JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Cardiovascular Disease Risk With Resting or Exercise Electrocardiography

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Cardiovascular disease (CVD) is the leading cause of death in the United States.

OBJECTIVE To review the evidence on screening asymptomatic adults for CVD risk using electrocardiography (ECG) to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, Cochrane Library, and trial registries through May 2017; references; experts; literature surveillance through April 4, 2018.

STUDY SELECTION English-language randomized clinical trials (RCTs); prospective cohort studies reporting reclassification, calibration, or discrimination that compared risk assessment using ECG plus traditional risk factors vs traditional risk factors alone. For harms, additional study designs were eligible. Studies of persons with symptoms or a CVD diagnosis were excluded.

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality; qualitative synthesis of findings.

MAIN OUTCOMES AND MEASURES Mortality, cardiovascular events, reclassification, calibration, discrimination, and harms.

RESULTS Sixteen studies were included (N = 77 140). Two RCTs (n = 1151) found no significant improvement for screening with exercise ECG (vs no screening) in adults aged 50 to 75 years with diabetes for the primary cardiovascular composite outcomes (hazard ratios, 1.00 [95% CI, 0.59-1.71] and 0.85 [95% CI, 0.39-1.84] for each study). No RCTs evaluated screening with resting ECG. Evidence from 5 cohort studies (n = 9582) showed that adding exercise ECG to traditional risk factors such as age, sex, current smoking, diabetes, total cholesterol level, and high-density lipoprotein cholesterol level produced small improvements in discrimination (absolute improvements in area under the curve [AUC] or C statistics, 0.02-0.03, reported by 3 studies); whether calibration or appropriate risk classification improves is uncertain. Evidence from 9 cohort studies (n = 66 407) showed that adding resting ECG to traditional risk factors produced small improvements in discrimination (absolute improvement in AUC or C statistics, 0.001-0.05) and appropriate risk classification for prediction of multiple cardiovascular outcomes, although evidence was limited by imprecision, quality, considerable heterogeneity, and inconsistent use of risk thresholds used for clinical decision making. Total net reclassification improvements ranged from 3.6% (2.7% event; 0.6% nonevent) to 30% (17% event; 19% nonevent) for studies using the Framingham Risk Score or Pooled Cohort Equations base models. Evidence on potential harms (eg, from subsequent angiography or revascularization) in asymptomatic persons was limited.

CONCLUSIONS AND RELEVANCE RCTs of screening with exercise ECG found no improvement in health outcomes, despite focusing on higher-risk populations with diabetes. The addition of resting ECG to traditional risk factors accurately reclassified persons, but evidence for this finding had many limitations. The frequency of harms from screening is uncertain.

JAMA. 2018;319(22):2315-2328. doi:10.1001/jama.2018.6897

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Cardiovascular disease (CVD) is the leading cause of death in US adults.[1,2] Traditional risk factors for CVD are male sex, older age, cigarette smoking, hypertension, dyslipidemia, and diabetes. Risk prediction equations, such as the Framingham Risk Score (FRS) or Pooled Cohort Equations (PCE), that integrate and weight these traditional risk factors are used commonly in clinical practice to assess 10-year risk of CVD events and to guide treatment decisions. The US Preventive Services Task Force (USPSTF) recommends using the PCE to calculate 10-year risk for adults aged 40 to 75 years to inform clinical decisions, for example, about statin use (B recommendation for those with 10-year risk ≥10%) and aspirin use (B recommendation for adults aged 50-59 years with 10-year risk ≥10%) for primary prevention.[3-5] The PCE include age, sex, race, cholesterol levels, systolic blood pressure, antihypertension treatment, presence of diabetes, and smoking status as risk factors and focus on prediction of hard outcomes such as heart attack and death from coronary heart disease (CHD), ischemic stroke, and stroke-related death.[4] None of the currently recommended equations include electrocardiography (ECG) findings.

Because many patients do not have symptoms of CVD or a prior diagnosis of CVD before a serious first event (eg, myocardial infarction [MI], stroke), identifying high-risk, asymptomatic individuals may reduce future morbidity and mortality.[6,7] Screening with ECG could potentially reclassify people (into higher- or lower-risk categories) in a manner that results in treatment changes that improve health outcomes. In 2012, the USPSTF recommended against screening with ECG in asymptomatic adults at low risk for CHD events (D recommendation) and concluded that evidence was insufficient to assess the balance of benefits and harms of screening for those at intermediate or high risk (I statement). To inform an updated recommendation by the USPSTF, the evidence on adding resting or exercise ECG to traditional risk factor assessment (vs using traditional risk factor assessment alone) for screening asymptomatic adults for CVD risk in populations and settings relevant to US primary care was reviewed.

Methods

Scope of Review

Detailed methods and additional details of results and analyses are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cardiovascular-disease-risk-screening-with-electrocardiography. **Figure 1** shows the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published through May 2017. Search strategies are listed in the eMethods in the Supplement. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry platform were searched for unpublished studies. To supplement electronic searches, investigators reviewed reference lists of pertinent articles, studies suggested by peer and federal partner reviewers, and comments received during public commenting periods. Since May 2017, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on April 4, 2018, and identified no additional eligible studies.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria for each KQ (eTable 1 in the Supplement). Disagreements were resolved by discussion. The review included English-language studies of adults conducted in countries categorized as "very high" on the United Nations Human Development Index. Only studies rated as good or fair quality were included. Studies that focused on adults with a history of CVD or symptoms suggesting CVD were excluded.

For all KQs, randomized clinical trials (RCTs) and nonrandomized controlled intervention studies comparing groups that were screened using ECG with groups that were not screened (ie, comparing risk stratification using ECG plus traditional risk factors vs risk stratification using traditional risk factors alone) were eligible. For KQ1 (direct evidence that screening improves health outcomes), eligible outcomes included all-cause mortality, cardiovascular mortality, and cardiovascular events (MI, angina, stroke, congestive heart failure, composite cardiovascular outcomes).

For KQ2 (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 not required to specifically use the PCE or FRS to be eligible, although such studies have greatest applicability to current practice. 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 and will not have an event) (eTable 2 in the Supplement). Studies that only assessed the association between ECG findings and outcomes (eg, with adjusted hazard ratios) were excluded.

For KQ3 (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, cardiovascular events, or injuries from exercise ECG; anxiety; labeling; and harms of subsequent interventions initiated as a result of screening. For studies reporting rates of harms from exercise ECG or subsequent interventions, large registries or multicenter studies without a control group that report rates of harms for asymptomatic persons were eligible.

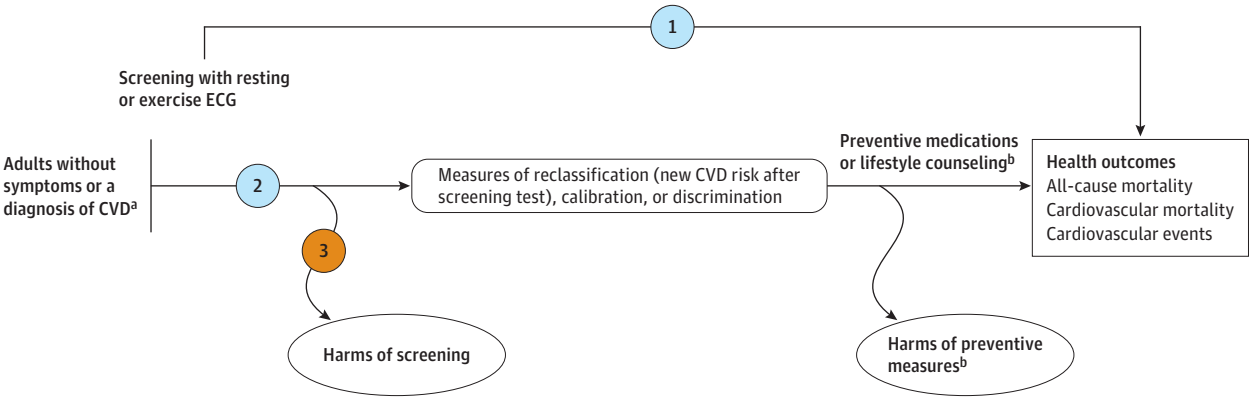
Data Extraction and Quality Assessment

For each included study, 1 investigator extracted pertinent information about the populations, tests or treatments, comparators, outcomes, settings, and designs, and a second investigator reviewed this information for completeness and accuracy. Two independent investigators assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (eMethods in the Supplement).[8] Disagreements were resolved by discussion. Individual study quality ratings are reported in the eResults and eTables 3-8 in the Supplement.

Data Synthesis and Analysis

Findings for each question were summarized in tabular and narrative format. To determine whether meta-analyses were appropriate, clinical heterogeneity and methodological heterogeneity were

Figure 1. Analytic Framework and Key Questions: Screening for Cardiovascular Disease Risk With Resting or Exercise Electrocardiography



Key questions

1 a. Does the addition of screening with resting or exercise ECG improve health outcomes compared with traditional CVD risk factor assessment alone in asymptomatic adults?

b. Does improvement in health outcomes vary for subgroups defined by baseline CVD risk (eg, low, intermediate, or high risk), age, sex, or race or 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 (eg, high-, intermediate-, and low-risk groups) or improve measures of calibration and discrimination?

3 a. What are the harms of screening with resting or exercise ECG, including harms of subsequent procedures or interventions initiated as a result of screening?

b. Do the harms vary for subgroups defined by baseline CVD risk (eg, low, intermediate, or high risk), age, sex, or race or ethnicity?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. Outcomes of interest are depicted using a rectangle; intermediate outcomes are in rounded rectangles and health outcomes have squared corners. Further details are available from the USPSTF procedure manual.[8] CVD indicates cardiovascular disease; ECG, electrocardiography.

[a] 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 level, high low-density lipoprotein cholesterol level, or low high-density lipoprotein cholesterol level), and diabetes.

[b] This systematic review does not include KQs about the benefits and harms of preventive medications to reduce cardiovascular risk (ie, 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.

assessed following established guidance.[9] For KQ1, pooled effects were not estimated because fewer than 3 similar studies were found, but risk ratios and 95% CIs were calculated for binary outcomes reported by the included RCTs. Statistical significance was assumed when 95% CIs did not cross the null. All testing was 2-sided.

For KQ2, considerable heterogeneity was found for ECG findings assessed, base prediction models, outcomes, and duration of follow-up; therefore, the results are presented in tabular format and in figures. Results are presented separately for exercise and resting ECG. Within the studies of resting ECG, results were stratified by whether studies evaluated the addition of a constellation of ECG abnormalities vs single or 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 (eg, FRS or PCE), or as "model development." For KQ2, the C statistic (Harrell C) and area under the curve (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. Analyses were conducted and figures were produced using Stata version 14 (StataCorp) and Microsoft Excel.

The overall strength of the body of evidence was assessed for each KQ as high, moderate, low, or insufficient using methods developed for the USPSTF (and the Evidence-based Practice Center program), based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias.[8]

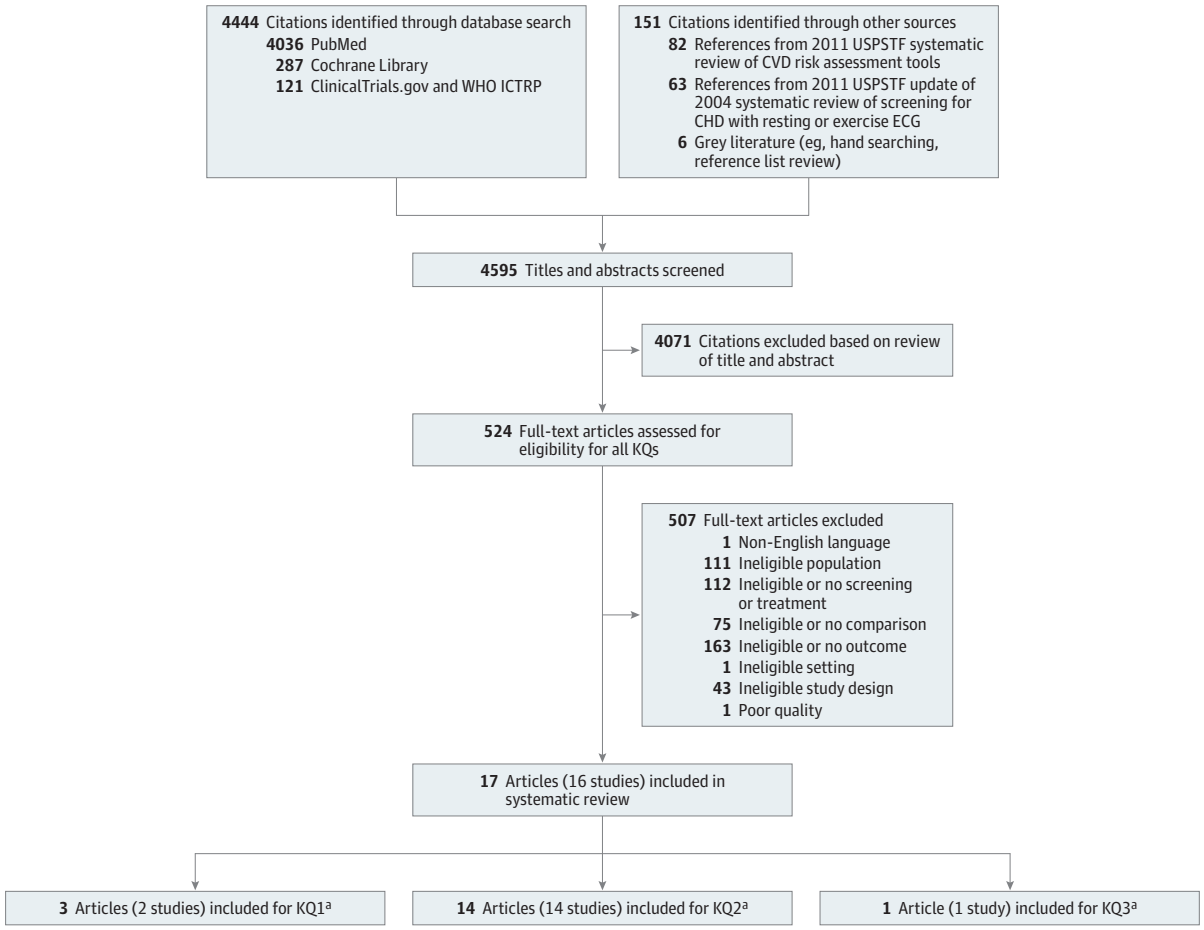
Results

A total of 16 studies (17 articles) with 77 140 participants were included (**Figure 2**).

Benefits of Screening

Key Question 1a. Does the addition of screening with resting or exercise ECG improve health outcomes compared with traditional CVD risk factor assessment alone in asymptomatic adults?

Figure 2. Literature Search and Flow Diagram: Screening for Cardiovascular Disease Risk With Resting or Exercise Electrocardiography



CHD indicates coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiography; ICTRP, International Clinical Trials Registry Platform; KQ, key question; USPSTF, US Preventive Services Task Force; WHO, World Health Organization.

[a] The sum of the number of studies per KQ exceeds the total number of studies because some studies were applicable to multiple KQs.

Key Question 1b. Does improvement in health outcomes vary for subgroups defined by baseline CVD risk (eg, low, intermediate, or high risk), age, sex, or race/ethnicity?

No eligible trials evaluated screening with resting ECG. Two fair-quality RCTs (DYNAMIT [Do You Need to Assess Myocardial Ischemia in Type-2 Diabetes][10] and DADDY-D [Does Coronary Atherosclerosis Deserve to Be Diagnosed Early in Diabetic Patients][11]) with a total of 1151 participants that evaluated screening with exercise ECG in high-risk, asymptomatic adults aged 50 to 75 years with diabetes were included (**Table 1**). DYNAMIT evaluated a bicycle exercise test,[10] whereas DADDY-D evaluated an exercise treadmill test.[11] Neither trial reached its sample size target.

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, cardiovascular-related mortality, MI, heart failure, or stroke—although findings were imprecise (**Figure 3**; eTable 9 in the Supplement). In DYNAMIT, there was no significant difference between groups for the primary composite end point—death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention (28 vs 26 events; hazard ratio, 1.00 [95% CI, 0.59-1.71]). In DADDY-D, there was no significant difference between groups for the primary outcome—cardiac events defined as a composite of nonfatal MI or cardiac death (12 vs 14 events; hazard ratio, 0.85 [95% CI, 0.39-1.84]). Subgroup analyses from the DADDY-D trial found no statistically significant differences between groups based on sex, age, or cardiovascular risk for the primary outcome.

Discrimination, Calibration, and Reclassification

Key Question 2. Does the addition of screening with resting or exercise ECG to traditional CVD risk factor assessment accurately reclassify persons into different risk groups (eg, high-, intermediate-, and low-risk groups) or improve measures of calibration and discrimination?

Exercise ECG

Of the 14 included studies for KQ2, 5 fair-quality cohort studies (9582 participants) evaluated exercise ECG (**Table 2**).[12-16] All participants were from cardiology or prevention centers in hospitals. Four of the studies reported that all participants were asymptomatic; 1 reported that 16.5% had atypical chest pain symptoms and had undergone both

Table 1. Characteristics of Randomized Clinical Trials That Evaluated Screening With Exercise ECG vs No Screening (KQ1 and KQ3)[a]

Source	Source of Patients	Screening Approach	Age, Mean (SD) [Range], y	No. (%)			Mean (SD)			Mean Follow-up, y
				Women	Hypertension	Smokers	10-y CV Risk, %	HbA_{1c}, %	BMI[b]	
DYNAMIT Lievre et al, 2011[10] (France)	45 Hospitals; ambulatory patients who consulted a diabetes specialist	Bicycle exercise ECG (or dipyridamole SPECT, 31%)[c] 316 Screened 315 Not screened	63.9 (5.1) [55-75]	NR (45)	NR (88.8)	NR (16.6)[d]	NR	8.6 (2.1)	30.6 (5)	3.5
DADDY-D Turrini et al,[11] 2015 (Italy)	2 Diabetes outpatient clinics at 1 center	Exercise ECG[e] 262 Screened 258 Not screened	61.9 (5) [50-70]	53 (20)	NR[f]	104 (38.7)	20 (9)[g]	7.7 (2)	30.1 (6)	3.6

Abbreviations: 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; HbA_{1c}, glycated hemoglobin; KQ, key question; NR, not reported; SPECT, single-photon emission computed tomography.

[a] Both studies were of fair quality. Neither study reported data on patient race/ethnicity.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] SPECT was used in patients unable to perform the exercise test, with a submaximal negative exercise test finding, or with ECG abnormalities impairing interpretation of the exercise test. Those with positive findings were referred to cardiologists, and all subsequent investigations and treatments were at the cardiologist's discretion (ie, no protocol for that part of the process related to angiography vs no angiography; pragmatic approach).

[d] Tobacco consumption (not specified in the article if limited to smoking).

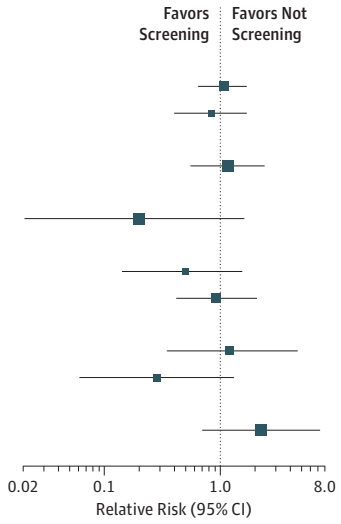
[e] Maximal symptom-limited exercise treadmill test performed following American Heart Association guidelines. Submaximal test findings were considered not diagnostic and did not lead to any further investigations. Coronary angiography was proposed to all patients with positive exercise treadmill test findings; choices to perform stenting or surgery were determined according to the European Guidelines by 2 interventional cardiologists and a cardiac surgeon after reviewing coronary anatomy.

[f] Antihypertensive treatment received by 74.3% of study patients; mean systolic blood pressure, 140 mm Hg.

[g] Required cardiovascular risk score of ≥10% for eligibility, risk determined according to Italian risk chart (includes sex, diabetic status, age, cigarette smoking status, systolic blood pressure, serum cholesterol level).

Figure 3. Main Results of Included Randomized Clinical Trials Reporting Health Outcomes (KQ1)

Source	Intervention Group		Control Group		Relative Risk (95% CI)
	Persons With Event, No.	Persons Without Event, No.	Persons With Event, No.	Persons Without Event, No.	
Primary composite outcome					
DYNAMIT,[10] 2011	28	288	26	289	1.07 (0.64-1.79)
DADDY-D,[11] 2015	12	250	14	244	0.84 (0.40-1.79)
All-cause mortality					
DYNAMIT,[10] 2011	15	301	13	302	1.15 (0.56-2.38)
Cardiovascular-related mortality					
DADDY-D,[11] 2015	1	261	5	253	0.20 (0.02-1.67)
Myocardial infarction					
DYNAMIT,[10] 2011	4	312	8	307	0.50 (0.15-1.64)
DADDY-D,[11] 2015	11	251	12	246	0.90 (0.41-2.01)
Heart failure					
DYNAMIT[10] 2011	5	311	4	311	1.25 (0.34-4.60)
DADDY-D,[11] 2015	2	260	7	251	0.28 (0.06-1.34)
Stroke					
DYNAMIT,[10] 2011	9	307	4	311	2.24 (0.70-7.21)



Size of data markers indicates relative number of events in the study compared with other studies reporting the same outcome. For the DYNAMIT (Do You Need to Assess Myocardial Ischemia in Type-2 Diabetes) trial, the primary composite outcome was defined as death from all causes, nonfatal myocardial infarction, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention. DYNAMIT did not report data for cardiovascular-related deaths. For other cardiovascular events, DYNAMIT reported no significant differences between groups for revascularization (18 vs 21, $P = .61$). For the DADDY-D (Does Coronary Atherosclerosis Deserve to Be Diagnosed Early in Diabetic Patients) trial, the primary composite outcome was defined as first cardiac event, specifically nonfatal myocardial infarction or cardiac death. DADDY-D reported 19 total deaths (6 cardiac and 13 noncardiac) and 7 total strokes but did not report in which group those occurred. Relative risks (RRs) and 95% CIs calculated using the numbers of events reported by the trials. The trials also reported hazard ratios (HRs) for the primary outcomes (HR, 1.00 [95% CI, 0.59-1.71] in DYNAMIT; HR, 0.85 [95% CI, 0.39-1.84] in DADDY-D). KQ indicates key question.

coronary artery calcium scoring and single-photon emission computed tomography for "clinically indicated reasons."[13] Mean baseline FRS score was 10.8 to 12.3 in studies reporting it.[13-15] The frequency of abnormal exercise test findings across included studies ranged from 6.4% to 16.7% (eTable 10 in the Supplement). Mean duration of follow-up ranged from 6 to 8 years in 4 studies; 1 had 26 years of follow-up.[16]

Results of the included studies are shown in **Figure 4** and **Figure 5**, and in eTable 5 and eFigures 1 and 2 in the Supplement. All

Table 2. Characteristics of Studies That Evaluated Discrimination, Calibration, or Reclassification With the Addition of Exercise ECG (KQ2)[a]

Source	Sample Size	ECG Findings Evaluated	Model Type[b]	Base Model	CV Risk	Mean (SD)		No. (%)					Follow-up, y
						Age, y	BMI	Women	Nonwhite Race/ Ethnicity	Hypertension	Diabetes Mellitus	Smokers	
Preventive Medicine Section of Cleveland Clinic (1990-2002) Aktas et al,[12] 2004 (United States)	3554	Bruce (or modified Bruce) protocol; ischemic ST-segment abnormality using 12-lead, symptom-limited exercise ECG[c]	Published coefficient	SCORE[d]	SCORE: 1st tertile: median, 0.14 (IQR, 0.87-1.8) 2nd tertile: median, 3.0 (IQR, 2.5-3.5) 3rd tertile: median, 6.6 (IQR, 5.2-9.2)	57 (4)	28 (4)	683 (19)	63 (2)	NR (mean systolic blood pressure, 128 mm Hg)	89 (3)	382 (10)	8 (mean)
Methodist Hospital, Houston Texas (1995-2006) Chang et al,[13] 2015 (United States)	988 (946 with follow-up)	Bruce protocol; stress-induced ischemia identified via ECG during symptom-limited exercise treadmill testing; METS and DTS[e]	Model development	FRS variables[f]	Mean FRS, 11.1 (SD, 6.5) Low risk (<6%): 16.9% Intermediate risk (6%-20%): 69.2% High risk (>20%): 13.9%	57.5 (9.3)	NR	234 (25)	NR	469 (49.6)	91 (9.6)	440 (46.5)	6.9 (median)
Preventive cardiology unit of a teaching hospital (1995-1999) Cournot et al,[14] 2006 (France)	1051	Symptom-limited exercise ECG[g]	Published coefficient	FRS[h]	FRS: All: mean, 12.3 (median, 10.4) Negative exercise test, n = 962: mean, 12.1 (median, 10.4) Positive exercise test, n = 89: mean, 14.7 (median, 11.4)	51.6 (10.3)	26.1 (4.5)	379 (36)	NR	576 (54.8)	115 (11.0)	255 (24.3)	6 (mean)
Preventive cardiology unit of a teaching hospital (1996-2004) Cournot et al,[15] 2009 (France)	2709 (2561 with baseline data)	Symptom-limited exercise ECG test with orthogonal and V_1 to V_6 leads[i]	Published coefficient	FRS[h]	Mean FRS, 10.8 (SD, 7.8)	51.6 (10.5)	26.0 (4.4)	978 (38)	NR	1235 (48.2)	175 (6.8)	613 (23.9)	6 (median)
University Hospital of Oslo (1972-1975) Erikssen et al,[16] 2004 (Norway)	2014	Resting ECG and a symptom-limited bicycle exercise ECG test[j]	Model development	Classical risk factor model[k]	NR	49.8 (5.5)	NR	0	NR	0	0	NR (43.8)	26

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DTS, Duke treadmill score; ECG, electrocardiogram; FRS, Framingham Risk Score; METS, metabolic equivalents; KQ, key question; NR, not reported; SCORE, Systematic Coronary Risk Evaluation.

[a] All studies in table were of fair quality.

[b] Model types were categorized as published coefficient models when they preserved the coefficients of published models that have been externally validated (eg, FRS or Pooled Cohort Equations) or as model development when they did not.

[c] An ischemic ST-segment abnormality, which was assessed visually by 2 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 ≥3 consecutive beats in ≥2 contiguous leads.

[d] SCORE provides 10-year risk for cardiovascular mortality and includes age, sex, total cholesterol level, systolic blood pressure, and smoking status (this study used the high-risk coefficients from it).

[e] Ischemia was defined as ≥1-mm ST-segment depression occurring >80 ms after the J point. High and low risk were defined as the presence and absence of ischemia, respectively.

[f] Authors attempted to calculate FRS as published, but continuous blood pressure and cholesterol measurements were not available, so these predictors were dichotomized (hyperlipidemia = total cholesterol 200-239 mg/dL and hypertension = systolic blood pressure 140-159 mm Hg).

[g] Positive exercise test finding was defined as a horizontal or downsloping ST-segment depression ≥1.0 mm at 80 ms after the J point, in ≥2 contiguous leads, occurring at any time of exercise or recovery period.

[h] Used Anderson 1991: 10-year FRS function that includes age, sex, current smoking, diabetes, total cholesterol level, and high-density lipoprotein cholesterol level.

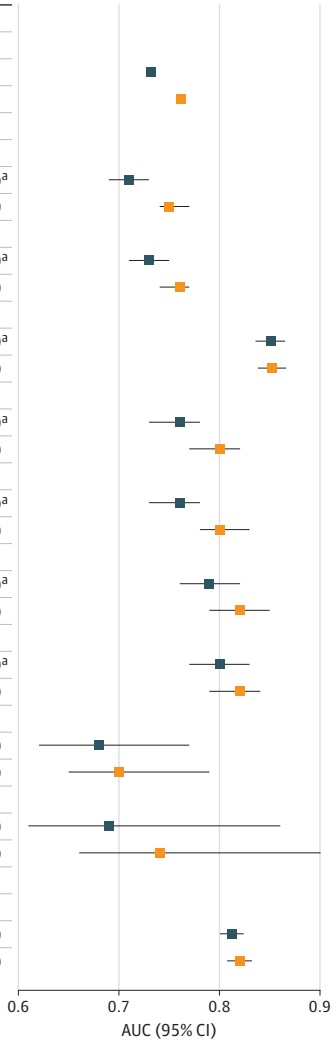
[i] Positive exercise test finding was defined as a horizontal or downsloping ST-segment depression ≥1.0 mm at 80 ms after the J point, in ≥2 contiguous leads, occurring at any time during exercise or the recovery period.

[j] 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 80 ms after the J point, regardless of ST-segment morphology).

[k] Model included age, total cholesterol level, systolic blood pressure, and smoking status. The study included men only. The study also excluded persons with prevalent diabetes and persons receiving blood pressure–lowering therapy at baseline. High-density lipoprotein cholesterol level was not accounted for in the model.

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

Source	Outcome	Specific ECG Findings Evaluated	Base Model	No. of Persons With Event	No. of Persons Total	AUC (95% CI)
Exercise ECG						
Cournot et al,[15] 2009	Coronary events	Positive exercise test	FRS	94	2709	
Base model						0.73 (NR)
Base model + ECG						0.76 (NR)
Resting ECG: multiple changes						
Shah et al,[24] 2016	All-cause mortality	ECG risk equation	FRS	810	6329	
Base model						0.71 (0.69-0.73)[a]
Base model + ECG						0.75 (0.74-0.77)
Shah et al,[24] 2016	All-cause mortality	ECG risk equation	PCE	810	6329	
Base model						0.73 (0.71-0.75)[a]
Base model + ECG						0.76 (0.74-0.77)
Badheka et al,[18] 2013	CVD mortality	Major or minor changes	FRS	739	6025	
Base model						0.85 (0.84-0.87)[a]
Base model + ECG						0.85 (0.84-0.87)
Shah et al,[24] 2016	CVD mortality	ECG risk equation	FRS	282	6329	
Base model						0.76 (0.73-0.78)[a]
Base model + ECG						0.80 (0.77-0.82)
Shah et al,[24] 2016	CVD mortality	ECG risk equation	PCE	282	6329	
Base model						0.76 (0.73-0.78)[a]
Base model + ECG						0.80 (0.78-0.83)
Shah et al,[24] 2016	Fatal IHD	ECG risk equation	FRS	166	6329	
Base model						0.79 (0.76-0.82)[a]
Base model + ECG						0.82 (0.79-0.85)
Shah et al,[24] 2016	Fatal IHD	ECG risk equation	PCE	166	6329	
Base model						0.80 (0.77-0.83)[a]
Base model + ECG						0.82 (0.79-0.84)
Denes et al,[20] 2007	CVD events	Major or minor changes	FRS	595	1264	
Base model						0.68 (0.62-0.77)
Base model + ECG						0.70 (0.65-0.79)
Denes et al,[20] 2007	CHD events	Major or minor changes	FRS	246	1264	
Base model						0.69 (0.61-0.86)
Base model + ECG						0.74 (0.66-0.90)
Resting ECG: single change						
Badheka et al,[19] 2013	CVD mortality	T-wave amplitude in aVR	FRS	1226	7928	
Base model						0.81 (0.80-0.82)
Base model + ECG						0.82 (0.81-0.83)



Black data markers indicate base model; orange data markers, base model plus electrocardiography (ECG). AUC indicates area under the curve; CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; IHD, ischemic heart disease; NR, not reported; PCE, Pooled Cohort Equations.

[a] Study reported C statistic rather than AUC.

3 of the studies reporting discrimination for the addition of exercise ECG variables to traditional risk factors[12,13,15] reported small absolute improvements in AUC or C statistics (0.02-0.03). None of the studies reported CIs, and only 1 reported a *P* value; that value indicated no statistically significant difference between models (*P* = .3).[13] Of the 4 studies that reported calibration or overall performance of models that added exercise ECG findings to traditional risk factors,[13-16] none reported figures such as calibration plots, but 1 provided a table of predicted and observed events for quintiles of risk.[16] All 4 studies reported different measures, and results were inconsistent (eResults and eTable 11 in the Supplement).

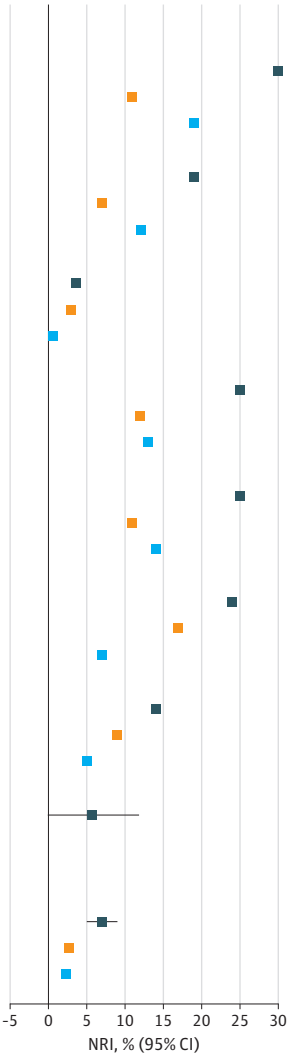
The 1 study that reported on reclassification from adding exercise ECG to traditional CVD risk factor assessment (Chang et al, 2015[13]; 988 participants) used categories defined by 10-year risk of cardiac events of less than 6%, 6% to 20%, and more than 20%.[13] Although adding exercise testing variables to the base model (FRS variables) did not significantly improve discrimination (change in AUC, 0.02; *P* = .3), the study found that adding the presence or absence of stress-induced ischemia detected during symptom-limited exercise treadmill testing to the base model improved risk classification in participants both overall (total NRI, 9.6%; *P* = .007) and in the intermediate-risk group (18.9%; *P* = .01). It did not report event NRI and nonevent NRI.

Resting ECG

Of the included studies for KQ2, 9 (68 475 participants) evaluated resting ECG (**Table 3**).[17-25] Five evaluated multiple ECG changes, including either a constellation of major and minor ECG changes or an ECG risk equation (that included multiple ECG changes).[17,18,20,23,24]

Figure 5. Effect on Reclassification of Adding Resting ECG Variables to Framingham Risk Score or Pooled Cohort Equations Base Models

Source	Outcome	Specific ECG Findings Evaluated	Base Model	No. of Persons With Event	No. of Persons Total	NRI, % (95% CI)
Resting ECG: multiple changes						
Shah et al,[24] 2016	All-cause mortality	ECG risk equation	FRS	810	6329	
Total NRI[a]						30 (NR)
Event NRI[a]						11 (NR)
Nonevent NRI[a]						19 (NR)
Shah et al,[24] 2016	All-cause mortality	ECG risk equation	PCE	810	6329	
Total NRI[a]						19 (NR)
Event NRI[a]						7 (NR)
Nonevent NRI[a]						12 (NR)
Badheka et al,[18] 2013	CVD mortality	Major or minor changes	FRS	739	6025	
Total NRI[b]						3.6 (NR)
Event NRI[b]						3.0 (NR)
Nonevent NRI[b]						0.6 (NR)
Shah et al,[24] 2016	CVD mortality	ECG risk equation	FRS	282	6329	
Total NRI[a]						25 (NR)
Event NRI[a]						12 (NR)
Nonevent NRI[a]						13 (NR)
Shah et al,[24] 2016	CVD mortality	ECG risk equation	PCE	282	6329	
Total NRI[a]						25 (NR)
Event NRI[a]						11 (NR)
Nonevent NRI[a]						14 (NR)
Shah et al,[24] 2016	Fatal IHD	ECG risk equation	FRS	166	6329	
Total NRI[a]						24 (NR)
Event NRI[a]						17 (NR)
Nonevent NRI[a]						7 (NR)
Shah et al,[24] 2016	Fatal IHD	ECG risk equation	PCE	166	6329	
Total NRI[a]						14 (NR)
Event NRI[a]						9 (NR)
Nonevent NRI[a]						5 (NR)
Auer et al,[17] 2012	CHD events	Major or minor changes	FRS	351	2192	
Total NRI[c]						5.7
						(−0.4 to 11.8)
Resting ECG: single change						
Badheka et al,[19] 2013	CVD mortality	T-wave amplitude in aVR	FRS	1226	7928	
Total NRI[b]						7.0 (5.0 to 9.0)
Event NRI[b]						2.7 (NR)
Nonevent NRI[b]						2.3 (NR)



Total net reclassification improvement (NRI; black data markers) indicates the sum of the event NRI (net upward reclassification among persons who had an event; orange data markers) and the nonevent NRI (net downward reclassification among persons who did not have an event; blue data markers). For some studies, only the total NRI is provided because the data for event and nonevent NRI were not reported. Nonevent NRI 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. Event NRI is calculated as the proportion of persons with an event who were appropriately reclassified into a higher risk group minus the proportion of those with an event who were inappropriately reclassified into a lower risk group. Although an overall positive value of NRI indicates net appropriate reclassification, the clinical implications can be very different if the majority of patients are those with events being shifted into higher-risk categories (event NRI), vs those without events being shifted into lower-risk categories (nonevent NRI). The addition of electrocardiographic (ECG) abnormalities to conventional risk factors improves total NRI in both cases, but one might lead to an increase in preventive medications, while the other suggests a possible reduction in the use of preventive medications. CHD indicates coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; NR, not reported; PCE, Pooled Cohort Equations.

[a] Categories of 10-year risk: <1%, 1% to <5%, 5% to <10%, ≥10%.

[b] Categories of 10-year risk: <5%, 5% to <10%, 10% to <20%, ≥20%.

[c] Categories of 10-year risk: <7.5%, 7.5% to <15%, ≥15%.

Four evaluated only single ECG changes.[19,21,22,25] Duration of follow-up ranged from 6[20] to 19 years.[24] Overall, the studies reported little or no information about participants' baseline symptoms.

Of the 5 studies that evaluated the addition of multiple ECG abnormalities to traditional risk factors,[17,18,20,23,24] 4 used FRS or PCE base models (with published coefficients) for some analyses.[17,18,20,24] The frequency of ECG abnormalities across these studies ranged from 31% to 55% (eTable 12 in the Supplement). The studies reported absolute improvements in AUC or C statistics of 0.001 to 0.05 (Figure 4; eFigure 1 in the Supplement). Of the 3 studies that reported calibration or overall performance for the addition of multiple ECG abnormalities,[17,18,20] none reported figures such as calibration plots. The studies reported a variety of measures indicating improved calibration among the 2 studies using published coefficients of FRS[18,20] but poor calibration

Table 3. Characteristics of Studies That Evaluated Discrimination, Calibration, or Reclassification With the Addition of Resting ECG (KQ2)[a]

Source	Sample Size	ECG Findings Evaluated	Model Type[b]	Base Model	Mean (SD)		No. (%)					Follow-up, y
					Age, y	BMI[c]	Women	Nonwhite Race/Ethnicity	Hypertension	Diabetes Mellitus	Smokers	
Health ABC Study (1997-98) Auer et al,[17] 2012 (United States)	2192	Major and minor 12-lead ECG abnormalities[d]	Published coefficient and model development[e]	FRS	73.5 (2.8)	27.4 (4.9)	1211 (55)	900 (41)	1257 (57.3)	292 (13.3)	Past: 956 (43.6) Current: 221 (10.1)	8.2 (median)
NHANES-III (1988-1994) Badheka et al,[18] 2013 (United States)	6025	Major and minor 12-lead ECG abnormalities[f]	Published coefficient	FRS	58.7 (13)	27.2 (5)	NR (54)	NR (12)	NR (40)	0	NR (24)	13 (mean)
NHANES-III (1988-1994) Badheka et al,[19] 2013 (United States)	7928	12-lead ECG ST-T wave abnormalities in lead aVR	Published coefficient	FRS	59.9 (13.4)	27.6 (5.5)	NR (55)	NR (9.2)	NR (43.8)	NR (10.9)	NR (23.1)	13.5 (mean)
WHI Study (estrogen + progestin trial) (1993-1998) Denes et al,[20] 2007 (United States)	1264[g]	Major, minor, and incident 12-lead ECG changes[h]	Published coefficient	FRS	63	28-29 (5.6-6.2)	1264 (100)	NR (16)	NR (55-75)	NR (4)	Past: NR (40) Current: NR (10)	5.6 (mean)
ARIC (1987-1989) Folsom et al,[21] 2003 (United States)	14 054	LVH using 12-lead ECG and Cornell score	Model development	FRS variables[i]	Median: 55 (range 45-64)	NR	7983 (57)	NR	NR	1500 (10.7)	NR	10.2 (median)
Jichi Medical School Cohort (1992-1995) Ishikawa et al,[22] 2015 (Japan)	10 643	Prolonged corrected QT (QTc) intervals and LVH on 12-lead ECG[j]	Model development	FRS variables plus alcohol intake and heart rate[k]	55.4 (11.2)	23.1 (3.1)	NR (62)	NR	NR (33.9)	NR (3.6)	NR (22.6)	10.7 (mean)
Copenhagen City Heart Study (1976-1978) Jorgensen et al,[23] 2014 (Denmark)	6991	Major and minor 12-lead ECG abnormalities; outcomes for some single ECG changes[l]	Model development	FRS variables[m]	70 (4)	26 (4.3)	4112 (59)	NR	NR	359 (5)	3249 (47)	9.8-11.9 (median across outcomes)
NHANES I (1971-1975) and NHANES III (1988-1994) Shah et al,[24] 2016 (United States)	9969 (derivation, 3640; validation, 6329)	ECG Risk Score including frontal T axis, corrected QT interval, T axis, heart rate, age, sex, age×sex interaction[n]	Published coefficient and model development	FRS, PCE, and FRS variables[o]	Total: 55.3 (10.1)	NR	5255 (53)	Derivation: 402 (11) Validation: 1681 (26.6)	272 (7.5); 1288 (20.4)	178 (4.9); 1049 (16.6)	1250 (34.3); 1612 (25.5)	18.8 (median, derivation) 10 (median, validation)

(*continued*)

Table 3. Characteristics of Studies That Evaluated Discrimination, Calibration, or Reclassification With the Addition of Resting ECG (KQ2)[a] (continued)

Source	Sample Size	ECG Findings Evaluated	Model Type[b]	Base Model	Mean (SD)		No. (%)					Follow-up, y
					Age, y	BMI[c]	Women	Nonwhite Race/Ethnicity	Hypertension	Diabetes Mellitus	Smokers	
ARIC (1987-1989) Tereshchenko et al,[25] 2014 (United States)	15 375	Resting 12-lead, P-wave morphology (DTNPV1)	Model development	FRS variables[p]	54 (5.8)	28 (5.5)	8510 (55)	4127 (27)	3861 (25)	1494 (10)	4001 (26)	14 (median)

[a] All studies were of fair quality except for Auer et al, which was good quality. When this table includes a range, the data were not reported for the full sample but were reported separately for different groups.

[b] Model types categorized as published coefficient models when they preserved the coefficients of published models that have been externally validated (eg, FRS or PCE) or as model development when they did not.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Criteria for major prevalent ECG abnormalities were any of the following, using the Minnesota Coding (MC) System: 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). Criteria for minor prevalent ECG abnormalities were minor ST-T changes (MC 4-3, 4-4, 5-3, and 5-4). Participants with both were classified as having major abnormalities. Participants without minor or major ECG abnormalities were classified as having marginal or no abnormalities and their ECG findings were considered normal.

[e] Model development comprised 2 models: (1) FRS variables and diabetes and (2) FRS variables only. FRS variables were age, sex, total and HDL cholesterol levels, systolic blood pressure, and smoking.

[f] Individuals with any of the following at baseline, classified using the MC System, were considered to have ECG abnormalities: possible or probably myocardial infarction, cardiac infarction or injury score ≥10, possible or probable left ventricular hypertrophy, any axis deviation, and any rhythm abnormalities other than sinus.

[g] Participant characteristics were reported for the larger sample of 14 749 postmenopausal women in the WHI estrogen + progestin trial but not for the subset of 1264 in the WHI blood subsample corresponding to the results relevant for this review.

[h] Criteria for major prevalent ECG abnormalities were any of the following, using the Novacode criteria: (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) Q-wave myocardial infarction, (7) isolated ischemic abnormalities, (8) left ventricular hypertrophy with ST-T abnormalities, and (9) miscellaneous arrhythmias (eg, supraventricular tachycardia, ventricular preexcitation, ventricular tachycardia) with <5 participants being included in the analysis and not listed individually. Women with both major and minor abnormalities were classified as having major abnormalities. Criteria for minor prevalent ECG abnormalities were any of the following, using the Novacode criteria: (1) first- and second-degree atrioventricular block, (2) borderline prolonged ventricular excitation, (3) prolonged ventricular repolarization, (4) isolated minor Q-wave 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. Criteria for incident ECG abnormalities were any of the following, using the Novacode criteria: (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 myocardial infarction, and (6) new ischemic ST-T evolution.

[i] Model included age, race, total and HDL cholesterol levels, systolic blood pressure, use of antihypertensive medication, and smoking status.

[j] QTc determined by Bazett QTc intervals of ≥440 ms in men and ≥460 ms in women on a 12-lead ECG. LVH diagnosed with Cornell product of ≥244 mVxms.

[k] Model included age, sex, BMI, current smoking, alcohol intake >20 g/d, systolic blood pressure, antihypertensive medication use, diabetes, hyperlipidemia, and heart rate.

[l] Reported outcomes for major or minor ECG changes, T-wave changes, ventricular conduction delay, LVH, Q waves, ST depressions, resting heart rate; classified using MC.

[m] Model included age, systolic blood pressure, total cholesterol, sex, current smoking, and diabetes.

[n] Selected from major and minor abnormalities. Major ECG abnormalities were defined as follows: major Q/QS-waves (MC 1.1, 1.2), ST-segment depression (MC 4.1, 4.2), negative T waves (MC 5.1, 5.2), ventricular conduction defect (MC 7.1, 7.2, or 7.4), atrial fibrillation/flutter (MC 8.3), or ST-segment elevation (MC9.2). Minor ECG abnormalities were defined as having minor Q waves (MC 1.2.8 or 1.3), high R waves (MC 3.1 or 3.3), minor ST-segment changes (MC 4.3 or 4.4), minor T-wave changes (MC 5.3 or 5.4), prolonged PR interval (MC 6.3), RR' in V_1 or V_2 (MC 7.3 or 7.5), or left anterior fascicular block (MC 7.7).

[o] FRS model includes age, sex, systolic and diastolic blood pressure, diabetes, tobacco use, total and HDL cholesterol levels, and use of antihypertensives.

[p] FRS components: age, sex, systolic blood pressure, diabetes, total and HDL cholesterol levels, smoking, and blood pressure–lowering therapy.

in 1 model development of older adults aged 70 to 79 years[17] (eResults and eTable 13 in the Supplement).

Four of the 5 studies evaluating multiple ECG changes reported NRI, and all but 1[23] provided event NRI or nonevent NRI data (or the data to calculate them) for some models (Figure 5; eResults, eTable 13, and eFigure 2 in the Supplement).[17,18,23,24] One study used the base model for risk prediction (ie, PCE) and some risk thresholds corresponding to current USPSTF recommendations for preventive medications.[24] Overall, total net reclassification improvements ranged from 3.6% (2.7% event; 0.6% nonevent) to 30% (17% event; 19% nonevent) for studies using FRS or PCE base models (95% CIs were rarely reported) (Figure 5). Evidence was limited by imprecision (or unknown precision), quality, and considerable heterogeneity. Consistency of findings for specific risk thresholds is unknown because all studies used different risk categories. Results of studies that evaluated single ECG changes are provided in the eResults in the Supplement.

Harms of Screening

Key Question 3a. What are the harms of screening with resting or exercise ECG, including harms of subsequent procedures or interventions initiated as a result of screening?

Key Question 3b. Do the harms of screening vary for subgroups defined by baseline CVD risk (eg, low, intermediate, or high risk), age, sex, or race/ethnicity?

One RCT described in KQ1, the DADDY-D trial, was included for this KQ. It reported on harms from subsequent interventions initiated as a result of screening.[11] Twenty of 262 participants (7.6%) in the screened group had positive exercise treadmill test findings. Of those 20 participants, 17 underwent coronary angiography (6.5% of the 262 in the screened group). Angiography revealed critical stenosis (not defined) in 12 of those 17 (71%), and all patients with critical stenosis underwent revascularization procedures (7 percutaneous and 5 surgical). One patient undergoing 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 later.

The other trial described in KQ1 (DYNAMIT) reported the number of some subsequent tests but did not report whether any of the tests or interventions resulted in harms.[10]

Discussion

Table 4 provides the summary of findings. The overall strength of evidence was low or insufficient for each of the questions 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 those trials were limited by not reaching sample size targets. Evidence on whether the addition of exercise ECG to traditional CVD risk factors results in accurate reclassification is lacking. For resting ECG, the addition of multiple abnormalities to traditional CVD risk factors accurately reclassified persons and improved discrimination and calibration, but evidence was limited by imprecision, quality, considerable heterogeneity, and inconsistent use of risk thresholds that align with recommendations and current clinical practice.

Two RCTs evaluated screening with exercise ECG. The participants were higher-risk groups that would be, in theory, more likely to benefit from screening to identify silent ischemia. However, screening with exercise ECG, followed by referral to cardiology (DYNAMIT) or recommendation for coronary angiography (DADDY-D) for those with abnormal exercise ECG findings, did not improve health outcomes. Some key limitations of the trials include not reaching sample size targets and only following up participants for about 3.5 years. Findings from the 2 studies were consistent, but 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.

Limited direct evidence was found on harms of screening asymptomatic adults. Potential harms of screening with exercise or resting ECG include mortality, arrhythmia, cardiovascular events, injuries, anxiety, labeling, and harms of subsequent procedures or interventions. Both DYNAMIT and DADDY-D reported on subsequent interventions after abnormal exercise test findings, but only DADDY-D reported whether any of those resulted in harms (1/12 had an MI). No other eligible studies reported 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 or interventions specifically for asymptomatic persons. This approach excluded a single-site study of 377 asymptomatic military officers (mean age, 37 years) that reported no complications during exercise testing.[26]

Many other studies have reported rates of angiography (but no information on harms) for asymptomatic persons after exercise ECG, ranging from 0.6% to 13%, and usually less than 3%.[12,14,26-34] Rates of subsequent revascularization have also been reported by some, with those studies estimating lower rates than those reported by DADDY-D and DYNAMIT (eg, 0.1%-0.5% in 2 studies with 1051-3554 participants).[12,14] Little is known about the harms of revascularization procedures for adults without symptoms or a prior diagnosis of CVD (eContextual Questions in the Supplement). Regardless of symptom status, some tests that follow an abnormal ECG finding expose patients to radiation, including coronary angiography, computed tomography angiography, and myocardial perfusion imaging.[35] Coronary angiography can expose patients to as much radiation as 600 to 800 chest radiographs.[36]

Studies that focused on *symptomatic* adults have reported rates of harms of exercise ECG and harms of subsequent interventions. Recommendations for exercise laboratories estimate a complication rate of 1 in 10 000,[37] referencing a review that reported rates of sudden cardiac death from 0 to 5 per 100 000 tests.[37,38] The recommendations also provided estimates from survey data for hospitalization including serious arrhythmias (≤0.2%), MI (0.04%), or sudden cardiac death (0.01%).[37,39]

No consensus exists for the thresholds that should be considered clinically significant changes in discrimination, calibration, or reclassification. Appropriate reclassification has the most direct clinical meaning, but studies must use meaningful risk categories (ie, that correspond to clinical decisions, such as 7.5% or 10% 10-year risk) to provide NRI results applicable to current clinical practice.

For exercise ECG, although evidence from cohort studies shows that the addition of exercise ECG to traditional CVD risk factors results in small absolute improvements in discrimination, 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. Also, there was an absence of evidence related to exercise ECG for healthy, low-risk persons (eg, mean baseline FRS was 10.8-12.3 in studies reporting it).

Table 4. Summary of Evidence for Screening With ECG

No. of Studies (No. of Participants)	Summary of Main Findings (Including Consistency and Precision)	Strength of Evidence	Limitations (Including Reporting Bias)	Applicability
KQ1: Benefits of Screening With ECG				
2 RCTs (fair quality) (n = 1151)	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.	Low for no benefit of screening with exercise ECG; insufficient for resting ECG; no studies	Neither trial reached sample size targets; stopped early because of trouble recruiting. Not clear that 3.5 y of follow-up is sufficient. Masking of outcome assessors and amount of missing data NR in 1 trial.[11] Reporting bias not detected.	Asymptomatic adults aged 50-75 y with diabetes undergoing exercise ECG; both trials enrolled high-risk populations
KQ2: Reclassification, Calibration, and Discrimination for Exercise ECG				
5 Cohort studies (fair quality) (n = 9582)				
Discrimination	3 studies: small absolute improvement in AUC or C statistics (0.02-0.03); none reported 95% CIs; 1 reported $P = .3$ (no significant difference between models). Consistent; imprecise.	Low for small improvement	CIs for calibration or discrimination NR (5 studies); mean duration of follow-up <10 y[d] (4 studies), reclassification NR (4 studies); unknown masking of outcome assessors (4 studies); not reporting both discrimination and calibration (3 studies); model development studies (2 studies); unclear handling and amount of missing data (2 studies). 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.	Adults without a history of CVD; mean age of participants 50-58 y; range of females was 0%-38%; race/ethnicity NR in most (4 studies). Mean baseline FRS score was 10.8-12.3 in studies reporting it (3 studies); intermediate risk, on average
Calibration or performance	4 studies; 2 studies FRS base model; all 4 used different metrics;[b] none reported figures such as calibration plots;[c] 3 studies reported improvement with addition of exercise ECG variables; mixed results for the 2 with FRS base models. Inconsistent; imprecise.	Insufficient		
Reclassification	1 model development study, n = 988: total NRI, 9.6% ($P = .007$); intermediate-risk NRI, 18.9% ($P = .01$). Consistency unknown; imprecise.	Insufficient		
KQ2: Reclassification, Calibration, and Discrimination for Resting ECG				
9 Cohort studies (8 fair, 1 good quality) (n = 66 407)				
Discrimination	7 studies; 4 studies FRS or PCE base model; 4 studies multiple ECG changes: very small to small absolute improvement in AUC or C statistics (0.001-0.05); few (3 studies) reported whether differences were statistically significant. Consistent; imprecise.	Low for very small to small improvement	Limited reporting on assessment of symptoms; unclear what proportion of participants were truly asymptomatic; masking of outcome assessors NR (8 studies), confidence intervals for calibration or discrimination NR (5 studies), not reporting calibration (5 studies), model development studies (4 studies), amount of missing data NR (2 studies), and mean duration of follow-up less than 10 y (2 studies). For reclassification, few (3 studies) included a threshold between risk categories corresponding to the recommendations for preventive medications (ie, 7.5% or 10% 10-y risk).	Adults without a history of CVD; mean age of participants, 54-73 y; majority were women in all studies; range of nonwhite participants in those who reported race/ethnicity (6 studies) was 9%-41%. Mean baseline risk ranging from low to high across studies.
Calibration or performance	4 studies; 2 studies FRS + major/minor ECG changes; 1 study FRS + specific T-wave change: no studies reported calibration plots; variety of metrics used; good calibration with addition of major or minor changes (2 studies) or T-wave amplitude in lead aVR (1 study) to FRS. Poor calibration with addition of major or minor changes to FRS variables (1 model development study of adults aged 70-79 y). Consistent among 3 studies using published coefficients; imprecise.	Low for improvement		
Reclassification	7 studies, 59 123 participants; 3 studies FRS or PCE + multiple ECG changes; 1 study FRS + specific T-wave change. Overall, total NRIs range from 3.6% (2.7% event; 0.6% nonevent) to 30% (17% event; 19% nonevent) for studies using FRS or PCE base models (95% CIs rarely reported).[f] 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.	Low for improvement		
KQ3: Harms of Screening With ECG				
1 RCT (fair quality) (n = 520)	1 patient of 12 (8.3%) undergoing revascularization procedures after positive exercise treadmill test in the DADDY-D trial had a nonfatal acute MI 3 d after percutaneous revascularization and underwent a second percutaneous angioplasty.[g] Consistency unknown (single study); imprecise.	Insufficient	Trial focused on assessing benefits; did not reach sample size target; not clear that mean of 3.6 y of follow-up is sufficient; masking of outcome assessors NR and amount of missing data NR. Reporting bias not detected.	Asymptomatic adults aged 55- 75 y with diabetes undergoing screening with exercise ECG

[a] For the primary composite outcomes, hazard ratios 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, Brier score, and Hosmer-Lemeshow χ^2; global χ^2; and predicted and observed events.

[c] One model development study provided a table of predicted and observed events for quintiles of risk.[16]

[d] The only study reporting longer follow-up covered 26 years, but it did not account for high-density lipoprotein cholesterol levels in analyses.[16]

[e] Of these, 16.5% had atypical chest pain, and participants were a subset of those having coronary artery calcium score and single-photon emission computed tomography for "clinically indicated reasons."[13]

[f] For multiple ECG changes (on resting 12-lead ECG), total NRIs for studies using any base model ranged from 1.9% (−0.2% event NRIs; 0.6% nonevent NRIs) to 30% (17% event NRIs; 19% nonevent NRIs).

[g] The DADDY-D trial reported that 20/262 participants (7.6%) in the screened group had positive exercise treadmill test findings. Of those 20, 17 underwent coronary angiography (6.5% of 262). Angiography revealed critical stenosis (not defined) in 71% (12/17), and all patients with critical stenosis underwent revascularization (7 percutaneous, 5 surgical). The DYNAMIT trial (included in KQ1) reported the number of some subsequent tests but did not report whether any tests or interventions resulted in harms; adverse events during follow-up were not recorded.[10] Of 316 participants in the screened group, 68 (21.5%) had a definitely abnormal or uncertain result (exercise test or SPECT). Of those, 38 underwent coronary angiography (12% of 316) and 9 subsequently underwent coronary angioplasty (7/9 received stents) and 3 had CABG surgery.

For resting ECG, evidence from cohort studies shows that the addition of ECG findings to traditional CVD risk factors results in small improvements (at best) in discrimination and in improvements for calibration and appropriate risk classification for prediction of all-cause mortality, CVD mortality, CHD events, or CVD events. However, evidence was limited by imprecision, risk of bias, and considerable heterogeneity in prediction models, risk thresholds (all studies used different risk categories), type of ECG abnormalities, and outcomes assessed. 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, patient populations, and base models used.

Figure 5 might suggest potential value in reclassification based on the addition of major and minor resting ECG changes to existing models (PCE or FRS) 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, there are important limitations. First, no 2 studies evaluated the same model, risk category thresholds, and outcome. Second, no CIs were provided for most of those data. Third, NRI is highly dependent on risk category thresholds, which varied widely across studies. Fourth, evaluating risk reclassification using 4 categories to determine NRI may inflate the NRI because each reclassification increases NRI, regardless of whether the change would correspond to different treatment decisions. Fifth, a single study[24] accounts for 6 of the 9 rows in Figure 5. It reported NRI for 3 different base models for prediction of several mortality outcomes but did not evaluate prediction of CHD or CVD events because it used data that do not have that capability. The study did not report the full reclassification table to show how much of the NRI was accounted for by reclassification that should change clinical decisions (eg, from 5%-9.9% to ≥10%) vs how much was accounted for by reclassification that would have no effect on clinical decisions and outcomes (eg, from 1%-4.9% to <1% for persons without events).[24] It was also the only study that evaluated adding an ECG risk equation to base models. Sixth, another study[17] in Figure 5 had only 7.5 years of follow-up and focused on elderly participants aged 70 to 79 years. 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 persons of similar age[40] and the USPSTF I statement on initiation of aspirin for primary prevention for older adults.

Additionally, for the studies of resting ECG, it is unclear what proportion of participants was truly asymptomatic. The proportion with symptoms may 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.

To better understand whether risk classification is improved in a 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 informative. Use of the PCE is recommended by the USPSTF and American College of Cardiology/American Heart Association to inform decisions about preventive medications. Only 1 included study used the PCE as the base model. Studies of a constellation of resting ECG changes show greater potential than those of single ECG changes and could be the focus of future research. Future 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 use of additional or fewer preventive medications. 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 and should exclude those with a history of CVD. Measures of discrimination, calibration, and reclassification (including total, event, and nonevent NRI) and their corresponding CIs should be reported. Future studies detailing harms of screening are also needed.

Conclusions

RCTs of screening with exercise ECG found no improvement in health outcomes, despite focusing on higher-risk populations with diabetes. The addition of resting ECG to traditional risk factors accurately reclassified persons, but evidence for this finding had many limitations. The frequency of harms from screening is uncertain.

ARTICLE INFORMATION

Accepted for Publication: May 3, 2018.

Author Contributions: Dr Jonas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jonas, Asher.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Jonas, Reddy, Asher.
Statistical analysis: Jonas.
Obtained funding: Jonas.
Administrative, technical, or material support: Jonas, Reddy, Middleton, Barclay, Green, Baker.
Supervision: Jonas.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This research was funded under contract HHSA-290-2015-00011-I, Task Order 5, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the USPSTF.

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project, including AHRQ staff (Howard Tracer, MD; Elisabeth Kato, MD, MRP; and Tracy Wolff, MD, MPH) and RTI International–University of North Carolina Evidence-based Practice Center staff (Carol Woodell, BSPH; Christiane Voisin, MSLS; Sharon Barrell, MA; and Loraine Monroe). USPSTF members, expert consultants, peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions. Mss Woodell, Voisin, Barrell, and Monroe received compensation for their role in this project.

Additional Information: A draft version of the full evidence report underwent external peer review from 4 content experts (Joy Melnikow, MD, MPH, University of California, Davis; Amit Shah, MD, MSCR, Emory University; Fabrizio Turrini, MD, Nuovo Ospedale Civile Sant'Agostino Estense, AUSL Modena, Modena, Italy; Timothy Wilt, MD, University of Minnesota) and 1 federal partner

reviewer from the National Institutes of Health. Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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