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EXERCISE CAPACITY AND MORTALITY AMONG MEN REFERRED FOR EXERCISE TESTING

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ABSTRACT

Background Exercise capacity is known to be an important prognostic factor in patients with cardiovascular disease, but it is uncertain whether it predicts mortality equally well among healthy persons. There is also uncertainty regarding the predictive power of exercise capacity relative to other clinical and exercise-test variables.

Methods We studied a total of 6213 consecutive men referred for treadmill exercise testing for clinical reasons during a mean (\pm SD) of 6.2 ± 3.7 years of follow-up. Subjects were classified into two groups: 3679 had an abnormal exercise-test result or a history of cardiovascular disease, or both, and 2534 had a normal exercise-test result and no history of cardiovascular disease. Overall mortality was the end point.

Results There were a total of 1256 deaths during the follow-up period, resulting in an average annual mortality of 2.6 percent. Men who died were older than those who survived and had a lower maximal heart rate, lower maximal systolic and diastolic blood pressure, and lower exercise capacity. After adjustment for age, the peak exercise capacity measured in metabolic equivalents (MET) was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease. Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or non-use of beta-blockade and the predictive power of exercise capacity. Each 1-MET increase in exercise capacity conferred a 12 percent improvement in survival.

Conclusions Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease. (N Engl J Med 2002;346:793-801.)

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DURING the past two decades, exercise capacity and activity status have become well-established predictors of cardiovascular and overall mortality.^{1,2} The fact that exercise capacity is a strong and independent predictor of outcomes supports the value of the exercise test as a clinical tool; it is noninvasive, is relatively inexpensive, and provides a wealth of clinically relevant diagnostic and prognostic information.^{3,4} However, recent guidelines⁴ and commentaries on the topic^{5,6} have identified several areas related to the prognostic usefulness of exercise testing that are in need of further study. For example, the majority of previous studies have not clearly assessed the independent prognostic power of exercise capacity relative to other clinical variables and information from exercise testing. In addition, whereas the literature is filled with long-term follow-up studies conducted in relatively healthy populations,⁷⁻¹¹ few studies have focused on more clinically relevant populations — that is, patients referred for exercise testing for clinical reasons. Moreover, although exercise capacity expressed in terms of metabolic equivalents (MET) is the common clinical measure of exercise tolerance, exercise capacity is strongly influenced by age and activity status. It is not known which has greater prognostic value: the absolute peak exercise capacity (measured in MET) or exercise capacity expressed as a percentage of the value predicted on the basis of age. Finally, the use of beta-blocker therapy is common among the patients who are typically referred for exercise testing; although beta-blockade improves survival, it can also reduce exercise capacity. Data related to the influence of beta-blockade on the prognostic value of exercise tolerance are sparse.

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In the present study, we assessed the prognostic value of exercise capacity among patients referred for exercise testing for clinical reasons. We addressed the questions of whether exercise capacity is an independent predictor of the risk of death; whether it is as strong a marker of risk as other established cardiovascular risk factors; whether the percentage of age-predicted exercise capacity achieved is a better marker of risk than the absolute peak exercise capacity; and whether beta-blockade influences the prognostic value of exercise capacity.

METHODS

Exercise Testing

The study population consisted of 6213 consecutive men referred for exercise testing for clinical reasons. Beginning in 1987, a thorough clinical history, current medications, and risk factors in these subjects were recorded prospectively on computerized forms at the time of the exercise tests.^{12,13} After providing written informed consent, the subjects underwent symptom-limited treadmill testing according to standardized graded¹⁴ or individualized¹⁵ ramp-treadmill protocols. Before testing, the subjects were given a questionnaire, which we used to estimate their exercise capacity; the use of this estimate allowed most subjects to reach maximal exercise capacity within the recommended range of 8 to 12 minutes.¹⁶ We have previously observed that this protocol results in the closest relation between the measured and estimated exercise capacity.¹⁵ (One MET is defined as the energy expended in sitting quietly, which is equivalent to a body oxygen consumption of approximately 3.5 ml per kilogram of body weight per minute for an average adult.) Subjects were discouraged from using the handrails for support. Target heart rates were not used as predetermined end points. Subjects were placed in a supine position as soon as possible after exercise.¹⁷ Medications were not changed or stopped before testing.

ST-segment depression was measured visually. Ventricular tachycardia was defined as a run of three or more consecutive premature ventricular contractions, and if 10 percent or more of all ventricular contractions were premature, the subject was considered to have frequent premature ventricular contractions.¹⁸ Exercise capacity (in MET) was estimated on the basis of the speed and grade of the treadmill.¹⁹ Subjects with either a decrease of 10 mm Hg in systolic blood pressure after an initial increase with exercise or a decrease to 10 mm Hg below the value measured while standing before testing were considered to have exertional hypotension.²⁰

No test results were classified as indeterminate.²¹ The exercise tests were performed, analyzed, and reported according to a standardized protocol and with the use of a computerized data base.²² Normal standards for age-predicted exercise capacity were derived from regression equations developed on the basis of results in veterans who were referred for exercise testing²³ and the predicted peak exercise capacity was calculated as $18.0 - (0.15 \times \text{age})$. The percentage of normal exercise capacity achieved was defined as follows: $(\text{achieved exercise capacity} \div \text{the predicted energy expenditure}) \times 100$.

We defined subjects with cardiovascular disease as those with a history of angiographically documented coronary artery disease, myocardial infarction, coronary bypass surgery, coronary angioplasty, congestive heart failure, peripheral vascular disease, or an abnormal result on an exercise test that was suggestive of coronary artery disease (ST-segment depression of ≥ 1.0 mm, exercise-induced angina, or both). Seven percent of the population (435 subjects) had a history of mild pulmonary disease and were included in the group with an abnormal exercise-test result, a history of cardiovascular disease, or both, which included a total of 3679 subjects. The other 2534 subjects, who had no evidence of cardiovascular disease, were classified as normal.

Follow-up

The Social Security death index was used to match all subjects to their records according to name and Social Security number. Vital status was determined as of July 2000.

Statistical Analysis

NCSS software (Salt Lake City) was used for all statistical analyses. Overall mortality was used as the end point for survival analysis. Censoring was not performed, since data on interventions were not available for all subjects. Survival analysis was performed with the use of Kaplan–Meier curves for the comparison of variables and cutoff points, and a Cox proportional-hazards model was used to determine which variables were independently and significantly associated with the time to death. Analyses were adjusted for age in single years as a continuous variable.

In order to compare our results with those of previous studies, the relative risk of death was calculated for each quintile of exercise capacity; subjects with an exercise capacity of less than 5 MET were considered to have a high risk of death, and those with an energy expenditure of more than 8 MET were considered to have a low risk. Receiver-operating-characteristic curves were constructed in order to compare the absolute exercise capacity achieved and exercise capacity expressed as a percentage of the age-predicted value in terms of their discriminatory accuracy in predicting survival. The receiver-operating-characteristic curves were compared with the use of the z statistic.

RESULTS

The mean (\pm SD) follow-up period was 6.2 ± 3.7 years, and the average annual mortality was 2.6 percent. No major complications occurred, although nonsustained ventricular tachycardia (three or more consecutive beats) occurred during 1.1 percent of the exercise tests. A total of 83 percent of the subjects who were classified as normal achieved a maximal heart rate that was at least 85 percent of the age-predicted value.

Demographic Characteristics

As compared with the normal subjects, subjects with cardiovascular disease were older, had a slightly lower body-mass index (defined as the weight in kilograms divided by the square of the height in meters), and had more extensive use of medicines in addition to more cardiovascular interventions (Table 1).

Exercise-Test Results

Age-adjusted demographic characteristics and the results of exercise testing in the subjects who survived and those who died in both groups are presented in Table 2. The regression equation that predicted the peak exercise capacity on the basis of age was $18.4 - (0.16 \times \text{age})$; with this equation, $r(\pm \text{SE}) = -0.50 \pm 0.31$, $P < 0.001$. The regression equation used to predict the maximal heart rate on the basis of age was $187 - (0.85 \times \text{age})$; with this equation, $r(\pm \text{SE}) = -0.39 \pm 0.23$, $P < 0.001$.

Predictors of Death from Any Cause

Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are present-

EXERCISE CAPACITY AND MORTALITY

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF NORMAL SUBJECTS AND SUBJECTS WITH CARDIOVASCULAR DISEASE.*

VARIABLE	ALL SUBJECTS (N=6213)	NORMAL SUBJECTS (N=2534)	SUBJECTS WITH CARDIOVASCULAR DISEASE (N=3679)	P VALUE
Demographic characteristics				
Age (yr)	59±11.2	55.5±11.8	61.5±10.1	<0.001
Height (in.)	69.2±4.1	69.4±3.4	69.2±3.6	0.02
Weight (lb)	191.2±39	193.7±37	188.8±36	<0.001
Body-mass index	28.0±5.2	28.4±5.1	27.3±5.0	<0.001
Medications (%)				
Digoxin	5.4	0	9.1	
Calcium antagonist	27.3	17.2	34.3	<0.001
Beta-blocker	18.9	12.0	23.7	<0.001
Nitrate	23.3	9.5	32.9	<0.001
Antihypertensive agent	24.0	19.3	27.3	<0.001
Medical history (%)				
Atrial fibrillation	3.1	0.8	2.7	<0.001
Pulmonary disease	6.9	0	11.7	
Stroke	3.6	0	6.1	
Claudication	5.3	0	8.9	
Typical angina	31.3	7	31.2	<0.001
Myocardial infarction	29.3	0	49.4	
Congestive heart failure	8.4	0	14.2	
Interventions (%)				
Coronary bypass surgery	9.3	0	14.1	
Percutaneous transluminal coronary angioplasty, stenting, or both	5.2	0	8.7	

*Plus-minus values are means ±SD. To convert values for height to centimeters, multiply by 2.54; to convert values for weight to kilograms, multiply by 0.45. For comparisons where no P value is given, the differences are due to the classification criteria specified in the study design.

TABLE 2. AGE-ADJUSTED CHARACTERISTICS AND EXERCISE-TEST RESPONSES AMONG SUBJECTS WHO DIED AND SUBJECTS WHO SURVIVED.*

VARIABLE	NORMAL SUBJECTS				SUBJECTS WITH CARDIOVASCULAR DISEASE			
	TOTAL (N=2534)	SURVIVED (N=2246)	DIED (N=288)	P VALUE	TOTAL (N=3679)	SURVIVED (N=2711)	DIED (N=968)	P VALUE
Age (yr)	55±12	55±12	62±10	<0.001	61±10	60±10	65±9	<0.001
Height (in.)	69.4±3.4	69.4±3.1	69.7±4.9	0.08	69.2±3.7	69.2±3.5	69.3±4.2	0.34
Weight (lb)	193.7±37.5	194.1±37.1	191.0±40.1	0.19	188.8±36.1	190.7±36.3	183.7±34.4	<0.001
Body-mass index	28.3±5.1	28.4±5.1	27.5±5.0	0.005	27.8±5.0	28.1±5.0	26.9±4.7	<0.001
Resting values								
Heart rate (beats/min)	78±16	78±16	83±16	<0.001	78±26	77±29	79±16	0.24
Blood pressure (mm Hg)								
Diastolic	84±12	84±12	83±13	0.16	82±18	82±19	80±12	<0.001
Systolic	132±20	133±20	131±21	0.13	134±23	135±23	132±24	<0.001
Maximal values								
Heart rate (beats/min)	145±24	145±23	140±25	<0.001	132±29	133±28	127±32	<0.001
Blood pressure (mm Hg)								
Diastolic	86±16	86±15	85±16	0.37	86±23	86±20	85±30	0.53
Systolic	184±28	184±27	178±32	<0.001	174±31	176±31	168±32	<0.001
Exercise capacity (MET)	9.5±3.8	9.7±3.7	8.4±3.5	<0.001	7.2±3.3	7.4±3.3	6.5±2.8	<0.001

*Plus-minus values are means ±SD. P values are for comparisons between the subjects who survived and those who died in each group. To convert values for height to centimeters, multiply by 2.54; to convert values for weight to kilograms, multiply by 0.45. MET denotes metabolic equivalents.

ed in Table 3. After adjustment for age, the best predictor of an increased risk of death among normal subjects was peak exercise capacity, followed by pack-years of smoking. Among subjects with cardiovascular disease, the best predictor of an increased risk of death from any cause was peak exercise capacity, followed by a history of congestive heart failure, history of myocardial infarction, pack-years of smoking, left ventricular hypertrophy on electrocardiography while at rest, pulmonary disease, and exercise-induced ST-segment depression. According to the model for the total group, every 1-MET increase in exercise capacity conferred a 12 percent improvement in survival.

The age-adjusted relative risks of death for subjects with each of the major risk factors among those achieving a peak exercise capacity of less than 5 MET and 5 to 8 MET, as compared with the fittest subjects (those achieving a peak of more than 8 MET), are shown in Figure 1. For subjects with any of these risk factors, the relative risk of death from any cause increased significantly as exercise capacity decreased. The age-adjusted relative risks of death from any cause for subjects in each quintile of fitness in each group are shown in Figure 2. In both groups, subjects with lower exercise capacity had a higher risk of death. The relative risk for the subjects in the lowest quintile of exercise capacity, as compared with those in the highest quintile, was 4.5 among the normal subjects and 4.1 among those with a history of cardiovascular or pulmonary disease, abnormal results on exercise testing, or both.

Absolute Exercise Capacity versus Percentage of Age-Predicted Value

Absolute peak exercise capacity (with or without adjustment for age) predicted survival more accurately than the percentage of age-predicted values achieved when entered into the proportional-hazards model. In addition, the area under the receiver-operating-characteristic curve was greater for absolute exercise capacity than for the percentage of age-predicted values (0.67 vs. 0.62, $P < 0.01$), indicating that the absolute value had greater discriminatory power. For subjects over 65 years of age, however, the areas under the receiver-operating-characteristic curves were similar (0.60). The survival curves for normal subjects who achieved an exercise capacity of less than 5 MET, 5 to 8 MET, and more than 8 MET are shown in Figure 3A; the survival curves for normal subjects who achieved an exercise capacity of less than 50 percent, 50 to 74 percent, 75 to 100 percent, and more than 100 percent of the age-predicted value are shown in Figure 3B. The corresponding curves for the subjects with cardiovascular disease are shown in Figures 3C and 3D. For both the absolute exercise capacity and the percentage of the age-predicted value, there were

TABLE 3. AGE-ADJUSTED RISK OF DEATH, ACCORDING TO CLINICAL AND EXERCISE-TEST VARIABLES.*

VARIABLE	HAZARD RATIO FOR DEATH (95% CI)	P VALUE
Normal subjects		
Peak exercise capacity (for each 1-MET increment)	0.84 (0.79–0.89)	<0.001
Pack-yr of smoking (for each 10-yr increment)	1.09 (1.03–1.14)	<0.001
History of hypertension	0.75 (0.56–1.02)	0.07
Diabetes	1.30 (0.84–2.00)	0.24
Total cholesterol level >220 mg/dl (5.7 mmol/liter)	1.21 (0.88–1.64)	0.25
Left ventricular hypertrophy	1.22 (0.57–2.63)	0.61
Exercise-induced ventricular arrhythmia	1.14 (0.64–2.01)	0.66
Maximal heart rate (for each increment of 10 beats/min)	1.00 (0.92–1.08)	0.93
Subjects with cardiovascular disease		
Peak exercise capacity (for each 1-MET increment)	0.91 (0.88–0.94)	<0.001
History of congestive heart failure	1.67 (1.37–2.04)	<0.001
History of myocardial infarction	1.60 (1.35–1.90)	<0.001
Pack-yr of smoking (for each 10-yr increment)	1.05 (1.02–1.08)	0.001
Left ventricular hypertrophy	1.50 (1.13–1.99)	0.005
Pulmonary disease	1.34 (1.06–1.68)	0.01
ST-segment depression	1.22 (1.03–1.44)	0.02
Total cholesterol level >220 mg/dl (5.7 mmol/liter)	0.88 (0.74–1.04)	0.14
Maximal heart rate (for each increment of 10 beats/min)	0.97 (0.93–1.01)	0.17
Exercise-induced ventricular arrhythmia	1.19 (0.92–1.53)	0.18
Diabetes	0.90 (0.69–1.16)	0.41
History of hypertension	1.07 (0.90–1.25)	0.47

*Data are from the Cox proportional-hazards model. Metabolic equivalents (MET) were calculated from the peak speed and grade of the treadmill and were evaluated as a continuous variable. Left ventricular hypertrophy was defined according to electrocardiographic criteria in a resting patient. Exercise-induced arrhythmia was defined as three or more premature ventricular contractions in succession, premature ventricular contractions that accounted for 10 percent or more of total beats during exercise, or both. Maximal heart rate was measured at peak exercise. ST-segment depression was defined as an exercise-induced change of 1.0 mm or more. CI denotes confidence interval.

significant differences in mortality rate among groups defined according to exercise level ($P < 0.001$), although the curves were shifted downward in the group with cardiovascular or pulmonary disease.

Effect of Beta-Blockade

There was no interaction between the use or non-use of beta-blockade and the predictive power of the peak exercise capacity; this was the case throughout the typical range of values for exercise capacity (2 to 10 MET). The results were similar when subjects were included in the beta-blockade subgroup only if they were taking a beta-blocker and had a blunted heart-rate response to exercise (a peak heart rate of less than 85 percent of the age-predicted value). The results were also similar (i.e., beta-blockade had no effect) when the survival curves were based on various cut-

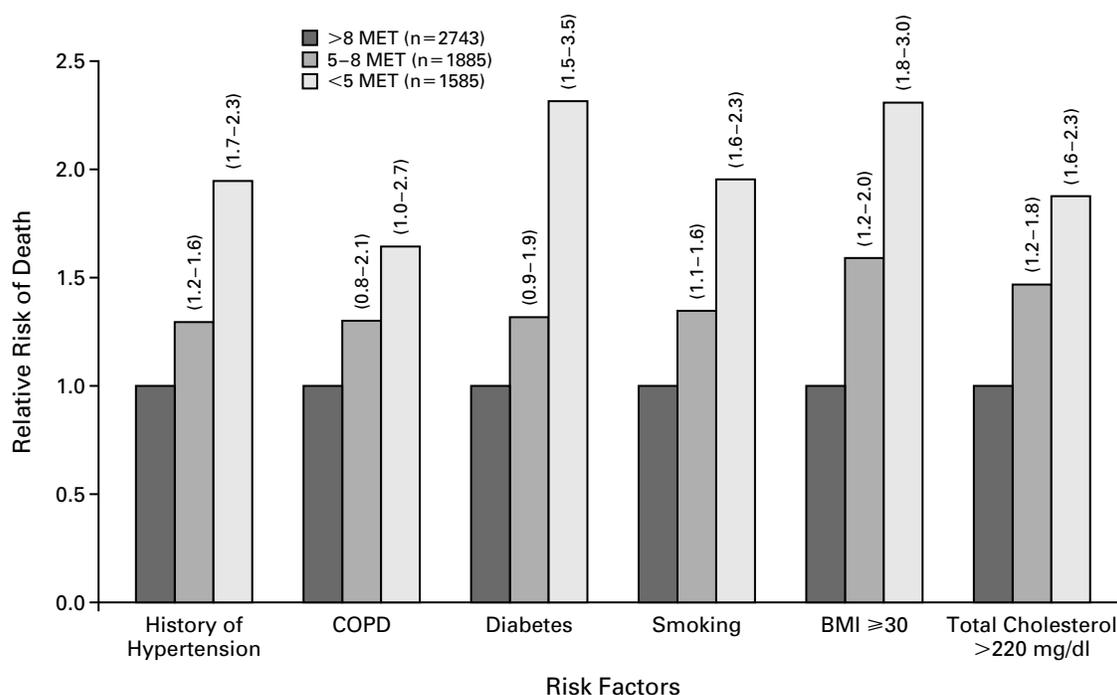


Figure 1. Relative Risks of Death from Any Cause among Subjects with Various Risk Factors Who Achieved an Exercise Capacity of Less Than 5 MET or 5 to 8 MET, as Compared with Subjects Whose Exercise Capacity Was More Than 8 MET.

Numbers in parentheses are 95 percent confidence intervals for the relative risks. BMI denotes body-mass index, and COPD chronic obstructive pulmonary disease.

off points for the percentage of age-predicted exercise capacity achieved (e.g., 50 percent or 75 percent of age-predicted values).

DISCUSSION

Our results demonstrate that exercise capacity is a strong predictor of the risk of death in patients referred for exercise testing for clinical reasons. The importance of exercise capacity, physical-activity status, or both in predicting survival has been reported in asymptomatic populations such as those of the Framingham Study,¹¹ the Aerobics Center Longitudinal Study,^{8,9} the Lipid Research Clinics Trial,⁷ and the Harvard Alumni study.²⁴ Our population was unique in that it afforded us the opportunity to assess subjects both with and without documented cardiovascular disease. Whereas the above-mentioned studies involved generally healthy populations, our data demonstrate that exercise capacity is a similarly important marker of risk in a clinically referred population and among men both with and without existing cardiovascular disease. Unlike the estimates of activity status or the submaximal exercise tests used in many studies, the maximal exercise testing used in the present study provided an objective measure of physical fitness.²⁵

In both healthy subjects and those with cardiovascular disease, the peak exercise capacity achieved was a stronger predictor of an increased risk of death than clinical variables or established risk factors such as hypertension, smoking, and diabetes, as well as other exercise-test variables, including ST-segment depression, the peak heart rate, or the development of arrhythmias during exercise. Our data also confirm the protective role of a higher exercise capacity even in the presence of other risk factors.^{7-9,24,25} In all subgroups defined according to risk factors, the risk of death from any cause in subjects whose exercise capacity was less than 5 MET was roughly double that of subjects whose exercise capacity was more than 8 MET (Fig. 1).

Poor physical fitness is a modifiable risk factor, and improvements in fitness over time have been demonstrated to improve prognosis.^{2,9} Our observation that every 1-MET increase in treadmill performance was associated with a 12 percent improvement in survival underscores the relatively strong prognostic value of exercise capacity. In addition, it confirms the presence of a graded, inverse relation between exercise capacity and mortality from any cause.⁷⁻¹¹ Recent long-term findings from the National Exercise and Heart Disease Project²⁶ among patients who had had a myocardial

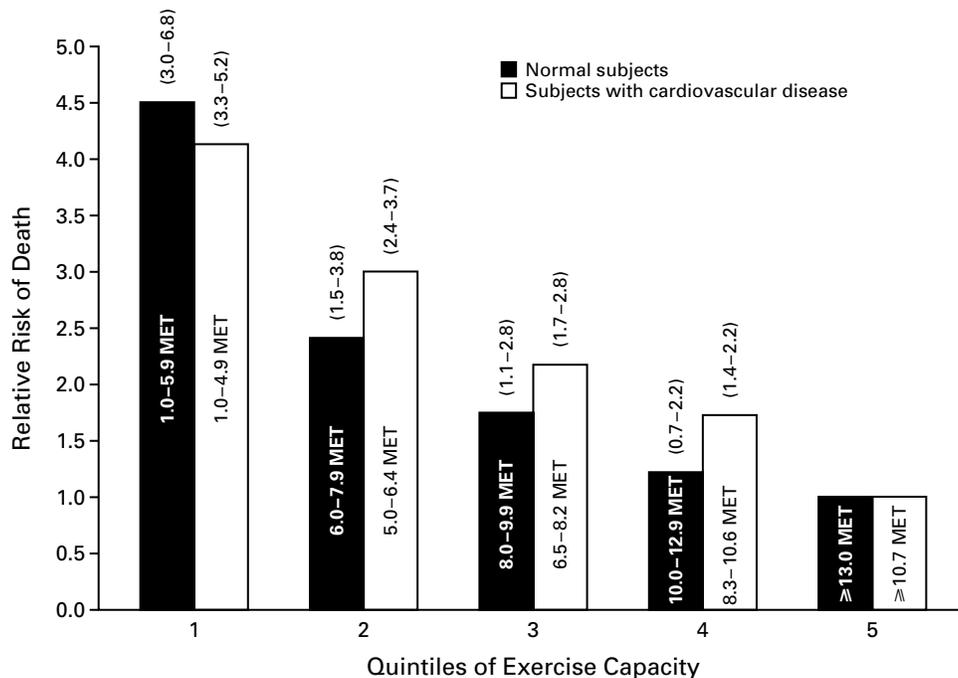


Figure 2. Age-Adjusted Relative Risks of Death from Any Cause According to Quintile of Exercise Capacity among Normal Subjects and Subjects with Cardiovascular Disease.

The subgroup of subjects with the highest exercise capacity (quintile 5) was used as the reference category. For each quintile, the range of values for exercise capacity represented appears within each bar; 95 percent confidence intervals for the relative risks appear above each bar.

infarction demonstrated that every 1-MET increase in exercise capacity after a training period was associated with a reduction in mortality from any cause that ranged from 8 percent to 14 percent over the course of 19 years of follow-up. In a study involving serial evaluations in nearly 10,000 men, Blair et al.⁹ observed a 7.9 percent reduction in mortality for every one-minute increase in treadmill time (roughly equivalent to the 1-MET change in our study).

In combination, these findings demonstrate that both a relatively high degree of fitness at base line and an improvement in fitness over time yield marked reductions in risk. The relative weight of exercise capacity in the model for assessing risk in both normal subjects and those with cardiovascular or pulmonary disease in our study, along with the fact that an improvement in exercise capacity lowers the risk of death,^{9,26} suggests that health professionals should incorporate into their practices strategies for promoting physical activity, in addition to the routine treatment of hypertension and diabetes, the encouragement of smoking cessation, and the like.

Our findings in normal subjects are similar to those of other studies^{8,27,28} in that we observed the most striking difference in mortality rates between the least-

fit quintile and the next-least-fit quintile. This observation concurs with the consensus (reflected in the recommendations of the Centers for Disease Control and Prevention and the American College of Sports Medicine² and the report of the Surgeon General on physical activity and health²⁹) that the greatest health benefits are achieved by increasing physical activity among the least fit. Among subjects with cardiovascular disease, however, we observed a nearly linear reduction in risk with increasing quintiles of fitness. Since most studies assessing the relation between fitness and mortality have excluded subjects with cardiovascular disease,³⁰ these findings require confirmation.

Few studies have similarly assessed the prognostic value of exercise tolerance among patients specifically referred for exercise testing for clinical reasons. Roger et al.³¹ retrospectively assessed 2913 men and women from Olmsted County, Minnesota, and reported that among exercise-test variables, exercise capacity had the strongest association with overall mortality and cardiac events among subjects of both sexes. More recently, this group addressed the association between clinical and exercise-test variables among young and elderly subjects in Olmsted County and observed that the peak workload achieved was the only treadmill-test

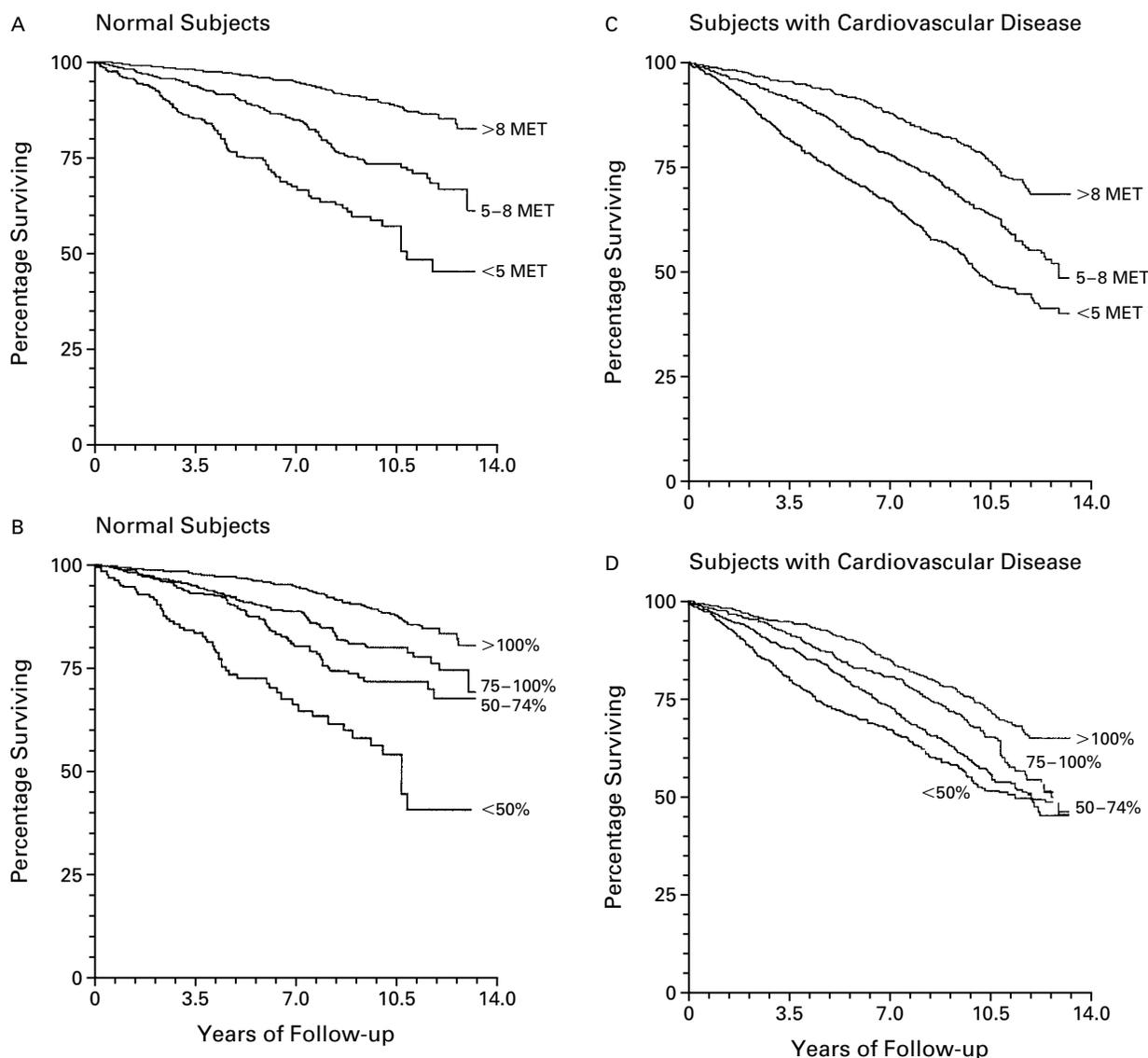


Figure 3. Survival Curves for Normal Subjects Stratified According to Peak Exercise Capacity (Panel A) and According to the Percentage of Age-Predicted Exercise Capacity Achieved (Panel B) and Survival Curves for Subjects with Cardiovascular Disease Stratified According to Peak Exercise Capacity (Panel C) and According to the Percentage of Age-Predicted Exercise Capacity Achieved (Panel D).

In all the analyses, the stratification according to exercise capacity discriminated among groups of subjects with significantly different mortality rates — that is, the survival rate was lower as exercise capacity decreased ($P < 0.001$).

variable that was significantly associated with mortality from any cause.³² These investigators also observed that each 1-MET increment in the peak treadmill workload was associated with a 14 percent reduction in cardiac events among younger subjects (those less than 65 years old) and an 18 percent reduction among elderly subjects.

In recent years, questions have been raised about which variable has superior prognostic power: exercise

capacity relative to age- and sex-predicted standards or absolute exercise capacity.³³⁻³⁵ We found that exercise capacity expressed as a percentage of the age-predicted value was not superior to the absolute peak exercise capacity in terms of predicting survival. Other studies in this area have focused only on patients with congestive heart failure and have had conflicting findings.³³⁻³⁵

We were also interested in whether our results

would be affected by beta-blockade, given that such treatment favorably influences survival and is known to either improve or inhibit exercise tolerance, depending on the presence or absence of symptoms during exercise, among other factors. Previous data in this area, although sparse, have demonstrated that beta-blockade does not interfere with the prognostic power of a finding of a low exercise capacity.^{36,37} Approximately 19 percent of the subjects in our study underwent exercise testing while receiving beta-blocker therapy, and the overall survival rate was slightly lower among those taking beta-blockers (18.4 percent vs. 21.0 percent among those not taking such drugs, $P=0.03$). Subjects achieving an exercise capacity of 5 MET or more had a higher survival rate than those achieving an exercise capacity of less than 5 MET, and this remained true when subjects were stratified according to the use or nonuse of a beta-blocker. Similarly, beta-blockade had no effect on survival within groups of subjects stratified according to exercise capacity within the clinically relevant range (2 to 10 MET). This issue has rarely been addressed in previous studies, although presumably a substantial proportion of subjects were taking beta-blockers in the Coronary Artery Surgery Study,³⁸ the Olmsted County Study,^{31,32} the Kuopio Ischemic Heart Disease Risk Factor Study,¹⁰ and other follow-up studies that quantified exercise tolerance and survival.

Our findings are applicable only to men, which is noteworthy, given that exercise-test results have been shown to differ significantly between men and women.³⁹ In addition, we had information only on death from any cause; we did not know the specific causes of death, nor were we able to censor data at the time of cardiovascular interventions. Finally, our exercise-capacity data were estimated on the basis of the speed and grade of the treadmill. Although this type of estimate is the most common clinical measure of exercise tolerance, directly measured exercise capacity (peak oxygen consumption) is known to be a more accurate and reproducible measure of exercise tolerance,⁴⁰ as well as a more robust predictor of outcomes.^{34,35}

The present results confirm the prognostic usefulness of exercise capacity in men. The prognostic power of exercise capacity is similar among apparently healthy persons and patients with cardiovascular conditions who are referred for exercise testing and similar among subjects who are taking beta-blockers and those who are not taking beta-blockers. Expressing exercise capacity as a percentage of the age-predicted value does not improve its prognostic power. Our findings demonstrate an association between exercise capacity and overall mortality, not necessarily a causal relation. Nevertheless, given the high prognostic value of exercise capacity relative to other markers of risk in this and other recent studies, clinicians who are reviewing ex-

ercise-test results should encourage patients to improve their exercise capacity. In terms of reducing mortality from any cause, improving exercise tolerance warrants at least as much attention as other major risk factors from physicians who treat patients with or at high risk for cardiovascular disease.

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