Usefulness of Exercise Testing in the Prediction of Coronary Disease Risk Among Asymptomatic Persons as a Function of the Framingham Risk Score

Gary J. Balady, MD; Martin G. Larson, SD; Ramachandran S. Vasan, MD; Eric P. Leip, MS; Christopher J. O’Donnell, MD, MPH; Daniel Levy, MD

Background—The purpose of this study is to determine the usefulness of exercise treadmill testing (ETT) among asymptomatic persons in predicting coronary heart disease (CHD) events over and above the Framingham CHD risk score.

Methods and Results—Subjects included 3043 members of the Framingham Heart Study offspring cohort without CHD (1431 men and 1612 women; age, 45±9 years) who underwent ETT and were followed up for 18.2 years. The risk of developing CHD was evaluated relative to 3 exercise test variables: (1) ST-segment depression ≥1 mm, (2) failure to achieve target heart rate (THR) of 85% predicted maximum, and (3) exercise capacity. In multivariable analyses that adjusted for age and Framingham CHD risk score, among men, ST-segment depression (hazard ratio [HR], 1.88; 95% CI, 1.21 to 2.91) and failure to achieve THR (HR, 1.70; 95% CI, 1.18 to 2.45) predicted higher CHD risk, whereas a greater exercise capacity predicted lower CHD risk (HR per MET, 0.94; 95% CI, 0.89 to 0.99). Although similar HRs were seen in women, those results were not statistically significant. Among men with 10-year predicted risk ≥20%, failure to reach THR and ST-segment depression both more than doubled the risk of an event (HR, 2.66 and HR, 2.11, respectively), and each MET increment in exercise capacity reduced risk by 13% (HR, 0.87).

Conclusions—Among asymptomatic men, ST-segment depression, failure to reach THR, and exercise capacity during ETT provided additional prognostic information in age- and Framingham risk score-adjusted models, particularly among those in the highest risk group (10-year predicted CHD risk of ≥20%). The evaluation of exercise test variables in women is limited, given our sample size and the few CHD events in women. (Circulation. 2004;110:1920-1925.)

Key Words: exercise ■ risk factors ■ cardiovascular diseases

Exercise tests are used for diagnostic and prognostic purposes and for monitoring the effects of therapeutic interventions in patients with known or suspected coronary artery disease.1–3 However, the clinical usefulness of exercise testing in asymptomatic individuals remains unsettled. Exercise testing, when used arbitrarily to screen for coronary artery disease, is limited by many potential problems with regard to its diagnostic accuracy and prognostic value. Accordingly, the use of such testing for routine screening of asymptomatic men and women for coronary artery disease is not recommended.1 The Bayesian issues posed by testing patients with a low probability of coronary heart disease (CHD) may be reduced by screening a higher-risk group, such as those patients with a higher burden of risk factors for CHD. However, the use of exercise testing in asymptomatic individuals without known or suspected CHD but with risk factors for its development is inconsistent and based on a few studies.4–12 Such testing may be useful in guiding the intensity of treatment of risk factors, whereby individuals with abnormalities on the exercise test receive more aggressive risk factor treatment.13,14 Furthermore, exercise testing may also be useful to evaluate individuals who are about to engage in a moderate- to vigorous-intensity exercise training program. This is particularly important because the promotion of exercise and physical activity has become part of our nation’s public health agenda.15 Several studies demonstrate that the risk of a coronary event during physical exertion or exercise is greater than during rest, particularly among those who are generally sedentary.1–3 Thus, health care providers are prone to use exercise testing as a pretraining screening tool for patients with CHD risk factors, despite the current class IIb recommendation in the American College of Cardiology/American Heart Association Guidelines for Exercise Testing.1
TABLE 1. Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1431)</td>
<td>(n=1612)</td>
</tr>
<tr>
<td>Age, y, mean ±SD (range)</td>
<td>45±9 (30–70)</td>
<td>45±9 (30–70)</td>
</tr>
<tr>
<td>Hypertension, † %</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension treatment, %</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>207±36</td>
<td>202±40</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>43±11</td>
<td>54±14</td>
</tr>
<tr>
<td>Diabetes, † %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Smoker, ‡ %</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>Predicted CHD risk, ‰</td>
<td>9.6±7.5 (2–53)</td>
<td>3.9±4.4 (1–27)</td>
</tr>
</tbody>
</table>

*Hypertension is defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg or on antihypertensive treatment.
†Diabetes is defined as under treatment with insulin or oral hypoglycemic agents or if fasting blood sugar was >140 mg/dL at first or second examination.
‡Smoker is defined as person who smoked regularly during the previous 12 months.

Methods

Study Sample

In 1971, 5124 offspring and spouses of offspring of original Framingham Heart Study participants were recruited.17 At the second examination of the Framingham Heart Study offspring cohort, conducted during the years 1979 to 1982, 3861 participants underwent a complete history and physical examination, resting ECG, and measurement of serum cholesterol and blood glucose levels. Subjects performed an exercise test, except for 122 with known CHD (3.2%) and 292 subjects (7.6%) who did not perform the exercise test for the following reasons: 33 had medical contra-indication to exercise; 69 were unable to walk on the treadmill; 14 refused to participate; 95 were rescheduled to a later date but never returned; and 81 for unspecified reasons. An additional 404 subjects were excluded from analysis: 259 (6.7%) were under 30 years of age; 24 (0.6%) had bundle-branch block on resting ECG; 87 (2.3%) were taking digoxin or a β-adrenergic blocking agent; and 34 (0.9%) failed to reach ≥70% maximum predicted heart rate on exercise testing. Thus, the study sample included 3043 subjects: 1431 men and 1612 women. Their characteristics are outlined in Table 1.

Exercise Testing

Exercise treadmill testing (ETT) was performed according to the standard Bruce protocol,2 aiming for the attainment of age- and sex-adjusted target heart rates (THRs) of 85% predicted maximal response. However, exercise was terminated when necessary for fatigue (n=172), significant angina (n=15), ischemic ST-segment depression ≥2 mm (n=10), significant ventricular ectopy (n=52), systolic blood pressure ≥250 mm Hg or decreased during exercise (n=3), or other or unspecified reasons (n=21). Peak exercise capacity from the treadmill test was estimated in METs using data from standard prediction equations.3 Twelve-lead ECGs were obtained at rest, at the end of each stage, and each minute for the first 4 minutes of recovery. The test was considered positive in the presence of ≥1-mm horizontal or downsloping ST-segment depression in 3 consecutive beats of a single lead.

Risk Factor Analysis and Determination of Framingham Risk Score

Using age, sex, history of smoking, presence of diabetes, systolic and diastolic blood pressure, fasting serum total cholesterol, and HDL cholesterol, as determined at the clinic examination when the exercise test was performed, data were entered into the Framingham CHD risk score algorithm.14 The risk score was then used to predict the 10-year risk of CHD for each individual subject using sex-specific prediction equations. Procedures and criteria for assessing risk factors, calculation of the sex-specific Framingham risk score, and prediction of 10-year CHD risk have been detailed previously.16

Events and Follow-Up

Follow-up information and vital status were available for up to 20 years after the exercise test on all 3043 subjects. Using standardized criteria for each cardiovascular outcome, decisions regarding diagnosis were made by a panel of Framingham investigators. CHD events were defined by the presence of one of the following: (1) new onset of angina pectoris, as demonstrated by a typical history of chest pain according to a physician-administered questionnaire; (2) coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic ECG abnormalities without serum enzyme elevations characteristic of myocardial necrosis; (3) myocardial infarction, determined by the presence of 2 out of 3 clinical criteria (diagnostic Q-wave ECG changes, prolonged chest discomfort, and diagnostic elevation of serum biomarkers); or (4) CHD death, if, on the basis of the available information, the cause of death was probably CHD and no other cause could be ascribed.18

Statistical Analysis

To examine the relations of ETT performance variables with risk of subsequent CHD, multivariable proportional-hazards regression models were used.19 Each ETT variable was considered individually. Hazard ratios (HRs) and 95% confidence intervals (CIs) for ETT variables were estimated using SAS software20 in sex-specific analyses adjusted for age alone, then age plus Framingham risk score (point total). Last, sex-specific, age- and risk score–adjusted, stepwise multivariable proportional-hazards regression models were used to assess the combined effects of the 3 ETT performance variables on risk of CHD. For statistical significance threshold, a 2-sided value of P<0.05 was used.

In men, the sample was divided into 10-year risk categories of <10%, 10% to 19%, and ≥20% using the Framingham risk score. These were called risk groups 1 to 3. Kaplan-Meier estimates of survival free of CHD were calculated within each group according to values of ETT performance variables. This risk-based analysis was not performed in women because of the low number of CHD events in women and the small number of women with 10-year CHD risk ≥10%.

Results

The study sample contained 3043 subjects (1431 men and 1612 women) whose mean age was 45±9 years (range, 30 to 70 years). The risk factor characteristics of the subjects are outlined in Table 1. Only 3% of men and 1% of women had diabetes. The predicted 10-year CHD risk using the Framingham risk score14 was 9.6% (range, 2% to 53%) for men and 3.9% (range, 1% to 27%) for women. Ischemic ST-segment depression occurred during exercise in 4.8% of men and 3.8% of women; also, 8.8% of men and 9.1% of women failed to reach THRs of 85% predicted maximal response. The mean peak MET level during exercise testing was 12.7±2.5 for men and 10.6±2.3 for women.
A total of 305 subjects developed CHD during a mean follow-up of 18.2 years (range, 0.07 to 20 years) (Table 2). The majority of events (73%) occurred in men, who had an event rate of 15.7%, compared with 5.0% in women. Angina and myocardial infarction were the 2 most common initial CHD events in men and women alike. Age-adjusted and age- and Framingham risk score–adjusted HRs for CHD events associated with ischemic ST-segment depression and with failure to reach THR are shown in Table 3. Ischemic ST-segment depression and failure to reach THR were associated with an increased HR in men but not in women. Each 1-MET increment of exercise capacity conferred significantly lower CHD risk in men, with a similar but nonsignificant trend in women. In men, when ischemic ST-segment depression and failure to reach THR were jointly entered into the age- and points-adjusted stepwise model, their effects were slightly attenuated (HR, 1.71, 95% CI, 1.10 to 2.68; and HR, 1.57, 95% CI, 1.07 to 2.31, respectively), compared with each alone (Table 3). No ETT performance variables entered the stepwise model in women.

To evaluate exercise test variables as predictors of outcome after adjustment for CHD risk score, an analysis was performed using categories of predicted CHD risk. Table 4 shows age-adjusted HR for CHD events for exercise test variables in men stratified accordingly. HRs for exercise test variables were significant only in risk group 2 and 3 men (ie, variables in men stratified accordingly). HRs for exercise test variables were slightly attenuated (HR, 1.71, 95% CI, 1.10 to 2.68; and HR, 1.57, 95% CI, 1.07 to 2.31, respectively), compared with each alone (Table 3). No ETT performance variables entered the stepwise model in women.

An analysis was performed to assess whether a difference existed between covariate HRs in the second 10 years of follow-up compared with the first 10 years. No differences over time in age-adjusted risk were found for any of the variables.

**Discussion**

Recent consensus statements from the American Heart Association and the American College of Cardiology promote the use of global CHD risk assessment in applying preventive therapies to patients. Accordingly, the most recent national cholesterol guidelines have incorporated a risk score based on the Framingham Heart Study into the lipid management algorithm. The present study assessed the incremental value of exercise testing among asymptomatic persons without known CHD relative to their predicted CHD risk, and it is the first to do so among men using the Framingham CHD risk score. These data on 3043 subjects demonstrate a broad risk range of CHD risk (10-year predicted CHD risk of 2% to 53% in men and 1% to 27% in women). Among asymptomatic men, the occurrence of ischemic ST-segment depression, failure to reach THR, and exercise capacity during ETT provided additional prognostic information in age- and Framingham risk score–adjusted models. The effects were greatest in the highest-risk group of men (10-year predicted CHD risk of ≥20%). The reported risk relations for each variable remained similar during both the first and the last 10 years of follow-up. In low-risk men (10-year predicted CHD risk of <10%) and in women, none of the exercise test variables yielded incremental prognostic information. However, the evaluation of exercise test variables in women is limited in the present study, given our sample size and the few CHD events in women.

Our finding regarding the inverse relation between measured exercise capacity and reduced cardiovascular risk are in concert with other population-based studies of asymptomatic men and women and those of men referred to clinical exercise testing laboratories. Although all of these studies controlled for the presence of CHD risk factors, none of the studies on men assessed subjects relative to a global CHD risk score, as was done in the present study. Although it seems obvious to conclude that healthier persons, who by their nature have better exercise capacity, will therefore live longer, a wealth of emerging data provide new and exciting insights into this relationship. Encouraging data from patients with cardiovascular disease dem-

**TABLE 2. Categorization of Initial CHD Events**

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1431)</th>
<th>Women (n=1612)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>224 (15.7%)</td>
<td>81 (5.0%)</td>
</tr>
<tr>
<td>Angina</td>
<td>111</td>
<td>45</td>
</tr>
<tr>
<td>Coronary insufficiency</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>CHD death</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are n (%).

**TABLE 3. Age and Framingham Risk Score–Adjusted Hazards Ratios for CHD Events According to ETT Variables**

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1431)</th>
<th>Women (n=1612)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted</td>
<td>Age- and Points-Adjusted</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>2.22 (1.44–3.42)</td>
<td>1.88 (1.21–2.91)</td>
</tr>
<tr>
<td>Failure to reach THR</td>
<td>2.00 (1.40–2.86)</td>
<td>1.70 (1.18–2.45)</td>
</tr>
<tr>
<td>METs (per 1 MET increment)</td>
<td>0.90 (0.85–0.95)</td>
<td>0.94 (0.89–0.99)</td>
</tr>
</tbody>
</table>

ETT indicates exercise treadmill testing; METs, metabolic equivalents; and THR, target heart rate.
onstrate that less fit or less active individuals may improve their survival if they increase their level of fitness or physical activity. Failure to achieve a predicted heart rate during exercise testing has been shown to be associated with an adverse CHD prognosis in previous clinical studies and population-based studies. Although the mechanisms for this observation are unclear, several hypotheses have been proposed.

The use of exercise testing in asymptomatic persons without known CHD but with certain cardiovascular disease risk factors has been addressed by previous studies. The Seattle Heart Watch study evaluated 2365 asymptomatic men, all of whom underwent a symptom-limited exercise test and were followed up for 5.6 years. The results of exercise testing were not predictive of the combined adverse outcome (angina, myocardial infarction, cardiac death) in the group as a whole. However, in patients with 1 or more risk factors and 2 or more abnormal features on exercise testing (chest pain, exercise time <6 minutes, attainment of <90% predicted heart rate, or ST-segment depression), there was a 30-fold increment in CHD risk. The broad application of these data is limited, because these latter high-risk subjects represented only 1% of the study group, subjects with diabetes or hypertension were excluded, and only a single ECG lead was monitored for analysis. Previous data from the Framingham Heart Study demonstrated that failure to reach THR and abnormal ST/heart rate indices were predictive of CHD events among asymptomatic individuals when controlled for age and cardiac risk factors. Neither of these exercise test variables was assessed relative to global CHD risk, as was done in the present study. Gibbons et al studied 25000 asymptomatic men (mean age, 42 years) who underwent maximal treadmill exercise testing and were followed up for 8 years for the occurrence of CHD death. CHD risk was assessed by counting the number of risk factors present in each subject. An abnormal exercise test response was defined collectively as the occurrence of angina, ST-segment depression, complex ventricular ectopy, or hypotension. Although CHD death in the entire group was low (0.6%), the age-adjusted relative risk of an abnormal exercise test was 21, 27, 54, and 80, respectively, in those with 0, 1, 2, and ≥3 risk factors. That study differed from others in that maximal exercise testing was used with full 12-lead ECG monitoring throughout the test and for 10 minutes after exercise. Unfortunately, the clinical usefulness of these data is limited, because the exercise test variables were analyzed as a composite rather than separately. In another study of 1083 asymptomatic subjects (mean age, 52 years), Rywik et al demonstrated that ≥1-mm horizontal or downsloping ST-segment depression during treadmill exercise testing yielded an odds ratio of 2.7 for the occurrence of CHD events (angina, myocardial infarction, death) when controlled for age, sex, and cholesterol level.

Two recent studies have provided important results in large numbers of asymptomatic women controlled for CHD risk who underwent treadmill testing. Gulati et al assessed 5721 female volunteers (mean age, 52 years) without known coronary artery disease who were followed up for 8 years. Exercise capacity in METs was an independent predictor of all-cause mortality when adjusted for Framingham Risk Score, whereby for each 1-MET increment, there was a 17% reduction in the risk of death. ST-segment depression was not predictive of mortality. These women were older and had a higher prevalence of diabetes (4.9%) than the women in our present study and thus represent a higher-risk group. Similarly, Mora et al assessed 2994 asymptomatic women in the Lipid Research Clinics Prevalence Study for the occurrence of total and cardiovascular mortality in 20-year follow-up after treadmill testing. After adjustment for cardiovascular risk factors, women who were below the median for both exercise capacity and heart rate recovery demonstrated a 3.5-fold increase in cardiovascular death. Although 95% of the women in that study were at low cardiovascular risk as determined by their Framingham risk score, those who were below the median for both exercise capacity and heart rate recovery demonstrated significantly increased risk of cardiovascular death compared with those above the median for both of these variables.

The present study is limited in that exercise testing was terminated when a subject achieved 85% of predicted maximum heart rate. Perhaps, if maximal testing had been performed and the ECG was monitored for longer duration after the test, ST-segment changes might have been more frequent, yielding a more powerful analysis for this variable. The occurrence of angina composed approximately half of the CHD events in both men and women. Thus, the number of nonfatal myocardial infarctions and CHD deaths was too low to allow for an analysis of exercise test variables in predicting the risk of hard CHD events. Also, the number of women with intermediate or higher predicted CHD risk was low, and there

### Table 4. Age-Adjusted Hazards Ratios for CHD Events According to ETT Variables Stratified for 10-Year Predicted Risk Groups: Men

<table>
<thead>
<tr>
<th>Risk Group 1, 10-year CHD Risk &lt;10%</th>
<th>Risk Group 2, 10-year CHD Risk 10%–19%</th>
<th>Risk Group 3, 10-year CHD Risk ≥20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/at risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72/863</td>
<td>93/413</td>
<td>59/144</td>
</tr>
<tr>
<td>Predicted CHD risk, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2 (2–8)</td>
<td>12.7 (10–16)</td>
<td>26.9 (20–53)</td>
</tr>
<tr>
<td>Hazard ratios (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.55 (0.56–4.28)</td>
<td>2.01 (1.01–3.99)</td>
<td>2.11 (1.06–4.20)</td>
</tr>
<tr>
<td>Failure to reach THR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.74 (0.23–2.36)</td>
<td>1.69 (0.96–2.98)</td>
<td>2.66 (1.52–4.67)</td>
</tr>
<tr>
<td>METs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.94 (0.85–1.03)</td>
<td>0.97 (0.88–1.06)</td>
<td>0.87 (0.78–0.96)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Women. Our study suggests that predicted CHD risk using the Framingham risk score should be taken into account before performing ETT in asymptomatic men, because such testing appears to have the greatest yield among those men with highest CHD risk.

Acknowledgments

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References


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