Exercise Tolerance Testing to Screen for Coronary Heart Disease: A Systematic Review for the U.S. Preventive Services Task Force

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Coronary heart disease 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 coronary heart disease. Coronary heart disease can also present as angina, but only 20% of acute coronary events are preceded by long-standing angina.[1] An estimated 1 to 2 million middle-aged men have asymptomatic but physiologically significant coronary artery obstruction, which puts them at increased risk for coronary heart disease events.[2,3] The economic burden of coronary heart disease is also substantial. The direct and indirect costs of coronary heart disease in the United States are projected to total $129.9 billion for 2003.[1] The clinical and economic impact of coronary heart disease is the basis for considerable public health interest in the development of effective strategies to reduce the incidence of coronary heart disease events.

In 1996, the U.S. Preventive Services Task Force considered use of resting electrocardiography or exercise tolerance testing to detect asymptomatic coronary artery disease and prevent coronary heart disease events.[4] The Task Force found insufficient evidence to recommend for or against using these tests to screen middle-aged and older men and women. They recommended against screening children, adolescents, or young adults.

To update the evidence review and recommendations on screening for asymptomatic coronary artery disease, the Task Force 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. The complete review considers resting electrocardiography, exercise tolerance testing, and electron-beam computed tomography for coronary calcium and is available at www.ahrq.gov/clinic/serfiles.htm.[5] This article describes the findings on exercise tolerance testing only. The recommendations and rationale of

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the Task Force on screening for asymptomatic coronary artery disease are available at www.preventiveservices.ahrq.gov.[6]

Clinicians can use 2 general approaches to prevention of morbidity and mortality from coronary heart disease. The first approach involves screening for and treating the traditional modifiable risk factors for coronary heart disease, such as hypertension, abnormal blood levels of lipids, diabetes, cigarette smoking, physical inactivity, and diet. Such an approach may incorporate explicit calculations of the patient's risk for coronary heart disease events by using risk prediction equations derived from the Framingham Heart Study or other cohort studies.[7] The second strategy involves supplementation of screening based on traditional risk factors with additional tests to provide further information about future risk for coronary heart disease or to detect severe blockages of the coronary arteries that might warrant treatment.

Detection of increased risk for future coronary heart disease events may lead to intensified use of risk-reducing treatments. Some risk-reducing treatments are directed at traditional risk factors (for example, therapy with statins for hyperlipidemia), whereas others are not (for example, aspirin therapy). Revascularization by using coronary artery bypass graft surgery or percutaneous coronary intervention seeks to treat blockages of the coronary arteries. Whether revascularization will reduce the risk for coronary heart disease events in persons identified by screening is unknown.

Exercise tolerance testing is widely used as a diagnostic test in the initial evaluation of patients with symptoms suggestive of myocardial ischemia and in persons with previously recognized coronary heart disease. Although exercise tolerance testing has been applied and studied as a screening or prognostic test in asymptomatic persons, its utility in this group is controversial. The best measure of the value of screening exercise tolerance testing would come from studies that examined whether patients randomly assigned to undergo such tests had fewer coronary heart disease events or received more appropriate risk-reducing therapies than did patients assigned to receive treatments after standard risk factor assessment.

Such direct evidence is not available. However, indirect evidence suggests that screening exercise tolerance testing may be helpful in guiding medical management.[8] In the Multiple Risk Factor Intervention Trial Research study, high-risk male participants were randomly assigned to receive a multimodal intervention to reduce cardiovascular risk or usual care. Among participants with an abnormal baseline result on exercise tolerance testing, those who received the intervention had a significantly lower rate of mortality from coronary heart disease during follow-up than did the group that received usual care. No effect was seen among men with a normal baseline result on exercise tolerance testing. It is not clear from the report of this post-hoc analysis whether the cardiovascular risk profiles of participants with an abnormal result on exercise tolerance testing at baseline differed significantly from those of participants with a normal result.

Because direct evidence on possible benefits of screening exercise tolerance testing is lacking, we used data from observational cohort studies to examine whether screening exercise tolerance testing could detect clinically significant asymptomatic obstructions of the coronary arteries or provide greater independent prognostic information about the risk for future coronary heart disease events than would be obtained solely by standard history, physical examination, and measurement of traditional risk factors. We also sought information about harms of screening, including the likelihood of false-positive results and the effect of labeling a person as being "at high risk."

Methods

Literature Review

To identify the relevant literature, we searched the MEDLINE database from 1966 through February 2003 by using the exploded Medical Subject Headings *coronary heart disease, exercise test,* and *mass screening* and the keywords *asymptomatic* and *screening.* We limited the search to English-language articles on human subjects. To supplement our literature searches, we hand-searched the bibliographies of key articles, used other recent systematic reviews when available, and included references provided by expert reviewers that had not been identified by other mechanisms.

Study Eligibility and Data Abstraction

Two reviewers examined the abstracts of the articles identified in the initial MEDLINE search and selected a subset for a full-text review. The same reviewers examined the full text of the selected articles to determine final eligibility. One reviewer extracted information from eligible articles into evidence tables, and another reviewer checked the tables. They resolved disagreements by consensus.

To be eligible, studies had to have been performed in participants with no history of cardiovascular disease or provide subset analysis for this group. Included studies on the detection of severe coronary artery obstruction reported the total number of persons screened to obtain the sample of persons with an abnormal result on exercise tolerance testing and the proportion of persons who were found to have coronary heart disease on angiography. The yield of exercise tolerance testing screening was determined by dividing the number of participants found to have abnormal results on angiography by the total number screened.

For the prognostic benefit of exercise tolerance testing, included studies reported the independent value of the test for predicting coronary heart disease events. We included studies that examined the prognostic benefit of exercise testing by using several variables, including ST-segment depression, functional capacity, chronotropic incompetence, heart rate recovery, and development of exercise-induced premature ventricular contractions. We also included studies that used nuclear medicine imaging to detect ischemia. We excluded studies that did not use statistical methods to control for the effect of other risk factors (such as age or systolic blood pressure) on the estimate of the prognostic strength of a positive result of exercise tolerance testing. Table 1 shows information on excluded studies.

The studies used different means of characterizing the prognostic benefit of screening with exercise tolerance testing. Many studies reported outcomes in terms of independent relative risk associated with a positive (versus a negative) screening test. Others 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 1 point in time.

To assess whether a relationship exists between sensitivity of exercise tolerance testing for future coronary heart disease and duration of follow-up, we examined the correlation between reported sensitivity and mean duration of follow-up by using STATA statistical software, version 7.0 (Stata Corporation, Chicago, Illinois).

Data Summary and Quality Assessment

We rated the quality of the included articles according to criteria developed by the U.S. Preventive Services Task Force Methods Work Group.[9] Tables 3 and 4 show information only from studies judged "good." For the studies shown in Table 2, we considered several factors that affect quality, chiefly the percentage of patients with a positive exercise tolerance testing who underwent catheterization and how completely outcomes were assessed. We used the final set of eligible articles to create evidence tables and produce the larger evidence report, which also included evaluation of resting electrocardiography and electron-beam computed tomography to detect coronary calcium. The full evidence report was subjected to external peer review and revised on the basis of the comments received; we used the revised report as the basis for this article.

Role of the Funding Agency

This evidence report was funded through a contract to the RTI-University of North Carolina Evidence-based Practice Center from the Agency for Healthcare Research and Quality. Staff of the funding agency contributed to the study design, reviewed draft and final manuscripts, and made editing suggestions.

Results

We identified 713 articles for review. We reviewed the abstracts and retained 55 articles that examined the diagnostic or prognostic significance of screening with exercise tolerance testing. After full article review, we kept 31 articles representing 29 studies that met the inclusion criteria.[10–40] We identified another 11 articles for inclusion through review of reference lists and input of expert reviewers.[8,41–50] Table 1 lists articles that were excluded during review of the full articles and the reason for exclusion.[51–74]

We found no studies that directly tested whether screening asymptomatic persons with exercise tolerance testing improves coronary heart disease and mortality. Similarly, we found no studies that examined the effect of screening with exercise tolerance testing on the subsequent use of risk-reducing interventions and behaviors. However, we identified fair- or good-quality observational cohort studies of asymptomatic adults that prospectively evaluated the value of exercise tolerance testing in detecting asymptomatic coronary artery obstruction[14–18,22,23,25,27,28,30,31,38,75] and predicting future coronary heart disease events, such as angina, myocardial infarction, and sudden death.[8,10–13,19–21,26,29,32–36,38–50] We also identified 3 good-quality studies that estimated the cost effectiveness of exercise tolerance testing to identify asymptomatic, severe, prevalent coronary heart disease.[24,28,37]

Exercise Tolerance Testing to Detect Asymptomatic Prevalent Disease

We identified 13 studies in 14 articles that examined the utility of exercise tolerance testing to detect asymptomatic coronary artery obstruction (Table 2).[14,15,18,22,23,25,27,28,30,31,38,75] In these studies, the prevalence of abnormal exercise tolerance testing, usually defined as exercise-induced ST-segment depression of 1 mm or more, ranged from about 3% among aviators who were presumed healthy[16] to 29% in a sample of diabetic persons in Finland.[15,75] A portion of the participants with a positive exercise tolerance testing in each study (1% to 60%) proceeded to evaluation with cardiac catheterization. Screening with exercise tolerance testing yielded angiographically demonstrable coronary heart disease, usually defined as greater than 50% stenosis of a major coronary artery, in a minority of the screened patients.

The yield of screening exercise tolerance testing was greater in higher-risk groups. Five studies in 6 articles evaluated diabetic persons,[15,75] those with multiple risk factors,[18,31] those with siblings with coronary heart disease,[17] and those who were prescreened by using a chest pain questionnaire.[25] In these studies, the yield of screening for angiographically demonstrable coronary heart disease ranged from 1.2%[31] to 9%.[15,18] Most cases of coronary artery obstruction identified by screening were single-vessel disease, but up to 2.7% of screened participants had significant left main or three-vessel disease,[18] and as many as 1.7% proceeded to revascularization after screening.[25] Eight studies screened unselected, low-risk patients.[14,16,22,23,27,28,30,38] These studies demonstrated a yield of 0.06% to 1.6% for asymptomatic coronary heart disease on angiography.

Cost Effectiveness

Three studies attempted to estimate the cost-effectiveness of screening to identify prevalent coronary artery obstruction. Sox and colleagues[24] used a decision-analysis model to estimate the clinical effectiveness and cost-effectiveness of exercise testing in asymptomatic adults. Their model was structured so that the benefit of screening was achieved through detection of patients with severe disease who would benefit from revascularization. Only direct costs were considered. Levels were based on reimbursement rates at the time of the study (late 1980s): $165 for exercise testing, $3,595 for angiography, and $31,178 for coronary artery bypass surgery. No discounting rate was given. Screening 60-year-old men had a cost per life-year saved of $24,600; for 60-year-old women, the cost was $47,606. For persons 40 years of age, the cost-effectiveness ratios were much higher: $80,349 per life-year saved for men and $216,496 per life-year saved for women.

The presence or absence of risk factors for coronary heart disease affected the cost-effectiveness ratios. The cost per life-year saved was $44,332 for

Table 1. Excluded Studies

Author, Year (Reference)	Reason for Exclusion
Allen et al, 1980[51]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Aronow et al, 1975[52,53]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Cumming et al, 1975[54]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Elamin et al, 1982[55]	Diagnostic use in symptomatic patients
Fadayomi et al, 1987[56]	Unclear ascertainment of end points
Froelicher et al, 1974[57]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Froelicher et al, 1977[58]	Did not report the total number of persons screened
Gerson et al, 1988[59]	Did not report the independent risk for a positive result on exercise tolerance testing
Gianrossi et al, 1989[60]	Diagnostic use in symptomatic patients
Goodman et al, 1989[61]	Participants had history of cardiovascular disease
Gupta et al, 1983[62]	Did not report independent risk for a positive result on exercise tolerance testing
Hopkirk et al, 1984[63]	Did not report the total number of persons screened
MacIntyre et al, 1981[64]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Manca et al, 1982[65]	Did not report the independent risk for a positive result on exercise tolerance testing
Mark et al, 1989[66]	Participants had history of cardiovascular disease
McHenry et al, 1984[67]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Melin et al, 1981[68]	Diagnostic use in symptomatic patients
Pedersen et al, 1991[69]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Roger et al, 1998[70]	Included symptomatic patients without sub-analysis
Rubler et al, 1987[71]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Selvester et al, 1996[72]	Used a screening protocol that employed multiple technologies
Tubau et al, 1989[73]	No adjustment for the effect of other risk factors on the relative risk for an abnormal result on exercise tolerance testing
Uhl et al, 1981[74]	Did not report the total number of persons screened

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease

Author, Year (Reference)	Sample	Exclusion Criteria	Test	Definition of Abnormal Exercise Electrocardiography Result	Prevalence of Abnormal Exercise Tolerance Test Result
Caralis et al, 1979[27]	3,496 men and women Mean age: NR % men NR	NR	Maximal exercise and thallium scintigraphy	≥2 mm of horizontal ST-segment depression	22/3496 (0.6%)
Piepgrass et al, 1982[16]	771 men in US Air Force flight crew Mean age ±SD, 42 ±5.2 y 100% men	Resting electrocardio-graphic abnormalities, history of chest pain, cardiovascular disease, marked hypertension	Maximal treadmill or two-step double Master's	≥0.1 mV of ST-segment depression 80 ms from the J point or exercise induced arrhythmia	27/771 (3.5%)
Hollenberg et al, 1985[38]	377 US Army officers Mean age 37 y % men NR	Known CHD	Maximal treadmill – US Air Force School Aerospace Medicine Protocol	≥1 mm ST depression during or after exercise or treadmill exercise score <5 units	45/377 (12%)
Boyle et al, 1987[14]	1,174 employees from 2 factories in the United Kingdom Mean age: NR Age range: 19–64 y 95% men	Symptoms of angina, orthopedic problems, hypertension with retinopathy, fainting, fibrillation	Treadmill	Maximal ST/heart rate slope value of >13 mm·beats^{-1} min 10^{-3}	68/1,174 (5.8%)

*Percentages were calculated by the authors of this report.

CAD, coronary artery disease; CHD, coronary heart disease; NR, not reported.

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)				
Definition of Abnormal Cardiac Catheterization Result	**Abnormal Catheterizations/ Total Catheterizations***	**Abnormal Catheterizations/ Abnormal Exercise Tolerance Test Result***	**Abnormal Exercise Tolerance Test Result and Abnormal Catheterizations/ All Screened Persons***	**Quality Grade**
NR	10/15 (66.7%)	10/22 (45.5%)	10/3,496 (0.3%)	Fair
NR	4/19 (21%)	4/27 (14.8%)	4/771 (0.5%) All cases were mild to moderate disease	Fair
≥50% narrowing of the luminal diameter of major epicardial artery	1/10 (10%)	1/45 (2%)	1/377 (0.3%) 1 had 1-vessel disease	Fair
≥75% stenosis of epicardial artery	9/24 (37.5%)	9/68 (13.2%)	9/1,174 (0.8%) 1 patient had coronary artery bypass graft surgery	Fair

continue

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Test	Definition of Abnormal Exercise Electrocardiography Result	Prevalence of Abnormal Exercise Tolerance Test Result
Okin et al, 1988[31]	606 men in the Army Reserve at moderate to high risk by Framingham Risk score Mean age: NR Age: >40 y 100% male	Known or suspected CHD or angina	Modified Balke-Ware with radionuclide scintigram for an abnormal exercise electrocardiogram	≥1 mm ST depression	10/606 (1.7) positive—abnormal exercise electro-cardiogram and scintigram; 52/606 (8.6) inconclusive—abnormal exercise electrocar-diogram and normal scintigram
Koistinen 1990[15,75]	136 diabetic patients in Finland Mean age: 49 y 62% men	Clinical evidence of CHD, use of lipid lowering agents, diabetes mellitus for less than 5 y, retinopathy, renal failure	Maximal bicycle ergometry and thallium scintigraphy	≥1 mm horizontal or downsloping ST-segment depression	40/136 (29%)
Dunn et al, 1991[30]	1,930 patients referred to Cleveland Clinic Foundation for screening exercise tolerance testing in 1987–1988 (5.6% had history of chest pain) Mean age: 49 y 85% men	Known CAD	Symptom-limited exercise electrocardio-graphy, then thallium scintography if results were abnormal	≥1 mm of horizontal or downsloping ST-segment depression, or arrhythmia	155/1,930 (8%)

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)

Definition of Abnormal Cardiac Catheterization Result	Abnormal Catheterizations/ Total Catheterizations*	Abnormal Catheterizations/ Abnormal Exercise Tolerance Test Result*	Abnormal Exercise Tolerance Test Result and Abnormal Catheterizations/ All Screened Persons*	Quality Grade
≥50% narrowing of the luminal diameter	7/10 (70%)	7/10 (70%)	7/606 (1.2%) 2 patients had 3-vessel disease, 2 had 2-vessel disease, 3 had 1-vessel disease	Good
Significant (≥50%) narrowing of the luminal diameter	12/34 (35%)	12/40 (30%)	12/136 (9%) 2 patients had 3-vessel disease, 5 had 2-vessel disease, 5 had 1-vessel disease	Fair
≥50% blockage of any major vessel	25/41 (61%)	25/155 (16.1%)	25/1,930 (1.3%) 6 patients had coronary artery bypass graft surgery	Fair

continue

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Test	Definition of Abnormal Exercise Electrocardiography Result	Prevalence of Abnormal Exercise Tolerance Test Result
Massie et al, 1993[18]	226 men from the San Francisco Veteran's Medical Center, all of whom had hypertension and at least 1 other cardiovascular risk factor Mean age ±SD, 61 ±8 y 100% men	Known cardiac disease history or symptoms, resting electrocardiography abnormalities, paced rhythm, noncardiac limitation to exercise	Standard Bruce with thallium scintigraphy	≥0.1 mV of additional horizontal or downsloping ST-segment depression at 80 ms after the J point	Abnormal exercise electro-cardiogram 67/226 (30%) Abnormal scintigram 41/226 (18%)
Davies et al, 1996[23]	5,000 men from the United Kingdom Mean age: NR 100% men	NR	Modified Balke	1 mV of horizontal or downsloping depression persisting for ≥5 complexes	162/5,000 (3.2%)
Cameron et al, 1997[25]	229 Australians who responded to questionnaire about chest pain Mean age: NR 43% men	Known CAD or negative screening questionnaire	Modified Bruce	Flat ST-segment depression ≥0.15 mV	Men 15/98 (15.3%) women 17/131 (13%)
Pilote et al, 1998[28]	4,334 patients referred to Cleveland Clinic Foundation for screening exercise tolerance testing in 1990–1993 Median age: 51 y 89% men	History of chest pain, heart failure, valvular or congenital heart disease, arrhythmia or digitalis use	Bruce or modified Bruce	≥1 mm horizontal or downsloping ST-segment depression, ≥1 mm ST elevation in leads other than aVR or V1, decrease in blood pressure ≥10 mmHg, typical chest pain, failure to reach target heart rate	633/4,334 (15%)

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)

Definition of Abnormal Cardiac Catheterization Result	Abnormal Catheterizations/ Total Catheterizations*	Abnormal Catheterizations/ Abnormal Exercise Tolerance Test Result*	Abnormal Exercise Tolerance Test Result and Abnormal Catheterizations/ All Screened Persons*	Quality Grade
Intraluminal lesion of ≥50% diameter of vessel in 2 projections	14/26 (54%) 18/21 (86%)	14/67 (21%) 18/29 (62%)	20/226 (9%) 6 patients had left main disease or 3-vessel disease; 5 had 2-vessel disease; 7 had 1-vessel disease	Fair
≥75% stenosis epicardial artery	67/86 (78%)	67/162 (41.4%)	67/5,000 (1.3%) 26 patients had coronary artery bypass graft surgery	Fair
NR	10/13 (77%)	10/32 (31%)	10/229 (4%) 4 patients had coronary artery bypass graft surgery	Fair
Coronary artery disease ≥1 coronary segment with ≥50% stenosis	71/126 (56%)	71/633 (11%)	71/4,334 (1.6%) 19 patients had left main disease or 3-vessel disease	Fair

continue

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)					
Author, Year (Reference)	**Sample**	**Exclusion Criteria**	**Test**	**Definition of Abnormal Exercise Electrocardiography Result**	**Prevalence of Abnormal Exercise Tolerance Test Result**
Livschitz et al, 2000[22]	4,900 male soldiers in the Israeli army ≥39 y Mean age ±SD 43 ±3 y 100% men	Angina, heart failure, valvular disease, congenital heart disease, arrhythmia	Bruce	≥1 mV of horizontal or downsloping ST-segment depression or ≥1.5 mV upsloping ST-segment depression	299/4,900 (6.1%)
Blumenthal et al, 2003[17]	734 primarily white healthy siblings of persons with CAD diagnosed before age 60 in Baltimore Mean age: NR but <60 y "Primarily male"	Known CAD, limitations that precluded testing	Modified Bruce and thallium scintigraphy	NR for exercise tolerance testing	153/734 (21%) (Abnormal exercise electrocardio-gram, scan, or both)

Table 2. Studies of the Use of Exercise Electrocardiography to Detect Asymptomatic Prevalent Coronary Heart Disease (cont)

Definition of Abnormal Cardiac Catheterization Result	Abnormal Catheterizations/ Total Catheterizations*	Abnormal Catheterizations/ Abnormal Exercise Tolerance Test Result*	Abnormal Exercise Tolerance Test Result and Abnormal Catheterizations/ All Screened Persons*	Quality Grade
NR	3/4 (75%)	3/299 (1%)	3/4900 (0.06%) 1 patient had coronary artery bypass graft surgery 2 had 1-vessel disease	Good
Clinically significant CAD: intraluminal lesion of ≥50% diameter	41/105 (39%)	41/153 (27%)	41/734 (5.5%)	Good

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Abnormal Test Result	
					Definition	Prevalence
Giagnoni et al, 1983[36]	514 factory workers in Italy Age range: 18–65 y 73% men	Positive history and physical exam for CVD, resting blood pressure ≥160/95 mm Hg, abnormal resting electrocardiogram	6 y	Submaximal supine cycle ergometry	≥1 mm of horizontal/ downsloping ST-segment depression during or after exercise	NR
MRFIT Trial Research Group, 1985[8] Rautaharju et al, 1986[50]	6,205 men in the upper 10% to 15% Framingham risk score distribution Age range: 35–57 y 100% men	Clinical heart disease, life-limiting conditions, diastolic blood pressure ≥115 mm Hg, cholesterol ≥350 mg/dL	7 y	Submaximal	Computer code ST-segment depression 16 muV-s or more in leads CS5, aVL, aVF, V5 during or after exercise (in electrocardiogram with less than 6 muV-s depression at rest)	12.2%
Gordon et al, 1986[41] Ekelund et al, 1989[26]	3,640 white men in Lipid Research Clinics Prevalence Survey in United States and Canada Mean age: 47 y Age range: 35–59 y 100% men	Evidence of CHD by history, resting electrocardiogram, and physician exam. Secondary hyperlipidemia, BMI >32.1 kg/m^2, blood pressure ≥165/105 mm Hg with antihypertensive or cardiovascular medication; diabetes mellitus	8.1 y	Submaximal modified Bruce	≥1 mm of ST-segment depression or elevation or computer-ST integral decreased or increased ≥10 muV-s from resting value	8.3%

*CHD death.

† All-cause death.

‡ For CHD events occurring during exercise.

§ Minnesota code 11.1 = ≥1 mm J-point depression with flat or downsloping ST segment in most complexes in any lead except aVR; Minnesota code 11.2 = horizontal or downsloping ST-segment depression of 0.5–1.0 mm; Minnesota code 11.4 = J-point depression of ≥1 mm with upslopng ST; Minnesota code 11.5 = ST-segment depression at rest that worsens to 11.1 during exercise.

‖ Values are odds ratios (95% CI).

Note: Events are CHD events unless otherwise indicated.

BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRFIT, Multiple Risk Factor Intervention Trial Research Group; NA, not applicable; NR, not reported; NS, not significant.

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)				
Cumulative Event Rate	**Adjusted Relative Risk (95% CI) for CHD Events with Abnormal ST-Segment Response**	**Sensitivity for CHD Events**	**Positive Predictive Value of Abnormal ST Response**	**Variables for Which Relative Risk Was Adjusted**
Normal exercise test 3.4% Abnormal exercise test result 15.6%*	5.5 (2.8–11.2)	62%	15%	Age, systolic blood pressure, smoking, coronary risk index
Normal exercise test result 2/1,000 person years* Abnormal exercise test result 7.6/1,000 person years*	3.5 (*P* <0.05)* 1.61 (*P* <0.01)†	NR	36%	Age, diastolic blood pressure, cholesterol, number of cigarettes smoked daily
Placebo group Normal exercise test result 13/1,000 person years* Abnormal exercise test result 1.9/1,000 person years*	*Placebo group* 5.7 (2.7–12.2)* 3.3 (1.8–5.9)*	30%	7.1%	Age, LDL cholesterol level, HDL cholesterol level, systolic blood pressure, smoking, family history
Cholestyramine group Normal exercise test result 7.2/1,000 person years* Abnormal exercise test result 1.5/1,000 person years*	*Cholestyramine group* 4.9 (2.2–10.8)* 2.9 (1.6–5.2)†			

continue

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Abnormal Test Result: Definition	Abnormal Test Result: Prevalence
Fleg et al, 1990[19]	407 residents of Baltimore, Maryland (mainly white) Mean age ±SD 60 ±11 y Range: 40–90 y 71% men	NR	4.6 y	Maximal treadmill with thallium modified Balke	≥1 mm of horizontal/ downsloping ST-segment during or after exercise	Abnormal electro-cardiogram only 16.0% Abnormal thallium scan only 14% Both tests abnormal 6.0%
Okin et al, 1991[40]	3,168 participants in the Framingham Offspring Study Mean age ±SD, 44 ±10 y Age range: 17–70 y 48% male	Medical contraindications to exercise, history of myocardial infarction, CHF, valvular disease, syncope, conduction abnormalities, digoxin use, atrial fibrillation	4.3 y	Standard Bruce	ST segment corrected for heart rate index >1.6 muV per beat per min or abnormal rate recovery loop	416/3168 13% (either test abnormal)
Siscovick et al, 1991[12]	3,617 white men in the Lipid Research Clinics Prevalence Survey Mean age: NR Age range: 35–59 y 100% male	Clinical evidence of CHD or CHF on history, various resting electrocardiogram abnormalities	7.4 y	Submaximal modified Bruce	Visual code ≥1 mm ST-segment depression or elevation or computer code ≥10 muV 1/N s	6.6%

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)				
Cumulative Event Rate*	**Adjusted Relative Risk (95% CI) for CHD Events with Abnormal ST-Segment Response**	**Sensitivity for CHD Events**	**Positive Predictive Value of Abnormal ST Response**	**Variables for Which Relative Risk Was Adjusted**
Both test results normal, 7%	1.0			Age, sex, hypertension, fasting blood glucose, total cholesterol, BMI, smoking, exercise duration
Abnormal electrocardiogram only, 12%	2.4 (*P* <0.05)	40%	24%	
Abnormal thallium scan only, 3%	1.4 (NS)	NA	NA	
Both tests abnormal, 48%	3.6 (1.6–8.1)	28%	48%	
Both tests normal 1.6%	1.0			Age, sex, smoking, diastolic blood pressure, total cholesterol level, fasting blood glucose, left ventricular hypertrophy on electrocardiography
Either test abnormal 4.1%	1.6 (1.1–2.5)	23%	4%	
Both tests abnormal 9.8%	2.7 (1.8–4.0)	8%	10%	
Overall 2%‡	2.6 (1.3–5.2)‡	18%	5%	Age, LDL cholesterol level, HDL cholesterol level, smoking, physical activity, workload achieved, family history of CHD, BMI, alcohol consumption

continue

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Abnormal Test Result: Definition	Abnormal Test Result: Prevalence
Blumenthal et al, 1996[32]	264 healthy siblings of individuals with CAD before age 60 in Baltimore, Maryland Mean age ±SD, 46 ±8 Age range: 37–59 y 69% men	Known CAD, corticosteroids, collagen vascular disease, decreased life expectancy, functional status limitations	6.2 y	Modified Bruce and thallium scintigraphy	≥1 mm (≥2 mm for women) of horizontal or downsloping depression in 3 consecutive beats during exercise or first 3 min of recovery	Abnormal exercise electrocardiogram 5.4% Abnormal plus thallium scan 18.1% Abnormal exercise electrocardiogram and scan 4.6%
Okin et al, 1996[39]	5,940 men in the usual care group of MRFIT Mean age: NR Age range: 35–57 y 100% men	No evidence of CHD by history, physical examination, or resting electrocardiography	7 y	Submaximal treadmill	ST segment corrected for heart rate index >1.6 muV per beats per min	729/5,940 (12.3%)
Katzel et al, 1999[29]	170 healthy sedentary obese men living in the Baltimore-Washington, DC area (96% white) Mean age: NR Age range: 45–79 y 100% men	History or laboratory evidence of CAD, diabetes mellitus, hypertension, hyperlipidemia	7.3 y	Maximal Bruce	≥1 mm of horizontal or downsloping ST-segment depression in 2 or more leads	37/170 (22%)

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)				
Cumulative Event Rate*	**Adjusted Relative Risk (95% CI) for CHD Events with Abnormal ST-Segment Response**	**Sensitivity for CHD Events**	**Positive Predictive Value of Abnormal ST Response**	**Variables for Which Relative Risk Was Adjusted**
Normal 3%	1.0			Age, sex
Abnormal exercise electrocardiogram 7%	1.5 (0.2–12.5)	NA	NA	
Abnormal thallium scan 13%	3.6 (1.1–11.4)	63%	20%	
Abnormal exercise electrocardiogram and scan 50%	14.5 (4.2–50.2)	32%	50%	
Normal exercise test result 1.3%* Abnormal exercise test result 5.4%*	3.6 (2.4–5.4)*	36%	5%	Age, diastolic blood pressure, cholesterol level, smoking
Overall 18%	4.23 (2.03–8.83)	55%	46%	Age, BMI, maximal VO2, fasting glucose level

continue

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Abnormal Test Result: Definition	Abnormal Test Result: Prevalence
Gibbons et al, 2000[33]	25,927 patients of a preventive medicine clinic in Texas (mainly white) Mean age: 42.9 Age range 20–82 y 100% men	Evident CHD, severe aortic stenosis, acute systemic illness, uncontrolled atrial or ventricular arrhythmias, pericarditis, myocarditis, thrombophlebitis or exercise-limiting orthopedic problems	8.4 y	Maximal treadmill modified Balke	Chest pain and ≥1 mm ST-segment depression or elevation, exercise induced-decrease ≥10 mm in systolic blood pressure, systolic blood pressure >250 mm Hg, diastolic blood pressure >120 mm Hg, ventricular tachycardia, left bundle-branch block, right bundle-branch block, super-ventricular tachycardia	No risk factors, 3.0%
						>1 risk factor, 7.1%
Josephson et al, 1990[11] Rywik et al, 2002[21]	1,083 participants in the Baltimore Longitudinal Study of Aging Mean age ±SD, 52 ±18 y 57% men	History of angina or heart failure, Q wave on resting electrocardio-graphy, valvular disease, use of anti-arrhythmic drugs, inability to achieve 85% of maximal heart rate	7.9 y	Modified Balke	Normal	
					Minnesota Code 11.1§	20%
					Minnesota Code 11.5§	5.5%
					Minnesota Code 11.2§	7%
					Minnesota Code 11.4§	11.5%

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Cumulative Event Rate*	Adjusted Relative Risk (95% CI) for CHD Events with Abnormal ST-Segment Response	Sensitivity for CHD Events	Positive Predictive Value of Abnormal ST Response	Variables for Which Relative Risk Was Adjusted
No risk factors Normal exercise test result 0.08/1000 person years* Abnormal ETT 2.8/1000 person years*	21 (6.9–63.3)*	60%	2.2%	Age
>1 risk factor Normal ETT 0.5/1000 person years* Abnormal exercise test result 7.6/1000 person years*	9*	61%	7.7%	
Men 4% Women 3%	1.0 ǁ	Men 74% Women 68%	Men 16% Women 7%	Age, cholesterol, sex, exercise duration
Men 17% Women 8%	2.7 (1.6–4.7) ǁ			
Men 17% Women 11%	2.7 (1.05–7.10) ǁ			
Men 10% Women 5%	1.8 (0.6–5.4) ǁ			
Men 17% Women 3%	1.3 (0.6–2.9) ǁ			

continue

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Abnormal Test Result	
					Definition	Prevalence
Jouven and Ducimetiere, 2000[45]	6,101 Frenchmen in Paris Civil Service Age range: 42–53 y 100% men	Known or suspected CVD, resting systolic blood pressure ≥180 mm Hg, resting electro-cardiographic abnormality	23	Bicycle ergometry	J-point depression of at least 1 mm with a flat or downsloping ST-segment during exercise or recovery	4.4%
Laukkanen et al, 2001[20]	1,769 participants, population in Kupio Ischemic Heart Disease Study base sample of Finnish men Mean age ±SD, 52 ±5.2 y 100% men	Known CHD or symptoms suggestive of CHD	10	Maximal bicycle ergometry	>1 mm ST-segment depression during exercise	10.7%
Rutter et al, 2002[13]	86 diabetic patients in the United Kingdom Mean age ±SD, 62 ±7 y Age range: 46–74 y 72% men	History of CAD	2.8	Treadmill	>1 mm of horizontal or downsloping ST-segment depression for 3 consecutive beats	52%
Mora et al, 2003[42]	2994 women enrolled in the Lipid Research Clinics Prevalence Study Age range 30–80 0% men	Pregnancy or significant cardiovascular disease	20.3	Maximal Bruce	≥1 mm horizontal or downsloping ST-segment depression at 0.08 seconds after the J-point during recovery or exercise	4.7%

Table 3. Association Between Abnormal ST-Segment Response to Exercise and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Cumulative Event Rate*	Adjusted Relative Risk (95% CI) for CHD Events with Abnormal ST-Segment Response	Sensitivity for CHD Events	Positive Predictive Value of Abnormal ST Response	Variables for Which Relative Risk Was Adjusted
Normal exercise test result, 6.4% Abnormal exercise test result 16.7%*	2.6 (1.93–3.59)*	10%	17–25%	Age, BMI, heart rate at rest, smoking, physical activity, diabetes mellitus, total cholesterol level, premature ventricular complex
Normal exercise test result 9.2% 2.4%* Abnormal 15.3% 7.9%*	1.7 (1.1–2.6) 3.5 (1.9–6.5)*	16%	15%	Age, examination year, smoking, systolic blood pressure, alcohol consumption, BMI, max oxygen uptake, diabetes mellitus, LDL cholesterol level, HDL cholesterol level
Both normal and abnormal exercise test results 17%	21 (2–204)	100%	20%	Ankle brachial index, microalbuminuria, Framingham 10-y CHD risk >30%, fibrinogen level
Both normal and abnormal exercise tolerance test results 5%* 14%†	0.88 (0.48–1.61)* 0.69 (0.45–1.04)†			Age, smoking, diabetes, family history of premature heart disease, obesity, HDL cholesterol level, LDL cholesterol level, triglyceride level, hypertension

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Definition of Abnormal Test Result	Prevalence of Predictor
Ekelund et al, 1988[35]	3,106 (healthy white men) in Lipid Research Clinics Prevalence Survey in United States and Canada Age range: 30–69 y 100% men	Men with CVD symptoms or hypertension were analyzed separately	8.5	Modified submaximal Bruce	Heart rate during stage 2 of exercise tolerance test and exercise time	Increase of 2 SD in stage 2 heart rate Decrease of 2 SD in time on the treadmill
Lauer et al, 1996[44]	1,575 subjects in Framingham Offspring Study (predominantly white) Mean age: 43 y 100% men	Prevalent CAD, inability to reach stage 2 in Bruce protocol, use of beta-blockers at time of exercise tolerance test	7.7	Submaximal Bruce	Failure to achieve age- and sex-predicted target heart rate on exercise tolerance test	21%
Wei et al, 1999[48] Blair et al, 1996[49]	25,714 patients at a preventive med clinic in Texas Aerobic s Center Longitudinal Study (>95% white), 10% of men with known CVD Mean age: 43.8 y 100% men	History of cancer, BMI <18.5 kg/m^2, age <20 y, or <1 y of follow-up	24	Maximal treadmill	Low fitness using age-based MET cut points on exercise tolerance test	Normal weight: 10% Overweight: 19% Obese: 51%

*CHD death.

†All-cause death.

Note: Events are CHD events unless otherwise indicated.

BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MET, metabolic equivalent; NA, not applicable; NR, not reported.

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)				
Cumulative Event Rate	**Relative Risk for CHD Events with Positive Test**	**Sensitivity for CHD Events**	**Positive Predictive Value of Abnormal Test**	**Relative Risk for the Following Variables**
0.26–1.69%*	3.2 (1.5–6.7) for abnormal heart rate recovery 2.8 (1.3–6.1) for decrease in exercise time	NR	NR	Age, smoking, HDL cholesterol level, LDL cholesterol level, systolic blood pressure
3% for those who reached target heart rate† 6% for those who failed to reach heart rate†	No significant association of predictor with all cause death 1.75 (1.11–2.74)*	46%	14%	Age, ST-segment response, physical activity, BMI, smoking, hypertension, hypertension medication, diabetes mellitus, total cholesterol level/HDL cholesterol level
Overall 1.7/1,000 person years†	Normal Weight 1.7 (1.1–2.5)* 1.6 (1.3–2.1)†	36%	4.6%	Diabetes mellitus, cholesterol level, hypertension, current smoking, history of CVD, abnormal electrocardiogram at rest, age, BMI, parental history of CVD, examination year
	Overweight 1.9 (1.4–2.5)* 1.7 (1.4–2.6)†	52%	5.4%	
	Obese 2.0 (1.2–3.6)* 2.3 (1.5–3.4)†	79%	3.4%	

continue

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Definition of Abnormal Test Result	Prevalence of Predictor
Cole et al, 2000[34]	5,234 in Lipid Research Clinics Prevalence Survey in United States and Canada Mean age: >30 y 39% men	Age <30 y, use of beta-blockers, digoxin, antiarrhythmic agents or nitrates, history of cardiovascular disease, unable to reach stage 2	12	Bruce or modified submaximal Bruce	Abnormal heart rate recovery defined as heart rate change of 42 beats/min or less from peak exercise to that measured 2 min later	33%
Jouven and Ducimetiere, 2000[45]	6,101 French men in Paris civil service Age range: 42–53 y 100% men	Known or suspected CVD, systolic blood pressure ≥180 at rest, or resting electrocardio-graphic abnormality	23	Bicycle ergometry	Premature ventricular complex constituting more than 10% of all ventricular depolarizations during exercise	2.3%
Morshedi-Meibodi et al, 2002[47]	2,967 participants in Framingham Offspring Study Mean age ±SD: 43 ±10 y 47% men	Prevalent CVD, chronic obstructive pulmonary disease, use of digoxin or beta-blockers, resting electrocardio-graphic abnormalities, inability to complete stage 1 of exercise	15	Submaximal Bruce	Heart rate recovery index – decrease in peak heart rate to 2 min of <42 beats/min	NA

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Cumulative Event Rate	Relative Risk for CHD Events with Positive Test	Sensitivity for CHD Events	Positive Predictive Value of Abnormal Test	Relative Risk for the Following Variables
Normal heart rate recovery 4% died Abnormal heart rate recovery 10% died	1.95 (1.11–3.42)* 1.55 (1.22–1.98)†	54%	10%	Age, sex, BMI, ethnicity, systolic blood pressure, hypertension medication, exercise habits, physical fitness, smoking, diabetes mellitus, lipids, ST-segment response, heart rate, chronotropic index, socioeconomic status
Normal exercise tolerance test result 6.4% Abnormal exercise tolerance test result 16.1%*	2.53 (1.65–3.88)* 1.1 (0.8–1.5)	5%*	17%*	Age, BMI, heart rate, systolic blood pressure, tobacco use, level of physical activity, diabetes mellitus, total cholesterol, presence or absence of premature ventricular depolarizations before or after exercise
Overall 7.2%	0.8 (0.5–1.1)†	NA	NA	Age, BMI, smoking, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication, diabetes mellitus, total cholesterol level, HDL cholesterol level, resting heart rate and peak heart rate

continue

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Definition of Abnormal Test Result	Prevalence of Predictor
Rywik et al, 2002[21]	1,083 participants in the Baltimore Longitudinal Study of Aging Mean age ±SD: 52 ±18 y 57% men	History of angina or heart failure, Q wave on rest electrocardio-gram, valvular disease, use of antiarrhythmic drugs, inability to achieve 85% of max heart rate	7.9	Modified Balke	Duration of exercise	NA
Frolkis et al, 2003[46]	29,244 persons referred to Cleveland Clinic for exercise tolerance testing Mean age ±SD: 56 ±11 y 70% men	Age <30 y, symptomatic heart failure, use of digoxin, valvular disease, end-stage renal disease, pacer, atrial fibrillation, heart block, frequent ventricular ectopic arrhythmia at rest, heart transplant, concurrent evaluation for an arrhythmia	5.3	Submaximal Bruce	Frequent ventricular ectopic arrhythmia (≥7 ventricular premature contractions/ min), ventricular bigeminy or trigeminy, ventricular couplets or triplets, ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation	No ventricular ectopic arrhythmia Frequent ventricular ectopic arrhythmia during recovery 2% Frequent ventricular ectopic arrhythmia during exercise 3%

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Cumulative Event Rate	Relative Risk for CHD Events with Positive Test	Sensitivity for CHD Events	Positive Predictive Value of Abnormal Test	Relative Risk for the Following Variables
Overall 7%	0.87 (0.79–0.96) (For CHD event for 1 minute increase in exercise duration)	NR	NR	Age, cholesterol, sex, ST-segment changes
5%†	1.0			Age, sex, diabetes mellitus, hypertension, smoking, previous CAD, medication use, BMI, resting heart rate, systolic blood pressure, ST-segment changes, chronotropic incompetence, abnormal heart rate recovery, peak exercise capacity
11%†	1.5 (1.1–1.9)†	3%	12%	
9%†	1.1 (0.9–1.3)†	4%	9%	

continue

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Author, Year (Reference)	Sample	Exclusion Criteria	Mean Years of Follow-up	Test	Definition of Abnormal Test Result	Prevalence of Predictor
Mora et al, 2003[42]	2994 women enrolled in the Lipid Research Clinics Prevalence Study Age range 30–80 y 0% men	Pregnancy or significant cardiovascular disease	20.3	Maximal Bruce	Low exercise capacity (<7.5 METS) and low heart rate recovery (<55 beats/minute)	31%
Gulati et al, 2003[43]	5721 women from the Chicago area (86% white) Mean age 52 y 0% men	Self reported CHD, percutaneous coronary intervention, coronary bypass surgery, congestive heart failure	9	Maximal Bruce	Exercise capacity, in METS	NA

Table 4. Association Between Exercise Predictors and Coronary Heart Disease Events in Asymptomatic Persons (cont)

Cumulative Event Rate	Relative Risk for CHD Events with Positive Test	Sensitivity for CHD Events	Positive Predictive Value of Abnormal Test	Relative Risk for the Following Variables
Normal and abnormal results on exercise tolerance test 5%* 14%†	3.52 (1.57–7.86)* 2.11 (1.47–3.04)†	71%	11%	Age, smoking, diabetes, family history of premature heart disease, obesity, HDL cholesterol level, LDL cholesterol level, triglycerides, hypertension
3.2%†	0.83 (0.78–0.89) for each 1 MET increase in exercise capacity			Framingham Risk Score

60-year-old men with no risk factors and $20,504 for those with 1 or more risk factors. The investigators concluded that routine screening was not warranted in general but that it may be beneficial for persons at increased risk for coronary heart disease (for example, older men with 1 or more risk factors). An earlier cost-effectiveness analysis of screening exercise tolerance testing had similar findings.[37]

Pilote and colleagues[28] performed a cost analysis of data from their study of the clinical yield of screening exercise tolerance testing to detect unsuspected severe coronary artery obstruction. They sampled more than 4,000 persons referred to the Cleveland Clinic for screening exercise tolerance testing. Data on cost were obtained from 1994 Medicare reimbursement rates: $110 for exercise testing, $1,780 for angiography, and $27,270 for coronary artery bypass surgery. Screening identified 19 patients with severe coronary artery obstruction (0.44% of the cohort); of these, 14 had subsequent coronary artery bypass graft surgery. The investigators estimated a cost of $39,623 to identify 1 case of severe coronary artery disease by screening exercise tolerance testing. The estimated cost per year of life saved was $55,274.

On the basis of these studies, it appears that screening with exercise treadmill testing and performing bypass surgery on persons with severe obstructions is relatively cost effective compared with other, better-accepted types of preventive care, such as mammography in women 50 to 69 years of age.[76]

Exercise Tolerance Testing as a Prediction Tool for Risk for Coronary Heart Disease Events

Exercise tolerance testing can be used to provide information about a person's risk for a future coronary heart disease event that may augment the predictive ability of traditional risk assessment. Better risk assessment may help clinicians and patients make better decisions about interventions for intermediate- and long-term risk reduction.

ST-segment Response

Traditionally, studies of the predictive value of exercise tolerance testing on future coronary heart disease have examined ST-segment response to exercise as the risk predictor. Most of these studies reported the total number of coronary heart disease events (fatal and nonfatal myocardial infarction, new-onset stable or unstable angina, and coronary death) as their main outcome. Others reported death from coronary heart disease or from all causes as the main outcome or as secondary outcomes. The mortality rate from coronary heart disease, and particularly the total mortality rate, may be less subject to ascertainment bias than is the total number of coronary heart disease events and, hence, may be more valid measures. However, whether from coronary heart disease or other causes, death is uncommon in the generally healthy, asymptomatic patients enrolled in these studies, making it difficult to estimate the ability of exercise tolerance testing to predict such events.

We identified 15 studies in 18 articles that examined the relationship between ST-segment response to exercise and risk for future coronary heart disease events (Table 3).[8,11–13,19–21,26,29,32,33,36,39–42,45,50] Thirteen of these studies (in 16 articles) found that ST-segment response during exercise predicted future coronary heart disease events.[8,11–13,19–21,26,29,33,36,39–41,45,50] In 1 of these studies, only coronary heart disease events occurring during exercise were considered as the outcome;[12] we therefore excluded them from analysis of the predictive utility for coronary heart disease events. Two studies found that ST-segment response to exercise alone did not predict future coronary heart disease events.[32,42]

Of the studies that found ST-segment response to be predictive of future coronary heart disease events, 6 (published in 8 articles) selected persons for participation on the basis of the presence of 1 or more risk factors: diabetes,[13] multiple risk factors,[8,33,39,50] hyperlipidemia,[26,41] and sedentary lifestyle and obesity.[29] The prevalence of an abnormal exercise tolerance testing, usually defined as ST-segment depression of 1 mm or more, ranged from 12% to 52%. After adjustment for other risk factors, the independent relative risk for coronary heart disease events associated with an abnormal ST-segment response to exercise in these higher-risk groups ranged from 3.5[8,50] to 21.0.[13] Sensitivity for occurrence of coronary heart disease events over the duration of the studies (3 to 8 years) ranged from 30% to 100%. The positive predictive value of an abnormal exercise tolerance testing ranged from 7.1%[26,41] to 46%.[29]

Seven studies (published in 8 articles) found ST-segment response to exercise to be predictive of future coronary heart disease events in an unselected, low-risk sample.[11,19–21,33,36,40,45] The prevalence of an abnormal test tended to be lower than that in the higher-risk sample, ranging from 3%[33] to 20%.[11,21] The independent relative risk for coronary heart disease events associated with an abnormal exercise tolerance testing ranged from 1.6[40] to 21,[33] with the majority of the values between 2.0 and 5.0. Gibbons and colleagues[33] reported a higher relative risk in low-risk persons (21.0) than did the other investigators; however, the absolute event rate was low (0.08 to 2.8 events/1000 person-years) and the confidence interval was wide (6.9 to 63.3). The sensitivity of exercise tolerance testing for coronary heart disease events was 10%[45] to 70%.[11,21] The positive predictive values ranged from 2.2%[33] to 24%.[19]

Two of the studies added nuclear perfusion imaging to exercise electrocardiography.[19,32] These studies reported positive predictive values of about 50%. However, imaging is likely to increase screening program costs.[19,32]

As might be expected, the sensitivity of an abnormal exercise tolerance testing decreased as the duration of follow-up increased ($r = -0.56$). Data from these cohort studies suggest that the majority of asymptomatic persons with an abnormal exercise tolerance testing do not go on to have coronary heart disease events, at least within the time frame of follow-up. Persons who do have events often develop angina rather than experience myocardial infarction or sudden death. The prevalence of an abnormal result on exercise tolerance testing and its predictive value among asymptomatic persons is greater in those at higher risk. These data are consistent with those of other investigators and policymakers who have suggested that the value of exercise tolerance testing is greater when it is applied to patients with 1 or more risk factors for coronary heart disease because selection of a higher-risk cohort for screening increases the prevalence of disease and positive predictive value.[10] Bruce and associates[10] reported that, in the Seattle Heart Watch Study of 4,158 asymptomatic men and women, a positive result on exercise tolerance testing in the absence of risk factors provided little predictive value. However, among patients with 1 or more other risk factors for coronary heart disease, the occurrence of 2 different types of abnormal response to exercise tolerance testing (exercise risk predictors) was associated with a 15-fold increase in risk compared with patients who had a normal result.

Other Exercise Predictors

More recent studies of the value of exercise testing in asymptomatic persons have examined the utility of other exercise-associated risk markers, including functional capacity, chronotropic incompetence, heart rate recovery, and development of exercise-induced premature ventricular contractions, for predicting patients' risk for coronary heart disease events or death (Table 4).[21,34,35,42–49] In contrast to ST-segment response, these exercise indicators may not directly detect ischemic myocardium, but they probably indicate other cardiovascular derangements, such as abnormal autonomic regulation, that predict coronary heart disease events. In general, these findings are associated with moderate increases in risk for coronary heart disease after adjustment for other risk factors for coronary heart disease (relative risk, 1.7 to 3.5). Some factors are common: For example, failure to achieve target heart rate was noted in 21% of patients in the Framingham Offspring Study.[44]

Exercise Tolerance Testing in Women

Two recent studies contribute important information on the predictive value of exercise tolerance testing in asymptomatic women.[42,43] The majority of other studies that we identified did not include women or did not provide subgroup analysis of the predictive value of screening exercise tolerance testing for women. Mora and colleagues[42] analyzed data from the female participants in the Lipid Research Clinics Prevalence Study, many of whom had hyperlipidemia. They found that, unlike in studies whose samples comprised predominantly men, ST-segment response did not predict future risk for coronary heart disease events (relative risk, 0.88 [95% CI, 0.48 to 1.61]) in women.[42] Low exercise capacity, along with low heart-rate recovery after exercise, was an independent predictor of death from coronary heart disease (relative risk, 3.52 [95% CI, 1.57 to 7.86) and of all-cause death (relative risk, 2.11 [95% CI, 1.47 to 3.04]) in women.

Gulati and coworkers[43] sampled asymptomatic female volunteers living in the Chicago area. They found that exercise capacity predicts risk for all-cause death in women. For every increase in exercise capacity of 1 metabolic equivalent, the relative risk for death was 0.83 (95% CI, 0.78 to 0.89). The predictive utility of exercise markers other than ST-segment response in these 2 studies of women is consistent with the results of similar studies in which most participants were men.

Exercise Tolerance Testing Before Beginning an Exercise Program

Exercise tolerance testing is frequently used as part of an evaluation of middle-aged persons before they begin an exercise program. Few data are available to determine the effectiveness of this approach in reducing the risk for activity-related coronary heart disease events. Siscovick and colleagues[12] analyzed the effectiveness of exercise tolerance testing to predict activity-related coronary heart disease events in the Lipid Research Clinics cohort of asymptomatic hypercholesterolemic men. After an initial exercise tolerance test, the cohort was followed for an average of 7.4 years; during that time, the investigators used retrospective record review to identify coronary heart disease events that were associated with moderate or intense activity. The cumulative incidence of activity-related coronary heart disease events during follow-up was 2%. An abnormal ST-segment response to exercise at the time of entry into the study was associated with a relative risk of 2.6 (95% CI, 1.3 to 5.2) for activity-related coronary heart disease events. The sensitivity of exercise testing for predicting the events was 18%, and the predictive value of a positive test for coronary heart disease events during exercise was 4%. Of the persons who had an activity-associated coronary heart disease event, 80% had an initially normal ST-segment response to exercise; 94% of persons with abnormal ST-segment response to exercise did not have an activity-associated event during follow-up. Thus, exercise testing appears to have limited ability to detect persons who will have exercise-related coronary heart disease events.

Adverse Effects of Screening Exercise Tolerance Testing

Other than information on the frequency of false-positive results, we found no studies that examined the potential harms of screening. No study reported rates of complications from angiography of asymptomatic persons, measures of anxiety from knowledge of an abnormal test result, or adverse events from medical therapy initiated because of an abnormal test result.

Discussion

We identified no randomized trials that examined the effect of screening exercise tolerance testing to guide management and improve health outcomes of coronary heart disease or affect the use of risk-reducing treatments in asymptomatic adults. Exercise tolerance testing of asymptomatic persons rarely detects previously unrecognized, clinically important coronary artery obstruction (up to 2.7% of screened persons). It does provide some independent prognostic information in at least some persons (relative risk of approximately 2.0 to 5.0 for coronary heart disease events associated with an abnormal result) above and beyond the prognostic information that can be gained from traditional assessment of risk factors. The effect of this additional information on clinical decision making, however, has not been studied. The potential benefits of screening exercise tolerance testing are likely to be small for groups in which the prevalence of the disease is low, such as young adults; such screening would also produce many cases of false-positive results. In such cases, the costs and harms associated with additional testing may exceed any benefits from screening.

The value of screening exercise tolerance testing rests in large part on the underlying incidence of coronary heart disease events and the prevalence of serious artery obstructions in the screened sample. Exercise tolerance testing will probably perform better when applied to higher-risk groups, such as persons with 1 or more risk factors for coronary heart disease. Selection of a higher-risk group for screening increases the prevalence of disease in those screened and, thus, the predictive value of a positive test result. Whether the benefits of such tests exceed the disadvantages, including costs, in higher-risk groups is still unclear at present and requires investigation.

For persons at low risk for coronary heart disease events, a positive result on exercise tolerance testing is much more likely to be false positive than true positive. False-positive results in this context are concerning because they can lead to unnecessary, and possibly injurious, additional procedures.

Screening has been advocated for people with high-risk occupations, but we did not identify new studies on the effect of screening such patients. Data from studies of patients with known coronary heart disease but no ischemic symptoms suggest that treatment with medications, such as beta-blockers, or revascularization can improve outcomes over no treatment, but whether patients with no history of coronary heart disease would have the same results is unclear.[77]

Exercise tolerance testing can be normal or nondiagnostic in an important proportion of patients who will experience a coronary heart disease event, as evidenced by the sensitivity values of 10% to 74% in the studies that evaluated ST-segment depression as a risk marker (Table 3). In a defined cohort of low-risk patients, a larger absolute number of coronary heart disease events occurs among those with an initially normal result on exercise tolerance testing than among those with an initially abnormal result. The suboptimal sensitivity of ST-segment response for predicting coronary heart disease events may be explained in part by the fact that ST-segment depression on exercise tolerance testing detects ischemia from obstructed coronary arteries, but many acute coronary heart disease events result from sudden occlusion of a previously unobstructed segment of artery.[78] Use of other measures than the exercise test that are not as dependent on identification of atherosclerotic obstructions may mitigate this dilemma.[79]

The primary tangible harm of screening exercise tolerance testing is the potential for medical complications related to cardiac catheterization done to further evaluate a positive result. Coronary angiography is generally considered a safe procedure. Of all persons undergoing outpatient coronary angiography, however, an estimated 0.08% will die as a result of the procedure, and 1.8% will experience a complication.[80] Complications of coronary angiography include myocardial infarction, stroke, arrhythmia, dissection of the aorta and coronary artery, retroperitoneal bleeding, femoral artery aneurysm, renal dysfunction, and systemic infection. Rates of complications are likely to be somewhat lower in asymptomatic persons, but no good data are available. A positive result on exercise tolerance testing may also be an impetus to initiate risk-reducing therapy; hence, another potential harm of screening is use of therapies such as aspirin or statins to over-treat persons who would not otherwise require treatment (that is, would be considered low risk) if they did not have an abnormal result on exercise tolerance testing. Other potential harms, including the psychological consequences of a false-positive test result, also have not been well studied.

Our findings are consistent with those of the American Heart Association/American College of Cardiology (AHA/ACC) expert panel, which also examined the effectiveness of screening exercise tolerance testing.[33] The panel recommended against routine exercise tolerance testing in asymptomatic adults because of concerns about the positive and negative predictive value of screening exercise tolerance testing and the potential harms of false-positive results. AHA/ACC found that screening exercise tolerance testing for persons with multiple risk factors to guide to risk-reduction therapy or for sedentary middle-aged adults who wish to start a vigorous exercise program is controversial but potentially beneficial.

Further studies are required to determine the balance of benefits and harms of screening exercise tolerance testing for patients with different degrees of risk for coronary heart disease. An adequately powered randomized trial of screening exercise tolerance testing compared with management based on traditional risk factors would greatly inform clinical decision making. Such a study should compare a traditional global coronary heart disease risk assessment tool to a screening strategy that also incorporates exercise tolerance testing. A broad spectrum of patients should be enrolled, including a sufficient number of women. Studies examining how providers and patients actually apply the additional information from exercise tolerance testing also will be helpful. Finally, better information about the adverse effects of screening is required if researchers are to perform well-informed cost-effectiveness analyses of exercise tolerance testing screening plus risk-factor-based decision making compared with risk-factor-based decision making alone.

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References

1. American Heart Association. Heart Disease and Stroke Statistics—2003 Update. Dallas, TX, American Heart Association; 2002.
2. Thaulow E, Erikssen J, Sandvik L, Erikssen G, Jorgensen L, Cohn PF. Initial clinical presentation of cardiac disease in asymptomatic men with silent myocardial ischemia and angiographically documented coronary artery disease (the Oslo Ischemia Study). *Am J Cardiol.* 1993;72:629–633.
3. Cohn PF. Detection and prognosis of the asymptomatic patient with silent myocardial ischemia. *Am J Cardiol.* 1988;61:4B–6B.
4. U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd ed. Washington, DC: Office of Disease Prevention and Health Promotion; 1996.
5. Fowler-Brown A, Pignone M, Pletcher M, Tice JA, Sutton SF, Lohr KN. *Screening for Asymptomatic Coronary Artery Disease: A Systematic Review for the U.S. Preventive Services Task Force.* Systematic Evidence Review No. 22 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011). Rockville, MD: Agency for Healthcare Research and Quality. February 2004. (Available on the AHRQ Web site at: www.ahrq.gov/clinic/serfiles.htm.)
6. U.S. Preventive Services Task Force. Screening for coronary heart disease: recommendation statement. *Ann Intern Med*. 2004;140:569–572.
7. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847.
8. Exercise electrocardiogram and coronary heart disease mortality in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Am J Cardiol.* 1985;55:16–24.
9. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20:21–35.
10. Bruce RA, Hossack KF, DeRouen TA, Hofer V. Enhanced risk assessment for primary coronary heart disease events by maximal exercise testing: 10 years' experience of Seattle Heart Watch. *J Am Coll Cardiol.* 1983;2:565–573.
11. Josephson RA, Shefrin E, Lakatta EG, Brant LJ, Fleg JL. Can serial exercise testing improve the prediction of coronary events in asymptomatic individuals? *Circulation.* 1990;81:20–24.
12. Siscovick DS, Ekelund LG, Johnson JL, Truong Y, Adler A. Sensitivity of exercise electrocardiography for acute cardiac events during moderate and strenuous physical activity. The Lipid Research

Clinics Coronary Primary Prevention Trial. *Arch Intern Med*. 1991;151:325–330.

13. Rutter MK, Wahid ST, McComb JM, Marshall SM. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *J Am Coll Cardiol.* 2002;40:56–61.

14. Boyle RM, Adlakha HL, Mary DA. Diagnostic value of the maximal ST segment/heart rate slope in asymptomatic factory populations. *J Electrocardiol.* 1987;20 Suppl:128–134.

15. Koistinen MJ. Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. *BMJ*. 1990;301:92–95.

16. Piepgrass SR, Uhl GS, Hickman JR Jr, Hopkirk JA, Plowman K. Limitations of the exercise stress test in the detection of coronary artery disease in apparently healthy men. *Aviat Space Environ Med.* 1982;53:379–382.

17. Blumenthal RS, Becker DM, Yanek LR, et al. Detecting occult coronary disease in a high-risk asymptomatic population. *Circulation*. 2003;107:702–707.

18. Massie BM, Szlachcic Y, Tubau JF, O'Kelly BF, Ammon S, Chin W. Scintigraphic and electrocardiographic evidence of silent coronary artery disease in asymptomatic hypertension: a case-control study. *J Am Coll Cardiol*. 1993;22:1598–1606.

19. Fleg JL, Gerstenblith G, Zonderman AB, et al. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers. *Circulation.* 1990;81:428–436.

20. Laukkanen JA, Kurl S, Lakka TA, et al. Exercise-induced silent myocardial ischemia and coronary morbidity and mortality in middle-aged men. *J Am Coll Cardiol*. 2001;38:72–79.

21. Rywik TM, O'Connor FC, Gittings NS, Wright JG, Khan AA, Fleg JL. Role of nondiagnostic exercise-induced ST-segment abnormalities in predicting future coronary events in asymptomatic volunteers. *Circulation.* 2002;106:2787–2792.

22. Livschitz S, Sharabi Y, Yushin J, et al. Limited clinical value of exercise stress test for the screening of coronary artery disease in young, asymptomatic adult men. *Am J Cardiol.* 2000;86:462–464.

23. Davies B, Ashton WD, Rowlands DJ, et al. Association of conventional and exertional coronary heart disease risk factors in 5,000 apparently healthy men. *Clin Cardiol.* 1996;19:303–308.

24. Sox HC Jr, Littenberg B, Garber AM. The role of exercise testing in screening for coronary artery disease. *Ann Intern Med.* 1989;110:456–469.

25. Cameron JD, Jennings GL, Kay S, et al. A self-administered questionnaire for detection of unrecognised coronary heart disease. *Aust N Z J Public Health.* 1997;21:545–547.

26. Ekelund LG, Suchindran CM, McMahon RP, et al. Coronary heart disease morbidity and mortality in hypercholesterolemic men predicted from an exercise test: the Lipid Research Clinics Coronary Primary Prevention Trial. *J Am Coll Cardiol*. 1989;14:556–563.

27. Caralis DG, Bailey I, Kennedy HL, Pitt B. Thallium-201 myocardial imaging in evaluation of asymptomatic individuals with ischaemic ST segment depression on exercise electrocardiogram. *Br Heart J.* 1979;42:562–567.

28. Pilote L, Pashkow F, Thomas JD, et al. Clinical yield and cost of exercise treadmill testing to screen for coronary artery disease in asymptomatic adults. *Am J Cardiol*. 1998;81:219–224.

29. Katzel LI, Sorkin JD, Goldberg AP. Exercise-induced silent myocardial ischemia and future cardiac events in healthy, sedentary, middle-aged and older men. *J Am Geriatr Soc.* 1999;47:923–929.

30. Dunn RL, Matzen RN, VanderBrug-Medendorp S. Screening for the detection of coronary artery disease by using the exercise tolerance test in a preventive medicine population. *Am J Prev Med*. 1991;7:255–262.

31. Okin PM, Kligfield P, Milner MR, Goldstein SA, Lindsay J Jr. Heart rate adjustment of ST-segment depression for reduction of false positive electrocardiographic responses to exercise in asymptomatic men screened for coronary artery disease. *Am J Cardiol.* 1988;62:1043–1047.

32. Blumenthal RS, Becker DM, Moy TF, Coresh J, Wilder LB, Becker LC. Exercise thallium tomography predicts future clinically manifest

coronary heart disease in a high-risk asymptomatic population. *Circulation*. 1996;93:915–923.

33. Gibbons LW, Mitchell TL, Wei M, Blair SN, Cooper KH. Maximal exercise test as a predictor of risk for mortality from coronary heart disease in asymptomatic men. *Am J Cardiol*. 2000;86:53–58.

34. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med.* 2000;132:552–555.

35. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med.* 1988;319:1379–1384.

36. Giagnoni E, Secchi MB, Wu SC, et al. Prognostic value of exercise EKG testing in asymptomatic normotensive subjects. A prospective matched study. *N Engl J Med.* 1983 ;309:1085–1089.

37. Stason WB, Fineberg HV. Implications of alternative strategies to diagnose coronary artery disease. *Circulation*. 1982;66:III80–86.

38. Hollenberg M, Zoltick JM, Go M, et al. Comparison of a quantitative treadmill exercise score with standard electrocardiographic criteria in screening asymptomatic young men for coronary artery disease. *N Engl J Med.* 1985;313:600–606.

39. Okin PM, Grandits G, Rautaharju PM, et al. Prognostic value of heart rate adjustment of exercise-induced ST segment depression in the multiple risk factor intervention trial. *J Am Coll Cardiol.* 1996;27:1437–1443.

40. Okin PM, Anderson KM, Levy D, Kligfield P. Heart rate adjustment of exercise-induced ST segment depression. Improved risk stratification in the Framingham Offspring Study. *Circulation.* 1991;83:866–874.

41. Gordon DJ, Ekelund LG, Karon JM, et al. Predictive value of the exercise tolerance test for mortality in North American men: the Lipid Research Clinics Mortality Follow-up Study. *Circulation.* 1986;74:252–261.

42. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA.* 2003;290:1600–1607.

43. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation.* 2003;108:1554–1559.

44. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation.* 1996;93:1520–1526.

45. Jouven X, Ducimetière P. Recovery of heart rate after exercise [Letter]. *N Engl J Med.* 2000;342:662–663.

46. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. *N Engl J Med.* 2003;348:781–790.

47. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk for cardiovascular disease events (The Framingham Heart Study). *Am J Cardiol.* 2002;90:848–852.

48. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA*. 1999;282:1547–1553.

49. Blair SN, Kampert JB, Kohl HW 3rd, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA.* 1996;276:205–210.

50. Rautaharju PM, Prineas RJ, Eifler WJ, et al. Prognostic value of exercise electrocardiogram in men at high risk for future coronary heart disease: Multiple Risk Factor Intervention Trial experience. *J Am Coll Cardiol*. 1986;8:1–10.

51. Allen WH, Aronow WS, Goodman P, Stinson P. Five-year follow-up of maximal treadmill stress test in asymptomatic men and women. *Circulation.* 1980;62:522–527.

52. Aronow WS, Allen WH, De Cristofaro D, Ungermann S. Follow-up of mass screening for coronary risk factors in 1817 adults. *Circulation.* 1975;51:1038–1045.

53. Aronow WS, Allen WH, De Cristofaro D, et al. Mass screening for coronary risk factors in 2,524 asymptomatic adults. *J Am Geriatr Soc.* 1975;23:121–126.

54. Cumming GR, Samm J, Borysyk L, Kich L. Electrocardiographic changes during exercise in asymptomatic men: 3-year follow-up. *Can Med Assoc J.* 1975;112:578–581.

55. Elamin MS, Boyle R, Kardash MM, et al. Accurate detection of coronary heart disease by new exercise test. *Br Heart J.* 1982;48:311–320.

56. Fadayomi MO, Akinroye KK. Implications of positive treadmill exercise tests in asymptomatic adult African blacks. *Eur Heart J.* 1987;8:611–617.

57. Froelicher VF Jr, Thomas MM, Pillow C, Lancaster MC. Epidemiologic study of asymptomatic men screened by maximal treadmill testing for latent coronary artery disease. *Am J Cardiol.* 1974;34:770–776.

58. Froelicher VF Jr, Thompson AJ, Wolthuis R, et al. Angiographic findings in asymptomatic aircrewmen with electrocardiographic abnormalities. *Am J Cardiol.* 1977;39:32–38.

59. Gerson MC, Khoury JC, Hertzberg VS, Fischer EE, Scott RC. Prediction of coronary artery disease in a population of insulin-requiring diabetic patients: results of an 8-year follow-up study. *Am Heart J.* 1988;116:820–826.

60. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation*. 1989;80:87–98.

61. Goodman S, Rubler S, Bryk H, Sklar B, Glasser L. Arm exercise testing with myocardial scintigraphy in asymptomatic patients with peripheral vascular disease. *Chest.* 1989;95:740–746.

62. Gupta R, Gupta S. Value of maximal treadmill exercise test to screen asymptomatic persons for coronary artery disease. *J Assoc Physicians India.* 1983;31:783–785.

63. Hopkirk JA, Uhl GS, Hickman JR Jr, Fischer J, Medina A. Discriminant value of clinical and exercise variables in detecting significant coronary artery disease in asymptomatic men. *J Am Coll Cardiol.* 1984;3:887–894.

64. MacIntyre NR, Kunkler JR, Mitchell RE, Oberman A, Graybiel A. Eight-year follow-up of exercise electrocardiograms in healthy, middle-aged aviators. *Aviat Space Environ Med.* 1981;52:256–259.

65. Manca C, Barilli AL, Dei Cas L, Bernardini B, Bolognesi R, Visioli O. Multivariate analysis of exercise ST depression and coronary risk factors in asymptomatic men. *Eur Heart J.* 1982;3:2–8.

66. Mark DB, Hlatky MA, Califf RM, et al. Painless exercise ST deviation on the treadmill: long-term prognosis. *J Am Coll Cardiol.* 1989;14(4):885–892.

67. McHenry PL, O'Donnell J, Morris SN, Jordan JJ. The abnormal exercise electrocardiogram in apparently healthy men: a predictor of angina pectoris as an initial coronary event during long-term follow-up. *Circulation.* 1984;70:547–551.

68. Melin JA, Piret LJ, Vanbutsele RJ, et al. Diagnostic value of exercise electrocardiography and thallium myocardial scintigraphy in patients without previous myocardial infarction: a Bayesian approach. *Circulation.* 1981;63:1019–1024.

69. Pedersen F, Sandoe E, Laerkeborg A. Prevalence and significance of an abnormal exercise ECG in asymptomatic males. Outcome of thallium myocardial scintigraphy. *Eur Heart J.* 1991;12:766–769.

70. Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, Gersh BJ. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. *Circulation*. 1998;98:2836–2841.

71. Rubler S, Gerber D, Reitano J, Chokshi V, Fisher VJ. Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. *Am J Cardiol.* 1987;59:1310–1313.

72. Selvester RH, Ahmed J, Tolan GD. Asymptomatic coronary artery disease detection: update 1996. A screening protocol using 16-lead high-resolution ECG, ultrafast CT, exercise testing, and radionuclear imaging. *J Electrocardiol*. 1996;29 Suppl:135–144.

73. Tubau JF, Szlachcic J, Hollenberg M, Massie BM. Usefulness of thallium-201 scintigraphy in predicting the development of angina pectoris in

hypertensive patients with left ventricular hypertrophy. *Am J Cardiol.* 1989;64:45–49.

74. Uhl GS, Kay TN, Hickman JR Jr. Computer-enhanced thallium scintigrams in asymptomatic men with abnormal exercise tests. *Am J Cardiol.* 1981;48:1037–1043.

75. Koistinen MJ, Huikuri HV, Pirttiaho H, Linnaluoto MK, Takkunen JT. Evaluation of exercise electrocardiography and thallium tomographic imaging in detecting asymptomatic coronary artery disease in diabetic patients. *Br Heart J.* 1990;63:7–11.

76. Salzmann P, Kerlikowske K, Phillips K. Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. *Ann Intern Med.* 1997;127:955–965.

77. Conti CR, Bourassa MG, Chaitman BR, et al. Asymptomatic cardiac ischemia pilot (ACIP). *Trans Am Clin Climatol Assoc*. 1994;106:77–83.

78. Coplan NL, Fuster V. Limitations of the exercise test as a screen for acute cardiac events in asymptomatic patients. *Am Heart J.* 1990;119:987–990.

79. Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. *Lancet.* 2000;356:1592–1597.

80. Bashore TM, Bates ER, Berger PB, et al. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert\ Consensus Documents. *J Am Coll Cardiol.* 2001;37:2170–2214.

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