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Screening for Cardiovascular Disease Risk With Electrocardiography: An Evidence Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Purpose: To systematically review the evidence on screening asymptomatic adults for cardiovascular disease (CVD) risk using resting or exercise electrocardiography (ECG) for populations and settings relevant to primary care in the United States.

Data Sources: PubMed/MEDLINE, the Cochrane Library, and trial registries through May 30, 2017; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through October 2017.

Study Selection: Two investigators selected English-language studies using a priori criteria. Eligible studies focused on the use of resting or exercise ECG for adults without symptoms or a diagnosis of CVD. Eligible designs included controlled trials comparing ECG screening with no ECG screening and prospective cohort studies reporting reclassification, calibration, or discrimination that compared risk assessment using ECG plus traditional risk factors versus traditional risk factors alone. For harms of ECG, prospective cohort studies, large retrospective cohort studies, and case-control studies were also eligible. For harms from exercise ECG or subsequent procedures/interventions, large registries or multicenter studies without a control group were also eligible.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: Sixteen studies (77,140 participants) were included. Two randomized, controlled trials (RCTs) (1,151 participants) found no significant improvement in all-cause mortality, cardiovascular-related mortality, myocardial infarction (MI), heart failure, or stroke for screening with exercise ECG in asymptomatic adults ages 50 to 75 years with diabetes compared with no screening. In addition, there was no significant improvement for their primary composite outcomes (hazard ratio [HR] 1.00 [95% confidence interval [CI], 0.59 to 1.71] for all-cause mortality, nonfatal MI, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention, and HR 0.85 [95% CI, 0.39 to 1.84] for nonfatal MI or cardiac death). No controlled trials evaluated screening with resting ECG. Although potential harms of exercise or resting ECG include arrhythmias, acute MI, sudden cardiac death, and harms of subsequent angiography or revascularization procedures after an abnormal test, evidence on their frequency in asymptomatic persons was scant. Evidence from five cohort studies (9,582 participants; mean baseline Framingham Risk Score [FRS] 10.8 to 12.3 in studies reporting it) shows that the addition of exercise ECG abnormalities to traditional CVD risk factors results in small improvements in discrimination (absolute improvement in area under the curve (AUC) or C-statistics 0.02 to 0.03; 95% CIs rarely reported), but it is uncertain whether calibration or appropriate risk classification improves. Evidence from nine cohort studies (66,407 participants; mean baseline risk ranging from low to high across studies) shows that the addition of resting ECG findings to traditional CVD risk factors results in very small or small improvements in discrimination (absolute improvement in AUC or C-statistics 0.001 to 0.05) and improvements for calibration and appropriate risk classification for prediction of multiple outcomes (e.g., all-cause mortality, CVD mortality, CHD events). Total net reclassification improvements (event;

nonevent) ranged from 3.6 percent (2.7%; 0.6%) to 30 percent (17%; 19%) for studies using Framingham Risk Score (FRS) or pooled cohort equation (PCE) base models (95% CIs were rarely reported).

Limitations: The RCTs that evaluated exercise ECG in asymptomatic diabetic patients did not reach sample size targets and were stopped early because of trouble recruiting; both followed participants for about 3.5 years. For risk prediction with the addition of ECG, evidence was limited by imprecision, quality, and considerable heterogeneity. Consistency of findings for specific risk thresholds is unknown because all studies used different risk categories. About half of the included risk prediction studies did not use the published coefficients of externally validated base models such as FRS or PCE; only one used the PCE as a base model. For risk prediction with resting ECG, it is unclear what proportion of participants was truly asymptomatic because most studies did not report any assessment of symptoms.

Conclusions: The overall strength of evidence was low or insufficient for each of the questions and outcomes evaluated. RCTs of screening with exercise ECG in asymptomatic participants found no improvement in health outcomes despite focusing on higher risk populations with diabetes. For asymptomatic persons without a history of CVD, the harms of exercise or resting ECG can include arrhythmias, acute MI, sudden cardiac death, and harms of subsequent angiography or revascularization procedures after an abnormal test, but the frequency of these harms is uncertain. Evidence on whether the addition of exercise ECG to traditional CVD risk factors results in accurate reclassification is lacking. Cohort studies found that the addition of multiple resting ECG abnormalities to traditional CVD risk factors accurately reclassifies persons, and improves discrimination and calibration, but evidence was limited by imprecision, quality, considerable heterogeneity, and inconsistent use of risk thresholds that align with clinical decisions and recommendations.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to inform an update of its 2012 recommendation on screening asymptomatic adults with electrocardiogram (ECG) for the prediction of cardiovascular disease (CVD) events.[1] In 2012, the USPSTF recommended against screening with resting or exercise ECG for the prediction of coronary heart disease (CHD) events in asymptomatic adults at low risk for CHD events (D recommendation). For asymptomatic adults at intermediate or high risk, the USPSTF concluded that evidence was insufficient to assess the balance of benefits and harms of screening (I statement). The purpose of this report is to systematically evaluate the current evidence on using resting or exercise ECG to screen asymptomatic adults for CVD risk for populations and settings relevant to primary care in the United States. This report summarizes the evidence on the benefits and harms of adding screening with resting or exercise ECG to traditional CVD risk factor assessments compared with using traditional CVD risk factor assessments alone. This report also summarizes the evidence on whether the addition of ECG accurately reclassifies persons into different risk groups or improves measures of calibration and discrimination.

Condition Definition

CVD is a broad term encompassing atherosclerotic conditions that affect the heart and blood vessels.[2-4] CVD generally refers to atherosclerosis, including but not limited to CHD (also called ischemic heart disease), cerebrovascular disease, and peripheral artery disease (PAD). In patients with CVD, plaques form within the arteries, causing reduced blood flow and/or arterial blockage. Serious CVD events (sometimes described as hard outcomes) include myocardial infarction (MI), heart failure, stroke, and sudden cardiac death. Less severe CVD events (sometimes called soft outcomes) include angina, claudication, transient ischemic attack (TIA), and revascularization.

Etiology and Natural History

In CVD, atherosclerotic plaque is deposited over many years within the endothelial lining of the coronary arteries, which provide oxygenated blood to the myocardium. The development of the plaque, containing not only lipids but other molecules secreted from various types of cells, is induced by a cascade of mechanisms including inflammatory processes.[5, 6] Some sites, such as branch points and the inner curves of arteries, are more susceptible to deposition of atherosclerotic plaque.[7] Sudden plaque rupture, or intra-luminal thrombosis related to the exposure of the ruptured plaque's thrombogenic core, is associated (though not invariably) with acute coronary syndrome, MI, and sudden cardiac death.[7, 8] Progression of atherosclerosis and of CVD is influenced by a variety of risk factors, some of them modifiable and thus targets for intervention.

Evidence of obstructive CHD, upon evaluation by coronary angiography, has been considered to be prognostic of significant morbidity and mortality; however, it has been demonstrated that culprit lesions, in patients who experience acute coronary events due to plaque rupture or acute thrombosis, may not be those angiographically observed to significantly occlude the vessel.[8, 9] Some persons do not experience symptoms before major first CVD events[10] because major first events can result from plaque rupture in vessels without significant stenosis.

Risk Factors

Traditional risk factors for CVD are male sex, older age, cigarette smoking, hypertension, dyslipidemia (high total or low-density lipoprotein cholesterol or low high-density lipoprotein [HDL] cholesterol), and diabetes. They are independently associated with risk of CVD and are included in the traditional Framingham risk assessment model.[11, 12] Some risk factors are modifiable and could be targets for treatment in patients identified as being at higher risk. Prevalence of risk factors is high in the United States: as of 2014, 16.9 percent of U.S. adults smoked cigarettes; as of 2012, 69 percent were overweight or obese, 13.1 percent had serum total cholesterol levels ≥240 mg/dL, 32.6 percent were hypertensive, and 8.5 percent of adults had diagnosed diabetes mellitus (another 3.3% had undiagnosed diabetes mellitus).[13] More than 90 percent of CVD events occur in persons with one or more risk factors.[14] Other factors, some behavioral and others biomarkers, are not included among the major independent traditional risk factors. Although they increase CVD risk to varying degrees, they have not been shown to consistently improve risk prediction in a clinically meaningful way beyond traditional risk factors; these include family history of early CVD, obesity, physical inactivity, atherogenic diet, and presence of prothrombic and proinflammatory factors.[12, 13, 15]

To help providers operationalize the large number of factors that need to be considered, risk prediction equations that integrate and weight the traditional risk factors are used commonly in clinical practice to assess 10-year risk of CVD events and to guide treatment decisions. The USPSTF recommends using the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations (PCEs) to calculate 10-year risk for adults ages 40 to 75 years to inform decisions about statin use for prevention of CVD and to inform decisions about aspirin use for primary prevention.[2, 16, 17] The USPSTF noted that concerns have been raised about the PCE's potential to overpredict risk and their moderate discrimination, but also that they are the only U.S.-based, externally validated equations that report risk as a combination of cerebrovascular and CHD events.[2, 17] The PCE approach takes into account age, sex, race, cholesterol levels, systolic blood pressure level, antihypertension treatment, presence of diabetes, and smoking status as risk factors and focuses on prediction of hard outcomes, specifically, heart attack and death from CHD, ischemic stroke, and stroke-related death.[16] Using the PCE and National Health and Nutrition Examination Survey data from 2011–2012, an estimated 9.4 percent of adults ages 40 to 79 years without a history of CVD have a 10-year risk greater than 20 percent.[18] Age has a large influence on the PCE's predicted risk, and it is estimated that 41 percent of men and 27 percent of women ages 60 to 69 years without a history of CVD will have a 10-year risk of at least 10 percent.[19]

Prevalence and Burden

CVD is the leading cause of death in U.S. adults and causes about a third of all deaths.[13, 18] In the United States, an estimated 580,000 persons have a first MI each year and about 610,000 have a first stroke.[20] Adult CVD prevalence increases with each decade of life, with higher prevalence among men than women.[13] The average annual incidence of first major cardiovascular (CV) event increases from around 25 cases per 1,000 in men ages 35 to 44 years to 80 cases per 1,000 in men age 85 years or older. For women (compared with men), similar incidence rates are observed about 10 years later in life, although the gap narrows for women ages 75 to 84 years and is reversed by age 85 years or older. Prevalence of CHD and stroke were nearly 3 to 4 times greater for adults age 65 years or older than for those ages 45 to 64 years (19.8% vs. 7.1% and 8.3% vs. 2.9%, respectively).[21, 22] Disparities exist with regard to mortality from and prevalence of CVD. Mortality rates are lowest for white women and highest for black men, and prevalence is highest for American Indians/Alaska Natives and blacks.[21, 22] CVD is a major source of direct and indirect health care costs in the United States. The estimated total cost of CVD in 2015 was $182 billion, which is predicted to double by 2030.[13]

Rationale for Screening and Screening Strategies

Because many patients do not have any symptoms of CVD before a serious first event, such as MI or stroke, identifying asymptomatic individuals for treatment with preventive medications may reduce risk for future CVD morbidity and mortality. Approximately 30 percent of patients presenting with acute coronary syndromes do not have a prior diagnosis of CVD.[10, 23] For screening with resting or exercise ECG to be effective, it must be able to reclassify individuals in a manner that results in treatment changes that improve health outcomes. For example, screening with ECG might reclassify persons into higher or lower risk categories. Appropriately reclassifying such individuals could help target use of preventive interventions to those most likely to benefit or could reduce use of preventive interventions for those least likely to benefit. However, if reclassification was inappropriate, it could lead to an increase in overtreatment or undertreatment.

Potential screening strategies include both resting and exercise ECG. Resting ECG records cardiac electrical activity over a short time, typically 10 seconds. Clinicians interpret the recorded ECG waveforms to look for evidence of conduction problems and/or myocardial ischemia. Resting or exercise ECGs have long been used as tests for the diagnostic evaluation of suspected CVD, which has led to consideration of their use for screening asymptomatic individuals and risk prediction. Although the most common method of exercise testing is the exercise treadmill test, other methods include bicycles and ergometers. Both resting and exercise ECG may show markers of unrecognized previous MI, silent or inducible myocardial ischemia, and other cardiac abnormalities (such as left ventricular hypertrophy, bundle branch block, or arrhythmias) that may be associated with CVD or may predict future CVD events.

Treatment Approaches

If screening for CVD risk results in appropriate risk reclassification, intensified preventive interventions focus on lipid-lowering therapy and aspirin, which have been demonstrated to reduce risk as assessed by a variety of outcomes.[24-28] Other preventive interventions (smoking cessation, blood pressure control, and weight management) would not be significantly affected by reclassification of risk (e.g., recommendations for smoking cessation are the same regardless of risk classification). Current USPSTF recommendations for statins and aspirin for primary prevention are based on the 10-year CVD risk as estimated by the PCE.[2, 17] The USPSTF recommends initiating use of low- to moderate-dose statins in adults ages 40 to 75 years without a history of CVD who have one or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD risk of 10 percent or greater (B recommendation) and selectively offering statins to adults ages 40 to 75 years without a history of CVD who have one or more CVD risk factors and a calculated 10-year risk of 7.5 percent to 10 percent (C recommendation). For aspirin, the USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and colorectal cancer in adults ages 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 (B recommendation). The USPSTF also has a C recommendation for initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults ages 60 to 69 years who have a 10 percent or greater 10-year CVD risk. The ACC and AHA jointly released guidelines (2014) recommending that moderate- to high-intensity statin therapy should be used in persons ages 40 to 75 years without a history of clinical CVD or diabetes and with an estimated 10-year risk of 7.5 percent or greater (Grade A, strong recommendation).[29] The ACC/AHA also recommended moderate-intensity statins when risk is 5 percent to less than 7.5 percent (Grade C, weak recommendation).

Recommendations and Clinical Practice in the United States

Numerous organizations recommend against routine screening of asymptomatic adults for CVD with resting or exercise ECG, including the American College of Physicians,[30] the American Academy of Family Physicians,[31] and the American College of Preventive Medicine (**Appendix A Table 1**).[32-34] Screening of special populations is recommended by some groups. For example, the American Academy of Family Physicians recommends screening otherwise low-risk patients who have certain occupations in which undetected CVD could significantly affect the public (e.g., airline pilots),[35] and the American College of Sports Medicine recommends screening moderate-risk patients who are beginning a new exercise regimen.[36]

Many risk prediction equations (i.e., tools, models, scores, calculators) are available and have been recommended in various countries for use in clinical practice to guide treatment decisions (**Appendix A Table 2**). The USPSTF and the ACC/AHA recommend using the PCE to calculate 10-year risk. The existing equations that have been externally validated vary in the risk factors included and predicted outcomes (e.g., global CVD outcomes vs. mortality vs. CHD-specific outcomes). The Framingham Risk Score (FRS) was the first widely used multivariable risk assessment tool[33, 34, 37] and included sex, age, total and high-density lipoprotein cholesterol

(HDL-C), blood pressure, diabetes, and smoking. A variety of Framingham-based risk equations have been externally validated.[27, 33, 34, 37-39] One early Framingham model (1991)[33] included left ventricular hypertrophy (LVH) (determined by ECG) along with traditional risk factors, but it was dropped from later models. None of the currently recommended prediction equations include ECG.

Despite recommendations, use of risk assessment in clinical practice may be suboptimal. For example, a survey of over 900 U.S. physicians found that although more than 80 percent agreed that risk calculation is useful, only 41 percent reported that they use it in practice.[40] Among those who use it, the majority use it to guide lipid-lowering therapy recommendations (69%) and aspirin therapy recommendations (54%).[40] Limited data are available on using ECGs to assess CVD risk in asymptomatic persons, but a population-based retrospective cohort study of Canadian adults reported that 21.5 percent had an ECG within 30 days of an annual health exam.[41] The proportion varied widely across 679 primary care practices (from 1.8% to 76.1%).

Chapter 2. Methods

Key Questions and Analytic Framework

The Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and key questions (KQs). **Figure 1** shows the analytic framework and KQs that guided the review. Three KQs were developed for this review:

1. Does the addition of screening with resting or exercise electrocardiography (ECG) improve health outcomes compared with traditional CVD risk factor assessment alone in asymptomatic adults? 1a. Does improvement in health outcomes vary for subgroups defined by baseline CVD risk (e.g., low, intermediate, or high risk), age, sex, or race/ethnicity?
2. Does the addition of screening with resting or exercise ECG to traditional CVD risk factor assessment accurately reclassify persons into different risk groups (e.g., high-, intermediate-, and low-risk groups) or improve measures of calibration and discrimination?
3. What are the harms of screening with resting or exercise ECG, including harms of subsequent procedures or interventions initiated as a result of screening? 3a. Do the harms of screening vary for subgroups defined by baseline CVD risk (e.g., low, intermediate, or high risk), age, sex, or race/ethnicity?

In addition to addressing our KQs, evidence related to two Contextual Questions was assessed. The first focused on what medications (i.e., aspirin, lipid-lowering therapy) are recommended for persons in each CVD risk category and the fidelity to prescribing and taking the recommended medications. The second focused on the harms and benefits of revascularization procedures in adults without symptoms or a prior diagnosis of CVD. These Contextual Questions were not a part of the systematic review. They are intended to provide additional background information. Literature addressing these questions is summarized in **Appendix A**.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published from January 2009 through May 30, 2017. Medical Subject Headings were used as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. The search relied primarily on the 2011 systematic review for the USPSTF[42] to identify potentially relevant studies published before 2009 (we reassessed all articles included in that systematic review using the eligibility criteria). Complete search terms and limits are listed in **Appendix B-1**. Targeted searches for unpublished literature were conducted by searching ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. To supplement electronic searches, the reference lists of pertinent review articles and studies that met the inclusion criteria were reviewed and all previously unidentified relevant articles were added. All literature suggested by peer reviewers or public comment respondents will be reviewed and eligible studies incorporated into the final review. Literature surveillance will also be conducted

through article alerts and targeted searches of high-visibility journals to identify studies published in the interim that may affect conclusions. All literature search results were managed using EndNote™ version 7.4 (Thomson Reuters, New York, NY).

Study Selection

Inclusion and exclusion criteria were developed for populations, interventions, comparators, outcomes, settings, and study designs with input from the USPSTF (**Appendix B-2**). English-language studies of adults age 18 years or older without symptoms or a diagnosis of CVD were included. Studies of children, adolescents, and persons with a history of CVD or symptoms suggesting CVD were excluded. Studies assessing resting ECG or exercise ECG were included and studies that assessed radiology tests, echocardiography, and vectorcardiography were excluded. Eligible studies recruited participants from primary care settings, occupational medicine settings, or the general population in countries categorized as "very high" on the Human Development Index.

For all KQs, controlled clinical trials and randomized, controlled trials (RCTs) comparing groups that were screened with groups that were not screened (i.e., comparing risk stratification using ECG plus traditional risk factors vs. risk stratification using traditional risk factors alone) were eligible. For KQ 1 (direct evidence that screening improves health outcomes), eligible outcomes included all-cause mortality, CV mortality, and CV events (MI, angina, stroke, congestive heart failure, composite CV outcomes).

For KQ 2 (calibration, discrimination, and reclassification), prospective cohort studies comparing CVD risk assessment models that included ECG findings with those that did not include ECG findings were also eligible. Studies were required to report reclassification (ability to correctly reassign persons into clinically meaningful risk categories), calibration (agreement between observed and predicted outcomes), or discrimination (ability to distinguish between persons who will vs. will not have an event). Detailed descriptions of the specific test performance measures are provided in **Table 1**. These measures assess performance of risk prediction models or the comparative performance of models. Studies that only assessed the association between ECG findings and outcomes (e.g., with adjusted hazard ratios) were excluded. The review focused on the benefits and harms of adding ECG to the current standard practice of CVD risk prediction using traditional risk factors: male sex, older age, cigarette smoking, hypertension, dyslipidemia (high total cholesterol, high low-density lipoprotein cholesterol, or low HDL-C), and diabetes. In current clinical practice, the PCE or FRS is typically used for risk prediction. Studies were not required to specifically use the PCE or FRS to be eligible, although such studies have greatest applicability to current practice. Eligible base models included age, sex, systolic blood pressure, antihypertensive medication use, total cholesterol, HDL, and current smoking or restricted samples to remove some of these variables. Models were not required to include diabetes or race/ethnicity, but models were eligible that included them. Comparisons that would not allow us to isolate the effect attributable to ECG were not eligible.

For KQ 3 (harms), prospective cohort studies, large retrospective cohort studies, and well-

designed case-control studies (only for rare events) were also eligible. Eligible harms included mortality, arrhythmia, CV events, or injuries from exercise ECG; anxiety; labeling; and harms of subsequent procedures or interventions initiated as a result of screening (e.g., subsequent angiography or revascularization procedures resulting in harm). For harms of subsequent procedures/interventions, studies that compare the procedure/intervention with no procedure/intervention were also eligible. For studies reporting rates of harms from exercise ECG or subsequent procedures/interventions, large registries or multicenter studies without a control group that report rates of harms for asymptomatic persons were also eligible.

Two investigators independently reviewed titles and abstracts; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. Two investigators independently reviewed the full text to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

The quality of trials and cohort studies was assessed as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B-3**). For risk prediction studies (KQ 2), predefined criteria from the Checklist for Critical Appraisal and Data Extraction for Systematic Review of Prediction Modelling Studies (CHARMS)[43] were used and adapted for this topic (**Appendix B-3**). Two independent investigators assigned quality ratings for each study. Disagreements were resolved by discussion. Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. A second team member reviewed all data extractions for completeness and accuracy.

Data Synthesis and Analysis

Findings for each KQ were qualitatively synthesized by summarizing the characteristics and results of included studies in tables, figures, and narrative format. To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed following established guidance.[44] The populations, tests, treatments, comparators, outcomes, and study designs were assessed qualitatively, looking for similarities and differences. At least three similar studies had to be available to estimate pooled effects. For KQ 1, pooled effects were not estimated because fewer than three similar studies were found, but risk ratios and 95 percent confidence intervals were calculated for binary outcomes reported by the included RCTs and a forest plot showing the results was created. For KQ 2, considerable heterogeneity of ECG findings assessed, base prediction models used, outcomes (e.g., all-cause mortality, CV mortality, CVD events, fatal ischemic heart disease), and duration of followup was found; therefore, the results are presented in tabular format and in figures. Results were stratified by ECG findings evaluated, separating results for exercise ECG and resting ECG. Within the studies of resting ECG results were stratified to separate those that evaluated the addition of a

constellation of ECG abnormalities from those that evaluated single/specific ECG changes. Results were categorized by the base models used as "published coefficient models," meaning the model preserved the coefficients of original published models that have been externally validated (e.g., FRS or PCE), or as "model development." For KQ 2, the C-statistic (Harrell's C) and AUC were used as the primary measures of discrimination and were summarized together. Measures of overall performance were summarized with those of calibration. Net reclassification improvement (NRI) was the primary measure of reclassification, with event and nonevent NRIs reported separately when possible. To describe the magnitude of changes in discrimination and reclassification, a range of 0.001 to 0.009 was considered to be very small, a range of 0.01 to 0.09 was considered to be small, and a range of 0.1 to 0.9 was considered to be moderate. Analyses were conducted and figures were produced using Stata version 14 (StataCorp) and Microsoft Excel.

Two independent reviewers assessed the overall strength of the body of evidence for each KQ as high, moderate, low, or insufficient using methods developed for the USPSTF (based on methods of the EPC program[45, 46]), based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias. The applicability of the findings to U.S. primary care populations and settings was also assessed. Discrepancies were resolved through consensus discussion.

Expert Review and Public Comment

A draft report was reviewed by content experts, representatives of federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments, as appropriate. It will also be posted for public comment.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and members of the USPSTF participated in developing the scope of work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

In total, 4,595 unique records were identified and 524 full texts assessed for eligibility (**Figure 2**). In total, 507 articles were excluded for various reasons detailed in **Appendix C**, and 16 studies (described in 17 articles) of good or fair quality were included. Of the included studies, two were studies of the benefits of ECG screening (KQ 1); 14 were studies of reclassification, calibration, or discrimination; and one study was of harms of ECG screening (KQ 3, which was also included for KQ 1). Compared with the previous evidence review for the USPSTF,[42] the current review includes three studies[47-49] that were in both reviews and 13 studies that are only in the current review. The previous review included many additional studies reporting associations (e.g., adjusted hazard ratios) between ECG findings and outcomes that were not eligible for this review because they did not report discrimination, calibration, or reclassification. It also included two studies related to harms of exercise ECG that were not eligible for the current review (one was an uncontrolled single center report of military officers getting stress tests;[50] the other described survey data on harms, focusing on symptomatic participants[51]); both studies are described in the discussion of this report. Details of quality assessments of included studies and studies excluded because of poor quality are provided in **Appendix D**.

Results

KQ 1. Does the Addition of Screening With Resting or Exercise ECG Improve Health Outcomes Compared With Traditional CVD Risk Factor Assessment Alone in Asymptomatic Adults? KQ 1a. Does Improvement in Health Outcomes Vary for Subgroups Defined by Baseline CVD Risk, Age, Sex, or Race/Ethnicity?

Summary

No eligible studies compared screening with resting ECG and no screening, and none evaluated the use of screening with ECG for the purpose of risk reclassification to inform decisions about preventive medications. Two RCTs (DYNAMIT and DADDY-D) with a total of 1,151 participants evaluated screening with exercise ECG in high risk, asymptomatic adults ages 50 to 75 years with diabetes. Both RCTs reported no statistically significant improvement in health outcomes, but were limited by not reaching sample size targets.

Detailed Results: Characteristics of Included Trials

We included two fair-quality RCTs: Do You Need to Assess Myocardial Ischemia in Type-2 diabetes (DYNAMIT)[52] and Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients (DADDY-D).[53] The characteristics of the included studies are summarized in **Table 2**. Both trials compared screening with exercise ECG with no screening exercise ECG.

The DYNAMIT study was a multicenter randomized trial that randomized 631 ambulatory patients who consulted a diabetes specialist to screening versus no screening.[52] Those in the screening arm were referred for detection of silent ischemia using a bicycle exercise test or Dipyridamole Single Photon Emission Computed Tomography (SPECT). SPECT was used in patients unable to perform the exercise test, with a submaximal negative exercise test, or with ECG abnormalities impairing the interpretation of the exercise test (31% ultimately had SPECT). Those with positive exercise or SPECT tests were referred to cardiologists, and all subsequent investigations and treatments were left to the judgment of the cardiologists (i.e., no protocol for that part of the process related to angiography vs. no angiography; pragmatic approach). The DADDY-D trial randomized 520 participants from a single center (2 diabetes outpatient clinics) to screening or no screening.[53] Participants were required to have a normal ECG to get into the study. Those in the screening arm underwent maximal symptom-limited exercise treadmill test (ETT). Submaximal tests were considered not diagnostic and did not lead to any further investigations. Coronary angiography was proposed to all patients with positive ETTs, and choices to perform stenting or surgery were reportedly determined according to the European Guidelines by two interventional cardiologists and a cardiac surgeon after reviewing coronary anatomy.

DYNAMIT was conducted in France, and the DADDY-D trial was conducted in Italy. Mean duration of followup for both trials was 3.5 to 3.6 years. Both enrolled ambulatory patients with a clinical diagnosis of type 2 diabetes. Mean hemoglobin A1cs were 8.6 (DYNAMIT) and 7.7 (DADDY-D), respectively. DYNAMIT enrolled patients ages 55 to 75 years; mean age was 64. DADDY-D enrolled patients ages 50 to 70 years; mean age was 62. Less than half of the participants (20–45%) were women in both trials. Neither trial reported information about race or ethnicity of participants. DADDY-D did not report baseline prevalence of hypertension (but 74% were on antihypertensive medications) or PAD; they were 89 percent and 14 percent for DYNAMIT, respectively. The prevalence of heart failure in both trials was less than 1 percent. Less than half of the participants (17–39%) in both trials were smokers.

Both trials were rated as fair quality. Neither trial reached the sample size targets. DYNAMIT was stopped early because of trouble recruiting and a lower than expected event rate (it randomized 631 of the planned 3,000). DADDY-D aimed for 364 per group but enrolled about 260 per group; because the target number of participants could not be achieved, the followup period was extended from two years to 3.5 years for those who had been enrolled (the authors reported a power of 77%). For DADDY-D, masking of outcome assessors was not reported and amount of attrition was unclear.

Results of Included Trials

The main results are shown in **Figure 3** and **Appendix E Table 1**. Overall, neither study found a statistically significant reduction in any category of events for screening compared with no screening, including their primary composite outcomes, all-cause mortality, CV-related mortality, MI, heart failure, or stroke, although findings were imprecise.

In the DYNAMIT trial, 28 participants in the screening group and 26 in the unscreened arm experienced at least one primary endpoint (composite of death from all causes, nonfatal MI,

nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention) (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.59 to 1.71). In the same trial, 13 in the screening arm and 15 in the unscreened arm experienced coronary events (fatal or nonfatal MI, hospitalized unstable angina, or heart failure requiring hospitalization or emergency service intervention) (HR, 0.77; 95% CI, 0.37 to 1.63). In the DADDY-D trial, 12 in the screened arm and 14 in the unscreened arm experienced a primary outcome, cardiac events defined as a composite of nonfatal MI or cardiac death (HR, 0.85; 95% CI, 0.39 to 1.84).

Subgroup analyses were performed by gender, age, and CV risk for multiple outcomes in the DADDY-D trial. No statistically significant differences were found between groups based on gender, age, or CV risk for the primary outcome of cardiac events. For heart failure, no significant differences were found between those screened and those not screened based on gender, age, or having a CV risk $\geq$20, but a difference was found for those with a CV risk <20 (0 vs. 5 events, p=0.022). For cardiac death, no significant differences were found between those screened and those not screened based on gender, CV risk, or being less than 60 years of age, but a difference was found for those $\geq$60 years of age. Fewer cardiac deaths were reported for those older than 60 years who were screened than those who were not screened (0 vs. 4 events, p=0.044). No significant differences were found between those screened and not screened based on gender, age, or CV risk for nonfatal MI. The study did not report interaction tests for the subgroup analyses, no adjustments were made for multiple testing, and it is unclear whether the subgroup analyses were planned a priori. The positive subgroup analysis findings are likely due to chance.

KQ 2. Does the Addition of Screening With Resting or Exercise ECG to Traditional CVD Risk Factor Assessment Accurately Reclassify Persons Into Different Risk Groups or Improve Measures of Calibration and Discrimination?

Summary

Fourteen good- or fair-quality studies were included.[47] Five evaluated exercise ECG[47, 48, 54-56] and nine evaluated resting ECG.[49, 57-64] Of those nine, five evaluated multiple ECG changes (a group of major and minor changes)[49, 57-60] and four evaluated only single ECG changes.[61-64] Of the studies evaluating exercise ECG, three used published coefficient base models (2 FRS and 1 SCORE).[47, 48, 55] Of the studies evaluating resting ECG, five reported some analyses using published coefficient base models (5 FRS; 1 also used PCE).[49, 57-59, 63]

For exercise ECG, although evidence from five cohort studies (9,582 participants) shows that the addition of exercise ECG abnormalities to traditional CVD risk factors results in small improvements in discrimination (absolute improvement in AUC or C-statistics 0.02 to 0.03), it is uncertain whether calibration or appropriate risk classification improves. For resting ECG, evidence from nine cohort studies (66,407 participants) shows that the addition of ECG findings to traditional CVD risk factors results in very small or small improvements in discrimination (absolute improvement in AUC or C-statistics 0.001 to 0.05) and improvements for calibration and appropriate risk classification for prediction of multiple outcomes (e.g., all-cause mortality,

CVD mortality, CHD events, or CVD events), but evidence was limited by imprecision, quality, considerable heterogeneity, and the risk categories evaluated.

Characteristics of Studies Evaluating Exercise ECG

Five cohort studies evaluated whether adding exercise ECG to traditional CVD risk prediction could improve discrimination, calibration, or risk reclassification (**Tables 3 and 4**).[47, 48, 54-56] The studies evaluated a total of 9,582 participants. Sample sizes ranged from 988[54] to 3,554.[47] One enrolled participants in the 1970s;[56] the other four enrolled participants in the 1990s. Two studies were conducted in the United States,[47, 54] two in France,[48, 55] and one in Norway.[56] Mean duration of followup ranged from 6 to 8 years in four studies; one had 26 years of followup.[56] The five studies used data from five different cohorts (although the 2 studies from France may have some overlap in a subset of the participants). For the base model, two used the FRS (with published coefficients of the original model),[48, 55] one used the European SCORE (with published coefficients),[47] one model development study used FRS variables,[54] and one model development study used some of the traditional risk factors (age, total cholesterol, systolic blood pressure, and smoking status) and restricted its sample to eliminate other risk factors (excluded women, those with prevalent diabetes, and those on blood pressure-lowering therapy at baseline) but did not account for HDL.[56]

All were prospective cohorts with participants from cardiology or prevention centers in urban hospitals. Participants were self-referred or referred by providers to a preventive cardiology unit in two studies,[48, 55] participants presented for executive physicals in one study,[47] participants were a subset of those from a study evaluating coronary artery calcium and SPECT in one study,[54] and participants were recruited from five governmental agencies in one study.[56] Four of the studies reported that all participants were asymptomatic. One study reported that 16.5 percent of participants had atypical chest pain symptoms and that the participants were a subset of persons having both coronary artery calcium score (CACS) and SPECT for "clinically indicated reasons";[54] it is unclear what proportion of participants were truly asymptomatic and what the clinically indicated reasons for testing were. The mean age of participants ranged from 50 to 58 years. Most participants in all trials were men, with the proportion of female participants ranging from 0 to 38 percent. Four studies did not report information about race/ethnicity; one reported that 2 percent of participants were nonwhite.[47] The baseline prevalence of hypertension and diabetes ranged from 0 to 55 percent and 0 to 11 percent, respectively. The percentage of smokers ranged from 10 to 47 percent. Mean baseline FRS score was 10.8 to 12.3 in studies reporting it.[48, 54, 55]

Study end points included all-cause mortality,[47] coronary events (cardiac deaths, sudden deaths, acute MI, and stable or unstable angina),[48, 55] cardiac events (cardiac death, nonfatal MI, and the need for coronary revascularization following the development of symptomatic CAD),[54] and CHD mortality (deaths caused by ischemic heart disease and sudden, unexpected deaths).[56]

All five of the included studies received fair-quality ratings (**Appendix D**). The most common methodological concerns were not reporting CIs for calibration or discrimination (5/5), not reporting measures of reclassification (4/5), selective inclusion of participants in the model based on data availability (4/5), unknown masking of outcome assessors (4/5), unknown if predictors

were assessed masked for the outcome (4/5), not reporting both discrimination and calibration (3/5), unclear handling and amount of missing data (2/5), uncertain validity and reliability of method used for measuring outcomes (2/5), using base model equations that have not been externally validated (i.e., model development studies) (2/5), and mean duration of followup less than 10 years (4/5), despite the risk prediction being focused on 10 years. The study with the longest followup (26 years) did not account for one of the traditional risk factors (HDL).[56] In addition, the only study reporting reclassification did not use the risk categories commonly used in current practice for making treatment decisions (it used <6% vs. 6 to 20% vs. >20%) and may have included many symptomatic participants (16.5% had atypical chest pain and participants were a subset of those having CACS and SPECT for "clinically indicated reasons").[54]

Results of Studies Evaluating Exercise ECG

For the comparison of interest to this review, one model development study reported reclassification,[54] four reported calibration,[48, 54-56] and three reported discrimination.[47, 54, 55] Results of the included studies are shown in **Table 5** and **Figures 4**–**7**. The frequency of abnormal exercise tests across included studies ranged from 6.4 to 16.7 percent (**Appendix E Table 3**).

Discrimination

Three studies reported discrimination for the addition of exercise ECG variables to traditional risk factors;[47, 54, 55] one of the three used FRS with published coefficients for the base model[55] and two were model development studies. Main results are shown in **Figures 4** and **5**, illustrating the AUC or C-statistic for the base model (black squares in the figures) and the AUC or C-statistic for the base model plus exercise ECG (white squares in the figures). Figure 4 is limited to the studies that used FRS or PCE with published coefficients for the base model whereas Figure 5 also shows model development studies. In addition to the AUC or C-statistic results, the columns of the figures show the outcome, ECG findings evaluated, base model used, sample size, and number of participants with an event. All three studies reported small absolute improvements in AUC or C-statistics (0.02 to 0.03), and none of them reported CIs for the discrimination data. One of the three reported a p-value indicating no statistically significant difference between a model with exercise testing variables and the base model with FRS variables (p=0.3).[54]

Calibration or Overall Performance

Four studies reported calibration or overall performance of models that added exercise ECG results to traditional risk factors (**Table 5**).[48, 54-56] Two of the studies used the FRS (with published coefficients) in base models[48, 55] and two were model development studies.[54, 56] None of the studies reported figures such as calibration plots, but one provided a table of predicted and observed events for quintiles of risk.[56] All four studies reported different measures: likelihood ratio test;[48] Akaike information criteria (AIC), Brier's score, and Hosmer-Lemeshow χ^2;[55] global χ^2;[54] and numbers of predicted and observed events.[56]

The two studies that used the FRS were both conducted in France and focused on prediction of

coronary events.[48, 55] One study (1,051 participants) reported that model performance was not improved for the full sample with the addition of symptom-limited exercise ECG to the model (p=0.13).[48] For the subgroup with pretest Framingham risk of 10.4 percent or greater, the authors reported a statistically significant improvement for adding exercise ECG to some base models, but not when the base model was FRS (n=526, p=0.06). The other study (2,709 participants) reported improved goodness of fit with the addition of exercise ECG, indicated by lower AIC (748.9 vs. 727.8) and Brier's score (0.035 vs. 0.033); the Hosmer-Lemeshow test showed no difference between the models (p, 0.99 vs. 0.99).[55]

Two studies developed new models rather than using published coefficients of existing models (e.g., FRS and PCE). The study described below under Risk Reclassification (Chang et al, 2015[54]) reported better calibration for the model that included exercise testing results than for the base model (global chi-square 16.16 vs. 11.72, p=0.04).[54] The study conducted in Norway (2,014 participants) reported numbers of predicted and observed events for models with and without exercise testing (**Table 5**).[56] Although both models (with and without exercise testing) show steep and similar gradients in age-adjusted CHD mortality (indicating good calibration), the model with exercise testing showed a slightly steeper gradient across quintiles of risk, with slightly better correspondence of predicted and observed events.

Risk Reclassification

One study (Chang et al, 2015[54]; 988 participants) reported on the reclassification from adding exercise ECG to traditional CVD risk factor assessment for predicting cardiac events.[54] It did not use the current common clinical thresholds to reclassify risk; instead, it used categories defined by 10-year risk of <6 percent, 6 to 20 percent, and >20 percent. For the base model, the authors were not able to calculate the FRS as published because blood pressure and cholesterol measurements were not available (so these predictors were dichotomized based on history of hyperlipidemia and hypertension). Therefore, it was considered a model development study with FRS variables in the base model (i.e., rather than a study using the externally validated FRS coefficients in the base model). The study found that adding the presence or absence of stress-induced ischemia detected during symptom-limited exercise treadmill testing to the base model increased the total NRI in subjects overall (9.6%; p=0.007) and in the intermediate risk group (18.9%; p=0.01). It did not report event NRI and nonevent NRI. The study also reported absolute and relative integrated discrimination improvement (IDI). For all patients, the IDI was small but statistically significant (absolute IDI, 1.4%, p=0.006; relative IDI, 110%, p<0.0001). The IDI was also improved significantly for the intermediate risk category (absolute IDI%, 1.7 [p=0.01]; relative IDI, 92% [p=0.004]). The study authors also reported on calibration, finding better calibration for the model that included exercise testing results than for the base model (global chi-square 16.16 vs. 11.72, p=0.04). However, adding exercise testing variables to the base model did not significantly improve discrimination (change in AUC, 0.02, p=0.3).

Characteristics of Studies Evaluating Resting ECG

Nine studies of resting ECG met inclusion criteria (**Tables 6** and **7**).[49, 57-64] Eight were cohort studies and one used data from an RCT.[49] Five evaluated multiple ECG changes: either a constellation of major and minor ECG changes based on the Minnesota code or an ECG risk

equation (that included multiple ECG changes).[49, 57-60] Four only evaluated single ECG changes.[61-64] Some studies that evaluated multiple ECG changes also reported findings for single/specific ECG changes. Three studies reported results from the National Health and Nutrition Examination Survey (NHANES),[57, 59, 63] two studies reported results from the Atherosclerosis Risk in Community study,[62, 64] and the remaining studies reported results from the Health, Aging, Body Composition Study,[58] the Women's Health Initiative,[49] the Jichi Medical School Cohort,[61] and the Copenhagen City Heart Study.[60] Excluding double-counted populations, the studies evaluated a total of 68,475 subjects. Sample sizes ranged from 1,264[49] to 15,375.[62] One study enrolled participants in the 1970s;[60] seven enrolled participants in the late 1980s and/or the 1990s, and one used a derivation cohort from the 1970s and a validation cohort from the 1980s and 1990s.[59] Seven studies were conducted in the United States, one in Japan,[61] and one in Denmark.[60] Duration of followup ranged from 6[49] to 19 years.[59]

For the base model, three studies used the FRS (with published coefficients of the original model),[49, 57, 63] one used the FRS and the PCE (with published coefficients; it also included model development analyses using FRS variables),[59] one focused on model development (with traditional risk factors) but also used FRS (with published coefficients) in some secondary analyses,[58] and four were model development studies using FRS variables (one of those also included alcohol intake and heart rate[61]).[60-62, 64]

All were population-based studies. Overall, the studies provided little or no information about any evaluation of whether participants had symptoms at baseline. It is unclear what proportion of participants were truly asymptomatic. One study reported excluding those with angina or claudication.[57] Another study included participants with symptoms of angina or claudication, counting them among the 5 percent with prevalent CHD enrolled in the study.[62] The studies either excluded those with a history of CVD or enrolled a small percentage of persons with a history of CVD. The mean age of participants ranged from 54 to 73 years. The majority of participants in all studies were women and one study enrolled only women.[49] Three studies did not report information about race/ethnicity; the range of nonwhite participants in those that did report race/ethnicity was 9 to 41 percent. The baseline prevalence of diabetes ranged from 0 to 13 percent. The percentage of smokers ranged from 22 to 54 percent. Mean baseline CVD risk was not reported by most studies.

Study end points included all-cause mortality,[57, 59, 60] CV mortality,[57, 59, 60, 63] CHD events,[49, 58, 60, 64] stroke events,[61] CVD events,[49, 60] sudden cardiac death,[62] and ischemic heart disease mortality.[59]

One study was rated as good quality,[58] and the others were rated as fair (**Appendix D**). The most common methodological concerns were selective inclusion of participants in the model based on data availability (9/9), unknown masking of outcome assessors (8/9), unknown if predictors were assessed masked for the outcome (7/9), not reporting CIs for either calibration or discrimination (5/9), not reporting calibration (5/9), using base model equations that have not been externally validated (i.e., model development studies) (4/9),[58, 60, 61, 64] not reporting the amount of missing data (2/9), and mean duration of followup less than 10 years (2/9).[49, 58] In addition, of the studies reporting reclassification, just three included a threshold between risk categories corresponding to the current USPSTF recommendations for initiating preventive medications (i.e., 7.5% or 10%

10-year risk).[57-59] Of the three, one reported using cut points between categories of 1, 5, and 10 percent;[59] one used <5, 5 to 9.9, 10 to 19.9, and 20 or greater;[57] and one used <7.5 percent, 7.5 percent to 15 percent, and >15 percent.[58] The study that used cut points of 1, 5 and 10 percent cited the European Society of Cardiology recommendations (from 2012) for lipid management as the rationale for the chosen cut points; those recommendations are based on SCORE (which predicts CVD death), and the recommendations describe that a 5 percent SCORE risk of CVD death equates to a 10 to 25 percent 10-year FRS risk of total CVD, depending on which of the several Framingham models is chosen.[65] One study based NRI cut points for risk categories on the distribution of the data rather than using a priori cut points.[60] One study included alcohol use and heart rate in addition to traditional risk factors in its base model.[61]

Among the five studies that evaluated multiple ECG changes, the most common methodological concerns (**Appendix D**) were selective inclusion of participants in the model based on data availability (5/5), unknown masking of outcome assessors (4/5), unknown if predictors were assessed masked for the outcome (4/5), not reporting CIs for either calibration or discrimination (3/5), not reporting the amount of missing data (2/5), not reporting calibration (2/5), using base model equations that have not been externally validated (i.e., model development studies) (2/5),[58, 60] and mean duration of followup less than 10 years (2/5).[49, 58] In addition, two studies reporting reclassification did not use the risk categories commonly used in current practice in the United States for making treatment decisions.[59, 60] One study based NRI cut points for risk categories based on the distribution of the data rather than using a priori cut points.[60]

Results of Studies Evaluating Resting ECG: Multiple ECG Changes

Five studies evaluated the effect of adding major or minor ECG abnormalities or an ECG risk equation (that included multiple ECG abnormalities) to traditional risk factors.[49, 57-60] Four of the five evaluated the incremental improvement of adding major or minor ECG abnormalities to the FRS or PCE (with published coefficients) for some of the outcomes reported.[49, 57-59] Three studies evaluated CHD events,[49, 58, 60] two studies evaluated CVD events,[49, 60] three studies evaluated CVD mortality,[57, 59, 60] three studies evaluated all-cause mortality,[57, 59, 60] and one evaluated ischemic heart disease mortality.[59] The frequency of ECG abnormalities across these studies ranged from 31 to 55 percent (**Appendix E Table 4**).

Discrimination

All five studies reported discrimination for the addition of ECG variables to traditional risk factors. Three of the five reported it using FRS or PCE with published coefficients.[49, 57, 59] Main results are shown in **Figure 4** and **Figure 5**, illustrating the AUC or C-statistic for the base model (black squares in the figures) and the AUC or C-statistic for the base model plus ECG changes (white squares in the figures). **Figure 4** is limited to the studies that used FRS or PCE with published coefficients for the base model whereas **Figure 5** also shows model development studies. In addition to the AUC or C-statistic results, the columns of the figures show the outcome, ECG findings evaluated, base model used, sample size, and number of participants with an event. All five studies reported very small (0.001)[57] to small (0.01 to 0.05) absolute improvements in AUC or C-statistics. Two studies reported p-values, with one study indicating statistically significant differences between models with ECG abnormalities and a base model

with conventional risk factors for outcomes of fatal CVD and combined fatal and nonfatal CVD ($p<0.001$);[60] the other study approached statistical significance ($p=0.05$).[57]

Calibration or Overall Performance

Three studies reported calibration or overall performance of models that added multiple changes from resting ECG to traditional risk factors (**Appendix E Table 2**).[49, 57, 58] Two of the studies used the FRS (with published coefficients) in base models,[49, 57] and one was a model development study (it reported reclassification for the addition of ECG variables to FRS, but only reported calibration for a model with ECG and FRS variables).[58] None of the studies reported figures such as calibration plots. The measures reported included likelihood ratio $\chi 2$ test,[49, 58] Hosmer-Lemeshow $\chi 2$,[57, 58] and Bayes information criterion (BIC).[57]

The two studies that used the FRS were both conducted in the United States and focused on prediction of CV mortality[57] or CHD events and CVD events.[49] One study (6,025 participants) using NHANES data reported that the addition of major and minor ECG changes improved calibration and performance for predicting CV mortality (Hosmer-Lemeshow χ^2 decreased from 15.14 to 10.98, p-values 0.05 and 0.2, respectively; BIC decreased from 3,360.54 to 3,358.28).[57] The other study (1,264 participants) reported that the addition of major and minor ECG abnormalities to FRS improved model performance for predicting both CHD and CVD events (likelihood ratio chi square test: $p=0.004$ and $p=0.02$, respectively).

The one model development study that reported calibration for a model with ECG and FRS variables was conducted in the United States and used the Health ABC Study cohort of 2,192 adults ages 70 to 79 years.[58] The study reported that a model with traditional risk factors (FRS variables) did not show a good calibration and was not improved by the addition of ECG abnormalities (Hosmer-Lemeshow χ^2 increased with the addition of ECG abnormalities from 67.6 to 87.9, likelihood ratio $p<0.00005$, goodness of fit p-values 0.03 for FRS variables vs. 0.01 for FRS variables plus ECG).[58]

Risk Reclassification

Four of the five studies evaluating multiple ECG changes reported results on reclassification when adding resting ECG to traditional risk factors (**Appendix E Table 2** and **Figures 6** and **7**).[57-60] **Figures 6** and **7** show the NRI results, with black squares indicating the total NRI (sum of the event NRI and nonevent NRI), gray squares indicating the event NRI (net upward reclassification among persons who had an event), and white squares representing nonevent NRI (net downward reclassification among persons who did not have an event). For some studies, only the total NRI (black square) is provided because the data for event and nonevent NRI were not reported. Figure 6 shows model development studies and studies that used FRS or PCE with published coefficients for the base model, whereas Figure 7 is limited to studies that used FRS or PCE with published coefficients for the base model. In addition to the NRI results, the columns of the figures show the outcome, ECG findings evaluated, base model used, sample size, number of participants with an event, and the risk categories used for analyses. Three of the studies used the FRS (with published coefficients) in base models,[57-59] one also used PCE (with published coefficients) and a model with FRS variables (not using published coefficients),[59] and one was a

model development study.[60] All four studies reported NRI and all but one[60] provided event NRI or nonevent NRI data (or the table to allow us to calculate it) for some models. Two studies reported IDI (**Appendix E Table 2**).[58, 59]

For studies using published coefficient models, **Figure 7** shows the net reclassification results. Three studies reported outcomes of reclassification and IDI. One study of adults in the NHANES population used four risk categories (<5%, 5 to 10%, 10 to 20%, and >20%) to calculate reclassification indices.[57] Investigators reported an overall NRI of 3.6 percent, where the NRI for those with events was 3 percent and the NRI for those without events was 0.6 percent, indicating a net appropriate reclassification of those with CVD mortality upward into higher risk categories. This study also reported a clinical NRI for intermediate risk patients of 13.6 percent, although this estimate was not corrected for bias.[66] The absolute value of the IDI was low, although statistically significant. (0.0001, p<0.001). A study of older adults in the Healthy Aging and Body Composition (Healthy ABC) study also reported an improved overall NRI and IDI when ECG abnormalities were added to FRS (NRI 5.7% [95% CI, -0.4 to 11.6], IDI, 1.03% [95% CI, 0.56% to 1.50%]), although specific NRIs for events and nonevents were not provided for the comparison with FRS.[58] The third study evaluated the addition of an ECG risk equation (that included frontal T axis, QT interval, and heart rate) to FRS, PCE, or a model with traditional risk factors.[59] It used NHANES I data to derive the risk equation and validated the model with NHANES III.[59] The clinical risk thresholds were based on the European Society of Cardiology (1%, 5%, and 10%). Adding the ECG risk equation to the FRS, PCE, or conventional risk factors resulted in improved classification. Categorical NRIs ranged from 4 to 30 percent, and continuous NRI ranged from 33 to 57 percent. Absolute IDI ranged from 0.2 to 2.6 percent, and relative IDIs ranged from 7 percent to 47 percent.

Three model development studies examined improvement in CV risk prediction when any ECG abnormality was added to conventional CV risk factors, which included diabetes in addition to the risk factors of the FRS variables.[58-60] Two of them also evaluated published coefficient models (FRS or PCE) as described in the previous paragraph.[58, 59] Two studies were conducted in older adult populations with mean age ranging from 70 to 74 years. The Healthy ABC study looked at the outcome of CHD,[58] while a study of the Copenhagen City Heart Study examined outcomes of fatal CVD events, fatal and nonfatal CVD events, and all-cause mortality.[60] The third study used NHANES cohorts to evaluate the addition of an ECG risk score to several base models.[59] All three studies reported improvements in discrimination and reclassification for all outcomes examined.

The models using the Healthy ABC cohort reported an NRI for those with events of -0.9 percent, indicating inappropriate reclassification of patients with CHD events to lower risk categories. The NRI for persons without events was 8.3 percent, indicating appropriate reclassification of patients without CHD events to lower risk categories. The study authors reported on reclassification of intermediate risk participants using an unadjusted and adjusted clinical NRI (13.6% and 6.7%, respectively). The Copenhagen City Heart Study reported improved categorical NRIs and continuous NRIs, although event and nonevent component NRIs were not reported for the former (**Appendix E Table 2** and **Figure 6**).[60] The study that evaluated the addition of an ECG risk equation (that included frontal T axis, QT interval, heart rate, age, and sex) to a model with traditional risk factors used NHANES I data to derive the risk equation and

validated the model with NHANES III.[59] The clinical risk thresholds were based on the European Society of Cardiology (1%, 5%, and 10%). Adding the ECG risk equation to conventional risk factors resulted in improved classification. Categorical NRIs ranged from 4 percent (for fatal ischemic heart disease) to 11 percent (for all-cause mortality), with reclassification to higher categories for persons with events accounting for most of the total NRI (i.e., event NRIs were greater than nonevent NRIs).

Results of Studies Evaluating Resting ECG: Single ECG Changes

Five studies evaluated the effect of adding a single ECG abnormality to traditional risk factors. Studies evaluated a range of outcomes including CVD events,[60] CHD events,[64] stroke,[61] CVD mortality,[60, 63] sudden cardiac death,[62] and all-cause mortality.[60] Three studies evaluated T wave changes and other ventricular repolarization abnormalities, three studies examined LVH, and the remaining two studies looked at a variety of ECG changes. The frequency of ECG abnormalities across the studies that evaluated single ECG changes ranged from 1 to 24 percent (**Appendix E Table 4**).

T Wave Changes and Other Ventricular Repolarization Abnormalities

One study using NHANES III data examined the effect of adding observed T wave amplitude greater than -0.2 mV in lead aVR to the FRS on risk prediction of CV mortality.[63] Investigators observed an improvement in discrimination (C-statistic 0.812 to 0.820), good calibration, and overall categorical NRI of 0.07 using clinical risk categories of <5 percent, 5 to 10 percent, 10 to 20 percent, and >20 percent. Net reclassification of subjects with events was 2.7 percent, and net reclassification of subjects without events was 2.3 percent, indicating participants were appropriately reclassified to higher or lower risk categories. IDI was reported as 0.012 ($p<0.01$).

The Copenhagen City Heart study examined the addition of any T wave changes or ventricular conduction delay (VCD) to conventional CV risk factors. For both repolarization abnormalities, the C-statistic improved from 0.705 to 0.716 (T wave) or 0.706 (VCD) for the outcome of fatal CVD events. For the combined outcome of nonfatal and fatal CVD events, discrimination improved from 0.651 to 0.658 for any T wave abnormality, but there was no change for VCD. Calibration results were not reported. Different risk thresholds were used for outcomes of fatal CVD events and fatal and nonfatal CVD events (**Appendix E Table 2** and **Figure 6**) when calculating categorical NRIs, and separate event and nonevent NRIs were not reported. Adding T wave changes to conventional risk factors resulted in an overall continuous NRI of 29.2 percent and a categorical NRI of 5.4 percent for fatal CVD events and 20.3 percent and 2.7 percent for fatal and nonfatal CVD events, respectively. Addition of VCD to conventional risk factors resulted in small but significant NRIs for fatal CVD events (overall continuous NRI of 12.1% and categorical NRI of 1.1%) but nonsignificant or no change for fatal and nonfatal CVD events.

Finally, prolonged QTc interval was added to conventional risk factors to participants in the Jichi Medical School Cohort. Discrimination and calibration results were not reported. Adding prolonged QTc to conventional risk factors resulted in a categorical NRI of 0.026 (event NRI, 1.35%; nonevent NRI, 1.22%) and nonsignificant IDI (0.291; $p=0.80$).[61]

Left Ventricular Hypertrophy

Three studies added LVH to conventional risk factors.[60, 61, 64] In the Copenhagen City Heart study, the addition of LVH to conventional risk factors resulted in increased discrimination of fatal CVD events and continuous and categorical NRIs of 2.8 and 1.1 percent, respectively.[60] There was no improvement in discrimination or significant NRI findings for fatal or nonfatal CVD events. Calibration and IDI results were not reported for this study. In a study of the Atherosclerosis Risk in Communities (ARIC) cohort, LVH was examined as a continuous measure using the Cornell score, as well as a categorical variable, by gender and diabetes subgroups.[64] For women, adding continuous or categorical LVH ECG findings to conventional risk factors worsened discrimination of CHD events (0.707 and 0.709, respectively vs 0.711) among those with diabetes and did not change discrimination in those without diabetes (0.777 for all models). For men, there was no or minimal improvement in discrimination. Calibration, reclassification, and IDI outcomes were not reported. The Jichi Medical School Cohort did not report discrimination or calibration outcomes but did report a categorical NRI of 0.020 (event NRI, 1.01%; nonevent NRI, 1.01%) and IDI of 0.004 (p=0.75) for a model that included LVH.[61]

Other ECG Changes

The remaining studies evaluated different individual ECG changes combined with conventional risk factors.[60, 62] One study examined the effect of adding the finding of a deep terminal negativity of the P wave in lead V1 to conventional risk factors and reported a categorical NRI of 0.028 for clinical risk thresholds of 5 percent and 15 percent.[62] Event NRI was 0.028, indicating participants who had events were primarily reclassified to higher risk categories. Discrimination, calibration, and IDI were not reported.

In the Copenhagen City Heart Study, Q waves, ST segment depressions, and resting heart rate were added to conventional risk factors with improvements in discrimination compared with conventional risk factors alone for fatal CVD events and fatal or nonfatal CVD events[60] (**Appendix E Table 2**). However, categorical NRIs were only significant for ST segment depressions (3.1% for fatal CVD, 2.2% for all CVD events), and event and nonevent NRIs were not reported separately. Calibration and IDI were also not reported.

KQ 3. What Are the Harms of Screening With Resting or Exercise ECG, Including Harms of Subsequent Procedures or Interventions Initiated as a Result of Screening? KQ 3a. Do the Harms of Screening Vary for Subgroups Defined by Baseline CVD Risk, Age, Sex, or Race/Ethnicity?

Summary

One eligible study reported on harms from subsequent procedures or interventions initiated as a result of screening. It reported that one person out of 12 undergoing revascularization had a nonfatal MI. No other eligible studies reported rates of harms from screening asymptomatic adults with resting or exercise ECG. We searched for, but did not find, other studies evaluating

potential harms such as mortality, arrhythmia, CV events, injuries, anxiety, labeling, and harms of subsequent procedures or interventions initiated as a result of screening.

Detailed Results

One of the fair-quality RCTs described in KQ 1, the DADDY-D trial, reported some results eligible for this KQ.[53] Twenty out of 262 participants (7.6%) in the screened group had positive ETTs. Of those 20, 17 underwent coronary angiography (6.5% of the 262 in the screened group). Angiography revealed critical stenosis (not defined) in 71 percent (12/17), and all patients with critical stenosis underwent revascularization procedures (7 percutaneous and 5 surgical). One patient having percutaneous revascularization had a nonfatal acute MI 3 days after the procedure and underwent a second percutaneous angioplasty. His ejection fraction was reported to be normal 6 months after the event.

The other trial described in KQ 1 (DYNAMIT) reported the number of some subsequent tests but did not report whether any of the tests or interventions resulted in harms; adverse events that occurred during followup were not recorded.[52] Sixty-eight of the 316 participants (21.5%) in the screened group had a definitely abnormal or an uncertain screening test (exercise test or SPECT) result. Of those, 38 underwent coronary angiography (12% of the 316 in the screened group) and nine subsequently underwent coronary angioplasty (7 of those 9 received stents) and three had coronary artery bypass graft.

Chapter 4. Discussion

Summary of Evidence

Tables 8 and **9** provide a summary of findings in this evidence review. **Table 8** is organized by KQ and provides a summary of the main findings along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability. For KQ 2, the summary of evidence for exercise ECG and resting ECG was separated. The overall strength of evidence was low or insufficient for each of the questions and outcomes evaluated. No RCTs of screening with resting ECG were found; RCTs of exercise ECG in asymptomatic participants found no improvement in health outcomes despite focusing on higher risk populations with diabetes, although they were limited by not reaching sample size targets. Scant direct evidence on harms of screening asymptomatic persons with ECG was found. Evidence on whether the addition of exercise ECG to traditional CVD risk factors results in accurate reclassification is lacking. Cohort studies found that the addition of multiple resting ECG abnormalities to traditional CVD risk factors accurately reclassifies persons, and improves discrimination and calibration, but evidence was limited by imprecision, quality, considerable heterogeneity, and inconsistent use of risk thresholds that align with clinical decisions and recommendations.

Evidence for the Benefits and Harms of Screening With Resting or Exercise ECG

No eligible studies compared screening with resting ECG and no screening, and none evaluated the use of screening with ECG for the purpose of risk reclassification to inform decisions about whether to initiate preventive medications. Two RCTs (DYNAMIT and DADDY-D, total of 1,151 participants) evaluated screening with exercise ECG in asymptomatic adults ages 50 to 75 years with diabetes compared with no screening and found no statistically significant improvement in health outcomes, including their primary composite outcomes, all-cause mortality, CV-related mortality, MI, heart failure, or stroke. Findings from the two studies were consistent but imprecise. For the primary composite outcomes, HRs were 1.00 (95% CI, 0.59 to 1.71) for a composite of death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention and 0.85 (95% CI, 0.39 to 1.84) for a composite of nonfatal MI or cardiac death. Some key limitations of the trials include not reaching sample size targets and stopping early because of trouble recruiting. Both trials followed participants for about 3.5 years, and longer followup may be needed to adequately evaluate screening with exercise ECG. The overall strength of evidence for whether screening with exercise ECG improves health outcomes was low (for no benefit) because of imprecision and risk of bias.

The participants in the included trials were higher risk groups that would be, in theory, more likely to benefit from screening with exercise ECG to identify silent ischemia. For example, in DYNAMIT, participants had diabetes plus two of the following additional risk factors: urinary albumin excretion above a threshold, hypertension, hyperlipidemia, history of PAD (14%), history of TIA (4 to 5%), tobacco consumption, or family history of premature CVD. However,

even among these higher risk groups of asymptomatic diabetics, screening with exercise ECG (followed by referral to cardiology [DYNAMIT] or recommendation for coronary angiography [DADDY-D] for those with abnormal exercise ECGs) did not improve health outcomes.

Potential harms of screening asymptomatic adults with resting or exercise ECG include mortality, arrhythmia, CV events, injuries, anxiety, labeling, and harms of subsequent procedures or interventions initiated as a result of screening (e.g., subsequent angiography or revascularization procedures resulting in harm). Both DYNAMIT and DADDY-D reported numbers of subsequent tests and interventions after abnormal exercise tests, but just one (DADDY-D) reported whether any of the tests or interventions resulted in harms (1/12 [8.3%] undergoing percutaneous revascularization had a nonfatal acute MI 3 days later). Among asymptomatic diabetics, DADDY-D and DYNAMIT reported that 7.6 percent (20/262 screened) had abnormal ETTs and 21.5 percent (68/316 screened) had definitely abnormal or uncertain bicycle exercise or SPECT results, respectively. Most of those with abnormal screening tests underwent coronary angiography (DADDY-D: 17/262, 6.5%; DYNAMIT 38/316, 12%), and some had revascularization procedures (12/262, 4.6% and 12/316, 3.8%, respectively).

No other eligible studies reported rates of harms for asymptomatic adults. Studies without control groups were eligible if they were multicenter studies or registries that reported rates of harms from exercise ECG or subsequent procedures/interventions specifically for asymptomatic persons. A single site study of 377 asymptomatic military officers (mean age 37) at one station in the Midwestern United States reported that none had complications during exercise testing.[50] Of the 377, 45 (11.9%) had abnormal exercise test results and 10 (2.7%) underwent coronary angiography. Of those, one was reported to have "mild CAD." Many other studies have reported rates of angiography (but no information on harms) for asymptomatic persons after exercise ECG; rates have ranged from 0.6 percent to 13 percent, although most reported rates less than 3 percent.[47, 48, 50, 67-74] Rates of subsequent revascularization have also been reported by some, with those studies estimating lower rates than reported by DADDY-D and DYNAMIT. For example, two studies (with 3,554 and 1,051 participants, respectively) reported rates of 0.1 percent to 0.5 percent undergoing revascularization after screening exercise ECG.[47, 48] Little is known about the harms of revascularization procedures for adults without symptoms or a prior diagnosis of CVD (**Appendix A, Contextual Question 2**). Regardless of symptom status, some tests that follow an abnormal ECG expose patients to radiation, including coronary angiography, computed tomography angiography, and myocardial perfusion imaging.[75] Coronary angiography can expose patients to as much radiation as 600 to 800 chest X-rays.[76]

Studies that focused on *symptomatic* adults have reported rates of harms of exercise ECG and harms of subsequent procedures/interventions. The scientific statement from the AHA with recommendations for clinical exercise laboratories reports that the complication rate is usually considered to be approximately 1 in 10,000[51] (0.0001%). It references a review of eight studies estimating sudden cardiac death during exercise testing that reported rates from zero to 0.005 percent (5 per 100,000 tests).[51, 77] The statement also notes that survey data provide estimates of rates for complications: hospitalization including serious arrhythmias (0.2% or less), acute MI (0.04%), or sudden cardiac death during or immediately after an exercise test (0.01%).[51, 78]

Reclassification, Calibration, and Discrimination With the Addition of Resting or Exercise ECG to Traditional CVD Risk Factor Assessment

No consensus exists for the thresholds that should be considered clinically significant changes in discrimination (e.g., AUC, C-statistic), calibration, or reclassification (e.g., NRI). Changes in these measures are important to evaluate in the context of each other, but appropriate reclassification (NRI) has the most direct clinical meaning. Nevertheless, studies must use clinically meaningful risk categories (i.e., that correspond to clinical decisions, such as 7.5% or 10% 10-year risk) to allow for the potential clinical significance of NRI results to be assessed. Further, interpreting NRI is not simple because it is unfamiliar to many and it is calculated from four proportions. For more clear interpretation, focusing on the event NRI and nonevent NRI components may help. For example, nonevent NRI is the net downward reclassification (i.e., appropriate reclassification) among persons who did not have an event; it is calculated as the proportion of persons without an event who were appropriately reclassified into a lower risk group minus the proportion of those without an event who were inappropriately reclassified into a higher risk group.

For exercise ECG, although evidence from five cohort studies (9,582 participants) shows that the addition of exercise ECG results to traditional CVD risk factors results in small improvements in discrimination (absolute improvement in AUC or C-statistics 0.02 to 0.03), it is uncertain whether calibration or appropriate risk classification improves. Evidence was limited by imprecision and risk of bias for all outcomes and by inconsistency or unknown consistency for calibration and reclassification outcomes. Some important limitations of the evidence include that CIs for calibration or discrimination were not reported; mean duration of followup was less than 10 years in four of the five studies; reclassification was only reported by one study; unknown masking of outcome assessors in four studies; and not reporting both discrimination and calibration in three studies. The only study reporting reclassification was a model development study (i.e., used FRS variables but did not use published coefficients) that used risk categories of <6 percent, 6 to 20 percent, and >20 percent and may have included many symptomatic participants (because 16.5% had atypical chest pain and participants were a subset of those having CACS and SPECT for "clinically indicated reasons").[54] Also, we found an absence of evidence related to exercise ECG for healthy, low risk persons (e.g., mean age was 50 to 58 and mean baseline FRS score was 10.8 to 12.3 in studies reporting it).

For resting ECG, evidence from nine cohort studies (66,407 participants) shows that the addition of ECG findings to traditional CVD risk factors results in very small or small improvements in discrimination (absolute improvement in AUC or C-statistics 0.001 to 0.05) and in improvements for calibration and appropriate risk classification for prediction of all-cause mortality, CVD mortality, CHD events, or CVD events. Total NRIs (event; nonevent) range from 3.6 percent (2.7%; 0.6%) to 30 percent (17%; 19%) for studies using FRS or PCE base models (95% CIs were rarely reported). However, evidence was limited by imprecision and risk of bias for all outcomes and by incomplete and inconsistent reporting of discrimination, calibration, and reclassification measures. For reclassification, although evidence consistently showed improved NRI, the estimates of NRI and the outcomes assessed were inconsistent, and the consistency of findings is unknown for specific risk thresholds because all studies used different risk categories. The body of evidence also had considerable heterogeneity in baseline prediction models used,

type of ECG abnormalities added to base models, and outcomes assessed (e.g., all-cause mortality, CVD mortality, CHD events). The reported discrimination of base models varied widely, ranging from inadequate to excellent (AUC or C-statistics from 0.58 to 0.85) likely because of the different outcomes, different patient populations, and different base models used. Only one study used the base model for risk prediction (i.e., the PCE) that the USPSTF and ACC/AHA currently recommend to inform clinical decisions about preventive medications.

An important limitation of the evidence was a lack of reporting on any assessment of symptoms; it is unclear what proportion of participants was truly asymptomatic in most of the studies of resting ECG. Perhaps the proportion with symptoms is likely to be relatively low given that the studies were population based and most of them excluded persons with a history of CVD, but it is uncertain whether enrolling even a small percentage of symptomatic participants could artificially inflate estimates of appropriate reclassification. Other important limitations included unknown masking of outcome assessors in eight studies, CIs for calibration or discrimination were not reported in five studies, calibration or overall performance was not reported in five studies, and not using established risk prediction models with published coefficients in four studies (i.e., model development studies).

For NRI, event and nonevent NRI components were often not reported as recommended. Although an overall positive value of NRI indicates net appropriate reclassification into appropriate risk strata, the clinical implications can be very different if the majority of patients are those with events being shifted into higher risk categories (event NRI) as opposed to those without events being shifted into lower risk categories (nonevent NRI). Although the addition of ECG abnormalities to conventional risk factors improves total NRI in both cases, one might lead to an increase in preventive medications, while the other suggests a possible reduction in the use of preventive medications.

For reclassification with resting ECG, few studies included a threshold between risk categories corresponding to the USPSTF recommendations for preventive medications (i.e., 7.5% or 10% 10-year risk). The potential for appropriate reclassification based on the addition of major and minor ECG changes to existing models (PCE or FRS) initially looks promising when viewing **Figure 7** because studies reported increases in total appropriate reclassification (total NRI), appropriate reclassification of persons with events to higher risk categories (event NRI), and appropriate reclassification of persons without events to lower risk categories (nonevent NRI). However, several cautions should be noted: (1) no two studies evaluated the same model, risk category thresholds, and outcome. Therefore, none of the models that included ECG variables have been validated in more than one study; (2) no CIs were provided for most of that data; (3) NRI is highly dependent on risk category thresholds, which varied widely across these studies; (4) evaluating risk reclassification using four categories to determine NRI is potentially not clinically meaningful (or is less clinically meaningful than using fewer categories) and may artificially make the reclassification look better because each reclassification counts as a positive move for the NRI if someone with an event moves from any lower to any higher category regardless of whether the change would correspond to different treatment decisions (likewise for someone without an event who moves into any lower risk category); (5) a single study[59] accounts for six of the nine rows in **Figure 7**. It reported NRI for three different base models for prediction of several mortality outcomes but did not evaluate prediction of CHD or CVD events

because it used NHANES data that do not have that capability. The study is limited by using risk category thresholds of 1, 5, and 10 percent and not reporting the full reclassification table to allow determination of how much of the NRI was accounted for by reclassification that should change clinical decisions (e.g., from 5 to 9.9% to 10% or greater risk for persons with events) versus how much was accounted for by reclassification that would have no effect on clinical decisions and outcomes (e.g., from 1 to 4.9% to <1% for persons without events). The study[59] is also the only study that evaluated adding an ECG risk equation to base models; (6) another study[58] in **Figure 7** is limited by only having 7.5 years of followup. It also focused on elderly participants ages 70 to 79 years and did not report event NRI or nonevent NRI (or the data to calculate those) for the addition of ECG changes to the FRS base model (those were reported for a model development part of the study and showed net inappropriate reclassification for persons who had events, event NRI -0.9%). It is uncertain whether risk reclassification could provide clinically useful information for this population given recent evidence on lack of benefit of statins for primary prevention in elderly persons of similar age[79] and given the USPSTF I statement on initiation of aspirin for primary prevention in adults age 70 years or older.

Limitations

This review did not evaluate the evidence on preventive medications (i.e., aspirin and lipid lowering therapy) that could be initiated based on risk reclassification or the evidence on benefits and harms of lifestyle counseling to reduce CV risk. Other systematic reviews for the USPSTF have evaluated that evidence. But one of the contextual questions (**Appendix A**) summarizes what medications (i.e., aspirin, lipid-lowering therapy) are recommended for persons in various CVD risk categories. This review did not systematically review the benefits and harms of revascularization procedures; contextual question 2 (**Appendix A**) summarizes information on the harms and benefits of revascularization procedures for adults without symptoms or a prior diagnosis of CVD.

For KQ 2 (reclassification, calibration, and discrimination), it was sometimes challenging to determine whether studies used published coefficients (e.g., used the FRS or PCE) or whether they were model development studies that used the FRS variables. Study authors were contacted to clarify the uncertainty, but some did not respond. Therefore, some studies could be misclassified (regarding model development vs. published coefficients). For KQ 2, we used qualitative terms (i.e., very small, small, and moderate) to describe the magnitude of changes in discrimination and reclassification (corresponding to 0.001 to 0.009, 0.01 to 0.09, and 0.1 to 0.9, respectively). These qualitative terms are meant only to be descriptive of specific numeric ranges and are not intended to indicate a corresponding clinically meaningful benefit for health outcomes. No consensus exists for the thresholds that should be considered clinically meaningful changes in the AUC/C-statistic or NRI.

For KQ 3 (harms of screening), for studies without control groups to be eligible for this review, studies were required to be multicenter studies or from large registries. This approach excluded a single center study of 377 asymptomatic military officers[50]; that study is described above in the Discussion. This review did not evaluate harms from ECG or subsequent procedures/interventions for symptomatic populations.

This review was limited to studies assessing resting ECG or exercise ECG. A previously published meta-analysis evaluated any screening test for coronary artery disease in persons with type 2 diabetes.[80] It identified five trials (including DYNAMIT and DADDY-D) with a total of 3,315 participants. The trials that were not eligible for our review evaluated stress scintigraphy, coronary CT angiography, or stress echocardiography with exercise ECG. Pooled analyses found no statistically significant association with all-cause mortality (RR, 0.95; 95% CI, 0.66 to 1.35) or cardiac events (RR, 0.72; 95% CI, 0.49 to 1.06).

Future Research Needs

To better understand whether risk classification is improved in a clinically useful way that is likely to improve health outcomes, risk prediction studies that evaluate the addition of ECG abnormalities to the PCE (as the base model) would be most useful because the PCE is the approach currently recommended by the USPSTF and ACC/AHA to assess 10-year risk and to inform decisions about preventive medications. Only one included study used the PCE as the base model. Studies of a constellation of resting ECG changes (e.g., major and minor changes based on the Minnesota code) show greater promise than those of single ECG changes and should likely be the focus of future research. Future risk studies should use clinically meaningful risk categories that correspond to recommendations about preventive medications to determine how many persons are appropriately reclassified in a manner that would lead to additional or fewer preventive medication treatments. Specifically, when considering the USPSTF recommendations for statins and aspirin, evaluating NRI related to the 10% 10-year risk threshold is of great interest. Future studies should evaluate asymptomatic populations (with some assessment of symptom status to avoid enrolling those with angina, atypical chest pain, or dyspnea, for example) and should exclude those with a history of CVD. Measures of discrimination, calibration, and reclassification (including total NRI, event NRI, and nonevent NRI) and their corresponding CIs should be reported.

Conclusion

The overall strength of evidence was low or insufficient for each of the questions and outcomes evaluated. Controlled trials of screening with exercise ECG in asymptomatic diabetic patients found no improvement in health outcomes over about 3.5 years but were limited by not reaching sample size targets and stopping early because of trouble recruiting. No controlled trials evaluated screening with resting ECG for asymptomatic adults. Potential harms of exercise ECG include arrhythmias, acute MI, and sudden cardiac death. Potential harms of both exercise and resting ECG include harms of subsequent angiography or revascularization procedures after an abnormal test, but little evidence exists to determine their frequency in asymptomatic persons. Some evidence suggests that the addition of exercise ECG to traditional risk factors results in small improvements in discrimination, but it is uncertain whether calibration or appropriate risk classification improves. Cohort studies found that the addition of multiple resting ECG findings to traditional risk factors improves discrimination (small absolute improvement in AUC or C-statistics), calibration, and appropriate risk classification (small to moderate improvement in total

NRI), but evidence was limited by imprecision, quality, considerable heterogeneity, and unknown consistency for specific risk thresholds because studies used different risk categories.

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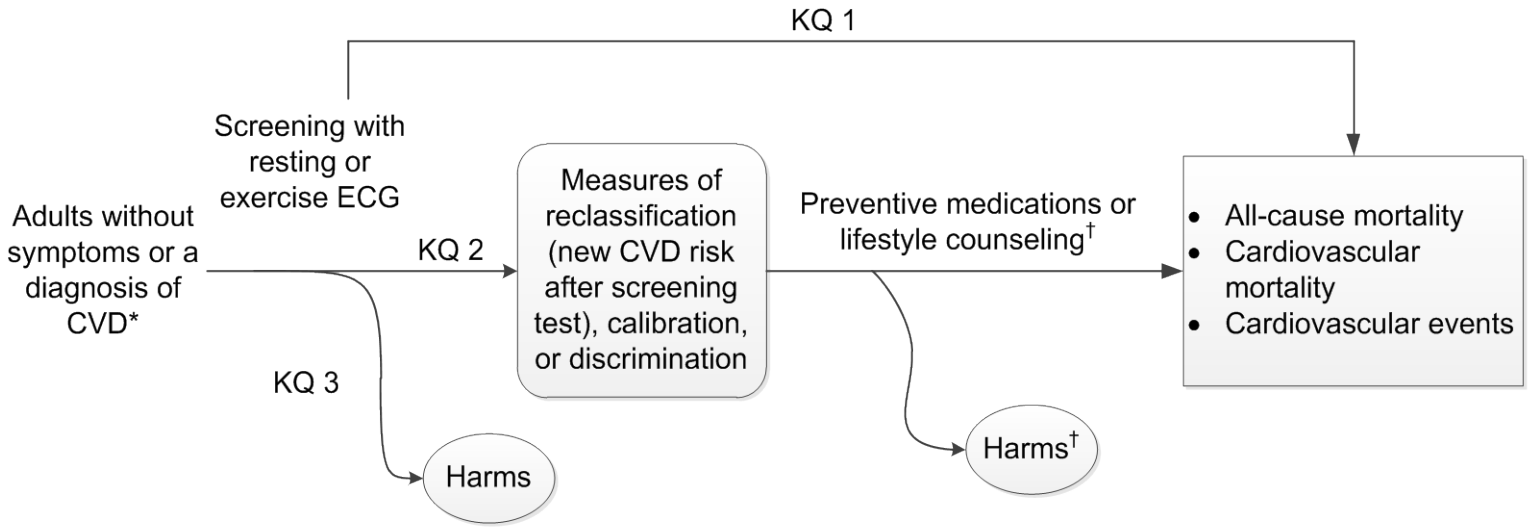
Figure 1. Analytic Framework



* Includes adults regardless of their CVD risk (those with low, intermediate, or high risk are eligible) as assessed by traditional risk factors (those included in Framingham risk models): male sex, older age, cigarette smoking, hypertension, dyslipidemia (high total cholesterol, high low-density lipoprotein cholesterol, or low high-density lipoprotein cholesterol), and diabetes.

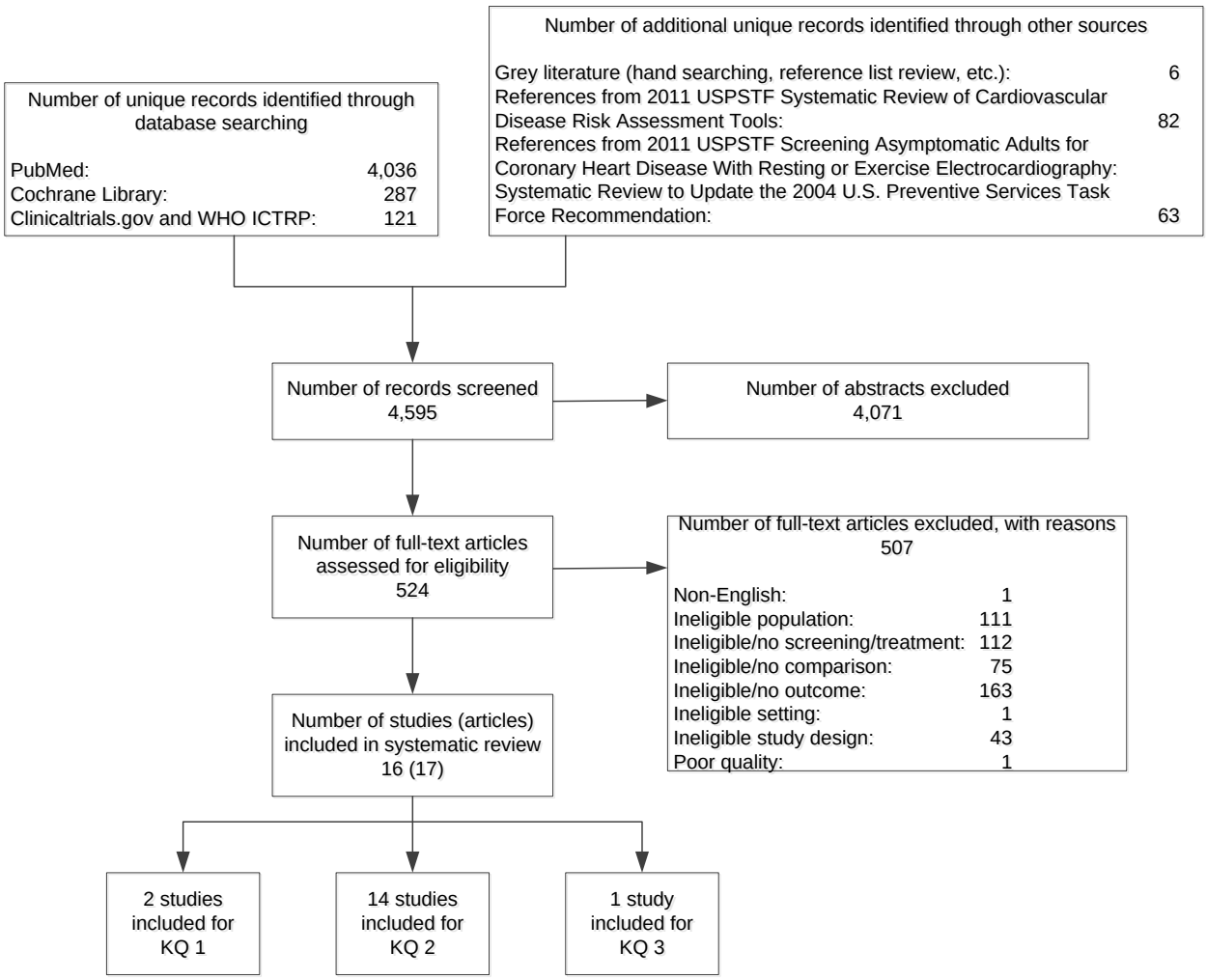
† This systematic review does not include key questions about the benefits and harms of preventive medications to reduce cardiovascular risk (i.e., aspirin and lipid-lowering therapy) or the benefits and harms of lifestyle counseling, because those have been addressed by other systematic reviews for the USPSTF.

Abbreviations: CVD = cardiovascular disease; ECG = electrocardiography; KQ – key question.

Key Questions to Be Systematically Reviewed

1. Does the addition of screening with resting or exercise electrocardiography (ECG) improve health outcomes compared with traditional cardiovascular disease (CVD) risk factor assessment alone in asymptomatic adults?
   - 1a. Does improvement in health outcomes vary for subgroups defined by baseline CVD risk (e.g., low, intermediate, or high risk), age, sex, or race/ethnicity?
2. Does the addition of screening with resting or exercise ECG to traditional CVD risk factor assessment accurately reclassify persons into different risk groups (e.g., high-, intermediate-, and low-risk groups) or improve measures of calibration and discrimination?
3. What are the harms of screening with resting or exercise ECG, including harms of subsequent procedures or interventions initiated as a result of screening?
   - 3a. Do the harms vary for subgroups defined by baseline CVD risk (e.g., low, intermediate, or high risk), age, sex, or race/ethnicity?

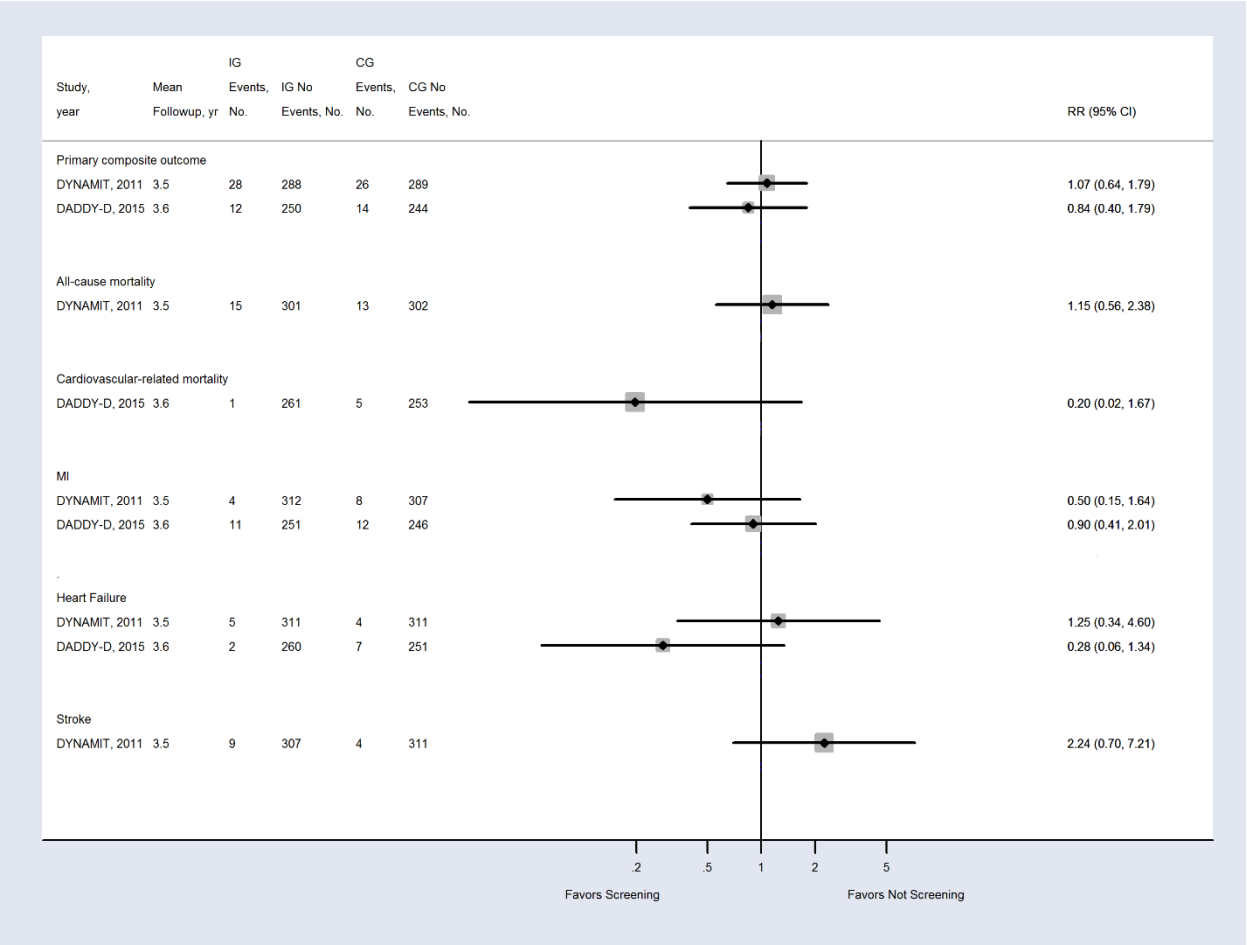
Figure 2. Summary of Evidence Search and Selection Diagram



Note: The sum of the number of studies per KQ exceeds the total number of studies because some studies are applicable to multiple KQs.

Abbreviations: ICTRP= International Clinical Trials Registry Platform; KQ=key question; USPSTF=U.S. Preventive Services Task Force; WHO=World Health Organization.

Figure 3. Main Results of Included Randomized, Controlled Trials Reporting Health Outcomes (KQ 1)



DYNAMIT, primary composite outcome was defined as death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention.

DADDY-D, primary composite outcome was defined as first cardiac event, specifically nonfatal MI or cardiac death.

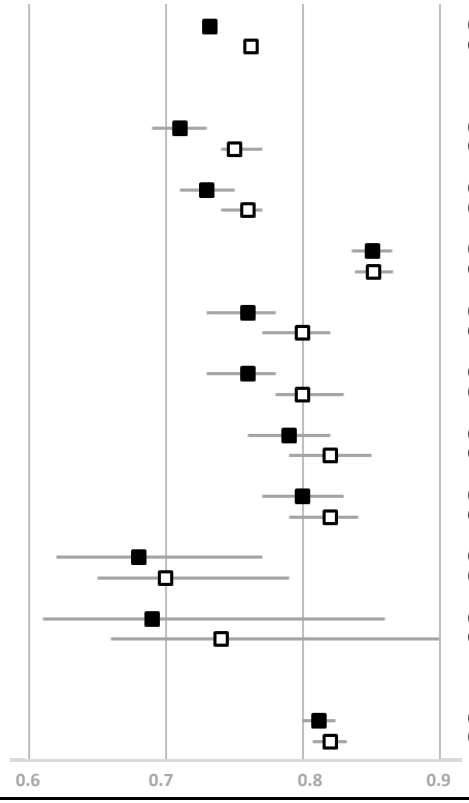
DYNAMIT did not report data for CV-related deaths. For other CV events, the DYNAMIT trial reported no significant differences between arms for revascularization (18 vs. 21, p=0.61).

The DADDY-D trial reported 19 total deaths (6 cardiac and 13 noncardiac) and seven total strokes but did not report which group those occurred in.

Abbreviations: CV=cardiovascular; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; MI=myocardial infarction.

Figure 4. Effect on Discrimination of Adding Exercise or Resting ECG Variables to Framingham Risk Score or Pooled Cohort Equation Base Models

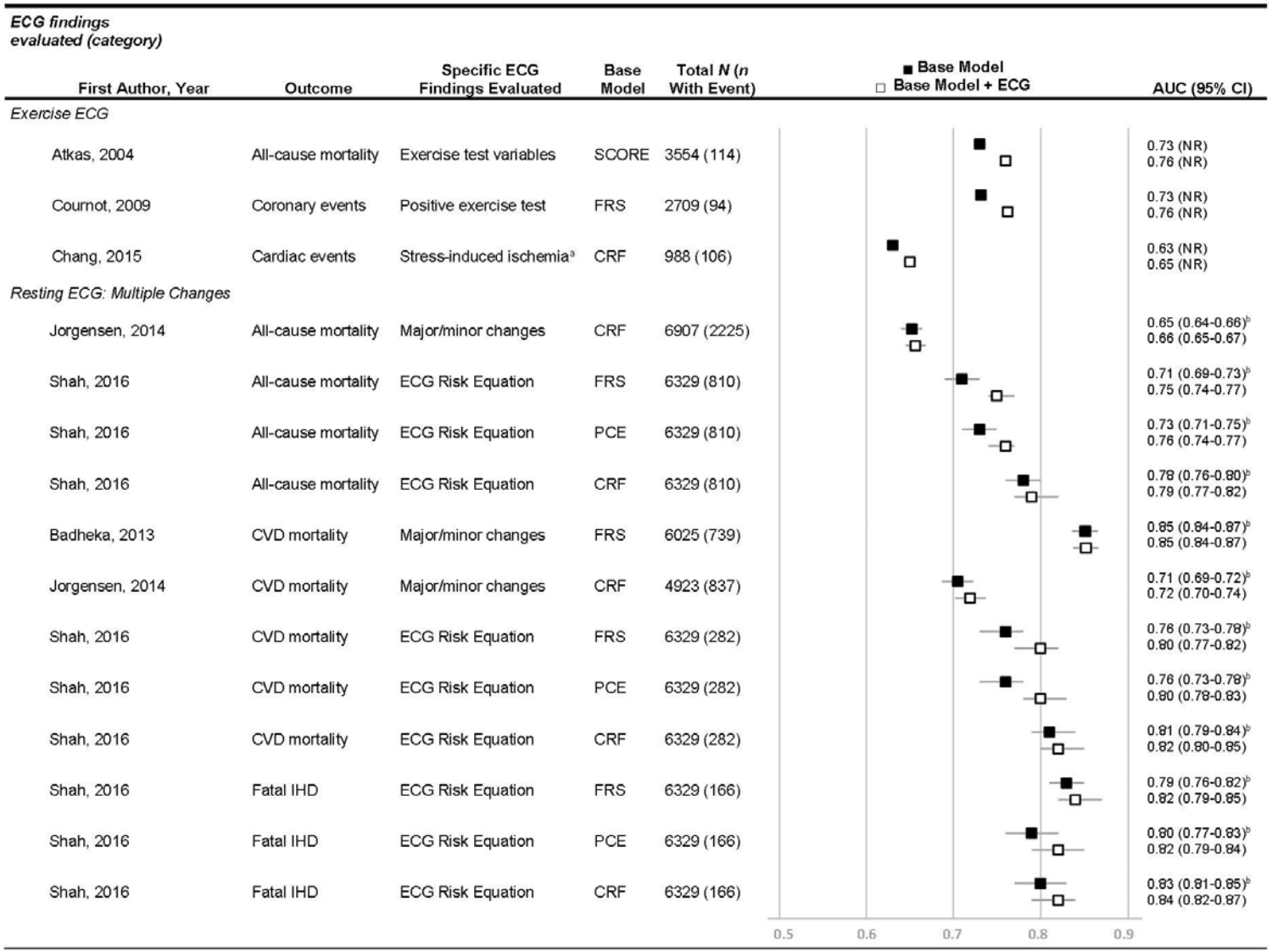
ECG findings evaluated (category) / First Author, Year	Outcome	Specific ECG findings evaluated	Base model	Total *N* (*n* with event)	AUC (95% CI)
Exercise ECG					
Cournot, 2009	Coronary events	Positive exercise test	FRS	2709 (94)	0.73 (NR) 0.76 (NR)
Resting ECG: Multiple Changes					
Shah, 2016	All-cause mortality	ECG Risk Equation	FRS	6329 (810)	0.71 (0.69-0.73)[b] 0.75 (0.74-0.77)
Shah, 2016	All-cause mortality	ECG Risk Equation	PCE	6329 (810)	0.73 (0.71-0.75)[b] 0.76 (0.74-0.77)
Badheka, 2013	CVD mortality	Major/minor changes	FRS	6025 (739)	0.85 (0.84-0.87)[b] 0.85 (0.84-0.87)
Shah, 2016	CVD mortality	ECG Risk Equation	FRS	6329 (282)	0.76 (0.73-0.78)[b] 0.80 (0.77-0.82)
Shah, 2016	CVD mortality	ECG Risk Equation	PCE	6329 (282)	0.76 (0.73-0.78)[b] 0.80 (0.78-0.83)
Shah, 2016	Fatal IHD	ECG Risk Equation	FRS	6329 (166)	0.79 (0.76-0.82)[b] 0.82 (0.79-0.85)
Shah, 2016	Fatal IHD	ECG Risk Equation	PCE	6329 (166)	0.80 (0.77-0.83)[b] 0.82 (0.79-0.84)
Denes, 2007	CVD events	Major/minor changes	FRS	1264 (595)	0.68 (0.62-0.77) 0.70 (0.65-0.79)
Denes, 2007	CHD events	Major/minor changes	FRS	1264 (246)	0.69 (0.61-0.86) 0.74 (0.66-0.90)
Resting ECG: Single Change					
Badheka, 2013	CVD mortality	T wave amplitude in aVR	FRS	7928 (1226)	0.81 (0.80-0.82) 0.82 (0.81-0.83)



[a] Model included metabolic equivalent (MET) and Duke treadmill score (DTS).
[b] Study reported c-statistic rather than AUC.

Abbreviations: AUC=area under the curve; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; FRS=Framingham Risk Score; LVH=left ventricular hypertrophy; NR=not reported; PCE=pooled cohort equation.

Figure 5. Effect on Discrimination of Adding Exercise or Resting ECG Variables to Framingham Risk Score, Pooled Cohort Equation, Systemic Coronary Risk Evaluation, or Conventional Risk Factor Base Models



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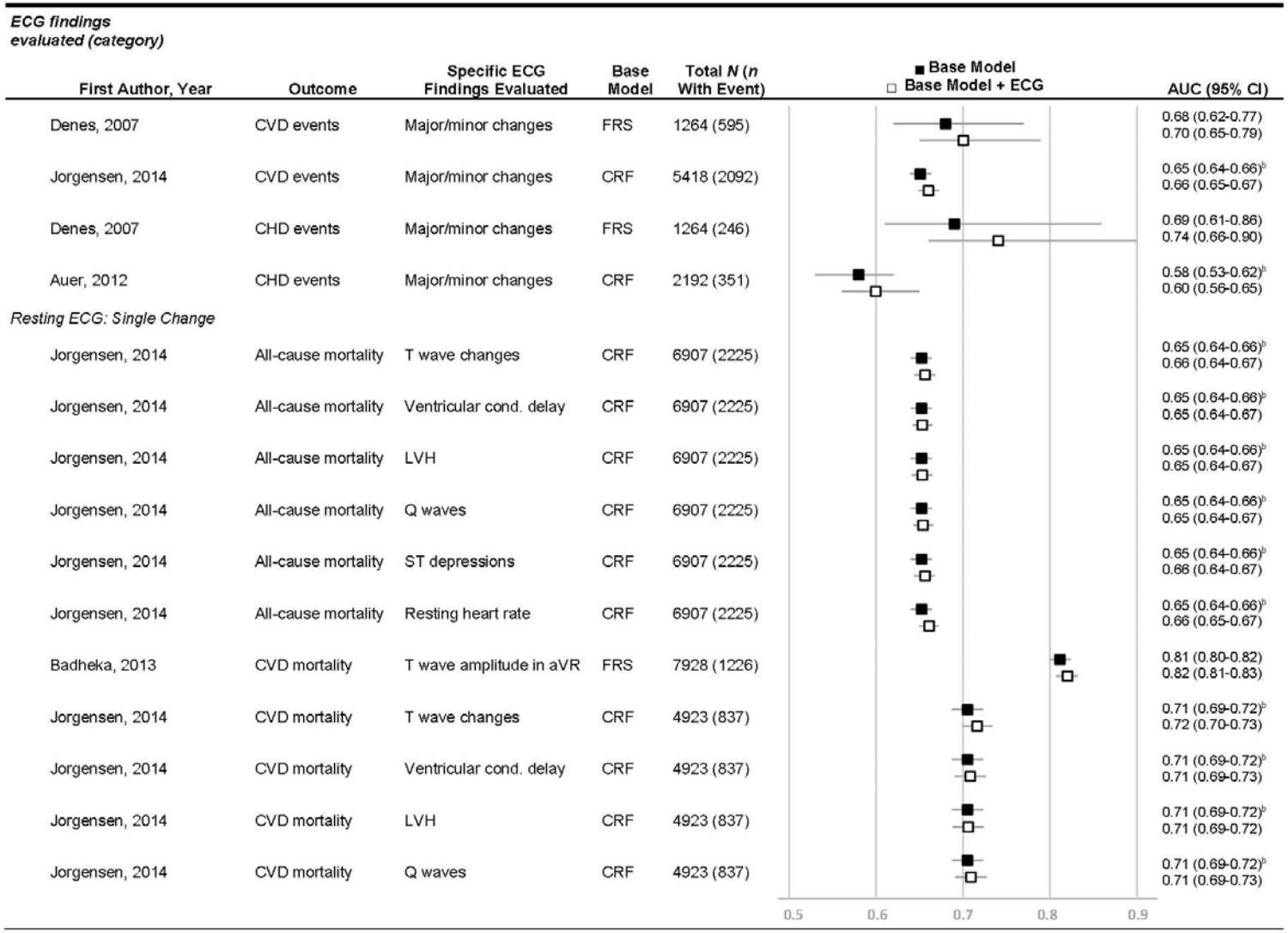
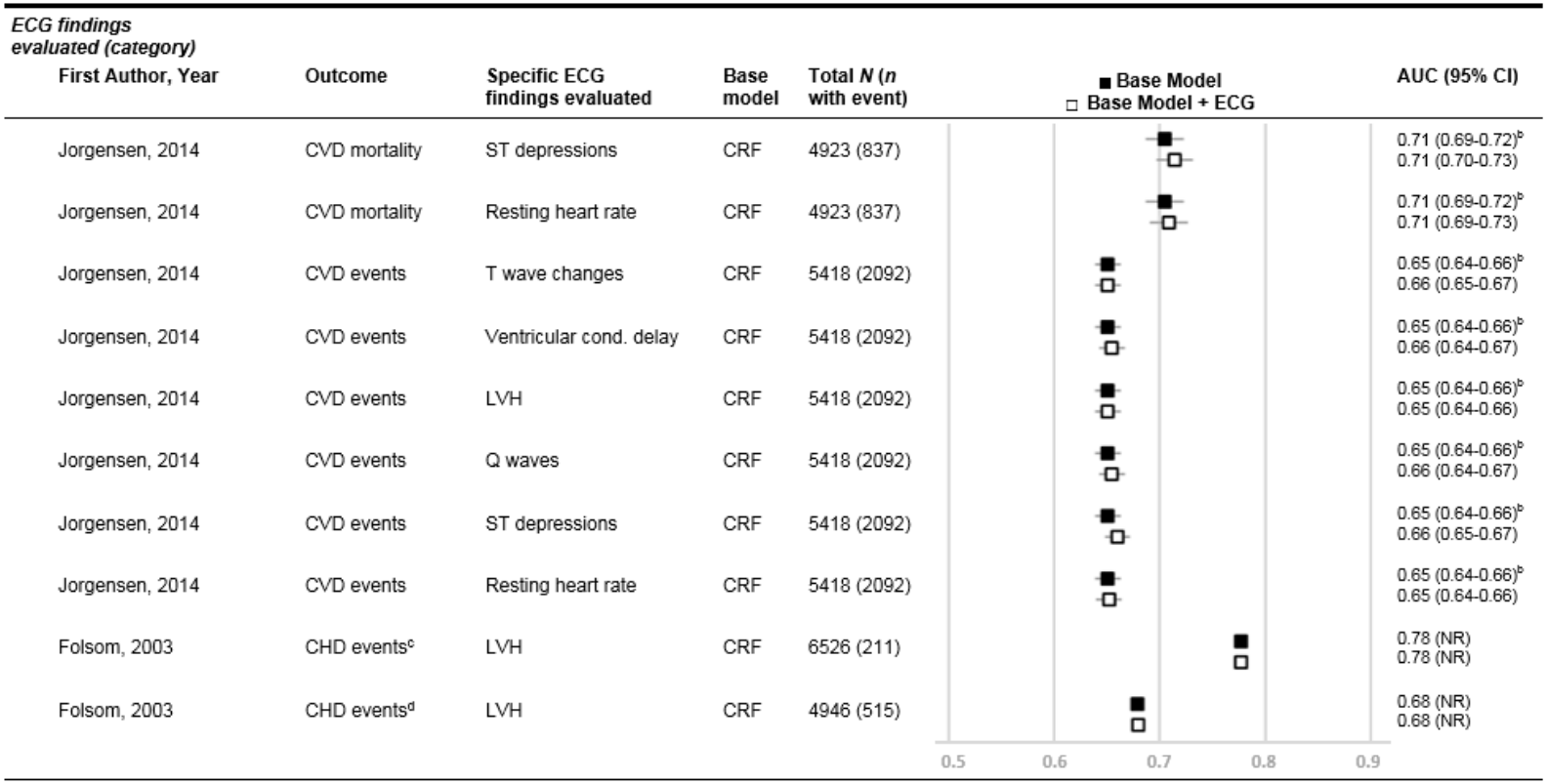


Figure 5. Effect on Discrimination of Adding Exercise or Resting ECG Variables to Framingham Risk Score, Pooled Cohort Equation, Systemic Coronary Risk Evaluation, or Conventional Risk Factor Base Models



[a] Model also included metabolic equivalent (MET) and Duke treadmill score (DTS).
[b] Study reported c-statistic rather than AUC.
[c] In women without diabetes mellitus.
[d] In men without diabetes mellitus.

Abbreviations: AUC=area under the curve; CHD=coronary heart disease; CI=confidence interval; CRF=conventional risk factors; CVD=cardiovascular disease; ECG=electrocardiography; FRS=Framingham Risk Score; IHD=ischemic heart disease; LVH=left ventricular hypertrophy; NR=not reported; PCE=pooled cohort equation; SCORE=Systemic Coronary Risk Evaluation.

Figure 6. Effect on Reclassification of Adding Exercise or Resting ECG Variables to Framingham Risk Score, Pooled Cohort Equation, or Conventional Risk Factor Base Models

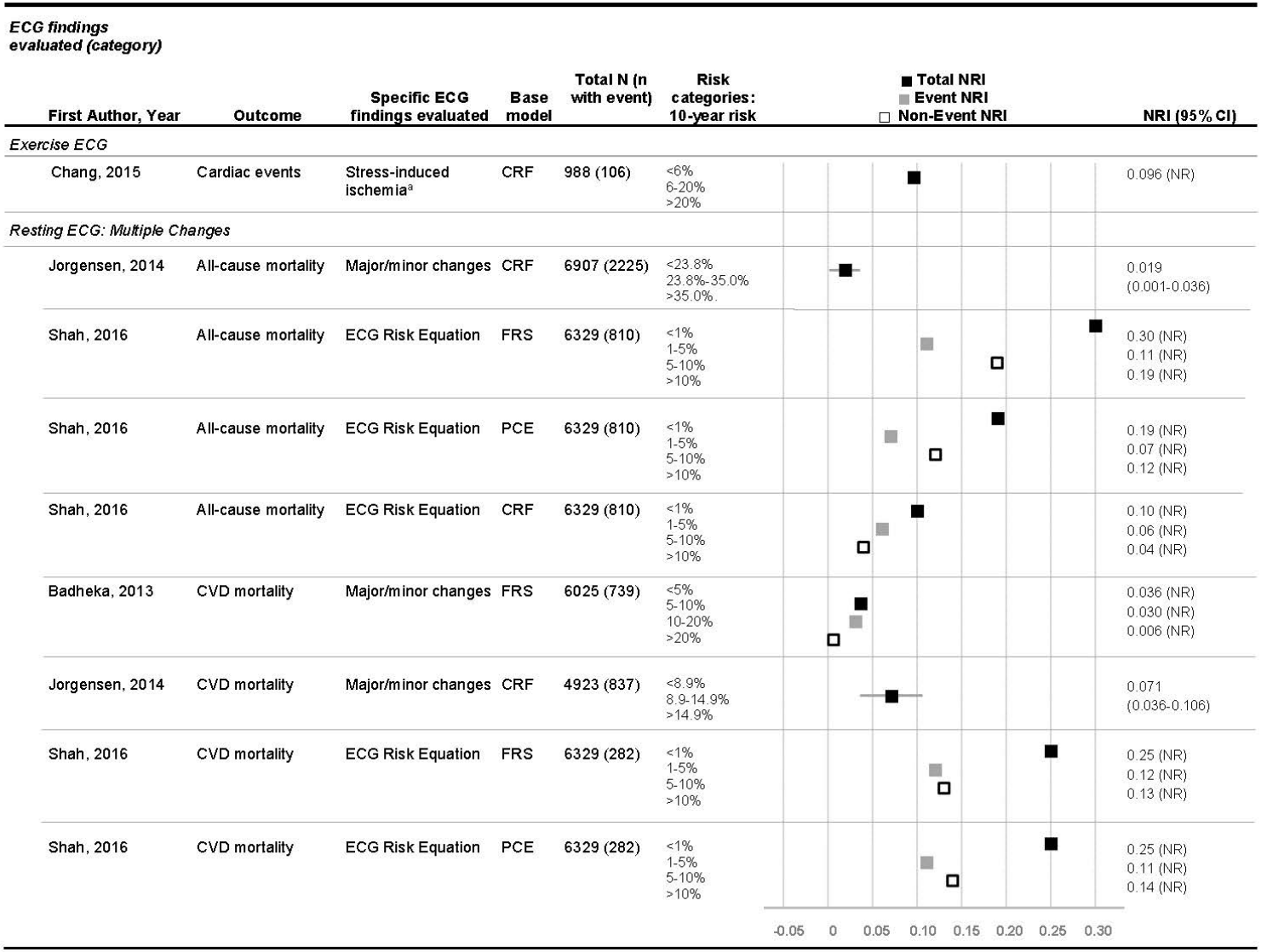
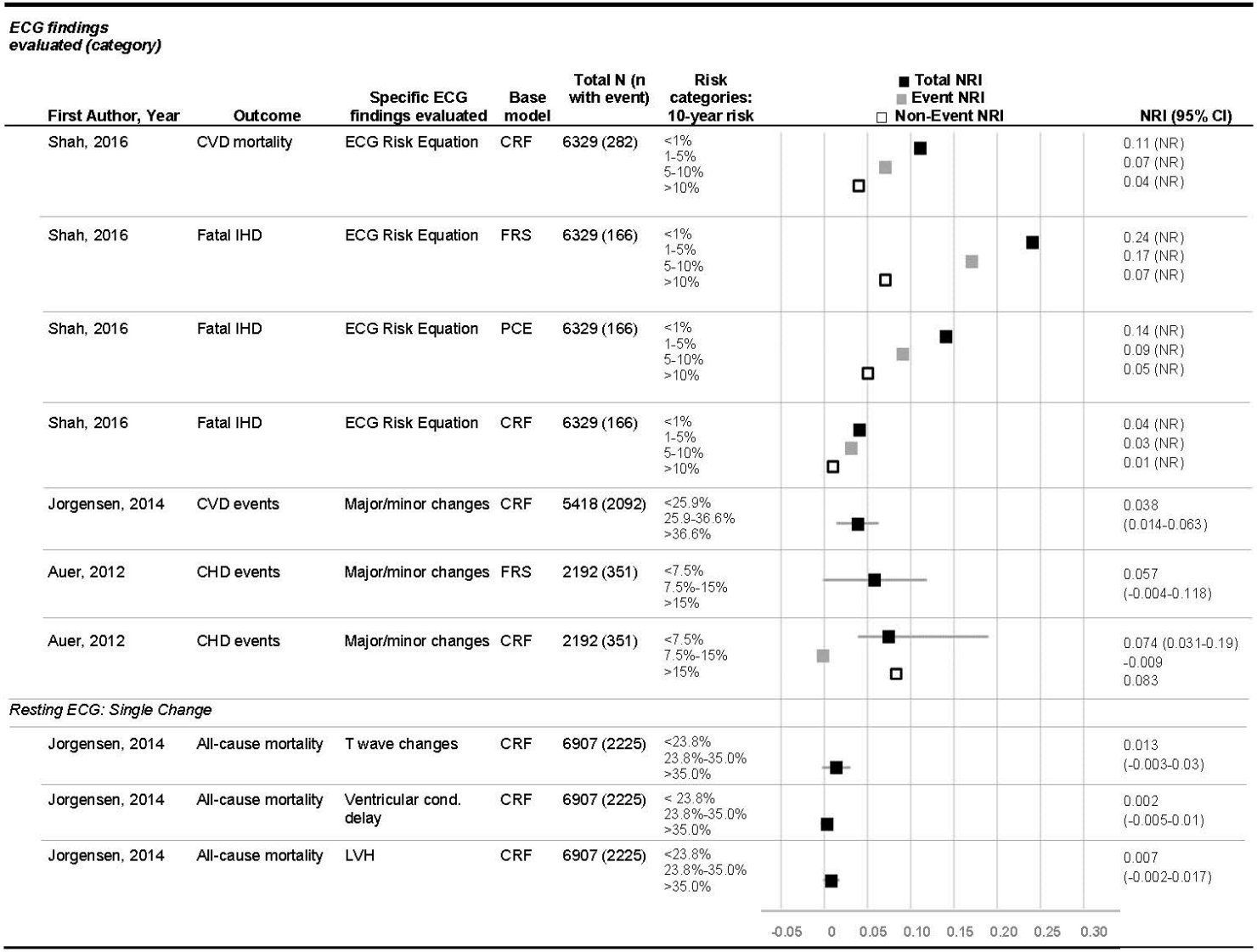


Figure 6. Effect on Reclassification of Adding Exercise or Resting ECG Variables to Framingham Risk Score, Pooled Cohort Equation, or Conventional Risk Factor Base Models



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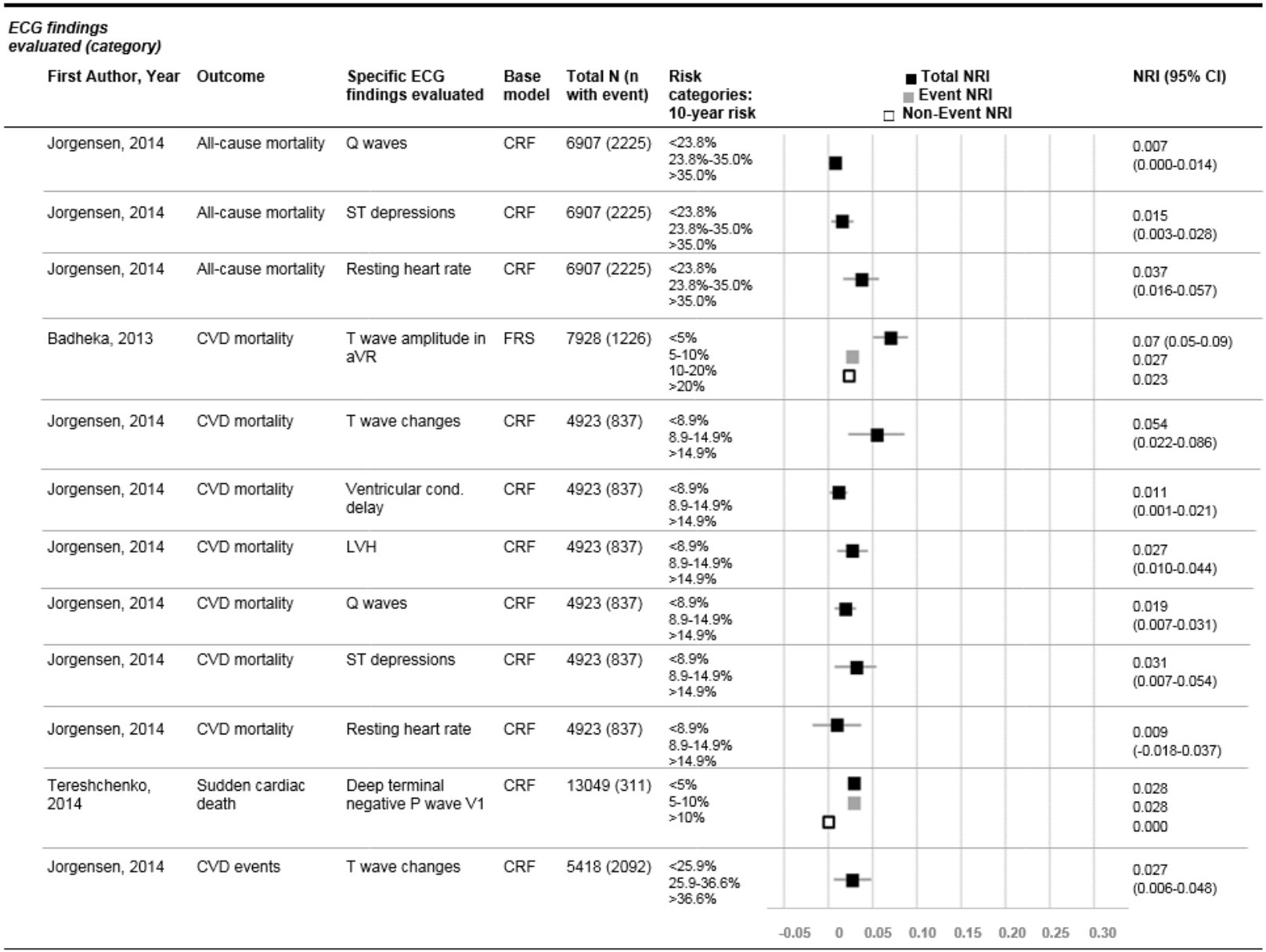
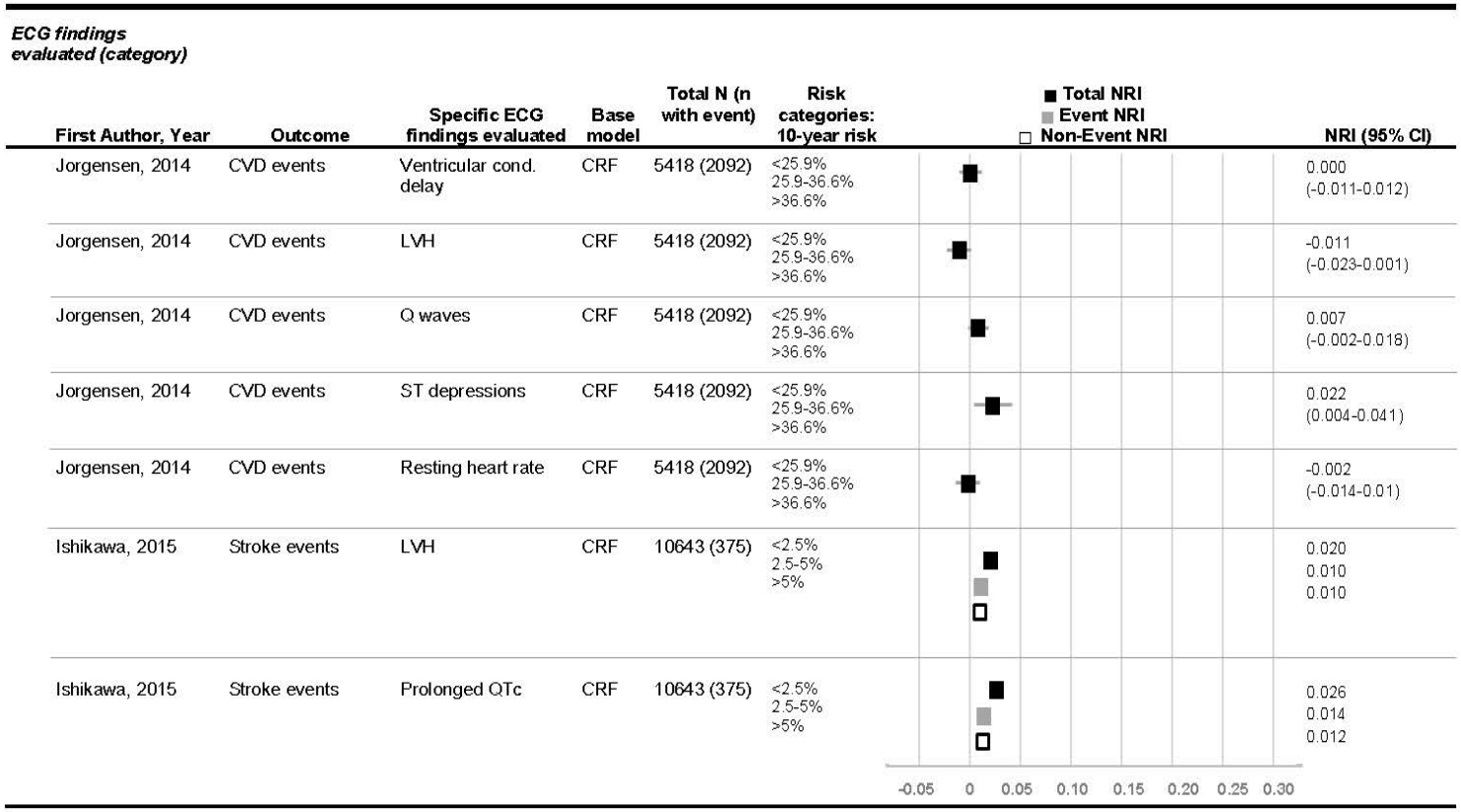


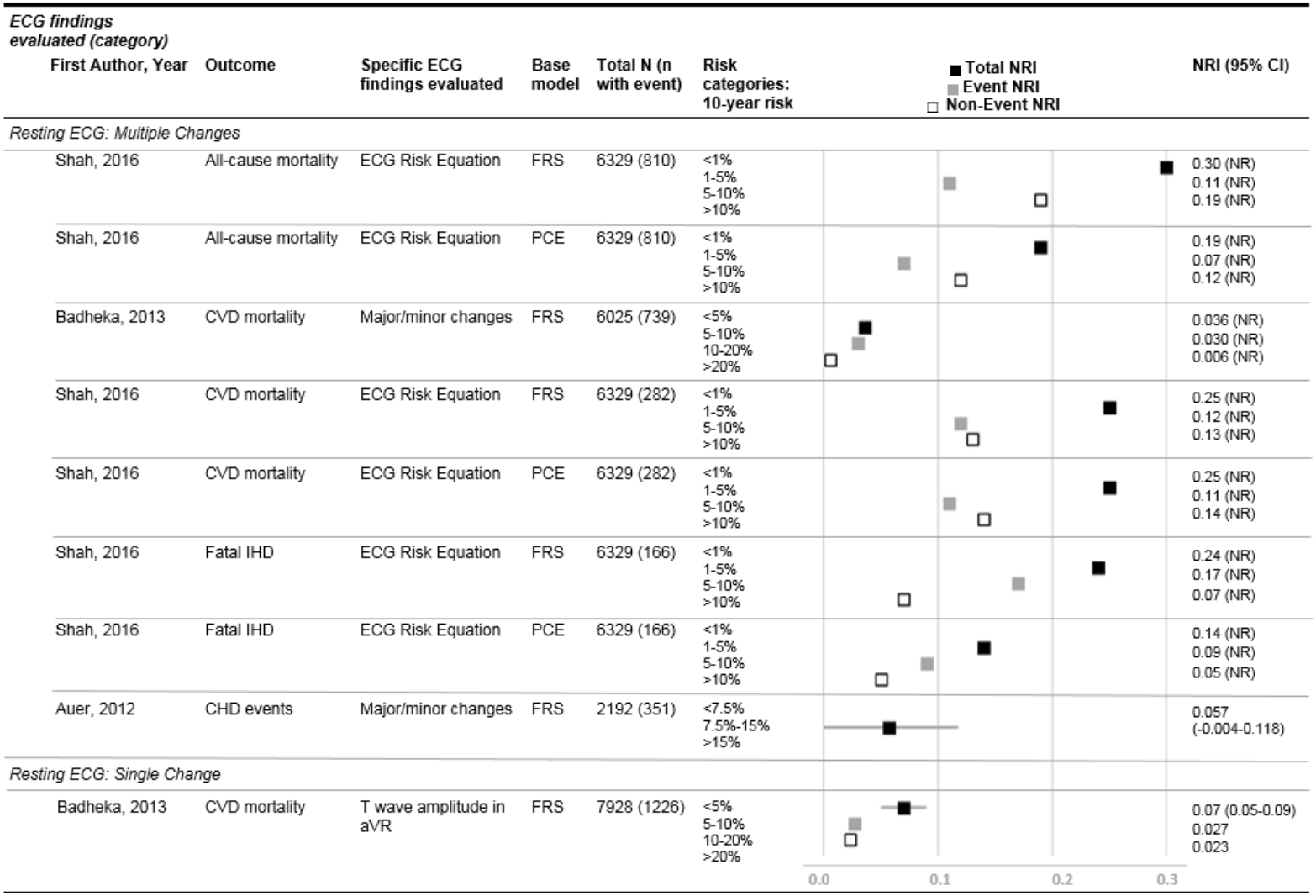
Figure 6. Effect on Reclassification of Adding Exercise or Resting ECG Variables to Framingham Risk Score, Pooled Cohort Equation, or Conventional Risk Factor Base Models



[a] Model also included metabolic equivalent (MET) and Duke treadmill score (DTS).

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CRF=conventional risk factors; CVD=cardiovascular disease; ECG=electrocardiography; FRS=Framingham Risk Score; LVH=left ventricular hypertrophy; NR=not reported; NRI=net reclassification index; PCE=pooled cohort equation.

Figure 7. Effect on Reclassification of Adding Resting ECG Variables to Framingham Risk Score or Pooled Cohort Equation Base Models



Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; FRS=Framingham Risk Score; NR=not reported; NRI=net reclassification index; PCE=pooled cohort equation.

Table 1. Test performance measures for comparing risk assessment or prediction models

Purpose of Outcome Measure	Example Measures of Test Performance	Description
Discrimination	c-statistic or AUC; change in c-statistic or AUC	The probability that, for a randomly selected pair of individuals, one with disease and the other without, that the person with disease will have the higher estimated disease probability according to the model. 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. The Harrell's C-statistic is an extension of the AUC for survival analysis allowing for right-censored data and variable time to followup. 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.
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 (e.g., groups defined by deciles or risk strata); a significant p-value signals poor fit. The test is sensitive to how groups are constructed and sensitive to sample size, often being nonsignificant for small N and significant for large N.
Overall performance (captures both calibration and discrimination aspects)	Akaike information criterion (AIC) and Bayes information criterion (BIC)	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, though 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.
	Likelihood ratio χ^2	Likelihood ratio χ^2 is a global test of model fit and is 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). A global χ^2 is generally the same as a likelihood χ^2 (twice the log likelihood ratio).
	R^2	There are a number of ways to calculate an R^2 for a logistic regression. Nagelkerke's generalized R^2 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. The R^2 is more helpful than the Brier score because it can be compared across models/studies.
	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.
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 with a cardiovascular disease outcome, plus the proportion moving down minus those moving up without an outcome. 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 of limited value in comparing models with different risk categories.
	Integrated discrimination improvement (IDI)	Integrates the NRI over all possible cut-offs; equivalent to difference in discrimination slopes of the two models and to the difference in R^2.

Note: Table was modified with permission of the authors from the Kaiser Permanente Evidence-based Practice Center; from a table in their report on nontraditional risk factors.

Abbreviations: AIC=Akaike information criterion; AUC=area under the curve; BIC=Bayes information criterion; FRS=Framingham risk score; IDI=integrated discrimination improvement; N=sample size; NRI=net reclassification index or improvement; PCE=pooled cohort equation; ROC=receiver operating characteristic.

Table 2. Characteristics of Included Randomized, Controlled Trials for KQ 1 and KQ 3

First Author, Year Trial Name	G1 (N) G2 (N)	Screening Approach	Source of Patients	Country	Years of Followup	Mean Age (SD)	% F	% Nonwhite	Mean CV Risk (SD)	Mean A1c (SD)	Mean BMI (SD)	% HTN % HF % TIA % PAD % PVD % Smokers	Quality
Lievre et al, 2011[52] DYNAMIT	Screened (316) Not screened (315)	Exercise ECG, bicycle exercise test (or dipyridamole SPECT, 31%)[a]	45 hospitals, ambulatory patients who consulted a diabetes specialist	France	Mean 3.5	63.9 (6.4)	45	NR	NR	8.6 (2.1)	30.6 (5)	88.8 0.5 4.6 14.1 NR 16.6[b]	Fair
Turrini et al, 2015[53] DADDY-D	Screened (262) Not screened (258)	Exercise ECG[c]	2 diabetes outpatient clinics	Italy	Mean 3.6	61.9 (5)	20	NR	20 (9)[d]	7.7 (2)	30.1 (6)	NR[e] 0 (excluded) NR NR 6 38.7	Fair

[a] SPECT was used in patients unable to perform the exercise test, with a submaximal negative exercise test, or with ECG abnormalities impairing the interpretation of the exercise test. Those with positive tests were referred to cardiologists, and all subsequent investigations and treatments were left at the cardiologist's discretion.
[b] Tobacco consumption
[c] Maximal symptom-limited exercise treadmill test (ETT) preformed following American Heart Association guidelines. Submaximal tests were considered not diagnostic and did not lead to any further investigations. Coronary angiography was proposed to all patients with positive ETT; choices to perform stenting or surgery were determined according to the European Guidelines by two interventional cardiologists and a cardiac surgeon after reviewing coronary anatomy.
[d] Required CV risk score ≥10% for eligibility, risk determined according to Italian risk chart (includes gender, diabetic status, age, cigarette smoking status, systolic blood pressure, serum cholesterol).
[e] 74.3% on antihypertensive treatment; mean SBP 140.

Abbreviations: A1c=glycosylated hemoglobin; BMI=body mass index; CV=cardiovascular; DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; ECG=electrocardiogram; ETT=exercise treadmill test; F=female; HF=heart failure; HTN=hypertension; KQ=key question; G=group; N=sample size; NR=not reported; PAD=peripheral artery disease; PVD=peripheral vascular disease; SBP=systolic blood pressure; SD=standard deviation; SPECT=Single Photon Emission Computed Tomography; TIA=transient ischemic attack.

Table 3. Characteristics of Included Studies for KQ 2 That Evaluated Exercise ECG, Part 1

First Author, Year, Quality	ECG Findings Evaluated	Model Type: Base Model	Cohort	Source of Patients	Country	Sample Size	Years of Followup
Aktas, 2004[47] Fair	Exercise ECG according to Bruce (or modified Bruce) protocol; ischemic ST abnormality[a] using a 12-lead, symptom-limited exercise ECG	Published coefficient: European SCORE[b]	From Preventive Medicine Section of Cleveland Clinic (1990–2002)	Consecutive participants presenting for an executive physical. Self-referred.	US	3,554	Mean: 8
Chang, 2015[54] Fair	Exercise ECG according to Bruce protocol; stress-induced ischemia[c] identified via ECG during symptom-limited exercise treadmill testing; METS and DTS	Model development: FRS[d] variables	From the Methodist Hospital, Houston Texas (1995–2006)	Persons who had both CACS and stress SPECT for clinically indicated reasons at the Heart and Vascular Center	US	988	Median: 6.9
Cournot, 2006[48] Fair	Symptom-limited exercise ECG[e]	Published coefficient: FRS[f]	From the preventive cardiology unit of a teaching hospital (1995–1999)	Consecutive asymptomatic persons self-referred or referred by PCPs and cardiologists for evaluation of risk factors and routine screening	France	1,051	Mean: 6
Cournot, 2009[55] Fair	A positive exercise test[g] during a symptom-limited exercise ECG with orthogonal and V_1 to V_6 leads	Published coefficient: FRS[f]	From the preventive cardiology unit of a teaching hospital (1996–2004)	Apparently healthy asymptomatic persons self-referred (20%) or referred by PCPs (27%) or other providers to a preventive cardiology unit	France	2,709	Median: 6
Erikssen, 2004[56] Fair	Resting ECG and a symptom-limited bicycle exercise ECG test[h]	Model development: Classical Risk Factor (CRF) regression model[i]	From the University Hospital of Oslo (1972–1975)	Apparently healthy males ages 40–60 years recruited from five governmental agencies who participated in a cardiovascular risk assessment	Norway	Assessment 1 (1972–1975): 2,014 Assessment 2 (1980–1982): 1,428	26

[a] An ischemic ST abnormality, which was assessed visually by two independent readers, was defined as a 1-mm horizontal or downsloping ST-segment depression occurring 80 ms after the J-point; ST-segment depression had to be noted in at least three consecutive beats in at least two contiguous leads.
[b] SCORE includes age, sex, total cholesterol, systolic blood pressure, and smoking status (this study used the high-risk coefficients from it).
[c] Ischemia was defined as ≥1 mm of ST-segment depression occurring >80 ms after the J-point. High and low risk were defined as the presence and absence of ischemia, respectively.
[d] Authors attempted to calculate FRS as published, but continuous BP and cholesterol measurements were not available, so these predictors were dichotomized (hyperlipidemia defined as total cholesterol 200–239 mg/dL and HTN defined as SBP 140–159 mm Hg).
[e] Positive ET was defined as a horizontal or downsloping ST-segment depression ≥1.0 mm at 80 ms after the J-point, in at least two contiguous leads, occurring at any time of exercise or recovery period.
[f] Used Anderson 1991: 10-year FRS function that includes age, sex, current smoking, diabetes, total cholesterol, and HDL-C.
[g] Positive exercise testing was defined as a horizontal or downsloping ST-segment depression ≥1.0 mm at 80 ms after the J-point, in at least two contiguous leads, occurring at any time during exercise or the recovery period.
[h] Exercise predictors were physical fitness (cumulative work during exercise divided by body weight), maximal heart rate, systolic blood pressure at the end of the first exercise load, and exercise ECG interpretation (ST-segment depression ≥1.0 mm at 0.08 s after the J-point regardless of ST-segment morphology).
[i] CRF model included age, total cholesterol, systolic blood pressure, and smoking status. The study included men only; therefore, sex was not needed in the model; the study also excluded persons with prevalent diabetes and persons on blood pressure–lowering therapy at baseline. High-density lipoprotein cholesterol was not accounted for in the model.

Table 3. Characteristics of Included Studies for KQ 2 That Evaluated Exercise ECG, Part 1

Abbreviations: BP=blood pressure; CACS=coronary artery calcium score; CRF=Classical Risk Factor; DTS=Duke treadmill score; ECG=electrocardiogram; ET= exercise test; FRS=Framingham Risk Score; HDL-C=high-density lipoprotein cholesterol; HTN= hypertension; METS=metabolic equivalents of task; KQ=key question; PCP=primary care physicians and cardiologists; SCORE=Systematic COronary Risk Evaluation; SPECT=single-photon emission computed tomography; U.S.=United States.

Table 4. Characteristics of Included Studies for KQ 2 That Evaluated Exercise ECG, Part 2

First Author, Year	% CVD	% With Symptoms	Mean Age (SD)	% F	% Nonwhite	CV Risk	Mean BMI (SD)	% HTN	% DM	% Smokers
Aktas, 2004[47]	0	0	57 (4)	19	2	SCORE,[a] median (25th–75th percentile) 1st tertile: 0.14 (0.87–1.8) 2nd tertile: 3.0 (2.5–3.5) 3rd tertile: 6.6 (5.2–9.2)	28 (4)	NR (mean SBP 128)	3	10
Chang, 2015[54]	0 (for CAD; NR for CVD)	16.5[b]	57.5 (9.3)	25	NR	FRS, mean (SD): 11.1 (6.5) Low risk (<6%): 16.9% Intermediate risk (6%–20%): 69.2% High risk (>20%): 13.9%	NR	49.6	9.6	46.5
Cournot, 2006[48]	0	0	Total: 51.6 (10.3)	36	NR	Mean (median) FRS All: 12.3 (10.4) Negative ET, n=962: 12.1 (10.4) Positive ET, n=89: 14.7 (11.4)	Total: 26.1 (4.5)	≥160/95 mm Hg: 33.0 ≥140/90 mm Hg: 54.8	11.0	24.3
Cournot, 2009[55]	0	0	Median: 51.6 (10.5)	38	NR	FRS, mean (SD): 10.8 (7.8)	26.0 (4.4)	48.2	6.8	23.9
Erikssen, 2004[56]	0	0	Assessment 1: 49.8 (5.5) Assessment 2: 56.6 (5.4)	0	NR	NR	NR	0 (treated HTN)	0	Assessment 1: 43.8 (NR) Assessment 2: 32.8 (NR)

[a] SCORE provides 10-year risk for cardiovascular mortality and includes age, sex, total cholesterol, systolic blood pressure, and smoking status (this study used the high-risk coefficients from it).
[b] Study reported 16.5% had atypical chest pain symptoms but does not report indications for other tests beyond stating that they were "clinically indicated reasons."

Abbreviations: BMI=body mass index; CAD=coronary artery disease; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; ECG=electrocardiogram; ET=exercise testing; F= female; FRS=Framingham Risk Score; HTN=hypertension; KQ=key question; n=sample size; NR=not reported; SBP=systolic blood pressure; SCORE=Systematic COronary Risk Evaluation; SD=standard deviation.

Table 5. Results of Included Studies for KQ 2 That Evaluated Exercise ECG

First Author, Year, Quality	Outcome	N (%) With Outcome	Discrimination	Calibration	Reclassification
Aktas, 2004[47] Fair	All-cause mortality	114 (3)	C-statistic (95% CI): SCORE: 0.73 (NR) SCORE + exercise test: 0.76 (NR), p NR	NR	NR
Chang, 2015[54] Fair	Cardiac events[a]	106 (11)[b]	AUC FRS variables: 0.63 (NR) FRS variables + ETT: NR FRS variables + DTS: NR FRS variables + METS: NR FRS variables + ETT + MET[c]+ DTS[d]: 0.65 (NR) p=0.3 (FRS variables + ETT + MET + DTS vs. FRS variables)	Global χ2 FRS variables: 11.72 FRS variables + ETT[e]: 16.16 p=0.04 (FRS + ETT vs. FRS) FRS variables + DTS: 14.59 p=0.24 (FRS + DTS vs. FRS) FRS variables + METS: 14.68 p=0.03 (FRS + METS vs. FRS)	**NRI % for FRS variables + ETT (p Value vs FRS variables)** All patients: 9.6 (0.007); Appropriate Use Cohort[f]: 11.1 (0.005) Low risk: 0 (1.0); Intermediate risk: 18.9 (0.01); High risk: 8.1 (0.38) **Absolute IDI % for FRS variables + ETT (p Value vs FRS variables)** All patients: 1.4 (0.006); Appropriate Use Cohort: 1.6 (0.006) Low risk: 0.1 (0.75); Intermediate risk: 1.7 (0.01); High risk: 0.88 (0.39) **Relative IDI % for FRS variables + ETT (p Value vs FRS variables)** All patients: 110 (<0.0001); Appropriate Use Cohort: 128 (<0.0001) Low risk: 591 (0.35); Intermediate risk: 92 (0.004); High risk: 522 (0.19)
Cournot, 2006[48] Fair	Total coronary events[g] (CE)	34 (3)[h]	NR	FRS Model vs. FRS Model + exercise test (ET) results Likelihood ratio test: *Whole sample (n=1051) p*=0.13[i] *Subgroup with pre-test Framingham risk ≥10.4% (n=526):* p=0.06[j]	NR
Cournot, 2009[55] Fair	Definite coronary events[k]	94 (4)[l]	FRS vs. FRS + femoral bruit + positive exercise test[m] *AUROC (95% CI):* 0.732 (NR) vs. 0.762 (NR), p NR *Sensitivity, %:* 3.2 vs. 8.5 *Specificity, %:* 99.4 vs. 98.6 *Positive predictive value, %:* 15.8 vs. 19.1 *Negative predictive value, %:* 96.4 vs. 96.6	FRS vs. FRS + femoral bruit + positive exercise test[m] *Hosmer-Lemeshow chi-square:* P=0.99 vs. P=0.99 *Akaike information criterion:* 748.9 vs. 727.8 *Brier's score:* 0.035 vs. 0.033	NR

Table 5. Results of Included Studies for KQ 2 That Evaluated Exercise ECG

First Author, Year, Quality	Outcome	N (%) With Outcome	Discrimination	Calibration	Reclassification
Erikssen, 2004[56] Fair	CHD Mortality[n]	300 (15)	NR	CRF vs. CRF+X models[o], Predicted (observed) events: *CRF, Assessment 1, 26-year follow-up* <8.9%: 30.1 (37) 8.9–11.3%: 41.3 (44) 1.4–15.2%: 54.2 (52) 15.3–20.0%: 70.4 (65) >20.0%: 104.1 (102) Total: 300.1 (300) *CRF+X, Assessment 1, 26-year follow-up* <7.2%: 24.8 (27) 7.2–10.2%: 37.2 (37) 10.3–14.1%: 49.2 (47) 14.2–20.8%: 67.8 (69) >20.8%: 121.2 (120) Total: 300.2 (300) *CRF, Assessment 2, 19-year follow-up* <8.9%: 14.7 (16) 8.9–11.3%: 19.9 (19) 1.4–15.2%: 24.9 (21) 15.3–20.0%: 32.4 (38) >20.0%: 51.0 (49) Total: 142.9 (143) *CRF+X, Assessment 2, 19-year follow-up* <7.2%: 10.7 (10) 7.2–10.2%: 15.9 (18) 10.3–14.1%: 21.8 (27) 14.2–20.8%: 30.6 (23) >20.8%: 64.0 (65) Total: 142.9 (143) *CRF, Assessment 1 with Insertion of Assessment 2 data for those who remained healthy (at 2), 19-year follow-up* <8.9%: 15.8 (18) 8.9–11.3%: 21.4 (20) 1.4–15.2%: 27.1 (25) 15.3–20.0%: 36.0 (32) >20.0%: 58.6 (48) Total: 158.9 (143) *CRF+X, Assessment 1 with Insertion of Assessment 2 data for those who remained healthy (at 2), 19-year follow-up* <7.2%: 8.0 (12)	NR

Table 5. Results of Included Studies for KQ 2 That Evaluated Exercise ECG

First Author, Year, Quality	Outcome	N (%) With Outcome	Discrimination	Calibration	Reclassification
				7.2–10.2%: 14.9 (15) 10.3–14.1%: 23.3 (30) 14.2–20.8%: 35.6 (31) >20.8%: 76.5 (55) Total: 158.3 (143)	

[a] Cardiac events were defined as a composite of cardiac death, nonfatal MI, and the need for coronary revascularization following the development of symptomatic CAD.
[b] The 106 events included 17 cardiac death, 16 nonfatal MIs, and 73 coronary revascularizations.
[c] Metabolic equivalents of task (peak exercise capacity was determined from the ETT to determine METs, and it was categorized as >8, 5 to 8, or <5).
[d] Duke treadmill score (it was categorized as low, 5 or more, intermediate, 4 to -10, or high, -11 or less)
[e] ETT is based on criteria for determining ischemia (separate from DTS or METs from the exercise test)
[f] Appropriate use cohort was 824 patients (87% of the total cohort) considered acceptable candidates for functional testing on the basis of recent appropriate use criteria (i.e., intermediate to high FRS risk and/or chest pain symptoms).
[g] Total coronary events included cardiac deaths, sudden deaths, acute MI, and stable or unstable angina.
[h] Including 6 cardiac deaths, 13 stable or unstable angina events, and 15 nonfatal MI. Number of sudden deaths NR.
[i] When adjusting for age, sex, current tobacco consumption, systolic blood pressure, total cholesterol, HDL cholesterol and diabetes (instead of 10-year Framingham risk of CHD), reported p was 0.10.
[j] When adjusting for age, sex, current tobacco consumption, systolic blood pressure, total cholesterol, HDL cholesterol and diabetes (instead of 10-year Framingham risk of CHD), reported p was 0.03.
[k] Definite coronary events included cardiac deaths, sudden deaths, acute MI, and stable or unstable angina. Revascularization (coronary artery bypass surgery or percutaneous coronary intervention) without clinical symptom was not considered as a coronary event.
[l] Study reported 8 with sudden death or fatal MI, 24 with nonfatal MI, 15 with acute coronary syndromes, and 47 with stable angina.
[m] All of the models considering the exercise test variable also included femoral bruit because it had been significant in adjusted HRs. The article provides data for FRS + femoral bruit also, showing that there was little to no change with its addition, e.g., AUROC 0.732 (same as for the model with FRS only).
[n] Deaths caused by ischemic heart disease and sudden, unexpected deaths were classified as coronary deaths. Cardiovascular deaths also include deaths caused by stroke and ruptured aortic aneurysms.
[o] Exercise predictors: Physical fitness (cumulative work during exercise divided by body weight), maximal heart rate, systolic blood pressure at end of the first exercise load (100 W), and exercise ECG interpretation (ST-depression of at least 1.0 mm 0.08 s after the J-point regardless of ST-segment morphology)

Abbreviations: AUC=area under the curve; AUROC=area under the receiver operating characteristic curve; CHD=coronary heart disease; CRF=classical risk factors; DTS=Duke treadmill score; ECG=electrocardiogram; ETT=exercise treadmill testing; MET=metabolic equivalents of task; FRS=Framingham Risk Score; IDI=integrated discrimination improvement; KQ=key question; N=sample; NR=not reported; NRI=net reclassification improvement; SCORE=Systematic COronary Risk Evaluation.

Table 6. Characteristics of Included Studies for KQ 2 That Evaluated Resting ECG, Part 1

First Author, Year Quality	ECG Findings Evaluated	Model Type: Base model	Cohort	Source of Patients	Country
Auer et al, 2012[58] Good	Major[a] and minor[b] 12-lead ECG abnormalities classified using the Minnesota Coding System	Both types evaluated Model development: (1) FRS variables[c] and diabetes (2) FRS variables only Published coefficient: FRS	Health, Aging, and Body Composition Study (Health ABC) Study)	Population-based cohort assessing body composition, long-term conditions, and incident mobility limitation in an older adult cohort (1997–98)	U.S.
Badheka et al, 2013[57] Fair	Major and Minor 12-lead ECG abnormalities classified using the Minnesota Coding System[d]	Published coefficient: FRS	NHANES-III	Population-based survey to collect information on the health and nutrition of U.S. households (1988–1994).	U.S.
Badheka et al, 2013[63] Fair	12-lead ECG ST-T wave abnormalities in lead aVR classified by the Minnesota Code	Published coefficient: FRS	NHANES-III	Population-based survey to collect information on the health and nutrition of U.S. households (1988–1994).	U.S.
Denes 2007[49] Fair	Major,[e] minor,[f] and incident[g] 12-lead ECG changes using the Novacode criteria	Published coefficient: FRS	WHI Study (estrogen + progestin trial)	Population-based study on common causes of morbidity/mortality among postmenopausal women (1993–1998).	U.S.
Folsom 2003[64] Fair	LVH using a 12-lead ECG and the Cornell score	Model development: FRS variables[h]	ARIC	Population-based study of 4 U.S. communities (1987–1989)	U.S.
Ishikawa 2015[61] Fair	Prolonged corrected QT (QTc) intervals[i] and LVH[j] on 12-lead ECG	Model development: FRS variables plus alcohol intake and heart rate[k]	The Jichi Medical School Cohort	Government-sponsored screening to clarify the risk factors for cardio/cerebrovascular diseases in the general population (1992-1995)	Japan
Jorgensen 2014[60] Fair	Major and Minor 12-lead ECG abnormalities classified using Minnesota Code; also reported outcomes for some single ECG changes[m]	Model development: FRS variables[l]	The Copenhagen City Heart Study	The Copenhagen City Heart Study (1976–1978)	Denmark
Shah, 2016[59] Fair	ECG Risk Score including frontal T axis, corrected QT interval, T axis, heart rate, age, sex, age*sex interaction term (selected from major[o] and minor[p] abnormalities)	Both types evaluated Published coefficient: FRS[n] and PCE Model development: FRS variables	NHANES I (development cohort) and NHANES III (validation cohort)	Population-based survey to collect information on the health and nutrition; NHANES I (1971–1975) and NHANES III (1988–1994)	U.S.
Tereshchenko, 2014[62] Fair	Resting 12-lead, P wave morphology (specifically DTNPV1[r])	Model development: FRS variables[q]	ARIC	Population-based study of 4 U.S. communities (1987–1989)	U.S.

[a] Criteria for major prevalent ECG abnormalities were any of the following: Q-QS wave abnormalities (MC 1-1 to 1-2-8); left ventricular hypertrophy (MC 3–1); Wolff-Parkinson-White syndrome (MC 6-4-1 or 6-4-2); complete bundle branch block or intraventricular block (MC 7-1-1, 7-2-1, 7–4, or 7–8); atrial fibrillation or atrial flutter (MC 8–3); or major ST-T changes (MC 4–1, 4–2, 5–1, and 5–2).

Table 6. Characteristics of Included Studies for KQ 2 That Evaluated Resting ECG, Part 1

[b] Criteria for minor prevalent ECG abnormalities were minor ST-T changes (MC 4– 3, 4-4, 5–3, and 5–4). Participants with both major and minor abnormalities were classified as having major abnormalities. Participants without minor or major ECG abnormalities were classified as having marginal or no abnormalities and their ECG was considered normal.
[c] FRS variables were age, sex, total and HDL-C systolic blood pressure, and smoking.
[d] Individuals with any of the following at baseline were considered to have ECG abnormalities: possible or probably MI, cardiac infarction/injury score of >=10, possible or probably left ventricular hypertrophy, any axis deviation, and any rhythm abnormalities other than sinus.
[e] Criteria for major prevalent ECG abnormalities were any of the following: (1) atrial fibrillation or atrial flutter; (2) high-degree atrioventricular dissociation; (3) left bundle-branch block; (4) right bundle-branch block; (5) indeterminate conduction delay; (6) Qwave MI; (7) isolated ischemic abnormalities; (8) left ventricular hypertrophy with ST-T abnormalities; and (9) miscellaneous arrhythmias (e.g., supraventricular tachycardia, ventricular preexcitation, ventricular tachycardia) with less than 5 participants being included in the analysis and not listed individually. Women with both major and minor abnormalities were classified as having major abnormalities.
[f] Criteria for minor prevalent ECG abnormalities were any of the following: (1) first- and second-degree atrioventricular block; (2) borderline prolonged ventricular excitation; (3) prolonged ventricular repolarization; (4) isolated minor Q and ST-T abnormalities; (5) left ventricular hypertrophy without ST-T abnormalities; (6) left atrial enlargement; (7) frequent atrial or ventricular premature beats; and (8) fascicular blocks.
[g] Criteria for incident ECG abnormalities were any of the following: (1) new atrial fibrillation or flutter; (2) new prolonged ventricular excitation; (3) new prolonged ventricular repolarization; (4) new left ventricular hypertrophy; (5) new Q-wave MI; and (6) new ischemic ST-T evolution.
[h] model included age, race, total & HDL cholesterol, systolic blood pressure, use of antihypertensive medication, and smoking status
[i] QTc determined by Bazett QTc intervals of ≥440 ms in men and ≥460 ms in women on a 12-lead ECG
[j] LVH diagnosed with Cornell product of >=244 mVxms
[k] model included age, sex, body mass index, current smoking, alcohol intake >20 g/d, systolic blood pressure, antihypertensive medication use, diabetes mellitus, hyperlipidemia, and heart rate.
[l] Model included age, systolic blood pressure, total cholesterol, sex, current smoking, and diabetes
[m] Reported outcomes for major or minor ECG changes, T wave changes, ventricular conduction delay, LVH, Q waves, ST depressions, resting heart rate
[n] FRS model includes age, sex, systolic and diastolic blood pressure, diabetes, tobacco use, total and HDL-C levels, and use of antihypertensives
[o] Major ECG abnormalities were defined based on Minnesota codes as follows: Major Q/QS waves (1.1, 1.2), ST depression (4.1, 4.2), negative T waves (5.1, 5.2), ventricular conduction defect (7.1, 7.2, or 7.4), atrial fibrillation/flutter (8.3), or ST elevation (9.2).
[p] Minor ECG abnormalities were defined as having Minnesota codes for Minor Q waves (1.2.8 or 1.3), high R waves (3.1 or 3.3), minor ST changes (4.3 or 4.4), minor T wave changes (5.3 or 5.4), prolonged PR interval (6.3), RR' in V1 or V2 (7.3 or 7.5), or left anterior fascicular block (7.7).
[q] FRS components: age, gender, systolic blood pressure, diabetes, HDL and total cholesterol, smoking, and blood pressure-lowering therapy)
[r] Deep terminal negativity of P wave in V1

Abbreviations: ARIC=Atherosclerosis Risk in Communities; ECG=electrocardiogram; FRS=Framingham Risk Score; HDL-C= high-density lipoprotein cholesterol; LVH=Left ventricular hypertrophy; NHANES-I= National Health and Nutrition Examination Survey-i; NHANES-III= National Health and Nutrition Examination Survey-III; PCE=pooled cohort equation; U.S.=United States; WHI=Women's Health Initiative.

Table 7. Characteristics of Included Studies for KQ 2 That Evaluated Resting ECG, Part 2

First Author, Year, Quality	Sample Size	Years of Follow-up	% CVD	% With Symptoms	Mean Age (SD)	% F	% Non-white	CV Risk	Mean BMI (SD)	% HTN	% DM	% Smokers
Auer et al, 2012[58] Good	2192	Median: 8.2	0	NR	73.5 (2.8)	55	41	FRS mean (SD): 12.6 (7.3[a]) Mean intermediate risk	27.4 (4.9)	57.3	13.3	Current: 10.1 Former: 43.6
Badheka et al, 2013[57] Fair	6025	Mean 13	0	NR[b]	58.7 (13)	54	12	<5: 3391 (59%) 5-10: 987 (17%) 10-20: 854 (15%) >20: 497 (9%) Most low risk	27.2 (5)	40	0	24
Badheka et al, 2013[63] Fair	7928	Mean13.5	CAD: 9.8 MI: 5.4 HF: 2.8 Stroke: 2.9 Total: 15.4	NR	59.9 (13.4)	55	9.2	<5: 2625 (35%) 5-10: 1221 (16%) 10-20: 1487 (20%) >20: 2176 (29%) Most low risk	27.6 (5.5)	43.8	10.9	23.1
Denes 2007[49] Fair	1,264[c]	Mean 5.6	0	NR	63	100	16	NR	28-29[d] (5.6-6.2)	55-75	4	Past: 40 Current: 10
Folsom 2003[64] Fair	14,054	Median: 10.2	0 with history of CHD	NR	Median: 55 (range 45-64)	57	NR[e]	NR	NR	NR	10.7	NR
Ishikawa 2015[61] Fair	10,643	Mean 10.7	Unclear, but likely small %[f]	NR	55.4 (11.2)	62	NR	<2.5: 4648 (55%) 2.5-5: 1819 (22%) >5: 1986 (23%) Most low stroke risk	23.1 (3.1)	33.9	3.6	22.6
Jorgensen 2014[60] Fair	6991[gi]	Median 11.9[h]	0	NR	70 (4)	59	NR	FRS[i] 25.9-33.4 Mean high risk	26 (4.3)	NR	5	47
Shah, 2016[59] Fair	9969 (derivation: 3640, validation: 6329)	Median: 18.8 (derivation), 10 (validation)	0	NR	Total: 55.3 (10.1)	53	Derivation: 11 Validation: 26.6	NHANES ECG risk equation scores: 9.02 (0.79); 8.96 (0.86) Possibly low risk	NR	Antihypertensive use: 7.5; 20.4	4.9; 16.6	34.3; 25.5[j]
Tereshchenko, 2014[62] Fair	15,375[k]	Median 14	CHD: 5% HF:5% MI: 4% Stroke: 2%	NR[l]	54 (5.8)	55	27	<5: 12,463 (96%) 5-20: 565 (4%) >20: 21 (0.2%) Most low SCD risk	28 (5.5)	25	10	26

[a] Breakdown by FRS Categories by % 10-year risk was as follows: <5.0: 297 (13.6); 5.0-9.9: 525 (23.9); 10.0-19.9: 853 (38.9); ≥20.0: 517 (23.6)
[b] Study excluded those with self-reported chest pain suggestive of angina or leg pain suggestive of claudication
[c] The number of participants shown here is the number in analyses eligible for our review. The authors used the 1,264 participants in the WHI blood subsample for the eligible analyses (the larger study included 14,749 participants, 7593 from the estrogen + progestin group and 7,156 from the placebo group).
[d] When this table includes a range, it means that the data were not reported for the full sample, but were reported separately for subgroups

Table 7. Characteristics of Included Studies for KQ 2 That Evaluated Resting ECG, Part 2

[e] % nonwhite was NR for full sample but the authors reported that 45% of diabetic participants were black.
[f] Exclusion criteria listed pacemaker implantation, atrial fibrillation, advanced or complete atrioventricular block, dextrocardia, complete left or right bundle block, heart rate over 150 bpm, and history of stroke or MI, but did not address history of CHD, TIA, angina, or PAD.
[g] For sample with >=10 years follow-up (sample used to calculate discrimination and reclassification outcomes): 4923 had >=10 years of follow-up for the endpoint of fatal CVD, 5418 had >=10 years of follow-up for the endpoint of fatal and nonfatal CVD, and 6907 had >=10 years of follow-up for the endpoint of all-cause mortality.
[h] Median for fatal CVD (primary outcome was 10.9); median for fatal or nonfatal CVD combined (secondary endpoint) was 9.8 years, and median for all-cause mortality was 11.9 years.
[i] Baseline risk from the SCORE Risk Model: For participants with no ECG Changes: 13.1 (8.0–21.1); for those with ECG Changes: 18.3 (10.7–29.6)
[j] When 2 numbers are present in these, they are for derivation cohort and the validation cohort
[k] 13,049 CVD-free persons were in the reclassification analyses
[l] The study defined prevalent CHD to include those with symptoms of angina or claudication as well as those with diagnoses of CHD.

Abbreviations: AUC=area under the curve; CAD=coronary artery disease; CHD=coronary heart disease; CV=cardiovascular; CVD-cardiovascular disease; DM=diabetes mellitus; FRS=Framingham Risk Score; HF=heart failure; HTN=hypertension; MI=myocardial infarction; NHANES=National Health and Nutrition Examination Survey; NR=not reported; SCD=spontaneous cardiac death; SD=standard deviation.

Table 8. Summary of Evidence for Screening with ECG

Key Question and Topic	No. of Studies & Study Design	N	Summary of Main Findings (Including Consistency and Precision)	Quality	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
1: Benefits of screening with ECG	2 RCTs	1,151	Neither study found a statistically significant reduction in events, including their primary outcomes,[a] all-cause mortality, cardiovascular-related mortality, MI, heart failure, or stroke. Findings were consistent and imprecise.	Fair	Neither trial reached sample size targets; stopped early because of trouble recruiting. Not clear that 3.5 years of followup is sufficient. Masking of outcome assessors and amount of missing data NR in 1.[53] Reporting bias not detected.	Low for no benefit of screening with exercise ECG Insufficient for resting ECG; no studies	Asymptomatic adults ages 50 to 75 years with diabetes undergoing exercise ECG; both trials enrolled high risk populations
2: Reclassification, calibration, and discrimination for exercise ECG	5 cohort studies	9,582	Discrimination (k=3): small absolute improvement in AUC or C-statistics (0.02–0.03); none reported 95% CIs; 1 reported p=0.3 (no significant difference between models). Consistent; imprecise. Calibration or performance (k=4 total; k=2 FRS base model): all 4 used different metrics;[b] none reported figures such as calibration plots;[c] k=3 reported improvement with addition of exercise ECG variables; mixed results for the 2 with FRS base models. Inconsistent; imprecise. Reclassification (k=1 model development study, 988 participants): Total NRI 9.6% (p=0.007); intermediate risk group NRI 18.9% (p=0.01). Consistency unknown; imprecise.	Fair	Confidence intervals for calibration or discrimination NR (k=5); mean duration of followup <10 years[d] (k=4), reclassification NR (k=4); unknown masking of outcome assessors (k=4); not reporting both discrimination and calibration (k=3); model development studies (k=2); unclear handling and amount of missing data (k=2); the 1 study reporting NRI was a model development study, used risk categories of <6% vs. 6–20% vs. >20% and may have included many symptomatic participants.[e] Reporting bias not detected.	Discrimination: Low for small improvement Calibration: Insufficient Reclassification: Insufficient	Adults without a history of CVD; mean age of participants 50–58 years; range of females was 0–38%; race/ethnicity NR in most (k=4); mean baseline FRS score was 10.8–12.3 in studies reporting it (k=3); intermediate risk, on average
2: Reclassification, calibration, and discrimination for resting ECG	9 cohort studies	66,407	Discrimination (k=7 total; k=4 FRS or PCE base model; k=4 multiple ECG changes): very small to small absolute improvement in AUC or C-statistics (0.001–0.05); Few (k=3) reported whether differences were statistically significant. Consistent; imprecise. Calibration or performance (k=4 total; k=2 FRS + major/minor ECG changes; k=1 FRS + specific T wave change): none reported calibration plots; variety of metrics used; good calibration with addition of major/minor	Fair[f]	Limited reporting on assessment of symptoms; unclear what proportion of participants were truly asymptomatic; masking of outcome assessors NR (k=8), confidence intervals for calibration or discrimination NR (k=5), not reporting calibration (k=5), model development studies (k=4), amount of missing data NR (k=2), and mean duration of followup less	Discrimination: Low for very small to small improvement Calibration: Low for improvement Reclassification: low for improvement	Adults without a history of CVD; mean age of participants 54–73; majority were women in all studies; range of nonwhite participants in those that reported race/ethnicity (k=6) was 9–

Table 8. Summary of Evidence for Screening with ECG

Key Question and Topic	No. of Studies & Study Design	N	Summary of Main Findings (Including Consistency and Precision)	Quality	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
			changes (k=2) or T wave amplitude in lead aVR (k=1) to FRS. Poor calibration with addition of major/minor changes to FRS variables (k=1 model development of older adults 70–79). Consistent among studies using published coefficients (k=3); imprecise. Reclassification (k=7 total with 59,123 participants; k=3 FRS or PCE + multiple ECG changes; k=1 FRS + specific T wave change). Overall, total NRIs (event; nonevent) range from 3.6% (2.7%; 0.6%) to 30% (17%; 19%) for studies using FRS or PCE base models (95% CIs rarely reported [**Figure 7**]).[g] Consistent in all showing improved NRI, but inconsistent for estimates of NRI and outcomes assessed; consistency unknown for specific risk categories because all studies used different risk categories; imprecise.		than 10 years (k=2). For reclassification, few studies (k=3) included a threshold between risk categories corresponding to the recommendations for preventive medications (i.e., 7.5% or 10% 10-year risk).		41%. Mean baseline risk ranging from low to high across studies
3: Harms of screening with ECG	1 RCT	520	One patient out of 12 (8.3%) undergoing revascularization procedures after positive exercise treadmill tests in the DADDY-D trial had a nonfatal acute MI 3 days after percutaneous revascularization and underwent a second percutaneous angioplasty.[h] Consistency unknown (single study); imprecise.	Fair	Trial focused on assessing benefits; did not reach sample size target; not clear that mean of 3.6 years of followup is sufficient; masking of outcome assessors NR and amount of missing data NR. Reporting bias not detected.	Insufficient	Asymptomatic adults ages 55 to 75 years with diabetes undergoing screening with exercise ECG

[a] For the primary composite outcomes, HRs were 1.00 (0.59 to 1.71) for a composite of death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention, and 0.85 (0.39 to 1.84) for a composite of nonfatal MI or cardiac death.
[b] Metrics included likelihood ratio test; Akaike information criteria (AIC), Brier's score, and Hosmer-Lemeshow $\chi 2$; global $\chi 2$; and numbers of predicted and observed events.
[c] One model development study provided a table of predicted and observed events for quintiles of risk.[56]
[d] The only study reporting longer followup covered 26 years, but it did not account for HDL in analyses.[56]
[e] 16.5% had atypical chest pain and participants were a subset of those having CACS and SPECT for "clinically indicated reasons." [54]
[f] One study was rated good quality. All others were rated fair quality.
[g] For multiple ECG changes (on resting 12-lead ECG), total NRIs (event NRIs; nonevent NRIs) for studies using any base model ranged from 1.9% (-0.2%; 0.6%) to 30% (17%; 19%).
[h] The DADDY-D trial reported that 20/262 participants (7.6%) in the screened group had positive ETTs. Of those 20, 17 underwent coronary angiography (6.5% of the 262). Angiography revealed critical stenosis (not defined) in 71% (12/17), and all patients with critical stenosis underwent revascularization procedures (7 percutaneous, 5 surgical). The DYNAMIT trial (included in KQ 1) reported the number of some subsequent tests but did not report whether any of the tests or interventions resulted in harms; adverse events that

Table 8. Summary of Evidence for Screening with ECG

occurred during followup were not recorded.[52] Sixty eight of the 316 participants (21.5%) in the screened group had a definitely abnormal or an uncertain screening test (exercise test or SPECT) result. Of those, 38 underwent coronary angiography (12% of the 316 in the screened group) and 9 subsequently underwent coronary angioplasty (7/9 received stents) and 3 had coronary artery bypass graft.

Abbreviations: AIC=Akaike information criteria; AUC=area under the curve; CACS=coronary artery calcium score; CI=confidence interval; CVD=cardiovascular disease; DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; ECG=electrocardiogram; FRS=Framingham Risk Score; HDL=high-density lipoprotein; HR=hazard ratio; k=number of studies; KQ=key question; MI=myocardial infarction; N=number; NR=not reported; NRI=net reclassification improvement; PCE=pooled cohort equation; RCT=randomized, controlled trial; SPECT=single-photon emission computed tomography.

Table 9. Snapshot to Assess Net Benefit

	KQ	Exercise ECG	Resting ECG	Considerations
Benefits	KQ 1: Benefits of screening	k=2; n=1,151 **No statistically significant difference** in primary composite outcomes, all-cause mortality, CV-related mortality, MI, heart failure, or stroke at 3.5 years	No evidence	Despite enrolling high-risk persons with diabetes, neither trial found benefit. But neither reached sample size targets; stopped early because of trouble recruiting. Findings were imprecise. Not clear that 3.5 years of followup is sufficient. Masking of outcome assessors and amount of missing data not reported in 1 trial.
	KQ 2: Calibration	k=4; n=6,762 **Mixed results** (and all 4 used different metrics)	k=4; n=17,409 **Improved calibration** among studies using published coefficients of FRS (k=3). Poor calibration in 1 model development of older adults ages 70–79 years.	Preferred measures rarely reported. **For resting ECG**: none reported calibration plots; limited reported on assessment of symptoms; unclear what proportion of participants were truly asymptomatic; majority of the resting ECG studies did not report calibration (k=5 out of 9); imprecise.
	KQ 2: Discrimination	k=3; n=7,251 **Small improvement**	k=7; n=44,699 **Very small to small improvement**	Overall, results were consistent but imprecise. **For exercise ECG**: 95% CIs were not reported (1 reported p=0.3, no significant difference between models). **For resting ECG:** k=4 FRS or PCE base model; few (k=3) reported whether differences were statistically significant.
	KQ 2: Reclassification	k=1; n=988 **Small improvement** (total NRI 9.6%, p=0.007; intermediate risk group NRI 18.9%, p=0.01)	k=7; n=59,123 **Small to moderate improvement** for studies using FRS or PCE base models (k=4): total NRIs (event; nonevent) range from 3.6% (2.7%; 0.6%) to 30% (17%; 19%)	Heterogeneity and applicability of risk thresholds; 95% CIs rarely reported. **For exercise ECG**: 1 model development study that used risk categories of <6% vs. 6–20% vs. >20% and may have included many symptomatic participants. **For resting ECG**: consistent in all showing improved NRI but inconsistent for estimates of NRI and outcomes assessed; consistency unknown for specific risk categories because all studies used different risk categories.
Harms	KQ 3: Screening	k=1; n=520 1/12 persons (8.3%) undergoing revascularization after positive exercise tests had a nonfatal acute MI 3 days after the procedure	No evidence	Only 1 study eligible with 1 event reported. More information about potential harms is in the Discussion and contextual question 2.

Abbreviations: CI=confidence interval; CV=cardiovascular; ECG=electrocardiogram; FRS=Framingham Risk Score; KQ=key question; MI=myocardial infarction; NRI=net reclassification improvement; PCE=pooled cohort equation.

Appendix A Table 1. Recent Recommendations on Screening for CVD Using ECG

Organization	Population	Recommendation
ACP, 2015[1]	Asymptomatic low-risk adults	Do not screen for cardiac disease in asymptomatic, low-risk adults with resting or stress ECG.
ACC Foundation/AHA/ASE/ ASNC/HFSA/HRS/SCAI/ SCCT/SCMR/STS, 2014[2]	Low global risk; regardless of ECG interpretability and ability to exercise Intermediate global risk; ECG interpretable and able to exercise	Exercise ECG is rarely an appropriate option because of the lack of a clear benefit/risk advantage. Exercise ECG may be an appropriate option because of variable evidence or agreement regarding the benefit/risk ratio, potential benefit based on practice experience in the absence of evidence, and/or variability in the population.
AAFP, 2012[3]	Asymptomatic low-risk adults	Do not order annual ECGs or any other cardiac screening.
ACPM, 2011[4]	General adult population	Do not routinely screen the general adult population using resting or exercise ECG.
ACC/AHA, 2010[5]	Asymptomatic adults **with** hypertension or diabetes Asymptomatic adults **without** hypertension or diabetes Intermediate-risk asymptomatic adults (including sedentary adults considering starting a vigorous exercise program)	A resting ECG is reasonable for cardiovascular risk assessment. A resting ECG may be considered for cardiovascular risk assessment. An exercise ECG may be considered for cardiovascular risk assessment, particularly when attention is paid to non-ECG markers such as exercise capacity.
AHA, 2005[6]	Asymptomatic adults	There is insufficient evidence to recommend exercise testing as a routine screening modality.

Abbreviations: AAFP=American Academy of Family Physicians; ACC=American College of Cardiology; ACP=American College of Physicians; ACPM=American College of Preventive Medicine; AHA=American Heart Association; ASA=American Stroke Association; ASE=American Society of Echocardiography; ASNC=American Society of Nuclear Cardiology; CVD=cardiovascular disease; ECG=electrocardiogram; HFSA=Heart Failure Society of America; HRS=Heart Rhythm Society; Royal College of Physicians of Edinburgh; SCAI=Society for Cardiovascular Angiography and Interventions; SCCT=Society of Cardiovascular Computed Tomography; SCMR=Society for Cardiovascular Magnetic Resonance; STS=Society of Thoracic Surgeons.

Appendix A Table 2. Characteristics of Available and Recommended Cardiovascular and Coronary Risk Assessment Models

Risk Score and Recommending Body	Risk Factors Included in the Model	Time Horizon and Outcome	Derivation and External Validation Cohorts	Limitations
ACC/AHA Pooled Cohort Equation, 2013[7] ACC/AHA[8]	• Age • Sex • Race/ethnicity • Treated or untreated SBP • TC • HDL-C • Current smoking • Diabetes Other CVD risk factors evaluated but not included[a]	10-year risk First hard CVD event (nonfatal MI, CHD death, fatal or nonfatal stroke)	Derivation Cohorts: ARIC, CHS, CARDIA, Framingham/Framingham Offspring External Validation Cohorts: REGARDS, MESA, Contemporary Cohort (ARIC, Framingham/ Framingham Offspring), Rotterdam Study, WHS, PHS, WHI Observational Study	Baseline exams for source cohorts conducted >25 years ago No equations for Hispanics or Asians; lack of large external datasets with needed covariate data to validate in these subpopulations Small numbers of events in validation cohorts, particularly in lower-risk groups Possible overprediction across risk strata
Framingham CVD, 2008[9] Canadian Cardiovascular Society[10]	• Age • Sex • TC • HDL-C • SBP • Antihypertensive medication use • Smoking • Diabetes • (Family history)[b]	10-year risk Any CVD event (coronary death, MI, coronary insufficiency, angina), cerebrovascular events, peripheral artery disease (intermittent claudication), and congestive heart failure	Derivation Cohort: Framingham External Validation Cohorts: MESA, WHI Observational Study	Not limited to "hard" outcomes Baseline exams for source cohorts conducted >40 years ago Derivation cohort predominately white with high proportion of smokers (~40%) Possible overprediction, potentially higher among men
QRISK2, 2008[11] NICE[12]	• Age • Sex • Race/ethnicity • Smoking status • SBP • TC:HDL-C ratio • Body mass index • Family history of CHD in first-degree relative aged <60 years • Townsend deprivation score • Treated hypertension • Rheumatoid arthritis • Chronic kidney disease • Diabetes • Atrial fibrillation	10-year risk CVD event (angina, MI, stroke, TIA)	Derivation Cohort: U.K. primary care database; 2/3 of participants randomly allocated to derivation dataset and 1/3 assigned to validation dataset External Validation Cohort: N/A	Not externally validated Derivation cohort predominantly white Recording of family history of CHD possibly not systematic Townsend deprivation score specific to the United Kingdom

Appendix A Table 2. Characteristics of Available and Recommended Cardiovascular and Coronary Risk Assessment Models

Risk Score and Recommending Body	Risk Factors Included in the Model	Time Horizon and Outcome	Derivation and External Validation Cohorts	Limitations
Reynolds, men, 2008[13] N/A	• Age • SBP • Smoking • TC • HDL-C • hs-CRP • Parental history of MI at <60 years of age	10-year risk CVD event (CVD death, MI, stroke, coronary revascularization)	Derivation Cohort: PHS External Validation Cohort: MESA	Derivation cohort predominately white Derivation cohort health professionals; health behaviors, access to health care, and SES may not be generalizable Data on blood pressure, obesity, and family history based on self-report Uncertain applicability in men <50 years old and those with diabetes
Reynolds, women, 2007[14] N/A	• Age • SBP • Smoking • TC • HDL-C • hs-CRP • Parental history of MI at <60 years of age • HbA1c if diabetic	10-year risk CVD events (CVD death, MI, stroke, coronary revascularization)	Derivation Cohort: WHS; 2/3 of participants assigned to model derivation dataset and 1/3 assigned to validation dataset External Validation Cohorts: MESA, WHI Observational Study	Derivation cohort predominately white Derivation cohort health professionals; health behaviors, access to health care, and SES may not be generalizable Data on blood pressure, obesity, and family history based on self-report Possible underprediction
ASSIGN, 2007[15] SIGN[16]	• 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)	Derivation Cohort: SHHEC External Validation Cohort: U.K. general practice database	Not externally validated in the United States Baseline exams for source cohort conducted >30 years ago Social deprivation index specific to Scotland High prevalence of smoking (~40%) and family history (~20%) in source cohort
ARIC, 2003[17] N/A	• Sex • Race • Cigarette smoking • TC • HDL-C • SBP • Antihypertensive medication use • Diabetes Other CVD risk factors evaluated but not included[c]	10-year risk CHD event (CHD death, MI, unrecognized MI defined by electrocardiogram readings, or coronary revascularization)	Derivation Cohort: ARIC External Validation Cohort: N/A	Not externally validated Baseline exams for source cohorts conducted >25 years ago Not limited to "hard" outcomes Race/ethnicity limited to blacks and whites Source cohort not inclusive of age <45 or >65 years

Appendix A Table 2. Characteristics of Available and Recommended Cardiovascular and Coronary Risk Assessment Models

Risk Score and Recommending Body	Risk Factors Included in the Model	Time Horizon and Outcome	Derivation and External Validation Cohorts	Limitations
SCORE, 2003[18] European Society of Cardiology[19]	• 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)	Derivation Cohort: Pooled dataset of population-based and occupational cohort studies from 12 European countries External Validation Cohorts: Externally validated in European cohorts (11 evaluation studies)	Not externally validated in the United States Baseline exams for source cohorts conducted >25 years ago Diabetes not included as a risk factor because it was not uniformly collected in source cohort
PROCAM, 2002[20] N/A	• Age • LDL-C • HDL-C • Triglycerides • Smoking • Diabetes • Family history of MI at age <60 years • SBP	10-year risk CHD event (sudden cardiac death, definite MI)	Derivation Cohort: Prospective German cohort of men External Validation Cohorts: Externally validated in several European cohorts	Not externally validated in the United States Baseline exams for source cohort conducted >30 years ago Excludes women and adults >65 years old Source cohort ~30% smokers
ATP III modification of Wilson Framingham model, 2002[21d] ATP III[21e]	• Age • Sex • TC • HDL-C • SBP • Treatment for hypertension • Smoking	10-year risk Hard CHD (MI death, CHD death)	Derivation Cohort: Framingham External Validation Cohorts: ATP III: MESA, WHI Observational Study Wilson: wide range of cohorts in United States, Europe, and Australia, including ARIC, PHS, HHP, PR, SHS, CHS	Baseline exams for source cohorts conducted >40 years ago Derivation cohort predominately white with high proportion of smokers (~40%) Most validation cohorts have an upper age range of ages 64 or 74 years Recent external validations of ATP III model suggest substantial overestimation, particularly among men Older validations of the Wilson model show underprediction in high-risk groups (people who have diabetes, have a strong family history of premature CVD, reside in regions with high incidence, have low SES) and overprediction in low-risk groups (Japanese American men, Hispanic men, Native American women)

Appendix A Table 2. Characteristics of Available and Recommended Cardiovascular and Coronary Risk Assessment Models

[a] ACC/AHA recommends that if risk based treatment is uncertain using this tool, then consider one or more of the following: family history, hs-CRP, coronary artery calcium score, or ankle-brachial index. Do not use carotid intima-media thickness for risk assessment. No recommendation for or against use of chronic kidney disease, apolipoprotein B, microalbuminuria, and cardiorespiratory fitness.
[b] Canadian Cardiovascular Society recommends a modified version of the model that includes family history of premature CHD.[10]
[c] Other CVD risk factors explored: age, body mass index, waist-to-hip ratio, sport activity index, forced expiratory volume, plasma fibrinogen, factor VII, factor VIII, von Willebrand factor, lipoprotein a, heart rate, Keys score, pack-years smoking, carotid intima-media thickness, fasting triglycerides, apolipoprotein A, apolipoprotein B, albumin, white blood cell count, and creatinine.
[d] There are additional Framingham-based risk assessment models with variations in outcomes predicted and risk factors included.[22-25] In this table we focused on models recommended by guideline bodies.[9, 21]
[e] Replaced by 2014 recommendations from the ACC/AHA.[8]

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; ARIC=Atherosclerosis Risk in Communities Study; ATP III=Adult Treatment Panel III; CARDIA=Coronary Artery Risk Development in Young Adults; CHD=coronary heart disease; CHS=Cardiovascular Health Study; CVD=cardiovascular disease; HbA1c=glycated hemoglobin; HDL-C=low-density lipoprotein cholesterol; HHP=Honolulu Heart Program; hs-CRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; MESA=Multi-Ethnic Study of Atherosclerosis; MI=myocardial infarction; N/A=not applicable; 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; 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; TIA=transient ischemic attack; UK=United Kingdom; U.S.=United States; WHI=Women's Health Initiative Observational Study; WHS=Women's Health Study.

CQ 1a. For people in each CVD risk category (or strata), what medications (i.e., aspirin, lipid-lowering therapy) are recommended?

Several organizations have recommendations for primary prevention of CVD, including the USPSTF, the ACC/AHA, and the American Academy of Family Physicians. European organizations have also weighed in on the subject. Most organizations consider aspirin and statin therapy for primary prevention, while some groups have also considered dietary supplement use.

Aspirin

The USPSTF released their recommendation[26] for the use of aspirin to prevent CVD in April 2016. They recommended initiating low-dose aspirin for adults ages 50 to 59 years with a 10-year CVD risk of 10 percent or greater and who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take daily aspirin for at least 10 years (B recommendation). The USPSTF recommended using the PCE for determination of 10-year risk. The USPSTF also has a C recommendation for adults ages 60 to 69 years (i.e., C recommendation indicating selectively offering this service based on professional judgment and patient preferences; at least moderate certainty that the net benefit is small). For adults less than age 50 years or 70 years or older, the USPSTF concluded there was insufficient evidence to assess the balance of benefits and harms (I statement).

Recommendations from the American Academy of Family Physicians about aspirin use for primary prevention have been consistent with those of the USPSTF. The American College of Chest Physicians suggests that patients older than 50 years without symptomatic CVD use low-dose aspirin for primary CVD prevention.[27] Both the ACC/AHA and the American Stroke Association recommend low-dose aspirin for adults with 10-year CVD risk greater than 6 percent,[28] while the American Diabetes Association[29] recommends low-dose aspirin in patients with both type 1 and 2 diabetes who have 10-year CVD risk greater than 10 percent and are not at increased risk for bleeding. The ADA does not recommend aspirin therapy in men younger than 50 years or most women younger than 60 years who have low CVD risk because the risk for bleeding outweighs the potential benefits of aspirin treatment.

Statins

In December 2016, the USPSTF[30] recommended low- to moderate-dose statins for primary prevention for adults ages 40 to 75 years with one or more CVD risk factors and a 10-year CVD risk of 10 percent or greater (B recommendation). For adults with 10-year CVD risk between 7.5 and 10 percent, the USPSTF made a C recommendation, noting that the likelihood of benefit within this risk category was smaller but some adults might benefit. For adults older than 75 years, the USPSTF concluded the evidence was insufficient to assess the balance of benefits and harms (I statement).

The 2013 ACC/AHA guidelines[31] recommend moderate- to high-intensity statin therapy for adults ages 40 to 75 years with LDL-C 70 to 189 mg/dL with a 10-year CVD risk greater than 7.5 percent as calculated by the PCE (strong recommendation) or if they have diabetes. For those with 10-year CVD risk of 5 percent to 7.5 percent, the ACC/AHA made a "weak recommendation" for using statins for primary prevention. For adults age 21 years or older with LDL-C greater than 190, they recommend statin therapy regardless of CVD risk (moderate recommendation).

The Canadian Cardiovascular Society recommends statins plus behavior modification for men age 40 years or older and women age 50 years or older without CVD risk factors and adults of any age with CVD risk factors who also have a 20 percent or greater 10-year CVD event risk (using FRS) or an LDL-C level of 135 to 19 0mg/dL and a 10 percent to 20 percent CVD event risk (based on the FRS).[10] The recommended treatment strategy is treatment-to-target rather than by therapy dose (e.g., 50% reduction in LDL-C level).[10]

The UK National Institute for Health and Care Excellence (NICE) recommends atorvastatin (20 mg) for primary prevention in adults (with or without type 2 diabetes) age 40 years or older with 10 percent or greater 10-year CVD risk (based on the QRISK2 tool).[12, 32] They note that for adults age 85 years or older, statins may reduce the risk of

nonfatal MI. They recommend statin treatment for adults with type 1 diabetes who are older than 40 years, have had diabetes more than 10 years, have nephropathy, or have other CVD risk factors.

Vitamin Supplements

The USPSTF recommends against the use of beta-carotene and vitamin E supplementation for CVD prevention (D recommendation). For multivitamin, single-, or paired-nutrient supplements, the USPSTF concluded there was insufficient evidence to assess the balance of benefits and harms for CVD prevention (I statement). In addition to beta-carotene and vitamin E, the AHA[33] recommends against the use of antioxidant vitamin supplements (e.g., vitamin C) and folic acid for primary CVD prevention.

Omega-3 Fatty Acids

The AHA[34] reported there were no RCTs to guide recommendations for the use of omega-3 fatty acids for primary CVD prevention in the general population. However, they found evidence there was no benefit for patients with or at risk for diabetes mellitus to prevent CVD. For patients with high CVD risk, the expert panel was split between recommending against omega-3 fatty acids use versus a weak recommendation that treatment in high-risk patients may be reasonable. NICE[35] recommends against use of omega-3 fatty acids for primary CVD prevention.

CQ 1b. What is the fidelity to prescribing and taking the recommended medications?

According to the National Ambulatory and National Hospital Ambulatory Medical Care Surveys from 2005 to 2008,[36] few patients were recommended to take aspirin in concordance with guideline recommendations. For example, in 2007 to 2008, among the population identified by the USPSTF to receive aspirin for prevention of CVD and stroke, it was recommended at only 16 percent of visits for males and 22 percent of visits for females.

In an analysis of the National Health and Nutrition Examination Survey (NHANES), 2011–2012,[37] patients without CVD were classified into high and low risk based on FRSs Approximately 40 percent of the high-risk group and 26 percent of the low-risk group reported being told by their physician to take aspirin. Between 76 percent and 79 percent of patients advised to take aspirin reported complying. Using the same dataset, Malayala et al[38] reported that about 35 percent of men ages 45 to 79 years who met USPSTF guideline recommendations for aspirin for primary prevention were advised by their providers to take aspirin and about 70 percent of that group reported compliance with the recommendation. Also using the 2011–2012 NHANES dataset, Fiscella et al[39] reported a slightly higher rate of aspirin recommendations for eligible women (i.e., ages 55 to 79 years), 42 percent, for primary CVD prevention.

The Reduction of Atherothrombosis for Continued Health (REACH)[40] Registry compiled data on over 25,000 U.S. outpatients with atherothrombosis or atherosclerotic risk factors between 2003 2004. Approximately 25 percent of the registry enrollees were asymptomatic and comprised the primary prevention cohort (n=6,600). For primary CVD prevention, 62 percent of the cohort were taking at least one antiplatelet agent, most often aspirin, and 77 percent were receiving a statin.

CQ 2. What are the harms and benefits of revascularization procedures for adults without symptoms or a prior diagnosis of CVD?

Precise estimates of benefits and harms of revascularization for asymptomatic adults were not available. Available data come from studies with mostly symptomatic people. For example, population-based registries including people with symptoms estimate that the risk for any serious harms from angiography (which is often done at the same time as revascularization) is about 1.7 percent, including arrhythmia (0.4%), death (0.1%), stroke (0.07%), or MI (0.05%).[41] After an abnormal screening ECG that is concerning for ischemia, some people without CHD would be sent for angiography without the possibility of benefit but would be subjected to potential harms. Even among a

large sample undergoing elective angiography (about 400,000 participants) that was mostly symptomatic (70%), an estimated 39 percent had no CHD on angiography.[42]

One registry study published in *JAMA Internal Medicine*'s Less is More series reported data from a preoperative referral population (for noncardiac surgery) that describes data for a sample with a majority of asymptomatic participants (60%): the National Cardiovascular Data Registry CathPCI Registry. It is a large, national registry of patients undergoing diagnostic cardiac catheterizations and/or percutaneous coronary interventions (PCI) that captures about 85 percent of PCI procedures from approximately 1,400 U.S. hospitals. The registry[43] contains data on nearly 195,000 patients who underwent preoperative evaluation prior to noncardiac surgery between July 2009 and December 2014. Approximately 60 percent of this cohort was reported to be clinically asymptomatic, although 58 percent had been taking antianginal medications within 2 weeks of the procedure; about 20 percent had atypical chest pain considered unlikely to be ischemic, and another 20 percent had stable angina. The sample excluded patients undergoing catheterization with suspected acute coronary syndrome, those who had unstable angina symptoms, and patients undergoing catheterization as part of a cardiac transplant evaluation.

The authors concluded that most patients undergoing diagnostic catheterization before noncardiac surgery are asymptomatic; the discovery of obstructive coronary artery disease is common; and although randomized, clinical trials have found no benefit in outcomes, revascularization is recommended in nearly half of these patients.

Obstructive disease was identified in 48 percent of the cohort overall, 40 percent of those who underwent diagnostic catheterization only, and 97 percent of those receiving PCI. Of patients with asymptomatic presentations, 48 percent were found to have obstructive disease. Approximately 16 percent of the cohort underwent PCI, and an additional 8 percent received CABG; revascularization was recommended in 23 percent of asymptomatic patients.

For the overall cohort, complications related to PCI were uncommon, including coronary artery dissection (1.3%), periprocedural MI (1.7%), vascular complications (0.4%), stroke (0.1%), and renal failure (0.4%). Death occurred in 14 patients on the same day as the procedure, eight of which occurred in the catheterization lab. Bleeding events within 72 hours of the procedure occurred in 371 patients (1.3%), primarily at the procedure access site. Adverse events for asymptomatic patients were not separately reported.

Benefits of revascularization in asymptomatic adults is uncommonly reported. McFalls et al[44] randomized patients scheduled for vascular surgery at 18 Veterans Affairs medical centers to receive preoperative coronary artery revascularization or no revascularization. Of these, 510 participants were randomized, and 240 participants underwent either PCI (n=141) or CABG (n=99). Notably, about half of all participants had prior CAD. After 2.7 years of followup, mortality was no different between groups (RR, 0.97; 95% CI, 0.69 to 1.36). In high-risk subgroups of participants, CABG did not confer a survival benefit. The vast majority of participants were taking beta-blockers, aspirin, ACE inhibitors, and statins up to 24 months after randomization, and their use did not differ between groups.

Appendix B1. Search Strategies

PubMed, 7/13/16

Search	Query	Items found
#1	Search ("Electrocardiography"[Mesh] OR electrocardiography OR EKG OR ECG OR "Exercise Test"[Mesh] OR (treadmill AND test) OR (treadmill AND ett))	256656
#2	Search ("Myocardial Ischemia"[Mesh] OR "coronary heart disease"[tiab] OR "coronary disease"[tiab] OR "coronary disease"[mh] OR "coronary artery disease"[tiab] OR "Atherosclerosis"[Mesh] OR atherosclerosis[tiab])	500580
#3	Search (#1 and #2)	67866
#4	Search (("Mass Screening"[Mesh] OR screen*[tiab]))	591681
#5	Search (#3 and #4)	1397
#6	Search (#3 and #4) Filters: Humans	1347
#7	Search (#3 and #4) Filters: Humans; English	1115
#8	Search (#3 and #4) Filters: Humans; English; Adult: 19+ years	843
#9	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "Controlled Clinical Trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	642180
#10	Search (#8 and #9)	81
#11	Search (#8 and #9) Filters: Humans	81
#12	Search (#8 and #9) Filters: Humans; English	81
#13	Search (#8 and #9) Filters: Publication date from 2009/01/01 to 2016/12/31; Humans; English	13
#14	Search (#3 and #4) Filters: Systematic Reviews; Humans; English; Adult: 19+ years	18
#15	Search (#3 and #4) Filters: Systematic Reviews; Meta-Analysis; Humans; English; Adult: 19+ years	18
#16	Search (#3 and #4) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	10
#17	Search ("adverse effects" [Subheading] OR "Long Term Adverse Effects"[Mesh] OR "Patient Harm"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR death[tiab] OR mortality[tiab] OR "medical errors"[mh] OR "iatrogenic disease"[mh] OR "false positive reactions"[mh] OR "Syncope"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Myocardial Infarction"[Mesh] OR "heart attack"[tiab] OR "Anxiety"[Mesh] OR labeling[tiab] OR labelling[tiab] OR "Coronary Angiography"[Mesh] OR "Myocardial Revascularization"[Mesh])	3631548
#18	Search (#8 and #17)	560
#19	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))	1903256
#20	Search (#18 and #19) Publication date from 2009/01/01 to 2016/12/31	92
#21	Search (#8 and #17) Filters: Systematic Reviews	13
#22	Search (#8 and #17) Filters: Systematic Reviews; Meta-Analysis	13
#23	Search (#8 and #17) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2009/01/01 to 2016/12/31	8
#24	Search ("Coronary Angiography"[Mesh] OR "Myocardial Revascularization"[Mesh])	121744
#25	Search (#2 and #24)	86047
#26	Search ("adverse effects" [Subheading] OR "Long Term Adverse Effects"[Mesh] OR "Patient Harm"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR death[tiab] OR mortality[tiab] OR "medical errors"[mh] OR "iatrogenic disease"[mh] OR "false positive reactions"[mh] OR "Syncope"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Myocardial Infarction"[Mesh] OR "heart attack"[tiab] OR "Anxiety"[Mesh] OR labeling[tiab] OR labelling[tiab])	3574617
#27	Search (#25 and #26)	49909
#28	Search (#25 and #26) Filters: Humans	49313
#29	Search (#25 and #26) Filters: Humans; English	42245
#30	Search (#25 and #26) Filters: Humans; English; Adult: 19+ years	32017
#31	Search (#25 and #26) Filters: Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	11463
#32	Search (#25 and #26) Filters: Systematic Reviews; Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	266
#33	Search (#25 and #26) Filters: Systematic Reviews; Meta-Analysis; Publication date from	267

Appendix B1. Search Strategies

Search	Query	Items found
	2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	
#34	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])	1511006
#35	Search (#33 not #34)	266

PubMed KQ 2 – Risk/Harms search, 7/13/16

Search	Query	Items found
#1	Search ("Electrocardiography"[Mesh] OR electrocardiography OR EKG OR ECG OR "Exercise Test"[Mesh] OR (treadmill AND test) OR (treadmill AND ett))	256656
#2	Search ("Mortality"[Mesh] OR "mortality"[Subheading] OR death[tiab] OR mortality[tiab] OR "Myocardial Infarction"[Mesh] OR "heart attack"[tiab] OR "Myocardial Ischemia"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "Coronary Disease"[MeSH] OR "Coronary Disease"[mh] OR "coronary heart disease"[tiab] OR "coronary artery disease"[tiab] OR "coronary disease"[tiab] OR "Heart Failure"[Mesh] OR "heart failure"[tiab] OR "Stroke"[Mesh])	1944815
#3	Search (#1 and #2)	95297
#4	Search ("Risk"[Mesh:NoExp] OR "Logistic Models"[Mesh] OR "Risk Assessment"[Mesh] OR "Risk Factors"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Kaplan-Meier Estimate"[Mesh] OR "risk prediction"[tiab] OR reclass*[tiab] OR Framingham[tiab] OR "risk score"[tiab] OR "risk scores"[tiab])	1099100
#5	Search (#3 and #4)	17436
#6	Search (#3 and #4) Filters: Humans	17238
#7	Search (#3 and #4) Filters: Humans; English	15162
#8	Search (#3 and #4) Filters: Humans; English; Adult: 19+ years	12007
#9	Search (#3 and #4) Filters: Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	4971
#10	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "Controlled Clinical Trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	642180
#11	Search (#9 and #10)	496
#12	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))	1903256
#13	Search (#9 and #12)	3135
#14	Search (#3 and #4) Filters: Systematic Reviews; Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	81
#15	Search (#3 and #4) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	81

Appendix B1. Search Strategies

Cochrane Library Searches KQ 1 and KQ 3, 7/13/16

ID	Search	Hits
#1	[mh Electrocardiography] or electrocardiography or EKG or ECG or [mh "Exercise Test"] or (treadmill and test) or (treadmill and ett)	20976
#2	[mh "Myocardial Ischemia"] or "coronary heart disease":ti,ab or "coronary disease":ti,ab or "coronary disease":kw or "coronary artery disease":ti,ab or [mh Atherosclerosis] or atherosclerosis:ti,ab	32974
#3	#1 and #2	5808
#4	[mh "Mass Screening"] or screen*:ti,ab	26321
#5	#3 and #4 Publication Year from 2009 to 2016, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	13
#6	((controlled:ti or controlled:ab) and (trial:ti or trial:ab)) or "controlled clinical trial" or "randomized controlled trial":pt or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	574189
#7	#5 and #6	9
#8	[mh /AE] or [mh "Long Term Adverse Effects"] or [mh "Patient Harm"] or [mh Mortality] or [mh /MO] or death:ti,ab or mortality:ti,ab or "medical errors":kw or "iatrogenic disease":kw or "false positive reactions":kw or [mh Syncope] or [mh "Arrhythmias, Cardiac"] or [mh "Myocardial Infarction"] or "heart attack":ti,ab or [mh Anxiety] or labeling:ti,ab or labelling:ti,ab or [mh "Coronary Angiography"] or [mh "Myocardial Revascularization"]	184054
#9	#5 and #8	12
#10	[mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh "Follow-up Studies"] or "prospective cohort" or [mh "prospective studies"] or (prospective* and cohort and (study or studies))	139076
#11	#9 and #10	9
#12	[mh "Coronary Angiography"] or [mh "Myocardial Revascularization"]	11381
#13	#2 and #12	7785
#14	[mh /AE] or [mh "Long Term Adverse Effects"] or [mh "Patient Harm"] or [mh Mortality] or [mh /MO] or death:ti,ab or mortality:ti,ab or "medical errors":kw or "iatrogenic disease":kw or "false positive reactions":kw or [mh Syncope] or [mh "Arrhythmias, Cardiac"] or [mh "Myocardial Infarction"] or "heart attack":ti,ab or [mh Anxiety] or labeling:ti,ab or labelling:ti,ab	179573
#15	#13 and #14 Publication Year from 2009 to 2016, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	215

Cochrane Library Searches KQ 2, Risk, 7/13/16

ID	Search	Hits
#1	[mh Electrocardiography] or electrocardiography or EKG or ECG or [mh "Exercise Test"] or (treadmill and test) or (treadmill and ett)	20976
#2	[mh Mortality] or [mh /MO] or death:ti,ab or mortality:ti,ab or [mh "Myocardial Infarction"] or "heart attack":ti,ab or [mh "Myocardial Ischemia"] or [mh ^"Cardiovascular Diseases"] or [mh "Coronary Disease"] or "Coronary Disease":kw or "coronary heart disease":ti,ab or "coronary artery disease":ti,ab or "coronary disease":ti,ab or [mh "Heart Failure"] or "heart failure":ti,ab or [mh Stroke]	101003
#3	#1 and #2	8278
#4	[mh ^Risk] or [mh "Logistic Models"] or [mh "Risk Assessment"] or [mh "Risk Factors"] or [mh "Predictive Value of Tests"] or [mh "Kaplan-Meier Estimate"] or "risk prediction":ti,ab or reclass*:ti,ab or Framingham:ti,ab or "risk score":ti,ab or "risk scores":ti,ab	44070
#5	#3 and #4	1239
#6	#3 and #4 Publication Year from 2009 to 2016	539
#7	#6 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	33
#8	((controlled:ti or controlled:ab) and (trial:ti or trial:ab)) or "controlled clinical trial" or "randomized controlled trial":pt or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	574189
#9	#6 and #8	493
#10	[mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh "Follow-up Studies"] or "prospective cohort" or [mh "prospective studies"] or (prospective* and cohort and (study or studies))	139076
#11	#6 and #10	281
#12	#9 or #11 Publication Year from 2009 to 2016	209

Appendix B1. Search Strategies

PubMed KQ 1 and KQ 3, 5/30/17

Search	Query	Items Found
#1	Search ("Electrocardiography"[Mesh] OR electrocardiography OR EKG OR ECG OR "Exercise Test"[Mesh] OR (treadmill AND test) OR (treadmill AND ett))	264065
#2	Search ("Myocardial Ischemia"[Mesh] OR "coronary heart disease"[tiab] OR "coronary disease"[tiab] OR "coronary disease"[mh] OR "coronary artery disease"[tiab] OR "Atherosclerosis"[Mesh] OR atherosclerosis[tiab])	518274
#3	Search (#1 and #2)	69195
#4	Search (("Mass Screening"[Mesh] OR screen*[tiab]))	630082
#5	Search (#3 and #4)	1445
#6	Search (#3 and #4) Filters: Humans	1390
#7	Search (#3 and #4) Filters: Humans; English	1156
#8	Search (#3 and #4) Filters: Humans; English; Adult: 19+ years	875
#9	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "Controlled Clinical Trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	672674
#10	Search (#8 and #9)	84
#11	Search (#8 and #9) Filters: Humans	84
#12	Search (#8 and #9) Filters: Humans; English	84
#13	Search (#8 and #9) Filters: Publication date from 2016/01/01 to 2017/12/31; Humans; English	4
#14	Search (#3 and #4) Filters: Systematic Reviews; Humans; English; Adult: 19+ years	19
#15	Search (#3 and #4) Filters: Systematic Reviews; Meta-Analysis; Humans; English; Adult: 19+ years	19
#16	Search (#3 and #4) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	1
#17	Search ("adverse effects" [Subheading] OR "Long Term Adverse Effects"[Mesh] OR "Patient Harm"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR death[tiab] OR mortality[tiab] OR "medical errors"[mh] OR "iatrogenic disease"[mh] OR "false positive reactions"[mh] OR "Syncope"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Myocardial Infarction"[Mesh] OR "heart attack"[tiab] OR "Anxiety"[Mesh] OR labeling[tiab] OR labelling[tiab] OR "Coronary Angiography"[Mesh] OR "Myocardial Revascularization"[Mesh])	3790291
#18	Search (#8 and #17)	577
#19	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))	2023668
#20	Search (#18 and #19) Publication date from 2016/01/01 to 2017/12/31	14
#21	Search (#8 and #17) Filters: Systematic Reviews	13
#22	Search (#8 and #17) Filters: Systematic Reviews; Meta-Analysis	13
#23	Search (#8 and #17) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2009/01/01 to 2016/12/31	0
#24	Search ("Coronary Angiography"[Mesh] OR "Myocardial Revascularization"[Mesh])	125817
#25	Search (#2 and #24)	89049
#26	Search ("adverse effects" [Subheading] OR "Long Term Adverse Effects"[Mesh] OR "Patient Harm"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR death[tiab] OR mortality[tiab] OR "medical errors"[mh] OR "iatrogenic disease"[mh] OR "false positive reactions"[mh] OR "Syncope"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Myocardial Infarction"[Mesh] OR "heart attack"[tiab] OR "Anxiety"[Mesh] OR labeling[tiab] OR labelling[tiab])	3731590
#27	Search (#25 and #26)	51715
#28	Search (#25 and #26) Filters: Humans	51104
#29	Search (#25 and #26) Filters: Humans; English	43976
#30	Search (#25 and #26) Filters: Humans; English; Adult: 19+ years	33495
#31	Search (#25 and #26) Filters: Publication date from 2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	1221
#32	Search (#25 and #26) Filters: Systematic Reviews; Publication date from 2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	22
#33	Search (#25 and #26) Filters: Systematic Reviews; Meta-Analysis; Publication date from	22

Appendix B1. Search Strategies

	2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	
#34	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])	1566106
#35	Search (#33 not #34)	22

PubMed KQ 2 – Risk/Harms, 5/30/17

Search	Query	Items Found
#1	Search ("Electrocardiography"[Mesh] OR electrocardiography OR EKG OR ECG OR "Exercise Test"[Mesh] OR (treadmill AND test) OR (treadmill AND ett))	264065
#2	Search ("Mortality"[Mesh] OR "mortality"[Subheading] OR death[tiab] OR mortality[tiab] OR "Myocardial Infarction"[Mesh] OR "heart attack"[tiab] OR "Myocardial Ischemia"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "Coronary Disease"[MeSH] OR "Coronary Disease"[mh] OR "coronary heart disease"[tiab] OR "coronary artery disease"[tiab] OR "coronary disease"[tiab] OR "Heart Failure"[Mesh] OR "heart failure"[tiab] OR "Stroke"[Mesh])	2043386
#3	Search (#1 and #2)	97776
#4	Search ("Risk"[Mesh:NoExp] OR "Logistic Models"[Mesh] OR "Risk Assessment"[Mesh] OR "Risk Factors"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Kaplan-Meier Estimate"[Mesh] OR "risk prediction"[tiab] OR reclass*[tiab] OR Framingham[tiab] OR "risk score"[tiab] OR "risk scores"[tiab])	1099100
#5	Search (#3 and #4)	18197
#6	Search (#3 and #4) Filters: Humans	17983
#7	Search (#3 and #4) Filters: Humans; English	15883
#8	Search (#3 and #4) Filters: Humans; English; Adult: 19+ years	12604
#9	Search (#3 and #4) Filters: Publication date from 2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	509
#10	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "Controlled Clinical Trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	672674
#11	Search (#9 and #10)	51
#12	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))	2023668
#13	Search (#9 and #12)	334
#14	Search (#3 and #4) Filters: Systematic Reviews; Publication date from 2009/01/01 to 2016/12/31; Humans; English; Adult: 19+ years	8
#15	Search (#3 and #4) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	8

Appendix B1. Search Strategies

Cochrane Library Searches KQ 1 and KQ 3, 5/30/17

ID	Search	Hits
#1	[mh Electrocardiography] or electrocardiography or EKG or ECG or [mh "Exercise Test"] or (treadmill and test) or (treadmill and ett)	22891
#2	[mh "Myocardial Ischemia"] or "coronary heart disease":ti,ab or "coronary disease":ti,ab or "coronary disease":kw or "coronary artery disease":ti,ab or [mh Atherosclerosis] or atherosclerosis:ti,ab	35404
#3	#1 and #2	6048
#4	[mh "Mass Screening"] or screen*:ti,ab	31391
#5	#3 and #4 Publication Year from 2016 to 2017, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	7
#6	((controlled:ti or controlled:ab) and (trial:ti or trial:ab)) or "controlled clinical trial" or "randomized controlled trial":pt or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	663873
#7	#5 and #6	6
#8	[mh /AE] or [mh "Long Term Adverse Effects"] or [mh "Patient Harm"] or [mh Mortality] or [mh /MO] or death:ti,ab or mortality:ti,ab or "medical errors":kw or "iatrogenic disease":kw or "false positive reactions":kw or [mh Syncope] or [mh "Arrhythmias, Cardiac"] or [mh "Myocardial Infarction"] or "heart attack":ti,ab or [mh Anxiety] or labeling:ti,ab or labelling:ti,ab or [mh "Coronary Angiography"] or [mh "Myocardial Revascularization"]	201669
#9	#5 and #8	6
#10	[mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh "Follow-up Studies"] or "prospective cohort" or [mh "prospective studies"] or (prospective* and cohort and (study or studies))	150064
#11	#9 and #10	4
#12	[mh "Coronary Angiography"] or [mh "Myocardial Revascularization"]	11848
#13	#2 and #12	8118
#14	[mh /AE] or [mh "Long Term Adverse Effects"] or [mh "Patient Harm"] or [mh Mortality] or [mh /MO] or death:ti,ab or mortality:ti,ab or "medical errors":kw or "iatrogenic disease":kw or "false positive reactions":kw or [mh Syncope] or [mh "Arrhythmias, Cardiac"] or [mh "Myocardial Infarction"] or "heart attack":ti,ab or [mh Anxiety] or labeling:ti,ab or labelling:ti,ab	197054
#15	#13 and #14 Publication Year from 2016 to 2017, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	4

Cochrane Library Searches KQ 2, Risk, 5/30/17

ID	Search	Hits
#1	[mh Electrocardiography] or electrocardiography or EKG or ECG or [mh "Exercise Test"] or (treadmill and test) or (treadmill and ett)	22891
#2	[mh Mortality] or [mh /MO] or death:ti,ab or mortality:ti,ab or [mh "Myocardial Infarction"] or "heart attack":ti,ab or [mh "Myocardial Ischemia"] or [mh ^"Cardiovascular Diseases"] or [mh "Coronary Disease"] or "Coronary Disease":kw or "coronary heart disease":ti,ab or "coronary artery disease":ti,ab or "coronary disease":ti,ab or [mh "Heart Failure"] or "heart failure":ti,ab or [mh Stroke]	115133
#3	#1 and #2	8800
#4	[mh ^Risk] or [mh "Logistic Models"] or [mh "Risk Assessment"] or [mh "Risk Factors"] or [mh "Predictive Value of Tests"] or [mh "Kaplan-Meier Estimate"] or "risk prediction":ti,ab or reclass*:ti,ab or Framingham:ti,ab or "risk score":ti,ab or "risk scores":ti,ab	47503
#5	#3 and #4	1334
#6	#3 and #4 Publication Year from 2009 to 2016	55
#7	#6 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	2
#8	((controlled:ti or controlled:ab) and (trial:ti or trial:ab)) or "controlled clinical trial" or "randomized controlled trial":pt or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	663874
#9	#6 and #8	54
#10	[mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh "Follow-up Studies"] or "prospective cohort" or [mh "prospective studies"] or (prospective* and cohort and (study or studies))	150064
#11	#6 and #10	27
#12	#9 or #11 Publication Year from 2016 to 2017	54

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	Adults age ≥18 years without symptoms or a diagnosis of CVD; studies of mixed populations of asymptomatic and symptomatic persons are eligible if results are reported separately for asymptomatic persons or <20% of the sample is symptomatic[a]	Persons with a history of atherosclerotic disease or symptoms suggesting coronary heart disease; children and adolescents
Screening tests	Resting ECG, exercise ECG	Radiology tests (e.g., thallium scan, scintigraphy, computed tomography), echocardiography, and vectorcardiography[b]
Comparisons	All KQs: Screened vs. nonscreened groups (i.e., risk stratification using ECG plus traditional risk factors vs. risk stratification using traditional risk factors alone) KQ 2: CVD risk assessment models that include ECG findings compared with those that do not KQ 3: For harms of subsequent procedures/interventions, studies that compare the procedure/intervention to no procedure/intervention are also eligible. For studies reporting rates of harms from exercise ECG or subsequent procedures/interventions, large registries or multicenter studies without a control group that report rates of harms for asymptomatic persons are also eligible.	No comparison, nonconcordant historical control, comparative studies with other novel risk factors (e.g., comparing ECG vs. C-reactive protein); studies that compare the risk for subsequent events between persons with and without ECG abnormalities and report associations (e.g., prospective cohort studies that report hazard ratios for outcomes associated with baseline T-wave abnormalities)
Outcomes	KQ 1: All-cause mortality, cardiovascular mortality, and cardiovascular events (myocardial infarction, angina, stroke, congestive heart failure, composite cardiovascular outcomes) KQ 2: Reclassification, calibration (the degree to which predicted and observed risk estimates agree, goodness-of-fit statistics), and discrimination (C-statistic/area under the curve) KQ 3: Mortality, arrhythmia, cardiovascular events, or injuries from exercise ECG; anxiety; labeling; harms of subsequent procedures or interventions initiated as a result of screening (e.g., subsequent angiography or revascularization procedures resulting in harm)	KQ 2: Studies assessing the association between ECG findings and outcomes (e.g., with adjusted hazard ratios)
Study designs	All KQs: Randomized, controlled trials or controlled clinical trials KQs 2, 3: Prospective cohort studies are also eligible KQ 3: Well-designed large retrospective cohort studies and well-designed case-control studies (only for rare events) are also eligible	All other designs, narrative reviews, systematic reviews[c] case reports, case series, editorials, letters, cross-sectional studies
Setting	Studies performed in primary care or occupational medicine settings, studies that recruit participants from the general population	Studies performed in specialty settings, studies of patients undergoing preoperative evaluation
Country	Studies conducted in countries categorized as "Very High" on the 2014 Human Development Index (as defined by the United Nations Development Program)	
Language	English	Non-English
Study quality	Good or fair	Poor (according to design-specific USPSTF criteria)

[a] The a priori plan for mixed populations was to include studies if the results were reported separately for asymptomatic persons or if less than 10 percent of the sample was symptomatic, and to systematically determine whether that approach would result in the exclusion of any studies in which 10 to 50 percent of the population was symptomatic that should be considered for inclusion. We only identified one such study (16.5% of participants had atypical chest pain[45]) and decided to include the study because of the uncertainty around the appropriate threshold (for proportion of symptomatic patients that would alter study findings and substantially limit their applicability for the review questions).

[b] Vectorcardiography is a method of recording the magnitude and direction of the electrical forces that are generated by the heart by means of a continuous series of vectors that form curving lines around a central point.

[c] We will not abstract data from systematic reviews and will not include them in the results, but we will conduct separate searches for systematic reviews and search the references lists of all potentially relevant systematic reviews to identify relevant primary studies that our electronic searches did not identify.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Sources: U.S. Preventive Services Task Force, Procedure Manual, Appendix VI
https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes
Harris et al, 2001[46]

Specific Questions Used to Guide Assessment of Included Studies

Items used to assess quality of RCTs for KQs 1 and 3

1. Was randomization adequate?
2. Was allocation concealment adequate?
3. Were groups similar at baseline?
4. Was intervention fidelity adequate?
5. What was the reported adherence to the intervention?
6. What was the overall attrition?
7. What was the differential attrition?
8. Did the study have differential attrition or overall high attrition raising concern for bias?
9. Did the study have cross-overs or contamination raising concern for bias?
10. Were outcome measurements equal, valid, and reliable?
11. Were patients masked?
12. Were providers masked?
13. Were outcome assessors masked?
14. Was the duration of followup adequate to assess the outcome?
15. What was the method used to handle missing data?
16. Did the study use acceptable statistical methods?
17. Quality Rating

Additional Items used to assess quality of RCTs that address harms, KQ3

1. Were harms prespecified and defined?
2. Were ascertainment techniques for harms adequately described?
3. Were ascertainment techniques for harms equal, valid, and reliable?
4. Was duration of follow-up adequate for harms assessment?
5. Quality Rating

Items used to assess quality of relevant studies reporting reclassification, calibration, and discrimination, KQ 2

1. Does study sample adequately capture the population of interest (participant eligibility and recruitment)?
2. Was there selective inclusion of participants in the model based on data availability?
3. If participants are from a treatment RCT, is treatment accounted for?
4. Enrolled consecutive patients or a random sample?
5. Were selection criteria clearly described?
6. Is a valid and reliable definition and method for measurement of the outcomes reported?
7. Was the same outcome definition (and method for measurement) used in all patients?
8. Were the outcomes assessed without knowledge of the candidate predictors (i.e., blinded)?
9. Is a valid and reliable definition and method for measurement and classification of candidate predictor(s) (ECG and risk factors) reported?
10. Were predictors assessed blinded for the outcome, and for each other (if relevant)?
11. How was the predictor of interest (ECG) handled in the modelling?
12. Number (%) participants with missing data (include predictors and outcomes)
13. Did the study have high attrition raising concern for bias?
14. How was missing data handled?
15. Were multiple measures of performance used (e.g., global fit, discrimination, calibration, net reclassification)?
16. Were both calibration and discrimination measures reported? Were confidence intervals reported?
17. Were a priori cut points used for classification measures (e.g., sensitivity, specificity, predictive values, NRI)?
18. Was a bias-corrected NRI used?
19. If net reclassification was assessed, were appropriate clinical thresholds used to reclassify risk?
20. Method used for testing model performance: development dataset only or separate external validation?
21. In what way was the population a separate external validation from the FRS or PCE?
22. Was the FRS or PCE recalibrated in the population before ECG was added to the model?
23. Quality

Appendix C. Excluded Studies

X1: Non-English
X2: Ineligible population
X3: Ineligible/no screening/treatment
X4: Ineligible/no comparison
X5: Ineligible/no outcome
X6: Ineligible setting
X7: Ineligible study design
X8: Appears to meet all criteria but ineligible country
X9: Appears to meet all criteria but abstract only
X10: Poor quality

1. Summaries for patients. Adding electrocardiography to medical history and physical examination for evaluation before sports participation in college athletes. *Ann Intern Med*. 2010 Mar 2;152(5):I13. doi: 10.7326/0003-4819-152-5-201003020-00001. PMID: 20194228. Exclusion Code: X7.
2. Abudiab M, Aijaz B, Konecny T, et al. Use of functional aerobic capacity based on stress testing to predict outcomes in normal, overweight, and obese patients. *Mayo Clin Proc*. 2013 Dec;88(12):1427-34. doi: 10.1016/j.mayocp.2013.10.013. PMID: 24290116. Exclusion Code: X2.
3. Acampa W, Petretta M, Evangelista L, et al. Myocardial perfusion imaging and risk classification for coronary heart disease in diabetic patients. The IDIS study: a prospective, multicentre trial. *Eur J Nucl Med Mol Imaging*. 2012 Mar;39(3):387-95. doi: 10.1007/s00259-011-1983-x. PMID: 22109666. Exclusion Code: X3.
4. Adabag AS, Grandits GA, Prineas RJ, et al. Relation of heart rate parameters during exercise test to sudden death and all-cause mortality in asymptomatic men. *Am J Cardiol*. 2008 May 15;101(10):1437-43. doi: 10.1016/j.amjcard.2008.01.021. PMID: 18471455. Exclusion Code: X5.
5. Agarwal SK, Chao J, Peace F, et al. Premature ventricular complexes on screening electrocardiogram and risk of ischemic stroke. *Stroke*. 2015 May;46(5):1365-7. doi: 10.1161/strokeaha.114.008447. PMID: 25873602. Exclusion Code: X5.
6. Agarwal SK, Heiss G, Rautaharju PM, et al. Premature ventricular complexes and the risk of incident stroke: the Atherosclerosis Risk In Communities (ARIC) Study. *Stroke*. 2010 Apr;41(4):588-93. doi: 10.1161/strokeaha.109.567800. PMID: 20167922. Exclusion Code: X5.
7. Agarwal SK, Simpson RJ, Jr., Rautaharju P, et al. Relation of ventricular premature complexes to heart failure (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol*. 2012 Jan 1;109(1):105-9. doi: 10.1016/j.amjcard.2011.08.009. PMID: 21945138. Exclusion Code: X5.
8. Ahmed HM, Al-Mallah MH, McEvoy JW, et al. Maximal exercise testing variables and 10-year survival: fitness risk score derivation from the FIT Project. *Mayo Clin Proc*. 2015 Mar;90(3):346-55. doi: 10.1016/j.mayocp.2014.12.013. PMID: 25744114. Exclusion Code: X2.
9. Ahmed T, Steward JA, O'Mahony MS. Dyspnoea and mortality in older people in the community: a 10-year follow-up. *Age Ageing*. 2012 Jul;41(4):545-9. doi: 10.1093/ageing/afs049. PMID: 22522776. Exclusion Code: X2.
10. Al Rifai M, Patel J, Hung RK, et al. Higher Fitness Is Strongly Protective in Patients with Family History of Heart Disease: The FIT Project. *Am J Med*. 2017 Mar;130(3):367-71. doi: 10.1016/j.amjmed.2016.09.026. PMID: 27751899. Exclusion Code: X4.
11. Al Rifai M, Schneider AL, Alonso A, et al. sRAGE, inflammation, and risk of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Diabetes Complications*. 2015 Mar;29(2):180-5. doi: 10.1016/j.jdiacomp.2014.11.008. PMID: 25499973. Exclusion Code: X3.
12. Aladin AI, Whelton SP, Al-Mallah MH, et al. Relation of resting heart rate to risk for all-cause mortality by gender after considering exercise capacity (the Henry Ford exercise testing project). *Am J Cardiol*.

2014 Dec 1;114(11):1701-6. doi: 10.1016/j.amjcard.2014.08.042. PMID: 25439450. Exclusion Code: X2.

13. Albayrak S, Ozhan H, Aslantas Y, et al. Predictors of major adverse cardiovascular events; results of population based MELEN study with prospective follow-up. *Eur Rev Med Pharmacol Sci*. 2015 Apr;19(8):1446-51. PMID: 25967720. Exclusion Code: X5.
14. Al-Mallah MH, Keteyian SJ, Brawner CA, et al. Rationale and design of the Henry Ford Exercise Testing Project (the FIT project). *Clin Cardiol*. 2014 Aug;37(8):456-61. doi: 10.1002/clc.22302. PMID: 25138770. Exclusion Code: X2.
15. Al-Zaiti SS, Carey MG. The Prevalence of Clinical and Electrocardiographic Risk Factors of Cardiovascular Death Among On-duty Professional Firefighters. *J Cardiovasc Nurs*. 2015 Sep-Oct;30(5):440-6. doi: 10.1097/jcn.0000000000000165. PMID: 24874885. Exclusion Code: X7.
16. Al-Zaiti SS, Fallavollita JA, Wu YW, et al. Electrocardiogram-based predictors of clinical outcomes: a meta-analysis of the prognostic value of ventricular repolarization. *Heart Lung*. 2014 Nov-Dec;43(6):516-26. doi: 10.1016/j.hrtlng.2014.05.004. PMID: 24988910. Exclusion Code: X7.
17. Andersen K, Rasmussen F, Held C, et al. Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study. *Bmj*. 2015;351:h4543. doi: 10.1136/bmj.h4543. PMID: 26378015. Exclusion Code: X5.
18. Anttila I, Nikus K, Nieminen T, et al. Prevalence and prognostic value of poor R-wave progression in standard resting electrocardiogram in a general adult population. The Health 2000 Survey. *Ann Med*. 2010 Mar;42(2):123-30. doi: 10.3109/07853890903555334. PMID: 20166814. Exclusion Code: X5.
19. 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 Jul 5;46(1):158-65. doi: 10.1016/j.jacc.2005.02.088. PMID: 15992651. Exclusion Code: X3.
20. Arbel Y, Birati EY, Shapira I, et al. T-wave amplitude is related to physical fitness status. *Ann Noninvasive Electrocardiol*. 2012 Jul;17(3):214-8. doi: 10.1111/j.1542-474X.2012.00512.x. PMID: 22816540. Exclusion Code: X7.
21. Armstrong AW, Azizi S, Wu J, et al. Psoriasis, electrocardiographic characteristics, and incidence of atrial fibrillation. *Arch Dermatol Res*. 2013 Dec;305(10):891-7. doi: 10.1007/s00403-013-1419-5. PMID: 24166719. Exclusion Code: X4.
22. Aro AL, Anttonen O, Tikkanen JT, et al. Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population. *Circ Arrhythm Electrophysiol*. 2011 Oct;4(5):704-10. doi: 10.1161/circep.111.963561. PMID: 21841194. Exclusion Code: X5.
23. Aro AL, Anttonen O, Tikkanen JT, et al. Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. *Circulation*. 2012 May 29;125(21):2572-7. doi: 10.1161/circulationaha.112.098681. PMID: 22576982. Exclusion Code: X4.
24. Aro AL, Huikuri HV. Electrocardiographic predictors of sudden cardiac death from a large Finnish general population cohort. *J Electrocardiol*. 2013 Sep-Oct;46(5):434-8. doi: 10.1016/j.jelectrocard.2013.06.016. PMID: 23871401. Exclusion Code: X7.
25. Aro AL, Huikuri HV, Tikkanen JT, et al. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. *Europace*. 2012 Jun;14(6):872-6. doi: 10.1093/europace/eur393. PMID: 22183749. Exclusion Code: X4.
26. Artero EG, Jackson AS, Sui X, et al. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality. *J Am Coll Cardiol*. 2014 Jun 3;63(21):2289-96. doi: 10.1016/j.jacc.2014.03.008. PMID: 24703924. Exclusion Code: X3.
27. Asia Pacific Cohort Studies C, Barzi F, Patel A, et al. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health*. 2007 Feb;61(2):115-21. doi: 10.1136/jech.2005.044842. PMID: 17234869. Exclusion Code: X3.
28. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular

Munster (PROCAM) study. *Circulation*. 2002 Jan 22;105(3):310-5. PMID: 11804985. Exclusion Code: X3.

29. Assmann G, Schulte H, Cullen P, et al. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study. *Eur J Clin Invest*. 2007 Dec;37(12):925-32. doi: 10.1111/j.1365-2362.2007.01888.x. PMID: 18036028. Exclusion Code: X3.
30. Assmann G, Schulte H, Seedorf U. Cardiovascular risk assessment in the metabolic syndrome: results from the Prospective Cardiovascular Munster (PROCAM) Study. *Int J Obes (Lond)*. 2008 May;32 Suppl 2:S11-6. doi: 10.1038/ijo.2008.29. PMID: 18469834. Exclusion Code: X3.
31. Bachmann TN, Skov MW, Rasmussen PV, et al. Electrocardiographic Tpeak-Tend interval and risk of cardiovascular morbidity and mortality: Results from the Copenhagen ECG study. *Heart Rhythm*. 2016 Apr;13(4):915-24. doi: 10.1016/j.hrthm.2015.12.027. PMID: 26707793. Exclusion Code: X5.
32. Badheka AO, Rathod A, Marzouka GR, et al. Isolated nonspecific ST-segment and T-wave abnormalities in a cross-sectional United States population and Mortality (from NHANES III). *Am J Cardiol*. 2012 Aug 15;110(4):521-5. doi: 10.1016/j.amjcard.2012.04.023. PMID: 22608358. Exclusion Code: X4.
33. Badheka AO, Singh V, Patel NJ, et al. QRS duration on electrocardiography and cardiovascular mortality (from the National Health and Nutrition Examination Survey-III). *Am J Cardiol*. 2013 Sep 1;112(5):671-7. doi: 10.1016/j.amjcard.2013.04.040. PMID: 23726176. Exclusion Code: X2.
34. Bakhoya VN, Kurl S, Laukkanen JA. T-wave inversion on electrocardiogram is related to the risk of acute coronary syndrome in the general population. *Eur J Prev Cardiol*. 2014 Apr;21(4):500-6. doi: 10.1177/2047487312460022. PMID: 22952285. Exclusion Code: X2.
35. Balady GJ, Larson MG, Vasan RS, et al. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. *Circulation*. 2004 Oct 5;110(14):1920-5. doi: 10.1161/01.CIR.0000143226.40607.71. PMID: 15451778. Exclusion Code: X5.
36. Bandorski D, Bogossian H, Ecke A, et al. Evaluation of the prognostic value of electrocardiography parameters and heart rhythm in patients with pulmonary hypertension. *Cardiol J*. 2016;23(4):465-72. doi: 10.5603/CJ.a2016.0044. PMID: 27367480. Exclusion Code: X5.
37. Barmpouletos D, Stavens G, Ahlberg AW, et al. Duration and type of therapy for diabetes: impact on cardiac risk stratification with stress electrocardiographic-gated SPECT myocardial perfusion imaging. *J Nucl Cardiol*. 2010 Dec;17(6):1041-9. doi: 10.1007/s12350-010-9293-4. PMID: 20963539. Exclusion Code: X3.
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39. Bates RE, Omer M, Abdelmoneim SS, et al. Impact of Stress Testing for Coronary Artery Disease Screening in Asymptomatic Patients With Diabetes Mellitus: A Community-Based Study in Olmsted County, Minnesota. *Mayo Clin Proc*. 2016 Nov;91(11):1535-44. doi: 10.1016/j.mayocp.2016.07.013. PMID: 27720456. Exclusion Code: X4.
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41. Becker A, Leber A, Becker C, et al. Predictive value of coronary calcifications for future cardiac events in asymptomatic individuals. *Am Heart J*. 2008 Jan;155(1):154-60. doi: 10.1016/j.ahj.2007.08.024. PMID: 18082507. Exclusion Code: X3.
42. Becker A, Leber AW, Becker C, et al. Predictive value of coronary calcifications for future cardiac events in asymptomatic patients with diabetes mellitus: a prospective study in 716 patients over 8 years. *BMC Cardiovasc Disord*. 2008 Oct 10;8:27. doi: 10.1186/1471-2261-8-27. PMID: 18847481. Exclusion Code: X3.
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of Cardiovascular Disease: A Systematic Review. *Clin Pharmacol Ther*. 2016 Nov;100(5):500-12. doi: 10.1002/cpt.438. PMID: 27449968. Exclusion Code: X2.

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46. Berry JD, Willis B, Gupta S, et al. Lifetime risks for cardiovascular disease mortality by cardiorespiratory fitness levels measured at ages 45, 55, and 65 years in men. The Cooper Center Longitudinal Study. *J Am Coll Cardiol*. 2011 Apr 12;57(15):1604-10. doi: 10.1016/j.jacc.2010.10.056. PMID: 21474041. Exclusion Code: X5.
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55. Bouzas-Mosquera A, Peteiro J, Alvarez-Garcia N, et al. Prediction of mortality and major cardiac events by exercise echocardiography in patients with normal exercise electrocardiographic testing. *J Am Coll Cardiol*. 2009 May 26;53(21):1981-90. doi: 10.1016/j.jacc.2009.01.067. PMID: 19460612. Exclusion Code: X2.
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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix D Table 1. Quality Assessment of Randomized, Controlled Trials (KQs 1 and 3): Part 1

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported intervention fidelity?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?
Lievre, 2011[47] DYNAMIT	Yes	Yes	Yes	NR	NR	1.1% mortality 2.5% primary composite outcome	1.2%	No
Turrini, 2015[48] and Turrini, 2009[49] DADDY-D	Yes	Yes	Yes	17/20 (85%) with positive exercise test underwent angiography	Yes, 44 (17%) in the no screening group had non-protocol exercise testing (but unclear if those were indicated because of incident symptoms)	NR	NR	Unclear

Abbreviations: DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; KQ=key question; NR=not reported.

Appendix D Table 2. Quality Assessment of Randomized, Controlled Trials (KQs 1 and 3): Part 2

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Lievre, 2011[47] DYNAMIT	Yes	No	No	Yes	Unclear (3.5 years)	None (complete case analysis)	Yes	Fair	Trial stopped early because of trouble recruiting (randomized 631 of the planned 3,000). Not clear that 3.5 years of followup is sufficient. Applicability: high risk population of diabetics with 2 risk factors (urinary albumin excretion above a threshold, hypertension, hyperlipidemia, PAD, history of TIA, tobacco consumption, and family history of premature CVD); Table 1 shows 14% with PAD, 4–5% with history of TIA; patients referred to a diabetes specialist in a hospital. Study left subsequent investigations after stress test to judgment of cardiologists (no protocol; pragmatic approach for decisions about e.g., angiography or not, various treatments).
Turrini, 2015[48] and Turrini, 2009[49] DADDY-D	Yes	No	No	NR	Unclear (3.6 years)	NR Complete case	Yes	Fair	Study did not reach sample size goal (aimed for 364 per group and got about 260); not clear that 3.6 years of followup is sufficient; amount of missing data NR (flow diagram may indicate no missing data though); masking of outcome assessors NR. Applicability: setting was 2 diabetes outpatient clinics, and participants had to have a normal ECG to get into the study.

Abbreviations: CVD=cardiovascular disease; DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; ECG=electrocardiogram; KQ=key question; NR=not reported; PAD=peripheral artery disease; TIA=transient ischemic attack.

Appendix D Table 3. Quality Assessment of Randomized, Controlled Trials: Additional Questions for Studies Reporting Harms (KQ 3)

First Author, Year Trial Name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating	Comments
Turrini, 2015[48] and Turrini, 2009[49] DADDY-D	Yes for post-procedure MI. No for other potential harms.	No	Unclear	Yes	Fair (for MI) but poor for other harms	Study reports that one patient had an MI 3 days after a revascularization procedure and that there were no other harms/events for those who underwent revascularization; limited assessment of harms and no mention of, for example, postintervention hematomas or infections. Other than MI, no methods on how harms were defined or measured, if they were measured at all.

Abbreviations: DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; KQ=key question; MI=myocardial infarction.

Appendix D Table 4. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 1

First Author, Year	Does study sample adequately capture the 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?	Enrolled consecutive patients or a random sample?	Were selection criteria clearly described?	Is a valid and reliable definition and method for measurement of the outcomes reported?	Was the same outcome definition (and method for measurement) used in all patients?	Were the outcomes assessed without knowledge of the candidate predictors (i.e., blinded)?	Is a valid and reliable definition and method for measurement and classification of candidate predictor(s) (ECG and risk factors) reported?
Chang, 2015[45]	Uncertain, possibly not, see comments	No (although unclear if the 4% without adequate followup were included in analyses)	NA	Unknown	No, "clinically indicated reasons" for CACS and stress SPECT not defined except for the 16% with atypical chest pain	Yes	Yes	Yes	Yes for most risk factors and ECG/ETT. No, cholesterol and blood pressure were not available, and conservative values were imputed based on history of hypertension or hyperlipidemia.
Ishikawa, 2015[50]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unknown	Yes
Tereshchenko, 2014[51]	Yes, but uncertain how many had CVD at baseline depending on overlap or lack thereof for those with history of CAD, MI, HF, and stroke (could be as low as 5% or as high as 14%)	Yes	NA	Yes	Yes	Yes	Yes	Unknown	Yes
Jorgensen, 2014[52]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unknown	Yes

Appendix D Table 4. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 1

First Author, Year	Does study sample adequately capture the 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?	Enrolled consecutive patients or a random sample?	Were selection criteria clearly described?	Is a valid and reliable definition and method for measurement of the outcomes reported?	Was the same outcome definition (and method for measurement) used in all patients?	Were the outcomes assessed without knowledge of the candidate predictors (i.e., blinded)?	Is a valid and reliable definition and method for measurement and classification of candidate predictor(s) (ECG and risk factors) reported?
Badheka, 2013[53]	Somewhat unclear; NHANES III sample; symptoms not assessed; just under 10% with CAD	Yes	NA	Complex, nonrandom, multistage stratified sample design (NHANES III)	Yes	Yes	Yes	Unknown	Yes
Badheka, 2013[54]	Yes	Yes for discrimination and calibration. No for NRI calculations; those excluded 5% with missing data).	NA	Complex, nonrandom multistage stratified sample design	Yes	Yes	Yes	Unknown	Yes
Auer, 2012[55]	Yes	Yes (but little missing data)	NA	Yes	Yes	Yes	Yes	Yes	Yes
Cournot, 2009[56]	Yes, regarding asymptomatic status, but they were self-referred (20%) or referred by PCPs (27%) or other providers to a preventive cardiology unit	Yes (but little missing data)	NA	No (referrals and from media)	Yes	Uncertain (questionnaire or phone call to patients and physicians)	Yes	Unknown	Yes

Appendix D Table 4. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 1

First Author, Year	Does study sample adequately capture the 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?	Enrolled consecutive patients or a random sample?	Were selection criteria clearly described?	Is a valid and reliable definition and method for measurement of the outcomes reported?	Was the same outcome definition (and method for measurement) used in all patients?	Were the outcomes assessed without knowledge of the candidate predictors (i.e., blinded)?	Is a valid and reliable definition and method for measurement and classification of candidate predictor(s) (ECG and risk factors) reported?
Shah, 2016[57]	Probably; NHANES I and III samples; symptoms not assessed, but self-reported CVD excluded	Yes (3,640/4,192 with ECG data for derivation cohort, NHANES I; 6,329/6,927 with ECG for validation cohort (III)	NA	Complex, nonrandom, multistage, stratified sample (NHANES I and III)	Yes	Yes	Yes	Unknown	Yes
Denes, 2007[58]	Yes (but only females with intact uterus in WHI)	Yes (<10% of the larger sample had measured cholesterol data allowing calculation of FRS)	Yes	No	Yes	Yes for CVD; unclear whether inclusion of silent MI from ECGs within the CHD composite outcome is valid and reliable	Yes	Unknown	Yes
Aktas, 2004[59]	Yes, no CVD and asymptomatic (but executive physical participants may not be representative)	NR	NA	Yes	Yes	Yes	Yes	NR	Yes

Appendix D Table 4. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 1

First Author, Year	Does study sample adequately capture the 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?	Enrolled consecutive patients or a random sample?	Were selection criteria clearly described?	Is a valid and reliable definition and method for measurement of the outcomes reported?	Was the same outcome definition (and method for measurement) used in all patients?	Were the outcomes assessed without knowledge of the candidate predictors (i.e., blinded)?	Is a valid and reliable definition and method for measurement and classification of candidate predictor(s) (ECG and risk factors) reported?
Cournot, 2006[60]	Yes, regarding asymptomatic status, but they were self-referred or referred by PCPs and cardiologists to a preventive cardiology unit	Yes	NA	Yes	Yes	Uncertain (questionnaire or phone call to patients and physicians for initial ascertainment)	Yes	Unknown	Yes
Strom Moller, 2007[61]	Population-based, but uncertain how many people with prior ASCVD or symptoms were included	Yes	NA	Yes	Yes	Yes	Yes	Unknown	Yes
Erikssen, 2004[62]	Yes	Unknown (full sample, survey 1), yes (survey 2)	NA	Yes	Yes	Yes	Yes	Unknown	Yes
Folsom, 2003[63]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unknown	Yes

Abbreviations: ASCVD=arteriosclerotic cardiovascular disease; CACS=coronary artery calcium score; CAD=coronary artery disease; CVD=cardiovascular disease; ECG=electrocardiogram; ETT=exercise treadmill test; FRS=Framingham Risk Score; KQ=key question; HF=heart failure; NA=not applicable; NHANES=National Health and Nutrition Examination Survey; NRI=Net reclassification index or improvement; PCP=primary care physician; RCT=randomized, controlled trial; SPECT=single-photon emission computed tomography; WHI=Women's Health Initiative.

Appendix D Table 5. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 2

First Author, Year	Were predictors assessed blinded for the outcome and for each other (if relevant)?	How was the predictor of interest (ECG) handled in the modeling?	Number of (%) Participants With Missing Data (Include Predictors and Outcomes)	Did the study have high attrition raising concern for bias?	How was missing data handled?	Were multiple measures of performance used (e.g., global fit,discrimination, calibration, net reclassification)?	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?
Chang, 2015[45]	Yes	Categorized (ETT showing presence or absence of ischemia; i.e., high or low risk)	4% missing followup for outcomes; 100% missing cholesterol and blood pressure numbers; NR for other predictors	No, not for lost to followup (but concern for missing data on some predictors)	Imputation for cholesterol and blood pressure based on history of diagnosis of hypertension or hyperlipidemia; unclear for missing outcome data (likely complete case analysis)	Yes	Both reported, no CIs (p-values given)	Yes	Unknown
Ishikawa, 2015[50]	Yes	Categorized and continuous (both were done in separate models)	Overall <14%; No ECG (n=1,285), Incomplete data (n=5) No followup data (n=84)	No	Complete-case analysis	Yes	Neither reported	Yes	NA
Tereshchenko, 2014[51]	Unknown	Categorized	2.6%	No	Complete-case analysis	Yes	Neither reported for eligible comparisons	Yes	Unknown
Jorgensen, 2014[52]	Unknown	Categorized	NR	Unknown	Other (complete-case analysis except that missing HDLs imputed by setting to mean of remaining participants)	Yes	Discrimination only reported, with CIs	No, NRI cut points for risk categories were based on the data	NA

Appendix D Table 5. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 2

First Author, Year	Were predictors assessed blinded for the outcome and for each other (if relevant)?	How was the predictor of interest (ECG) handled in the modeling?	Number of (%) Participants With Missing Data (Include Predictors and Outcomes)	Did the study have high attrition raising concern for bias?	How was missing data handled?	Were multiple measures of performance used (e.g., global fit,discrimination, calibration, net reclassification)?	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?
Badheka, 2013[53]	Unknown	Categorized	62 (<1%) missing mortality (n=4) or ST-T data (n=58)	No	Complete-case analysis (related to ST-T and mortality; some multiple imputation used for other variables)	Yes	Both reported, with CIs only for discrimination (also given for NRI)	Yes	NA
Badheka, 2013[54]	Unknown	Categorized (ECG abnormalities absent vs. present)	5% (breakdown NR)	No	Multiple imputation	Yes	Both reported, CI only reported for discrimination	Yes	NA
Auer, 2012[55]	Yes	Categorized	For main analyses, excluded those with missing data on traditional risk factors (n=41, <2%); for secondary analyses of people with followup ECGs at 4 years, excluded 424 (24%) with missing followup ECGs	No	Complete-case analysis	Yes	Calibration: p-values Discrimination with CIs	Yes	Yes

Appendix D Table 5. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 2

First Author, Year	Were predictors assessed blinded for the outcome and for each other (if relevant)?	How was the predictor of interest (ECG) handled in the modeling?	Number of (%) Participants With Missing Data (Include Predictors and Outcomes)	Did the study have high attrition raising concern for bias?	How was missing data handled?	Were multiple measures of performance used (e.g., global fit,discrimination, calibration, net reclassification)?	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?
Cournot, 2009[56]	Unknown	Categorized	87 (3.4%)	No	Complete-case analysis	Yes	Both reported, no CIs	Unclear (cut point reported, but unclear if a priori decision)	NA
Shah, 2016[57]	Unknown	Some variables categorized and some continuous	641 (6%) missing ECG data NR for outcomes	No	Complete-case analysis	Yes	Both reported, with CIs for discrimination only	Yes	NA
Denes, 2007[58]	Unknown	Categorized (normal, minor abnormalities, or major abnormalities)	91% (breakdown NR) for the only eligible results (Figure 3 and the related text)	Unknown (for the sample of interest to us)	Complete-case analysis	No (only discrimination)	Discrimination only reported, with CIs	NA	NA
Aktas, 2004[59]	NR	Categorized	NR	NR	NR	No	Discrimination only reported, no CIs	NA	NA
Cournot, 2006[60]	Unknown	Categorized	Lost to followup n=138 (11%); missing predictors unknown	No	Complete-case analysis	No	Calibration reported without CIs; discrimination not reported	Cut point used and reported but not a priori (was based on median FRS score)	NA

Appendix D Table 5. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 2

First Author, Year	Were predictors assessed blinded for the outcome and for each other (if relevant)?	How was the predictor of interest (ECG) handled in the modeling?	Number of (%) Participants With Missing Data (Include Predictors and Outcomes)	Did the study have high attrition raising concern for bias?	How was missing data handled?	Were multiple measures of performance used (e.g., global fit,discrimination, calibration, net reclassification)?	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?
Strom Moller, 2007[61]	Yes for the outcome, NR for each other	Categorized	For the 70-year-old cohort, 1,139/2,239 (51%) had ECGs and were included (1,139/1,681, 68%, of those who had been invited)	Yes	Complete case	No	Discrimination only reported, no CIs (data only for the subgroup who had followup ECGs at age 70)	NA	NA
Erikssen, 2004[62]	Unknown	Categorized	Not reported (survey 1); for survey 2 586/2,014 (29%) not included	Not reported	Not reported	No	Calibration reported without CIs (number of predicted and observed events); discrimination not reported	Yes	NA
Folsom, 2003[63]	Unknown	Categorized	11%	No	Complete-case analysis	Yes	Both reported, no CIs	Unknown	NA

Abbreviations: CI=confidence interval, ECG=electrocardiogram; ETT=exercise treadmill test; FRS=Framingham Risk Score; HDL=high-density lipoprotein cholesterol; KQ=key question; NA=not applicable; NR=not reported; NRI=net reclassification improvement.

Appendix D Table 6. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 3

First Author, Year	If net reclassification was assessed, were appropriate clinical thresholds used to reclassify risk?	Method used for testing model performance: development dataset only or separate external validation?	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 ECG was added to the model?	Quality	Comments
Chang, 2015[45]	Used <6% vs. 6–20% vs. >20% (not 7.5% or 10%)	Developmental dataset only	Entirely different population (but NA because did not use original FRS coefficients)	Yes (unable to use original FRS coefficients because of missing blood pressure and cholesterol values)	Fair	Moderate concern that the population may have limited applicability to our question; men and women with no history of CAD who had coronary artery calcium and stress SPECT performed for "clinically indicated reasons"; 16.5% with atypical chest pain and unclear how many had other symptoms; risk of misclassification due to imputing unavailable/missing data for all cholesterol and blood pressure measurements based on prior diagnoses of hypertension and hyperlipidemia (measurements were not available so they calculated FRS using conservative imputations; page 135); did not use current clinical thresholds for reclassification; followup was 6.9 years; this is a derivation study without external validation. Calibration NR, p-values for discrimination.
Ishikawa, 2015[50]	No, used <2.5%, 2.5–5%, >5%	Development dataset only	NA	NA (did not use FRS or PCE; used model with traditional risk factors plus heart rate and alcohol use as base model)	Fair	Base model included alcohol use and heart rate in addition to traditional risk factors; unclear why these particular clinical thresholds were chosen (<2.5%, 2.5–5%, >5%). Unknown if predictors were assessed blinded for outcomes; ECG QTc (predictor) determined by hand.
Tereshchenko, 2014[51]	Used <5%, 5–<20% and ≥20% (not 10% or 7.5%)	Developmental dataset only	Entirely different population (used ARIC)	Yes (FRSs were not directly used due to possible issues of the applicability to different ethnic groups; the authors adjusted for race)	Fair	Did not report calibration or discrimination for eligible comparison (ECG finding+traditional risk factors vs. traditional risk factors alone); unclear masking; did not use 10% or 7.5% threshold in classifications of risk groups

Appendix D Table 6. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 3

First Author, Year	If net reclassification was assessed, were appropriate clinical thresholds used to reclassify risk?	Method used for testing model performance: development dataset only or separate external validation?	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 ECG was added to the model?	Quality	Comments
Jorgensen, 2014[52]	No, used cut points determined by the data (low risk: <8.9%; intermediate risk: 8.9%–14.9; high risk: >14.9%).[a]	Developmental dataset only	Entirely different population (but NA because did not use FRS or PCE)	NA, used different base model with conventional risk factors	Fair	NRI cut points for risk categories were based on the data; calibration NR; unknown masking; amount of missing ECG data NR
Badheka, 2013[53]	Used FRS 5%–20% for intermediate risk category (not 7.5% or 10%)	Developmental dataset	Entirely different population (NHANES III)	Unknown (but seems that it was not)	Fair	Unclear proportion of population with symptoms; masking not reported; used 5%–20% for intermediate risk category
Badheka, 2013[54]	Yes	Developmental dataset only (no split of data)	Entirely different population (used NHANES)	Unknown	Fair	
Auer, 2012[55]	Yes	Developmental dataset only (no split of data)	NA	Yes	Good	Applicability to older patients, ages 70–79 years at baseline; good internal validity but developmental dataset and no validation set; did not use FRS because it has not been validated in adults over age 75, but adjusted for traditional risk factors included in FRS and diabetes; used 7.5% to 15% risk thresholds over 7.5 years (attempting to correspond with 10–20% 10-year risk); mean followup was 6.4 years
Cournot, 2009[56]	NA	Developmental dataset with respect to FRS + exercise ECG models; for models with FRS alone, could be considered external validation of FRS	Entirely different population	No	Fair	Masking of outcome assessors and assessors of relevant exposures NR; uncertain validity of outcome assessment procedures (relied primarily on questionnaire and phone calls for initial ascertainment); some measures of discrimination and calibration reported, but without CIs, and reclassification NR; duration of followup median 6 years. The relevant models also included femoral bruit in addition to adding exercise ECG.

Appendix D Table 6. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 3

First Author, Year	If net reclassification was assessed, were appropriate clinical thresholds used to reclassify risk?	Method used for testing model performance: development dataset only or separate external validation?	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 ECG was added to the model?	Quality	Comments
						Perhaps limited applicability of the selected population that included many referrals
Shah, 2016[57]	Used 1%, 5%, and 10% based on recommendation by the European Society of Cardiology for lipid management	Developmental dataset (NHANES I) and validation (NHANES III)	Entirely different population	Yes and no (appears that they ran analyses both ways)	Fair	Masking NR; some uncertainty about symptom status of participants
Denes, 2007[58]	NA	Developmental dataset only (no split of data)	Entirely different population (used WHI)	No	Fair	High proportion of missing data for the analyses eligible for our questions; less than 10% of the sample was included in the analyses eligible for our questions (due to lack of measured cholesterol information for most participants); complete-case analysis; only reports C-statistic
Aktas, 2004[59]	NA	Developmental dataset only with respect to SCORE + exercise ECG models (for models with SCORE alone, could be considered external validation)	Entirely different population (but NA because did not use FRS or PCS; used SCORE)	NA (did not use FRS or PCS for the parts eligible for our evaluation; used SCORE)	Fair	Provides limited information relevant to our questions (just some discrimination statistics without CIs); masking NR, amount and handling of missing data NR; mean followup of only 8 years (less than desired for 10-year risk prediction). Population referred for executive physical.
Cournot, 2006[60]	NA	Developmental dataset with respect to FRS + exercise ECG models; for models with FRS alone, could be considered external validation of FRS	Entirely different population	No	Fair	Masking of outcome assessors and assessors of relevant exposures NR; uncertain validity of outcome assessment procedures (relied primarily on questionnaire and phone calls for initial ascertainment); calibration reported, but without CIs, and reclassification and discrimination NR; duration of followup mean 6 years. Perhaps limited applicability of the selected population that included many referrals.

Appendix D Table 6. Quality Ratings for Studies Reporting Reclassification, Calibration, and Discrimination (KQ 2): Part 3

First Author, Year	If net reclassification was assessed, were appropriate clinical thresholds used to reclassify risk?	Method used for testing model performance: development dataset only or separate external validation?	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 ECG was added to the model?	Quality	Comments
Strom Moller, 2007[61]	NA	Developmental dataset	NA	NA	Poor	Very high attrition. Study started at age 50. The only eligible analysis/outcome is the part where they report discrimination (ROC curve) for FRS (traditional risk factors) vs. FRS + ECG indicating ischemia for a subgroup of the cohort who had repeated ECGs (20 years later) at age 70 (n=1,139 of the 2.239, 51%); they had 12-year followup after age 70. No similar analyses provided for the full cohort of 2,239 participants. Also, unclear selection criteria; unclear what proportion of the population had prior CVD or symptoms at baseline for the 50-year-old initial cohort or for the 70-year-old subgroup.
Erikssen, 2004[62]	NA	Developmental dataset only	NA	NA	Fair	Masking of outcome assessors NR, lack of multiple measures (calibration only; did not report discrimination or reclassification), missing data NR
Folsom, 2003[63]	NA	Developmental dataset only	Entirely different population (ARIC)	NA (did not use FRS or PCE)	Fair	Masking NR; developmental set only; unclear if cut points for LVH were defined a priori; reclassification NR

[a] Supplement table 2 reported different risk categories for categorical NRI – low risk < 23.8%, intermediate 23.8–35%, high >35%

Abbreviations: ARIC=Atherosclerosis Risk in Communities study; CAD=coronary artery disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiogram; KQ=key question; LVH=left ventricular hypertrophy; NA=not applicable; NHANES=National Health and Nutrition Examination Survey; NR=not reported; PCE=pooled cohort equation; RCT=randomized, controlled trial; ROC=receiver operating characteristic; SCORE=Systematic COronary Risk Evaluation; SPECT=single-photon emission computed tomography; WHI=Women's Health Initiative.

Appendix E Table 1. Results of Included Randomized, Controlled Trials Reporting Health Outcomes (KQ 1)

First Author, Year Trial Name	G1 (N) G2 (N)	All-Cause Mortality G1 N (%) G2 N (%) HR (95% CI)	CV Mortality G1 N (%) G2 N (%) HR (95% CI)	MI G1 N (%) G2 N (%) HR (95% CI)	Heart Failure G1 N (%) G2 N (%) HR (95% CI)	Stroke G1 N (%) G2 N (%) HR (95% CI)	Other CV Events G1 N (%) G2 N (%) HR (95% CI)	Composite CV Outcome G1 N (%) G2 N (%) HR (95% CI)
Lievre, 2011[47] DYNAMIT	Screened (316) Not screened (315)	15 (4.7) 13 (4.1) NR, NS	NR	4 (1.3) 8 (2.5) NR, NS	Hospitalized cardiac failure: 5 (1.6) 4 (1.3) NR, NS	9 (2.8) 4 (1.3) NR, NS	Revasculari-zation 18 (5.7) 21 (6.7) p=0.61	Main endpoint[a] 28 (8.9) 26 (8.3) 1.00 (0.59 to 1.71) Coronary events[b] 13 (4.1) 15 (4.8) 0.77 (0.37 to 1.63)
Turrini et al, 2015[48] DADDY-D	Screened (262) Not screened (258)	NR by group. Total of 19 deaths reported (6 cardiac and 13 non-cardiac)	*All* 1 (0.4) 5 (1.9) 0.197 (0.023 to 1.683) *Female* 0/53 (0) 3/51 (5.9) NA, p=0.077 *Male* 1/209 (0.5) 2/207 (1) 0.497 (0.045 to 5.483) *≥60 years* 0/182 (0) 4/181 (2.2) NA, p=0.044 <*60 years* 1/80 (1.3) 1/77 (1.3) 0.993 (0.062 to 15.87) *CV risk≥20* 1/115 (0.9) 2/112 (1.8) 0.494 (0.045 to 5.443) *CV risk<20* 0/147 (0) 3/146 (2.1)	Non-fatal MI: *All* 11 (4.2) 12 (4.7) 0.908 (0.400 to 2.057) *Female* 5/53 (9.4) 1/51 (2) 4.916 (0.573 to 42.142) *Male* 6/209 (2.9) 11/207 (5.3) 0.535 (0.198 to 1.446) *≥60 years* 7/182 (3.8) 8/181 (4.4)0.859 (0.311 to 2.370) <*60 years* 4/80 (5) 4/77 (5.2) 0.999 (0.249 to 3.981) *CV risk≥20* 4/115 (3.5) 6/112 (5.4) 0.656 (0.185 to 2.325) *CV risk<20*	*All* 2 (0.8) 7 (2.7) 0.273 (0.57 to 1.314) *Female* 0/53 (0) 3/51 (5.9) NA, p 0.065 *Male* 2/209 (1) 4/207 (1.9) 0.485 (0.89 to 2.647) *≥60 years* 2/182 (1.1) 4/181 (2.2) 0.476 (0.087 to 2.599) <*60 years* 0/80 (0) 3/77 (3.9) NA, p 0.08 *CV risk≥20* 2/115 (1.7) 2/112 (1.8) 0.961 (0.135 to 6.822) *CV risk<20* 0/147 (0) 5/146 (3.4)	NR by group. Total of 7 strokes	NR	Cardiac events (primary outcome; composite of nonfatal MI or cardiac death) *All* 12 (4.6) 14 (5.4) 0.849 (0.393 to 1.837) *Female* 5/53 (9.4) 3/51 (5.9) 1.653 (0.395 to 6.928) *Male* 7/209 (3.3) 11/207 (5.3) 0.625 (0.242 to 1.614) *≥60 years* 7/182 (3.8) 10/181 (5.5) 0.687 (0.261 to 1.805) <*60 years* 5/80 (6.3) 4/77 (5.2) 1.264 (0.339 to 4.707) *CV risk≥20* 5/115 (4.3) 6/112 (5.4) 0.822 (0.251 to 2.692) *CV risk<20* 7/147 (4.8) 8/146 (5.5)

Appendix E Table 1. Results of Included Randomized, Controlled Trials Reporting Health Outcomes (KQ 1)

First Author, Year Trial Name	G1 (N) G2 (N)	All-Cause Mortality G1 N (%) G2 N (%) HR (95% CI)	CV Mortality G1 N (%) G2 N (%) HR (95% CI)	MI G1 N (%) G2 N (%) HR (95% CI)	Heart Failure G1 N (%) G2 N (%) HR (95% CI)	Stroke G1 N (%) G2 N (%) HR (95% CI)	Other CV Events G1 N (%) G2 N (%) HR (95% CI)	Composite CV Outcome G1 N (%) G2 N (%) HR (95% CI)
			NA, p=0.08	7/147 (4.8) 6/146 (4.1) 1.176 (0.393 to 3.505)	NA, p=0.022			0.879 (0.318 to 2.426)

[a] Composite endpoint of death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention.
[b] Defined as fatal or nonfatal MI, hospitalized unstable angina, or heart failure requiring hospitalization or emergency service intervention.

Abbreviations: CI=confidence interval; CV=cardiovascular; DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; KQ=key question; G=group; HR=hazard ratio; MI=myocardial infarction; N=sample size; NA=not applicable; NR=not reported; NS=not significant.

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
Auer, 2012[55] Fair	CHD events[a]	Total: 351 (16.0) CHD deaths: 96 (4.4) Acute MIs: 101 (4.6) Hospitalizations for angina or coronary revascularization: 154 (7.0)	Base model: CVRF Harrell C index Calibration NRI Adjusted clinical NRI IDI Base model: FRS NRI IDI	1. CVRF model (used FRS variables)[b] 2. CVRF + any ECG abnormality 3. FRS model 4. FRS + any ECG abnormality	Harrell C Index (95% CI) CVRF model: 0.58 (0.53–0.62) CVRF + ECG: 0.60 (0.56–0.65)	Hosmer-Lemeshow chi-square CVRF model: 67.6 CVRF + ECG: 87.9 Likelihood ratio: p≤0.00005 Goodness of fit p value CVRF model: 0.03 CVRF model + ECG: 0.01	CVRF + ECG vs. CVRF Overall sample NRI: 7.4% (3.1%–19.0%) Event NRI: -0.9% Nonevent NRI: 8.3% Adjusted clinical NRI 6.7% (95% CI, 1.2% to 19.3%) IDI: 0.99% (0.32%–2.15%) For the Intermediate Risk Category: NRI 13.6% FRS + ECG vs. FRS NRI 5.7% (-0.4%–11.8%) IDI: 1.03% (0.56%–1.50%) Reclassification with Addition of ECG For those who experience a CHD event <7.5%, no change: 4 <7.5% to 7.5-<15%: 2 <7.5% to ≥15%: 0 Total: 6 7.5-<15.0% to <7.5%: 7 7.5-<15.0%, no change: 91 7.5-<15% to ≥15%: 27 Total: 125 ≥15.0% to <7.5%: 0 ≥15.0% to 7.5-<15.0%: 25 ≥15%, no change: 195 Total: 220 For those who do not experience a CHD event <7.5%, no change: 74 <7.5% to 7.5-<15%: 17 <7.5% to ≥15%: 0 Total: 91 7.5-<15.0% to <7.5%: 129

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							7.5-<15.0%, no change: 678 7.5-<15% to ≥15%: 149 Total: 956 ≥15.0% to <7.5%: 0 ≥15.0% to 7.5-<15.0%: 189 ≥15%, no change: 605 Total: 794
Badheka, 2013[54] Fair	CV mortality All-cause mortality	CV mortality: 739 (12.3) All-cause mortality: 1,824 (30.3)	AUC IDI Calibration NRI	Model A: FRS[c] Model B: FRS + ECG abnormalities	C-statistic Model A: 0.851 (0.836–0.865) Model B: 0.852 (0.838–0.866) p=0.05	Hosmer-Lemeshow chi-square Model A: 15.14 p=0.05 Model B: 10.98 p=0.2 Goodness of fit Likelihood ratio test: p=0.001 Bayesian information criterion Model A: 3360.54 Model B: 3358.28	Overall NRI: 3.6%, p=0.0001; NRI for Those with Events: 3.0% p=0.03 NRI for Those without Events: NRI: 0.6% p=0.11 Absolute IDI: 0.0001, p≤0.001 For the Intermediate Risk Category: NRI 13.2% Reclassification with Addition of ECG Abnormalities For Those with Events <5%, no change: 92 <5% to 5-10%: 11 <5% to 10–20%: 0 <5% to >20%: 0 Total: 103 5-10% to <5%: 4 5-10%, no change: 98 5-10% to 10–20%: 26 5-10% to >20%: 0 Total: 128 10-20% to <5%: 0 10-20% to 5–10%: 14 10-20%, no change: 205 10-20% to >20%: 21 Total: 240 >20% to <5%: 0 >20% to 5-10%: 0 >20% to 10–20%: 19 >20%, no change: 208

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							Total: 227 Risk Reclassified Higher from Each Category For Those with Events <5%: 11 (10.7%) 5% to <10%: 26 (20.3%) 10% to <20%: 21 (8.8%) >20%: NA Total: 58 (8.3%) Risk Reclassified Lower from Each Category For Those with Events <5%: NA 5% to <10%: 4 (3%) 10% to <20%: 14 (5.8%) ≥20%: 19 (8.4%) Total: 37 (5.3%) For Those with no Events <5%, no change: 3209 <5% to 5–10%: 79 <5% to 10–20%: 0 <5% to >20%: 0 Total: 3,288 5-10% to <5%: 104 5-10%, no change: 702 5-10% to 10–20%: 53 5-10% to >20%: 0 Total: 859 10-20% to <5%: 0 10-20% to 5–10%: 65 10-20%, no change: 512 10-20% to >20%: 37 Total: 614 >20% to <5%: 0 >20% to 5–10%: 0 >20% to 10–20%: 31 >20%, no change: 239

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							Total: 270 Risk Reclassified Higher No Events <5%: 79 (2.4%) 5% to <10%: 53 (6.2%) 10% to <20%: 37 (6.0%) >20%: NA Total: 169 (3.4%) Risk Reclassified Lower No Events <5%: NA 5% to <10%: 104 (12.1%) 10% to <20%: 65 (10.6%) ≥20%: 31 (11.5%) Total: 200 (4.0%) Intermediate Risk Cohort: NRI: 13.24% 137 (2.4%) and 187 (3.3%) were reclassified to higher and lower risk groups, respectively
Badheka, 2013[53] Fair	CV mortality	1,226 (15.5)	C-statistic AUROC Calibration Reclassification IDI NRI	Model A: FRS only Model B: FRS plus the variable T-wave amplitude in lead aVR	C-statistic Model A: 0.832 (0.822–0.841) Model B: 0.838 (0.828–0.848) p<0.01 AUROC Model A: 0.812 (0.800–0.824) Model B: 0.820 (0.807–0.832) p<0.01	Hosmer-Lemeshow chi-square Model A: 13.7 Model B: 16.7 Goodness of fit Likelihood ratio test: p<0.01 Bayesian information criterion Model A: 5240.0 Model B: 5172.2	Overall NRI: 0.07 (0.05–0.09) p<0.01 Reclassification of subjects with events: 2.7% p<0.01 Reclassification of subjects without events: 2.3% p<0.01 Absolute IDI 0.012 (0.009–0.015), p<0.01 Relative IDI 0.11 Participants with CVD disease events <5%, no change: 53 <5% to 5–<10%: 11 <5% to 10–<20%: 0 <5% to >20%: 0 Total: 64 5-<10% to <5%: 6 5-<10%, no change: 50

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							5-<10% to 10–<20%: 22 5-<10% to >20%: 0 Total: 78 10-<20% to <5%: 0 10-<20% to 5–<10%: 13 10-<20%, no change: 148 10-<20% to >20%: 60 Total: 221 >20% to <5%: 0 >20% to 5–<10%: 0 >20% to 10-<20%: 42 >20%, no change: 754 Total: 796 Participants with CVD disease events reclassified as higher risk from each category <5%: 11 5%–<10%: 22 10%–<20%: 60 >20%: NA Total: 93 Participants with CVD disease events reclassified as lower risk from each category <5%: NA 5%–<10%: 6 10%–<20%: 13 >20%: 42 Total: 61 Participants without CVD disease events <5%, no change: 2,426 <5% to 5–<10%: 135 <5% to 10–<20%: 0 <5% to >20%: 0 Total: 2,561

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							5–<10% to <5%: 221 5–<10%, no change: 764 5–<10% to 10–<20%: 158 5–<10% to >20%: 0 Total: 1,143 10–<20% to <5%: 0 10–<20% to 5-<10%: 216 10–<20%, no change: 898 10–<20% to >20%: 152 Total: 1,266 >20% to <5%: 0 >20% to 5-<10%: 0 >20% to 10–<20%: 158 >20%, no change: 12,22 Total: 1,380 Participants without CVD disease events reclassified as higher risk from each category <5%: 135 5%–<10%: 158 10%–<20%: 152 >20%: NA Total: 445 Participants without CVD disease events reclassified as lower risk from each category <5%: NA 5%–<10%: 221 10%–<20%: 216 >20%: 158 Total: 595 Intermediate risk cohort (5% to <20% risk): 60 (20%) of subjects with events and 219 (9.1%) of subjects without events were reclassified appropriately to

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							higher and lower risk categories, respectively
Denes, 2007[58] Fair	Incident CHD[d] Incident CVD events[e]	CHD events: 246 (1.7) CVD events: 595 (4)	AUC Calibration/ overall performance	FRS FRS + ECG abnormality	AUROC (95% CI) FRS for CHD: 0.69 (0.61–0.86) FRS + ECG abnormality for CHD: 0.74 (0.66–0.90) FRS for CVD: 0.68 (0.62-0.77) FRS + ECG abnormality for CVD: 0.70 (0.65–0.79)	Likelihood ratio chi square test FRS + ECG abnormality CHD: p=0.004 CVD: p=0.02	NR
Folsom, 2003[63] Fair	CHD events[f]	Total: 954 (6.8) Among 707 women with diabetes: 99 (14.0) Among 6,526 women without diabetes: 211 (3.2) Among 566 men with diabetes: 129 (22.8) Among 4,946 men without diabetes: 515 (10.4)	AUROC Calibration	Basic model Basic + LVH model	AUROC *Basic Model* Women with diabetes: 0.711 Women without diabetes: 0.777 Men with diabetes: 0.680 Men without diabetes: 0.679 *Basic + LVH Model (yes/no)* Women with diabetes: 0.709 Women without diabetes: 0.777 Men with diabetes: 0.681 Men without diabetes: 0.679	NR	NR
Ishikawa, 2015[50] Fair	Stroke events	Total: 375 (3.5) Cerebral hemorrhages: 85 (0.8) Ischemic strokes: 242 (2.3) Subarachnoid	NRI IDI	Traditional CV risk factor model[h] (model) Model with ECG-LVH	NR	NR	IDI The model with and without QTc Interval (as a continuous variable) IDI= 0.292, p=0.80 The model with and without

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
		hemorrhages: 47 (0.4) Unknown cause: 1		without QTc interval Model with ECG-LVH with QTc interval Model without QTc interval (as a continuous variable) Model with QTc interval (as a continuous variable) Model without ECG-LVH Model with ECG-LVH Model without ECG-LVH or QTc interval Model with ECG-LVH and QTc interval			ECG-LVH IDI= 0.004, p=0.75 The model with and without ECG-LVH and/or QTc interval IDI=0.006, p=0.63 <u>NRI, Frequency (Percentage)</u> The model with and without QTc Interval (as a continuous variable) Categorical NRI= 0.026, p<0.001 Event NRI 1.35% Nonevent NRI 1.22% *Reclassification of subjects with stroke events using the model with QTc interval* <2.5% to <2.5%: 41 (91.1) <2.5% to 2.5–5.0%: 2 (3.4) <2.5% to >5.0%: 0 (0.0) Total: 43 2.5–5.0% to <2.5%: 4 (8.9) 2.5–5.0% to 2.5–5.0%: 51 (87.9) 2.5–5.0% to >5.0%: 11 (5.7) Total: 66 >5.0% to <2.5%: 0 (0.0) >5.0% to 2.5–5.0%: 5 (8.6) >5.0% to >5.0%: 183 (94.3) Total: 188 *Reclassification of subjects without stroke events using the model with QTc interval* <2.5% to <2.5%: 4,401 (95.5) <2.5% to 2.5–5.0%: 162 (9.2) <2.5% to >5.0%: 2 (0.1) Total: 4,565

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							2.5–5.0% to <2.5%: 205 (4.5) 2.5–5.0% to 2.5–5.0%: 1,384 (78.2) 2.5–5.0% to >5.0%: 165 (9.3) Total: 1,754 >5.0% to <2.5%: 0 (0.0) >5.0% to 2.5–5.0%: 224 (12.7) >5.0% to >5.0%: 1,613 (90.6) Total: 1,837 The model with and without ECG-LVH Categorical NRI= 0.020, p<0.001 Event NRI 1.01% Nonevent NRI 1.01% *Reclassification of subjects with stroke events using the model with ECG-LVH* <2.5% to <2.5%: 41 (95.3) <2.5% to 2.5–5.0%: 2 (3.2) <2.5% to >5.0%: 0 (0.0) Total: 43 (14.5) 2.5–5.0% to <2.5%: 2 (4.7) 2.5–5.0% to 2.5–5.0%: 56 (88.9) 2.5–5.0% to >5.0%: 8 (4.2) Total: 66 (22.2) >5.0% to <2.5%: 0 (0.0) >5.0% to 2.5–5.0%: 5 (7.9) >5.0% to >5.0%: 183 (95.8) Total: 188 (63.3) *Reclassification of subjects without stroke events using the model with ECG-LVH*

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							<2.5% to <2.5%: 4,495 (97.6) <2.5% to 2.5-5.0%: 70 (4.0) <2.5% to >5.0%: 0 (0.0) Total: 4,565 (56.0) 2.5–5.0% to <2.5%: 110 (2.4) 2.5–5.0% to 2.5-5.0%: 1,551 (88.3) 2.5–5.0% to >5.0%: 93 (5.2) Total: 1,754 (21.5) >5.0% to <2.5%: 0 (0.0) >5.0% to 2.5-5.0%: 135 (7.7) >5.0% to >5.0%: 1,702 (94.8) Total: 1,837 (22.5) The model with and without ECG-LVH and/or QTc interval Categorical NRI=0.035, p<0.001 *Reclassification of subjects with stroke events using the model with ECG-LVH and QTc interval* <2.5% to <2.5%: 40 (87.0) <2.5% to 2.5–5.0%: 3 (5.5) <2.5% to >5.0%: 0 (0.0) Total: 43 (14.5) 2.5–5.0% to <2.5%: 6 (13.0) 2.5–5.0% to 2.5–5.0%: 44 (80.0) 2.5–5.0% to >5.0%: 16 (8.2) Total: 66 (22.2) >5.0% to <2.5%: 0 (0.0) >5.0% to 2.5–5.0%: 8 (14.5) >5.0% to >5.0%: 180 (91.8) Total: 188 (63.3)

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							Reclassification of subjects without stroke events using the model with ECG-LVH and QTc interval <2.5% to <2.5%: 4403 (94.8) <2.5% to 2.5–5.0%: 157 (9.0) <2.5% to >5.0%: 5 (0.3) Total: 4,565 (56.0) 2.5–5.0% to <2.5%: 242 (5.2) 2.5–5.0% to 2.5–5.0%: 1,316 (75.9) 2.5–5.0% to >5.0%: 196 (11.0) Total: 1,754 (21.5) >5.0% to <2.5%: 0 (0.0) >5.0% to 2.5–5.0%: 262 (15.1) >5.0% to >5.0%: 1,575 (88.7) Total: 1,837 (22.5)
Jorgensen, 2014[52] Fair	Fatal CVD events Fatal or Nonfatal CVD events (combined) All-cause mortality	Fatal CVD events: 2,236 (32.0) Fatal or nonfatal CVD events: 3,849 (55.0) All-cause mortality: 5,626 (80.5) For sample with ≥10 years followup (used to calculate discrimination and reclassification outcomes): Fatal CVD	C-statistic Continuous NRI Categorical NRI	Conventional risk factors Conventional risk factors and major/minor ECG changes	Any ECG changes C-Index for Fatal CVD Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG changes: 0.719 (0.702–0.737) p<0.001 Conventional risk factors and ECG changes with increasing severity: 0.719 (0.702–0.736) p<0.001 C-Index for Fatal or Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–	NR	Any ECG changes Continuous NRI for fatal CVD events Conventional risk factors and ECG changes as present or not: 42.3 (34.7–50.0) p<0.001 Conventional risk factors and ECG changes with increasing severity: 42.3 (34.7–50.0) p<0.001 Categorical NRI for fatal CVD events Conventional risk factors and ECG changes as present or not: 7.1 (3.6–10.6) p<0.001 Conventional risk factors and ECG changes with increasing severity: 7.2 (3.7–10.7) p<0.001

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
		events: 837 (17) Fatal or nonfatal CVD events: 2,092 (38.6) All-cause mortality: 2,225 (32.2)			0.663) Conventional risk factors and ECG changes as present or not: 0.660 (0.648–0.672) p<0.001 Conventional risk factors and ECG changes with increasing severity: 0.660 (0.648–0.671) p<0.001 C-Index for all-cause mortality Conventional risk factors: 0.652 (0.640–0.664) Conventional risk factors and ECG changes: 0.656 (0.645–0.668) p<0.001 Conventional risk factors and ECG changes with increasing severity: 0.656 (0.645–0.668) p<0.001 C-Index for Fatal CVD Events (From Table 3, model validation) Conventional risk factors: 0.705 (0.703–0.707) Adjusted for optimism: 0.706 Conventional risk factors and ECG changes: 0.719		Continuous NRI for Fatal or Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 29.1 (23.6–34.7) p<0.001 Conventional risk factors and ECG changes with increasing severity:29.2 (23.7–34.8) p<0.001 Categorical NRI for Fatal or Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 3.8 (1.4–6.3) p<0.001 Conventional risk factors and ECG changes with increasing severity: 4.2 (1.8–6.7) p<0.001 Continuous NRI for All-Cause Mortality Conventional Risk Factors and ECG Changes as Present or Not: 22.7 (17.5–27.8) p<0.001 Categorical NRI for All-Cause Mortality Conventional Risk Factors and ECG Changes as Present or Not: 1.9 (0.1–3.6) p<0.001 Conventional Risk Factors and ECG Changes for Fatal CVD Events (From Table 3, validation)

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					(0.717–0.721) Adjusted for optimism: 0.720 p<0.001 Fatal or Nonfatal CVD Events (From Table 3, validation) Conventional risk factors: 0.651 (0.649–0.653) Adjusted for optimism: 0.652 Conventional risk factors and ECG changes: 0.660 (0.658–0.662) Adjusted for optimism: 0.660 p<0.001 T wave changes C-Index for Fatal CVD Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG change: 0.716 (0.699–0.734) p<0.001 C-Index for Fatal and Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–0.663) Conventional risk factors and ECG change: 0.658 (0.647–0.670)		Continuous NRI: 42.3 (42.0–42.4) Adjusted for optimism: 42.3 p<0.001 Categorical NRI: 7.1 (6.7–9.0) Adjusted for optimism: 8.6 p<0.001 Conventional Risk Factors and ECG Changes for Fatal or Nonfatal CVD Events (From Table 3, validation) Continuous NRI: 29.2 (28.4–29.2) Adjusted for optimism: 29.2 p<0.001 Categorical NRI: 4.2 (3.5–5.6) Adjusted for optimism: 4.7 p<0.001 T wave changes Continuous NRI for Fatal CVD Events Conventional Risk Factors and ECG Changes as Present or Not: 29.2 (21.5–36.8) p<0.001 Categorical NRI for Fatal CVD Events Conventional Risk Factors and ECG Changes as Present or Not: 5.4 (2.2–8.6) p<0.01 Continuous NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 20.3 (14.7–25.9)

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					p<0.001 C-Index for All-Cause Mortality Conventional risk factors: 0.652 (0.640–0.664) Conventional risk factors and ECG change: 0.656 (0.644–0.668) p<0.01 Ventricular conduction delay C-Index for Fatal CVD Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG change: 0.708 (0.690–0.726) p>0.05 C-Index for Fatal and Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–0.663) Conventional risk factors and ECG change: 0.655 (0.643–0.667) p>0.05 C-Index for All-Cause Mortality Conventional risk factors: 0.652 (0.640–0.664)		p<0.001 Categorical NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 2.7 (0.6–4.8) p<0.05 Continuous NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 16.5 (11.4–21.7) p<0.001 Categorical NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 1.3 (-0.3–3.0) p>0.05 Ventricular conduction delay Continuous NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 2.8 (-4.9–10.4) p>0.05 Categorical NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 1.1 (0.1–2.1) p<0.05 Continuous NRI for Fatal and

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					Conventional risk factors and ECG change: 0.653 (0.642–0.665) p>0.05 LVH C-Index for Fatal CVD Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG change: 0.706 (0.688–0.724) p>0.05 C-Index for Fatal and Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–0.663) Conventional risk factors and ECG change: 0.651 (0.639–0.663) p>0.05 C-Index for All-Cause Mortality Conventional risk factors: 0.652 (0.640–0.664) Conventional risk factors and ECG change: 0.653 (0.641–0.665) p>0.05 Q waves C-Index for Fatal CVD		Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 5.5 (-0.1–11.1) p>0.05 Categorical NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 0.0 (-1.1– 1.2) p>0.05 Continuous NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 3.2 (-2.0–8.4) p>0.05 Categorical NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 0.2 (-0.5–1.0) p>0.05 LVH Continuous NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 12.1 (4.5–19.8) p<0.01 Categorical NRI for Fatal CVD Events Conventional risk factors and

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG change: 0.709 (0.691–0.727) p<0.05 C-Index for Fatal and Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–0.663) Conventional risk factors and ECG change: 0.655 (0.643–0.667) p<0.01 C-Index for All-Cause Mortality Conventional risk factors: 0.652 (0.640–0.664) Conventional risk factors and ECG change: 0.654 (0.643–0.666) p<0.05 ST depressions C-Index for Fatal CVD Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG change: 0.714 (0.697–0.732)		ECG changes as present or not: 2.7 (1.0–4.4) p<0.01 Continuous NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 6.7 (1.1–12.3) p<0.05 Categorical NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: -1.1 (-2.3–0.1) p>0.05 Continuous NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 7.0 (1.8–12.1) p<0.01 Categorical NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 0.7 (-0.2–1.7) p>0.05 Q waves Continuous NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 5.3 (-0.02–12.9) p>0.05

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					p<0.001 C-Index for Fatal and Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–0.663) Conventional risk factors and ECG change: 0.660 (0.648–0.672) p<0.001 C-Index for All-Cause Mortality Conventional risk factors: 0.652 (0.640–0.664) Conventional risk factors and ECG change: 0.656 (0.644–0.667) p<0.01 Resting heart Rate C-Index for Fatal CVD Events Conventional risk factors: 0.705 (0.687–0.723) Conventional risk factors and ECG change: 0.709 (0.691–0.727) p<0.001 C-Index for Fatal and Nonfatal CVD Events Conventional risk factors: 0.651 (0.639–0.663) Conventional risk		Categorical NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 1.9 (0.7–3.1) p<0.01 Continuous NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 3.9 (-1.6–9.5) p>0.05 Categorical NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 0.7 (-0.2–1.8) p>0.05 Continuous NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 4.7 (-0.4–9.9) p>0.05 Categorical NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 0.7 (0.0–1.4) p<0.05 ST depressions Continuous NRI for Fatal CVD Events

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					factors and ECG change: 0.652 (0.640–0.664) p>0.05 C-Index for All-Cause Mortality Conventional risk factors: 0.652 (0.640–0.664) Conventional risk factors and ECG change: 0.661 (0.649–0.672) p<0.001		Conventional risk factors and ECG changes as present or not: 18.0 (10.4–25.6) p<0.001 Categorical NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 3.1 (0.7–5.4) p<0.01 Continuous NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 14.7 (9.1–20.3) p<0.001 Categorical NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 2.2 (0.4–4.1) p<0.01 Continuous NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 11.1 (6.0–16.3) p<0.001 Categorical NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 1.5 (0.3–2.8) p<0.01

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							Resting heart Rate Continuous NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 14.1 (6.4–21.7) p<0.001 Categorical NRI for Fatal CVD Events Conventional risk factors and ECG changes as present or not: 0.9 (-1.8–3.7) p>0.05 Continuous NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: 7.3 (1.8–12.9) p<0.05 Categorical NRI for Fatal and Nonfatal CVD Events Conventional risk factors and ECG changes as present or not: -0.2 (-1.4–1.0) p>0.05 Continuous NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 21.4 (16.2–26.6) p<0.001

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							Categorical NRI for All-Cause Mortality Conventional risk factors and ECG changes as present or not: 3.7 (1.6–5.7) p<0.001
Shah, 2016[57] Fair	Primary: CVD death Secondary outcomes: 10-year ischemic heart disease (IHD) death and all-cause death	Derivation cohort: CVD death: 574 (15.8) Validation cohort: CVD death: 282 (4.4) Fatal IHD: 166 (2.6) All-cause death: 810 (12.8)	C-statistic IDI Calibration (only for base models) Reclassification NRI	NHANES ECG risk score model FRS model FRS model + ECG risk equation PCE model PCE model + ECG risk equation FRS variables model FRS variables model + ECG risk equation	<u>C-statistic (95% CI)</u> *NHANES ECG risk score model* Fatal IHD: 0.80 (0.77–0.83) Fatal CVD: 0.79 (0.76–0.81) All-cause death: 0.75 (0.73–0.77) *FRS model* Fatal IHD: 0.79 (0.76–0.82) Fatal CVD: 0.76 (0.73–0.78) All-cause death: 0.71 (0.69–0.73) *FRS model + ECG risk equation* Fatal IHD: 0.82 (0.79–0.85) Fatal CVD: 0.80 (0.77–0.82) All-cause death: 0.75 (0.74–0.77) *Difference between FRS model and FRS model + ECG risk equation* Fatal IHD: 0.03 (0.01–0.05) Fatal CVD: 0.04 (0.02–0.06)	<u>Hosmer-Lemeshow chi-square values</u> NHANES ECG risk score model IHD Death: 185 CVD Death: 281 Death: 600 FRS model IHD Death: 175 CVD Death: 237 Death: 458 Pooled cohort model (ACC-AHA) IHD Death: 152 CVD Death: 222 Death: 447 Calibration statistics for the NHANES ECG risk score for CVD death were adequate with p=0.08 in the derivation cohort and p=0.22 in the validation cohort.	<u>NRI, Total (Event NRI; Nonevent NRI), %</u> FRS model *Categorical NRI* Fatal IHD: 24 (17; 7) Fatal CVD: 25 (12; 13) All-cause death: 30 (11; 19) *Continuous NRI* Fatal IHD: 57 (22; 35) Fatal CVD: 56 (21; 35) All-cause death: 53 (20; 33) ACC-AHA pooled cohort equation model *Categorical NRI* Fatal IHD: 14 (9; 5) Fatal CVD: 25 (11; 14) All-cause death: 19 (7; 12) *Continuous NRI* Fatal IHD: 41 (17; 24) Fatal CVD: 54 (20; 34) All-cause death: 35 (18; 17) Framingham variables model *Categorical NRI* Fatal IHD: 4 (3; 1) Fatal CVD: 11 (7; 4) All-cause death: 10 (6; 4) *Continuous NRI* Fatal IHD: 37 (9; 28) Fatal CVD: 35 (7; 28) All-cause death: 33 (8; 25) <u>IDI, %</u> FRS model *Absolute IDI*

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					All-cause death: 0.04 (0.03–0.05) *PCE model* Fatal IHD: 0.80 (0.77–0.83) Fatal CVD: 0.76 (0.73–0.78) All-cause death: 0.73 (0.71–0.75) *PCE model + ECG risk equation* Fatal IHD: 0.82 (0.79–0.84) Fatal CVD: 0.80 (0.78–0.83) All-cause death: 0.76 (0.74–0.77) *Difference between PCE model and PCE model + ECG risk equation* Fatal IHD: 0.02 (0.01–0.03) Fatal CVD: 0.04 (0.03–0.06) All-cause death: 0.03 (0.02–0.03) 19 *FRS variables model* Fatal IHD: 0.83 (0.81–0.85) Fatal CVD: 0.81 (0.79–0.84) All-cause death: 0.78 (0.76–0.80) *FRS variables model + ECG risk equation* Fatal IHD: 0.84		Fatal IHD: 1.0 Fatal CVD: 1.6 All-cause death: 2.6 *Relative IDI* Fatal IHD: 25 Fatal CVD: 35 All-cause death: 38 ACC-AHA pooled cohort equation model *Absolute IDI* Fatal IHD: 0.7 Fatal CVD: 2.0 All-cause death: 1.9 *Relative IDI* Fatal IHD: 19 Fatal CVD: 47 All-cause death: 25 Framingham variables model *Absolute IDI* Fatal IHD: 0.2 Fatal CVD: 0.8 All-cause death: 2.0 *Relative IDI* Fatal IHD: 7 Fatal CVD: 13 All-cause death: 8

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
					(0.82–0.87) Fatal CVD: 0.82 (0.80–0.85) All-cause death: 0.79 (0.77–0.82) *Difference between Framingham variables model and Framingham variables model + ECG risk equation* Fatal IHD: 0.01 (0.01–0.02) Fatal CVD: 0.01 (0.01–0.02) All-cause death: 0.01 (0.01–0.02)		
Tereshchenko, 2014[51] Fair	Sudden cardiac death	SCD: 311 (2.0)	Reclassification NRI	Modified FRS[i]+DTNPV1 vs. modified FRS	NR	NR	DTNPV discrimination ability NRI estimate=0.028, p=0.06 Event NRI: 0.028 (2.8%) Nonevent NRI: 0.0002 (0.02%) Appropriately reclassified participants with SCD outcome into the higher risk categories: 3.4% appropriately reclassified into a higher risk group, 0.3% reclassified into a higher risk group inappropriately. Reclassification with addition of DTNPV1 for those with SCD events <5%, no change:135 <5% to 5–20%: 3 (2.2%) <5% to ≥20%: 0 Total: 138 5%–20% to <5%:1 (2.6%)

Appendix E Table 2. Results of Included Studies for KQ 2 That Evaluated Resting ECG

First Author, Year Quality	Outcome	N (%) With Outcome(s)	Outcome Measures	Models	Discrimination	Calibration	Reclassification
							5%–20%, no change: 34 5%–20% to ≥20%: 3 (7.8%) Total: 38 ≥20% to <5%:0 ≥20% to 5-20%: 0 ≥20%, no change: 3 Total: 3 Classification based on modified FRS+ DTNPV1, Total <5%:136 5–20%: 37 ≥20%: 6 Total: 179 Reclassification for those without SCD events <5%, no change <5%: 12,298 <5% to 5–20%: 27 (0.22%) <5% to ≥20%: 0 Total: 12,325 5%–20% to <5%:35 (6.6%) 5%–20%, no change: 485 5%–20% to ≥20%: 7 (1.3%) Total: 527 ≥20% to <5%:0 ≥20% to 5–20%: 1 (5.6%) ≥20%, no change: 17 Total: 18 Classification based on modified FRS+ DTNPV1, Total <5%:12333 5–20%: 513 ≥20%: 24 Total: 12,870

[a] Adjudicated CHD events including hard CHD Events (acute MI and CHD deaths) and soft CHD events (hospitalization for angina and coronary revascularization).
[b] FRS variables were age, sex, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking.

[c] FRS model included age, sex, systolic blood pressure, smoking history, serum cholesterol level, and serum high density lipoprotein level.
[d] CHD defined as acute MI necessitating overnight hospitalizations, silent MI identified on serial ECGs, or death due to CHD.
[e] CVD end points included CHD (CHD death and nonfatal MI), coronary artery bypass graft surgery/percutaneous transluminal coronary angioplasty and stroke.
[f] A CHD event was defined as a validated definite or probable hospitalized myocardial infarction, a definite CHD death, an unrecognized myocardial infarction defined by ARIC ECG readings, or coronary revascularization.
[g] model included age, race, total & HDL cholesterol, systolic blood pressure, use of antihypertensive medication, and smoking status
[h] Model included age, sex, body mass index, current smoking, alcohol intake >20 g/d, systolic blood pressure, antihypertensive medication use, diabetes mellitus, hyperlipidemia, and heart rate.
[i] Modified FRS in this used the CHD Framingham risk score with age, gender, SBP, DM, HDL and total cholesterol, smoking, and BP-lowering therapy; they note that calculated FRS scores were not directly used due to possible issues of the applicability to different ethnic groups and were adjusted for race

Abbreviations: ACC=American College of Cardiology AHA=American Heart Association; AUC=area under the curve; AUROC=area under the receiver operating characteristic curve; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; CVRF=cardiovascular risk factors; ECG=electrocardiogram; DTNPVI=Deep Terminal Negativity of the P Wave in V1 ; FRS=Framingham Risk Score; IDI=integrated discrimination improvement; IHD=ischemic heart disease; KQ=key question; LVH= left ventricular hypertrophy; MI=myocardial infarction; NA=not applicable; NHANES=National Health and Nutrition Examination Survey; NRI=net reclassification improvement; PCE=pooled cohort equation; QTc=corrected QT interval; SCD=sudden cardiac death.

Appendix E Table 3. Number and Percentage of Execise ECGs With Abnormalities in Studies Included for KQ 2

First Author, Year	Sample Size	n (%) with Abnormalities	ECG Findings Evaluated	Source of Patients	Country
Aktas, 2004[59]	3,554	371 (10.4%) had ischemic ST-segment changes 549 (15.4%) had abnormal based on functional capacity or HR recovery	Exercise ECG according to Bruce (or modified Bruce) protocol; ischemic ST abnormality using a 12-lead, symptom-limited exercise ECG	Consecutive participants presenting for an executive physical. Self-referred.	U.S.
Chang, 2015[45]	988 (946 with followup)	116/946 (12.3%) with followup had ischemic exercise ECG; 75% with >8 METs; 22% 5-8 METs; <5 METs	Exercise ECG according to Bruce protocol; stress-induced ischemia identified via ECG during symptom-limited exercise treadmill testing; METs and DTS	People who had both CACS and stress SPECT for clinically indicated reasons at the Heart and Vascular Center	U.S.
Cournot, 2006[60]	1,051	89 (8.5%) had positive exercise test	Symptom-limited exercise ECG	Consecutive asymptomatic people self-referred or referred by PCPs and cardiologists for evaluation of risk factors and routine screening	France
Cournot, 2009[56]	2,709	163 (6.4%) had positive exercise test	A positive exercise test[9] during a symptom-limited exercise ECG with orthogonal and V_1 to V_6 leads	Apparently healthy asymptomatic people self-referred (20%) or referred by PCPs (27%) or other providers to a preventive cardiology unit	France
Erikssen, 2004[62]	Assessment 1 (1972–1975): 2,014 Assessment 2 (1980–1982): 1,428	205 (10.2%) positive exercise test 238 (16.7%) positive exercise test	Resting ECG and a symptom-limited bicycle exercise ECG test	Apparently healthy males ages 40–60 years recruited from five governmental agencies who participated in a cardiovascular risk assessment	Norway

Abbreviations: CACS=coronary artery calcium score; DTS=Duke treadmill score; ECG=electrocardiogram; HR=hazard ratio; METs=metabolic equivalents; PCPs=primary care physicians; SPECT=Single Photon Emission Computed Tomography; U.S.=United States.

Appendix E Table 4. Number and Percentage of Resting ECGs With Abnormalities in Studies Included for KQ 2

First Author, Year Quality	Sample Size	n (%) With Abnormalities	ECG Findings Evaluated	Source of Patients	Country
Auer et al, 2012[55]	2,192	782 (36%) any abnormality 506 (23%) major 276 (13%) minor 1,410 (64%) no abnormality	Major[a] and minor[b] 12-lead ECG abnormalities classified using the Minnesota Coding System	Population-based cohort assessing body composition, long-term conditions, and incident mobility limitation in an older adult cohort (1997–1998)	U.S.
Badheka et al, 2013[54]	6,025	3,291 (54.6%) had any ECG abnormalities	Major and Minor 12-lead ECG abnormalities classified using Minnesota Code[d]	Population-based survey to collect information on the health and nutrition of U.S. households (1988–1994)	U.S.
Badheka et al, 2013[53]	7,928	1,919 (24.2%) ST-segment elevation (>8 mV) in aVR; 1,459 (18.4%) T-wave amplitude 0.1 mV or greater in aVR	12-lead ECG ST-T wave abnormalities in lead aVR classified by the Minnesota Code	Population-based survey to collect information on the health and nutrition of U.S. households (1988–1994)	U.S.
Denes, 2007[58]	1,264[c]	Data only reported for the larger WHI sample of 14,749: 910 (6.2%) major 4,095 (27.8%) minor 9,744 (66.1%) none	Major,[e] minor,[f] and incident[g] 12-lead ECG changes using the Novacode criteria	Population-based study on common causes of morbidity/ mortality among postmenopausal women (1993–1998)	U.S.
Folsom, 2003[63]	14,054	NR	LVH using a 12-lead ECG and the Cornell score	Population-based study of 4 U.S. communities (1987–1989)	U.S.
Ishikawa, 2015[50]	10,643	162 (1.5%) had prolonged QTc intervals	Prolonged corrected QT (QTc) intervals[i] and LVH[j] on 12-lead ECG	Government-sponsored screening to clarify the risk factors for cardio/ cerebrovascular diseases in the general population (1992-1995)	Japan
Jorgensen, 2014[52]	6,991[g]	2,140 (30.6%) any ECG abnormalities 1,163 (16.6%) major 353 (5.0%) intermediate 624 (8.9%) minor	Major and Minor 12-lead ECG abnormalities classified using Minnesota Code; also reported outcomes for some single ECG changes[m]	The Copenhagen City Heart Study (1976–1978)	Denmark
Shah, 2016[57]	9,969 (derivation: 3,640, validation: 6,329)	NR (reported mean and SD for the variables in the ECG Risk Score)	ECG Risk Score including frontal T axis, corrected QT interval, T axis, heart rate, age, sex, age*sex interaction term (selected from major[o] and minor[p] abnormalities)	Population-based survey to collect information on health and nutrition; NHANES I (1971–1975) and NHANES III (1988–1994)	U.S.
Tereshchenko, 2014[51]	15,375[k]	167 (1.1%) had the specific DTNPV1 abnormality	Resting 12-lead, P wave morphology (specifically DTNPV1[r])	Population-based study of 4 U.S. communities (1987–1989)	U.S.

Abbreviations: DTNPVI=Deep Terminal Negativity of the P Wave in V1; ECG=electrocardiogram; LVH=left ventricular hypertrophy; NHANES=National Health and Nutrition Examination Survey; NR=not reported; QTc=corrected QT interval; SD=standard deviation; U.S.=United States; WHI=Women's Health Initiative.

Appendix E Table 5. Results of Included Randomized Controlled Trials Reporting Harms (KQ 3)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality Due to Screening G1 N (%) G2 N (%) HR (95% CI)	Arrhythmia G1 N (%) G2 N (%) HR (95% CI)	CV Events Due to Screening G1 N (%) G2 N (%) HR (95% CI)	Injuries G1 N (%) G2 N (%) HR (95% CI)	Anxiety G1 N (%) G2 N (%) HR (95% CI)	Labeling G1 N (%) G2 N (%) HR (95% CI)	Harms of Subsequent Procedures/Interventions G1 N (%) G2 N (%) HR (95% CI)
Lievre et al, 2011[47] DYNAMIT	Screened (316) Not screened (315)	NR (all-cause mortality described in KQ 1)	NR	NR	NR	NR	NR	NR (number of revascularizations reported in KQ 1, but NR whether any resulted in harms; 18 vs. 21)
Turrini et al, 2015[48] DADDY-D	Screened (262) Not screened (258)	NR (all-cause mortality described in KQ 1)	NR	NR	NR	NR	NR	20/262 (7.6%) patients who underwent ETT had a positive result. Of those, 17 underwent coronary angiography. It was positive for critical stenosis in 12/17 (70.6%), and all 12 underwent revascularization procedures (7 percutaneous and 5 surgery). One patient having percutaneous revascularization had an acute MI (nonfatal) 3 days after the procedure.

Abbreviations: CI=confidence interval; CV=cardiovascular; DADDY-D=Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients; DYNAMIT=Do You Need to Assess Myocardial Ischemia in Type-2 diabetes; ETT=exercise treadmill test; G=group; HR=hazard ratio; KQ=key question; MI=myocardial infarction; N=sample size; NR=not reported.

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