Composition study; HTN = hypertension; IPD MA = individual participant data meta-analyses; JNC-V = the fifth Joint National Committee; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; PCE = Pooled Cohort Equations; PPV = positive predictive value; SBP = systolic blood pressure; TC = total cholesterol; Tx = treatment

Table 14. Calibration and Overall Performance Measures in Included ABI Risk Prediction Studies (KQ2)

Measure	Author, Year	Model type: Base model	Study name	N	Outcome‡	Subgroup	Base model	Base model P-Value	Extended model	Extended model P-Value	Between model P-Value	Calculated change between models
AIC	Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration	5,869	Hard CHD	Women†	6689.92	--	6662.06	--	--	-27.86
	Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration	5,632	Hard CHD	Men†	9541.82	--	9521	--	--	-20.82
	Velescu, 2015[91]	Published coefficient: FRS	REGICOR	5,248	Soft CVD	All Participants	2571	--	2562.2	--	--	-8.8
	Velescu, 2015[91]	Published coefficiens: FRS	REGICOR	5,248	Soft CHD	All Participants	1653	--	1650.2	--	--	-2.8
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	1796.7	--	1795.6	--	--	-1.1
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	3102.6	--	3100.2	--	--	-2.4
BIC	Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration	5,869	Hard CHD	Women†	6693.93	--	6678.09	--	--	-15.84
	Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration	5,632	Hard CHD	Men†	9546.22	--	9538.61	--	--	-7.61
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	1839.3	--	1859.5	--	--	20.2
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	3145.2	--	3164.1	--	--	18.9
Hosmer-Lemeshow test	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	4.8	0.85	10.64	0.3	--	5.84
	Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study	659	Soft CVD	Women	9.26	0.321	14.75	0.064	--	5.49
	Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study*	582	Soft CVD	Men	7.08	0.528	NR	NR	--	--
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	4.23	0.9	15.01	0.09	--	10.78
Likelihood ratio $\chi 2$	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	27.48	<0.001	36.56	<0.001	NR	9.08

Table 14. Calibration and Overall Performance Measures in Included ABI Risk Prediction Studies (KQ2)

Measure	Author, Year	Model type: Base model	Study name	N	Outcome‡	Subgroup	Base model	Base model P-Value	Extended model	Extended model P-Value	Between model P-Value	Calculated change between models
	Kavousi, 2012[82]	Model development: FRS variables	Rotterdam	5,933	Hard CHD	All Participants	230.49	NR	3.7	NR	<0.05	-226.79
	Kavousi, 2012[82]	Model development: FRS variables	Rotterdam	3,525	Hard CHD	Women	NR	NR	0.1	NR	>0.05	--
	Kavousi, 2012[82]	Model development: FRS variables	Rotterdam	2,408	Hard CHD	Men	NR	NR	5.6	NR	<0.05	--
	Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study	659	Soft CVD	Women	15.81	0.003	24.55	<0.001	NR	8.74
	Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study*	582	Soft CVD	Men	35.85	<0.001	NR	NR	NR	--
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	35.31	<0.001	45.8	<0.001	NR	10.49
R^2	Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study	659	Soft CVD	Women	6.2	--	9.6	--	--	3.4
	Holewijn, 2014[95]	Model development: FRS variables	Nijmegen Biomedical Study*	582	Soft CVD	Men	12.5	--	NR	--	--	--
	Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration	5,869	Hard CHD	Women†	0.0353	--	0.0475	--	--	0.0122
	Fowkes, 2014[66]	Published coefficient: FRS	ABI Collaboration	5,632	Hard CHD	Men†	0.1138	--	0.1241	--	--	0.0103

* Extended model risk prediction statistics NR for men because HR analysis showed that ABI had no significant additional predictive value on top of traditional cardiovascular risk factors.

† Development Dataset

‡ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; AIC = Akaike information criterion; BIC = Bayesian information criterion; CHD = coronary heart disease; CVD = cardiovascular disease; FRS=Framingham Risk Score; Health ABC = Health, Aging, and Body Composition study; HR = hazard ratio; NR = not reported; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry)

Table 15. Discrimination Outcomes in Included ABI Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome§§	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
Published coefficient: PCE	Yeboah, 2016[90]	MESA II	Hard CVD	All Participants	5,185	0.74 (NR to NR)	0.75 (NR to NR)	0.01 (NR to NR)	0.55
Published coefficient: FRS	Geisel, 2017[114]	HNR	Hard CVD	All Participants	3,108	0.693 (0.661 to 0.726)	0.687 (0.653 to 0.721)	-0.006 (NR to NR)	0.54
	Geisel, 2017[114]	HNR	Hard CVD	Low risk	1,694	0.658 (0.602 to 0.713)	0.666 (0.608 to 0.724)	0.008 (NR to NR)	0.45
	Geisel, 2017[114]	HNR	Hard CVD	Intermediate risk	1,022	0.575 (0.520 to 0.629)	0.596 (0.541 to 0.651)	0.021 (NR to NR)	0.32
	Geisel, 2017[114]	HNR	Hard CVD	High risk	392	0.556 (0.482 to 0.629)	0.608 (0.521 to 0.694)	0.052 (NR to NR)	0.28
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Women¶	5,869	0.661 (0.587 to 0.728)	0.681 (0.607 to 0.746)	0.02 (NR to NR)	NR
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Women#	6,459	0.578 (0.492 to 0.661)	0.69 (0.605 to 0.764)	0.112 (NR to NR)	NR
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Women**	5,872	0.676 (0.599 to 0.745)	0.71 (0.633 to 0.775)	0.034 (NR to NR)	NR
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Men¶	5,632	0.715 (0.655 to 0.768)	0.721 (0.661 to 0.773)	0.006 (NR to NR)	NR
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Men#	4,962	0.672 (0.599 to 0.737)	0.685 (0.612 to 0.749)	0.013 (NR to NR)	NR
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Men**	5,638	0.721 (0.664 to 0.722)	0.721 (0.664 to 0.722)	0 (NR to NR)	NR
	Yeboah, 2016[90]	MESA II	Hard CHD	All Participants	5,185	0.74 (NR to NR)	0.75 (NR to NR)	0.01 (NR to NR)	0.042
	Velescu, 2015[91]	REGICOR††	Soft CVD	All Participants	5,248	0.787 (NR to NR)	0.795 (NR to NR)	0.008* (0.001* to 0.017*)	0.049*
	Velescu, 2015[91]	REGICOR††	Soft CHD	All Participants	5,248	0.795 (NR to NR)	0.797 (NR to NR)	0.002* (-0.001* to 0.007*)	0.529*
Model development: FRS variables	Murphy, 2012[79]	ARIC	Hard CVD	All Participants	11,594	0.756 (0.739 to 0.773)†	0.758 (0.741 to 0.775)	0.002 (NR to NR)	0.23
	Price, 2007[80]	EAS	Hard CVD	All Participants	1,007	0.614 (0.56 to 0.67)	0.64 (0.59 to 0.69)	0.026 (NR to NR)	0.02
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Women#	6,459	0.788 (0.709 to 0.85)	0.791 (0.712 to 0.852)	0.003 (NR to NR)	NR
	Fowkes, 2014[66]	ABI Collaboration	Hard CHD	Men#	4,962	0.683 (0.611 to 0.748)	0.69 (0.618 to 0.754)	0.007 (NR to NR)	NR
	Murphy, 2012[79]	ARIC	Hard CHD	All Participants	11,594	NR	NR	NR	NS
	Rodondi, 2010[81]	Health ABC	Hard CHD	All Participants	1,515	0.6 (NR to NR)	0.612 (NR to NR)	0.012 (NR to NR)	NR

Table 15. Discrimination Outcomes in Included ABI Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome§§	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
	Kavousi, 2012[82]	Rotterdam	Hard CHD	All Participants	5,933	0.73 (0.71 to 0.75)	NR	0.00* (0.00* to 0.00*)	NR
	Kavousi, 2012[82]	Rotterdam	Hard CHD	Women	3,525	NR	NR	0.00* (0.00* to 0.00*)	NR
	Kavousi, 2012[82]	Rotterdam	Hard CHD	Men	2,408	NR	NR	0.010* (0.00* to 0.01*)	NR
	Yeboah, 2012[75]	MESA	Soft CVD	Intermediate risk	1,330	0.623 (NR to NR)	0.65 (NR to NR)	0.027 (NR to NR)	0.01
	Holewijn, 2014[95]	Nijmegen Biomedical Study	Soft CVD	Women	659	0.691 (NR to NR)	0.726 (NR to NR)	0.036* (NR to NR)	0.26*
	Holewijn, 2014[95]	Nijmegen Biomedical Study	Soft CVD	Men	582	0.748 (NR to NR)	NR (NR to NR)	NR (NR to NR)§	NR
	Rodondi, 2010[81]	Health ABC	Soft CHD	All Participants	1,515	0.611 (NR to NR)	0.624 (NR to NR)	0.013 (NR to NR)	NR
	Yeboah, 2012[75]	MESA	Soft CHD	Intermediate risk	1,330	0.623 (NR to NR)	0.65 (NR to NR)	0.027 (NR to NR)	0.01

* Calculated as Extended-Base except where noted; asterisk indicates reported (not calculated) change

† Sensitivity, specificity, also reported for use of FRS alone and a two-step risk assessment where those with ABI <0.9 and who are in the intermediate FRS group 'move up.'

§ Extended model AUC NR because HR analysis showed that ABI had no significant additional predictive value on top of traditional cardiovascular risk factors.

‖ Recalibrated by including the PCE in the Cox model predicting Hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events

¶ Development dataset

External validation dataset

** Internal validation dataset

†† Recalibrated by replacing Framingham means of risk factors and average event rate with those of Girona population (Marrugat, 2003)[160].

§§ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EAS = Edinburgh Artery Study; FRS=Framingham Risk Score; Health ABC = Health, Aging, and Body Composition study; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement; NS= not significant; PCE = Pooled Cohort Equations; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry)

Table 16. Reclassification Outcomes in Included ABI Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome ¶¶	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	Risk categories (High, Intermediate, Low) 10-yr risk
Published coefficient: PCE	Yeboah, 2016[90]	MESA	5,185	Hard CVD	All Participants	0.017 (-0.031 to 0.058)*	0.013 (-0.034 to 0.051)*	0.004 (-0.004 to 0.011)*	≥7.5%, <7.5%
Published coefficient: FRS	Geisel, 2017[114]	HNR	3,108	Hard CVD	All Participants	0.190 (0.102 to 0.278)	NR	NR	Continuous NRI used
	Geisel, 2017[114]	HNR	1,694	Hard CVD	Low risk (<10% FRS)	0.041 (-0.062 to 0.144)	NR	NR	Continuous NRI used
	Geisel, 2017[114]	HNR	1,022	Hard CVD	Intermediate risk (10-20% FRS)	0.129 (0.014 to 0.245)	NR	NR	Continuous NRI used
	Geisel, 2017[114]	HNR	392	Hard CVD	High risk (>20% FRS)	0.455 (0.212 to 0.698)	NR	NR	Continuous NRI used
	Fowkes, 2014[66]	ABI Collaboration‡	6,459	Hard CHD	Women	0.096 (0.061 to 0.164)§¶	0.145 (0.101 to 0.189)§	-0.051 (-0.059 to -0.043)§	≥20%, 10-19%, <10%
	Fowkes, 2014[66]	ABI Collaboration‡	552	Hard CHD	Women, Intermediate Risk	0.288 (0.064 to 0.513)†#‖‖	NR	NR	≥20%, 10-19%, <10%
	Fowkes, 2014[66]	ABI Collaboration‡	4,962	Hard CHD	Men	0.043 (0.008 to 0.076)§**	0.026 (-0.005 to 0.058)§	0.016 (0.004 to 0.027)§	≥20%, 10-19%, <10%
	Fowkes, 2014[66]	ABI Collaboration‡	1,851	Hard CHD	Men, Intermediate Risk	0.051 (-0.016 to 0.119)† ††‖‖	NR	NR	≥20%, 10-19%, <10%
	Yeboah, 2016[90]	MESA	5,185	Hard CHD	All Participants	0.039 (-0.011 to 0.109)	0.041 (-0.01 to 0.108)	-0.003 (-0.008 to 0.004)	>20%, 10-20%, <10%
	Yeboah, 2016[90]	MESA	201	Hard CHD	Intermediate Risk	0.11 (-0.138 to 0.357)†	NR	NR	>20%, 10-20%, <10%
	Velescu, 2015[91]	REGICOR	5,182	Soft CVD	All Participants	0.029 (0.014 to 0.045)	0.006 (-0.007 to 0.022)	0.023 (0.017 to 0.029)	≥10%, 5-10%, 0-5%
	Velescu, 2015[91]	REGICOR	1,201	Soft CVD	Intermediate Risk	0.061 (0.024 to 0.098)†	NR	NR	≥10%, 5-10%, 0-5%
	Velescu, 2015[91]	REGICOR	5,182	Soft CHD	All Participants	0.001 (-0.06 to 0.058)	-0.01 (-0.07 to 0.045)	0.011 (0.007 to 0.017)	≥10%, 5-10%, 0-5%
	Velescu, 2015[91]	REGICOR	935	Soft CHD	Intermediate Risk	0.021 (-0.061 to 0.103)†	NR	NR	≥10%, 5-10%, 0-5%
Model development: FRS variables	Murphy, 2012[79]	ARIC	11,594	Hard CVD	All Participants	0.008 (-0.015 to 0.03)	0.003 (-0.019 to 0.025)‖	0.005 (0 to 0.009)‖	≥20%, ≥6% to <19%, <6%
	Murphy, 2012[79]	ARIC	3,376	Hard CVD	Intermediate Risk	0.011 (-0.021 to 0.042)†	NR	NR	≥20%, ≥6% to <19%, <6%
	Fowkes, 2014[66]	ABI Collaboration‡	6,459	Hard CHD	Women	0.011 (-0.019 to 0.04)§	NR	NR	≥20%, 10-19%, <10%

Table 16. Reclassification Outcomes in Included ABI Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome ¶¶	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	Risk categories (High, Intermediate, Low) 10-yr risk
	Fowkes, 2014[66]	ABI Collaboration‡	552	Hard CHD	Women, Intermediate Risk	0.024 (-0.03 to 0.105)§	NR	NR	≥20%, 10-19%, <10%
	Fowkes, 2014[66]	ABI Collaboration‡	4,962	Hard CHD	Men	0.02 (-0.023 to 0.042)§	NR	NR	≥20%, 10-19%, <10%
	Fowkes, 2014[66]	ABI Collaboration‡	1,851	Hard CHD	Men, Intermediate Risk	0.077 (0 to 0.13)§	NR	NR	≥20%, 10-19%, <10%
	Rodondi, 2010[81]	Health ABC	1,985	Hard CHD	All Participants	0.079 (NR to NR)	NR	NR	≥15%, 7.5 to <15%, <7.5%‡‡
	Rodondi, 2010[81]	Health ABC	1,020	Hard CHD	Intermediate Risk	0.193 (NR to NR)	NR	NR	≥15%, 7.5 to <15%, <7.5%‡‡
	Kavousi, 2012[82]	Rotterdam	5,933	Hard CHD	All Participants	0.006 (-0.018 to 0.029)	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Intermediate Risk	0.073 (0.029 to 0.117)	0.047 (NR to NR)	0.026 (NR to NR)	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	3,525	Hard CHD	Women	-0.009 (-0.027 to 0.01)	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Women, Intermediate Risk	-0.012 (-0.042 to 0.017)	-0.016 (NR to NR)	0.004 (NR to NR)	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	2,408	Hard CHD	Men	-0.016 (-0.065 to 0.033)	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Men, Intermediate Risk	0.065 (-0.011 to 0.141)	0.046 (NR to NR)	0.019 (NR to NR)	>20%, 10-20%, <10%
	Yeboah, 2012[75]	MESA	1,330	Soft CVD	Intermediate Risk	0.068 (NR to NR)	0.041 (NR to NR)	0.027 (NR to NR)	<3.4%, 3.4 to 21.1%, >21.1%‡‡
	Holewijn, 2014[95]	Nijmegen Biomedical Study	659	Soft CVD	Women	0.159 (NR to NR) p= 0.056	NR	NR	≥20%, 10-20%, <10%§§
	Holewijn, 2014[95]	Nijmegen Biomedical Study	NR	Soft CVD	Women, Intermediate Risk	0.60 (NR to NR)	NR	NR	≥20%, 10-20%, <10%§§
	Holewijn, 2014[95]	Nijmegen Biomedical Study	582	Soft CVD	Men	-0.011 (NR to NR) p=0.686	NR	NR	≥20%, 10-20%, <10%§§
	Holewijn, 2014[95]	Nijmegen Biomedical Study	NR	Soft CVD	Men, Intermediate Risk	0.136 (NR to NR)	NR	NR	≥20%, 10-20%, <10%§§

Table 16. Reclassification Outcomes in Included ABI Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome ¶¶	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	Risk categories (High, Intermediate, Low) 10-yr risk
	Rodondi, 2010[81]	Health ABC	1,985	Soft CHD	All Participants	0.033 (0.0004 to 0.065)	0.022 (NR to NR)	0.01 (NR to NR)	≥15%, 7.5 to <15%, <7.5%‡‡
	Rodondi, 2010[81]	Health ABC	1,020	Soft CHD	Intermediate Risk	0.038 (-0.028 to 0.104)†	NR	NR	≥15%, 7.5 to <15%, <7.5%‡‡
	Yeboah, 2012[75]	MESA	1,330	Soft CHD	Intermediate Risk	0.036 (NR to NR)	0.021 (NR to NR)	0.015 (NR to NR)	<2.0%, 2.0 to 15.4%, >15.4%‡‡

* Sensitivity analysis using 3 categories (0-5%, 5-7.5%, >7.5%) produced similar results
† Bias-corrected NRI_{INT} calculated using simple variance method
‡ All reclassification analyses conducted in external validation datasets
§ Calculated using Kaplan-Meier estimates reported in study.
‖ Event and nonevent NRI calculated using simple variance method
¶ Sensitivity analyses using wider intermediate risk group of 5-19% showed NRI of 0.204 (0.116 to 0.225; p<0.001)
# Sensitivity analyses using wider intermediate risk group of 5-19% showed NRI of 0.130 (0.073 to 0.179; p<0.001).
** Sensitivity analyses using wider intermediate risk group of 5-19% showed NRI of 0.031 (0.006 to 0.064; p=0.018).
†† Sensitivity analyses using wider intermediate risk group of 5-19% showed NRI of 0.079 (0.037 to 0.115; p<0.001).
‡‡ 7.5-yr risk
§§ Time horizon NR
‖‖ Calculated from Kaplan-Meier estimates
¶¶ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; AIC = Akaike information criterion; BIC = Bayesian information criterion; CHD = coronary heart disease; CVD = cardiovascular disease; FRS=Framingham Risk Score; Health ABC = Health, Aging, and Body Composition study; HR = hazard ratio; NR = not reported; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry)

Table 17. A Comparison of Cohorts in Included hsCRP Risk Prediction Studies With Emerging Risk Factors Collaboration IPD Meta-Analysis (KQ2)

Cohort	2012 IPD meta-analysis[65]*	Publications not included in IPD meta-analysis
AFTCAPS	n=5,613	
ARIC	n=9,326	Folsom, 2006[110]; n=1,511
British Regional Heart Study		Wannamethee, 2011[102]; n=2,893
BRUN	n=817	
BWHHS	n=2,652	
CaPS	n=816	
CHS	4,211	
COPEN	n=7,772	
EAS	n=741	Shah, 2009[78]; n=962
EISNER		Rana, 2012[99]; n=1,286
EPIC-Norfolk	n=15,902	Rana, 2009[104]; n=2,550
ESTHER	n=4,738	
FINRISK-92	n=891	
FINRISK-97	n=1,150	
FHS		Wilson, 2005[85]; n=4,446
Framingham Offspring	n=2,713	Wilson, 2005[85] n=4,446; Wilson, 2008[107]; n=3,006; Zhou, 2013[97]; n=1,687
Health ABC		Rodondi, 2010[81]; n=2,191
Heinz Nixdorf Recall		Mohlenkamp, 2011[103]; n=3,966
HISAYAMA	n=2,577	
HOORN	n=525	
Inter99		Seven, 2015[92]; n=6,502
KIHD	n=2,020	
LEADER	n=437	
MESA	n=6,722	Yeboah, 2016[90] n=5,185; Yeboah, 2012 n=1,330[75]
MONICA 1	n=873	Koenig, 2004[84]; n=3,435
MONICA 2	n=1,265	Koenig, 2004[84]; n=3,435
MONICA 3	n=3,150	Koenig, 2004[84]; n=3,435
MONICA Goteborg	n=740	
MONICA Copenhagen		Lyngbaek, 2013[96]; n=2,315
NHANES III	n=2,359	
NPHS-II		Shah, 2009[78]; n=2,479
NSHS	n=1,324	
PREVEND	n=5,819	
PROSPER	n=3,180	Sattar, 2007[108]; n=3,165
QUEBEC	n=1,219	
RANCHO	n=1,381	
REYK	n=14,927	Danesh, 2004[87]; n=6,428
ROTTERDAM	n=4,437	Kavousi, 2012[82], n=3,029; Elias-Smale, 2010[76], n=2,028
Scottish Health Survey		Hamer, 2009[105]; n=5,944
SHIP		Schneider, 2012[100]; n=3,967
SHS	n=3,112	
Singapore Chinese Health Study		Salim, 2013[109]; n=1,493
TARFS	n=1,673	
ULSAM	n=926	
PHS-II	n=10,715	
WHITE (Whitehall I)	n=3,808	
WHITE II (Whitehall II)	n=7,326	
WHS	n=23,287	Cook, 2006[83]; n=26,927
WOSCOPS	n=5,452	Welsh, 2013[98]; n=4,128
49 total included cohorts; 11 unique cohorts not represented in IPD MA		

*(k=38 for discrimination; k=22 for reclassification)

Abbreviations: AFTCAPS = Air Force / Texas Coronary Atherosclerosis Prevention Study; ARIC = Atherosclerosis Risk in Communities study; BRUN = Bruneck Study; BWHHS = British Womens Heart and Health Study; CaPS = Caerphilly Prospective Study; CHS = Cardiovascular Health Study; COPEN = Copenhagen City Heart Study; EAS = Edinburgh Artery Study; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; EPIC = European

Table 17. A Comparison of Cohorts in Included hsCRP Risk Prediction Studies With Emerging Risk Factors Collaboration IPD Meta-Analysis (KQ2)

Prospective Investigation into Cancer and Nutrition; ESTHER = *Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung* (Epidemiological investigations of the chances of preventing, recognizing early and optimally treating chronic diseases in an elderly population); FINRISK = national FINRISK study; FHS = Framingham Heart Study; Health ABC = Health, Aging, and Body Composition study; HISAYAMA = Hisayama study; HNR = Heinz Nixdorf Recall study; hsCRP = high sensitivity C-reactive protein; HOORN = Hoorn study; IPD MA = individual participant data meta-analyses; KIHD = Kuopio Ischemic Heart Disease Study; LEADER = Lower Extremity Arterial Disease Event Reduction Trial; MESA = Multi-Ethnic Study of Atherosclerosis; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NHANES = National Health and Nutrition Examination Survey; NPHS = Northwick Park Heart Study; NSHS = Nova Scotia Health Survey; PHS = Physicians' Health Study; PREVEND = Prevention of Renal and Vascular End Stage Disease Study; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; QUEBEC = Quebec CV Study; RANCHO = Rancho Bernardo Study; REYK = Reykjavik Study; ROTTERDAM = Rotterdam study; SHIP = the Study of Health in Pomerania; SHS = Strong Heart Study; TARFS = Turkish Adult Risk Factor Study; ULSAM = Uppsala Longitudinal Study of Adult Men study; WHITE = Whitehall study; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study

Table 18. Study Design and Participant Characteristics in Included hsCRP Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Country	N	F/U, mean (yrs); Range	Mean age	% Women	% White	% DM	% HTN (% treated)	% Chol meds*	% Current Smoker	Mean hsCRP, mg/L	hsCRP Elevated Threshold, mg/L (% Elevated hsCRP)
Yeboah, 2016†[90]*	Published coefficient: PCE	MESA	United States	5,185	10; NR	61.2	53.1	38	9.8	NR (32.5)	0	13.6	1.9§	NR (NR)
	Published coefficient: FRS	MESA	United States	5,185	10; NR	61.2	53.1	38	9.8	NR (32.5)	0	13.6	1.9§	NR (NR)
Zhou, 2013[97]	Published coefficient: FRS	Framingham Offspring	United States	1,687	NR; NR	NR	100	NR	NR	NR (NR)	NR	NR	NR	NR (NR)
Lyngbaek, 2013[96]	Published coefficient: FRS	MONICA - Copenhagen	Denmark	2,315	12.7§; 4.0-13.4 (5/95 percentile)	53.9	50.5	NR	3.7	NR (NR)	NR	46.1	1.73§	approx. ≥3.0 (NR)
Rana, 2009[104]	Published coefficient: FRS	EPIC-Norfolk**	United Kingdom	2,550	6; NR	65	36.1	NR	3.1	NR (NR)	0	10.9	1.8§	NR (NR)
Hamer, 2009[105]*	Published coefficient: FRS	Scottish Health Survey	United Kingdom	5,944	7.1; NR	53.6	55.5	NR	2.6	26.1 (NR)	NR	25.8	3.58	≥3 (32.1)
Koenig, 2004[84]*	Published coefficient: FRS††	MONICA - Augsburg	Germany	3,435	6.6; NR	56.4	0	100	5.8	NR (NR)	NR	27.4	1.69	>3.0 (29)
Salim, 2016[109]	Model development: FRS variables	Singapore Chinese Health Study**	Singapore	1,493	NR; NR	64	35.4	NR	0	NR (29.1)	NR	25.1	1.14‡‡	NR (NR)
Seven, 2015[92]	Model development: FRS variables	Inter99	Denmark	6,502	11.4; NR	45.9	51.9	NR	1.9	NR (6)	3	39	0.9§	NR (NR)
Welsh, 2013[98]*	Model development: FRS variables	WOSCOPS	United Kingdom	4,128§§	14.7§; NR	NR	0	NR	NR	NR (NR)	NR‡	NR	1.73	>3.65 (NR)
Rana, 2012‖‖[99]	Model development: FRS variables	EISNER	United States	1,286	4.1; NR	58.6	47.2	NR	8.1	57.9 (NR)	NR	5.4	5.0	NR (NR)
Emerging Risk Factors Collaboration, 2012[65]	Model development: FRS variables	ERFC IPD MA¶¶	Multi-national	166,596	8.8§; 2.9 to 23.3 (5/95 percentile)	59.7	51	NR	6	NR (NR)	NR	21	0.59##	NR (NR)
Yeboah, 2012[75]‖‖*	Model development: FRS variables	MESA	United States	1,330	7.6§; 7.3-7.8 (IQR)	63.8	33.3	35.7	0	NR (38.2)	14.1	16.5	1.62§	NR (NR)
Kavousi, 2012†[82]	Model development: FRS variables	Rotterdam	Netherlands	3,029	6.8§; 5.8-8.1 (IQR)	69.1	59.4	NR	12.9	NR (23.5)	10.2	17.5	2.3§	NR (NR)

Table 18. Study Design and Participant Characteristics in Included hsCRP Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Country	N	F/U, mean (yrs); Range	Mean age	% Women	% White	% DM	% HTN (% treated)	% Chol meds*	% Current Smoker	Mean hsCRP, mg/L	hsCRP Elevated Threshold, mg/L (% Elevated hsCRP)
Schneider, 2012[100]	Model development: FRS variables	SHIP	Germany	3,967	10.0§; 9.3, 10.0 (IQR)	49§	52.3	NR	7.2	NR (26.5)	NR	33.2	1.38§	NR (NR)
Wannamethee, 2011[102]	Model development: FRS variables	British Regional Heart Study	United Kingdom	2,893***	9; 8-10	68.2	0	>99	10.6	NR (NR)	NR	12.4	1.67†††	NR (NR)
Mohlenkamp, 2011‖‖[103]*	Model development: FRS variables	HNR	Germany	3,966	5.1; NR	59.3	52.8	NR	7.2	54.2 (31.7)	9.1	22.6	1.4§	>3 (22.6)
Rodondi, 2010‡‡‡[81]	Model development: FRS variables	Health ABC	United States	2,191	8.2§; (Max 10.2)	73.5	55.3	58.9	13.3	46.1 (12.5‖‖‖)	10.5	10.1	NR	>3.0 (NR)
Elias-Smale, 2010‖‖[76]	Model development: FRS variables	Rotterdam	Netherlands	2,028	9.2§; 8.3-10.0 (IQR)	69.6	57.4	NR	NR	NR (27.6)	14	16.8	NR	NR (NR)
Shah, 2009[78]*	Model development: FRS variables	EAS	Scotland	962	17; NR	NR	NR	NR	NR	NR (NR)	NR	NR	1.93†††	>3 (33.3)
Shah, 2009[78]	Model development: FRS variables	NPHS II	United Kingdom	2,479	10; NR	NR	0	NR	NR	NR (NR)	NR	NR	2.46†††	>3 (43.9)
Wilson, 2008[107]*	Model development: FRS variables	Framingham Offspring	United States	3,006	12††††; NR	45.5	52.4	NR	2.4	NR (9.9)	NR	36	2.5	>3 (21.9)
Sattar, 2007[108]	Model development: FRS variables	PROSPER	Multi-national	3,165§§§§	3.2; NR	75.4	51.7	NR	10.7	61.8 (NR)	0	26.8	3.1†††	>3 (52)
Folsom, 2006[110]*	Model development: FRS variables	ARIC‖‖‖‖	United States	1,511	7.3§; NR	NR	NR	72.7 ‖‖‖‖‖‖	NR	NR (NR)	NR	NR	3.08	NR (NR)
Cook, 2006[83]*	Model development: FRS variables‖	WHS	United States	26,927	10; NR	54	100	NR	0	14.8 (12)	NR	12.2	1.5§	NR (NR)
Wilson, 2005[85]	Model development: FRS variables	FHS and Framingham offspring	United States	4,446	8; NR	58.1	56.2	NR	7.3	NR (20.6)	NR	19.5	NR	>3.0 (38.4)

Table 18. Study Design and Participant Characteristics in Included hsCRP Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Country	N	F/U, mean (yrs); Range	Mean age	% Women	% White	% DM	% HTN (% treated)	% Chol meds*	% Current Smoker	Mean hsCRP, mg/L	hsCRP Elevated Threshold, mg/L (% Elevated hsCRP)
Danesh, 2004[87]	Model development: FRS variables	Reykjavik**	Iceland	6,428 *****	19.4†††††; NR	55.7	29.7	NR	2.3	NR (NR)	NR	52.2	1.46† ††††	2 (37.1)

* Explicitly states that a high-sensitivity assay was used to measure CRP
† Also a study of ABI and CAC
‡ 100% with hyperlipidemia at baseline
§ Median
‖2 models; 1 de novo, 1 full recalibration of ATP III
** Nested case-control study
†† FRS entered categorically, not continuously. This will underestimate the prognostic value of the published FRS and overestimate the prognostic value of CRP.[63]
‡‡ Weighted geometric mean
§§ Only abstracted data for "clean CVD cohort" which excluded those with minor ECG abnormalities, angina, those taking nitrates, those with IC, or history of CVD (673, 16.3% excluded)
‖‖ Also a study of CAC
¶¶ 38 cohorts for Hard CVD; 37 for Hard CHD: Air Force/Texas Coronary Atherosclerosis Study, ARIC, Bruneck Study, British Women's Heart and Health Study, Caerphilly Prospective Study, CHS, Copenhagen City Heart Study, EAS, EPIC Norfolk Study, ESTHER, Finrisk 1992 Cohort, Finrisk 1997 Cohort, FHS Offspring, Hisayama Study, Hoorn Study, Kuopio Ischemic Heart Disease Study, Lower Extremity Arterial Disease Event Reduction Trail, MESA, MONICA/KORA Augsburg Survey 1, MONICA/KORA Augsburg Survey 2, MONICA/KORA Augsburg Survey 3, MONICA Goteborg Study, NHANES III, Nova Scotia Health Survey, Prevention of Renal and Vascular End Stage Disease Study, Prospective Study of Pravastatin in the Elderly at Risk, Quebec Cardiovascular Study, Rancho Bernardo Study, Reykjavik Study, Rotterdam, SHS, Turkish Adult Risk Factor Study, Uppsala Longitudinal Study of Adult Men, PHS II, Whitehall I Study, Whitehall II Study, WHS, West of Scotland Coronary Prevention Study
log CRP
*** Participants without prevalent CVD (an additional 756 with CVD are reported in the paper in stratified analyses)
††† Geometric mean
‡‡‡ Also a study of ABI
‖‖‖ ACE inhibitors are the only anti-HTN drug class reported
¶¶¶ Tzoulaki, 2007 reports that 1,010 of 1,592 in original cohort had CRP measurement; based on Ns in Shah, 2009 inferring that 48 individuals did not have valid CRP measurement and 43 did not have other variables to calculate FRS
**** 3,012 in original cohort, inferring 533 had no valid CRP measurement and 67 had missing FRS variable data
†††† Unclear whether this is mean, median, or maximum
§§§§ N for cohort with no history of vascular disease; total cohort with CRP data=5,680
‖‖‖‖ Case-cohort study
***** 376 (5.8%) with baseline ECG abnormalities or history of angina
††††† F/U averaged between cases (17.5 years) and controls (20.6 years)
‡‡‡‡‡ hsCRP values are log-transformed and presented as geometric mean
‖‖‖‖‖ In overall ARIC population, as reported on the study's website: https://www2.cscc.unc.edu/aric/system/files/CohortCharacteristics.pdf

Abbreviations: ABI = ankle-brachial index; ATP III = Adult Treatment Panel III; ARIC = Atherosclerosis Risk in Communities study; CAC = coronary artery calcium; CHD = coronary heart disease; Chol = cholesterol; CVD = cardiovascular disease; DM = diabetes mellitus; EAS = Edinburgh Artery Study; ECG = echocardiogram; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC IPD MA= Emerging

Table 18. Study Design and Participant Characteristics in Included hsCRP Risk Prediction Studies (KQ2)

Risk Factors Collaboration individual participant data meta-analysis; FRS = Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; IQR = inter-quartile range; meds = medications; MESA = Multi-Ethnic Study of Atherosclerosis; mg/L = milligrams per Liter; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; NR = not reported; PCE = Pooled Cohort Equations; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SHIP = the Study of Health in Pomerania; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study; yr(s) = year(s)

Table 19. Base Models for Included hsCRP Risk Prediction Studies (KQ2)

Author, Year	Base model: Model type	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	TC: HDL ratio	DM	Predicted outcomes‡‡‡: N (%)	Handling of hsCRP in extended model
Yeboah, 2016*[90]	Published coefficient: PCE (Goff, 2014)†	MESA	x	x	x	x	x	x	x	x		x	Hard CVD: 320 (6.2)	Log-transformed
Yeboah, 2016*[90]	Published coefficient: FRS†	MESA	x	x		x	x‡		x	x		x	Hard CHD: 194 (3.7)	Log-transformed
Lyngbaek, 2013[96]	Published coefficient: FRS (Wilson, 1998)	MONICA - Copenhagen	x	x		x	x‡	x	x	x		x	Hard CVD: 302 (13.0)	Categorical by tertile (mg/L): men (0.12-1.12, 1.13-2.81, 2.82-92.55); women (0.13-1.00, 1.01-2.97, 2.98-98.45)
Zhou, 2013[97]	Published coefficient: FRS (Wilson, 1998)	Framingham Offspring	x	x		x	x‡		x	x		x	Soft CVD§: 261 (15.5)	Log-transformed
Rana, 2009[104]	Published coefficient: FRS (Wilson, 1998)	EPIC-Norfolk	x	x		x	x‡		x	x		x	Soft CHD: 921 (36.1)	Log-transformed
Hamer, 2009[105]	Published coefficient: FRS (D'Agostino, 2008)	Scottish Health Survey	x	x		x	x	x	x	x		x	Soft CVD: 308 (5.2) Soft CHD: 240 (4.0) Fatal CVD: 138 (2.3)	Log-transformed and categorical for discrimination: <1 mg/L, 1 to <3 mg/L, ≥3 mg/L
Koenig, 2004[84]	Published coefficient: FRS (Wilson, 1998)‖	MONICA - Augsburg	x	x		x	x‡		x	x		x	Hard CHD: 191 (5.6)	Categorical: <1, 1-3, >3 mg/L
Salim, 2016[109]	Model development: FRS variables	Singapore Chinese Health Study	x	x		x	x		x	x			Hard CHD: 441 (29.5)	Log-transformed for men, quadratic for women
Seven, 2015[92]	Model development: FRS variables#	Inter99	x	x		x	x	x	x	x		x	Soft CVD: 493 (8.0)	Log-transformed**
Welsh, 2013[98]	Model development: FRS variables#	WOSCOPS	x	††		x	x		x	x		x	Soft CVD: 1357 (32.9) Soft CHD: 779 (18.9) Fatal CVD: 253 (6.1) Fatal CHD: 171 (4.1)	Log-transformed
Emerging Risk Factors Collaboration, 2012[65]	Model development: FRS variables	ERFC IPD MA	x	x		x	x		x	x		x	Hard CVD: 13568 (8.1) Hard CHD: 8816 (5.3)	Log-transformed

Table 19. Base Models for Included hsCRP Risk Prediction Studies (KQ2)

Author, Year	Base model: Model type	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	TC: HDL ratio	DM	Predicted outcomes‡‡‡: N (%)	Handling of hsCRP in extended model
Yeboah, 2012*[75]	Model development: FRS variables‡‡	MESA	x	x	x	x	x	x	x	x			Soft CVD: 123 (9.2) Soft CHD: 94 (7.1)	Log-transformed
Kavousi, 2012*[82]	Model development: FRS variables§§	Rotterdam	x	x		x	x	x	x	x		x	Hard CHD: 347 (5.8)	Continuous
Rana, 2012‖‖[99]	Model development: FRS variables	EISNER	x	x		x	x	x	x	x		x	Soft CVD: 35 (2.7)	Continuous
Schneider, 2012[100]	Model development: FRS variables	SHIP	x	x		x	x	x	x	x		x	Fatal CVD: 91 (2.5)	Log-transformed
Wannamethee, 2011[102]	Model development: FRS variables	British Regional Heart Study	x	††		x	x		x	x		x	Hard CVD: 402 (13.9) Hard CHD: 194 (6.7) Fatal CVD: 223 (7.7) Fatal CHD: 119 (4.1)	Log-transformed
Mohlenkamp, 2011‖‖[103]	Model development: FRS variables	HNR	x	x		x	x			x¶¶		x	Hard CHD: 91 (2.3)	Continuous##
Elias-Smale, 2010‖‖[76]	Model development: FRS variables	Rotterdam	x	x		x	x	x	x	x		x	Hard CHD: 135 (6.6)	Continuous
Rodondi, 2010***[81]	Model development: FRS variables	Health ABC	x	x		x	x	x	x	x		x	Hard CHD: 197 (9.0) Soft CHD: 351 (16.0)	Categorical: <1, 1-3, >3 mg/L
Shah, 2009[78]	Model development: FRS variables	Edinburgh Artery Study	x	x		x	x		x	x		x	Hard CHD: 147 (15.3)	Log-transformed
Shah, 2009[78]	Model development: FRS variables	Northwick Park Heart Study II	x	††		x	x		x			x	Hard CHD: 162 (6.5)	Log-transformed
Wilson, 2008[107]	Model development: FRS variables	Framingham Offspring	x	x		x	x	x	x	x		x	Hard CHD: 129 (4.3) Soft CVD: 286 (9.5)	Log-transformed
Sattar, 2007[108]	Model development: FRS variables†††	PROSPER	x	x		x	x	x		x¶¶		x	Hard CVD: 373 (11.8) Hard CHD: NR (NR)	Log-transformed

Table 19. Base Models for Included hsCRP Risk Prediction Studies (KQ2)

Author, Year	Base model: Model type	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	TC: HDL ratio	DM	Predicted outcomes‡‡‡: N (%)	Handling of hsCRP in extended model
Cook, 2006[83]	Model development: FRS (NCEP ATP III, 2002)‡‡‡	WHS	x	††		x	x	x	x	x			Soft CVD: NR (NR)§§§	Log-transformed
Cook, 2006[83]	Model development: FRS variables‖‖‖	WHS	x	††		x	x	x¶¶¶	x	x			Soft CVD: 390 (2.6)###	Log-transformed
Folsom, 2006[110]	Model development: FRS variables	ARIC	x	x	x	x	x	x	x	x		x	Soft CHD: 666 (44.1)	Log-transformed
Wilson, 2005[85]	Model development: FRS	FHS and Framingham offspring	x	x		x	x				x	x	Hard CVD: 283 (6.4) Hard CHD: 160 (3.6) Soft CVD: 466 (10.5)	Categorical: <1, 1-3, >3 mg/L
Danesh, 2004[87]	Model development: FRS variables****	Reykjavik	x	x		x	x		x				Hard CHD: 2,459 (38.2)	Log-transformed††††

* Also a study of ABI and CAC
† Recalibration accomplished by including the PCE (or FRS in that corresponding model) in the Cox model predicting hard CVD events (or hard CHD in FRS model); created a calibrated PCE which used the BL survival estimated from MESA data
‡ BP categories as defined in JNC-V; includes DBP
§ CVD definition is not specified; assuming soft CVD based on number of events
‖ FRS was entered categorically, not continuously in the model. Two categorizations reported for 10-yr risk of hard CHD: 1) 3 risk categories: <6%, 6% to 19%, and ≥20%; and 2) 5 risk categories, <6%, 6% to 10%, 11% to 14%, 15% to 19%, and ≥20%. Models were additionally adjusted for survey year.
Also adjusted for intervention arm
** Assumed log-transformation since hsCRP distribution was skewed; no other details reported
†† Sex not included as a predictor as sample was entirely Men or entirely Women
‡‡ FRS (NCEP ATP III, 2002) plus addition of race/ethnicity served as the base model
§§ Additionally adjusted for CAC scanner type
‖‖ Also a study of CAC
¶¶ Also included LDL
Assumed continuous for relevant analyses, though categorical analyses also presented for association data (HR analyses)
*** Also a study of ABI
††† Also adjusted for randomized treatment and country
‡‡‡ ATP III beta-coefficients recalculated for all traditional risk factors before adding CRP to the model to be conservative and allow best possible fit.
§§§ Reported for model development cohort only
‖‖‖ For generalizability, predicted probabilities were calibrated to observed risk from the Framingham Heart Study.
¶¶¶ SBP included as two variables: (SBP-125) and $(SBP-125)^2$
Among model development population of 15,048 women with data on all variables who were not taking HRT
**** Also adjusted for enrollment year. Inclusion of predictors in the base model derived from Figure 1.
†††† Assumed log-transformed for relevant analyses, though categorical analyses also present for association data (OR analyses)

Table 19. Base Models for Included hsCRP Risk Prediction Studies (KQ2)

‡‡‡‡ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; ATP III = Adult Treatment Panel III; ARIC = Atherosclerosis Risk in Communities study; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; EAS = Edinburgh Artery Study; ECG = echocardiogram; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC IPD MA= Emerging Risk Factors Collaboration individual participant data meta-analysis; FRS = Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HDL = high-density lipoprotein; HNR = Heinz Nixdorf Recall study; HR = hazard ratio; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis; mg/L = milligrams per Liter; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; NR = not reported; OR = odds ratio; PCE = Pooled Cohort Equations; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SBP = systolic blood pressure; SHIP = the Study of Health in Pomerania; TC = total cholesterol; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study

Table 20. Calibration and Overall Performance Measures in Included hsCRP Risk Prediction Studies (KQ2)

Measure	Author, Year	Model Type: Base model	Study name	N	Outcome‡‡	Subgroup	Base model	Base model P-Value	Extended model	Extended model P-Value	Between model P-Value	Calculated change between models
AIC	Shah, 2009[78]	Model development: FRS variables	Edinburgh Artery Study*	962	Hard CHD	All Participants	2397.6	--	2390.5	--	<0.001	-7.1
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	1796.7	--	1800.5	--	--	3.8
	Koenig, 2004[84]	Published coefficient: FRS†	MONICA - Augsburg	3,435	Hard CHD	All Participants	2816	--	2797	--	--	-19‡
	Shah, 2009[78]	Model development: FRS variables	NPHS-II§	2,479	Hard CHD	All Participants	2368.6	--	2355.8	--	<0.001	-12.8
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	3102.6	--	3104.8	--	--	2.2
	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	6942.74	--	6928.58	--	--	-14.16
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHSII	15,048	Soft CVD	All Participants	6941.84	--	6928.53	--	--	-13.31
BIC	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	1839.3	--	1859.1	--	--	19.8
	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	6974.46	--	6964.28	--	--	-10.18
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHSII	15,048	Soft CVD	All Participants	6969.60	--	6960.26	--	--	-9.34
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	3145.2	--	3163.3	--	--	18.1
Brier score	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	0.01964	--	0.01959	--	--	-0.00005
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHSII	15,048	Soft CVD	All Participants	0.01965	--	0.01960	--	--	-0.00005
Gronnesby-Borgan goodness-of-fit	Lyngbaek, 2013[96]	Published coefficient: FRS	MONICA - Copenhagen	2,315	Hard CVD	All Participants	NR	>0.05	NR	>0.05	--	--
Hosmer-Lemeshow test	Shah, 2009[78]	Model development: FRS variables	Edinburgh Artery Study*	962	Hard CHD	All Participants	NR	0.65	NR	0.65	--	--
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	4.80	0.85	7.96	0.54	--	--

Table 20. Calibration and Overall Performance Measures in Included hsCRP Risk Prediction Studies (KQ2)

Measure	Author, Year	Model Type: Base model	Study name	N	Outcome‡‡	Subgroup	Base model	Base model P-Value	Extended model	Extended model P-Value	Between model P-Value	Calculated change between models
	Mohlenkamp, 2011[103]	Model development: FRS variables	HNR	3,966	Hard CHD	All Participants	11.5	0.18	NR	NR	--	--
	Shah, 2009[78]	Model development: FRS variables	NPHS-II§	2,479	Hard CHD	All Participants	NR	0.82	NR	0.90	--	--
	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	NR	0.79¶	NR	0.71¶	--	--
	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	NR	0.008#	NR	0.25#	--	--
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHSII	15,048	Soft CVD	All Participants	NR	0.59¶	NR	0.19¶	--	--
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHSII	15,048	Soft CVD	All Participants	NR	0.039#	NR	0.23#	--	--
	Rana, 2009[104]	Published coefficient: FRS	EPIC-Norfolk	2,550	Soft CHD	All Participants	18.0	0.02	20.3	0.009	NR	2.3
	Rana, 2009[104]	Published coefficient: FRS	EPIC-Norfolk	1,008	Soft CHD	Intermediate Risk	12.9	0.1	10.8	0.2	NR	-2.1
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	4.23	0.90	13.86	0.13	NR	9.63
Likelihood ratio χ^2	Sattar, 2007[108]	Model development: FRS variables	PROSPER	3,165	Hard CVD	All Participants	NR**	NR**	NR**	NR**	NR**	--
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Hard CHD	All Participants	27.48	<0.001	29.62	0.002	NR	2.14
	Kavousi, 2012	Model development: FRS variables	Rotterdam	3,029	Hard CHD	All Participants	230.49††	NR	4.8††	NR	<0.05††	-225.69††
	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	542.54	NR	558.69	NR	<0.001	16.15
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHSII	15,048	Soft CVD	All Participants	541.44	NR	556.75	NR	<0.001	15.31
	Rodondi, 2010[81]	Model development: FRS variables	Health ABC	1,515	Soft CHD	All Participants	35.31	<0.001	41.87	<0.001	NR	6.56
-2 log likelihood	Rana, 2009[104]	Published coefficient: FRS	EPIC-Norfolk	2,550	Soft CHD	All Participants	3284.6	NR	3242.7	NR	NR	-41.9
	Rana, 2009[104]	Published coefficient: FRS	EPIC-Norfolk	1,008	Soft CHD	Intermediate Risk	1253.6	NR	1225.9	NR	NR	-27.7

Table 20. Calibration and Overall Performance Measures in Included hsCRP Risk Prediction Studies (KQ2)

Measure	Author, Year	Model Type: Base model	Study name	N	Outcome‡‡	Subgroup	Base model	Base model P-Value	Extended model	Extended model P-Value	Between model P-Value	Calculated change between models
R^2	Cook, 2006[83]	Model development: FRS variables (ATP III Full Recalibration)	WHS	26,927	Soft CVD	All Participants	8.84	NR	8.97	NR	NR	0.13
	Cook, 2006[83]	Model development: FRS variables (WHS Model)	WHS‖	15,048	Soft CVD	All Participants	8.92	NR	9.05	NR	NR	0.13

* Figure 1 reports ratio of predicted:observed events by quintile. Predicted:observed ratio for base model, by quintile: 1.30, 0.96, 0.98, 1.05, 0.97. Predicted:observed ratio for extended model, by quintile: 1.31, 0.81, 1.26, 0.90, 0.99

† FRS entered categorically, not continuously; 3-category model abstracted

‡ AIC difference between models was 13 using FRS with 5 risk categories.

§ Figure 1 reports ratio of predicted:observed events by quintile. Predicted:observed ratio for base model, by quintile: 0.93, 1.00, 1.21, 1.24, 0.86. Predicted:observed ratio for extended model, by quintile: 0.85, 1.20, 1.28, 1.00, 0.92.

‖ Calibration plot shown but O:E NR. Calibration plot shows that the model without CRP overpredicts risk in the 14-15% risk group and calibration is improved with addition of CRP. In the 16-17% risk group; overprediction appears to worsen in the model with CRP. Other risk groups look reasonably similar.

¶ Hosmer-Lemeshow test based on deciles.

Hosmer-Lemeshow test based on 10 categories defined by 2-percentage point increments in predicted risk (from 0-2% risk to 18% or greater risk).

** Reports probability values for likelihood ratio test for inclusion of term representing deciles of predicted risk into the model (based on models either including or excluding log CRP); the corresponding p-value is unclear but authors report "no significant miscalibration in the models either before or after addition of CRP."

†† P-value indicates statistically significant improvement in model fit. Base model is "model likelihood chi-square" Extended model statistic is "increase in model fit after extending the base model." Power not enough to perform sex-specific analyses for CRP.

‡‡ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; AIC = Akaike information criterion; ARIC = Atherosclerosis Risk in Communities study; BIC = Bayesian information criterion; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC IPD MA= Emerging Risk Factors Collaboration individual participant data meta-analysis; FRS = Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; HRT = hormone replacement therapy; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; MESA = Multi-Ethnic Study of Atherosclerosis; mg/L = milligrams per Liter; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; NR = not reported; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SHIP = the Study of Health in Pomerania; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study

Table 21. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome† ††	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
Published coefficient: PCE†	Yeboah, 2016[90]	MESA	Hard CVD	All Participants	5,185	0.74 (NR to NR)	0.74 (NR to NR)	0 (NR to NR)	0.25
Published coefficient: FRS	Lyngbaek, 2013[96]	MONICA - Copenhagen	Hard CVD	Women	1,168	0.717 (0.674 to 0.759)	0.724 (0.679 to 0.769)	0.007 (NR to NR)	0.262
	Lyngbaek, 2013[96]	MONICA - Copenhagen	Hard CVD	Men	1,147	0.722 (0.686 to 0.757)	0.734 (0.699 to 0.769)	0.012 (NR to NR)	0.037
	Yeboah, 2016[90]	MESA†	Hard CHD	All Participants	5,185	0.74 (NR to NR)	0.74 (NR to NR)	0 (NR to NR)	0.925
	Koenig, 2004[84]	MONICA - Augsburg‡	Hard CHD	All Participants	3,435	0.713 (NR to NR)§	0.740 (NR to NR)§	0.027 (NR to NR)	0.0077
	Zhou, 2013[97]	Framingham Offspring	Soft CVD	All Participants	1,687	0.776 (NR to NR)	0.778 (NR to NR)	0.002* (-0.005* to 0.01*)	NR
	Zhou, 2013[97]	Framingham Offspring	Soft CVD	Intermediate Risk	193	NR	NR	0.037* (-0.054* to 0.13*)	NR
	Hamer, 2009[105]	Scottish Health Survey	Soft CVD	All Participants	5,944	0.777 (0.754 to 0.800)	0.781 (0.758 to 0.804)	0.004 (NR to NR)	NR
	Rana, 2009[104]	EPIC-Norfolk	Soft CHD	All Participants	2,550	0.59 (0.57 to 0.61)	0.65 (0.59 to 0.64)	0.03* (0.01* to 0.05*)	0.005
	Rana, 2009[104]	EPIC-Norfolk	Soft CHD	Intermediate Risk	1,008	0.54 (0.50 to 0.57)	0.61 (0.57 to 0.65)	0.08* (0.03* to 0.12*)	<0.001
	Hamer, 2009[105]	Scottish Health Survey	Soft CHD	All Participants	5,944	0.766 (0.740 to 0.792)	0.768 (0.742 to 0.793)	0.002 (NR to NR)	NR
Model development: FRS variables	Wannamethee, 2011[102]	British Regional Heart Study	Hard CVD	All Participants	2,893	0.686 (NR to NR)	0.695 (NR to NR)	0.009 (NR to NR)	0.06
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	All Participants	166,596	0.7139 (0.7097 to 0.7182)	0.7179 (0.7136 to 0.7221)	0.0039* (0.0028* to 0.0050*)	<0.0001
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	Women	4,535 cases¶	NR	NR	0.0007* (-0.0007* to 0.0021*)	Interaction p<0.001 vs Men***
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	Men	5,755 cases¶	NR	NR	0.0077* (0.0058* to 0.0096*)	Interaction p<0.001 vs Women***
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	With diabetes	1,580 cases¶	NR	NR	0.0026* (-0.0015* to 0.0067*)	Interaction p=0.48 vs without diabetes***
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	Without diabetes	11,418 cases¶	NR	NR	0.0042* (0.0029* to 0.0055*)	Interaction p=0.48 vs

Table 21. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome† ††	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
									with diabetes***
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	Non-Whites	539 cases¶	NR	NR	-0.0008* (-0.0056* to 0.0039*)	Interaction p=0.274 vs Whites***
	ERFC, 2012[65]	ERFC IPD MA	Hard CVD	Whites	3,544 cases¶	NR	NR	0.0021* (-0.0002* to 0.0044*)	Interaction p=0.274 vs Non-whites***
	Wilson, 2005[85]	FHS and Framingham offspring	Hard CVD	All Participants‖	4,446	0.78 (0.76 to 0.80)	0.78 (0.75 to 0.80)	0 (NR to NR)	NR
	Sattar, 2007[108]	PROSPER	Hard CVD	All Participants	3,165	0.58 (NR to NR)	0.69 (NR to NR)	0.11 (NR to NR)	NR
	Sattar, 2007[108]	PROSPER	Hard CVD	Placebo group only	1,654#	0.630 (NR to NR)	0.637 (NR to NR)	0.007 (NR to NR)	0.020
	Wannamethee, 2011[102]	British Regional Heart Study	Hard CHD	All Participants	2,893	0.686 (NR to NR)	0.690 (NR to NR)	0.004 (NR to NR)	0.49
	Shah, 2009[78]	Edinburgh Artery Study	Hard CHD	All Participants	962	0.68 (0.64 to 0.71)**	0.67 (0.63 to 0.71)**	-0.01 (NR to NR)**	NR
	ERFC, 2012[65]	ERFC IPD MA	Hard CHD	All Participants	165,586	NR	NR (NR to NR)	0.0051* (0.0035* to 0.0066*)	NR
	Wilson, 2005[85]	FHS and Framingham offspring	Hard CHD	All Participants	4,446	0.80 (0.77 to 0.83)	0.80 (0.77 to 0.83)	0 (NR to NR)	NR
	Wilson, 2008[107]	Framingham Offspring	Hard CHD	All Participants	3,006	0.863 (NR to NR)	0.865 (NR to NR)	0.002 (NR to NR)	NR
	Rodondi, 2010[81]	Health ABC	Hard CHD	All Participants	1,515	0.600 (NR to NR)	0.592 (NR to NR)	-0.008 (NR to NR)	NR
	Mohlenkamp, 2011[103]	Heinz Nixdorf Recall (HNR)	Hard CHD	All Participants	3,966	0.719 (0.671 to 0.767)	0.732 (0.684 to 0.780)	0.013 (NR to NR)	0.12
	Shah, 2009[78]	Northwick Park Heart Study II	Hard CHD	All Participants	2,479	0.62 (0.60 to 0.65)**	0.66 (0.63 to 0.68)**	0.04 (NR to NR)**	NR
	Sattar, 2007[108]	PROSPER	Hard CHD	Placebo group only	1,654#	0.655 (NR to NR)	0.663 (NR to NR)	0.008 (NR to NR)	0.028
	Danesh, 2004[87]	Reykjavik	Hard CHD	All Participants	6,428††	0.64 (0.63 to 0.65)	0.65 (0.64 to 0.67)	0.01 (NR to NR)	NR
	Elias-Smale, 2010[76]	Rotterdam	Hard CHD	All Participants	2,028	0.72 (NR to NR)	0.72 (NR to NR)	0 (NR to NR)	0.31

Table 21. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome† ††	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
	Kavousi, 2012[82]	Rotterdam	Hard CHD	All Participants	3,029	0.73 (0.71 to 0.75)	NR	0.00* (-0.01* to 0.00*)	NR
	Salim, 2016[109]	Singapore Chinese Health Study	Hard CHD	Women	528	0.778 (0.729 to 0.827)	0.780 (0.731 to 0.829)	0.002 (NR to NR)	NR
	Salim, 2016[109]	Singapore Chinese Health Study	Hard CHD	Men	965	0.679 (0.644 to 0.714)	0.689 (0.654 to 0.724)	0.01 (NR to NR)	NR
	Rana, 2012[99]	EISNER	Soft CVD	All Participants	1,286	0.73 (0.66 to 0.82)	0.73 (0.65 to 0.82)	0 (NR to NR)	0.95
	Wilson, 2005[85]	FHS and Framingham offspring	Soft CVD	All Participants	4,446	0.78 (0.76 to 0.80)	0.78 (0.76 to 0.80)	0 (NR to NR)	NR
	Wilson, 2008[107]	Framingham Offspring	Soft CVD	All Participants	3,006	0.795 (NR to NR)	0.799 (NR to NR)	0.004 (NR to NR)	NR
	Seven, 2015[92]	Inter99	Soft CVD‡‡	All Participants	6,138§§	0.697 (NR to NR)	0.701 (NR to NR)	0.004 (NR to NR)	0.26
	Yeboah, 2012[75]	MESA	Soft CVD	Intermediate Risk	1,330	0.623 (NR to NR)	0.640 (NR to NR)	0.017 (NR to NR)	0.03
	Cook, 2006[83]	WHS (WHS model)‖‖	Soft CVD	All Participants	15,048	0.811 (NR to NR)	0.813 (NR to NR)	0.002 (NR to NR)	NR
	Cook, 2006[83]	WHS (ATP III full recalibration)¶¶	Soft CVD	All Participants	26,927	0.809 (NR to NR)	0.810 (NR to NR)	0.001 (NR to NR)	NR
	Welsh, 2013[98]	WOSCOPS	Soft CVD	All Participants	4,128	0.582 (0.57 to 0.60)##	0.588 (0.57 to 0.60)##	0.006 (NR to NR)##	<0.001
	Folsom, 2006[110]	ARIC	Soft CHD	All Participants	1,511	0.767 (NR to NR)	0.770 (NR to NR)	0.003* (NR to NR)	>0.05
	Rodondi, 2010[81]	Health ABC	Soft CHD	All Participants	1,515	0.611 (NR to NR)	0.622 (NR to NR)	0.011 (NR to NR)	NR
	Yeboah, 2012[75]	MESA	Soft CHD	Intermediate Risk	1,330	0.623 (NR to NR)	0.640 (NR to NR)	0.017 (NR to NR)	0.03
	Schneider, 2012[100]	Study of Health in Pomerania	Fatal CVD	All participants	3,602	0.898 (0.873 to 0.923)	0.906 (0.881 to 0.93)	0.008 (NR to NR)	NR

* Calculated as Extended-Base except where noted; asterisk indicates reported (not calculated) change

† Recalibrated by including the PCE in the Cox model predicting Hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events

‡ FRS entered categorically, not continuously. 3-category model abstracted.

§ Authors also report AUC and p-value for FRS model stratified into 5 risk categories: base model AUC=0.735, extended model AUC=0.750; p=0.0163.

‖ Table 7, which calculates FRS as published by D'Agostino, shows that tertiles of CRP were able to discriminate in low-risk individuals (<10% 10-yr risk) but not intermediate or high-risk individuals.

¶ Only studies with information on all subgroups used.

Table 21. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Reported in Table 3 of Shepherd, 2002.
** Sensitivity analyses conducted using AUC instead of Harrell's c gave similar results.
†† No change in findings when 376 (5.8%) of participants with baseline ECG abnormalities or angina were excluded from analysis (data not shown)
‡‡ Assumed since primary outcome
§§ Assumed from Table 5
‖‖ For generalizability, predicted probabilities were calibrated to observed risk from the Framingham Heart Study.
¶¶ ATP III beta-coefficients recalculated for all traditional risk factors before adding hsCRP to the model to be conservative and allow best possible fit.
C-statistics take into account competing risk of non-CVD death
*** Exploratory subgroup analyses
††† Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; AIC = Akaike information criterion; ARIC = Atherosclerosis Risk in Communities study; BIC = Bayesian information criterion; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC IPD MA= Emerging Risk Factors Collaboration individual participant data meta-analysis; FRS = Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; HRT = hormone replacement therapy; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; MESA = Multi-Ethnic Study of Atherosclerosis; mg/L = milligrams per Liter; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; NR = not reported; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SHIP = the Study of Health in Pomerania; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study

Table 22. Reclassification Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome ###	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	Risk categories (High, Intermediate, Low) 10 yr-risk
Published coefficient: PCE	Yeboah, 2016[90]	MESA	5,185	Hard CVD	All Participants	0.024 (-0.015 to 0.067)*	0.028 (-0.013 to 0.077)*	-0.005 (-0.015 to 0.003)*	≥7.5%, <7.5%
Published coefficient: FRS	Lyngbaek, 2013[96]	MONICA - Copenhagen	1,168	Hard CVD	Women	-0.083 (-0.354 to 0.189)	NR	NR	Continuous NRI
	Lyngbaek, 2013[96]	MONICA - Copenhagen	1,147	Hard CVD	Men	0.308 (0.081 to 0.534)	NR	NR	Continuous NRI
	Yeboah, 2016[90]	MESA	5,185	Hard CHD	All Participants	0.003 (-0.028 to 0.026)	0.005 (-0.027 to 0.027)	-0.002 (-0.007 to 0.001)	>20%, 10-20%, <10%
	Yeboah, 2016[90]	MESA	204	Hard CHD	Intermediate Risk	-0.003 (-0.138 to 0.132)‡	NR	NR	>20%, 10-20%, <10%
	Rana, 2009[104]	EPIC-Norfolk	2,550	Soft CHD	All Participants	0.120 (NR to NR)	0.021 (NR to NR)	0.099 (NR to NR)	>20%, 10-20%, <10%
	Rana, 2009[104]	EPIC-Norfolk	1,008	Soft CHD	Intermediate Risk	0.284 (NR to NR)	0.129 (NR to NR)	0.155 (NR to NR)	>20%, 10-20%, <10%
Model development: FRS variables	Wannamethee, 2011[102]	British Regional Heart Study	2,854	Hard CVD	All Participants	0.063 (0.019 to 0.108)§	0.056 (0.014 to 0.097)	0.008 (-0.008 to 0.023)	≥20%, 10-19%, <10%***
	Wannamethee, 2011[102]	British Regional Heart Study	1,005	Hard CVD	Intermediate Risk	0.094 (0.003 to 0.185)‡	NR	NR	≥20%, 10-19%, <10%***
	ERFC, 2012[65]	ERFC IPD MA‖	72,574	Hard CVD	All Participants	0.0152 (0.0078 to 0.0227)	0.0146 (0.0073 to 0.0219)	0.0006 (-0.0009 to 0.0022)	≥20%, 10-20%, <10%***
	ERFC, 2012[65]	ERFC IPD MA	10,412	Hard CVD	Intermediate Risk	0.027 (0.007 to 0.047)‡	NR	NR	≥20%, 10-20%, <10%***
	ERFC, 2012[65]	ERFC IPD MA¶	25,157	Hard CVD	Women	0.0036 (-0.007 to 0.0142)	NR	NR	≥20%, 10-20%, <10%***
	ERFC, 2012[65]	ERFC IPD MA¶	19,467	Hard CVD	Men	0.0124 (-0.002 to 0.0269)	NR	NR	≥20%, 10-20%, <10%***
	Shah, 2009[78]	Edinburgh Artery Study	919	Hard CHD	All Participants	0.088 (-0.013 to 0.189)	0.035 (-0.594 to 0.130)#	0.053 (0.016 to 0.089)#	≥15%, 10-15%, 5-10%, 0-<5%
	Shah[78], 2009	Edinburgh Artery Study	919	Hard CHD	All Participants	0.03 (-0.030 to 0.092)	0.042 (-0.016 to 0.101)#	-0.012 (-0.029 to 0.006)#	≥15%, 0-15%
	Shah, 2009[78]	Edinburgh Artery Study	532	Hard CHD	Intermediate Risk	0.103 (-0.038 to 0.243)‡	NR	NR	≥15%, 10-15%, 5-10%, 0-<5%
	Wilson, 2008[107]	Framingham Offspring	3,006	Hard CHD	All Participants	0.1177 (0.030 to 0.205)**	0.1091 (0.022 to 0.196)**	0.0086 (0.0003 to 0.017)**	>20%, 6-20%, 0-6%†††
	Wilson, 2008[107]	Framingham Offspring	448	Hard CHD	Intermediate Risk	0.130 (-0.005 to 0.265)‡	NR	NR	>20%, 6-20%, 0-6%†††

Table 22. Reclassification Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome ###	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	Risk categories (High, Intermediate, Low) 10 yr-risk
	Mohlenkamp, 2011[103]	Heinz Nixdorf Recall (HNR)	3,966	Hard CHD	All Participants	0.105 (NR to NR); p=0.026	NR	NR	>20%, 10-20%, <10%
	Shah, 2009[78]	Northwick Park Heart Study II	2,412	Hard CHD	All Participants	0.085 (-0.013 to 0.183)	0.088 (-0.007 to 0.184)#	-0.003 (-0.025 to 0.020)#	≥15%, 10-15%, 5-10%, 0-<5%
	Shah, 2009[78]	Northwick Park Heart Study II	2,412	Hard CHD	All Participants	0.049 (0.008 to 0.090)	0.057 (0.016 to 0.098)#	-0.008 (-0.014 to -0.001)#	≥15%, 0-15%
	Shah, 2009[78]	Northwick Park Heart Study II	1,235	Hard CHD	Intermediate Risk	0.076 (-0.065 to 0.216)‡	NR	NR	≥15%, 10-15%, 5-10%, 0-<5%
	Kavousi, 2012[82]	Rotterdam	3,029	Hard CHD	All Participants	0.020 (-0.023 to 0.064)	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Intermediate Risk	0.092 (0.002 to 0.180)	0.019 (NR to NR)‡‡	0.073 (NR to NR)‡‡	>20%, 10-20%, <10%
	Salim, 2016[109]	Singapore Chinese Health Study	528	Hard CHD	Women	NR	0.015 (NR to NR); p=0.157§§	0.000 (NR to NR); p=1.0§§	>20%, 10-20%, <10%
	Salim, 2016[109]	Singapore Chinese Health Study	965	Hard CHD	Men	NR	0.032 (NR to NR); p=0.020§§	0.002 (NR to NR); p=0.759§§	>20%, 10-20%, <10%
	Wilson, 2008[107]	Framingham Offspring	3,006	Soft CVD	All Participants	0.0559 (0.011 to 0.100)‖	0.0498 (0.007 to 0.093)‖‖	0.0061 (-0.005 to 0.018)‖‖	>20%, 6-20%, 0-6%†††
	Wilson, 2008[107]	Framingham Offspring	1,042	Soft CVD	Intermediate Risk	0.058 (-0.015 to 0.131)‡	NR	NR	>20%, 6-20%, 0-6%†††
	Seven, 2015[92]	Inter99	6,138	Soft CVD¶¶	All Participants	0.039 (NR to NR); p=0.012	NR	NR	>15%, 5-15%, <5%§§§
	Yeboah, 2012[75]	MESA	1,330	Soft CVD	Intermediate Risk	0.037 (NR to NR)	0.016 (NR to NR)	0.021 (NR to NR)	<3.4%, 3.4 to 21.1%, >21.1%‖‖‖
	Welsh, 2013[98]	WOSCOPS	4,128	Soft CVD	All Participants	0.010 (0.002 to 0.018)	NR	NR	≥20%, <20%***
	Welsh, 2013[98]	WOSCOPS	4,128	Soft CVD	All Participants	0.065 (-0.001 to 0.129)	0.017 (NR to NR)	0.048 (NR to NR)	Continuous NRI of improvements across integer % thresholds for >0% risk
	Rodondi, 2010[81]	Health ABC	NA	Soft CHD	All Participants	NR##	NR##	NR##	≥20%, 10 to <20%, <10%

Table 22. Reclassification Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome ###	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	Risk categories (High, Intermediate, Low) 10 yr-risk
	Yeboah, 2012[75]	MESA	1,330	Soft CHD	Intermediate Risk	0.079 (NR to NR)	0.043 (NR to NR)	0.036 (NR to NR)	<2.0%, 2.0 to 15.4%, >15.4%‖‖‖
	Schneider, 2012[100]	Study of Health in Pomerania	3,602	Fatal CVD	All Participants	0.0471 (-0.0270 to 0.1592)	NR	NR	SCORE: >9%, 2-9%, <2%¶¶¶

* Sensitivity analysis using 3 categories (0-5%, 5-7.5%, >7.5%) produced similar results
† Category-free NRI
‡ Bias-corrected NRI_{INT} calculated using simple variance method
§ Using calculated overall NRI instead of reported NRI because there are internal inconsistencies and % calculation errors in the reclassification table (reported NRI=0.038, p=0.07).
‖Reclassification data is from 22 studies with >10 yrs F/U reporting both fatal and nonfatal CVD events.
¶ Based on 15 studies with at least 10 years of followup in both men and women (2784/19467 first CV events in men; 2323/25157 first CV events in women). Discussion states that subpopulation analyses were exploratory.
# CIs calculated for event and nonevent NRI.
** CIs were calculated for overall, event, and nonevent NRI using simple variance method. Reported NRI are statistically adjusted from 12 years to 10 years of followup interval which resulted in smaller number of events, n=110 (instead of 129 events at 12-years).
‡‡ Event and nonevent NRI calculated
§§ Reported as 'case NRI' and 'noncase NRI'; because of case-control design we did not combine to calculate total NRI
‖‖ CIs were calculated for overall, event, and nonevent NRI using simple variance method. Reported NRI are statistically adjusted from 12 years to 10 years of followup interval which resulted in smaller number of events, n=241 (instead of 286 events at 12-years).
¶¶ Assumed since the primary outcome
Not reported because CRP was not strongly related with CHD events and did not improve global measures of predictive accuracy.
*** 10-yr CVD risk
††† 10-yr CHD risk
§§§ time horizon NR
‖‖‖ 7.5-yr risk
¶¶¶ 10-yr risk of fatal CVD
Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities study; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC IPD MA= Emerging Risk Factors Collaboration individual participant data meta-analysis; FRS=Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; hsCRP = high sensitivity C-reactive protein; HRT = hormone replacement therapy; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; MESA = Multi-Ethnic Study of Atherosclerosis; mg/L = milligrams per Liter; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; NR = not reported; NRI = net reclassification improvement; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SHIP = the Study of Health in Pomerania; WHS = Women's Health Study; WOSCOPS = the West of Scotland Coronary Prevention Study; yr = year

Table 23. Study Design and Participant Characteristics in Included CAC Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Country	N	F/U, mean (yrs); Range	Mean Age	% Women	% White	% DM	% HTN (% treated)	% Hyper-lipidemia (% treated)	% Current smoker	Mean CAC score	Elevated CAC score threshold (% elevated CAC score)
Yeboah, 2016†[90]	Published coefficient: PCE	MESA	United States	5,185	10; NR	61.2	53.1	38	9.8	NR (32.5)	NR (0)	13.6	0§	NR (NR)
Fudim, 2016[112]	Published coefficient: PCE	MESA	United States	6,742	7.5§; NR	62.0	52.7	38.5	NR	NR (NR)	NR (NR)	NR	NR	NR (NR)
Geisel, 2017[114]	Published coefficient: FRS	HNR	Germany	3,108	10.3; NR	59.2	52.9	NR	11.5	NR (31.6)	NR (9.2)	22.6	11.3§	≥100 (26.5)
Yeboah, 2016†[90]	Published coefficient: FRS	MESA	United States	5,185	10; NR	61.2	53.1	38	9.8	NR (32.5)	NR (0)	13.6	0§	NR (NR)
Erbel, 2010[74]	Published coefficient: FRS	HNR	Germany	4,129	5.1; NR	59.4	52.7	NR	7.4	38.2 (32.1)	45.6# (9)	22.8	168.3	≥400 (10.2)
Wong, 2009[106]	Published coefficient: FRS	EISNER + Cardiac Research Database‖‖‖‖	United States	2,303	4.4; 0.8 to 7.8	55.7	38	NR‡‡	7	NR (NR)	NR (NR)	7	NR	≥400 (8.2)
Greenland, 2004[86]	Published coefficient: FRS	South Bay Heart Watch	United States	1,029	6.3; 0.12 to 8.5	65.7	9.9	84.9	0	41.4 (NR)	NR (NR)	17.7	NR	≥301 (21.5)
Kavousi, 2016[111]	Model development: PCE variables	Pooled Analysis of 5 Cohorts¶¶¶ of Low Risk Women (<7.5% 10-yr PCE risk)	United States, Germany, Netherlands	6,739	10.5*****; 7.0 to 11.6	54.1	100	NR	4.8	NR (17.2)	NR (0)	13.7	0.24§	>0 (36.1)
Bos, 2015[89]	Model development: PCE variables	Rotterdam	Netherlands	2,408	6.6***; NR	69.5	52.4	NR	12.5	73.8 (39.3)	48.6# (22.8)	15.4	52.3§†††	Prevalence of any CAC (82.1)
Polak, 2017[113]	Model development: FRS variables	MESA	United States	6,500	10.2§; 97 to 10.7 (IQR)	62.1	52.6	38.9	9.5	NR (36.5)	NR (16.1)	13.1	NR	>0 (50.1)
Kavousi, 2016[111]	Model development: FRS variables	Pooled Analysis of 5 Cohorts¶¶¶ of Low Risk Women (<10% 10-yr FRS risk)	United States, Germany, Netherlands	7,772	10.5*****; 7.0 to 11.6	54.1	100	NR	4.8######	NR (17.2)	NR (0)	13.7	0.24§	>0 (36.1)
Hoffmann, 2016[88]	Model development: FRS variables	Framingham Heart Study Offspring and 3rd Generation	United States	3,486‖‖	8; NR	50	50.9	100	5.3	42.9 (16.2)	21.4 (11.5)	12.5	0§¶¶	>300¶¶ (8.1)

Table 23. Study Design and Participant Characteristics in Included CAC Risk Prediction Studies (KQ2)

Author, Year	Model type: Base model	Study name	Country	N	F/U, mean (yrs); Range	Mean Age	% Women	% White	% DM	% HTN (% treated)	% Hyper-lipidemia (% treated)	% Current smoker	Mean CAC score	Elevated CAC score threshold (% elevated CAC score)
Chang, 2015[93]	Model development: FRS variables ‡‡‡	Houston Methodist DeBakey Heart and Vascular Center cohort	United States	946§§§	6.9§; 4.7-8.8 (IQR)	57.5	24.7	NR	9.6	49.6 (NR)	57.1 (NR)	46.5	118§	>400 (25.2)
Yeboah, 2014‖‖‖[94]	Model development: FRS variables	MESA and HNR	United States and Germany	1,343	8.5; NR	63	44	53	100	NR (59)	NR (23)	16	272	>400 (NR)
Yeboah, 2012[75]†	Model development: FRS variables	MESA	United States	1,330	7.6§; 7.3-7.8 (IQR)	63.8	33.3	35.7	0	NR (38.2)	NR (14.1)	16.5	7.0§	NR (NR)
Kavousi, 2012†[82]	Model development: FRS variables	Rotterdam	Netherlands	3,678	6.8§; 5.8-8.1 (IQR)	69.1	59.4	NR	12.9	NR (23.5)	NR (10.2)	17.5	65.8§	NR (NR)
Rana, 2012###[99]	Model development: FRS variables	EISNER	United States	1,286	4.1; NR	58.6	47.2	NR	8.1	57.9 (NR)	NR (NR)	5.4	116.3	NR (NR)
Malik, 2011[101]	Model development: FRS variables	MESA	United States	6,603	6.4§; 0-7.8	62.9	52.6	38.4	13.3 ††††	44.7 (37)	37.0 (15.8)	13	146.8	≥400 (10)
Mohlenkamp, 2011###[103]	Model development: FRS variables	HNR	Germany	3,966	5.1; NR	59.3	52.8	NR	7.2	54.2 (31.7)	NR (9.1)	22.6	14.9§	≥100 (26.6)
Erbel, 2010[74]	Model development: FRS variables	HNR	Germany	4,129	5.1; NR	59.4	52.7	NR	7.4	38.2 (32.1)	45.6# (9)	22.8	168.3	≥400 (10.2)
Elias-Smale, 2010###[76]	Model development: FRS variables	Rotterdam	Netherlands	2,028	9.2§; 8.3-10.0 (IQR)	69.6	57.4	NR	NR	NR (27.6)	NR (14)	16.8	84§	Prevalence of any CAC (89.5)
Polonsky, 2010[77]	Model development: FRS variables	MESA	United States	5,878	5.8§; 5.6-5.9 (IQR)	62	54	NR	0	NR (33)	NR (16)	50	NR	NR (NR)

† Also a study of ABI and CRP
§ Median
# Defined as TC≥240 mg/dL or lipid-lowering drugs
‡‡ Reported as "mainly Caucasian"
‖‖ Baseline participant characteristics are for 3217 participants without CVD
¶¶ Modified Agatston score
*** Estimated from 15773 p-y F/U and N of 2408
††† CAC volume (mm^3); calcium density not measured

Table 23. Study Design and Participant Characteristics in Included CAC Risk Prediction Studies (KQ2)

‡‡‡ Authors attempted to calculate FRS as published, but continuous BP and cholesterol measurements not available so these predictors were dichotomized (hyperlipidemia defined as TC 200-239 mg/dL and HTN defined as SBP 140-159 mm Hg)
§§§ 16.5% had atypical chest pain
‖‖‖ ABI and CRP also considered as part of predictor selection during model development, but variables were ultimately not included in the final model based on a priori thresholds, so analyses of these NTRFs not reported
Also a study of CRP
†††† 25% of population with MetS
‖‖‖‖ 43% (N=999) of participants from EISNER RCT; 57% (N=1,304) from cardiac research database of physician- or self-referred clinical patients
¶¶¶ Five pooled cohorts: DHS, FHS, HNR, MESA, and Rotterdam
Participants with diabetes excluded from the FRS analysis
***** Estimated from median and interquartile range

Abbreviations: ABI = ankle-brachial index; BP = blood pressure; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DHS = Dallas Heart Study; DM = diabetes mellitus; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FHS = Framingham Heart Study; FRS = Framingham Risk Score; F/U = follow up; HNR = Heinz Nixdorf Recall study; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; IQR = inter-quartile range; MESA = Multi-Ethnic Study of Atherosclerosis; MetS = metabolic syndrome; mg/dL = Milligrams per Deciliter; mg/L = milligrams per Liter; NR = not reported; NRI = net reclassification improvement; NTRF = non-traditional risk factor; RCT = randomized controlled trial; SBP = systolic blood pressure; TC = total cholesterol

Table 24. Base Models for Included CAC Risk Prediction Studies (KQ2)

Author, Year	Base model	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	DM	Predicted outcome‖‖‖‖‖: N (%)	Handling of CAC in extended model
Yeboah, 2016*[90]	Published coefficient: PCE (Goff, 2014)†	MESA	X	X	X	X	X	X	X	X	X	Hard CVD: 320 (6.2)	Log-transformed; log (CAC+1)
Fudim, 2016[112]	Published coefficient: PCE	MESA	X	X	X	X	X	X	X	X	X	Hard CVD: 296 (4.4)	Log-transformed; log (CAC+1)
Yeboah, 2016*[90]	Published coefficient: FRS (D'Agostino, 2001)†	MESA	X	X		X	X‡		X	X	X	Hard CHD: 194 (3.7)	Log-transformed; log (CAC+1)
Geisel, 2017[114]	Published coefficient: FRS	HNR	X	X		X	X	X	X	X	X	Hard CVD: 223 (7.2)	Log-transformed; log (CAC+1) for discrimination analyses; Categorical: ≥100, <100 for reclassification analyses
Erbel, 2010[74]	Published coefficient: FRS (Wilson, 1998)	HNR	X	X		X	X‡			X§	X	Hard CHD: 93 (2.2)	Log-transformed; log (CAC+1)‖
Erbel, 2010[74]	Published coefficient: FRS (NCEP ATP III, 2002)¶	HNR	X	X		X	X	X	X	X		Hard CHD: 93 (2.2)	Log-transformed; log (CAC+1)‖
Wong, 2009[106]	Published coefficient: FRS (NCEP ATP III, 2002)#	EISNER + Cardiac Research Database	X	X		X	X	X	X	X		Hard CHD: 16 (0.7) Soft CVD: 47 (2.0) Soft CHD: 41 (1.8)	Categorical: 0-9, 10-99, 100-399, ≥400**
Greenland, 2004[86]	Published coefficient: FRS (NCEP ATP III, 2002)	South Bay Heart Watch	X	X		X	X	X	X	X		Hard CHD: 84 (8.2)	Continuous
Kavousi, 2016[111]	Model development: PCE variables	Pooled analysis of 5 cohorts§§§ of low risk women (<7.5% 10-yr PCE risk)	X			X	X	X	X	X	X	Hard CVD: 165 (2.4)	Log-transformed; log (CAC+1)
Bos, 2015[89]	Model development: PCE variables	Rotterdam	X	X	X	X	X	X	X	X	X	Fatal CVD: 84 (3.5)	Log-transformed; ln (CAC+1)
Polak, 2017[113]	Model development: FRS variables	MESA	X	X	X	X	X		X	X	X	Soft CHD: 429 (6.6)	Categorical: 0, >0

Table 24. Base Models for Included CAC Risk Prediction Studies (KQ2)

Author, Year	Base model	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	DM	Predicted outcome‖‖‖‖: N (%)	Handling of CAC in extended model
Kavousi, 2016[111]	Model development: FRS variables	Pooled analysis of 5 cohorts§§§ of low risk women (<10%10-yr FRS risk)	X			X	X	X	X	X		Hard CHD: 150 (1.9)	Log-transformed; ln (CAC+1)
Hoffmann, 2016[88]	Model development: FRS variables (categorical and continuous models)	Framingham Heart Study Offspring and 3rd Generation	X	X		X	X	X	X	X	X	Hard CHD: 59 (1.7) Hard CVD: 107 (3.1)	Primary analysis: categorical (0, 1-100, 101-300, >300); secondary analysis: log-transformed
Chang, 2015[93]	Model development: FRS variables§§	Houston Methodist DeBakey Heart and Vascular Center cohort	X	X		X	X		X		X	Soft CHD: 106 (11.2)	Log-transformed
Yeboah, 2014¶¶[94]	Model development: FRS variables##	MESA and HNR	X	X		X	X		X	X	X	Hard CHD: 85 (6.3)	Log-transformed; log(CAC+25)
Yeboah, 2012[75]*	Model development: FRS variables	MESA	x	x	x	x	x	x	x	x		Soft CVD: 123 (9.2) Soft CHD: 94 (7.1)	Log-transformed; ln (CAC+1)
Kavousi, 2012*[82]	Model development: FRS variables***	Rotterdam	X	X		X	X	X	X	X	X	Hard CHD: 347 (5.8)	Log-transformed; ln (CAC+1)
Rana, 2012†††[99]	Model development: FRS variables	EISNER	x	x		x	x	x	x	x	x	Soft CVD: 35 (2.7)	Log-transformed; log (CAC+1)
Malik, 2011[101]	Model development: FRS variables	MESA	X	X	X	X	X	X	X	X		Soft CVD: 410 (6.2) Soft CHD: 299 (4.5)	Continuous‡‡‡
Mohlenkamp, 2011†††[103]	Model development: FRS variables	HNR	X	X		X	X			X§	X	Hard CHD: 91 (2.3)	Log-transformed; log (CAC+1)
Erbel, 2010[74]	Model development: FRS variables	HNR	X	X		X	X			X§	X	Hard CHD: 93 (2.2)	Log-transformed; log (CAC+1)
Elias-Smale, 2010†††[76]	Model development: FRS variables	Rotterdam	X	X		X	X	X	X	X	X	Hard CHD: 135 (6.6)	Log-transformed; ln (CAC+1)

Table 24. Base Models for Included CAC Risk Prediction Studies (KQ2)

Author, Year	Base model	Study name	Age	Sex	Race/ ethnicity	Smoking	SBP	Anti-HTN Tx	TC	HDL	DM	Predicted outcome[IIIII]: N (%)	Handling of CAC in extended model
Polonsky, 2010[77]	Model development: FRS variables	MESA	X	X	X	X	X	X	X	X		Soft CHD: 209 (3.6)	Log-transformed; ln (CAC+1)

* Also a study of ABI and CRP
† Recalibration accomplished by including the PCE (or FRS in that corresponding model) in the Cox model predicting hard CVD events (or hard CHD in FRS model); created a calibrated PCE which used the BL survival estimated from MESA data
‡ BP categories as defined in JNC-V; includes DBP
§ Also included LDL
¶ Analyzed as ATP III categories where persons with risk equivalents (symptomatic carotid stenosis, stroke, PAD, or diabetes) allocated to high-risk group
# Participants with diabetes automatically assigned a risk score of 20% (or higher if so calculated)
** Limited results reported for sensitivity analyses using log-transformed CAC
§§ Authors attempted to calculate FRS as published, but continuous BP and cholesterol measurements not available so these predictors were dichotomized (hyperlipidemia defined as TC 200-239 mg/dL and HTN defined as SBP 140-159 mm Hg)
‖ Assumed log-transformed for relevant analyses, though categorical data used elsewhere in analysis. Patients were classified as having normal (≤10), mild (11 to 100), moderate (101 to 400), or severe (>400) calcification.
¶¶ ABI and CRP also considered as part of predictor selection during model development, but variables were ultimately not included in the final model based on a priori thresholds, so analyses of these NTRFs not reported
Base model discrimination reported for FRS as published; but not for an extended model of FRS+CAC. Because of poor calibration using the FRS as published in this population, the model was entirely refit with new coefficients.
*** Model additionally included adjustment for CAC scanner type
††† Also a study of CRP
‡‡‡ Assumed that CAC was included as a continuous variable for relevant analyses using "zCAC" which was calculated by subtraction of the mean and division by the SD of each measurement. Categorical CAC included in other analyses (categories defined by 0, 1-99, 100-399, ≥400)
§§§ Five pooled cohorts: DHS, FHS, HNR, MESA, and Rotterdam
‖‖ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; BP = blood pressure; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DHS = Dallas Heart Study; DM = diabetes mellitus; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FHS = Framingham Heart Study; FRS = Framingham Risk Score; F/U = follow up; HDL = high-density lipoprotein; HNR = Heinz Nixdorf Recall study; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; IQR = inter-quartile range; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis; MetS = metabolic syndrome; mg/dL = Milligrams per Deciliter; mg/L = milligrams per Liter; NR = not reported; NRI = net reclassification improvement; NTRF = non-traditional risk factor; PCE = Pooled Cohort Equations; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; Tx = treatment

Table 25. Calibration and Overall Performance Measures in Included CAC Risk Prediction Studies (KQ2)

Measure	Author, Year	Model type: Base model	Study name	N	Outcome§	Subgroup	Base model	Base model p-value	Extended model	Extended model p-value	Between model p-value	Calculated change between models
AIC	Bos, 2015[89]	Model development: PCE variables	Rotterdam	2,408	Fatal CVD	All Participants	1195.57	--	1176.93	--	--	-18.64
BIC	Fudim, 2016[112]	Published coefficient: PCE	MESA	3,556	Hard CVD	Women	NR	NR	Very Strong‡	NR	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	3,186	Hard CVD	Men	NR	NR	Very Strong‡	NR	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	1,850	Hard CVD	African American	NR	NR	Very Strong‡	NR	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	2,599	Hard CVD	Caucasian	NR	NR	Very Strong‡	NR	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	801	Hard CVD	Chinese American	NR	NR	Positive‡	NR	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	1,492	Hard CVD	Latino	NR	NR	Very Strong‡	NR	NR	NR
Hosmer-Lemeshow test	Fudim, 2016[112]	Published coefficient: PCE	MESA	3,556	Hard CVD	Women	NR	NR	16.715	0.033	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	3,186	Hard CVD	Men	NR	NR	8.587	0.38	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	1,850	Hard CVD	African American	NR	NR	11.0	0.20	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	2,599	Hard CVD	Caucasian	NR	NR	11.9	0.16	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	801	Hard CVD	Chinese American	NR	NR	4.9	0.77	NR	NR
	Fudim, 2016[112]	Published coefficient: PCE	MESA	1,492	Hard CVD	Latino	NR	NR	12.3	0.14	NR	NR
	Bos, 2015[89]	Model development: PCE variables	Rotterdam	2,408	Fatal CVD	All Participants	6.27	0.71	2.84	0.97	--	-3.43
	Erbel, 2010[74]	Model development: FRS variables	HNR	4,129	Hard CHD	All Participants	15.5	0.05	9.1	0.33	--	-6.4
	Mohlenkamp, 2011[103]	Model development: FRS variables	HNR	3,966	Hard CHD	All Participants	11.5	0.18	NR	NR	--	--
	Polonsky, 2010[77]	Model development: FRS variables	MESA	5,878	Soft CHD	All Participants	6.72	0.46	9.15	0.24	--	2.43

Table 25. Calibration and Overall Performance Measures in Included CAC Risk Prediction Studies (KQ2)

Measure	Author, Year	Model type: Base model	Study name	N	Outcome§	Subgroup	Base model	Base model p-value	Extended model	Extended model p-value	Between model p-value	Calculated change between models
Likelihood ratio χ2	Elias-Smale, 2010[76]	Model development: FRS variables	Rotterdam	2,028	Hard CHD	All Participants	83.93	NR	120.32	NR	<0.001	36.39
	Kavousi, 2012[82]	Model development: FRS variables	Rotterdam	3,678	Hard CHD	All Participants	230.49*	NR	60.9†	NR	<0.05	-169.59
	Kavousi, 2012[82]	Model development: FRS variables	Rotterdam	NR	Hard CHD	Women	NR	NR	22.6†	NR	<0.05	--
	Kavousi, 2012[82]	Model development: FRS variables	Rotterdam	NR	Hard CHD	Men	NR	NR	41.2†	NR	<0.05	--
Global χ2	Chang, 2015[93]	Model development: FRS variables	Houston Methodist DeBakey Heart and Vascular Center	946	Soft CHD	All Participants	11.72	NR	45.33	NR	<0.0001	33.61

* Model likelihood chi-square

† Extended model statistic is "increase in model fit after extending the base model."

‡ Reported as "BIC support for model with CAC". From correspondence with Fudim, improvement in BIC are defined: 0-2 = negligible; 2-6 = positive; 6-10 = strong; and >10 = very strong.

§ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: AIC = Akaike information criterion; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; FRS = Framingham Risk Score; HNR = Heinz Nixdorf Recall study; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; PCE = Pooled Cohort Equations

Table 26. Discrimination Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome¶¶	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
Published coefficient: PCE	Yeboah, 2016[90]†	MESA	Hard CVD	All Participants	5,185	0.74 (NR to NR)	0.76 (NR to NR)	0.02 (NR to NR)	0.04
	Fudim, 2016[112]	MESA	Hard CVD	Women	3,556	0.766 (NR to NR)	0.784 (NR to NR)	0.018* (NR to NR)	0.19
	Fudim, 2016[112]	MESA	Hard CVD	Men	3,186	0.705 (NR to NR)	0.730 (NR to NR)	0.025* (NR to NR)	0.047
	Fudim, 2016[112]	MESA	Hard CVD	African American	1,850	0.707 (NR to NR)	0.740 (NR to NR)	0.033* (NR to NR)	0.11
	Fudim, 2016[112]	MESA	Hard CVD	Caucasian	2,599	0.734 (NR to NR)	0.753 (NR to NR)	0.019* (NR to NR)	0.18
	Fudim, 2016[112]	MESA	Hard CVD	Chinese American	801	0.734 (NR to NR)	0.747 (NR to NR)	0.013* (NR to NR)	0.66
	Fudim, 2016[112]	MESA	Hard CVD	Latino	1,492	0.800 (NR to NR)	0.809 (NR to NR)	0.009* (NR to NR)	0.45
Published coefficient: FRS	Geisel, 2017[114]	HNR	Hard CVD	All participants	3,108	0.693 (0.661 to 0.726)	0.731 (0.699 to 0.763)	0.038 (NR to NR)	0.02
	Geisel, 2017[114]	HNR	Hard CVD	Low risk (<10%)	1,694	0.658 (0.602 to 0.713)	0.738 (0.684 to 0.792)	0.08 (NR to NR)	0.01
	Geisel, 2017[114]	HNR	Hard CVD	Intermediate risk (10-20%)	1,022	0.575 (0.520 to 0.629)	0.665 (0.610 to 0.720)	0.09 (NR to NR)	0.004
	Geisel, 2017[114]	HNR	Hard CVD	High risk (>20%)	392	0.556 (0.482 to 0.629)	0.617 (0.534 to 0.700)	0.061 (NR to NR)	0.18
	Erbel, 2010[74]	HNR	Hard CHD (Wilson, 1998)	All Participants	4,129	0.681 (0.629 to 0.733)	0.749 (0.682 to 0.8)	0.068 (NR to NR)	0.003
	Erbel, 2010[74]	HNR	Hard CHD (ATPIII model)	All Participants	4,129	0.653 (0.606 to 0.7)	0.755 (0.705 to 0.805)	0.102 (NR to NR)	0.0001
	Erbel, 2010[74]	HNR	Hard CHD (Wilson, 1998)	Women	2,177	0.671 (0.582 to 0.76)	0.711 (0.621 to 0.8)	0.04 (NR to NR)	0.25
	Erbel, 2010[74]	HNR	Hard CHD (ATPIII model)	Women	2,177	0.668 (0.606 to 0.731)	0.729 (0.654 to 0.804)	0.061 (NR to NR)	0.23
	Erbel, 2010[74]	HNR	Hard CHD (Wilson, 1998)	Men	1,952	0.628 (0.558 to 0.698)	0.730 (0.667 to 0.802)	0.102 (NR to NR)	0.0003
	Erbel, 2010[74]	HNR	Hard CHD (ATPIII model)	Men	1,952	0.583 (0.523 to 0.644)	0.727 (0.665 to 0.788)	0.144 (NR to NR)	<0.0001
	Yeboah, 2016[90]	MESA	Hard CHD†	All Participants	5,185	0.74 (NR to NR)	0.78 (NR to NR)	0.04 (NR to NR)	0.001
	Greenland, 2004[86]	South Bay Heart Watch	Hard CHD	All Participants	1,029	0.63 (0.628 to 0.632)‡	0.68 (0.678 to 0.682)‡	0.05 (NR to NR)	<0.001
	Wong, 2009[106]	EISNER + Cardiac	Hard CHD	All Participants	2,303	0.757 (NR to NR)§	0.834 (NR to NR)§	0.077 (NR to NR)	0.1

Table 26. Discrimination Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome¶¶	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
		Research Database							
	Wong, 2009[106]	EISNER + Cardiac Research Database	Soft CVD	All Participants	2,303	0.763 (NR to NR)‖	0.851 (NR to NR)‖	0.088 (NR to NR)‖	0.006
	Wong, 2009[106]	EISNER + Cardiac Research Database	Soft CHD	All Participants	2,303	0.748 (NR to NR)¶	0.857 (NR to NR)¶	0.109 (NR to NR)¶	0.004
Model development: PCE variables	Kavousi, 2016[111]	Pooled analysis of 5 cohorts‖‖ of low risk women (<7.5% 10-yr PCE risk)	Hard CVD	All Participants	6,739	0.73 (0.69 to 0.77)	0.77 (0.74 to 0.81)	0.02* (0.0 to 0.05)	0.08
	Bos, 2015[89]	Rotterdam	Fatal CVD	All Participants	2,408	0.78 (0.73 to 0.83)	0.81 (0.76 to 0.86)	0.03 (NR to NR)	NR
Model development: FRS variables	Kavousi, 2016[111]	Pooled analysis of 5 cohorts‖‖ of low risk women (<10% 10-yr FRS risk)	Hard CHD	All Participants (DM excluded)	7,772	0.79 (0.70 to 0.88)	0.83 (0.73 to 0.93)	0.04* (0.01 to 0.07)	NR
	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	Hard CVD	All Participants	3,319#	0.8 (NR to NR)**	0.82 (NR to NR)**	0.02 (NR to NR)**	>0.05**
	Erbel, 2010[74]	HNR	Hard CHD	All Participants	4,129	0.712 (0.664 to 0.76)	0.763 (0.714 to 0.812)	0.051 (NR to NR)	0.004
	Elias-Smale, 2010[76]	Rotterdam	Hard CHD	All Participants	2,028	0.72 (NR to NR)	0.76 (NR to NR)	0.04 (NR to NR)	<0.001
	Kavousi, 2012[82]	Rotterdam	Hard CHD	All Participants	3,678	0.73 (0.71 to 0.75)	NR	0.05* (0.02* to 0.06*)	NR
	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	Hard CHD	All Participants	3,340#	0.78 (NR to NR)††	0.82 (NR to NR)††	0.04 (NR to NR)††	<0.05
	Mohlenkamp, 2011[103]	HNR	Hard CHD	All Participants	3,966	0.719 (0.671 to 0.767)	0.763 (0.715 to 0.812)	0.044 (NR to NR)	0.0067
	Kavousi, 2012[82]	Rotterdam	Hard CHD	Women	NR	NR	NR	0.05* (0.03* to 0.07*)	NR

Table 26. Discrimination Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	Outcome¶¶	Subgroup	N	Base model c-statistic (95% CI)	Extended model c-statistic (95% CI)	Change in discrimination (95% CI)*	Change P-Value
	Kavousi, 2012[82]	Rotterdam	Hard CHD	Men	NR	NR	NR	0.06* (0.03* to 0.09*)	NR
	Yeboah, 2014[94]	MESA and HNR	Hard CHD	With diabetes	1,343	0.6964 (0.64 to 0.75)‡‡	0.7575 (NR to NR)	0.061 (NR to NR)	NR
	Rana, 2012[99]	EISNER	Soft CVD	All Participants	1,286	0.73 (0.66 to 0.82)	0.84 (0.78 to 0.91)	0.11 (NR to NR)	0.003
	Yeboah, 2012[75]	MESA	Soft CVD	Intermediate risk	1,330	0.623 (NR to NR)	0.784 (NR to NR)	0.161 (NR to NR)	<0.001
	Malik, 2011[101]	MESA	Soft CVD	With diabetes, MetS, or neither§§	4,036	NR	NR	NR	<0.0001
	Chang, 2015[93]	Houston Methodist DeBakey Heart and Vascular Center	Soft CHD	All Participants	946	0.63 (NR to NR)	0.7 (NR to NR)	0.07 (NR to NR)	0.01
	Polonsky, 2010[77]	MESA	Soft CHD	All Participants	5,878	0.76 (0.72 to 0.79)	0.81 (0.78 to 0.84)	0.05 (NR to NR)	<0.001
	Yeboah, 2012[75]	MESA	Soft CHD	Intermediate risk	1,330	0.623 (NR to NR)	0.784 (NR to NR)	0.161 (NR to NR)	<0.001
	Malik, 2011[101]	MESA	Soft CHD	No diabetes or MetS	4,036	0.73 (NR to NR)	0.8 (NR to NR)	0.07 (NR to NR)	<0.0001
	Malik, 2011[101]	MESA	Soft CHD	With diabetes	881	0.72 (NR to NR)	0.78 (NR to NR)	0.06 (NR to NR)	<0.0001

* Calculated as Extended-Base except where noted; asterisk indicates reported (not calculated) change

† Recalibrated by including the PCE in the Cox model predicting Hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events

‡ CIs calculated from standard deviations

§ For categorical CAC analyses; p=0.08 for LogCAC analyses (AUCs NR); p=0.07 for LogCAC volume analyses (AUCs NR).

‖ For categorical CAC analyses; p=0.004 for LogCAC analyses (AUCs NR); p<0.01 for LogCAC volume analyses (AUCs NR).

¶ For categorical CAC analyses; p=0.002 for LogCAC analyses (AUCs NR); p=0.02 for LogCAC volume analyses (AUCs NR).

N assumed based on NRI analyses

** Same results obtained for entry of CAC continuously in the model (log transformed) and when entered categorically in the model (0, 1-100, 101-300, >300)

†† CAC entered continuously in the model (log-transformed). Results were similar when CAC entered categorically in the model (0, 1-100, 101-300, >300): base model 0.78 (NR to NR); extended model 0.83 (NR to NR); change in discrimination: 0.05 (NR to NR).

‡‡ AUC for published coefficient FRS in this population was 0.6797; CAC not added to published coefficient FRS. AUC for published coefficient PCE was 0.637; CAC not added to published coefficient PCE.

§§ For all analyzed groups (diabetes, MetS, neither), C-statistics improved from 0.73-0.74 to 0.78-0.79 (all p<0.0001) but which c-statistics belong to which groups NR.

‖‖ Five pooled cohorts: DHS, FHS, HNR, MESA, and Rotterdam

Table 26. Discrimination Outcomes in Included CAC Risk Prediction Studies (KQ2)

¶¶ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; ATP III = Adult Treatment Panel III; AUC = area under the concentrated curve; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DHS = Dallas Heart Study; DM = diabetes mellitus; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FHS = Framingham Heart Study; FRS = Framingham Risk Score; F/U = follow up; HNR = Heinz Nixdorf Recall study; MESA = Multi-Ethnic Study of Atherosclerosis; MetS = metabolic syndrome; NR = not reported; NRI = net reclassification improvement; PCE = Pooled Cohort Equations

Table 27. Reclassification Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome‡‡	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	10-Year risk categories (High, Intermediate, Low)
Published coefficient: PCE	Yeboah, 2016[90]	MESA	5,185	Hard CVD	All Participants	0.119 (0.08 to 0.256)*	0.178 (0.08 to 0.256)*	-0.059 (-0.075 to 0.03)*	≥7.5%, <7.5%
	Fudim, 2016[112]	MESA	3,556	Hard CVD	Women	0.095 (NR to NR); p=0.039	NR	NR	≥5.25%, <5.25% 7-year risk
	Fudim, 2016[112]	MESA	3,556	Hard CVD	Women	0.488 (NR to NR); p<0.001	NR	NR	Continuous NRI
	Fudim, 2016[112]	MESA	3,186	Hard CVD	Men	0.080 (NR to NR); p=0.037	NR	NR	≥5.25%, <5.25% 7-year risk
	Fudim, 2016[112]	MESA	3,186	Hard CVD	Men	0.437 (NR to NR); p<0.001	NR	NR	Continuous NRI
	Fudim, 2016[112]	MESA	1,850	Hard CVD	African American	0.111 (NR to NR); p=0.082	NR	NR	≥5.25%, <5.25% 7-year risk
	Fudim, 2016[112]	MESA	1,850	Hard CVD	African American	0.500 (NR to NR); p<0.001	NR	NR	Continuous NRI
	Fudim, 2016[112]	MESA	2,599	Hard CVD	Caucasian	0.111 (NR to NR); p=0.02	NR	NR	≥5.25%, <5.25% 7-year risk
	Fudim, 2016[112]	MESA	2,599	Hard CVD	Caucasian	0.587 (NR to NR); p<0.001	NR	NR	Continuous NRI
	Fudim, 2016[112]	MESA	801	Hard CVD	Chinese American	-0.121 (NR to NR); p=0.11	NR	NR	≥5.25%, <5.25% 7-year risk
	Fudim, 2016[112]	MESA	801	Hard CVD	Chinese American	0.701 (NR to NR); p=0.003	NR	NR	Continuous NRI
	Fudim, 2016[112]	MESA	1,492	Hard CVD	Latino	0.024 (NR to NR); p=0.61	NR	NR	≥5.25%, <5.25% 7-year risk
	Fudim, 2016[112]	MESA	1,492	Hard CVD	Latino	0.472 (NR to NR); p<0.001	NR	NR	Continuous NRI
Published coefficient: FRS	Geisel, 2017[114]	HNR	3,108	Hard CVD	All participants	0.551 (0.416 to 0.686)	NR	NR	Continuous NRI
	Geisel, 2017[114]	HNR	1,694	Hard CVD	Low risk (<10%)	0.414 (0.177 to 0.652)	NR	NR	Continuous NRI

Table 27. Reclassification Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome‡‡	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	10-Year risk categories (High, Intermediate, Low)
	Geisel, 2017[114]	HNR	1,022	Hard CVD	Intermediate risk (10-20%)	0.446 (0.246 to 0.646)	NR	NR	Continuous NRI
	Geisel, 2017[114]	HNR	392	Hard CVD	High risk (<20%)	0.181 (-0.100 to 0.462)	NR	NR	Continuous NRI
	Yeboah, 2016[90]	MESA	5,185	Hard CHD	All Participants	0.084 (0.024 to 0.196)	0.119 (0.045 to 0.239)	-0.034 (-0.053 to 0.017)	>20%, 10-20%, <10%
	Yeboah, 2016[90]	MESA	211	Hard CHD	Intermediate Risk	0.041 (-0.197 to 0.28)†	NR	NR	>20%, 10-20%, <10%
Model development: PCE variables	Kavousi, 2016[111]	Pooled analysis of 5 cohorts## of low risk women (<7.5% 10-yr PCE risk)	6,739	Hard CVD	All Participants	0.20 (0.09 to 0.31)	NR	NR	Continuous NRI
	Bos, 2015[89]	Rotterdam	2,408	Fatal CVD	All Participants	0.55 (0.33 to 0.76)	0.417 (NR to NR)	0.137 (NR to NR)	Continuous NRI
Model development: FRS variables	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	3,319	Hard CVD	All Participants	0.213 (0.088 to 0.337)‡§	0.232 (0.109 to 0.356)‡§	-0.02 (-0.032 to -0.008)‡§	≥10%, 6.5 to <10%, 2.5 to <6.5%, 0 to <2.5%§§
	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	3,319	Hard CVD	All Participants	0.2 (0.03 to 0.37)‖	0.21 (NR to NR)‖	-0.01 (NR to NR)‖	≥10%, 6.5 to <10%, 2.5 to <6.5%, 0 to <2.5%§§
	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	589	Hard CVD	Intermediate Risk	0.274 (0.058 to 0.491)†‡	NR	NR	≥10%, 6.5 to <10%, 2.5 to <6.5%, 0 to <2.5%§§
	Kavousi, 2016[111]	Pooled analysis of 5 cohorts## of low risk women (<10% 10-yr FRS risk)	7,772	Hard CHD	All Participants (excluded DM)	0.28 (0.18 to 0.39)	NR	NR	Continuous NRI
	Hoffmann, 2016[88]	Framingham Heart Study Offspring	3,340	Hard CHD	All Participants	0.22 (0.01 to 0.42)‖	0.24 (NR to NR)‖	-0.02 (NR to NR)‖	≥10%, 5 to <10%, 2.5 to <5%, 0 to <2.5%§§

Table 27. Reclassification Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome‡‡	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	10-Year risk categories (High, Intermediate, Low)
		and 3rd Generation							
	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	3,340	Hard CHD	All Participants	0.319 (0.141 to 0.497)‡¶	0.333 (0.156 to 0.511)‡¶	-0.014 (-0.026 to -0.003)‡¶	≥10%, 5 to <10%, 2.5 to <5%, 0 to <2.5%§§
	Hoffmann, 2016[88]	Framingham Heart Study Offspring and 3rd Generation	347	Hard CHD	Intermediate Risk	0.457 (0.093 to 0.821)†,‡	NR	NR	≥10%, 5 to <10%, 2.5 to <5%, 0 to <2.5%§§
	Erbel, 2010[74]	HNR	4,129	Hard CHD	All Participants	0.224 (0.091 to 0.356)#	0.226 (0.094 to 0.357)#	-0.002 (-0.019 to 0.015)#	>20%, 10-20%, <10%
	Erbel, 2010[74]	HNR	1,126	Hard CHD	Intermediate Risk	0.226 (-0.07 to 0.522)†	NR	NR	>20%, 10-20%, <10%**
	Mohlenkamp, 2011[103]	HNR	3,966	Hard CHD	All Participants	0.238 (NR to NR); p=0.0007	NR	NR	>20%, 10-20%, <10%
	Elias-Smale, 2010[76]	Rotterdam	2,028	Hard CHD	All Participants	0.14 (NR to NR); p<0.01	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	3,678	Hard CHD	All Participants	0.193 (0.125 to 0.262)	0.235 (0.168 to 0.301)††	-0.041 (-0.058 to -0.024)††	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Women	0.134 (0.039 to 0.229)	NNR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Women, Intermediate Risk	0.252 (0.064 to 0.44)	0.045 (NR to NR)††	0.207 (NR to NR)††	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	919	Hard CHD	Intermediate Risk	0.165 (0.041 to 0.29)†	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Men	0.241 (0.144 to 0.338)	NR	NR	>20%, 10-20%, <10%
	Kavousi, 2012[82]	Rotterdam	NR	Hard CHD	Men, Intermediate Risk	0.509 (0.337 to 0.681)	0.329 (NR to NR)††	0.18 (NR to NR)††	>20%, 10-20%, <10%
	Rana, 2012[99]	EISNER	1,279	Soft CVD	All Participants	0.35 (0.11 to 0.58)	0.286	0.06	>8%, 2.4 to 8%, <2.4%‖‖

Table 27. Reclassification Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model type: Base model	Author, Year	Study name	N	Outcome‡‡	Subgroup	Total NRI (95% CI)	Event NRI (95% CI)	Nonevent NRI (95% CI)	10-Year risk categories (High, Intermediate, Low)
							(0.035 to 0.536)††	(0.028 to 0.092)††	
	Rana, 2012[99]	EISNER	411	Soft CVD	Intermediate Risk	0.196 (-0.236 to 0.628)†	NR	NR	>8%, 2.4 to 8%, <2.4%‖‖
	Yeboah, 2012[75]	MESA	1,330	Soft CVD	Intermediate Risk	0.466 (NR to NR)	0.106 (NR to NR)	0.36 (NR to NR)	>21.1%, 3.4 to 21.1%, <3.4%¶¶
	Polak, 2017[113]	MESA	6,500	Soft CHD	All Participants	0.111 (0.064 to 0.159) †††	0.126 (0.080 to 0.172) †††	-0.015 (-0.027 to -0.002) †††	≥20%, 6-20%, <6%
	Polak, 2017[113]	MESA	2,634	Soft CHD	Intermediate Risk	0.073 (0.024 to 0.121)†	NR	NR	≥20%, 6-20%, <6%
	Chang, 2015[93]	Houston Methodist DeBakey Heart and Vascular Center	946	Soft CHD	All Participants	0.302 (NR to NR); p<0.0001	NR	NR	>20%, 6-20%, <6%
	Chang, 2015[93]	Houston Methodist DeBakey Heart and Vascular Center	655	Soft CHD	Intermediate Risk	0.286 (NR to NR); p<0.0001	NR	NR	>20%, 6-20%, <6%
	Polonsky, 2010[77]	MESA	5,878	Soft CHD	All Participants	0.25 (0.16 to 0.34)‡‡	0.225 (0.134 to 0.316)††	0.024 (0.01 to 0.037)††	≥10%, 3% to <10%, 0% to <3%§§
	Polonsky, 2010[77]	MESA	1,847	Soft CHD	Intermediate Risk	0.19 (0.05 to 0.33)†	NR	NR	≥10%, 3% to <10%, 0% to <3%§§
	Polonsky, 2010[77]	MESA	5,038	Soft CHD	Sensitivity analysis excluding 840 on lipid meds at baseline	0.26 (0.16 to 0.37)	NR	NR	≥10%, 3% to <10%, 0% to <3%
	Yeboah, 2012[75]	MESA	1,330	Soft CHD	Intermediate Risk	0.659 (NR to NR)	0.255 (NR to NR)	0.404 (NR to NR)	>15.4%, 2.0 to 15.4%, <2.0%

* Sensitivity analysis using 3 categories (0-5%, 5-7.5%, >7.5%) produced similar results

† Bias-corrected NRI_{INT} calculated using simple variance method

Table 27. Reclassification Outcomes in Included CAC Risk Prediction Studies (KQ2)

‡ CAC entered continuously in the model (log-transformed).
§ Calculated values in order to derive CIs for event and nonevent NRIs and there were small differences compared with reported values (method of CI calculation in paper NR). Study reported NRI (95% CI) w/ log CAC: 0.25 (0.08-0.41); event NRI: 0.27; and nonevent NRI: -0.02.
‖ CAC entered categorically in the model: 0, 1-100, 101-300, >300
¶ Calculated values in order to derive CIs for event and nonevent NRIs and there were small differences compared with reported values (method of CI calculation in paper NR). Study reported NRI (95% CI) w/ log CAC: 0.33 (0.11-0.53); Event NRI: 0.33; and Nonevent NRI: -0.02.
# Calculated Total NRI CIs, and event and nonevent NRIs. NRI was 0.196 (p=0.004) using categories of <6%, 6-20%, >20%. Also reports NRI for intermediate group where CAC scores <100 move an individual into low risk and CAC scores ≥400 move an individual to high risk (0.217 for 10-20% intermediate-risk group; 0.306 for 6-20% intermediate-risk group).
** Results for intermediate-risk group defined by 6-20% also available
†† Calculated event and nonevent NRI
‡‡ Sensitivity analysis including 883 with diabetes had NRI 0.27 (0.19 to 0.34)
§§ 5-year risk
‖‖ 4-year risk
¶¶ 7.5-year risk
Five pooled cohorts: DHS, FHS, HNR, MESA, and Rotterdam
††† Calculated event and nonevent NRI Cis
‡‡‡ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: AUC = area under the concentrated curve; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DHS = Dallas Heart Study; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FHS = Framingham Heart Study; FRS = Framingham Risk Score; F/U = follow up; HNR = Heinz Nixdorf Recall study; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement; PCE = Pooled Cohort Equations

Table 28. Radiation Exposure in Included CAC Harms Studies (KQ3)

Author, Year Quality	Cohort Year(s) of recruitment	N analyzed	Scanner type	Radiation exposure
Bos, 2015[89] Fair	Rotterdam 2003-2006	2,408	Electron-beam or Multi-detector CT	Estimated radiation dose: ≤2.1 mSv
Hoffmann, 2016[88] Fair	Framingham Offspring and 3rd Generation 1998-2001 or 2002-2005	3,486	Multi-detector CT	Effective radiation exposure range: 1.0 to 1.25 mSv
Messenger, 2016[115] Fair	MESA 2009	3,442	Multi-detector CT	Mean effective dose: 1.05 ± 0.45 mSv Effective dose range: 0.74-1.26 mSV
Rozanski, 2011[11] Fair	EISNER RCT 2001-2005	2,137	Electron-beam or multislice CT	Estimated radiation dose range: 1 to 2 mSv

Abbreviations: CT = computed tomography; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; MESA = Multi-Ethnic Study of Atherosclerosis; mSv = Millisievert; RCT = randomized controlled trial

Table 29. Psychological Outcomes in Included Harms Studies (KQ3)

Author, Year Quality	Cohort Year(s) of recruitment	N analyzed	Age	% Women	F/U	Outcome/instrument	IG Mean change (SE)	CG Mean change (SE)	p-value for between group difference
Nielsen, 2012[118] Fair	DanRisk 2009	1,169	50% were 50 yrs 50% were 60 yrs	53%	6 mo	Depression/MDI Score (range 0-50)	-1.4 (NR); p<0.0001*	NA	NA
O'Malley, 2003[119] Fair	US Active-Duty Army Personnel (RCT) Jan 1999 – Mar 2001	450 IG: 208 CG: 197	39-45 yrs Mean age: 42 yrs	21%	12 mo	Depression score/PRIME-MD†	-0.04 (0.21)	-0.13 (0.22)	0.75‖
						Anxiety score/PRIME-MD†	-0.19 (0.18)	-0.38 (0.21)	0.50‖
						Mental health functional status/SF-36§	0.44 (0.55)	1.01 (0.48)	0.44‖

Severity of depression estimated: 0 to 20 points (no depression); 21 to 25 points (mild depression); 26 to 30 points (moderate depression); >30 points (severe depression).
*Statistically significant at the 5% level after adjustment for multiple testing using the Bonferroni-Holm method.
† Continuous scores for depression and anxiety were obtained using the PRIME-MD based on the number and severity of symptoms reported in each domain. Higher scores indicate poorer mental health
‡ Stress was measured by the number and severity of responses to measures of 9 different domains of live (work, finances, relationships, caregiving burden, body image, sexuality, psychological support, health, and traumatic life experiences).
§ Mental health function status was measured with the Short Form-36
‖ Calculated from analysis of variance for between-group comparisons of change after 1-year followup

Abbreviations: CG = control group; DanRisk = the Danish Risk Score study; F/U = followup; IG = intervention group; Jan = January; Mar = March; MDI = Major Depression Inventory; mo = month(s); PRIME-MD = Primary Care Evaluation of Mental Disorders; RCT = randomized controlled trial; SF-36 = Short Form-36; yrs = years

Table 30. Adverse Cardiac Events and Outcomes in Included Harms Studies (KQ3)

Author, Year Quality	Cohort Year(s) of recruitment	N analyzed	Age	% Women	F/U	Outcome		IG N (%)	CG N (%)	Between group difference HR (95% CI); p-value
Chi, 2014[116] Fair	Administrative data Jan 2005–Aug 2011	3,006† IG: 2,139 CG: 867	18-64 yrs Mean (SD) = 52.76 (7.72)	40.5%	16-22 mo††	Adverse cardiac events during the entire f/u period	MI*	8 (0.49)	2 (0.37)	NR; 0.73‡
							Ischemic stroke§	4 (0.24)	0	NR; 0.58‡
							Hospital admission for unstable anginaǁ	4 (0.24)	3 (0.56)	NR; 0.42‡
Shreibati, 2014[117] Fair	Medicare Administrative data 2006-2011	8,358 CAC: 4,179 hs-CRP: 4,179	Mean (SD) = 73.2 yrs (6.05)	CAC: 59.1% hs-CRP: 60.6%	36 mo#	Outcomes for matched cohorts CAC and CRP	MI	40 (0.35)**	52 (0.46)**	0.68 (0.44-1.04)‡‡; 0.073
							Ischemic stroke	63 (0.56)**	88 (0.79)**	0.75 (0.54-1.04)‡‡; 0.092
							ACM	27 (0.24)**	31 (0.27)**	0.91 (0.48-1.70)‡‡; 0.77
	Medicare Administrative data 2006-2011	6,250 CAC: 3,125 Lipid Scrn: 3,125	Mean (SD) = 72.5 (5.85)	CAC: 59.1% Lipid Scrn: 57.9%	36 mo#	Outcomes for matched cohorts CAC and Lipid Screening	MI	36 (0.40)**	43 (0.48)**	0.81 (0.50-1.31)‡‡; 0.39
							Ischemic stroke	54 (0.61)**	66 (0.75)**	0.85 (0.58-1.23)‡‡; 0.39
							ACM	21 (0.23)**	23 (0.25)**	0.91 (0.50-1.64)‡‡; 0.76

* Acute myocardial infarction is defined as hospitalization with *ICD-9-CM* diagnosis codes 410.x0 or 410.x1 and a length of stay between 3 and 183 Days

† Patients were followed from the index date to the end of study period, end of plan enrollment, or first occurrence of any adverse cardiac event, whichever occurred first. Continuous eligibility following index date was not required for this analysis. Patients classified as high risk were excluded.

‡ Categorical variables: χ^2 or Fisher tests; mean followup time: 2-sample *t* tests; median followup time: Wilcoxon rank-sum tests

§ Ischemic stroke is defined as hospitalization with *ICD-9-CM* diagnosis code 433.x1 or 434.x1, and a length of stay between 3 and 183 days

ǁ Unstable angina pectoris was identified by *ICD-9-CM* diagnosis code 411.1x

median 3-year followup (interquartile range, 1.4-4.3 years).

** Number of events (Incidence rate per 100 person-years).

†† Median followup periods were 689 days for CAC and 501 days for Reference.

‡‡ Cox Proportional Hazards Regression; Univariate proportional hazards models account for matched data

Abbreviations: ACM = all-cause mortality; Aug = August; CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; Jan = January; MI = myocardial infarction; mo = months NR = not reported; Scrn = Screening

Table 31. Health Care Utilization Outcomes in Included Harms Studies (KQ3)

Author, Year Quality	Cohort Year(s) of recruitment	N analyzed	Age	% Women	F/U	Outcome		IG N (%)	CG N (%)	HR (95% CI); p-value
Chi, 2014[116] Fair	Administrative data Jan 2005 – Aug 2011	3,006† IG: 2,139 CG: 867	18-64 yrs Mean (SD) = 52.76 (7.72)	40.5%	6 mo**	Cardiac imaging tests	None	1496 (76.80)	585 (76.17)	NR; 0.52‡
							1 type of test	364 (18.69)	152 (19.79)	NR
							2 types of test	81 (4.16)	26 (3.39)	NR
							≥3 types of test	7 (0.36)	5 (0.65)	NR
							Stress echocardiography	257 (13.19)	112 (14.58)	NR; 0.34‡
							Myocardial nuclear imaging	187 (9.60)	64 (8.33)	NR; 0.30‡
							Cardiac magnetic resonance imaging	3 (0.15)	3 (0.39)	NR; 0.36‡
							Diagnostic cardiac cauterization	40 (2.05)	23 (2.99)	NR; 0.14‡
							Cardiac positron emission tomography	7 (0.36)	1 (0.13)	NR; 0.45‡
							Coronary CT angiography	43 (2.21)	13 (1.69	NR; 0.40‡
						Therapeutic intervention	Therapeutic intervention (CABG)	6 (0.31)	5 (0.65)	NR; 0.20‡
							Therapeutic intervention (PCI)	64 (3.29)	34 (4.43)	NR; 0.15‡
Rozanski, 2011[11] Fair	ELSNER RCT May 2001 – May 2005	1,840 IG: 1256 CG: 584	58.2 ± 8.4	47.5%	48 mo	Performed procedures	Resting ECG	767 (58.5)	380 (61.0%)	NR; 0.30
							Stress nuclear	169 (12.9)	62 (10.0%)	NR; 0.06
							Stress echocardiography	195 (14.9)	102 (16.4%)	NR; 0.39
							Any stress test*	454 (34.6)	211 (33.9%)	NR; 0.74
							Cardiac CT	101 (7.7)	44 (7.1%)	NR; 0.62
							Carotid ultrasound	167 (12.7)	88 (14.1%)	NR; 0.40
							Cardiac catheterization	43 (3.35)	18 (2.9%)	NR; 0.71
							Coronary revascularization	30 (2.3)	11 (1.8%)	NR; 0.46
Shreibati, 2014[117] Fair	Medicare Administrative data 2006-2011	8,358 CAC: 4,179 hs-CRP: 4,179	Mean (SD) = 73.2 yrs (6.05)	CAC: 59.1% hsCRP: 60.6%	6 mo**	Outcomes for matched cohorts CAC and CRP	Myocardial perfusion scintigraphy (MPS)	1014 (64.7)§	590 (33.7)§	2.15 (1.57-2.94)#; <0.001
							Exercise treadmill test (ETT)	292 (15.7)§	201 (10.6)§	2.04 (1.24-3.36)#; 0.005
							Stress transthoracic echocardiography (TTE)	160 (8.4)§	87 (4.5)§	3.00 (1.34-6.68)#; 0.007
							Coronary CT angiography (CCTA)	56 (2.9)§	40 (2.0)§	3.66 (1.02-13.14)#; 0.046

Table 31. Health Care Utilization Outcomes in Included Harms Studies (KQ3)

Author, Year Quality	Cohort Year(s) of recruitment	N analyzed	Age	% Women	F/U	Outcome		IG N (%)	CG N (%)	HR (95% CI); p-value
							Any Testǁ	1268 (86.1)§	474 (44.2)§	2.22 (1.68-2.93)#; <0.001
							Coronary angiography (Cath)	247 (13.2)§	112 (15.8)§	3.54 (1.91-6.55)#; <0.001
							Percutaneous coronary intervention (PCI)	90 (4.6)§	30 (1.5)§	8.5 (1.96-36.79)#; 0.004
							CABG	43 (2.2)§	17 (0.87)§	2.66 (0.70-10.05)#; 0.15
							PCI/CABG	128 (6.7)§	46 (2.4)§	4.80 (1.83-12.58)#; 0.001
	Medicare Administrative data 2006-2011	6,250 CAC: 3,125 Lipid Scrn: 3,125	Mean (SD) = 72.5 (5.85)	CAC: 59.1% Lipid Scrn: 57.9%	6 mo**	Outcomes for matched cohorts CAC and Lipid Screening	Myocardial perfusion scintigraphy (MPS)	711 (59.8)§	205 (14.7)§	4.81 (3.18-7.28)#; <0.001
							Exercise treadmill test (ETT)	224 (16.3)§	76 (5.3)§	2.83 (1.65-4.85)#; <0.001
							Stress transthoracic echocardiography (TTE)	120 (8.4)§	35 (2.4)§	2.60 (1.25-5.39)#; 0.010
							Coronary CT angiography (CCTA)	33 (2.3)§	3 (0.21)§	7.00 (0.86-56.89)#; 0.069
							Any Testǁ	902 (81.8)§	268 (20.8)§	4.30 (3.04-6.06)#; <0.001
							Coronary angiography (Cath)	185 (13.3)§	57 (4.0)§	4.23 (2.31-7.74)#; <0.001
							Percutaneous coronary intervention (PCI)	67 (4.6)§	20 (1.4)§	3.25 (1.06-9.96)#; 0.039
							CABG	34 (2.3)§	8 (0.55)§	4.50 (0.97-20.93)#; 0.054
							PCI/CABG	96 (6.7)§	27 (1.9)§	3.50 (1.41-8.67)#; 0.007

* Stress nuclear, stress echocardiography, or treadmill exercise electrocardiography

† Only patients who had 6-month continuous medical eligibility from index date and were classified as non-high-risk for CHD were included in analysis, regardless of whether there was an occurrence of cardiovascular event after index date

‡ P value for utilization was based on χ^2 / Fisher exact test; P value for cost was based on Wilcoxon rank-sum test

§ Number of events (Incidence rate per 1000 person-years).

ǁ indicate any noninvasive cardiac testing

Cox Proportional Hazards Regression; Univariate proportional hazards models account for matched data.

** following index date

Abbreviations: CABG = Coronary artery bypass surgery; CAC = coronary artery calcium; CI = confidence interval; CRP = c-reactive protein; CT = computed tomography; ECG = electrocardiography; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; MPS = myocardial perfusion scintigraphy

Table 32. Participant Characteristics of Included Treatment Studies (KQ4)

Trial name Author, Year	Quality	Country	N	Age, years (mean)	% Women	SBP/DBP, mm Hg (mean)*	TC, mg/dL (mean)	LDL, mg/dL	HDL, mg/dL	% with DM	% Current smokers	% with elevated NTRF	Mean NTRF	Annual risk of CVD Events (%)‡
AAA Fowkes, 2010[122]	Good	Scotland	3,350	62.0	71.5	148/84	238§	NR	NR	2.6	33.0	100 with ABI ≤0.95	ABI: 0.86	0.99
POPADAD Belch, 2008[123]	Good	Scotland	1,276	60.3	55.9	145/79	213¶	121¶	47¶	100†	31.1	100 with ABI ≤0.99	ABI: 0.90	2.53
St. Francis Heart Study Arad, 2005[121]	Fair	US	1,005	59.0	26.5	NR**	226	146	50	8.5	12.5	100 with CAC >80th percentile	CAC: 545.4	2.30
JUPITER Ridker, 2008[120]	Good	26 Countries	17,802	66.0¶	38.2	134/80¶	186¶	108¶	49¶	0	15.8	100 with CRP ≥2.0 mg/L	CRP: 4.2 mg/L¶	1.48

* In AAA, 15.2% were treated with a diuretic, 6.4% were treated with a nitrate or calcium channel blocker, 6.2% were treated with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, and 9.8% were treated with a beta blocker. Hypertension treatment was not reported in POPADAD.
† Mean HbA1c of 8.0%
‡ Data are from Berger 2011 meta-analysis[161] or similarly calculated as percent with cardiovascular events in control group/years of followup. Mean FRS not reported in any trial. Approximately half of the JUPITER population had FRS <10% (Figure 2)
§ 4.2% were on lipid-lowering treatment at baseline and 25% were treated at 5 years; use of lipid-lowering treatment was not reported in POPADAD.
¶ Median
** 40.5% with hypertension

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; CAC = coronary artery calcium score; CRP = c-reactive protein; CVD = cardiovascular disease; DBP = diastolic blood pressure; FRS – Framingham Risk Score; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein cholesterol; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein cholesterol; N = number; NR = not reported; NTRF = nontraditional risk factor; PAD = peripheral arterial disease; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; SBP = systolic blood pressure; TC = total cholesterol

Table 33. Methodological and Intervention Characteristics of Included Treatment Studies (KQ4)

Trial name Author, year	N	Study design	Inclusion	Recruitment	Pharmacotherapy dose & formulation	Duration & Mean followup	Primary endpoint	Secondary endpoints	Adherence & crossover
AAA Fowkes, 2010[122]	3,350	RCT	Men and women ages 50-75 years with no history of vascular disease and ABI ≤0.95	Community health registry and community volunteer	100 mg daily, tablet, enteric coated	8.2 years*	Composite outcome: initial fatal or nonfatal coronary event or CVA or revascularization	1) All initial vascular events, defined as a composite outcome: primary end point event or angina, intermittent claudication, or TIA; 2) all-cause mortality	Participants adhered to study medication for 60% of p-y of F/U. Effect on primary end point did not differ between those taking and not taking medication at 5 years
POPADAD Belch, 2008[123]	1,276	2x2 RCT, Antioxidant	Men and women age ≥40 years with diabetes, no symptomatic CVD, and ABI ≤0.99	Diabetes clinics	100 mg daily, tablet, not enteric coated	6.7 years†	2 composite end points: 1) death from CHD or CVA, nonfatal MI or CVA, above ankle amputation for critical limb ischemia; 2) death from CHD or CVA	All-cause mortality; nonfatal MI; and occurrence of other individual vascular events	At 1 year, 14% of participants stopped taking trial drugs; at 5 years, 50% (cumulative) of patients withdrew from trial therapy
St. Francis Heart Study Arad, 2005[121]	1,005	RCT	Men and women ages 50-70 years with no history, symptoms or signs of ASCVD and CAC score >80th percentile for age and gender	Mixed; population-based, health insurance, and community volunteer	Atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha tocopherol), 1,000 U daily, and aspirin 81 mg daily (aspirin given to both groups)	4.3 years*	Composite of all first ASCVD events: coronary death, nonfatal MI, surgical or percutaneous coronary revascularization procedures, non-hemorrhagic CVA, and peripheral vascular surgery	All coronary events; the sum of nonfatal MI and coronary deaths; and all events occurring >90 days after randomization	Consumption of ≥85% of study medication averaged 85% for atorvastatin or its matching placebo, 88% for vitamins C and E or their matching placebos and 79% for aspirin; 14% in control group began taking aspirin without a CVD event

Table 33. Methodological and Intervention Characteristics of Included Treatment Studies (KQ4)

Trial name Author, year	N	Study design	Inclusion	Recruitment	Pharmacotherapy dose & formulation	Duration & Mean followup	Primary endpoint	Secondary endpoints	Adherence & crossover
JUPITER Ridker, 2008[120]	17,802	RCT	Men ≥50 years and women ≥60 years with no history of CVD or DM and LDL-C <130 mg/dL and hs-CRP ≥2.0 mg/L	NR	Rosuvastatin 20 mg once daily	1.9 years*†	First major CVD event, defined as nonfatal MI, nonfatal CVA, hospitalization for unstable angina, arterial revascularization, or confirmed death from CVD causes	Components of the primary end point considered individually–arterial revascularization or hospitalization for unstable angina, MI, CVA, or death from CVD causes–and death from any cause	At the time the study was terminated, 75% of participants were taking their study pills

* Terminated early
† Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; ASA = aspirin; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CVA = cardiovascular accident; F/U = followup; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MI = myocardial infarction; N = number; PAD = peripheral arterial disease; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RCT = randomized controlled trial; p-y = patient years; TIA = transient ischemic attack

Table 34. Composite and Mortality Outcomes in Included Treatment Studies (KQ4)

Outcome	Trial name Author, Year	Mean F/U, years	IG N analyzed	IG N events (%)	CG N analyzed	CG N events (%)	IG vs. CG HR (95% CI)
Primary Composite CVD Outcome*	AAA Fowkes, 2010[122]	8.2	1,675	181 (10.8%)	1,675	176 (10.5%)	1.00 (0.81 to 1.23)†
	POPADAD Belch, 2008[123]	6.7‡	638	116 (18.2%)	638	117 (18.3%)	0.98 (0.76 to 1.26)
	St. Francis Heart Study Arad, 2005 [121]	4.3	490	34 (6.9%)	515	51 (9.9%)	0.70 (0.44 to 1.10) §‖, p=0.08¶#
	JUPITER Ridker, 2008 [120]	1.9‡	8,901	142 (1.6%)	8,901	251 (2.8%)	0.56 (0.46 to 0.69)
Composite Fatal Coronary Events + CVA + CVD Death	AAA Fowkes, 2010[122]	8.2	1,675	35 (2.1%)§	1,675	30 (1.8%)§	1.17 (0.72 to 1.89)§‖
	POPADAD Belch, 2008[123]	6.7‡	638	43 (6.7%)	638	35 (5.5%)	1.23 (0.79 to 1.93)
Composite Nonfatal MI + CVA	AAA Fowkes, 2010[122]	8.2	1,675	99 (5.9%)§	1,675	106 (6.3%)§	0.93 (0.72 to 1.22)§‖
	POPADAD Belch, 2008[123]	6.7‡	638	84 (13.2%)§	638	97 (15.2%)§	0.87 (0.66 to 1.14)§‖
	JUPITER Ridker, 2008 [120]	1.9‡	8,901	52 (0.6%)§	8,901	120 (1.3%)§	0.43 (0.31 to 0.60)§‖
All-Cause Mortality	AAA Fowkes, 2010[122]	8.2	1,675	176 (10.5%)	1,675	186 (11.1%)	0.95 (0.77 to 1.16)
	POPADAD Belch, 2008[123]	6.7‡	638	94 (14.7%)	638	101 (15.8%)	0.93 (0.71 to 1.24)
	JUPITER Ridker, 2008 [120]	1.9‡	8,901	198 (2.2%)	8,901	247 (2.8%)	0.80 (0.67 to 0.97)

* Defined in AAA as: initial fatal or nonfatal coronary event or CVA or revascularization; defined in POPADAD as death from CHD or CVA, nonfatal MI or CVA, above ankle amputation for critical limb ischemia; defined in St. Francis Heart Study as coronary death, nonfatal MI, surgical or percutaneous coronary revascularization procedures, non-hemorrhagic CVA, and peripheral vascular surgery; defined in JUPITER as nonfatal MI, nonfatal CVA, hospitalization for unstable angina, an arterial revascularization, or cardiovascular death.

† HR adjusted for baseline age, ankle-brachial index, cholesterol, systolic blood pressure, smoking, and socioeconomic status; unadjusted HR 1.03 (95% CI, 0.84 to 1.27)

‡ Median

§ Calculated

‖ RR

¶ Adjusted for standard risk factors: age, elevated total cholesterol, hypertension, diabetes, smoking, and family history of premature coronary artery disease (Arad, 2000)

All ASCVD events after 90 days also reported. IG: 30/486 (6.2%); CG: 47/511 (9.2%); p=0.07

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; Adj = adjusted; CG = control group; CI = confidence interval; CVA = cardiovascular accident; CVD = cardiovascular disease; HR = hazard ratio; IG = intervention group; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MI = myocardial infarction; N = population; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk

Table 35. Myocardial Infarction and CVA Outcomes in Included Treatment Studies (KQ4)

Outcome	Trial name Author, Year	Mean F/U, years	IG N analyzed	IG N events (%)	CG N analyzed	CG N events (%)	IG vs. CG HR (95% CI)
Nonfatal MI + Fatal Coronary Events	AAA Fowkes, 2010[122]	8.2	1,675	90 (5.4%)*	1,675	86 (5.1%)*	1.05 (0.77 to 1.40)*†
	POPADAD Belch, 2008[123]	6.7‡	638	90 (14.1%)*	638	82 (12.9%)*	1.10 (0.83 to 1.45)*†
	St. Francis Heart Study Arad, 2005 [121]	4.3	490	9 (1.8%)	515	17 (3.3%)	0.56 (0.22 to 1.32)*†, p=0.14
	JUPITER Ridker, 2008‖ [120]	1.9‡	8,901	31 (0.3%)	8,901	68 (0.8%)	0.46 (0.30 to 0.70)
Fatal Coronary Events	AAA Fowkes, 2010[122]	8.2	1,675	28 (1.7%)	1,675	18 (1.1%)	1.56 (0.86 to 2.80)*†
	POPADAD Belch, 2008[123]	6.7‡	638	35 (5.5%)	638	26 (4.1%)	1.35 (0.81 to 2.25)
Nonfatal MI	AAA Fowkes, 2010[122]	8.2	1,675	62 (3.7%)	1,675	68 (4.1%)	0.91 (0.65 to 1.28)*†
	POPADAD Belch, 2008[123]	6.7‡	638	55 (8.6%)	638	56 (8.8%)	0.98 (0.68 to 1.43)
	JUPITER Ridker, 2008‖ [120]	1.9‡	8,901	22 (0.2%)	8,901	62 (0.7%)	0.35 (0.22 to 0.58)
Total CVA	AAA Fowkes, 2010[122]	8.2	1,675	44 (2.6%)*	1,675	50 (3.0%)*	0.88 (0.59 to 1.31)*†
	POPADAD Belch, 2008[123]	6.7‡	638	37 (5.8%)*	638	50 (7.8%)*	0.74 (0.49 to 1.12)*†
	JUPITER Ridker, 2008 [120]	1.9‡	8,901	33 (0.4%)	8,901	64 (0.7%)	0.52 (0.34 to 0.79)
Fatal CVA	AAA Fowkes, 2010[122]	8.2	1,675	7 (0.4%)	1,675	12 (0.7%)	0.58 (0.23 to 1.48)*†
	POPADAD Belch, 2008[123]	6.7‡	638	8 (1.3%)	638	9 (1.4%)	0.89 (0.34 to 2.30)
	JUPITER Ridker, 2008 [120]	1.9‡	8,901	3 (0.03%)*	8,901	6 (0.07%)*	0.5 (0.08 to 2.34)*†
Nonfatal CVA	AAA Fowkes, 2010[122]	8.2	1,675	37 (2.2%)	1,675	38 (2.3%)	0.97 (0.62 to 1.52)*†
	POPADAD Belch, 2008[123]	6.7‡	638	29 (4.6%)	638	41 (6.4%)	0.71 (0.44 to 1.14)
	JUPITER Ridker, 2008 [120]	1.9‡	8,901	30 (0.3%)	8,901	58 (0.6%)	0.52 (0.33 to 0.80)
Total ischemic CVA	AAA Fowkes, 2010[122]	8.2	1,675	30 (1.8%)*	1,675	37 (2.2%)*	0.81 (0.50 to 1.31)*†

Table 35. Myocardial Infarction and CVA Outcomes in Included Treatment Studies (KQ4)

Outcome	Trial name Author, Year	Mean F/U, years	IG N analyzed	IG N events (%)	CG N analyzed	CG N events (%)	IG vs. CG HR (95% CI)
Fatal ischemic CVA	AAA Fowkes, 2010[122]	8.2	1,675	2 (0.1%)	1,675	7 (0.4%)	0.29 (0.06 to 1.37)*†
	POPADAD Belch, 2008[123]	6.7‡	638	3 (0.5%)	638	5 (0.8%)	0.60 (0.14 to 2.50)*†
Nonfatal ischemic CVA	AAA Fowkes, 2010[122]	8.2	1,675	28 (1.7%)	1,675	30 (1.8%)	0.93 (0.56 to 1.56)*†

*Calculated
†RR
‡Median
‖Reported as any MI

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; ASCVD = atherosclerotic cardiovascular disease; CG = control group; CI = confidence interval; CVA= cardiovascular accident; HR = hazard ratio; IG = intervention group; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; N = population; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk

Table 36. Age Subgroup Analyses for Primary Outcomes in Included Treatment Studies (KQ4)

Trial name Author, Year	Mean F/U, years	Type of analysis	Outcome	Age, years	IG N analyzed	IG N events (%)	CG N analyzed	CG N events (%)	IG vs. CG HR (95% CI)	P-Value for interaction
AAA Fowkes, 2010[122]	8.2	A priori	Primary composite: Initial fatal or nonfatal coronary event, CVA or revascularization	<62	NR	57 (NR)*	NR	70 (NR)†	0.85 (0.60 to 1.20)	NR
				≥62	NR	124 (NR)‡	NR	106 (NR)§	1.13 (0.87 to 1.47)	
POPADAD Belch, 2008[123]	6.7‖	Specification unclear	Primary composite: death from CHD or CVA, nonfatal MI or CVA, or above ankle amputation for critical limb ischemia	<60	297	38 (12.8%)	315	36 (11.4%)	1.11 (0.70 to 1.75)	0.77
				≥60	341	78 (22.9%)	323	81 (25.1%)	0.89 (0.65 to 1.21)	
JUPITER Ridker, 2008[120]	1.9‖	A priori	Primary end point: MI, CVA, hospitalization for unstable angina, arterial revascularization, or CVD death	≤65	NR	NR	NR	NR	NR	0.32
				>65	NR	NR	NR`	NR	NR	

*8.6 per 1,000 p-y (95% CI, 6.5 to 11.2)
†10.2 per 1,000 p-y (95% CI, 8.0 to 12.9)
‡18.8 per 1,000 p-y (95% CI, 15.6 to 22.4)
§16.6 per 1,000 p-y (95% CI, 13.6 to 20.1)
‖Median.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CHD = coronary heart disease; CVA = cardiovascular accident; HR = hazard ratio; IG = intervention group; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MI = myocardial infarction; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y: person-years

Table 37. Sex Subgroup Analyses for Primary Outcomes in Included Treatment Studies (KQ4)

Trial name Author, year	Mean F/U, years	Type of analysis	Outcome	Sex	IG N analyzed	IG N events (%)	CG N analyzed	CG N events (%)	IG vs. CG HR (95% CI)	P-Value for interaction
AAA Fowkes, 2010[122]	8.2	A priori	Primary composite: initial (earliest) fatal or nonfatal coronary event or CVA or revascularization	Men	481	96 (20.0%)	473	83 (17.5%)	1.15 (0.86 to 1.54)*†	NR
				Women	1,194	85 (7.1%)	1,202	93 (7.7%)	0.92 (0.68 to 1.23)*†	NR
				Women	352	17 (4.8%)	361	16 (4.4%)	1.09 (0.55 to 2.16)	
POPADAD Belch, 2008[123]	6.7‡	Specification unclear	Primary composite: death from CHD or CVA, nonfatal MI or CVA, or above ankle amputation for critical limb ischemia	Men	286	68 (23.8%)	277	62 (22.4%)	1.04 (0.74 to 1.47)	0.54
				Women	352	48 (13.6%)	361	55 (15.2%)	0.89 (0.60 to 1.31)	
JUPITER Ridker, 2008[120, 124]	1.9‡	A priori	Primary end point: MI, CVA, hospitalization for unstable angina, arterial revascularization, or CVD death	Men	5,475	103 (1.9%)	5,526	181 (3.3%)	0.58 (0.45 to 0.73)	0.80
				Women	3,426	39 (1.1%)	3,375	70 (2.1%)	0.54 (0.37 to 0.80)	

* Calculated
† RR
‡ Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CHD = coronary heart disease; CVA = cardiovascular accident; HR = hazard ratio; IG = intervention group; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MI = myocardial infarction; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y: person-years; RR = relative risk

Table 38. Outcomes in Included Harms Studies (KQ5)

Trial name Author, Year	Mean F/U, years	Outcome	IG N analyzed	IG N events (%)	CG N analyzed	CG N events (%)	IG vs. CG HR (95% CI)
AAA Fowkes, 2010[122]	8.2	Major Hemorrhage*	1,675	34 (2.0%)	1,675	20 (1.2%)	1.71 (0.99 to 2.97)
		Major GI Bleeding†	1,675	9 (0.5%)‡	1,675	8 (0.5%)‡	1.13 (0.44 to 2.91)‡§
		Total Hemorrhagic CVA	1,675	5 (0.3%)‡	1,675	4 (0.2%)‡	1.25 (0.34 to 4.65)‡§
		Fatal Hemorrhagic CVA	1,675	3 (0.2%)	1,675	3 (0.2%)	1.00 (0.20 to 4.95)‡§
		Nonfatal Hemorrhagic CVA	1,675	2 (0.1%)	1,675	1 (0.1%)	2.00 (0.18 to 22.04)‡§
		Intracranial Bleeding‖	1,675	6 (0.4%)‡§	1,675	3 (0.2%)‡§	2.00 (0.50 to 7.98)‡§
POPADAD Belch, 2008[123]	6.7¶	Fatal Hemorrhagic CVA	638	2 (0.3%)	638	3 (0.5%)	0.67 (0.11 to 3.98)‡§
JUPITER Ridker, 2008 [120]	1.9¶	Total Hemorrhagic CVA	8,901	6 (0.1%)	8,901	9 (0.1%)	0.67 (0.20 to 2.10)‡§; p=0.44
		Serious adverse event	8,901	1,352 (15.2%)	8,901	1,377 (15.5%)	0.98 (0.91 to 1.06)‡§
		Newly diagnosed diabetes (physician-reported)	8,901	270 (3.0%)	8,901	216 (2.4%)	1.25 (1.04 to 1.50)‡§

* Defined as nonfatal or fatal hemorrhagic CVA, fatal or nonfatal subarachnoid/subdural hemorrhage, GI bleed requiring admission, and other bleeding requiring hospital admission

† Defined as requiring admission to hospital to control bleeding; admission only to investigate bleeding not included

‡ Calculated.

§ RR

‖ Defined as fatal or nonfatal subarachnoid/subdural hemorrhage

¶ Median

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CVA = cardiovascular accident; GI = gastrointestinal; IG = intervention group; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; n = population; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk; HR = Hazard Ratio

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
KQ1: Direct evidence for screening	CVD events or mortality	k=1, n=2,137 1 RCT	No statistically significant difference in MI and/or mortality at 4 years between those who received CAC vs. those who did not receive CAC.	Not applicable Not applicable	Not applicable	Insufficient	1 Fair	Single trial; insufficient sample size and length of follow up to detect differences in patient health outcomes	U.S.-based trial, volunteer sample
KQ2: ABI Risk prediction	Calibration	k=5 n=26,286 1 IPD MA 4 cohorts	Based on one IPD MA, various measures demonstrate that the addition of ABI to FRS can improve model fit. However, it is unclear the clinical meaning of changes in these measures of calibration.	Reasonably consistent Unable to assess precision	Undetected	Low	1 Good 4 Fair	No preferred measures of calibration	No evidence for PCE, IPD MA in Whites only
	Discrimination	k=10 n=79,583 1 IPD MA 8 cohorts†	Based on one IPD MA, ABI can result in large improvement in discrimination when added to FRS in women, but not men, primarily due to poorer discrimination of the base model (using published coefficients) in women, but not men. The incremental benefit in IPD MA model development analyses was very small for both men and women, owing to improved base model discrimination.	Reasonably consistent Reasonably precise	Undetected	Moderate	1 Good 9 Fair	Adequate power for sex-stratified analyses limited to IPD MA; differences in study population, base models, and outcomes predicted limit direct comparison across studies	Limited evidence for PCE, IPD MA in Whites only
	Risk reclassification	k=9 n=46,979 1 IPD MA 7 cohorts†	Based on one IPD MA, ABI can result in improvement in reclassification when added to FRS (using published coefficients) in women, but not men;	Reasonably consistent Reasonably precise	Undetected	Moderate	1 Good 8 Fair	Adequate power for sex-stratified analyses limited to IPD MA; differences in study population, base models, and outcomes predicted	Limited evidence for PCE, IPD MA in Whites only, risk categories on which NRI analyses are

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
			most promising for women at intermediate risk for hard CHD events. However, examination of separate components of the NRI (event and nonevent NRI) suggests that improvement in reclassification comes from women who had events being appropriately reclassified as having a higher risk; in contrast, women who did not have a cardiovascular event (which is the majority of the population) were inappropriately reclassified as having a higher risk (i.e., a negative nonevent NRI). Improvement in NRI was not observed in the model development IPD MA.					limit direct comparison across studies. The NRI is not weighted for prevalence of events/nonevents, so the reclassification benefit may be overstated.	based can vary across studies and may not apply to current practice
KQ2: hsCRP Risk prediction	Calibration	k=9 n=50,343 8 cohorts‡ 1 nested case-control	Various measures demonstrate that the addition of hsCRP to traditional risk factors can improve model fit. However, it is unclear the clinical meaning of changes in these measures. In model development studies, calibration plots suggest that the addition of hsCRP can improve model fit in some but not all risk groups.	Reasonably consistent Unable to assess precision	Undetected	Low	2 Good, 7 Fair	No preferred measures for most studies (and none for published coefficient models); no calibration statistics for the IPD MA.	Limited evidence for PCE. Model development IPD MA only (calibration in model development less applicable to clinical practice)

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
	Discrimination	k=25 n=265,704 1 IPD MA 18 cohorts‡ 3 nested case-control studies 1 case-cohort study	At best, improvement in discrimination from the addition of hsCRP to traditional cardiovascular risk assessment is small and more likely to occur in the context of a poorly discriminating base model. IPD MA model development study found very small improvement in discrimination from the addition of hsCRP to FRS to predict hard CHD.	Inconsistent Reasonably precise for IPD MA	Undetected	Moderate	2 Good, 23 Fair	Limited reporting of confidence intervals and statistical significance; differences in study population, base models, and outcomes predicted limit direct comparison across studies	Limited evidence for PCE. Model development IPD MA only (changes in discrimination in model development may be less applicable to clinical practice)
	Risk reclassification	k=15 n=115,686 1 IPD MA 13 cohorts‡ 1 nested case-control study	NRI from the addition of hsCRP to FRS are inconsistent; 1 published coefficient PCE-based study suggested no improvement in reclassification. Best evidence from IPD MA showed statistically significant NRI of 0.0152 (95% CI, 0.0078 to 0.0227). Sex-stratified analyses suggest that reclassification occurs in men but not women. The bias-corrected NRI_{INT} from the IPD MA was 0.027 (95% CI, 0.007 to 0.047).	Inconsistent Reasonably precise for IPD MA	Undetected	Moderate	2 Good, 13 Fair	Comparisons across studies are limited by inconsistency in risk category definitions; sex-specific analyses reported rarely and more are needed to confirm the signal of effect modification by sex. Limited information on NRI_{INT}, as analyses often underpowered and often cannot be bias-corrected.	Limited evidence for PCE. Risk categories on which NRI analyses are based can vary across studies and may not apply to current practice. Estimates of reclassification in model development may be less applicable to clinical practice.
KQ2: CAC Risk prediction	Calibration	k=8 n=29,775 4 cohorts§	Limited model development studies using various measures demonstrate that the addition of CAC to traditional risk factors can improve model fit.	Inconsistent Unable to assess precision	Undetected	Insufficient	8 Fair	No preferred measures of calibration	No evidence for published coefficient models, calibration in model development

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
			However, it is unclear the clinical meaning of changes in these measures.						less applicable to clinical practice, limited evidence in context of PCE
	Discrimination	k=18 n=60,486 10 cohorts‖	CAC in addition to traditional risk factor assessment results in at least small improvements in discrimination, from changes of 0.02 to 0.102 in studies using published coefficients to 0.02 to 0.05 in model development studies. Discrimination is not consistently greater in men or women.	Reasonably consistent Reasonably precise	Undetected	Moderate	18 Fair	Smaller cohorts compared to ABI and hsCRP body of evidence. No IPD MA limits understanding in differences by sex. Differences in study population, base models, and outcomes predicted limit direct comparison across studies	Limited evidence in context of PCE. Non-population based cohorts may not be broadly applicable.
	Risk reclassification	k=15 n=58,289 9 cohorts¶	CAC resulted in NRIs of 0.084 to 0.35 when added to traditional risk factor assessment. Evaluation of separate components of the NRI shows that improvements in NRI are consistently driven by event NRIs much larger than nonevent NRIs, which were commonly negative (when reported), and sometimes statistically significant. Reclassification is not consistently greater in men or women.	Reasonably consistent Reasonably precise	Undetected	Moderate	15 Fair	Smaller cohorts compared to ABI and hsCRP body of evidence. No IPD MA limits understanding in differences by sex. Limited information on NRI_{INT}, as analyses often underpowered and often cannot be bias-corrected. Differences in study population, base models, and outcomes predicted limit direct comparison across studies. The NRI is not weighted for	Non-population based cohorts may not be broadly applicable. Risk categories on which NRI analyses are based can vary across studies and may not apply to current practice.

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
								prevalence of events/nonevents, so the reclassification benefit may be overstated.	
KQ3: Harms of screening	Radiation dose	k=4 n=11,473 3 cohorts 1 RCT	Effective dose of radiation per CT exam for screening CAC was low, ≤2.1 mSv.	Reasonably consistent Reasonably precise	Suspected	Moderate #	4 Fair	Only a limited subset of CAC studies included for KQ2 reported radiation dose. Dose not reported separately by EBCT vs MDCT	CT protocols evolve over time, most often reducing radiation exposure.
	Psychological outcomes	k=2 n=1,619 1 cohort 1 RCT	Screening CAC is not associated with subsequent depression, anxiety, or decline in overall mental health functioning up to 1 year.	Reasonably consistent Reasonably precise	Undetected	Moderate	2 Fair	No studies for ABI or hsCRP. Only one study with a comparator arm.	Baseline depression and anxiety scores were low in these studies. One study in a Danish cohort, the other in active military duty.
	CVD events	k=2 n=11,364 2 cohorts	No paradoxical increase in CVD events (MI, CVA, unstable angina) or all-cause mortality with screening CAC at approximately 1.5 to 3 years of follow up.	Reasonably consistent Reasonably precise	Undetected	Moderate	2 Fair	No studies for ABI or hsCRP. Retrospective analyses of administrative data. Limited length of follow up.	Large nationally representative samples.
	Health care utilization	k=3 n=13,204 2 cohorts 1 RCT	Best-quality evidence from 1 RCT found no statistically significant increase in cardiac imaging or revascularization for screening CAC at 4 years of follow up. Two retrospective cohort studies using differently	Inconsistent Imprecise	Undetected	Low	3 Fair	No studies for ABI or hsCRP. No studies of downstream utilization due to incidental findings on CT for CAC. 2 retrospective analyses of administrative data.	RCT may be less applicable to clinical practice.

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
			assembled control groups had mixed findings. One study using Medicare claims data found a higher number of cardiac imaging and revascularization procedures associated with CAC as opposed to CRP or lipid screening.						
KQ4: ABI-guided treatment benefit	CVD events	k=2 n=4,626 RCT	AAA and POPADAD found no benefit for ABI-guided low-dose aspirin (100 mg daily) in asymptomatic persons on composite CVD outcomes (MI, CVA, revascularization or amputation) at approximately 7 to 8 years of follow up.	Reasonably consistent Reasonably precise	Undetected	Moderate	2 Good	No ABI-guided statin trials	Nontraditional threshold for ABI used in both trials.
KQ4: hsCRP-guided treatment benefit	CVD events	k=1 n=17,802 RCT	JUPITER found a benefit for hsCRP-guided high-intensity statin (rosuvastatin 20mg daily) in asymptomatic persons on CVD outcomes. At 1.9 years follow up, 1.6% had a CVD event (MI, CVA, hospitalization for unstable angina, revascularization, or CVD mortality) in the statin group compared to 2.8% in the placebo group, HR 0.56 (95% CI, 0.46 to 0.69).	Not applicable Reasonably precise	Undetected	Moderate	1 Good	No hsCRP-guided aspirin treatment trials. Trial stopped early which may overestimate findings of benefit.	Threshold for hsCRP was 2.0 mg/L. Diverse population.

Table 39. Summary of Evidence

KQ	Outcome	No. of studies (k), no. of participants (n)* Study designs	Summary of findings by outcome	Consistency/ precision	Reporting bias	EPC SOE	Study quality	Body of evidence limitations	Applicability
KQ4: CAC-guided treatment benefit	CVD events	k=1 n=1,005 RCT	St. Francis Heart Study found no benefit for CAC-guided moderate-intensity statin (atorvastatin 20mg daily) in asymptomatic persons on composite CVD outcomes at approximately 4 years of follow up.	Not applicable Imprecise	Undetected	Low	1 Fair	No CAC-guided aspirin treatment trials. Trial not powered to detect a difference in outcomes.	All participants were taking aspirin. Threshold for CAC was based on age/sex. Mean hsCRP was lower in this trial compared to JUPITER.
KQ5: ABI-guided aspirin treatment harms	Major bleeding	k=2 n=4,626 RCT	AAA and POPADAD found no statistically significant difference in bleeding events between low-dose aspirin (100mg daily) and placebo. However, AAA found a trend for increased bleeding events in the aspirin group (2.0%) versus placebo (1.2%), HR 1.71 (95% CI 0.99, 2.97) at 8.2 years of follow up.	Reasonably consistent Imprecise	Undetected	Low	2 Good	Limited follow up. Likely not powered to detect a difference in bleeding events. POPADAD only reported on hemorrhagic CVA, and the event rate was very low.	These two trials should be interpreted in the context of the larger body of evidence on major bleeding from low-dose aspirin.
KQ5: hsCRP-guided statin treatment harms	Serious adverse events	k=1 n=17,802 1 RCT	JUPITER found a statistically significant increase in incident diabetes but not in other serious adverse events. There were 3.0% cases of diabetes in the rosuvastatin group compared to 2.4% cases in the placebo group, RR 1.25 (95% CI 1.04, 1.50) at 1.9 years of follow up.	Reasonably consistent Reasonably precise	Undetected	Moderate	1 Good	Limited follow up.	This trial should be interpreted in the context of the larger body of evidence on adverse events from high-intensity statins.

* Ns approximated by using the largest N analyzed in each cohort

† Two studies using the MESA cohort[75, 90]

‡ One study reported 2 cohorts separately[78]

Table 39. Summary of Evidence

§ Three studies using the Rotterdam cohort[76, 82, 89]; 2 studies using MESA[77, 112]; 2 studies using Heinz Nixdorf Recall cohort[74, 103]
‖ Four studies using the Rotterdam cohort[76, 82, 89, 111]; 7 studies using MESA[75, 77 607, 90, 94, 101, 111, 112]; 5 studies using the Heinz Nixdorf Recall cohort[74, 94, 103, 111, 114]
¶ Four studies using the Rotterdam cohort[76, 82, 89, 111]; 6 studies using MESA[75, 77, 90, 111-113]; 4 studies using the Heinz Nixdorf Recall cohort[74, 103, 111, 114]
# Footnote, likely high in the context of external literature summarized in the discussion

Abbreviations: AAA = the Aspirin for Asymptomatic Atherosclerosis trial; ABI = ankle-brachial index; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CT = computed tomography; CVA = cerebrovascular accident; CVD = cardiovascular disease; EBCT = electron-beam computed tomography; EPC SOE = Evidence-based Practice Center assessment of strength of evidence; ERFC = Emerging Risk Factors Collaboration; FRS = Framingham Risk Score; F/U = follow up; HR = hazard ratio; hsCRP = high sensitivity C-reactive protein; IPD MA = individual participant data meta-analyses; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KQ = key question; L = liter; MDCT = multidetector computed tomography; MESA = Multi-Ethnic Study of Atherosclerosis; mg = milligram; MI = myocardial infarction; mSv = millisievert; no = number; NR = not reported; NRI = net reclassification improvement; PCE = Pooled Cohort Equations; POPADAD = the Prevention of Progression of Arterial Disease and Diabetes trial; RCT = randomized controlled trial; RR = relative risk

Table 40. Snapshot to Assess Net Benefit

		ABI	hsCRP	CAC	Considerations
Benefits	KQ1: Direct evidence for nontraditional risk factor assessment	No evidence	No evidence	k=1; n=2,137 **No statistically significant difference** in MI and/or mortality at 4 years	Ongoing screening trials in progress; may not directly address incremental benefit over traditional risk factor assessment
	KQ2: Calibration	k=5; n=26,286 **Improved** calibration	k=9; n=50,343 **Improved** calibration	k=8; n=29,775 **Improved** calibration	Preferred measures rarely reported; clinical meaning of changes in calibration unclear
	KQ2: Discrimination*	k=10; n=79,583 **Generally no to small improvement, but large improvement** in women in IPD MA	k=25; n=265,704 Inconsistent, at most **very small to small** improvement	k=18; n=60,486 **At least small, sometimes large** improvement	Improvement likely influenced by discrimination of base model
	KQ2: Reclassification	k=9; n=46,979 **NRIs are at best <0.1 and are usually much smaller and often nonsignificant**; women without events inappropriately reclassified	k=15; n=115,686 **Inconsistent** improvement when added to FRS and best evidence shows NRI <0.02; **no improvement** when added to PCE	k=15; n=58,289 **NRIs of 0.084 to 0.35;** people without events inappropriately reclassified	NRI may overstate benefit; applicability of risk thresholds
	KQ4: Treatment guided by NTRF in addition to FRS/PCE	No evidence	No evidence	No evidence	Unlikely such a trial will occur due to required sample
	KQ4: Treatment guided by NTRF vs usual care	Aspirin: k=2; n=4,626 **No benefit** in CVD outcomes at 7-8 years	Statin: k=1; n=17,802 **Benefit** for high-intensity statin at 1.9 years of follow up	Statin: k=1; n=1,005 **No benefit** for moderate-intensity statin at 4 years of follow up	Results and conclusions not comparable across nontraditional risk factors
Harms	KQ3: Screening	No evidence	No evidence	Radiation**:** k=4; n=11,473 **Low effective dose**, ≤2.1 mSv Psychological outcomes: k=2; n=1,619 **No association with depression, anxiety, or decline in mental health** at 6 to 12 mo CVD outcomes: k=2; n=11,364 **No paradoxical increase in CVD events** approximately up to 2 to 3 y Health care utilization: k=3; n=13,204 **Mixed results for downstream cardiac testing/procedures**	Incidental findings not uncommon; unclear whether identification of incidental findings and/or increased health care utilization is a net benefit or net harm
	KQ5: Treatment guided by NTRF	Aspirin: k=2; n=4,626 **Mixed results** for increase in bleeding events	Statin: k=1; n=17,802 **Increase** in incident diabetes but not in other serious adverse events	No evidence	Larger body of evidence not included in this review informs harms of aspirin and statins; inappropriate reclassification addressed in KQ2.

Table 40. Snapshot to Assess Net Benefit

* For changes in the c-statistic, the term "large" is used to denote changes of 0.1 or greater, "moderate" for changes of 0.05-0.1, "small" for 0.025-0.05, and "very small" for changes less than 0.025.

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; FRS = Framingham Risk Score; hsCRP = high sensitivity C-reactive protein; KQ = key question; mo = month; NRI = net reclassification improvement; NTRF = non-traditional risk factor; PCE = Pooled Cohort Equations

Table 41. Selected Examples of Appropriate and Inappropriate Reclassification Using Current Treatment Thresholds (≥7.5% for the PCE and ≥10% for the FRS)

			People having CVD or CHD event				People not having CVD or CHD event			
			Absolute number of people reclassified		Per 100* people reclassified		Absolute number of people reclassified		Per 100* people reclassified	
Base model and predicted outcome	Threshold for treatment	NTRF	Appropriate ↑ Reclass.	Inappropriate ↓ Reclass.	Appropriate ↑ Reclass.	Inappropriate ↓ Reclass.	Appropriate ↓ Reclass.	Inappropriate ↑ Reclass.	Appropriate ↓ Reclass.	Inappropriate ↑ Reclass.
PCE† (Hard CVD)	≥7.5%	ABI	17	13	5	4	113	92	2	2
		hsCRP	18	9	6	3	98	120	2	2
		CAC	76	19	24	6	202	496	4	10
FRS† (Hard CHD)	≥10%	ABI	7	4	4	2	50	57	1	1
		ABI (Men)‡	14	17	3	4	260	174	6	4
		ABI (Women)‡	46	5	15	2	136	426	2	7
		hsCRP	1	1	1	1	16	28	0	1
		hsCRP§	162	131	2	2	993	922	2	1
		CAC	26	5	13	3	71	233	1	5

* Rounded to whole numbers

† MESA cohort from Yeboah, 2016[90] (N in reclassification analyses: 5,185)

‡ IPD MA study for ABI reported in ABI Collaboration, 2014[66] (N in reclassification analyses, Women: 6,459; Men: 4,962)

§ IPD MA study for CRP reported in Emerging Risk Factors Collaboration, 2012[65] (N in reclassification analyses: 72,574)

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; FRS = Framingham Risk Score; hsCRP = high-sensitivity c-reactive protein; IPD MA = individual participant data meta-analyses; NTRF = non-traditional risk factor; PCE = Pooled Cohort Equations; Reclass = reclassification

Appendix A Table 1. USPSTF Recommendations With Reference to CVD Risk Assessment

Type	Topic, Year [Grade] Recommendation*	Clinical Considerations Around CVD Risk Assessment
Screening	**Abnormal Glucose and Type 2 Diabetes Mellitus in Adults, 2015** [B] The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity.	The target population includes persons who are most likely to have glucose abnormalities that are associated with increased CVD risk and can be expected to benefit from primary prevention of CVD through risk factor modification.
	High Blood Pressure in Adults, 2015 [A] The USPSTF recommends screening for high blood pressure in adults aged 18 years or older. The USPSTF recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment.	Recommendation applies to adults without known hypertension. Blood pressure screening interval shorter for those with risk factors for hypertension: age ≥40 years, high-normal blood pressure, overweight or obese, and African American.
	Abdominal Aortic Aneurysm, 2014 [B] Men Ages 65 to 75 Years who Have Ever Smoked: The USPSTF recommends one-time screening for abdominal aortic aneurysm (AAA) with ultrasonography in men ages 65 to 75 years who have ever smoked. [C] Men Ages 65 to 75 Years who Have Never Smoked: The USPSTF recommends that clinicians selectively offer screening for AAA in men ages 65 to 75 years who have never smoked rather than routinely screening all men in this group. [I] Women Ages 65 to 75 Years who Have Ever Smoked: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for AAA in women ages 65 to 75 years who have ever smoked. [D] Women Who Have Never Smoked: The USPSTF recommends against routine screening for AAA in women who have never smoked.	Recommendation applies to older adults stratified by sex and smoking history. In nonsmokers, clinicians should consider a patient's risk factors and the potential for harm before screening. Risk factors for increased risk of AAA include: older age, first-degree relative with an AAA, history of other vascular aneurysms, known CVD, hyperlipidemia, obesity, and hypertension.
	Carotid Artery Stenosis, 2014 [D] The USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population.	Recommendation did not review new evidence for assessment of CIMT as a nontraditional risk factor in CVD risk assessment.
	PAD and CVD in Adults: Risk Assessment with ABI, 2013† [I] The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for peripheral artery disease (PAD) and cardiovascular disease (CVD) risk assessment with the ankle–brachial index (ABI) in adults.	Recommendation included ABI to screen for PAD as well as measurement of ABI as a nontraditional risk factor in CVD risk assessment.

Appendix A Table 1. USPSTF Recommendations With Reference to CVD Risk Assessment

Type	Topic, Year [Grade] Recommendation*	Clinical Considerations Around CVD Risk Assessment
	Coronary Heart Disease: Screening with ECG, 2012† [D] Adults at Low Risk: The USPSTF recommends against screening with resting or exercise electrocardiography (ECG) for the prediction of coronary heart disease (CHD) events in asymptomatic adults at low risk for CHD events. [I] Adults at Intermediate or High Risk: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening with resting or exercise ECG for the prediction of CHD events in asymptomatic adults at intermediate or high risk for CHD events.	Recommendation applies to all adults without known CVD, stratified by risk. Framingham ATP-III model referenced in clinical considerations. High risk defined as 10-year risk >20%, 10-20% as intermediate risk and <10% as low-risk.
Counseling	**Healthful Diet and Physical Activity for CVD Prevention in Adults with Cardiovascular Risk Factors, 2014** [B] The USPSTF recommends offering or referring adults who are overweight or obese and have additional cardiovascular disease (CVD) risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention.	Recommendation applies to adults who are overweight or obese and have existing CVD risk factors (hypertension, hyperlipidemia, impaired fasting glucose, or metabolic syndrome), or are considered to be at high risk based on CVD risk assessment.
	Healthful Diet and Physical Activity for CVD Prevention in Adults, 2017 [C] The USPSTF recommends that primary care professionals individualize the decision to offer or refer adults without obesity who do not have hypertension, dyslipidemia, abnormal blood glucose, or diabetes to behavioral counseling to promote a healthful diet and physical activity. Existing evidence indicates a positive but small benefit of behavioral counseling for the prevention of cardiovascular disease (CVD) in this population. Individuals who are interested and ready to make behavioral changes may be most likely to benefit from behavioral counseling.	Recommendation applies to adults ages 18 years or older who are normal weight or overweight, with a BMI between 18.5 and 30 kg/m^2. It does not apply to persons who have known CVD risk factors (hypertension, dyslipidemia, abnormal blood glucose, or diabetes) or persons who have obesity or are underweight.

Appendix A Table 1. USPSTF Recommendations With Reference to CVD Risk Assessment

Type	Topic, Year [Grade] Recommendation*	Clinical Considerations Around CVD Risk Assessment
Preventive Medication	**Statin Use for the Primary Prevention of Cardiovascular Disease in Adults, 2016** [B] The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (i.e., symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40 to 75 years. [C] Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10-year CVD event risk of less than 10%, the likelihood of benefit is smaller because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%. [I] The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years and older without a history of heart attack or stroke.	To determine whether a patient is a candidate for statin therapy, clinicians must first determine the patient's risk of having a future CVD event. However, clinicians' ability to accurately identify a patient's true risk is imperfect, because the best currently available risk estimation tool, which uses the Pooled Cohort Equations from the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the assessment of cardiovascular risk, has been shown to overestimate actual risk in multiple external validation cohorts. The reasons for this possible overestimation are still unclear. The Pooled Cohort Equations were derived from prospective cohorts of volunteers from studies conducted in the 1990s and may not be generalizable to a more contemporary and diverse patient population seen in current clinical practice. Furthermore, no statin clinical trials enrolled patients based on a specific risk threshold calculated using a CVD risk prediction tool; rather, patients had 1 or more CVD risk factors other than age and sex as a requirement for trial enrollment. Because the Pooled Cohort Equations lack precision, the risk estimation tool should be used as a starting point to discuss with patients their desire for lifelong statin therapy. The likelihood that a patient will benefit from statin use depends on his or her absolute baseline risk of having a future CVD event, a risk estimation that is imprecise based on the currently available risk estimation tool. Thus, clinicians should discuss with patients the potential risk of having a CVD event and the expected benefits and harms of statin use. Patients who place a higher value on the potential benefits than on the potential harms and inconvenience of taking a daily medication may choose to initiate statin use for reduction of CVD risk. The USPSTF has made several other recommendations relevant to the prevention of CVD in adults (see the "Other Approaches to Prevention" section).

Appendix A Table 1. USPSTF Recommendations With Reference to CVD Risk Assessment

Type	Topic, Year [Grade] Recommendation*	Clinical Considerations Around CVD Risk Assessment
	Aspirin for the Prevention of CVD and Colorectal Cancer, 2016 [B] The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. [C] The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. [I] The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. [I] The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	The primary risk factors for CVD include older age, male sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking. The USPSTF used a calculator derived from the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations to predict 10-year risk for first hard atherosclerotic CVD event (defined as nonfatal myocardial infarction [MI], coronary heart disease [CHD] death, and fatal or nonfatal stroke). Although concerns have been raised about the equations' potential to overpredict risk and their moderate discrimination, they are the only U.S.-based, externally validated equations that report risk as a combination of cerebrovascular and CHD events.

* The following CVD-related recommendations do not explicitly involve CVD risk assessment: Vitamin Supplementation to Prevent Cancer and CVD (2014); Obesity in Adults: Screening and Management (2012)†; Tobacco Use in Adults and Pregnant Women: Counseling and Interventions (2015)
† Update in progress

Abbreviations: AAA = abdominal aortic aneurysm; ABI = ankle-brachial index; ACC = American College of Cardiology; AHA = American Heart Association; ATP III = Adult Treatment Panel III; BMI = body mass index; CAC = coronary artery calcium; CHD = coronary heart disease; CRC = colorectal cancer; CVD = cardiovascular disease; DM = diabetes mellitus; kg/m = kilogram per meter; PAD = peripheral artery disease; USPSTF = United States Preventive Services Task Force

Literature Search Strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid MEDLINE(R) Daily Update <May 19, 2017>

Search Strategy:

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1 exp Cardiovascular Diseases/ ()
2 (heart or coronar* or cardiac* or cardio* or myocardi* or vascular* or CVD or cerebrovascular or stroke or cerebral or atheroscler*).ti. ()
3 (heart or coronar* or cardiac* or cardio* or myocardi* or vascular* or CVD or cerebrovascular or stroke or cerebral or atheroscler*).ti,ab. ()
4 limit 3 to ("in data review" or in process or "pubmed not medline") ()
5 1 or 2 or 4 ()
6 Ankle Brachial Index/ ()
7 Blood Pressure/ ()
8 Ankle/ ()
9 7 and 8 ()
10 Ankle/bs [Blood Supply] ()
11 Brachial Artery/ph, pp, us [Physiology, Physiopathology, Ultrasonography] ()
12 (brachial adj1 ankle adj4 (ratio* or index* or indices or gradient* or pressur*)).ti,ab. ()
13 (arm adj1 ankle adj4 (ratio* or index* or indices or gradient* or pressur*)).ti,ab. ()
14 ankle index*.ti,ab. ()
15 6 or 9 or 10 or 11 or 12 or 13 or 14 ()
16 C-Reactive Protein/ ()
17 (c-reactive protein or crp or hscrp).ti. ()
18 (c-reactive protein or crp or hscrp).ti,ab. ()
19 limit 18 to ("in data review" or in process or "pubmed not medline") ()
20 exp Biomarkers/ ()
21 exp Inflammation/ ()
22 18 and 20 and 21 ()
23 16 or 17 or 19 or 22 ()
24 Coronary Vessels/ ()
25 Coronary Artery Disease/ ()
26 Coronary Angiography/ ()
27 Tomography, X-Ray Computed/ ()
28 Four-Dimensional Computed Tomography/ ()\
29 Tomography, Spiral Computed/ ()
30 Multidetector Computed Tomography/ ()
31 24 or 25 or 26 or 27 or 28 or 29 or 30 ()
32 Calcinosis/ ()
33 Vascular Calcification/ ()
34 Calcium/ ()
35 32 or 33 or 34 ()
36 31 and 35 ()
37 (coronary adj3 calci*).ti,ab. ()
38 cac.ti,ab. ()

39 calcium scor*.ti,ab. ()
40 coronary computed tomographic angiogra*.ti,ab. ()
41 ccta.ti,ab. ()
42 36 or 37 or 38 or 39 or 40 or 41 ()
43 5 and 15 ()
44 limit 43 to yr="2012 -Current" ()
45 5 and 23 ()
46 limit 45 to yr="2007 -Current" ()
47 5 and 42 ()
48 limit 47 to yr="2008 -Current" ()
49 44 or 46 or 48 ()
50 Animal/ not (Human/ and Animal/) ()
51 49 not 50 ()
52 limit 51 to english language ()

PubMed [Publisher Supplied]

Search	Query
#19	Search #18 AND Publisher[sb] AND English[Language]
#18	Search #13 OR #15 OR #17
#17	Search #1 AND #11 Filters: Publication date from 2008/01/01 to 2017/12/31
#16	Search #1 AND #11
#15	Search #1 AND #5 Filters: Publication date from 2007/01/01 to 2017/12/31
#14	Search #1 AND #5
#13	Search #1 AND #4 Filters: Publication date from 2012/01/01 to 2017/12/31
#12	Search #1 AND #4
#11	Search #6 OR #7 OR #8 OR #9 OR #10
#10	Search ccta[tiab]
#9	Search "coronary computed tomographic angiography"[tiab] OR "coronary computed tomographic angiograph"[tiab] OR "coronary computed tomographic angiographic"[tiab] OR "coronary computed tomographic angiogram"[tiab]
#8	Search "calcium score"[tiab] OR "calcium scores"[tiab] OR "calcium scoring"[tiab]
#7	Search cac[tiab]
#6	Search coronary[tiab] AND (calcium*[tiab] OR calcify*[tiab] OR calcifi*[tiab] OR calcinos*[tiab])
#5	Search "c-reactive protein"[tiab] OR "c-reactive proteins"[tiab] OR crp[tiab] OR hscrp[tiab]
#4	Search #2 OR #3
#3	Search ankle[tiab] AND (brachial[tiab] OR arm[tiab])
#2	Search "ankle index"[tiab] OR "ankle indexes"[tiab] OR "ankle indices"[tiab]
#1	Search heart[ti] OR coronar*[ti] OR cardiac*[ti] OR cardio[ti] OR cardiog*[ti] OR cardiol*[ti] OR cardiom*[ti] OR cardiop*[ti] OR cardiov*[ti] OR myocardi*[ti] OR vascular*[ti] OR CVD[ti] OR cerebrovascular[ti] OR stroke[ti] OR cerebral[ti] OR atheroscler*[ti]

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#1 (heart or coronar* or cardiac* or cardio* or myocardi* or vascular* or CVD or cerebrovascular or stroke or cerebral or atheroscler*):ti
#2 ankle:ti,ab,kw near/2 brachial:ti,ab,kw
#3 arm:ti,ab,kw near/2 ankle:ti,ab,kw
#4 "ankle index":ti,ab,kw or "ankle indexes":ti,ab,kw or "ankle indices":ti,ab,kw
#5 #2 or #3 or #4
#6 "c-reactive protein":ti,ab,kw or "c-reactive proteins":ti,ab,kw or crp:ti,ab,kw or hscrp:ti,ab,kw
#7 coronary:ti,ab,kw near/3 calci*:ti,ab,kw
#8 cac:ti,ab,kw
#9 "calcium score":ti,ab,kw or "calcium scores":ti,ab,kw or "calcium scoring":ti,ab,kw
#10 "coronary computed tomographic angiography":ti,ab,kw or "coronary computed tomographic angiograph":ti,ab,kw or "coronary computed tomographic angiographic":ti,ab,kw or "coronary computed tomographic angiogram":ti,ab,kw
#11 ccta:ti,ab,kw
#12 #7 or #8 or #9 or #10 or #11
#13 #1 and #5 Publication Year from 2012 to 2017, in Trials
#14 #1 and (#6) Publication Year from 2007 to 2017, in Trials
#15 #1 and #12 Publication Year from 2008 to 2017, in Trials
#16 #13 or #14 or #15

NRI and Confidence Interval Calculations

When a study reported a full reclassification table, a cross-tabulation of risk categories between a base model (in this case, a model with traditional risk factors only) and an extended model (which adds a nontraditional risk factor of interest to the base model), we used these data to calculate event and nonevent NRI for the overall population when these separate measures were not reported. Additionally, the full reclassification table was used to calculate a bias-corrected NRI for the intermediate risk group (NRI_{INT}). Not having individual-level data, we derived confidence intervals using a simple variance formula, a conservative estimation when compared to bootstrapping techniques as shown by Paytner and Cook.[70]

To calculate the overall event and nonevent NRIs, we first defined the upward movement (*up*) as a change into higher category and downward movement (*down*) as a change into lower category, per Pencina and colleagues.[69]

Event NRI = P(up|event) - P(down|event)

Non-event NRI = P(down|nonevent) – P(up|nonevent)

Overall NRI = [Event NRI] + [Nonevent NRI]

NRIs can be calculated separately for individual risk strata reported in a study, and calculation of the NRI_{INT} is of the most clinical interest given potential treatment uncertainty in this group.

However, unlike the overall NRI for which the null hypothesis of reclassification table is symmetrical and the expected NRI overall is 0, the expected NRI for the intermediate-risk group is not 0 and nonsymmetrical.[70, 71] Thus, the intermediate-risk group NRI would be biased, overestimating the reclassification movements (potential increase in Type I error) if not corrected.

A bias-corrected NRI_{INT} was calculated by subtracting the expected NRI_{INT} from the biased NRI_{INT}.[70] Based on symmetry assumption, we constructed separate expected reclassification tables using the whole observed table for events and nonevents. The expected number in the diagonal cells equaled numbers in the diagonal cells of the observed table. The expected numbers of the off-diagonal cells would be the average of the observed number in row r, column c and in row c, column r.[70]

From the expected table, we calculated the expected NRI_{INT} as follows:

Expected NRI_{INT} = [P(INT_up| INT _event) – P(INT _down| INT _event)] + [P(INT _down| INT _nonevent) – P(INT _up| INT _nonevent)]

From the observed table, we calculated the biased NRI_{INT} the same way as for expected NRI_{INT}. Thus,

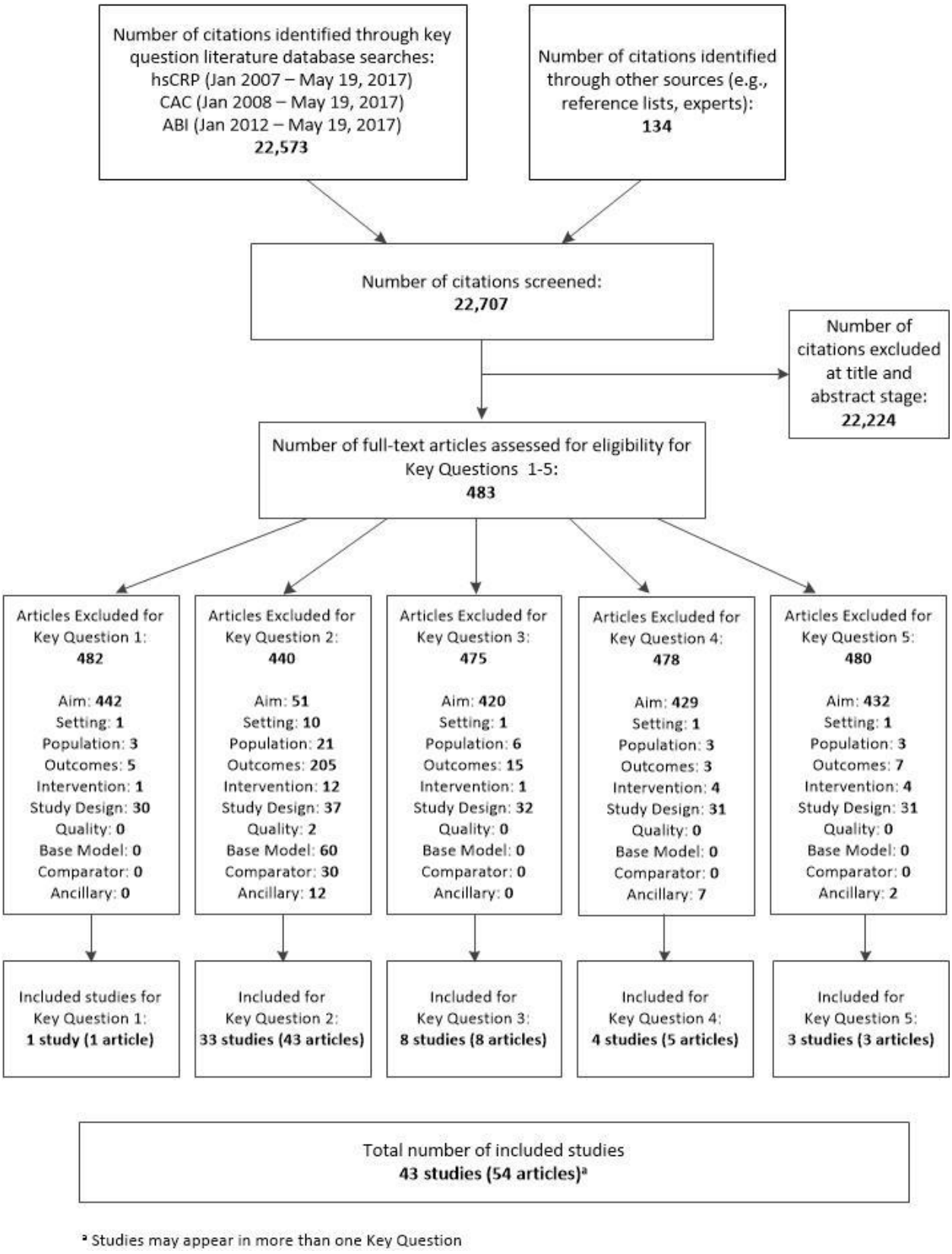
bias-corrected NRI_{INT} = biased NRI_{INT} – expected NRI_{INT}

Confidence intervals for the NRIs (above) were constructed using the simple variance estimator based n binary outcome data and derived from Z-statistics formula:[70]

Variance of NRI = [(P(up|event) + P(down|event)) / # events^2] + [(P(down|nonevent) + P(up|nonevent)) / #non-events^2]

95% confidence interval = NRI ± 1.96*$\sqrt{\text{variance of NRI}}$

Appendix B Figure 1. Literature Flow Diagram



Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CRP = C-reactive protein

Appendix B Table 1. Search Terms Used in the Abstract and Keywords Fields of EndNote

Search Terms in Abstract or Keyword Fields	Search Terms in Abstract Field Only†
Braz*	Animal*
Chin*	Bovin*
Egypt*	Canin*
India*	Felin*
Iran*	Mammal*
Iraq*	Mouse*
Keny*	Murine*
Mexic*	Pig*
Sahara*	Sprag*
Turk*	Swin*
Adoles*	
Autoimmun*	
Child*	
Infant*	
Mice*	
Neonat*	
Preg*	
Primat*	
Rheum*	
Sickle*	
Arthrit*	
Cancer*	
Hepati*	
HIV*	
Infect*	
Kidney*	
Lupus*	
Pancrea*	
Renal*	
Transplant*	
Cuba*	
Haiti*	
Lanka*	
Libya*	
Niger*	
Peru*	
Russ*	
South Africa*	
Ukrain*	
Wille*	

* Asterisk indicates truncation of search term

† Due to limited number of search terms and groups of search terms in EndNote, most animal-related terms only searched for in the abstract field

Appendix B Table 2. Inclusion Criteria

Category	Inclusion Criteria
Condition definition	Atherosclerotic cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, and peripheral artery disease
Populations	Adults without known cardiovascular disease • By sex, race/ethnicity, and diabetes
Risk Factors	High-sensitivity C-reactive protein, coronary artery calcium, ankle-brachial index
Treatments	KQs 4&5: interventions aimed at preventing CVD events (i.e., aspirin, HMG Co-A reductase inhibitors, antihypertension medications, and lifestyle modifications such as diet and/or exercise)
Comparisons	KQs 1–3: existing cardiovascular disease risk assessment models (focus on cardiovascular disease as opposed to coronary heart disease risk assessment) KQs 4&5: no treatment or usual care (as defined by the study)
Outcomes	KQs 1&4: CVD events (e.g., myocardial infarction, cerebrovascular accident) and/or mortality KQ 2: measures of reclassification (e.g., net reclassification index, integrated discrimination improvement), discrimination (e.g., area under the curve, c-statistic), and calibration (e.g., agreement between observed and predicted risks) KQs 3&5: serious adverse events from risk factor assessment or aggressive risk factor modification resulting in unexpected or unwanted medical attention (e.g., major bleeding, development of diabetes), exposure to radiation
Countries	Studies conducted in countries categorized as "Very High" on the 2014 Human Development Index (as defined by the United Nations Development Program)
Study designs	KQs 1&4: systematic review of trials, RCT, CCT KQ 2: systematic review of trials, RCT, CCT, well-designed large prospective cohort studies, risk prediction studies KQs 3&5: systematic reviews, RCT, CCT, well-designed large prospective or retrospective cohort studies, well designed case-control studies (only for rare events)
Language	English language only
Study Quality	"Fair" or "Good" quality only

Abbreviations: CCT = controlled clinical trial; CVD = cardiovascular disease; HMG Co-A reductase inhibitors = 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors; KQ = key question; RCT = randomized controlled trial

Appendix B Table 3. Quality Assessment Criteria

Study Design	Criteria
Randomized and nonrandomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[51]	• Valid random assignment? (NA for non-randomized controlled trials) • Was allocation concealed? • Were eligibility criteria specified? • Were groups similar at baseline? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable follow up? • Was there evidence of selective reporting of outcomes? • Was there risk of contamination?
Cohort studies, adapted from the Newcastle-Ottawa Scale[52]	• Was the exposed cohort(s) representative of the general population? • Was the non-exposed cohort selective from the same community as exposed cohort? • How was "exposure" ascertained? • Demonstrated that outcome of interest was not present at start of study? • Were the cohorts comparable on the basis of the design or analysis? • Were outcome assessors blind? • Was follow up long enough for outcomes to occur? • Was there adequate of follow up of cohorts?
Risk prediction study, adapted from CHARMS[53] with selected domains pertaining to IPD meta-analyses[54] (if applicable)	• *Does the IPD-MA a priori define the rationale, methods, and conduct of methods? If no, what don't they state? • *How does the IPD-MA identify relevant studies? • Source of data • Does study sample adequately represent population of interest (participant eligibility and recruitment)? • Was there selective inclusion of participants in the model based on data availability? • If participants are from a treatment RCT, is treatment accounted for? • Is a definition and method for measurement of the outcome reported? • Was the same outcome definition (and method for measurement) used in all patients? • Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)? • Time of outcome occurrence (average follow-up) and time horizon predicted • Is a definition and method for measurement of candidate predictors reported? • Were predictors assessed blinded for each other? • How was the predictor of interest (ABI, CAC, CRP) handled in the modelling? • Number of participants and number of outcomes/events • Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable) • Number of participants with any missing value (include predictors and outcomes) • How was missing data handled? • *Does IPD-MA use methods to investigate and account for between study heterogeneity? • Were both calibration and discrimination measures reported? Were confidence intervals reported? • Were a priori cut points used for classification measures (e.g., sensitivity, specificity, predictive values, NRI)? • Was a bias-corrected NRI used? This applies only to studies presenting NRI for a specific risk strata.

Appendix B Table 3. Quality Assessment Criteria

Study Design	Criteria
	• In what way was the population a separate external validation from the FRS or PCE? • Was the FRS or PCE recalibrated in the population before the NTRF was added to the model?

*Applicable for IPD meta-analyses only

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHARMS = Checklist for Critical Appraisal and Data Extraction for Systematic Review of Prediction Modelling Studies; CRP = C-reactive protein; FRS = Framingham Risk Score; IPD MA = individual participant data meta-analyses; NA = not applicable; NRI = net reclassification improvement; PCE = Pooled Cohort Equations; RCT = randomized controlled trial

Appendix C. Included Studies

Below is a list of included studies and ancillary publications; organized by Key Question and listed by Cohort*:

*Articles may appear under more than one Key Question

Key Question 1

EISNER

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Key Question 2

ABI Collaboration

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ARIC

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EAS

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EISNER

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EISNER + Referred Participant Database

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ERFC IPD MA

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Framingham + Framingham Offspring

Wilson PW, Nam BH, Pencina M, et al. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. Arch Intern Med. 2005;165(21):2473-8. PMID: 16314543. https://doi.org/10.1001/archinte.165.21.2473

Framingham Offspring

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Framingham Offspring + 3rd Generation

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Houston Methodist DeBakey Heart and Vascular Center

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MESA

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MONICA – Augsburg

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Lyngbaek S, Marott JL, Sehestedt T, et al. Cardiovascular risk prediction in the general population with use of suPAR, CRP, and Framingham Risk Score. Int J Cardiol. 2013;167(6):2904-11. PMID: 22909410. http://dx.doi.org/10.1016/j.ijcard.2012.07.018

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NPHS II

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WHS

Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med. 2006;145(1):21-9. PMID: 16818925.

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Pooled Analysis of 5 Cohorts of Low Risk Women (the Dallas Heart Study, the Framingham Heart Study (FHS), the Heinz Nixdorf Recall study (HNR), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study)

Kavousi M, Desai CS, Ayers C, et al. Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women: A Meta-analysis. JAMA. 2016;316(20):2126-34. PMID: 27846641. https://dx.doi.org/10.1001/jama.2016.17020

Key Question 3

Active-duty Army personnel

O'Malley PG, Feuerstein IM, Taylor AJ. Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: a randomized controlled trial. JAMA. 2003;289(17):2215-23. PMID: 12734132. https://doi.org/10.1001/jama.289.17.2215

EISNER

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Framingham Offspring + 3rd Generation

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MESA

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Rotterdam

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Key Question 4

AAA

Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303(9):841-8. PMID: 20197530. https://doi.org/10.1001/jama.2010.221

JUPITER

Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation. 2010;121(9):1069-77. PMID: 20176986. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.906479

Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207. PMID: 18997196. https://doi.org/10.1056/NEJMoa0807646

POPADAD

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Key Question 5

AAA

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JUPITER

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POPADAD

Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840. PMID: 18927173. https://doi.org/10.1136/bmj.a1840

Appendix D. Excluded Studies

Reason for Exclusion	
E1.	Aim
E2.	Setting
E3.	Population
E4.	Outcomes
*E4a.	Outcome of CVA only
*E4b.	Outcome of all-cause mortality only
†E4c.	Radiation dose only
E5.	Intervention
E6.	Study design
E7.	Quality
E8	Language
*E9.	Base model
E10.	Comparator
E11.	Ancillary article meeting criteria but not outcomes not abstracted

* KQ2-specific exclusion code

† KQ3-specific exclusion code

1. Abbott RD, Petrovitch H, Rodriguez BL, et al. Ankle/brachial blood pressure in men >70 years of age and the risk of coronary heart disease. Am J Cardiol. 2000;86(3):280-4. PMID: 10922433. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
2. Abbott RD, Rodriguez BL, Petrovitch H, et al. Ankle-brachial blood pressure in elderly men and the risk of stroke: the Honolulu Heart Program. J Clin Epidemiol. 2001;54(10):973-8. PMID: 11576807. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
3. AbouEzzeddine OF, McKie PM, Scott CG, et al. Biomarker-based risk prediction in the community. Eur J Heart Fail. 2016;18(11):1342-50. PMID: 27813304. **KQ1E1, KQ2E9, KQ3E1, KQ4E1, KQ5E1.**
4. Aboyans V, McClelland RL, Allison MA, et al. Lower extremity peripheral artery disease in the absence of traditional risk factors. The Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2011;214(1):169-73. PMID: 21067754. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
5. Agarwal S, Cox AJ, Herrington DM, et al. Coronary calcium score predicts cardiovascular mortality in diabetes: diabetes heart study. Diabetes Care. 2013;36(4):972-7. PMID: 23230101. **KQ1E1, KQ2E3, KQ3E1, KQ4E1, KQ5E1.**
6. Agarwal S, Morgan T, Herrington DM, et al. Coronary calcium score and prediction of all-cause mortality in diabetes: the diabetes heart study. Diabetes Care. 2011;34(5):1219-24. PMID: 21398528. **KQ1E1, KQ2E4b, KQ3E1, KQ4E1, KQ5E1.**
7. Agarwal SK, Chambless LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. Circ Heart Fail. 2012;5(4):422-9. PMID: 22589298. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
8. Ahmadi N, Hajsadeghi F, Blumenthal RS, et al. Mortality in individuals without known coronary artery disease but with discordance between the Framingham risk score and coronary artery calcium. Am J Cardiol. 2011;107(6):799-804. PMID: 21247539. **KQ1E1, KQ2E3, KQ3E1, KQ4E1, KQ5E1.**
9. Ahmadi-Abhari S, Luben RN, Wareham NJ, et al. Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. Eur J Epidemiol. 2013;28(7):541-50. PMID: 23821244. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
10. Al Rifai M, McEvoy JW, Nasir K, et al. Traditional cardiovascular disease risk factors associated with one-year all-cause mortality among those with coronary artery calcium scores >400. Atherosclerosis. 2015;241(2):495-7. PMID: 26091973. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
11. Alemao E, Cawston H, Bourhis F, et al. Comparison of cardiovascular risk algorithms in patients with vs without rheumatoid arthritis and the role of C-reactive protein in predicting cardiovascular outcomes in rheumatoid arthritis. Rheumatology (Oxford). 2017;56(5):777-86. PMID: 28087832. **KQ1E1, KQ2E3, KQ3E1, KQ4E1, KQ5E1.**

12. Allan GM, Garrison S, McCormack J. Comparison of cardiovascular disease risk calculators. Curr Opin Lipidol. 2014;25(4):254-65. PMID: 24977979. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
13. Alzamora MT, Fores R, Pera G, et al. Ankle-brachial index and the incidence of cardiovascular events in the Mediterranean low cardiovascular risk population ARTPER cohort. BMC Cardiovasc Disord. 2013;13:119. PMID: 24341531. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
14. Ambrose MS, Nagy CD, Blumenthal RS. Selective use of coronary calcification measurements in an expanded intermediate risk group. J Cardiovasc Comput Tomogr. 2008;2(4):209-13. PMID: 19083951. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
15. Ambrosius WT, Polonsky TS, Greenland P, et al. Design of the value of imaging in enhancing the wellness of your heart (VIEW) trial and the impact of uncertainty on power. Clinical Trials. 2012;9(2):232-46. PMID: 22333998. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
16. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur Heart J. 2006;27(6):713-21. PMID: 16497686. **KQ1E1, KQ2E10, KQ3E1, KQ4E1, KQ5E1.**
17. Andersson C, Vasan RS. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease?: Clinical risk scores are sufficient to define primary prevention treatment strategies among asymptomatic patients. Circ Cardiovasc Imaging. 2014;7(2):390-7; discussion 7. PMID: 24642921. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
18. Andersson J, Johansson L, Ladenvall P, et al. C-reactive protein is a determinant of first-ever stroke: prospective nested case-referent study. Cerebrovasc Dis. 2009;27(6):544-51. PMID: 19390179. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
19. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300(2):197-208. PMID: 18612117. **KQ1E1, KQ2E11, KQ3E1, KQ4E1, KQ5E1.**
20. Anonymous. Corrigendum to: Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnationalMulticenter (CONFIRM) Study. Eur Heart J. 2015;36(46):3287. PMID: 26063448. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
21. Arad Y, Goodman KJ, Roth M, et al. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol. 2005;46(1):158-65. PMID: 15992651. **KQ1E1, KQ2E10, KQ3E1, KQ4E1, KQ5E1.**
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132. Gibson AO, Blaha MJ, Arnan MK, et al. Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort. The MESA Study. Jacc: Cardiovascular Imaging. 2014;7(11):1108-15. PMID: 25459592. **KQ1E1, KQ2E4a, KQ3E1, KQ4E1, KQ5E1.**
133. Giugliano G, Sannino A, Brevetti L, et al. Ankle/brachial index to everyone. BMC Surgery. 2012;12 Suppl 1:S18. PMID: 23173985. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
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141. Halcox JP, Roy C, Tubach F, et al. C-reactive protein levels in patients at cardiovascular risk: EURIKA study. BMC Cardiovascular Disorders. 2014;14:25. PMID: 24564178. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
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144. Hamer M, Chida Y, Stamatakis E. Association of very highly elevated C-reactive protein concentration with cardiovascular events and all-cause mortality. Clinical Chemistry. 2010;56(1):132-5. PMID: 19884487. **KQ1E1, KQ2E11, KQ3E1, KQ4E1, KQ5E1.**
145. Han D, B OH, Gransar H, et al. Incremental benefit of coronary artery calcium score above traditional risk factors for all-cause mortality in asymptomatic Korean adults. Circulation Journal. 2015;79(11):2445-51. PMID: 26356835. **KQ1E1, KQ2E4b, KQ3E1, KQ4E1, KQ5E1.**
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148. Hartaigh BO, Valenti V, Cho I, et al. 15-Year prognostic utility of coronary artery calcium scoring for all-cause mortality in the elderly. Atherosclerosis. 2016;246:361-6. PMID: 26841073. **KQ1E1, KQ2E4b, KQ3E1, KQ4E1, KQ5E1.**
149. Hecht HS, Narula J, Chandrashekhar Y. In Sickness and in Health: Coronary Artery Calcium or Risk Factors. Jacc: Cardiovascular Imaging. 2015;8(12):1401-3. PMID: 26699109. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
150. Henein M, Granasen G, Wiklund U, et al. High dose and long-term statin therapy accelerate coronary artery calcification. International Journal of Cardiology. 2015;184:581-6. PMID: 25769003. **KQ1E1, KQ2E1, KQ3E1, KQ4E4, KQ5E1.**
151. Henein M, Granåsen G, Wiklund U, et al. High dose and long-term statin therapy accelerate coronary artery calcification. Int J Cardiol. 2017;184:581-6. PMID: 25769003. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
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153. Hermann DM, Gronewold J, Lehmann N, et al. Coronary artery calcification is an independent stroke predictor in the general population. Stroke. 2013;44(4):1008-13. PMID: 23449263. **KQ1E1, KQ2E4a, KQ3E1, KQ4E1, KQ5E1.**
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155. Hiatt WR, Zakharyan A, Fung ET, et al. A validated biomarker panel to identify peripheral artery disease. Vascular Medicine. 2012;17(6):386-93. PMID: 23086582. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
156. Hoffmann U, Massaro JM, Fox CS, et al. Defining normal distributions of coronary artery calcium in women and men (from the Framingham Heart Study). American Journal of Cardiology. 2008;102(9):1136-41, 41.e1. PMID: 18940279. **KQ1E1, KQ2E4, KQ3E4c, KQ4E1, KQ5E1.**
157. Hughes MF, Saarela O, Blankenberg S, et al. A multiple biomarker risk score for guiding clinical decisions using a decision curve approach. European Journal of Preventive Cardiology. 2012;19(4):874-84. PMID: 21775414. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
158. Hughes-Austin JM, Dominguez A, 3rd, Allison MA, et al. Relationship of Coronary Calcium on Standard Chest CT Scans With Mortality. Jacc: Cardiovascular Imaging. 2016;9(2):152-9. PMID: 26777213. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
159. Hulten E, Bittencourt MS, O'Leary D, et al. Cardiometabolic risk is associated with atherosclerotic burden and prognosis: results from the partners coronary computed tomography angiography registry. Diabetes Care. 2014;37(2):555-64. PMID: 24130364. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
160. Hulten E, Villines TC, Cheezum MK, et al. Calcium score, coronary artery disease extent and severity, and clinical outcomes among low Framingham risk patients with low vs high lifetime risk: results from the CONFIRM registry. Journal of Nuclear Cardiology. 2014;21(1):29-37; quiz 8-9. PMID: 24385134. **KQ1E1, KQ2E5, KQ3E1, KQ4E1, KQ5E1.**
161. Hung J, Knuiman MW, Divitini ML, et al. C-reactive protein and interleukin-18 levels in relation to coronary heart disease: prospective cohort study from Busselton Western Australia. Heart, Lung & Circulation. 2008;17(2):90-5. PMID: 17851127. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**

162. Ibebuogu UN, Ahmadi N, Hajsadeghi F, et al. Measures of coronary artery calcification and association with the metabolic syndrome and diabetes. Journal of the CardioMetabolic Syndrome. 2009;4(1):6-11. PMID: 19245510. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
163. Ijkema R, Aerde MA, Aalst CM, et al. A randomized controlled trial measuring the effectiveness of screening for cardiovascular disease using classic risk assessment and coronary artery calcium: The ROBINSCA study. European Journal of Preventive Cardiology. 2014;21(1 suppl. 1):S21. PMID: None. **KQ1E4, KQ2E1, KQ3E4, KQ4E1, KQ5E1.**
164. Iribarren C, Chandra M, Rana JS, et al. High-sensitivity cardiac troponin I and incident coronary heart disease among asymptomatic older adults. Heart. 2016;102(15):1177-82. PMID: 27030599. **KQ1E1, KQ2E10, KQ3E1, KQ4E1, KQ5E1.**
165. Ishisone T, Koeda Y, Tanaka F, et al. Comparison of utility of arterial stiffness parameters for predicting cardiovascular events in the general population. International Heart Journal. 2013;54(3):160-5. PMID: 23774240. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
166. Isma'eel H, Min D, Al-Shaar L, et al. Assessing Level of Agreement for Atherosclerotic Cardiovascular Disease Risk Categorization Between Coronary Artery Calcium Score and the American College of Cardiology/American Heart Association Cardiovascular Prevention Guidelines and the Potential Impact on Treatment Recommendations. Am J Cardiol. 2016;118(10):1480-5. PMID: 27642113. **KQ1E1, KQ2E6, KQ3E1, KQ4E1, KQ5E1.**
167. Isma'eel HA, Almedawar MM, Harbieh B, et al. Quantifying the impact of using Coronary Artery Calcium Score for risk categorization instead of Framingham Score or European Heart SCORE in lipid lowering algorithms in a Middle Eastern population. Journal of the Saudi Heart Association. 2015;27(4):234-43. PMID: 26557741. **KQ1E1, KQ2E2, KQ3E1, KQ4E1, KQ5E1.**
168. Iso H, Cui R, Date C, et al. C-reactive protein levels and risk of mortality from cardiovascular disease in Japanese: the JACC Study. Atherosclerosis. 2009;207(1):291-7. PMID: 19482283. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
169. Iso H, Noda H, Ikeda A, et al. The impact of C-reactive protein on risk of stroke, stroke subtypes, and ischemic heart disease in middle-aged Japanese: the Japan public health center-based study. Journal of Atherosclerosis & Thrombosis. 2012;19(8):756-66. PMID: 22785140. **KQ1E1, KQ2E9, KQ3E1, KQ4E1, KQ5E1.**
170. Jacobs PC, Prokop M, van der Graaf Y, et al. Comparing coronary artery calcium and thoracic aorta calcium for prediction of all-cause mortality and cardiovascular events on low-dose non-gated computed tomography in a high-risk population of heavy smokers. Atherosclerosis. 2010;209(2):455-62. PMID: 19875116. **KQ1E1, KQ2E4, KQ3E4c, KQ4E1, KQ5E1.**
171. Jain A, McClelland RL, Polak JF, et al. Cardiovascular imaging for assessing cardiovascular risk in asymptomatic men versus women: the multi-ethnic study of atherosclerosis (MESA). Circulation Cardiovascular imaging. 2011;4(1):8-15. PMID: 21068189. **KQ1E1, KQ2E9, KQ3E1, KQ4E1, KQ5E1.**
172. Jenny NS, Solomon C, Cushman M, et al. Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) and risk of cardiovascular disease in older adults: results from the Cardiovascular Health Study. Atherosclerosis. 2010;209(2):528-32. PMID: 19804884. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
173. Jha AK, Hwang U, Keyhani S, et al. Statins lower the risk of first cardiovascular event in patients with high C-reactive protein and normal LDL cholesterol (outcomes research in review). Journal of clinical outcomes management. 2009;16(1):09, 12-3. PMID: None. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
174. Jimenez MC, Rexrode KM, Glynn RJ, et al. Association Between High-Sensitivity C-Reactive Protein and Total Stroke by Hypertensive Status Among Men. Journal of the American Heart Association. 2015;4(9):e002073. PMID: 26391131. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
175. Johnson JE, Gulanick M, Penckofer S, et al. Does knowledge of coronary artery calcium affect cardiovascular risk perception, likelihood of taking action, and health-promoting behavior change? Journal of Cardiovascular Nursing. 2015;30(1):15-25. PMID: 24434820. **KQ1E1, KQ2E1, KQ3E4, KQ4E1, KQ5E1.**
176. Johnson KM, Dowe DA. The detection of any coronary calcium outperforms Framingham risk score as a first step in screening for coronary atherosclerosis. AJR American Journal of Roentgenology. 2010;194(5):1235-43. PMID: 20410409. **KQ1E1, KQ2E5, KQ3E1, KQ4E1, KQ5E1.**

Appendix D. Excluded Studies

177. Jones WS, Patel MR, Rockman CB, et al. Association of the ankle-brachial index with history of myocardial infarction and stroke. American Heart Journal. 2014;167(4):499-505. PMID: 24655698. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
178. Jorgensen T, Jacobsen RK, Toft U, et al. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. BMJ. 2014;348:g3617. PMID: 24912589. **KQ1E1, KQ2E1, KQ3E1, KQ4E5, KQ5E5.**
179. Joshi PH, Patel B, Blaha MJ, et al. Coronary artery Calcium predicts Cardiovascular events in participants with a low lifetime risk of Cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2016;246:367-73. PMID: 26841074. **KQ1E1, KQ2E11, KQ3E1, KQ4E1, KQ5E1.**
180. Jung CH, Lee MJ, Kang YM, et al. 2013 ACC/AHA versus 2004 NECP ATP III Guidelines in the Assignment of Statin Treatment in a Korean Population with Subclinical Coronary Atherosclerosis. PLoS ONE [Electronic Resource]. 2015;10(9):e0137478. PMID: 26372638. **KQ1E1, KQ2E5, KQ3E1, KQ4E1, KQ5E1.**
181. Kabagambe EK, Judd SE, Howard VJ, et al. Inflammation biomarkers and risk of all-cause mortality in the Reasons for Geographic And Racial Differences in Stroke cohort. American Journal of Epidemiology. 2011;174(3):284-92. PMID: 21685411. **KQ1E1, KQ2E4, KQ3E1, KQ4E1, KQ5E1.**
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Appendix E Table 1. Integrated Discrimination Improvement in Included ABI Risk Prediction Studies

Model Type: Base Model	Author, Year	Study Name	N	Outcome*	Subgroup	IDI (95% CI)	IDI p-value
Published coefficient: FRS	Velescu, 2015[91]	REGICOR	5,182	Soft CVD	All Participants	1.11 (0.67 to 1.55)	<0.001
	Velescu, 2015[91]	REGICOR	5,182	Soft CHD	All Participants	0.63 (0.32 to 0.95)	<0.001
Model development: FRS variables	Murphy, 2012[79]	ARIC	11,594	Hard CVD	All Participants	0.075 (NR to NR)	0.0002
	Holewijn, 2014[95]	Nijmegen Biomedical Study	659	Soft CVD	Women	0.025 (NR to NR)	0.087
	Holewijn, 2014[95]	Nijmegen Biomedical Study	582	Soft CVD	Men	0.013 (NR to NR)	0.263

* Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; ARIC = Atherosclerosis Risk in Communities study; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; FRS=Framingham Risk Score; IDI = integrated discrimination improvement; NR = not reported; NRI = net reclassification improvement; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry)

Appendix E Table 2. Integrated Discrimination Improvement in Included hsCRP Risk Prediction Studies

Model Type: Base Model	Author, Year	Study Name	N	Outcome*	Subgroup	IDI (95% CI)	IDI p-value
Published coefficient: FRS	Lyngbaek, 2013[96]	MONICA - Copenhagen	1,168	Hard CVD	Women	0.004 (-0.001 to 0.008)	0.058
	Lyngbaek, 2013[96]	MONICA - Copenhagen	1,147	Hard CVD	Men	0.018 (0.008 to 0.028)	<0.001
Model development: FRS variables	Wannamethee, 2011[102]	British Regional Heart Study	2,854	Hard CVD	All Participants	0.32 (NR to NR)	0.14
	ERFC, 2012[65]	ERFC IPD MA	72,574	Hard CVD	All Participants	0.0036 (0.0028 to 0.0043)	<0.0001
	Mohlenkamp, 2011[103]	HNR	3,966	Hard CHD	All Participants	0.0015 (NR to NR)	0.32
	Seven, 2015[92]	Inter99	6,138	Soft CVD	All Participants	0.003 (NR to NR)	<0.001

* Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; ERFC IPD MA= Emerging Risk Factors Collaboration individual participant data meta-analysis; IDI = integrated discrimination improvement; FRS = Framingham Risk Score; HNR = Heinz Nixdorf Recall study; hsCRP = high sensitivity C-reactive protein; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NR = not reported; NRI = net reclassification improvement

Appendix E Table 3. Integrated Discrimination Improvement in Included CAC Risk Prediction Studies

Model Type: Base Model	Author, Year	Study Name	N	Outcome‖	Subgroup	IDI (95% CI)	IDI p-value
Published coefficient: PCE	Fudim, 2016[112]	MESA	3,556	Hard CVD	Women	0.0069 (NR to NR)	0.032
	Fudim, 2016[112]	MESA	3,186	Hard CVD	Men	0.0117 (NR to NR)	<0.001
	Fudim, 2016[112]	MESA	1,850	Hard CVD	African American	0.014 (NR to NR)	<0.001
	Fudim, 2016[112]	MESA	2,599	Hard CVD	Caucasian	0.012 (NR to NR)	<0.001
	Fudim, 2016[112]	MESA	801	Hard CVD	Chinese American	0.005 (NR to NR)	0.27
	Fudim, 2016[112]	MESA	1,492	Hard CVD	Hispanic	0.006 (NR to NR)	0.23
Model development: PCE variables	Bos, 2015[89]	Rotterdam	2,408	Fatal CVD	All Participants	0.18 (0.07 to 0.3)*	NR
Model development: FRS variables	Erbel, 2010[74]	HNR	4,129	Hard CHD	All Participants	0.0152 (NR to NR)	<0.0001
	Mohlenkamp, 2011[103]	HNR	3,966	Hard CHD	All Participants	0.0148 (NR to NR)	<0.0001
	Rana, 2012[99]	EISNER	1,279	Soft CVD	All Participants	0.076 (NR to NR)	0.0001
	Chang, 2015[93]	Houston Methodist DeBakey Heart and Vascular Center	946	Soft CHD	All Participants	0.035 (NR to NR)†	<0.0001
	Chang, 2015[93]	Houston Methodist DeBakey Heart and Vascular Center	655	Soft CHD	Intermediate Risk	0.029 (NR to NR)‡	<0.0001
	Polonsky, 2010[77]	MESA	5,878	Soft CHD	All Participants	0.026 (NR to NR)§	<0.001

* Reported as relative IDI (ratio of the absolute difference in discrimination slopes of the 2 models over the discrimination slope of the reference model)
† Relative IDI=2.85
‡ Relative IDI=1.62
§ Relative IDI showed 81% improvement in discrimination slope
‖ Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; IDI = integrated discrimination improvement; FRS = Framingham Risk Score; HNR = Heinz Nixdorf Recall study; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported

Appendix F. Ongoing Studies

Study Reference Trial Identifier	Study Name	Location	Estimated N	Description	2017 Status
ISRCTN12157806	The Danish Cardiovascular Screening Trial (DANCAVAS)	Denmark	45,000 (men)	Population-based, randomized trial to evaluate the health benefits and cost-effectiveness of using noncontrast CT scans (to measure CAC and identify aortic/iliac aneurysms) and measurements of the ABI as part of a multicomponent screening and intervention program for CVD in men aged 65 to74 years.	Ongoing: Est Interim Publication Date 2018; Completion Date Jan 2026
NCT03228459 (Protocol) (project page)	Randomized intervention study to assess the prevalence of subclinical vascular disease and hidden kidney disease and its impact on morbidity and mortality: The ILERVAS project	Spain	14,600	Adults 45 to 70 years without previous history of CVD and with ≥1 CVD risk factor will be randomly selected from the primary health care centers across the province of Lérida. The following baseline tests will be given to the intervention group in a mobile screening unit: artery ultrasound (carotid, femoral, transcranial and abdominal aorta); ABI; spirometry; determination of advanced glycation end products; dried blood spot and urine spot tests.	Ongoing: Est Data Collection Completion Date 2017; Follow up through 2025
NR (Protocol) (project page)	Aragon Workers Health Study (AWHS)	Spain	5,400	Longitudinal cohort study based on the annual health exams of 5,400 workers of a car assembly plant in Spain. Study participants were recruited during a standardized clinical exam in 2009–2010 (participation rate 95.6%). Study participants will undergo annual clinical exams and laboratory assays, and baseline and triennial collection of biological materials for biobanking and cardiovascular imaging exams (carotid, femoral and abdominal ultrasonography, CAC, and ABI). Participants will be followed up for 10 years; specific cardiovascular events that will be monitored are not reported.	Ongoing: Est Completion Date Jan 2019
European Research Council Project ID: 294604 (project page)	Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA)[132]	The Netherlands	39,000	A large-scale, population-based RCT designed to investigate whether screening asymptomatic men and women for a high risk of cardiovascular disease by means of (1) the Systematic COronary Risk Evaluation (SCORE) model or (2) CAC is effective in reducing morbidity and mortality due to CHD. The trial is conducted in three regions of the Netherlands and planned follow up is 5 years.	Ongoing: Est Completion Date 2019 (Mid-term Report Summary)
NCT01428934	Improving Intermediate Risk Management. MARK Study (MARK)[162]	Spain	2,495	The purpose of this study is to analyze if ABI, measures of arterial stiffness, postprandial glucose, glycosylated hemoglobin, self-measured blood pressure, and presence of comorbidity are independently associated to incidence of vascular events and whether they can improve the predictive capacity of current risk equations in the intermediate-risk population. Planned follow up of 18 months, 5, and 10 years.	Ongoing as of 12/2017: Est Completion Date Dec 2016

Appendix F. Ongoing Studies

Study Reference Trial Identifier	Study Name	Location	Estimated N	Description	2017 Status
NCT00143923	Novel Strategies for Reducing Heart Disease Risk Disparities	US	2,000	Prospective cohort study of 2,000 residents of the state of Pennsylvania with approximately equal representation of whites and African Americans. All participants will undergo assessments of traditional and nontraditional risk factors to identify and determine the mechanisms of population disparities in cardiovascular risk. 800 participants who are at intermediate or high risk of cardiovascular disease will be randomly assigned to either (1) usual care/"advice only"; or (2) a multidisciplinary behavioral modification program to determine the most effective approach to reduce or eliminate racial, socioeconomic and geographic disparities in cardiovascular risk. The primary outcome is CVD events at 20 years follow up.	Ongoing: Est Completion Date Dec 2024

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHD; coronary heart disease; CT=computed tomography; CVD = cardiovascular disease; Dec = December; Est = estimated; Jan = January; Sept = September