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Systematic Evidence Review
Number 22

Screening for Asymptomatic Coronary Artery Disease: A Systematic Review for the U.S. Preventive Services Task Force

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, the Evidence-based Practice Center at Oregon Health Sciences University systematically reviews the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/clinic/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the USPSTF in print and on the Web. These are available through the AHRQ Web site and through the National Guideline Clearinghouse (http://www.ngc.gov).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850, or e-mail uspstf@ahrq.gov.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the current USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

Contents

Figure and Tables

Abstract

Background: We reviewed the evidence on the value of screening asymptomatic patients with resting electrocardiogram (ECG), exercise electrocardiogram treadmill test (ETT), or electron beam computerized tomography (EBCT).

Methods: We searched MEDLINE 1966 - June 2002 to identify studies examining the independent value of ECG, ETT, and EBCT in patients with no known history of cardiovascular events. We sought to identify studies that examined the use of these tests compared with traditional risk assessment of coronary heart disease (CHD) as a means of reducing CHD events, improving the use of CHD risk-reducing treatments, or producing more accurate assessments of actual CHD risk.

Results: No studies examined the effect of screening asymptomatic patients with ECG, ETT, or EBCT on CHD outcomes. Two fair quality studies examined the effect of a positive EBCT on self-reported adoption of risk-reducing behaviors and found mixed results. ECG, ETT, and EBCT each can provide independent prognostic information about the risk of CHD events, mainly in middle-aged or older adults, but the effect of this information on clinical decisionmaking is unclear. When the risk of CHD events is low, however, most positive findings will be false positives and may result in unnecessary further testing.

Conclusions: Although ECG, ETT, and EBCT can provide prognostic information about the risk of future CHD events, the effect of this information on clinical management or disease outcomes in asymptomatic patients is unclear.

Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States. Each year, more than 1 million Americans experience nonfatal or fatal myocardial infarction or sudden death from CHD. The estimated direct and indirect costs of CHD and stroke were $298.2 billion for 2001.[1] Angina is the most common presenting symptom of CHD, but in many persons the first manifestation may be myocardial infarction or sudden death.[2] An estimated 1 to 2 million middle-aged men have asymptomatic but physiologically significant coronary artery disease, which puts them at increased risk for CHD events.[3,4]

In 1996, the U.S. Preventive Services Task Force (USPSTF) considered the use of resting electrocardiography (ECG) or exercise electrocardiography treadmill testing (ETT) to detect asymptomatic coronary artery disease (ACAD).[5] The Task Force found insufficient evidence to recommend for or against screening middle-aged and older men and women with these tests. They recommended against screening children, adolescents, or young adults. Electron beam computerized tomography (EBCT) was not evaluated.

To update the evidence review and recommendations on screening for ACAD, the USPSTF and the Agency for Healthcare Research and Quality requested that the RTI International-University of North Carolina Evidence-based Practice Center perform an updated evidence review beginning in 2001. Figure 1 shows the analytic framework for our analysis.

Clinicians can use two approaches for preventing CHD morbidity and mortality. The first approach involves screening for, and treating, the traditional modifiable CHD risk factors, such as hypertension, abnormal blood lipids, diabetes, cigarette smoking, physical inactivity, and diet. Such an approach may incorporate explicit calculations of the patient's risk of CHD events,

using risk prediction equations derived from the Framingham Study or other cohort studies.[6] The second strategy involves supplementing risk factor-based screening with additional tests to provide further information about CHD risk. Some of these tests detect asymptomatic blockage of the coronary arteries, also known as ACAD; others provide indirect information about CHD risk. In this strategy, detection of ACAD or increased CHD risk would lead to additional use of risk-reducing treatments. Some of these treatments are directed at traditional risk factors (e.g., statins for hyperlipidemia); others are not (e.g., aspirin). Another potential rationale for screening for ACAD is to detect and treat (by bypass surgery or percutaneous coronary intervention) important blockages of the coronary arteries. Little information, however, is available to determine if such treatment is effective in asymptomatic populations.

The principal tests for detecting ACAD or increased CHD risk include resting and exercise electrocardiograms, which can provide evidence of unrecognized previous myocardial infarction, silent or inducible myocardial ischemia, or other evidence of cardiac abnormalities. Newer tests detect the presence of atherosclerotic plaque, including EBCT, the ankle-brachial index (ABI), and B-mode carotid Doppler ultrasound. In this review, we consider the role of ECG, ETT, and EBCT in the detection and prevention of CHD events. Carotid Doppler ultrasound and the ABI will be considered in other USPSTF reports. Other tests, including Thallium-201 scintigraphy, exercise or stress echocardiography, and ambulatory ECG (Holter monitoring) are less commonly used for screening purposes, have not been well studied in asymptomatic patients, and are not considered further here.

The best measure of the value of tests to identify ACAD or increased CHD risk would come from studies that examined whether patients randomized to receive such tests had fewer CHD events than patients randomized to receive standard risk factor assessment-guided

treatment. Because no such evidence is available, we used observational cohort studies to examine whether these screening tests either lead to greater use of effective risk-reducing treatments or provide independent prognostic information about the risk of future CHD events. Such an assessment is based on each test's ability to provide better information than would be obtained by the standard history, physical examination, and measurement of traditional risk factors and calculation of CHD risk using global CHD risk equations. In addition to information about benefits, we also searched for any information about harms of screening, including the likelihood of false-positive screening results and the effect of labeling an individual as being "high risk."

Methods

To identify the relevant literature, we searched MEDLINE from 1966 through June 2002. We used the following MeSH headings and keywords: (Coronary disease and asymptomatic) or (Myocardial Infarction and silent) and (electrocardiography or exercise test or tomography, x-ray computed or echocardiography) and (diagnosis or prognosis), limited to English language and human subjects. In addition to these general searches, we also searched MEDLINE for articles on several specific electrocardiographic findings, including left ventricular hypertrophy, ventricular arrythmias, and ST segment changes or T wave inversions. We also performed hand searches of the bibliographies of key articles and used other recent systematic reviews when available to supplement our literature searches.

Two reviewers examined the abstracts of the articles identified in the initial MEDLINE search and resolved disagreements about inclusion by consensus. Two reviewers examined the full text of the remaining articles to determine final eligibility. To be eligible, studies had to be

performed in patients with no previous history of cardiovascular disease and to report the independent effect of the test on the incidence of CHD events, the proportion of patients receiving CHD risk-reducing treatments, or the risk of future CHD events. When reporting the prognostic benefit of ECG, ETT, and EBCT, studies have used different means of characterizing results. Many studies have reported the outcomes in terms of independent relative risk associated with a positive (versus a negative) screening test. Others have used diagnostic test terminology, such as sensitivity and specificity or positive predictive value. In such cases, the terms are used to indicate test accuracy over the entire follow-up period, rather than at one point in time (e.g. sensitivity is the proportion of all patients who go on to have a CHD event that had positive screening tests at baseline; positive predictive value is the proportion of all patients screening positive that go on to have a CHD event).

We rated the quality of the included articles according to criteria developed by the USPSTF Methods Work Group.[7] We used the final set of eligible articles to create evidence tables and a draft report, which was submitted for external peer review and subsequently revised as appropriate (see Appendix for the list of peer reviewers).

Results

We examined the effect of screening for ACAD on health outcomes, the adoption of risk-reducing behaviors, and ability to predict independently the risk of CHD events.

Effect of Screening Tests on Health Outcomes

We identified no studies that examined the effect of screening tests for ACAD on CHD or other health outcomes. A subgroup analysis of the Multiple Risk Factor Intervention Trial

found that patients with an abnormal exercise treadmill test, defined by abnormal heart rate-corrected ST depression, had a lower risk for CHD mortality with risk factor modification than patients in usual-care control group who also had this finding but did not receive specific advice about risk factor reduction.[8]

Effect of Screening on Adoption of Risk-reducing Behaviors

We identified two studies of fair quality that examined the impact of EBCT results on subsequent risk-reducing behaviors.[9,10] Wong and colleagues conducted a nonrandomized study in which they administered questionnaires at baseline and 1 to 2 years after an EBCT scan to 703 asymptomatic men and women.[9] Using logistic regression to control for other CHD risk factors present at baseline, they found that the presence of calcium on EBCT (CAC score > 0) was associated with statistically significant increases in self-report of new aspirin use (relative risk [RR], 1.86), new lipid-lowering medication use (RR, 3.54), use of vitamin E (RR, 1.62), decreased consumption of dietary fat (RR, 1.58), and increased worry (RR, 2.73).

O'Malley and colleagues surveyed 144 asymptomatic smokers from a cohort of 3,035 individuals who underwent EBCT at the Walter Reed Army Medical Center.[10] Response rate was 69% (99 of 144). The mean response time was 8.4 months post-scan. Mean age was 50 and 68% were men; most (80%) were self-referred. Increased perception of CHD risk was more common among patients with positive scans than among those with no coronary calcium (40% vs. 12%). Many patients (59%) reported being more motivated to quit smoking after the scan but neither motivation nor stage of behavioral change was associated with the presence of calcium on the scan. Smoking cessation rates were similar in those with and without calcium on their scans (14% and 12%, respectively).

Effect of Screening on Risk of Future CHD Events

Many studies have examined the value of ECG, ETT, and EBCT in predicting risk of future CHD events. The next 3 sections of the report will consider this evidence.

Resting Electrocardiogram (ECG)

In a recent systematic review examining the role of ECGs in asymptomatic adults, Ashley and colleagues identified 22 cohort studies that were of at least 5 years' duration and investigated the prevalence of abnormal ECG findings and their ability to predict cardiovascular mortality.[11] Some studies specifically searched for and excluded patients with any symptoms of cardiovascular disease; others excluded only patients with diagnosed cardiovascular disease. In these studies, the prevalence of the most common ECG abnormalities (Q waves, left ventricular hypertrophy (LVH), bundle branch blocks, and ST segment depression) ranged from 1% to 10%. Abnormal results were more common in men and increased with age. Another common finding, the presence of unrecognized atrial fibrilliation, is not examined further here but may have important health benefits.

Each of the main ECG abnormalities was associated with increases in the risk of CVD mortality. No summary estimates of the magnitude of increased risk were calculated. The sensitivity of ECG abnormalities for all-cause mortality was low (32% for any major abnormality in one study), but the specificity was relatively high (87%).[11] Another review from 1995 found similar results.[12]

Our review identified a similar set of large, fair or good quality observational cohort studies that examined the prognostic importance of abnormal findings on the resting ECG of asymptomatic persons.[13-38] They are described below with respect to silent myocardial infarction

(Q waves), LVH, ST segment and T wave changes, and various combined ECG changes (Tables 1A - 1G).

Q waves or silent myocardial infarction. Abnormal Q waves on ECG are often considered evidence of prior myocardial infarction, although they will be seen in a small proportion of patients with angiographically normal coronary arteries.[39] The interim development of Q waves on ECG without clinical evidence of a myocardial infarction is considered a clinically unrecognized or "silent" myocardial infarction.

Several cohort studies have examined the incidence and prevalence of Q waves on ECG. Sheifer and colleagues performed a systematic review of these studies.[40] They found that 20% to 40% of all myocardial infarctions identifiable on ECG were clinically unrecognized. The presence of ECG findings that are diagnostic of myocardial infarction (e.g., Q waves) appears to portend a high risk of future CHD events that may approach that of patients after recognized myocardial infarction (Table 1A).[14-17,33,35,37]

As an example, Sigurdsson and colleagues examined the prevalence of unrecognized myocardial infarction in a large cohort study of men in Iceland.[35] On ECG, it was 0.5% at age 40 but increased to 5.5% at age 75. Unrecognized myocardial infarction was associated with a relative risk of 7.0 (95% Confidence Interval [CI], 4.9 - 10.0) for future death from CHD. Three other studies have reached similar results,[16,17,37] but at least one study found no relationship.[33]

Left ventricular hypertrophy (LVH). ECG can detect LVH, but its sensitivity is low.[41] The presence of LVH on ECG, however, is strongly associated with adverse CHD-related events.[38] We identified several studies examining the effect of ECG LVH on the relative risk for CHD events (Table 1B).[13,15,17-24,31,34]

Most studies examined LVH prevalence in terms of repolarization abnormalities (so-called LVH with strain, labeled VS in Table 1B); this finding is less common than LVH defined only by voltage criteria (VO) and is more strongly associated with risk of cardiovascular events and mortality. The prevalence of ECG LVH with repolarization abnormalities generally ranged from 1.0% to 10%. Studies that adequately adjusted for other risk factors found that the presence of LVH with repolarization abnormalities was associated with a relative risk of between 1.8 and 4.4 for CHD mortality.

A small number of studies investigated LVH defined by voltage-only criteria.[17,20,22] Using this definition, prevalence was higher: approximately 20% in men and 6% to 13% in women. The study by Larsen and colleagues, which was the only one to adjust for other CHD risk factors, found no increased risk from LVH defined by voltage criteria alone (RR, 1.07; 95% CI, 0.92 to 1.24).[22]

ST segment and T wave changes. Some studies examined the prognostic value of ST segment depression, T wave inversions, or both, on ECG (Tables 1C and 1D).[13-17,22,31,34,36] The overall prevalence of ST segment or T wave changes ranged from 1% to 10% and increased with age. After adjustment for other risk factors, these findings were generally associated with an increase in the relative risk for CHD events of 1.7 to 4.0.

As an example, Sigurdsson and colleagues examined the independent effect of ST segment depression detected in asymptomatic patients participating in the Reykjavik Heart Study, which began in 1967.[36] Prevalence was related to age: 2% at age 40, 4% at age 50, 9% at age 60, 17% at age 70, and 30% at age 80. After adjustment for other CHD risk factors, they reported that ST segment depression was associated with a relative risk of 1.6 (95% CI, 1.0 to 2.8) for future angina or myocardial infarction and 2.0 (95% CI, 1.6 to 2.5) for CHD death.

Ventricular ectopy. The presence of premature ventricular impulses (ventricular arrythmia) on ECG also predicts increased risk of future CHD events. We identified 6 studies that examined the prevalence of ventricular ectopy and its effect on future CHD events (Table 1E).[16,17,31-34] Prevalence varied from 0.8% to 11%. Relative risk of CHD death was increased in each study except one; the increase in risk ranged from 2.1[31,34] to 4.0.[32]

Grouped ECG abnormalities. In addition to individual ECG findings, several studies examined whether the incidence and prevalence of groups of "major" or "minor" ECG changes affected the risk of future CHD events.[13,25-29,31]

Studies that examined the impact of major ECG changes (principally major ST segment or T wave changes, conduction blocks, ventricular ectopy, and atrial fibrillation; Table 1F) found relative risks for CHD mortality of 2 to nearly 4.[13,25,31]

Minor or nonspecific ECG abnormalities (principally small changes in the ST segments and T waves or minor conduction abnormalities; Table 1G) have been associated with increased cardiovascular morbidity and mortality.[13,25-28,31] Daviglus et al. studied 1,673 men employed at the Western Electric Company in Chicago, Illinois, who had no history of CHD or definitive ECG evidence of previous CHD events.[29] All subjects had a baseline resting ECG and were followed for 29 years. For men who had minor, nonspecific abnormalities on three or more annual ECGs, the relative risk for dying of coronary heart disease was 2.39 (95% CI, 1.39 to 4.12). Kannel et al. examined the Framingham cohort of 5,127 men and women who were free of overt CHD at study entry and followed with biennial ECGs.[28] Subjects who had nonspecific ECG abnormalities on any of the first 4 biennial examinations (prevalence: men, 6.5%; women, 5.2%), had a 1.4-fold greater risk of developing CHD than those without such ECG findings.

Most ECG studies examined cohorts that were predominantly European in origin, but three studies included large numbers of African-American patients.[26,27,30] The Charleston Heart Study found that although major ECG abnormalities are more prevalent in black men, they may confer greater independent risk of CHD death in white men (RR, 2.72; 95% CI, 1.47 to 5.04) than in black men (RR, 1.95; 95% CI, 0.93 to 4.11).[27] Jones et al. reported that in the Artherosclerosis Risk in Communities (ARIC) study cohort, LVH with associated ST-T wave abnormalities on rest ECG was associated with a particularly high age-adjusted risk of CHD events in black women (Hazard Ratio [HR] 5.9; 95% CI 3.6 to 9.7).[30] Black men with LVH with associated ST-T wave abnormalities had an HR of 2.0 (95% CI, 1.1 to 3.6) for CHD events. LVH with associated ST-T wave abnormalities in white men and women was not found to be a statistically significant predictor of CHD events in this study. Available studies suggest that the prognostic value of noninvasive screening may differ somewhat by population groups, but further research is needed to better characterize them precisely.

Adverse effects. The main adverse effects of ECGs are the false-positive test results, which can lead to further unnecessary tests and treatments and the adverse events associated with these additional interventions. A positive result also labels the person as being at increased risk, which may itself have adverse outcomes. When applied in low-risk asymptomatic populations with a low prevalence of CHD and low risk of CHD events in the next 5 to 10 years, most positive test results will occur in patients who will not go on to have a CHD event over that time span. Because of the limited sensitivity of the resting ECG and the low prevalence of disease in asymptomatic adults, a majority of CHD events will occur among persons with an initially normal ECG.[42]

Exercise Treadmill Testing (ETT)

ETT is widely used as a diagnostic test in the initial evaluation of patients with symptoms suggestive of myocardial ischemia and for persons with previously recognized coronary heart disease. Although ETT has been applied and studied as a screening or prognostic test in asymptomatic persons, its utility in this patient population is controversial.

Several fair or good quality observational cohort studies of asymptomatic adults have prospectively evaluated the value of ETT in predicting future CHD events, such as angina, myocardial infarction, and death (Table 2).[43-53] Most studies reported total CHD events as their main outcome. Others reported CHD mortality or total mortality as their main outcomes, or in addition to reporting CHD events. CHD mortality and particularly total mortality are less subject to ascertainment bias than total CHD events. In these studies, the prevalence of an abnormal ETT, usually defined as ST segment depression of ≥ 1 mm, ranged from 5% to 25%. After adjustment for other risk factors, the independent relative risk of CHD events associated with a positive test generally ranged from 2.6 to 5.7, sensitivity for occurrence of CHD events over the length of the studies (3 to 12 years duration) ranged from 10% to 62%, and positive predictive value ranged from 6% to 48%.

More recent studies of the value of exercise testing in asymptomatic men have examined the utility of other risk markers, including functional capacity, chronotropic incompetence, heart rate recovery, and the development of exercise-induced premature ventricular contractions and the risk of CHD events or mortality.[45,47,54-59] In general, these findings are associated with moderate increases in CHD risk after adjustment for other CHD risk factors (relative risks 1.7 to 3.2). Some are quite common; failure to achieve target heart rate was noted in 21% of patients in the Framingham Offspring Study, for example.[54]

In addition to its ability to predict future CHD events, a positive ETT may be able to detect the small proportion of asymptomatic patients with severe coronary artery disease, such as left main or 3-vessel coronary artery obstruction, findings that may warrant immediate revascularization. Davies and colleagues examined the yield of exercise ECG in 5,000 asymptomatic middle-aged men in London; 162 men (3.2%) had an abnormal exercise ECG response.[60] Among the men with abnormal tests, 92 agreed to undergo further evaluation, and 67 had significant coronary artery disease on angiography, defined as at least 1 vessel with 50% stenosis. Of these 67 patients, 26 underwent revascularization for 3-vessel or left main coronary artery disease and 7 had angioplasty; the remaining 34 were treated medically. No data are available on the 70 patients who did not undergo further evaluation. Assuming those lost to follow-up did not have 3-vessel or left main coronary disease, the yield of ETT for detecting severe disease was approximately 0.5%. To detect these patients with severe coronary artery obstructions during screening, however, requires that all patients with positive ETT undergo cardiac catheterization, which may have other, untoward effects as well.

Although a positive ETT can provide useful prognostic information, using ETT in asymptomatic populations with low risk of CHD (often less than 1% per year) will lead to many false-positive results. For example, Hopkirk et al. reviewed the medical records of 225 asymptomatic air-crew members who had an abnormal ST segment response during screening exercise ECG and subsequently had a cardiac catheterization.[61] The authors found that only 29% of the men had angiographically demonstrable CAD.

In terms of CHD risk, the positive predictive values identified in the cohort studies discussed above were generally low (range: 6% to 48%). Many of the studies that found higher

pre-test and post-test probabilities of disease are older investigations that reflect the higher prevalence and seriousness of CHD in the 1980's and earlier.

Data from the prospective cohort studies suggest that the majority of asymptomatic persons with an abnormal ETT do not have CHD events, at least within the follow-up time frame, usually 3 to 8 years. Persons who do have events are more likely to develop angina than have myocardial infarction or sudden death.[52] Within a defined cohort of low-risk patients, a larger absolute number of CHD events occurs among patients with initially normal ETT results than among those with initially abnormal results.

Other investigators have developed sophisticated scoring systems for improving ETT accuracy.[62] Adding nuclear perfusion imaging to ECG analysis may increase sensitivity somewhat but may also increase costs.[63] However, the low predictive value of screening ETT is driven mainly by the low underlying prevalence of disease in asymptomatic patients, and hence it cannot be corrected solely by improving test accuracy.

Table 3 considers the effect of different levels of pretest probabilities (couched as underlying prevalence of disease) on the yield of a screening test (generally speaking, not specifically for ACAD). It presents 2 cases for 2 screening tests. In 1 case, the prevalence of disease is only 1%; in the other, it is 10%. The screening tests differ in terms of the assumed sensitivity and specificity, with test "B" having more favorable assumptions than test "A."

As shown in Case 1 (1% prevalence), the probability of disease in those testing positive ranges from 3.4% to 7.5%; the probability of disease in those testing negative ranges from 0.2% to 0.4%. Although test B performs better than test A, the differences on an absolute scale are small.

By contrast, in Case 2, the range of probability of disease in those testing positive is from 28% to 47% (and 2.4% to 4% for probability of disease in those testing negative). The numbers for true- and false-negative or -positive persons of course differ between the two cases (and by test), and the probabilities of disease (for those testing either positive or negative) are far higher for Case 2 than Case 1. These hypothetical results demonstrate the large impact of underlying prevalence (or pretest probabilities) on the yield of tests and highlight the caution that must be taken in interpreting screening test results.

Some investigators and policymakers have suggested that the value of ETT is greater when it is applied to patients with one or more CHD risk factors because selecting a higher-risk cohort for screening increases the prevalence of disease and positive predictive value. Bruce et al. reported that, in the Seattle Heart Watch Study of 4,158 asymptomatic men and women, a positive exercise ECG in the absence of risk factors provided little predictive value.[64] However, among patients with one or more other CHD risk factors, the occurrence of 2 different types of abnormal ETT response was associated with a 15-fold increase in risk compared to those with normal ETT.[65]

A large cohort study of 25,927 asymptomatic healthy middle-aged men in Texas found that an abnormal ETT in a man without risk factors conferred an age-adjusted relative risk for CHD death of 21 (95% CI, 6.9 to 63.3). Although the relative risk associated with a positive test was large, the post-test probability for patients with no risk factors was only 1.25%.[51] In a man with 3 or more conventional cardiac risk factors, a positive ETT conveyed an independent increase in relative risk of 8 for death from CHD.

In addition to false-positive results, ETT can be normal or nondiagnostic in an important proportion of patients who will go on to have a CHD event. Older studies reported sensitivity for

ST segment depression of 1 mm or greater to be 65% to 70%.[66,67] However, more recent investigators have questioned the accuracy and relevance of this older information for asymptomatic adults today, particularly because the spectrum of disease encountered now may be less severe and because of the presence of work-up bias in earlier studies.[68,69] In addition, most of the early investigations studied primarily male populations; test performance in women appears to be lower than for men, at least for symptomatic patients.[70] The suboptimal sensitivity of ETT for CHD events may be partly explained by the fact that ST segment depression on ETT detects ischemia from obstructive coronary arteries, but many acute CHD events result from sudden occlusion of a previously nonobstructed artery segment.[71] Use of other measures from the exercise test that are not as dependent on identifying atherosclerotic obstructions may partly mitigate this dilemma.[68]

Electron Beam Computed Tomography (EBCT)

Recent studies have examined the role of EBCT for the detection of coronary calcium as a potential screening test for CHD. EBCT can detect and quantify the amount of calcium deposited in the walls of coronary arteries. For symptomatic patients, EBCT has a sensitivity of 80% and specificity of 40% for detecting obstructed arteries when compared with coronary angiography.[72] Coronary calcium may be a marker for anatomic changes that are associated with an increased future risk of CHD. Conversely, the absence of coronary calcium may identify a low-risk cohort, at least for periods of time up to 3 to 5 years. Pletcher and colleagues recently conducted a systematic review and meta-analysis of the independent risk information available from EBCT for asymptomatic adults.[73] They identified 5 fair-quality studies that met their inclusion criteria.[74-78] They then applied data standardization measures to allow better comparison and meta-analysis of the different results. The 5 studies had follow-up periods of 32

to 72 months and enrolled middle-aged adults (mean ages ranged from 52 to 66 years; women accounted for 11% to 49% of participants). Most studies used crude measures of other CHD risk factors, mainly self-report of the presence or absence of smoking, hypertension, diabetes, and lipid disorders, although one study used direct measures of most risk factors.[75] In addition, the CHD outcomes measured usually included revascularization, which may be affected by the EBCT result itself.

After adjustment for other risk factors, higher calcium scores were associated with a higher risk of CHD events. Calcium scores of 1 to 100 were associated with a relative odds of 2.1 (95% CI, 1.6 to 2.9) compared with a score of 0. Scores above 100 were associated with higher risk, but the magnitude of the increased risk was smaller for the study that best measured other risk factors[75] than for those using crude measures. Patients with a calcium score of 0 generally had very low rates of CHD events over the defined follow-up period. Pletcher and colleagues concluded that EBCT may have a role in better defining the risk of CHD events for patients who are found to be at intermediate levels of risk based on traditional risk factors, but they did not identify any studies that examined if EBCT data affected clinical decision-making.

Potential adverse effects of screening for ACAD with EBCT include increased false-positive test results and labeling. As is the case with ECG and ETT, false-positive EBCT results often cause patients to undergo invasive diagnostic procedures such as coronary angiography, with resultant costs and risk of adverse events. Patients with obstructed arteries identified on angiography may then undergo revascularization, the efficacy of which is unclear.

Abnormal test results may also produce considerable anxiety until the test result is determined to be false. Labeling a person as suffering from coronary disease may also have negative consequences. Mixed evidence from hypertension screening suggests that being labeled

as having increased risk may be associated with poorer future health.[79] The studies by Wong et al. and O'Malley et al. suggest that patients with abnormal EBCT results are more worried about their health than those with negative results, but the impact of this finding on health and quality of life is unclear.[9,10]

Discussion

We identified no studies that examined the effect of screening for ACAD on health outcomes such as CHD events or mortality. Two studies of fair quality found mixed results with respect to the effect of EBCT results on self-reported adoption of CHD risk-reducing treatments. ECG, ETT and EBCT all appear to provide some independent prognostic information for at least some patients, above and beyond the prognostic information that can be gained from a traditional assessment of risk factors. The effect of this additional information on clinical decision-making, however, has not been assessed.

The additional value of screening for ACAD is likely to be small for patients in whom the prevalence of the disease is low, such as young adults; such screening would produce large numbers of false-positive results. In such cases, the costs and harms associated with additional testing and possibly labeling might exceed any benefits from screening. In older adults, for whom CHD risk is generally higher, the tests will perform better, but whether the benefits of such tests exceed the downsides in middle-aged and older adults is still unclear and awaits further investigation. Screening has been advocated for people with high-risk occupations, but we did not identify new studies examining the effect of screening such patients. Also uncertain is whether testing for ACAD leads to more effective and efficient use of risk-reducing strategies than would be the case for traditional risk factor analysis alone. Data from studies of patients

with known CHD but no ischemic symptoms suggest that treatment with medications, such as beta-blockers, or revascularization can improve outcomes over no treatment, but whether the same results would be found in a population of patients with no previous CHD history is unclear.[80]

Even if we assume that the additional information is helpful, few studies have examined the cost-effectiveness of screening for ACAD. In 1989, Sox and colleagues used a decision analysis model to estimate the effectiveness and cost-effectiveness of exercise testing in asymptomatic adults.[81] Their model was structured so that the main benefit of screening was achieved through detection of patients with severe disease who would benefit from revascularization.

They found that screening average 60 year old men had a cost per life-year saved of $24,600; for women, the cost was $47,606. For 40 year olds, the cost-effectiveness ratios were much larger: $80,349 per life year saved for men and $216,496 per life year saved for women. The presence or absence of CHD risk factors affected the cost-effectiveness ratios. For 60 year old men with no risk factors, the cost per life year saved was $44,332; for men with 1 or more CHD risk factors, it was $20,504. The authors concluded that routine screening was not warranted in general; for persons at increased risk for CHD (e.g., older men with one or more risk factors), however, it may be beneficial.

Although such projections about cost-effectiveness from models are helpful, a better appreciation of the actual benefit from screening would come from one or more adequately powered randomized trials of screening compared to traditional risk factor-based management using global CHD risk assessment and enrolling a broad spectrum of patients, including a sufficient number of women.

Future research also needs to examine the independent prognostic information from EBCT in the context of accurate measurement of traditional risk factors and a sufficient period of follow-up. The large Multi-Ethnic Study of Atherosclerosis (MESA) study,[82] which is currently ongoing, will help in this regard. Studies examining how providers and patients apply the additional information about risk from tests for ACAD would also be helpful. Finally, better information about the adverse effects of screening is required if researchers are to perform well-informed cost-effectiveness analyses of ACAD screening compared with risk-factor-based decisionmaking.

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Appendix
Peer Review

Peer Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. External reviewers comprised clinicians, researchers, representatives of professional societies, and potential users of the report. The peer reviewers were asked to provide comments on the content, structure, and format of the evidence report and to complete a checklist. The peer reviewers' comments and suggestions formed the basis of our revisions to the evidence report. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

Michael Lauer, MD

Mark Grunwald, MD

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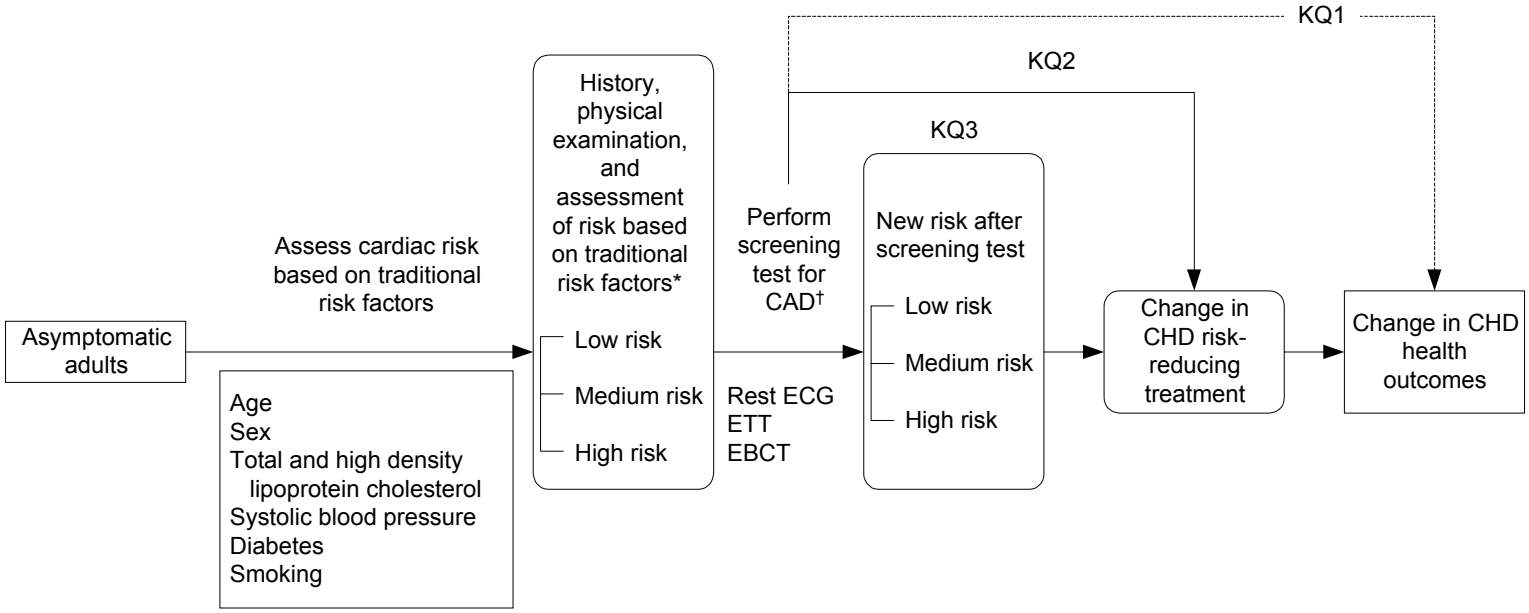
Victor Froelicher, MD

Euan Ashley, MD

Hal Sox, MD

Paolo Raggi, MD

Figure 1. Analytic Framework: Screening for Asymptomatic Coronary Artery Disease



KQ1: Does testing for asymptomatic CAD with ECG, ETT, or EBCT lead to improvement in CHD health outcomes?

KQ2: Does testing for asymptomatic CAD with ECG, ETT, or EBCT lead to increased use of CHD risk-reducing treatments?

KQ3: Do any of the screening tests for asymptomatic CAD (ECG, ETT, EBCT) provide additional prognostic information over and above that from the traditional risk factors?

* Using Framingham-based global CHD risk calculation.

† CAD, coronary heart disease; CHD, coronary heart disease; ECG, resting electrocardiogram; ETT resting electrocardiogram treadmill test; EBCT, electron beam computerized tomography.

Table 1A. Association Between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Q waves

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of Finding	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Pedoe et al., 1978[17]	8,228*	40-59 100%	Employed men in the UK	4	1.0%	4	None or not reported
Reunanen et al., 1978[33]	3,600*	30-59 100%	Men ages 30 to 59	5	Not reported	1	Age and follow-up time
Rose et al., 1978[16]	15,974†	40-64 100%	British civil servants living in London, England	5	1.6%	4.2‡ (2.3-8.0)	Age
Kannel and Abbott, 1986[37]	Not reported	Not reported	Framingham residents (mainly white)	10	Men 4.2%§ Women 2.5%§	Men, 3.2 Women, 4.8	Age
Sigurdsson et al., 1996[35]	9,139‖	35-60 100%	Residents of Reykjavik, Iceland	4-24	Not reported	7.0 (4.9-10.0)	Age, blood pressure, lipids, blood sugar, smoking
Menotti et al., 1997[14]	22,553	30-69 54%	Italians	6	Men 0.2-1.4%¶ Women 0.4-1.5%¶	1.25 (0.26-5.31) 9.88 (1.05-92.6)	ECG abnormality, age, SBP, chol, smoking, BMI
Menotti et al., 2001[15]	1,785	65-84 100%	Europeans	10	6.8%	2.25 (1.43-3.55)	Age, SBP, chol, BMI, smoking, cohort (country)

*Asymptomatic subset of study population.
†Approximate number of asymptomatic subjects.
‡Point estimate of relative risk and confidence intervals calculated by Sox et al., 1989.[42]
§Two-year cumulative incidence.
‖Total study population; performed subset analysis on group of asymptomatic men.
¶Varies with age.

Table 1B. Association Between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Left Ventricular Hypertrophy

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of LVH (VO) or LVH (VS)	Relative Risks for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Pedoe et al., 1978[17]	8,228	40-59 100%	Employed men in the UK	4.3	VO, 2.5%	1.6	Not reported
Rabkin et al., 1982[34]	3,983	15-64 100%	Pilots in the Royal Canadian Air Force during WWII	30	VS, 6.4%	3.1*	Age
Knutsen et al., 1988[31]	7,682	45-68 100%	Men of Asian descent living in Honolulu, Hawaii	12	VS, 0.6%	11.4 (5.9-22.5)	Age
Dunn et al., 1990[20]	3,275	Mean, 50 49%	Hypertensive patients of Glasgow Blood Pressure Clinic, UK	6.5	VO, men 21.7% VS, men 12.8% VO, women 12.7% VS, women 8.8%	2.7* 4.0* 2.0* 2.3*	Age
Kannel et al., 1992[18]	5,209	30-62	Framingham residents (mainly white)	30	VS, men 9.7% VS, women 5.6%	5.6* 4.7* (morbidity) 5.0* 7.4* (morbidity)	Age
Sullivan et al., 1993[23]	4,824	Mean, 55 57%	Memphis residents (mainly white)	5	VS, 5.2%†	1.9	Not reported
Sutherland et al., 1993[27]	642 Whites 328 Blacks	35-74 100%	Black and white men in Charleston, SC	30	VS, white 0.9% VS, black 9.8%	5.61 (1.25 – 25.22) 1.10 (0.46 – 2.68)	Age, SBP, chol, BMI, smoking, DM, education

Table 1B. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Left Ventricular Hypertrophy (continued)

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of LVH (VO) or LVH (VS)	Relative Risks for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Kahn et al., 1996[21]	459	75-85 35%	Bronx residents (mainly white)	6	VS, 9.2%	2.0 (1.16-3.46) 1.7 (0.90-3.27) (morbidity)	Age, sex, HTN, diabetes, BMI, cholesterol, digoxin use, cardiomegaly on chest x-ray, smoking, prior MI‡
Menotti et al., 1997[14]	22,553	30-69 54%	Italians	6	VO, men 5.1-7.4%§ VS, men 0.5% VO, women 1.5-4.2%§ VS, women 0.5%	1.62 (0.86-3.05) 6.51 (2.69-15.8) 5.14 (0.94-28.1) 14.6 (1.57-?)	ECG abnormality, age, SBP, chol, smoking, BMI
De Bacquer et al., 1998[13]	9,954	25-74 52%	Belgian residents (mainly white)	10	VS, men 0.8% VS, women 0.5%	1.8 (0.4-7.6) 1.9 (0.3-14.1)	Age, diabetes, BMI, SBP, total cholesterol, HDL, smoking, anti-HTN meds, other major ECG changes
Verdecchia et al., 1998[24]	1,717	Mean, 52 51%	Hypertensive Italians	3.3	VS, 17.8%‖	4.2 (2.1-8.7)	Age, diabetes, previous CVD events¶
Brown et al., 2000[19]	7,924	25-74 mean, 49.2 47.6%	NHANES II (1976-92) (10% black)	16.8	VS, 1.3%	2.0 (1.2-3.5)	Age, sex, diabetes, BMI, SBP, total cholesterol, smoking, history of CVD#
Menotti et al., 2001[15]	1,785	65-84 100%	Europeans	10	VO, 15% VS, 4.9%	1.05 (0.68–1.3) 1.65 (0.93-2.92)	Age, SBP, chol, BMI, smoking, cohort (country)

Table 1B. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Left Ventricular Hypertrophy (continued)

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of LVH (VO) or LVH (VS)	Relative Risks for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Jones et al., 2002[30]	10,368 white 3,694 blacks	45-64 43%	Blacks and whites in MD, NC, MN, MS	10	VS, white men 0.8% VS, white women 0.9% VS, black men 5.9% VS, black women 5.3%	1.6 (0.8-0 3.4)** 2.2 (0.8–5.9)** 2.0 (1.1–3.6)** 5.9 (3.6–9.7)**	Age
Larsen et al., 2002[22]	11,634	25-74 45%	Copenhagen City residents (mainly white)	21	VO, men 19.3% VS, men 1.1% VO, women 5.6% VS, women 0.6%	1.1 (0.9-1.2) 1.9 (1.5-2.5) 1.1 (0.9-1.2) 1.9 (1.5-2.5)	Sex, diabetes, BMI, DBP, heart rate, total cholesterol, smoking

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence intervals; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; HTN, hypertension; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; meds, medications; MI, myocardial infarction; SBP, systolic blood pressure; VO, Voltage only; VS, Voltage with Strain pattern.

*Confidence intervals not reported, but p value reported to be < 0.05.
†Includes LVH by voltage criterion only and persons with LVH by voltage criterion and strain pattern.
‡13.9% reported history of previous myocardial infarction.
§ Varies with age.
‖ LVH diagnosis using the Perugia score.
¶2% reported previous history of cardiovascular events.
#4% reported history of previous myocardial infarction.
**Hazard ratio for all CHD events (including mortality).

Table 1C. Association Between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: ST Segment Depression

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of ST Segment Depression	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Pedoe et al., 1978[17]	8,228	40-59 100%	Employed men in the UK	4.3	2.3%	3.5	Not reported
Rose et al., 1978[16]	15,974*	40-64 100%	British civil servants living in London, England	5	0.9%	2.4† (0.8-7.0)	Age
Rabkin et al., 1982[34]	3,983	15-64 100%	Pilots in the Royal Canadian Air Force during WWII	30	16.9%	4.7	Age
Knutsen et al., 1988[31]	7,682	45-68 100%	Men of Asian descent living in Honolulu, Hawaii	12	Major, 1.3% Minor, 0.5%	6.2 (3.5-11.1) 3.0 (1.9-4.8) (event) 3.1 (1.1-8.6) 2.1 (0.9-4.4) (event)	Age
Sutherland et al., 1993[27‡]	642 whites 328 blacks	35-74 100%	Black and white men in Charleston, SC	30	White 8.2 % Black 29.4%	1.77 (1.23-2.55) 1.12 (0.81-1.56)	Age, SBP, chol, BMI, smoking, DM, education
Sigurdsson et al., 1996[36]	9,139§	35-60 100%	Residents of Reykjavik, Iceland	4-24	2% to 30% varied by age	2.0 (1.6- 2.5)	Age, blood pressure, lipids, blood sugar, smoking
Menotti et al., 1997[14‡]	22,553	30-69 54%	Italians	6	Men 2.0-7.2%‖ Women 4.3-9.6%‖	3.76 (2.26-6.28) 1.03 (0.13-8.46)	ECG abnormality, age, SBP, chol, smoking, BMI
De Bacquer et al., 1998[13]	9,954	25-74 52%	Belgian residents (mainly white)	10	Men 1.6% Women 2.7%	3.5 (1.8-6.8) 2.6 (1.0-7.0) (event)	Age, BMI, SBP, total cholesterol, HDL, diabetes, smoking, anti-HTN meds, other major ECG changes

Table 1C. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: ST Segment Depression

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of ST Segment Depression	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Menotti et al., 2001[15‡]	1,785	65-84 100%	Europeans	10	22%	1.53 (1.09-2.15)	Age, SBP, chol, BMI, smoking, cohort (country)
Larsen et al., 2002[22]	11,634	25-74 45%	Residents of Copenhagen, Denmark (mainly white)	21	Men 1.2% Women 2.2%	1.7 (1.4-2.2) (death) 1.8 (1.4-2.3) (events)	SBP, DBP, HR, BMI, total cholesterol, diabetes, smoking, sex, alcohol use, physical exercise, family history of CHD

BMI, body mass index; CHD, coronary heart disease; CI, confidence intervals; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiographic; HDL, high-density lipoprotein cholesterol; HR, heart rate; HTN, hypertension; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; SBP, systolic blood pressure.

*Asymptomatic subset of study population.
†Point estimate of relative risk and confidence intervals calculated by Sox et al., 1989.[42]
‡Includes T-wave inversion
§Total study population; performed subset analysis on group of asymptomatic men.
‖Varies with age

Table 1D. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: T Wave Inversions

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of T Wave Inversion	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Pedoe et al., 1978[17]	8,228	40-59 100%	Employed men in the UK	4.3	6.0	3.8	Not reported
Rose et al., 1978[16]	15,974	40-64 100%	British civil servants living in London, England	5	3.3%	3.2* (1.9-5.3)	Age
Knutsen et al., 1988[31]	7,682	45-68 100%	Men of Asian descent living in Honolulu, Hawaii	12	Major, 2.3% Minor, 1.2%	5.1 (3.1-8.3) 2.5 (1.7-3.7) (event) 3.5 (1.7-7.5) 3.0 (1.8-5.0) (event)	Age
De Bacquer et al., 1998[13]	9,954	25-74 52%	Belgian residents (mainly white)	10	Men 6.1% Women 9.6%	2.1 (1.2-3.4) 1.9 (0.9-3.9)	Age, BMI, SBP, total cholesterol, HDL, diabetes, smoking, anti-HTN meds, other major ECG changes
Larsen et al., 2002[22]	11,634	25-74 45%	Residents of Copenhagen, Denmark (mainly white)	21	Men 5.3% Women 5.3%	1.5 (1.3-1.8) 1.5 (1.3-1.7) (event)	SBP, DBP, HR, BMI, total cholesterol, diabetes, smoking, sex, alcohol use, physical exercise, family history of CHD

BMI, body mass index; CHD, coronary heart disease; CI, confidence intervals; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiographic; HDL, high-density lipoprotein cholesterol; HTN, hypertension; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; SBP, systolic blood pressure.

*Point estimate of relative risk and confidence intervals calculated by Sox et al., 1989.[39]

Table 1E. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Ventricular Ectopic Activity

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of Ventricular Ectopy	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Pedoe et al., 1978[17]	8,228	40-59 100%	Employed men in the UK	4.3	1.3%	0.8 (0.04-12.3)	Not reported
Reunanen et al., 1978[33]	3,660*	Not reported	Men aged 30-59	5	Not reported	3.5	Not reported
Rose et al., 1978[16]	15,974†	40-64 100%	British civil servants living in London, England	5	1.3%	3.4‡ (1.5-7.5)	Age
Cullen et al., 1982[32]	1,497†	40-79 50%	Men and women	13	3%	2.1	Not reported
Rabkin et al., 1982[34]	3,983	15-64 100%	Pilots in the Royal Canadian Air Force during WWII	30	11%	4.0	Age
Knutsen et al., 1988[31]	7,682	45-68 100%	Men of Asian descent living in Honolulu, Hawaii	12	0.8%	4.0 (1.7-9.6) 1.4 (0.6-3.0) (event)	Age

*Approximate number of asymptomatic subjects.
†Asymptomatic subset of study population.
‡Point estimate of RR and confidence intervals calculated by Sox et al., 1989.[39]

Table 1F. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Major ECG Changes

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of Major ECG Changes	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Liao et al., 1988[25]*	17,633	40-64 66%	White residents of Chicago	11.5	Men 9.6% Women 12.9%	3.7† 1.9†	Age, diabetes, DBP, cholesterol, smoking, anti-HTN meds
Knutsen et al., 1988[31]‡	7,682	45-68 100%	Men of Asian descent living in Honolulu, Hawaii	12	5.6%	2.9 (1.9-4.4) 1.8 (1.4-2.4) (event)	Age
Hames et al, 1993[26]§	2,216	≥40 47%	Black and white residents of Evans Co., GA	20	Men 5-20%‖ Women 5-30%‖	1.9 (1.03-3.49)¶ 1.75 (0.87-3.49)¶	Age, SES, race, prevalent CHD, SBP, smoking, chol, BMI, minor ECG changes
Sutherland et al., 1993[27]§	642 Whites 328 Blacks	35-74 100%	Black and white men in Charleston, SC	30	White 6.9% Black 13.7%	2.72 (1.47-5.04) 1.95 (0.93-4.11)	Age, SBP, chol, BMI, smoking, DM, education, ECG abnormality
De Bacquer et al., 1998[13]*	9,954	25-74 52%	Belgian residents (mainly white)	10	Men 3.7% Women 3.1%	2.1 (1.2-3.7) 3.1 (1.4-6.9)	Age, diabetes, BMI, SBP, total cholesterol, HDL, smoking, anti-HTN meds, other ECG changes

BMI, body mass index; CHD, coronary heart disease; CI, confidence intervals; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; HTN, hypertension; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MC, Minnesota code; meds, medications; MI, myocardial infarction; SBP, systolic blood pressure.

*Major ECG changes defined as: Major ST depression (MC 4.1, 4.2), Major T wave inversion (MC 5.1, 5.2), CHB (MC 6.1), 2° AVB (MC 6.2), LBBB (MC 7.1), RBBB (C 7.2), frequent PVCs (MC 8.1), aflutter/afib (MC 8.3).

†No confidence interval reported, but $P < 0.01$.

‡Major ECG changes defined as: Major ST depression (MC 4.1, 4.2), Major T wave inversion (MC 5.1, 5.2), CHB (MC 6.1), 2° AV block (MC 6.2), LBBB (MC ;7.1), RBBB (MC 7.2), frequent PVCs (MC 8.1), unspecified intraventricular block (MC 7.4), aflutter/afib (MC 8.3).

§Major ECG changes defined as: Major ST depression (MC 4.1, 4.2), Major T wave inversion (MC 5.1, 5.2), LBBB (MC 7.1), RBBB (MC 7.2), frequent PVCs (MC 8.1), aflutter/afib (MC 8.3).

‖Varies with age and race.

¶Estimates for the 40 to 64 age range.

Table 1G. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Minor ECG Changes

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of Minor ECG Changes	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Kannel et al., 1987[28]*	5,127	44-74 44%	Framingham residents (mainly white)	30	Men 8.5% Women 7.7%	3.7† 2.0† (event) 3.0† 2.0† (event)	Age
Knutsen et al., 1988[31]‡	7,682	45-68 68%	Men of Asian descent living in Honolulu, Hawaii	12	10%	2.2 (1.5-3.2) 1.4 (1.1-1.7) (event)	Age
Liao et al., 1988[25]§	17,633	40-64 55%	White residents of Chicago	11.5	Men 7.3% Women 4.5%	2.1‖ 1.5¶	Age, DBP, cholesterol, smoking, diabetes, anti-HTN meds
Hames et al., 1993[26]§	2,216	≥40 47%	Black and white residents of Evans Co., GA	20	Men 20-40# Women 20-40%#	1.22 (0.78-1.92) 131 (0.56-2.57)	Age, SES, race, prevalent CHD, SBP, smoking, chol, BMI, major ECG changes
Sutherland et al., 1993[27]§	642 whites 328 blacks	35-74 100%	Black and white men in Charleston, SC	30	White 13.2% Black 16.0%	1.25 (0.92-1.70) 0.79 (0.52-1.19)	Age, SBP, chol, BMI, smoking, DM, education, ECG abnormality
De Bacquer et al., 1998[13]**	9,954	25-74 52%	Belgian residents (mainly white)	10	1.9% 1.5%	1.0 (0.6-1.6) 1.6 (0.8-3.1)	Age, diabetes, BMI, SBP, total cholesterol, HDL, smoking, anti-HTN meds, other ECG changes

Table 1G. Association between Resting ECG Abnormalities and Risk of Coronary Heart Disease Mortality in Asymptomatic Individuals: Minor ECG Changes (continued)

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Prevalence of Minor ECG Changes	Relative Risk for CHD Mortality (95% CI)	Relative Risk Adjusted for the Following Variables
Daviglus et al., 1999[29††]	1,673	40-55 100%	Men employed at the Western Electric Co. in Chicago	29	1.2%[#]	2.4 (1.4-4.1)	Age, education, SBP, smoking, cholesterol, BMI and BMI2

BMI, body mass index; CHD, coronary heart disease; CI, confidence intervals; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; HTN, hypertension; LDL, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MC, Minnesota code; MI, myocardial infarction; SBP, systolic blood pressure

*Minor ECG changes defined as: In the absence of high R wave, there was ST segment depression > 1 mm and/or abnormal T wave flattening or inversion.
†For ages 35-64 years. No confidence intervals reported, but $P < 0.001$.
‡Minor ECG changes defined as: Borderline Q wave (MC 1.3), borderline ST depression (MC 4.3), borderline T wave inversion (MC 5.3), 1° AVB (MC 6.3), high R wave (MC 3.1, 3.2), LAD (MC 2.1), RAD (MC 2.2).
§Minor ECG changes as defined as: Borderline Q wave (MC 1.3), borderline ST depression (MC 4.3), borderline T wave inversion (MC 5.3), 1° AVB (MC 6.3), high R wave (MC 3.1, 3.2), LAD (MC 2.1), RAD (MC 2.2), low QRS voltage (MC 9.1).
‖$P < 0.01$.
¶$P > 0.05$.
#Varies with age and race.
**Minor ECG changes defined as Borderline Q wave (MC 1.3), borderline ST depression (MC 4.3), borderline T wave inversion (MC 5.3), high R wave (MC 3.1, 3.2), LAD (MC 2.1), RAD (MC 2.2), low QRS voltage (MC 9.1).
††Minor ECG changes defined as: Mild ST depression (MC 4.3, 4.4), mild T wave abnormality (MC 5.3, 5.4).
‡‡The percentage of men with three or more ECG with minor abnormalities within the follow-up period.

Table 2. Association between Abnormal ST Segment Response to Exercise and CHD Events in Asymptomatic Individuals

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Technique	Prevalence of Abnormal Test (%)	Relative Risk for CHD Events with Abnormal ST Segment Response	Sensitivity for CHD Events	Positive Predictive Value of Abnormal ST Response	Relative Risk Adjusted for the Following Variables
Allen et al., 1980[44]	888	Adults 65%	Men and Women	5	Maximal Ellestad	Men 14% Women 5%	3.3* 1.8†	38 10	15.7 6	Not reported
Cumming et al., 1975[46]	510	40-65 100%	Civil servants in Canada	3	Maximal cycle ergometry	12.0%	10.0	42	25	Not reported
Ekelund et al., 1989;[47] Gordon, et al., 1986[43]	3,640	35-59 100%	Lipid Research Clinics Study (white men)	8.1	Submaximal Modified Bruce	8.3%	Placebo group 5.7 (2.7-12.2) Cholesty-ramine group 4.9 (2.2-10.8)	30‡	7.1‡	Age, LDL, HDL, SBP, smoking, family history
Fleg et al., 1990[48]	407	40-90 mean = 60	Residents of Baltimore, Maryland (mainly white)	4.6	Maximal treadmill with Thallium Modified Balke	6.0%§ 16.0%‖	3.6 (1.6-8.1) 2.4¶	28 40	48 24	Age, sex, HTN, FBS, total cholesterol, BMI, smoking, exercise duration

Table 2. Association between Abnormal ST Segment Response to Exercise and CHD Events in Asymptomatic Individuals (continued)

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Technique	Prevalence of Abnormal Test (%)	Relative Risk for CHD Events with Abnormal ST Segment Response	Sensitivity for CHD Events	Positive Predictive Value of Abnormal ST Response	Relative Risk Adjusted for the Following Variables
Froelicher et al., 1974[49]	1,390[#]	20-52	Aircrewmen in the US Air Force evaluated for flying status	6.3	Maximal treadmill	10.0%	14.3	60.9	20	Not reported
Giagnoni et al., 1983[50]	514	18-65 73%	Factory workers in Italy	6	Submaximal Supine cycle ergometry	Not reported	5.5 (2.8-11.2)	62	15	Age, SBP, smoking, coronary risk index
McHenry et al., 1984[52]	916	27-55 mean = 37 100%	Employees of the Indiana State Police Department	12.7	Maximal treadmill Modified Balke	2.5%	7.4	39	34	Not reported
Rautaharju et al., 1986[53]	6,205**	35-57 100%	MRFIT	7	Submaximal	12.2%	3.5[††]	Not reported	36[††]	Age, DBP, cholesterol, number of cigarettes smoked daily

Table 2. Association between Abnormal ST Segment Response to Exercise and CHD Events in Asymptomatic Individuals (continued)

Authors and Year	No. of Subjects in Study	Age Range (years) and Sex (% male)	Participants	Follow-up (years)	Technique	Prevalence of Abnormal Test (%)	Relative Risk for CHD Events with Abnormal ST Segment Response	Sensitivity for CHD Events	Positive Predictive Value of Abnormal ST Response	Relative Risk Adjusted for the Following Variables
Gibbons et al., 2000[51]	25,927	20-82 mean = 42.9 100%	Patients of a preventive medicine clinic in Texas (mainly white)	8.4	Maximal treadmill Modified Balke	No RF, 3.0%	21 (6.9-63.3)	60	2.2	Age
						>1 RF, 7.0%	9	61	7.7	
Jouven et al., 2000[45]	6,101	42-53 100%	Frenchmen in Paris Civil Service	23	Bicycle ergometry	4.4%	2.6 (1.93-3.59)[††]	10	17-25	Age, BMI, HR at rest, smoking, physical activity, DM, total chol, PVC's

[*]No confidence intervals reported, but reported statistically significant with $P < 0.05$.
[†]No confidence intervals reported, but reported not statistically significant with $P > 0.05$.
[‡]Sensitivity and positive predictive value for CHD death.
[§]Concordant positive results for both the thallium scintigraphy and exercise ECG.
‖Positive test for exercise ECG only.
¶Confidence interval not reported, but $P < 0.05$.
#Includes 63 subjects with history suggestive of CHD.
**Refers to the subset of patients randomized to usual care.
[††]Relative risk and positive predictive value for CHD death, $P < 0.05$.

Table 3. Yield of Screening Tests under Different Assumptions about Pretest Probabilities and Sensitivity and Specificity Rates

Case 1. Use of screening tests in a hypothetical cohort of 1,000 people in whom the prevalence of disease is 1% (i.e. 10 people have the disease, 990 do not)
1a. Using a screening test "A" with 70% sensitivity and 80% specificity, the following results will be expected: 7 people with the disease will be detected (true positives) 3 people with the disease will be missed (false negatives) 792 people without disease will test negative (true negatives) 198 people without disease will test positive (false positives) Probability of disease in those testing positive = 3.4% Probability of disease in those testing negative = 0.4%
1b. Using a better screening test "B" with 80% sensitivity and 90% specificity, the following results will be expected: 8 people with the disease will be detected (true positives) 2 people with the disease will be missed (false negatives) 891 people without disease will test negative (true negatives) 99 people without disease will test positive (false positives) Probability of disease in those testing positive = 7.5% Probability of disease in those testing negative = 0.2%
Case 2. Use of screening tests in a hypothetical cohort of 1,000 people in whom the prevalence of disease is 10% (i.e. 100 people have the disease, 900 do not).
2a. Using a screening test "A" with 70% sensitivity and 80% specificity, the following results will be expected: 70 people with the disease will be detected (true positives) 30 people with the disease will be missed (false negatives) 720 people without disease will test negative (true negatives) 180 people without disease will test positive (false positives) Probability of disease in those testing positive = 28% Probability of disease in those testing negative = 4%
2b. Using a better screening test "B" with 80% sensitivity and 90% specificity, the following results will be expected: 80 people with the disease will be detected (true positives) 20 people with the disease will be missed (false negatives) 810 people without disease will test negative (true negatives) 90 people without disease will test positive (false positives) Probability of disease in those testing positive = 47% Probability of disease in those testing negative = 2.4%