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

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Background: **Coronary heart disease is the leading cause of morbidity and mortality in the United States. Exercise tolerance testing has been proposed as a means of better identifying asymptomatic patients at high risk for coronary heart disease events.**

Purpose: **To review the evidence on the use of exercise tolerance testing to screen adults with no history of cardiovascular disease for coronary heart disease.**

Data Sources: **The MEDLINE database from 1966 through February 2003, hand-searching of bibliographies, and expert input.**

Study Selection: **Eligible studies evaluated the benefits or harms of exercise tolerance testing when added to traditional risk assessment for adults with no known history of cardiovascular events.**

Data Extraction: **One reviewer extracted information from eligible articles into evidence tables, and another reviewer checked the tables. Disagreements were resolved by consensus.**

Data Synthesis: **No study has directly examined the effect of screening asymptomatic patients with exercise tolerance testing on coronary heart disease outcomes or risk-reducing behaviors or therapies. Multiple cohort studies demonstrate that screening exercise tolerance testing identifies a small proportion of asymptomatic persons (up to 2.7% of those screened) with severe coronary artery obstruction who may benefit from revascularization. Several large prospective cohort studies, conducted principally in middle-aged men, suggest that exercise tolerance testing can provide independent prognostic information about the risk for future coronary heart disease events (relative risk with abnormal exercise tolerance testing, 2.0 to 5.0). However, when the risk for coronary heart disease events is low, most positive findings will be false and may result in unnecessary further testing or worry. The risk level at which the benefits of additional prognostic information outweigh the harms of false-positive results is unclear and requires further study.**

Conclusions: **Although screening exercise tolerance testing detects severe coronary artery obstruction in a small proportion of persons screened and can provide independent prognostic information about the risk for coronary heart disease events, the effect of this information on clinical management and disease outcomes in asymptomatic patients is unclear.**

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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 the 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 (5). This article describes the findings on exercise tolerance testing only. The recommendations and rationale of the Task Force on screening for asymptomatic coronary artery disease are available at www.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 to 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 different 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 on 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 "posi-

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 the 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 subanalysis
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

tive 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 Corp., 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). For the studies shown in **Table 2**, we considered several factors that affect quality, chiefly the percentage of patients with a positive result on 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 was revised on the basis of the comments received; we used the revised report as the basis for this article. **Tables 3** and **4** show information only from studies judged "good."

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.

DATA SYNTHESIS

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 prev-

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

Study, Year (Reference)	Sample	Exclusion Criteria	Test	Definition of Abnormal Exercise Electrocardiography Result
Caralis et al., 1979 (27)	3496 men and women; mean age NR; percentage of men NR	NR	Maximal exercise and thallium scintigraphy	≥2 mm of horizontal ST-segment depression
Piepgrass et al., 1982 (16)	771 men in U.S. Air Force flight crew; mean age ± SD, 42 ± 5.2 y; 100% men	Resting electrocardiographic abnormalities, history of chest pain, cardiovascular disease, marked hypertension	Maximal treadmill or 2-step double Master's	≥0.1 mV of ST-segment depression 80 ms from the J point, or exercise-induced arrhythmia
Hollenberg et al., 1985 (38)	377 U.S. Army officers; mean age, 37 y; percentage of men NR	Known CHD	Maximal treadmill—U.S. Air Force School of Aerospace Medicine Protocol	≥1 mm ST-segment depression during or after exercise, or treadmill exercise score < 5 units
Boyle et al., 1987 (14)	1174 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 >13 mm · beats^{-1} • min 10^{-3}
Okin et al., 1988 (31)	606 men in the U.S. Army Reserve at moderate to high risk by Framingham Risk score; mean age NR, but all participants > 40 y; 100% men	Known or suspected CHD or angina	Modified Balke–Ware with radionuclide scintigraphy after an abnormal result on exercise electrocardiography	≥1 mm ST-segment depression
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 <5 y, retinopathy, renal failure	Maximal bicycle ergometry and thallium scintigraphy	≥1 mm horizontal or down-sloping ST-segment depression
Dunn et al., 1991 (30)	1930 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 electrocardiography, then thallium scintigraphy if results were abnormal	≥1 mm of horizontal or down-sloping ST-segment depression, or arrhythmia
Massie et al., 1993 (18)	226 men from the San Francisco Veterans Administration Medical Center, all of whom had hypertension and at least 1 other cardiovascular risk factor; mean age ± SD, 61 ± 8 y; 100% men	Known history of cardiac disease or symptoms, abnormalities on resting electrocardiography, paced rhythm, noncardiac limitation to exercise	Standard Bruce with thallium scintigraphy	≥0.1 mV of additional horizontal or down-sloping ST-segment depression at 80 ms after the J point
Davies et al., 1996 (23)	5000 men from the United Kingdom; mean age NR; 100% men	NR	Modified Balke	1 mV of horizontal or down-sloping depression persisting for ≥5 complexes
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
Pilote et al., 1998 (28)	4334 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, digitalis use	Bruce or modified Bruce	≥1 mm horizontal or down-sloping ST-segment depression, ≥1 mm ST-segment elevation in leads other than aVR or V1, decrease in blood pressure ≥ 10 mm Hg, typical chest pain, failure to reach target heart rate
Livschitz et al., 2000 (22)	4900 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 down-sloping ST-segment depression or ≥1.5 μV up-sloping ST-segment depression
Blumenthal et al., 2003 (17)	734 primarily white healthy siblings of persons with CAD diagnosed before age 60 y 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

* CAD = coronary artery disease; CHD = coronary heart disease; NR = not reported.
† Percentages were calculated by the authors of this report.

alence 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 result on 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

Table 2—**Continued**

Definition of Abnormal Cardiac Catheterization Result	Prevalence of Abnormal Exercise Tolerance Test 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
	← *n/n (%)* →				
NR	22/3496 (0.6)	10/15 (66.7)	10/22 (45.5)	10/3496 (0.3)	Fair
NR	27/771 (3.5)	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	45/377 (12)	1/10 (10)	1/45 (2)	1/377 (0.3); 1 patient had 1-vessel disease	Fair
≥75 stenosis of epicardial artery	68/1174 (5.8)	9/24 (37.5)	9/68 (13.2)	9/1174 (0.8); 1 patient had coronary artery bypass graft surgery	Fair
≥50 narrowing of the luminal diameter	10/606 (1.7) positive-abnormal exercise electrocardiogram and scintigram; 52/606 (8.6) inconclusive-abnormal exercise electrocardiogram and normal scintigram	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	40/136 (29)	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	155/1930 (8)	25/41 (61)	25/155 (16.1)	25/1930 (1.3); 6 patients had coronary artery bypass graft surgery	Fair
Intraluminal lesion ≥50% diameter of vessel in 2 projections	Abnormal exercise electrocardiogram: 67/226 (30) Abnormal scintigram: 41/226 (18)	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 of epicardial artery	162/5000 (3.2)	67/86 (78)	67/162 (41.4)	67/5000 (1.3); 26 patients had coronary artery bypass graft surgery	Fair
NR	Men, 15/98 (15.3); women, 17/131 (13)	10/13 (77)	10/32 (31)	10/229 (4); 4 patients had coronary artery bypass graft surgery	Fair
Coronary artery disease in ≥1 coronary segment with ≥50% stenosis	633/4334 (15)	71/126 (56)	71/633 (11)	71/4334 (1.6); 19 patients had left main or 3-vessel disease	Fair
NR	299/4900 (6.1)	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 ≥50% diameter	153/734 (21) (abnormal exercise electrocardiogram, scan, or both)	41/105 (39)	41/153 (27)	41/734 (5.5)	Good

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, $3595 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 60-year-old men with

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

Study, Year (Reference)	Sample	Exclusion Criteria	Mean Duration of Follow-up	Test
			y	
Giagnoni et al., 1983 (36)	514 factory workers in Italy; age range, 18–65 y; 73% men	Positive history and physical examination for CVD, resting blood pressure ≥ 160/95 mm Hg, abnormal resting electrocardiogram	6	Submaximal supine cycle ergometry
MRFIT Research Group, 1985 (8); Rautaharju et al., 1986 (50)	6205 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 level ≥ 350 mg/dL	7	Submaximal
Gordon et al., 1986 (41); Ekelund et al., 1989 (26)	3640 white men in Lipid Research Clinics Prevalence Survey in the United States and Canada; mean age, 47 y (range, 35–59 y); 100% men	Evidence of CHD by history, resting electrocardiogram, and physician examination; secondary hyperlipidemia; BMI > 32.1 kg/m^2; blood pressure ≥ 165/105 mm Hg with antihypertensive or cardiovascular medication; diabetes mellitus	8.1	Submaximal modified Bruce
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	Maximal treadmill with thallium-modified Balke
Okin et al., 1991 (40)	3168 participants in the Framingham Offspring Study; men age ± SD, 44 ± 10 y (range, 17–70 y); 48% men	Medical contraindications to exercise, history of myocardial infarction, CHF, valvular disease, syncope, conduction abnormalities, digoxin use, atrial fibrillation	4.3	Standard Bruce
Siscovick et al., 1991 (12)	3617 white men in the Lipid Research Clinics Prevalence Survey; mean age NR (range, 35–59 y); 100% men	Clinical evidence of CHD or CHF on history, various resting electrocardiographic abnormalities	7.4	Submaximal modified Bruce
Blumenthal et al., 1996 (32)	264 healthy siblings of patients who developed CAD before age 60 y in Baltimore, Maryland; mean age ± SD, 46 ± 8 (range, 37–59 y); 69% men	Known CAD, corticosteroid use, collagen vascular disease, decreased life expectancy, functional status limitations	6.2	Modified Bruce and thallium scintigraphy
Okin et al., 1996 (39)	5940 men in the usual-care group of MRFIT; mean age NR (range, 35–57 y); 100% men	No evidence of CHD by history, physical examination, or resting electrocardiography	7	Submaximal treadmill
Katzel et al., 1999 (29)	170 healthy, sedentary, obese men living in Baltimore–Washington, DC area (96% white); mean age NR (range, 45–79 y); 100% men	History or laboratory evidence of CAD, diabetes mellitus, hypertension, hyperlipidemia	7.3	Maximal Bruce
Gibbons et al., 2000 (33)	25 927 patients of a preventive medicine clinic in Texas (mainly white); mean age, 42.9 y (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	Maximal treadmill modified Balke

Continued

Table 3—**Continued—Top Right**

Abnormal Test Result		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-Segment Response	Variables for Which Relative Risk Was Adjusted
Definition	Prevalence					
	% (n/n)			%		
≥1 mm of horizontal or down-sloping ST-segment depression during or after exercise	NR	Normal exercise test result, 3.4%; abnormal exercise test result, 15.6%†	5.5 (2.8–11.2)	62	15	Age, systolic blood pressure, smoking, coronary risk index
Computer code–ST-segment depression 16 μV-s or more in leads CS5, aVL, aVF, or V5 during or after exercise (in electrocardiogram with less than 6 μV-s of depression at rest)	12.2	Normal exercise test result, 2/1000 person-years†	3.5 ($P < 0.05$)†	NR	36	Age, diastolic blood pressure, cholesterol level, number of cigarettes smoked daily
		Abnormal exercise test result, 7.6/1000 person-years†	1.61 ($P < 0.01$)‡			
≥1 mm of ST-segment depression or elevation or computer-ST integral decreased or increased ≥ 10 μV-s from resting value	8.3	*Placebo group*:		30	7.1	Age, LDL cholesterol level, HDL cholesterol level, systolic blood pressure, smoking, family history
		Normal exercise test result, 13/1000 person-years†	5.7 (2.7–12.2)			
		Abnormal exercise test result, 1.9/1000 person-years†	3.3 (1.8–5.9)‡			
		Cholestyramine group:				
		Normal exercise test result, 7.2/1000 person-years†	4.9 (2.2–10.8)†			
		Abnormal exercise test result, 1.5/1000 person-years†	2.9 (1.6–5.2)‡			
≥1 mm of horizontal or down-sloping ST-segment depression during or after exercise		Both test results normal, 7%	1.0			Age, sex, hypertension, fasting blood glucose level, total cholesterol level, BMI, smoking, exercise duration
	Abnormal electrocardiogram only, 16.0	Abnormal electrocardiogram only, 12%	2.4 ($P < 0.05$)	40	24	
	Abnormal thallium scan only, 14	Abnormal thallium scan only, 3%	1.4	NA	NA	
	Both test results abnormal, 6.0	Both test results abnormal, 48%	3.6 (1.6–8.1)	28	48	
ST segment corrected for heart rate index > 1.6 μV per beats per min, or abnormal rate recovery loop		Both test results normal, 1.6%	1.0			Age, sex, smoking, diastolic blood pressure, total cholesterol level, fasting blood glucose level, left ventricular hypertrophy on electrocardiography
	Either test result abnormal, 13 (416/3168)	Either test result abnormal, 4.1%	1.6 (1.1–2.5)	23	4	
		Both test results abnormal, 9.8%	2.7 (1.8–4.0)	8	10	
Visual code ≥ 1 mm ST-segment depression or elevation, or computer code ≥ 10 μV–s	6.6	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
≥1 mm (≥2 mm for women) of horizontal or down-sloping ST-segment depression in 3 consecutive beats during exercise or first 3 min of recovery		Normal, 3%	1.0			Age, sex
	Abnormal exercise electrocardiogram, 5.4	Abnormal exercise electrocardiogram, 7%	1.5 (0.2–12.5)	NA	NA	
	Abnormal plus thallium scan, 18.1	Abnormal thallium scan, 13%	3.6 (1.1–11.4)	63	20	
	Abnormal exercise electrocardiogram and scan, 4.6	Abnormal exercise electrocardiogram and scan, 50%	14.5 (4.2–50.2)	32	50	
ST segment corrected for heart rate index > 1.6 μV per beats per min	12.3 (729/5940)	Normal exercise test result, 1.3%†	3.6 (2.4–5.4)†	36	5	Age, diastolic blood pressure, cholesterol level, smoking
		Abnormal exercise test result, 5.4%†				
≥1 mm of horizontal or down-sloping ST-segment depression in ≥2 leads	22 (37/170)	Overall, 18%	4.23 (2.03–8.83)	55	46	Age, BMI, maximal Vo_2, fasting glucose level
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, supraventricular tachycardia	No risk factors, 3.0	No risk factors: Normal exercise test result, 0.08/1000 person-years†; abnormal exercise test result, 2.8/1000 person-years†	21 (6.9–63.3)†	60	2.2	Age
	>1 risk factor, 7.1	>1 risk factor: normal exercise test result, 0.5/1000 person-years†; abnormal exercise test result, 7.6/1000 person-years†	9.0†	61	7.7	

Continued

Table 3—**Continued—Bottom Left**

Study, Year (Reference)	Sample	Exclusion Criteria	Mean Duration of Follow-up	Test
			y	
Josephson et al., 1990 (11); Rywik et al., 2002 (21)	1083 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 electrocardiography, valvular disease, use of antiarrhythmic drugs, inability to achieve 85% of maximal heart rate	7.9	Modified Balke
Jouven and Ducimetière, 2000 (45)	6101 French men in Paris Civil Service; age range, 42–53 y; 100% men	Known or suspected CVD, resting systolic blood pressure ≥ 180 mm Hg, resting electrocardiographic abnormality	23	Bicycle ergometry
Laukkanen et al., 2001 (20)	1769 participants 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
Rutter et al., 2002 (13)	86 diabetic patients in the United Kingdom; mean age ± SD, 62 ± 7 y (range, 46–74 y); 72% men	History of CAD	2.8	Treadmill
Mora et al., 2003 (42)	2994 women enrolled in the Lipid Research Clinics Prevalence Study; age range, 30–80 y; 0% men	Pregnancy or clinically significant cardiovascular disease	20.3	Maximal Bruce

* 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; LDL = low-density lipoprotein; MRFIT = Multiple Risk Factor Intervention Trial; NA = not applicable; NR = not reported.
† CHD death.
‡ All-cause death.
§ For CHD events occurring during exercise.
‖ Minnesota code 11.1 = ≥1 mm J-point depression with flat or down-sloping ST segment in most complexes in any lead except aVR; Minnesota code 11.2 = horizontal or down-sloping ST-segment depression of 0.5–1.0 mm; Minnesota code 11.4 = J point depression of ≥ 1 mm with up-sloping ST; Minnesota code 11.5 = ST-segment depression at rest that worsens to 11.1 during exercise.
¶ Values are odds ratios (95% CI).

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 4000 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, $1780 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

Table 3—**Continued—Bottom Right**

Abnormal Test Result		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-Segment Response	Variables for Which Relative Risk Was Adjusted
Definition	Prevalence					
	% (n/n)			%		
Normal		Men: 4% Women: 3%	1.0¶	Men: 74 Women: 68	Men: 16 Women: 7	Age, cholesterol level, sex, exercise duration
Minnesota code 11.1‖	20	Men: 17% Women: 8%	2.7 (1.6–4.7)¶			
Minnesota code 11.5‖	5.5	Men: 17% Women: 11%	2.7 (1.05–7.10)¶			
Minnesota code 11.2	7	Men: 10% Women: 5%	1.8 (0.6–5.4)¶			
Minnesota code 11.4‖	11.5	Men: 17% Women: 3%	1.3 (0.6–2.9)¶			
J-point depression of at least 1 mm with a flat or down-sloping ST segment during exercise or recovery	4.4	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
>1 mm ST-segment depression during exercise	10.7	Normal exercise test result, 9.2%; 2.4%† Abnormal exercise test result, 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, maximum oxygen uptake, diabetes mellitus, LDL cholesterol level, HDL cholesterol level
>1 mm of horizontal or down-sloping ST-segment depression for 3 consecutive beats	52	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
≥ 1 mm horizontal or down-sloping ST-segment depression at 0.08 s after the J point during recovery or exercise	4.7	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

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 was considered as the outcome (12); we therefore excluded it 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 result on 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 result on 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 coro-

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

Study, Year (Reference)	Sample	Exclusion Criteria	Mean Duration of Follow-up	Test
			y	
Ekelund et al., 1988 (35)	3106 healthy white men in the Lipid Research Clinics Prevalence Survey in the 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
Lauer et al., 1996 (44)	1575 persons in the Framingham Offspring Study (predominantly white); mean age, 43 y; 100% men	Prevalent CAD, inability to reach stage 2, or use of β-blockers at time of exercise tolerance test	7.7	Submaximal Bruce
Wei et al., 1999 (48); Blair et al., 1996 (49)	25 714 patients at a preventive medicine clinic in the Texas Aerobics 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
Cole et al., 2000 (34)	5234 persons in the Lipid Research Clinics Prevalence Survey in United States and Canada; mean age > 30 y; 39% men	Age < 30 y; use of β-blockers, digoxin, antiarrhythmic agents, or nitrates; history of cardiovascular disease; or inability to reach stage 2	12	Bruce or modified submaximal Bruce
Jouven and Ducimetière, 2000 (45)	6101 French men in Paris civil service; age range, 42–53 y; 100% men	Known or suspected CVD, resting systolic blood pressure ≥ 180 mm Hg, or resting electrocardiographic abnormality	23	Bicycle ergometry
Morshedi-Meibodi et al., 2002 (47)	2967 participants in the Framingham Offspring Study; mean age ± SD, 43 ± 10 y; 47% men	Prevalent CVD, chronic obstructive pulmonary disease, use of digoxin or β-blockers, resting electrocardiographic abnormalities, or inability to complete stage 1	15	Submaximal Bruce
Rywik et al., 2002 (21)	1083 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 electrocardiogram, valvular disease, use of antiarrhythmic drugs, those who did not achieve 85% of maximum heart rate	7.9	Modified Balke
Frolkis et al., 2003 (46)	29 244 persons referred to the 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 transplantation, or concurrent evaluation for an arrhythmia	5.3	Submaximal Bruce
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
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	Maximum Bruce

* 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.
† CHD death.
‡ All-cause death.

nary 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 result on exercise tolerance

Table 4—**Continued**

Definition of Abnormal Test Result	Prevalence of Predictor	Cumulative Event Rate	Relative Risk (95% CI) for CHD Events with Positive Test	Sensitivity for CHD Events	Positive Predictive Value of Abnormal Test Result	Variables for Which Relative Risk Was Adjusted
	%			%		
Heart rate during stage 2 of exercise tolerance test and exercise time	Increase of 2 SDs in stage 2 heart rate Decrease of 2 SDs in time on the treadmill	0.26–1.69%†	3.2 (1.5–6.7) for abnormal heart rate recovery 2.8 (1.3–6.1) for decrease exercise time	NR	NR	Age, smoking, HDL cholesterol level, LDL cholesterol level, systolic blood pressure
Failure to achieve age- and sex-predicted target heart rate on exercise tolerance test	21	3% for those who reached target heart rate (all-cause death) 6% for those who failed to reach target 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
Low fitness according to age-based MET cut-points on exercise tolerance test	Normal weight: 10 Overweight: 19 Obese: 51	Overall; 1.7/1000 person-years†	Normal weight 1.7 (1.1–2.5)† 1.6 (1.3–2.1)‡ Overweight 1.9 (1.4–2.5)† 1.7 (1.4–2.6)‡ Obese 2.0 (1.2–3.6)† 2.3 (1.5–3.4)‡	36 52 79	4.6 5.4 3.4	Diabetes mellitus, cholesterol level, hypertension, current smoking, history of CVD, abnormal resting electrocardiogram, age, BMI, parental history of CVD, examination year
Abnormal heart rate recovery, defined as heart rate change ≤42 beats/min from peak exercise to that measured 2 min later	33	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
Premature ventricular complex constituting >10% of all ventricular depolarizations during exercise	2.3	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
Heart rate recovery index: decrease in peak heart rate to 2 min of <42 beats/min	NA	Overall: 7.2%	0.8 (0.5–1.1)‡	NA	NA	Age, BMI, smoking, systolic blood pressure, diastolic blood pressure, antihypertension medication, diabetes mellitus, total cholesterol level, HDL cholesterol level, resting heart rate, peak heart rate
Duration of exercise	NA	Overall: 7%	0.87 (0.79–0.96) (for CHD event for 1-min increase in exercise duration)	NR	NR	Age, cholesterol level, sex, ST-segment changes
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	5%‡ 11%‡ 9%‡	1.0 1.5 (1.1–1.9)‡ 1.1 (0.9–1.3)‡	3 4	12 9	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
Low exercise capacity (< 7.5 METs) and low heart rate recovery (<55 beats/min)	31	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, triglyceride level, hypertension
Exercise capacity, in METs	NA	3.2%‡	0.83 (0.78–0.89) for each 1-MET increase in exercise capacity	–	–	Framingham Risk Score

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 result on 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 result on 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 are 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 4158 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 result 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 about 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 β-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 nonobstructed segment of artery (78). Use of other measures from 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 such therapies as aspirin or statins to overtreat 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 expert panel, which also examined the effectiveness of screening exercise tolerance testing (33). They 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. The American Heart Association/American College of Cardiology found

that screening exercise tolerance testing for persons with multiple risk factors to guide 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 will 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 exercise tolerance testing screening plus risk factor–based decision making compared with risk-factor–based decision making alone.

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