PATHOPHYSIOLOGY AND NATURAL HISTORY

EXERCISE TESTING

Predictive value of the exercise tolerance test for mortality in North American men: The Lipid Research Clinics Mortality Follow-up Study*

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ABSTRACT More than 3600 white men, from 30 to 79 years old and without a history of myocardial infarction, underwent submaximal treadmill exercise tolerance tests as part of their baseline evaluation for the Lipid Research Clinics Mortality Follow-Up Study. The exercise test was conducted according to a common protocol and coded centrally; depression of the ST segment by at least 1 mm (visual coding) and/or 10 μV·sec (ST integral, computer coding) signified a positive test. Concurrent measurements of age, blood pressure, history of cigarette smoking, and plasma levels of lipids, lipoproteins, and glucose, as well as other coronary risk factors, were obtained. Cumulative mortality from cardiovascular disease was 11.9% (22/185) over 8.1 years mean follow-up among men with a positive exercise test vs 1.2% (36/2993) over 8.6 years mean follow-up among men with a negative test. Three-quarters (43) of these deaths were due to coronary heart disease. The relative risk for cardiovascular mortality associated with a positive exercise test was 9.3 before and 4.6 after age adjustment. Cardiovascular mortality rates were especially elevated (relative risk 15.6 before and 5.1 after age adjustment) among the 82 men whose exercise tests were adjudged "strongly" positive based on degree and timing of the ischemic electrocardiographic response. A positive exercise test was also moderately associated with noncardiovascular mortality; the relative risk for all-cause mortality was 7.2 before and 3.4 after age adjustment. The relative risk for cardiovascular mortality associated with a positive exercise test was not appreciably altered by covariance adjustment for known coronary risk factors other than age. A positive exercise test was a stronger predictor of cardiovascular death than were high plasma levels of low-density lipoprotein cholesterol, low plasma levels of high-density lipoprotein cholesterol, smoking, hyperglycemia, or hypertension. Its impact on risk of cardiovascular death was equivalent to that of a 17.4 year increment in age.


EXERCISE tolerance tests are widely used in the evaluation of patients in whom coronary heart disease (CHD) is suspected.1 Subjecting an individual to a series of increasing workloads so as to gradually in-

crease his or her heart rate is a safe and noninvasive method of eliciting electrocardiographic signs of ischemia that are apparent at rest. In this way one may corroborate objectively a patient’s subjective symptoms. Exercise-induced electrocardiographic changes correlate well (although imperfectly) with the angiographic demonstration of coronary lesions2-4 and are highly prognostic of subsequent mortality in such patients.5,6 The predictive value of a positive exercise test for subsequent cardiovascular events in predominantly asymptomatic populations and how it might be influenced by known CHD risk factors such as smoking, blood pressure, and plasma lipids is more controversial.7-17 Since the prevalence of positive exercise tests and that of CHD are small in such populations, only a large study with several years of follow-up can address this issue adequately.
In one such study, involving more than 11,000 Italian workers followed for 5 to 10 years, the incidence rate of CHD events (coronary death, nonfatal myocardial infarction, and/or angina pectoris) in 135 asymptomatic normotensive subjects with reproducibly abnormal submaximal exercise tests (horizontal or downsloping ST segment depression of 1 mm or more) was 5.5 times higher than that in 379 matched controls. Since cases and controls were matched with respect to their “coronary risk index” (a linear combination of smoking, blood pressure, age, and serum cholesterol at baseline), the prognostic value of a positive exercise test appeared to be independent of these other risk factors. The authors did not report whether the risk ratio differed significantly between upper and lower strata of these risk factors. In another large study, a 10 year follow-up of 3611 men and 547 women initially free of clinical CHD, a positive exercise test was predictive of an increased incidence of manifestations of CHD only among participants with at least one other CHD risk factor (smoking, hypertension, hypercholesterolemia, diabetes, family history, angina pectoris) at baseline.

The present report concerns the ability of a single submaximal exercise test to predict death from CHD and from other cardiovascular and noncardiovascular causes in 1870 normolipidemic and 1770 hyperlipidemic 30- to 79-year-old white male participants in the Lipid Research Clinics (LRC) Prevalence Study. The constancy of the predictive value of the exercise test among various CHD risk factor strata, as well as its persistence after adjusting statistically for these risk factors, is examined.

Methods

Study participants. The LRC Prevalence Study, conducted between 1972 and 1976, consisted of a preliminary screening (visit 1) of men and women from predefined populations at 10 participating centers who were chosen by a complex sampling procedure (see below). In 1977, a mortality surveillance follow-up study of all visit 2 participants of age 30 or above was begun to assess the relationship of certain baseline characteristics to subsequent overall and cause-specific mortality. This surveillance was performed by mail and telephone contact. No treatment of any kind was provided, and no additional examinations were performed.

Because of the paucity of exercise test data in nonwhites and in the very elderly and because of the infrequency of cardiovascular death among women who were able to complete the exercise test, the present report is restricted to white men under age 80 at baseline. Fasting levels of plasma cholesterol and triglyceride were determined in 17,719 white men between the ages of 30 and 79 at visit 1 of the study. The following men were invited to return for visit 2: (1) 15% random sample of all visit 1 participants, (2) those whose visit 1 plasma cholesterol levels met or exceeded the following age-specific cutpoints: 240 mg/dl for ages 30 to 39, 260 mg/dl for ages 40 to 49, and 280 mg/dl for ages 50 +, (3) those whose visit 1 plasma triglyceride levels exceeded the following age-specific cutpoints: 250 mg/dl for ages 30 to 39, and 300 mg/dl for ages 40 +, (4) those who indicated at visit 1 that they were currently taking cholestryamine, colestipol, clofibrate, nicotinic acid, and/or "other lipid-lowering drugs," and (5) individuals with borderline elevations in cholesterol and/or triglyceride levels, the definition of which varied among the 10 participating centers. The 268 age-eligible white men in this variably defined group have been excluded from consideration in the present report.

Because of the “oversampling” of hyperlipidemic men from the parent population, special statistical procedures, which took sampling probabilities into account, were required to derive mortality rates that would apply to the parent population. For these procedures (described under Statistical Methods below), separately computed mortality rates were used for participants who met the criteria for hyperlipidemia specified under Nos. 2, 3, and 4 at visit 1 (hyperlipidemics) and for participants not meeting those criteria at visit 1 (normolipidemics). Note that the hyperlipidemic subpopulation included a portion of the 15% random sample (No. 1 above) as well as men who were selected because of their hyperlipidemia. Thus, if all invitees had attended visit 2, the normolipidemic and hyperlipidemic subpopulations at visit 2 would have represented 15% and 100%, respectively, of the normolipidemic and hyperlipidemic men who attended visit 1. The actual sampling data are shown in table 1. Actual response rates ranged from 86% to 92%, and the ratio of sampling frequencies was close to the expected 0.15 in all age groups.

Ascertainment of death. Beginning in 1977–78, participants were contacted annually. When a death was discovered, the death certificate and interviews with a witness or next of kin were obtained. Two members of a panel of five cardiologists, who were uninformed as to the identity or baseline characteristics of the cases they reviewed, assigned the cause of death as CHD, cardiovascular disease, or “other.” (Note that the cardiovascular disease category includes CHD.) Disagreements between the two primary reviewers were adjudicated by the full panel. Although the study is ongoing, the present report is based on deaths ascertained during or before the 1983–84 contact year, an average follow-up of 8.4 years. The vital status of all but five of the 4189 participants under consideration was established at least one time between 1977 and 1984. There have been 306 deaths, of which 103 were attributed by the panel to CHD and 58 to other cardiovascular causes.

The exercise test. A submaximal treadmill exercise test by a modified Bruce protocol was administered to participants judged fit to perform the test safely. The test consisted of a series of seven 3 min stages in which the speed and inclination were increased stepwise and during which the electrocardiogram was monitored continually for heart rate and voltage changes. The test was stopped when a preset target heart rate — 90% of the maximal heart rate predicted for the participant’s age and level of physical conditioning — was attained. The analysis of exercise test outcome as a predictor of mortality was restricted to those men who (1) were eligible for and performed at least 1 min of the standard exercise test protocol, (2) had no clinical or resting electrocardiographic evidence of ischemic myocardial damage or left ventricular hypertrophy, (3) were not using digitalis, and (4) had their vital status ascertained at least once between 1977 and 1984. The specific exclusion criteria and the number of men disqualified by each criterion are given in table 2. Men with angina pectoris (by Rose questionnaire) or with a history of exertional dyspnea were not specifically excluded; the prevalence of these findings among the remaining 3640 men were 2.9% and 12.9%, respectively.

Exercise tests were classified as positive or nonpositive for
testing despite physical or heart disease, hypertension, R-on-T includes only those electrocardiographic recordings (V4, V5, and V6) and Frank (X, Y, and Z) leads, from which tracings of representative portions were generated. Each test was coded both by certified technicians, who examined the degree of ST ischemia at the electrocardiographic coding center in Birmingham, AL, which applied uniform criteria for all tests performed at the 19 participating LRCs. The coding center received electromagnetic tapes of each exercise test containing continuous electrocardiographic recordings in the precordial (V4, V5, and V6) and Frank (X, Y, and Z) leads, from which tracings of representative portions were generated. Each test was coded both by certified technicians, who examined the degree of ST depression (or elevation) at 0.08 sec after the nadir of the J point, and by a computer program, which calculated the ST integral. In most cases the visual and computer codes were in agreement. Discrepant results were evaluated by a supervisor, and erroneous codes were corrected or deleted. A test was considered to be positive if (1) ST depression or elevation of 1 mm or more was recorded by the visual coder, (2) the ST integral fell by at least 10 μV·sec from its resting value to a value of 10 μV·sec or less, or (3) the ST integral rose by at least 10 μV·sec from its resting value. The prevalence of positive tests was 5.1% (185/3640). This low prevalence probably reflected the use of a submaximal (rather than maximal) exercise test and the disqualification of many participants with known heart disease from exercise testing.

Since a greater ST response or one that occurs at a lower workload is likely to be indicative of more severe functional impairment of the myocardial circulation, positive tests were subdivided further according to the degree of ST depression (or elevation) and by how early in the test it was observed. Positive tests in which the ST response was at least 2 mm or occurred during the first 6 min of the exercise test or at a heart rate at or below 163 - 0.66 · age were considered "strongly positive." Nonpositive tests that were not terminated due to other possible manifestations of cardiovascular disease (chest or leg pain, cerebral symptoms, hypotension, arrhythmia, or heart block) and in which the maximal heart rate was at least 180 - 0.66 · age were considered negative, since such tests demonstrated an ability to maintain a functionally adequate circulation at heart rates within 30 beats/min (and levels of oxygen consumption within 15% to 20%) of the expected physiologic limit. Other nonpositive tests (12.7% of all tests performed) were considered "inconclusive" and were not analyzed further.

**Risk factor measurements.** Plasma lipid, lipoprotein, and glucose levels were measured after 12 or more hours of fasting. Low-density lipoprotein cholesterol (LDL-C) levels were determined ultracentrifugally. Information on smoking history, alcohol consumption, medications, and physical activity was obtained by questionnaire. Height and weight were measured with the participant wearing light clothing but no shoes. Quetelet index was calculated by dividing weight (in grams) by the square of height (in centimeters). Blood pressure was measured after 5 min in a sitting position; the first of four readings was used.

Dichotomous classifications, based on medication consumption as well as clinical measurement, were constructed for blood pressure, plasma glucose, and plasma LDL-C. Participants with

### TABLE 1
Composition of study population — white men

<table>
<thead>
<tr>
<th>Age decade</th>
<th>Normal lipidemic men</th>
<th>Hyperlipidemic men*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up study</td>
<td>Selection ratio</td>
</tr>
<tr>
<td></td>
<td>Parent population</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>4621 (13.9%)</td>
<td>0.152</td>
</tr>
<tr>
<td>40–49</td>
<td>4732 (13.4%)</td>
<td>0.147</td>
</tr>
<tr>
<td>50–59</td>
<td>3755 (14.7%)</td>
<td>0.162</td>
</tr>
<tr>
<td>60–69</td>
<td>1612 (12.8%)</td>
<td>0.148</td>
</tr>
<tr>
<td>70–79</td>
<td>720 (13.1%)</td>
<td>0.141</td>
</tr>
<tr>
<td>Total age</td>
<td>15440 (13.8%)</td>
<td>2279 (90.6%)</td>
</tr>
</tbody>
</table>

*Men with plasma cholesterol and/or triglyceride levels above age-specific cutpoints and/or using lipid lowering drug(s) at initial screening (see text).

The ratio of the proportion of eligible normal lipidemic men in the parent population entered in the follow-up study to the proportion of eligible hyperlipidemic men in the parent population entered in the follow-up study.

### TABLE 2
Exclusions from analysis*

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to follow-up</td>
<td>5</td>
</tr>
<tr>
<td>No exercise test</td>
<td>379</td>
</tr>
<tr>
<td>Duration less than 1 minute</td>
<td>7</td>
</tr>
<tr>
<td>Nonstandard exercise test protocol†</td>
<td>8</td>
</tr>
<tr>
<td>Ineligible for exercise testing‡</td>
<td>90</td>
</tr>
<tr>
<td>Prior myocardial infarction§</td>
<td>9</td>
</tr>
<tr>
<td>On digoxis</td>
<td>15</td>
</tr>
<tr>
<td>History of heart surgery</td>
<td>4</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>5</td>
</tr>
<tr>
<td>ETT coding ambiguity</td>
<td>27</td>
</tr>
</tbody>
</table>

ETT = exercise tolerance test.

*For white male participants, 30 to 79 years old, derived by the sampling mechanism described in table 1. Exclusions are listed hierarchically so as to be mutually exclusive; for example, the 90 men listed as ineligible for exercise testing all performed at least 1 min of the standard exercise test.

†A preliminary stage with speed and inclination of the treadmill set below standard stage 1 levels was included for subjects unable to perform the standard test.

‡Subjects with signs of aortic stenosis, congestive heart failure, hypertension, R-on-T type premature ventricular contractions, ventricular tachycardia, a parasympathetic focus, atrial fibrillation or fibrillation, congenital heart disease, suspected acute myocardial injury or unhealed infarction, or physical impediments significantly impairing their ability to walk on the treadmill.

§By history and/or resting electrocardiogram. Note that this entry includes only those men who were eligible for and underwent exercise testing despite a prior myocardial infarction, and thus represents only a small fraction of the participants with this condition.
systolic blood pressures of at least 160 mm Hg and/or with
diastolic blood pressures of at least 95 mm Hg and/or who
reported using antihypertensive drugs (e.g., methyldopa, hy-
dralazine) or diuretics (e.g., thiazides) commonly used for low-
nering blood pressure, were counted in this category. Other
diuretics (such as furosemide) were not considered antihy-
tensive drugs unless explicitly said to have been prescribed for
that purpose; nine normotensive men who were using these
drugs were excluded from analyses involving blood pressure.

Of 552 "hypertensives," 344 (62%) had elevated diastolic
blood pressures, while 59 (11%) had isolated systolic hyperten-

sion. Among 240 men (43%) under treatment for hypertension, 149
had blood pressures below 160/95 mm Hg.

Men with plasma glucose levels above 115 mg/dl and/or
taking hypoglycemic drugs (e.g., insulin, tolbutamide, chloro-
propamide, phenformin) were classified as hyperglycemic. Of
299 hyperglycemic men, 81 (27%) had plasma glucose levels at
or above 140 mg/dl and 43 (14.4%) were taking hypoglycemic
drugs.

Men with plasma LDL-C levels at or above 180 mg/dl were
assigned to the "high LDL-C" category. Those with plasma
LDL-C below 180 mg/dl who were not taking lipid-lowering
drugs were assigned to the "low LDL-C" category. Men with
LDL-C levels of less than 180 mg/dl who were taking lipid-
lowering drugs were not assigned to either category, since
the original indication for treatment (high LDL-C or high triglyc-
ereide levels) could not generally be determined.

Statistical methods. Within the hyperlipidemic and normoli-
demic subpopulations, mortality rates were computed by di-
viding the number of deaths by person-years of follow-up. Age-
adjusted relative risks associated with exercise test outcome
within these subpopulations and failure curves for men with
positive and negative exercise tests were computed by the pro-
portional-hazards model. A standard statistical software pack-
age (the SAS PHGLM procedure) was used in these computa-
tions.

Since the performance of separate analyses for the hyperlipi-
demic and normolipidemic subpopulations was both cumber-
some and impractical in situations involving stratification with
respect to other risk factors, methods for computing summary
mortality rates and relative risks applicable to the original LRC
Prevalence Study population were required. To calculate mor-
tality rates, the numbers of deaths occurring in the hyperlipi-
demic and normolipidemic subpopulations were combined with
weights corresponding to the inverse of their relative probabil-

ities of sampling from the parent population. Person-years of
follow-up for the two subpopulations were similarly combined.
Summary (unadjusted) mortality rates were calculated as ratios
of these weighted sums of deaths and person-years.

Age-adjusted relative risks associated with exercise test out-
come were computed with a weighted discrete proportional-
hazards model, employing the weights described above for the
hyperlipidemic and normolipidemic subpopulations. The fol-
low-up period was subdivided into five 2 year intervals, con-
taining seven, 14, nine, nine, and four deaths from CHD; 10,
16, 13, 14, and five total deaths from cardiovascular disease;
and 10, 15, 17, 15 and 15 other deaths. It was assumed that the
mortality rate ratio associated with a positive vs a negative
exercise test was constant over time within each of the two
subpopulations (i.e., proportionality of hazards). No deaths had
occurred at follow-up times exceeding 10 years. Because of the
paucity of deaths from cardiovascular disease after 8 years of
follow-up, only the first four intervals were considered in mod-
eling CHD and cardiovascular disease mortality.

Note that the procedures described in this section were de-
signed to estimate the relationships that would be pertinent
in the parent population or in a uniform probability sample derived
therefrom. The weighting by sampling probabilities, despite its
superficial resemblance to direct adjustment, does not in itself
adjust for possible confounding of the relationship of exercise
test outcome and mortality by hyperlipidemia. Such adjust-
ment, when desired, was accomplished by incorporating the
lipid level of interest as a covariable in the weighted discrete
proportional-hazards model.

Results
The baseline characteristics and follow-up data for each of the exercise test categories are given in table 3. Among nearly 3000 men with negative exercise tests at baseline, 3.2% had died by mid-1984, 1.2% of cardio-
vascular causes (mostly CHD). By contrast, 25.6% of the men with strongly positive and 12.6% of those with
weakly positive exercise tests had died. The vast ma-
}

TABLE 3
Descriptive statistics for white 30- to 79-year-old men in LRC Follow-Up Study^a

<table>
<thead>
<tr>
<th>Exercise test outcome</th>
<th>n</th>
<th>Percent hyperlipidemic</th>
<th>Mean age (years)</th>
<th>Mean follow-up (years)</th>
<th>CHD</th>
<th>Cardiovascular disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly positive^a</td>
<td>82</td>
<td>56.1</td>
<td>58.1</td>
<td>7.85</td>
<td>14.6</td>
<td>20.7</td>
<td>25.6</td>
</tr>
<tr>
<td>Weakly positive</td>
<td>103</td>
<td>49.5</td>
<td>50.5</td>
<td>8.27</td>
<td>3.9</td>
<td>4.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Negative</td>
<td>2993</td>
<td>48.6</td>
<td>43.2</td>
<td>8.56</td>
<td>0.9</td>
<td>1.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Inconclusive^c</td>
<td>462</td>
<td>47.0</td>
<td>51.5</td>
<td>8.28</td>
<td>2.4</td>
<td>4.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Excluded (see table 2)</td>
<td>544</td>
<td>53.5</td>
<td>53.0</td>
<td>7.74</td>
<td>9.0</td>
<td>14.9</td>
<td>23.0</td>
</tr>
</tbody>
</table>

^aFive men who could not be recontacted and contributed no person-years of follow-up are omitted from this tabulation.
^bIncludes 38 tests with ≥2 mm (and/or ≥20 μV·sec) ST depression, 57 positive tests of duration ≤6 min (two stages), and 10
positive tests with heart rate ≥163 – 0.66·age. Note that these criteria are not mutually exclusive.
^cIncludes 270 nonpositive tests terminated at heart rate ≥180 – 0.66·age and 285 nonpositive tests terminated because of chest
or leg pain, cerebral symptoms, hypotension, arrhythmia, or heart block. Note that these criteria are not mutually exclusive.
that of the group with a negative exercise test. Mortality among men with an inconclusive exercise test was higher than among men with a negative test, although not as high as among those with a positive test. Mortality was very high in the excluded group, of which a high proportion (including most of those who were not tested) had known organic heart disease. There were also large differences in mean age among these groups; for example, the mean age of the strongly positive test group was nearly 15 years greater than that of the negative test group. Additionally, the strongly positive test group had the largest proportion of hyperlipidemics. Thus, one may not infer from table 3 alone that exercise test performance was an independent prognostic factor for mortality.

The mortality rates for men with a strongly positive or with any positive exercise test outcome at baseline are compared with those for men with a negative exercise test outcome in table 4 and in figure 1. Within both the hyperlipidemic and normolipidemic subpopulations, the crude mortality rates for CHD, cardiovascular disease, and for all causes were consistently highest among the men with a strongly positive test and lowest among the men with a negative exercise test (table 4). The gradient was steeper among hyperlipidemic than among normolipidemic men and was steeper for cardiovascular than for noncardiovascular deaths. After age adjustment, the relative risk of cardiovascular death for a man with a positive vs a negative exercise test was 5.7 in the hyperlipidemic and 4.0 in the normolipidemic subpopulation. The CHD, cardiovascular disease, and all-cause mortality curves for men with positive vs negative exercise tests appeared to diverge steadily throughout the period of follow-up in both subpopulations (figure 1). Thus, the relative risk associated with a positive test did not appear to vary over time.

A strongly positive exercise test conferred a substantial additional increment in risk of cardiovascular mortality in the hyperlipidemic population (relative risk increased to 10.1) but not in the normolipidemic population (relative risk remained at 4.0). However, the confidence intervals for these estimates of relative risk were very wide and overlapped considerably (table 4); no statistically significant interaction of hyperlipidemia and exercise test outcome could be demonstrated. When the results for the two subpopulations were combined (table 4), the relative risk of cardiovascular death was 4.6 for men with a positive exercise test and 5.1 for those with a strongly positive test. These relative risks as well as those for CHD and all-cause mortality differed highly significantly (p < .001) from unity.

The independence of the predictiveness of a positive exercise test for cardiovascular mortality from that of the known major CHD risk factors was further examined by estimating relative risk within strata of cigarette smoking, blood pressure, and plasma levels of glucose, LDL-C, and high-density lipoprotein cholesterol (HDL-C), in addition to age (table 5). Due to the limited number of cardiovascular deaths among men with positive exercise tests, it was not feasible to perform the analysis separately for the hyperlipidemic and normolipidemic subpopulations, to separate strongly positive from other positive tests, to separate CHD from other cardiovascular deaths, or to stratify on more than one risk factor at a time. A positive exercise test was associated with a 1.8- to 12.6-fold increase in risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Exercise test outcome</th>
<th>n</th>
<th>Deaths</th>
<th>Rate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative risk&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CHD</th>
<th>All cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemic subpopulation</td>
<td>Strongly positive</td>
<td>46</td>
<td>9</td>
<td>254 (21.0)</td>
<td>10.0 (3.6-27.6)</td>
<td>11</td>
<td>310 (22.6)</td>
</tr>
<tr>
<td></td>
<td>All positive</td>
<td>97</td>
<td>11</td>
<td>140 (11.6)</td>
<td>5.8 (2.4-14.3)</td>
<td>13</td>
<td>165 (12.0)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>1456</td>
<td>15</td>
<td>12.1</td>
<td>1.00</td>
<td>17</td>
<td>13.7</td>
</tr>
<tr>
<td>Normolipidemic subpopulation</td>
<td>Strongly positive</td>
<td>36</td>
<td>3</td>
<td>104 (11.4)</td>
<td>4.2 (1.0-17.1)</td>
<td>6</td>
<td>207 (14.4)</td>
</tr>
<tr>
<td></td>
<td>All positive</td>
<td>88</td>
<td>5</td>
<td>71 (7.8)</td>
<td>4.3 (1.4-13.2)</td>
<td>9</td>
<td>127 (8.8)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>1537</td>
<td>12</td>
<td>9.1</td>
<td>1.00</td>
<td>19</td>
<td>14.4</td>
</tr>
<tr>
<td>All subjects&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Strongly positive</td>
<td>82</td>
<td>12</td>
<td>127 (13.4)</td>
<td>5.0 (1.7-15.1)</td>
<td>17</td>
<td>224 (15.6)</td>
</tr>
<tr>
<td></td>
<td>All positive</td>
<td>185</td>
<td>16</td>
<td>81 (8.5)</td>
<td>4.6 (1.8-11.7)</td>
<td>22</td>
<td>133 (9.3)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>2993</td>
<td>27</td>
<td>9.5</td>
<td>1.00</td>
<td>36</td>
<td>14.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Per 10,000 person-years of follow-up, not age adjusted. The ratio of this rate to that in men with a negative exercise test is given in parentheses.

<sup>b</sup>Antilog (base e) of proportional-hazards regression coefficient for exercise test outcome, with covariance adjustment for age as a continuous variable. Ninety-five percent confidence intervals are given in parentheses. The relative risk for a negative exercise test is unity, by definition.

<sup>c</sup>Rates and relative risks are adjusted for unequal sampling of hyperlipidemic and normolipidemic men from parent population (see Methods).
for cardiovascular mortality within the risk factor strata examined, and was a highly significant independent predictor of cardiovascular mortality in each model. Note that the larger relative risks and Z scores associated with a positive exercise test in the stratified model for age reflect the fact that the dichotomous stratification used in this model only partially adjusted for the effect of age, as compared with the continuous age term used in the other models. In the models in which strata of age and LDL-C were used, the Z scores for interaction suggested that exercise test outcome might predict mortality most strongly in younger men and in men with lower plasma LDL-C levels, but in view of their marginal significance and the considerable number of statistical tests performed, neither result should be regarded as definitive.

In the absence of demonstrably strong interactions between exercise test outcome and other risk factors as predictors of cardiovascular mortality, a weighted discrete proportional-hazards multiple regression model with terms for all seven variables and no interaction terms was computed (table 6). Even after adjustment for these six other risk factors, a positive exercise test was associated with a 4.2-fold increase in risk of cardiovascular mortality. This relative risk was substantially greater than that associated with any of the dichotomous risk factors analyzed and was equal to that associated with a 17.4 year increment in age. In the model including no covariance adjustments other than age (table 4), the 4.6-fold increase in risk of cardiov-

### TABLE 4  
(Continued)

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Rate(^a)</th>
<th>Relative risk(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>367 (8.7)</td>
<td>3.2 (1.6–6.5)</td>
</tr>
<tr>
<td>16</td>
<td>203 (4.8)</td>
<td>2.0 (1.1–3.8)</td>
</tr>
<tr>
<td>52</td>
<td>41.9</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td>276 (8.3)</td>
<td>2.1 (0.9–4.6)</td>
</tr>
<tr>
<td>18</td>
<td>254 (7.6)</td>
<td>3.2 (1.8–5.8)</td>
</tr>
<tr>
<td>44</td>
<td>33.3</td>
<td>1.00</td>
</tr>
<tr>
<td>21</td>
<td>291 (8.4)</td>
<td>2.5 (1.3–4.7)</td>
</tr>
<tr>
<td>34</td>
<td>247 (7.2)</td>
<td>3.4 (2.0–5.8)</td>
</tr>
<tr>
<td>96</td>
<td>34.4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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FIGURE 1. Age-adjusted life table failure curves for men with positive and negative exercise tests within the hyperlipidemic (left) and normolipidemic (right) subpopulations. These six pairs of curves were generated from six separate proportional-hazards models, each containing age as a continuous variable and exercise test outcome as a categorical variable.
TABLE 5
Exercise test outcome and cardiovascular mortality among risk factor strata

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>StratumA</th>
<th>Exercise test outcome</th>
<th>n</th>
<th>Deaths</th>
<th>Relative riskB</th>
<th>Exercise test</th>
<th>Risk factor</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≥55</td>
<td>Positive</td>
<td>92</td>
<td>13</td>
<td>15.4</td>
<td>5.31</td>
<td>3.42</td>
<td>−1.74</td>
</tr>
<tr>
<td></td>
<td>&lt;55</td>
<td>Positive</td>
<td>93</td>
<td>9</td>
<td>12.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>396</td>
<td>12</td>
<td>3.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes</td>
<td>Smokers</td>
<td>Positive</td>
<td>42</td>
<td>6</td>
<td>12.0</td>
<td>3.82</td>
<td>3.01</td>
<td>−0.54</td>
</tr>
<tr>
<td></td>
<td>Nonsmokers</td>
<td>Positive</td>
<td>143</td>
<td>16</td>
<td>5.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>≥160/95</td>
<td>Positive</td>
<td>52</td>
<td>12</td>
<td>8.3</td>
<td>3.62</td>
<td>1.20</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>&lt;160/95</td>
<td>Positive</td>
<td>133</td>
<td>10</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(or on drug)</td>
<td>Negative</td>
<td>394</td>
<td>11</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(not on drug)</td>
<td>Negative</td>
<td>2593</td>
<td>25</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>&gt;115</td>
<td>Positive</td>
<td>31</td>
<td>7</td>
<td>11.6</td>
<td>3.16</td>
<td>0.94</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>≤115</td>
<td>Positive</td>
<td>211</td>
<td>8</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(or on drug)</td>
<td>Negative</td>
<td>153</td>
<td>15</td>
<td>3.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(not on drug)</td>
<td>Negative</td>
<td>2776</td>
<td>28</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma LDL-C (mg/dl)</td>
<td>≥180</td>
<td>Positive</td>
<td>55</td>
<td>12</td>
<td>8.4</td>
<td>4.24</td>
<td>3.80</td>
<td>−2.20</td>
</tr>
<tr>
<td></td>
<td>&lt;180</td>
<td>Positive</td>
<td>122</td>
<td>9</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(or on drug)</td>
<td>Negative</td>
<td>573</td>
<td>16</td>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(not on drug)</td>
<td>Negative</td>
<td>2380</td>
<td>20</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma HDL-C (mg/dl)</td>
<td>&gt;40</td>
<td>Positive</td>
<td>111</td>
<td>11</td>
<td>4.0</td>
<td>4.22</td>
<td>−2.86</td>
<td>−0.53</td>
</tr>
<tr>
<td></td>
<td>≤40</td>
<td>Positive</td>
<td>1697</td>
<td>13</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>73</td>
<td>11</td>
<td>17.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>1290</td>
<td>23</td>
<td>3.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A Strata for blood pressure, plasma glucose, and plasma LDL-C take into account pharmacologic treatment for elevations in these levels (see Methods).

B Estimated from weighted discrete proportional-hazards model containing dichotomous terms for exercise test outcome and risk factor covariate and their interaction and, except in the first model (in which age was the dichotomous covariate examined), a continuous term for age. The relative risk for a man with a negative exercise test in the low-risk stratum for each covariate is unity, by definition. Relative risk for other strata are obtained from antilogs (base e) of appropriate regression coefficients. Z scores were obtained by dividing each regression coefficient by its standard error; the conventional (two-sided, p = .05) threshold for statistical significance is ±1.96.

Cardiovascular mortality in men with a positive vs negative exercise test was equal to that associated with a 19.2 year increment in age. Thus the covariance adjustment for risk factors other than age had little impact on the prognostic significance of a positive exercise tolerance test.

The association of a positive exercise test with mortality from cardiovascular disease was also analyzed as a function of physical activity, alcohol consumption, body mass index, and plasma triglyceride levels. None of these factors was itself associated with mortality from cardiovascular disease in this group of LRC participants nor substantially altered the prognostic value of the exercise test. Further restriction of the study population to men free of angina pectoris and exertional dyspnea did not substantially alter our results. Because of the finding by Bruce et al. 15, 16 that the prognostic value of a positive exercise test was not significant in individuals with no other CHD risk factors, we attempted to analyze the subgroup of LRC participants lacking any of the CHD risk factors (smoking, hypertension, hypercholesterolemia, diabetes, a positive family history, or angina pectoris) defined by these investigators (table 7). The number of these risk factors and the broadness of their definition resulted in the exclusion of 66% of men with negative exercise tests, 78% of those with positive exercise tests (89% of those with strongly positive tests), and 93% of the men who died of cardiovascular disease. While it is not possible to make very much of a single cardiovascular death among 40 "low risk" men with positive exercise tests, it should be noted that only one of every 336 similarly low-risk men with negative exercise tests died of cardiovascular causes during 8.7 years of mean.
TABLE 6  
Weighted discrete proportional-hazards regression model for cardiovascular mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise tolerance test</td>
<td>4.2</td>
<td>2.0-8.9</td>
</tr>
<tr>
<td>Age (decades)</td>
<td>2.3</td>
<td>1.5-3.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.1</td>
<td>1.2-3.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8</td>
<td>0.8-3.9</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.5</td>
<td>0.7-3.6</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>2.6</td>
<td>1.3-5.3</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>2.9</td>
<td>1.5-5.7</td>
</tr>
</tbody>
</table>

*Multiple regression model with dichotomous (positive vs negative) term for exercise tolerance test outcome, continuous term for age (in decades), and dichotomous terms for the strata shown in table 5 for the remaining risk factor variables.

Follow-up. All-cause mortality, for which the data are less sparse, was also substantially higher among the 40 men with a positive exercise test at baseline than among the 1010 men with a negative test. Thus, these limited data do not support the notion that a positive exercise test carries no excess risk in this subgroup.

Discussion

Among predominantly asymptomatic 30- to 79-year-old white male participants in the LRC Prevalence Study, a positive exercise test was a powerful predictor of mortality, especially when death was attributed to cardiovascular disease. The strength of this association was similar whether consideration was restricted to deaths due to CHD or whether deaths due to other cardiovascular causes were included as well. Given that CHD accounted for 74% (43 of 58) of deaths from cardiovascular disease among men with a conclusive exercise test result, this similarity is not surprising. While the results suggest that the prognostic value of a positive exercise test is not restricted to CHD mortality, they do not prove that a positive exercise test is equally predictive of all forms of death from cardiovascular disease.

When cardiovascular disease mortality was subtracted from the all-cause rates in table 4, non–cardiovascular disease mortality was also higher in men with positive vs negative exercise tests (114 vs 20 deaths per 10,000 person-years). This association was considerably stronger among the normolipidemic men (127 vs 19 deaths per 10,000 person-years) than among the hyperlipidemic men (38 vs 28 deaths per 10,000 person-years). Since “non–cardiovascular disease mortality” comprises a mixture of diverse causes of death, its greater rate in men with positive vs negative exercise tests may be a nonspecific finding, attributable to the greater age and poorer overall health of the positive test group. After age adjustment, the overall relative risk associated with a positive exercise tolerance test fell from 4.6 to 3.4 when noncardiovascular as well as cardiovascular deaths were analyzed (table 4).

The increased risk associated with exercise-induced electrocardiographic ST depression was particularly marked when this response occurred in the first two stages of exercise or at a low heart rate or when ST depression exceeded 2 min (i.e., when the test was “strongly” positive). Cumulative cardiovascular disease mortality was more than four times as high (20.7% vs 4.9%) for men with strongly vs those with weakly positive exercise tests (table 3). Mortality from cardiovascular disease for men with positive tests was almost twice as high (224 vs 133 deaths per 10,000 person-years) when only men with a strongly positive exercise test rather than men with either a strongly or weakly positive test were considered (table 4). These findings are in general agreement with the report of Gibbons et al. 32 that a positive exercise test most strongly predicts CHD progression when the electrocardiographic abnormality occurs below 85% of the predicted maximum heart rate. In our study, a substantial portion of the incremental risk associated with a strongly vs a weakly positive exercise test (especially in the normolipidemic subpopulation) was attributable to the greater age of the men with strongly positive tests and was removed by age adjustment (table 4). However, even after age adjustment, the relative risk associated with a positive exercise test was greater (5.1 vs 4.6) when only strongly positive (rather than all positive) tests were considered.

TABLE 7  
Mortality in low-risk LRC Study participants

<table>
<thead>
<tr>
<th>Exercise test outcome</th>
<th>No. at risk</th>
<th>Mean follow-up (years)</th>
<th>CHD</th>
<th>Cardiovascular disease</th>
<th>All causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>40</td>
<td>8.70</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1010</td>
<td>8.68</td>
<td>1 (0.1%)</td>
<td>3 (0.3%)</td>
<td>12 (1.2%)</td>
</tr>
</tbody>
</table>

*White men, 30 to 79 years old, with none of the CHD risk factors specified by Bruce et al. 15, 16 Men who smoked, had plasma cholesterol levels above 250 mg/dl or systolic blood pressure above 140 mm Hg, were under treatment for hyperlipidemia, hypertension, or diabetes mellitus, had a positive Rose questionnaire for angina pectoris, or reported a history of CHD in a first-degree relative below age 60 were excluded.
We were unable to confirm the finding of Bruce et al.\textsuperscript{15, 16} that the exercise test had prognostic value only in individuals with other known risk factors. While our ability to examine this issue critically was limited by the presence in the LRC study population of only 40 low-risk men (by Bruce’s criteria) with positive exercise tests, the proportions of deaths in this group, just as in the entire study population, exceeded those among their counterparts with negative exercise tests. The absence of statistical significance of this association in the LRC population and in Bruce’s study is more likely a result of the low prevalence of men with a positive exercise test and no other CHD risk factors than a result of a true interaction effect. Stratification of the LRC study population with respect to individual risk factors (table 5) failed to yield any support for the hypothesis that the prognostic significance of a positive exercise test was contingent on the presence of other CHD risk factors. In fact, in the only instances in which the possibility of an interaction effect was suggested by the data (i.e., for age and LDL-C), the relative risk of death from cardiovascular disease associated with a positive vs negative exercise test decreased when the risk factor was present. Although one cannot rule out the possibility that significant interactions might emerge after additional follow-up, the data at this time suggest that the exercise tolerance test has similar prognostic value under a variety of conditions.

While the exercise test provides significant prognostic information in men without known CHD and probably even in those without other CHD risk factors, the present study and others like it cannot directly address the utility of the exercise test in screening an asymptomatic population. It would be incorrect to consider the 163 men (91%) with positive exercise tests who did not die of cardiovascular disease as “false positives,” since many men with known CHD could be expected to live longer than the 8.1 years mean duration of follow-up and some could be expected to die of other causes. Furthermore, since the exercise test was done only at baseline and could only measure the adequacy of the coronary circulation at the time it was done, the 36 men (1.2%) with negative exercise tests who later died of cardiovascular disease do not necessarily represent “false negatives.” Studies that assess the concordance of exercise test outcome with a concurrent “standard” measurement of the status of coronary arteries are in theory best able to address the utility of the exercise test in screening for CHD. However, because most such studies have used coronary angiography (an anatomic assessment) as their standard, they too must be interpreted with caution, since anatomic studies are rarely done in asymptomatic individuals and since discordance between a physiologic and an anatomic assessment of the coronary circulation need not imply that either is in error.\textsuperscript{33-35}

The results from the mortality follow-up to the LRC Prevalence Study are in essential agreement with those of the study of Giagnoni et al.,\textsuperscript{17} who also assessed the prognostic importance of the functional status of the coronary circulation in a primarily asymptomatic population. Despite important methodologic differences in the composition of the study population (27% female subjects), the mode of exercise testing (bicycle ergometer), the clinical end point (including nonfatal myocardial infarction and angina pectoris), and means of controlling for other risk factors (matching), their estimate of the relative risk associated with a positive test is quantitatively similar to that reported here. We conclude that a low ischemic threshold is a powerful predictor of mortality, especially that due to cardiovascular disease, independent of other known coronary risk factors.

We gratefully acknowledge the technical assistance of Bob McMahon, Timothy Rowles, Dawn Stewart, Kay Bobitt, Larry Sink, and Larry Wallman. We also thank Michael Criqui, Gerardo Heiss, and Al Tyroler for their valuable advice.

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