

# Prediction of Long-Term Prognosis in 12 169 Men Referred for Cardiac Rehabilitation

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**Background**—Predicting the risk of cardiac and all-cause death in patients with established coronary heart disease is important in counseling the individual and designing risk-stratified rehabilitation and secondary prevention programs. Cox proportional hazards and Kaplan-Meier survival curves were thus completed on initial assessment data obtained from patients referred to an outpatient cardiac rehabilitation center.

**Methods and Results**—A single-center prospective observational design took peak cardiorespiratory exercise test data for 12 169 male rehabilitation candidates aged  $55.0 \pm 9.6$  years (7096 myocardial infarctions [MIs], 3077 coronary artery bypass grafts [CABGs], and 1996 documented cases of ischemic heart disease [IHD]). A follow-up of 4 to 29 years (median, 7.9) yielded 107 698 man-years of experience. Entry data were tested for associations with time to cardiac and all-cause death. We recorded 1336 cardiac deaths (953 MI, 225 CABG, and 158 IHD) and 2352 all-cause deaths. A powerful predictor of cardiac and all-cause mortality was measured peak oxygen intake ( $\dot{V}O_{2\text{peak}}$ ). For the overall sample, values of  $<15$ ,  $15$  to  $22$ , and  $>22$  mL/kg per minute yielded respective multivariate adjusted hazard ratios of 1.00, 0.62, and 0.39 for cardiac and 1.00, 0.66, and 0.45 for all-cause deaths. For the separate diagnostic categories, apart from  $\dot{V}O_{2\text{peak}}$ , the only other significant predictors of cardiac death common to all 3 were smoking and digoxin, and for all-cause death, age, smoking, digoxin, and diabetes.

**Conclusions**—Exercise capacity, as determined by direct measurement of  $\dot{V}O_{2\text{peak}}$ , exerts a major long-term influence on prognosis in men after MI, CABG, or IHD and can play a valuable role in risk stratification and counseling. (*Circulation*. 2002;106:666-671.)

**Key Words:** exercise ■ prognosis ■ coronary disease ■ survival

Previous authors have discussed the predictive value of exercise test data in subjects with established heart disease. However, conclusions were generally based on submaximal tests or on an oxygen intake ( $\dot{V}O_2$ ) predicted from treadmill stages or times, with a limited follow-up period.<sup>1-7</sup> We therefore examined the prognostic importance of maximal cardiopulmonary exercise testing determined at entry to a large outpatient cardiac rehabilitation program, with the subjects followed over a median of 7.9 (range, 4 to 29) years.

## Methods

### Study Population

A total of 13 131 men were referred to an outpatient cardiac program between September 1, 1968, and December 31, 1994. Patients with noncoronary diagnoses (n=808) and in whom there were technical problems in respiratory gas collection (n=154) were excluded. This left a sample of 12 169 men (7096 myocardial infarctions [MIs], 3077 coronary artery bypass grafts [CABGs], and 1996 documented

cases of ischemic heart disease [IHD]), referred  $13.4 \pm 3.9$  weeks after the event.

### Follow-Up

As approved by the Institutional Committee on Human Experimentation, a questionnaire covering demographics and present health status was mailed to all patients. If an envelope was returned marked "address unknown," the new address was sought through contacts such as family members, employer, family physician, and cardiologist. If additional mailings elicited no response, a final search was made through a computer program (Pro-Phone) that lists all published Canadian telephone numbers and addresses.

Death certificates were examined for decedents resident in Ontario. For 56 decedents no longer resident in Ontario, cause of death was determined on the basis of our clinical interpretation of responses from a physician, spouse, or family.

### Cardiorespiratory Testing

Cardiorespiratory testing has been described previously.<sup>8</sup> The patients performed a progressive test (16.7 W/min) on an electrically braked cycle ergometer until subjective exhaustion, plateauing of oxygen intake, or clinical contraindications to continue.<sup>9</sup> All tests

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were directly supervised by a physician, with the same senior team of technical assistants in attendance throughout the period 1968 to 1994.<sup>10</sup> Patients continued with their usual medications on the day of the test.

### Statistical Methods

SAS Software version 8.2 was used for all statistical analyses. Univariate analysis examined clinically relevant variables, including cardiovascular drugs, and those that were statistically significant ( $P < 0.05$ ) were entered into a multivariate Cox Proportional Hazards model. This procedure was carried out for the group as a whole and for each of the diagnostic categories. Survival time was defined as from the time of the exercise test to the time of cardiac or all-cause death for each diagnostic category (MI, CABG, or IHD). Patients with a diagnosis of MI or IHD who subsequently underwent coronary revascularization were included up to the time of their procedure and then censored. Age and total cholesterol were treated as continuous variables, peak oxygen intake as a 3-level categorical and then a continuous variable, and all other variables as binary data. Exertional hypotension was defined as a drop in systolic blood pressure below resting value or failure to rise more than 10 mm Hg with 2 successive increases in workload (33.4 watts). Wald  $\chi^2$  was calculated, yielding 95% CIs and probability values for the relative risk of individual items after adjusting for other variables.

Kaplan-Meier survival curves were generated, providing a univariate expression of survival in relation to cardiac death, cardiac death for the 3 categories of  $\dot{V}O_{2\text{peak}}$ , and all-cause death. To determine whether a  $\dot{V}O_{2\text{peak}}$  estimated from peak work rate<sup>11</sup> possesses the same prognostic power as measured  $\dot{V}O_{2\text{peak}}$ , we tested the differences in the areas under the receiver operating characteristic curve using the z statistic of Hanley and McNeil.<sup>12</sup>

### Results

The median follow-up time was 7.9 (range, 4 to 29) years. We were unable to contact 583 patients (4.8% of our sample). During follow-up, 1336 cardiac deaths (953 MI, 225 CABG, and 158 IHD) and 2352 all-cause deaths (11.0% and 19.3%, respectively, of the original sample) were recorded.

### Clinical and Physiological Characteristics

Subjects were in their mid-50s, with body dimensions representative of sedentary men of the same age group (Table 1). Over one half of all patients were myocardial infarction survivors, and approximately one half were taking a  $\beta$ -blocker or a platelet inhibitor (most commonly aspirin).

The average  $\dot{V}O_{2\text{peak}}$  values were typical of postcoronary men in their mid-50s. The peak heart rates, respiratory exchange ratios, and Borg ratings of perceived exertion indicate that values were at or close to the individuals' maximal oxygen intake. Complex ventricular arrhythmias and significant ST-segment depression ( $\geq 0.2$  mV) occurred in 30% and 15% of patients, respectively.

### Predictors of Mortality

For the total group, and taking a peak  $\dot{V}O_2$  of  $< 15$  mL/kg per minute (4.3 METs) as baseline, multivariate analysis showed that values of 15 to 22 (4.3 to 6.3 METs) and  $> 22$  mL/kg per minute ( $> 6.3$  METs) yielded, respectively, a 38% and 61% reduction in the risk of cardiac death over the follow-up period (Table 2).

$\beta$ -Blockers and platelet inhibitors also exerted a protective effect (risk reductions of 13% and 31%, respectively). Significant adverse predictors of cardiac death ( $P < 0.01$ ) were age, diabetes, continuing smoking, exertional hypotension,

ST-segment depression, and taking various cardioactive drugs (Table 2).

Results for patients with MI, CABG, and IHD show that only  $\dot{V}O_{2\text{peak}}$ , smoking, and digoxin had significant effects common to all 3 diagnostic categories (Table 3).

In terms of all-cause deaths,  $\dot{V}O_{2\text{peak}}$ , platelet inhibitors, and  $\beta$ -blockade were significant favorable predictors for the group as a whole (Table 4); only  $\dot{V}O_{2\text{peak}}$ , smoking, diabetes, digoxin, and age were significant ( $P < 0.0001$ ) predictors common to all 3 diagnostic categories.

### Kaplan-Meier Curves

The Kaplan-Meier curves for all diagnostic categories show the 15-year probability of surviving a cardiac death was 81% (Figure 1), and death from all causes was 69% (Figure 2). The 15-year values for the individual diagnostic categories were similar, as follows: MI, 79% and 68%; CABG, 83% and 70%; and IHD, 85% and 74%.

Grouping data by initial  $\dot{V}O_{2\text{peak}}$ , there was a clear distinction of prognosis between the 3 initial categories of aerobic fitness. For cardiac deaths, the 15-year survival rates for patients with  $\dot{V}O_{2\text{peak}}$  values of  $< 15$ , 15 to 22, and  $> 22$  mL/kg per minute were  $\approx 65\%$ , 81%, and 88% (log-rank test,  $P < 0.001$ ) (Figure 3). Considering deaths from all causes, the corresponding figures were 48%, 69%, and 80% (log-rank test,  $P < 0.001$ ).

When treated as a continuous variable, a 1-mL/kg per minute increment in  $\dot{V}O_{2\text{peak}}$  could be equated with a 9% improvement in prognosis (hazard ratio, 0.91) or a 2.6-year advantage in prognosis for the lower half of the sample and a gain of 1.0 year in the upper half of the sample.

Survival prospects were substantially worsened by exertional hypotension (15-year survival from cardiac deaths, 67.7% versus 81.6%,  $P < 0.001$ ; from all-cause deaths, 53% versus 70%,  $P < 0.001$ ) and by continued smoking (15-year survival from cardiac deaths, 75% versus 83%,  $P < 0.001$ ; from all-cause deaths, 61% versus 72%,  $P < 0.001$ ).

Finally, receiver operating curve analysis showed that the values for areas under the curves for measured and predicted  $\dot{V}O_{2\text{peak}}$  were, respectively, 0.66 (0.64 to 0.69) and 0.66 (0.67 to 0.69). There was no significant difference between the areas under the curve ( $Z = 0.135$ ;  $P = 0.893$ ).

### Discussion

To our knowledge, this study contains the largest number of coronary patients investigated for the predictive value of cardiopulmonary exercise testing with the longest follow-up. The data demonstrate that the primary factor influencing prognosis in coronary heart disease patients is the individual's effort tolerance, as assessed objectively by the measurement of  $\dot{V}O_{2\text{peak}}$ . This substantiates the conclusions previously formed by Vanhees et al,<sup>13</sup> who examined the predictive power of measured  $\dot{V}O_{2\text{peak}}$  in a smaller sample over a shorter median follow-up. A more recent study involving a large group of men referred for exercise testing, some normal and some suffering from cardiovascular disease, also found exercise capacity, estimated on the basis of treadmill performance, to be a more powerful predictor of mortality than other established risk factors.<sup>7</sup> Observations in healthy men

**TABLE 1. Clinical Characteristics**

Variable	MI	CABG	IHD	Total
Diagnostic category	7096 (58.3)	3077 (25.3)	1996 (16.4)	12 169
Age at CPXT,* y	53.5±9.5	57.1±9.4	55.5±9.3	54.7±9.6
Body mass, kg	80.0±12.1	79.1±11.8	82.0±13.4	80.0±12.3
Body mass index, kg/m <sup>2</sup>	26.7±3.6	26.7±3.5	27.4±3.9	26.8±3.6
Resting heart rate, bpm	68.0±13.6	74.1±13.9	66.6±13.3	69.3±13.9
Resting systolic BP, mm Hg	128.3±18.0	134.8±19.2	134.1±19.5	130.9±18.8
Resting diastolic BP, mm Hg	82.9±11.0	85.6±11.7	84.1±11.5	83.8±11.4
Total cholesterol, mmol/L	5.8±1.2	5.7±1.3	5.7±1.2	5.7±1.2
Current smokers	1343 (19.0)	269 (8.7)	352 (17.7)	1964 (16.2)
Diabetes	376 (5.3)	273 (8.9)	131 (6.6)	780 (6.4)
β-Blockers	3536 (49.8)	1052 (34.2)	965 (48.3)	5553 (45.6)
Platelet inhibitor	2981 (42.0)	2253 (73.2)	1080 (54.1)	6314 (51.9)
Calcium antagonists	1472 (20.7)	286 (9.3)	892 (44.7)	2650 (21.8)
Diuretics	951 (13.4)	314 (10.2)	209 (10.5)	1474 (12.1)
Digoxin	687 (9.7)	405 (13.2)	81 (4.1)	1173 (9.6)
Antiarrhythmics	511 (7.2)	131 (4.3)	31 (1.5)	673 (5.5)
Antihypertensives	632 (8.9)	254 (8.2)	166 (8.3)	1052 (8.6)
Vasodilators	3119 (43.9)	50.5 (16.4)	1002 (51.2)	4646 (38.2)
Anticoagulants	241 (3.4)	72 (2.3)	33 (1.6)	346 (2.8)
Cardiopulmonary exercise test measurements				
Peak heart rate, bpm				
With β-blockers	117.1±18.8	117.0±19.6	110.9±18.1	116.0±19.0
Without β-blockers	137.8±18.8	142.4±17.3	136.8±20.4	139.0±18.7
Peak power output, watts	122.3±36.8	117.6±31.9	126.9±38.37	121.9±36.1
$\dot{V}O_{2peak}$ absolute, L/min	1.6±0.5	1.5±0.4	1.7±0.5	1.6±0.4
$\dot{V}O_{2peak}$ relative, mL/kg per minute	20.5±5.2	19.2±4.5	20.6±5.5	20.2±5.1
Ventilatory threshold (n=5419)	13.3±2.7	12.7±2.5	13.4±3.0	13.2±2.7
Respiratory exchange ratio	1.2±0.1	1.2±0.1	1.1±0.1	1.2±0.1
Borg rating of perceived exertion	18.6±1.7	18.4±1.8	18.7±1.7	18.6±1.7
ST-segment depression ≥0.2 mv	1008 (14.2)	369 (12.0)	417 (21.0)	1794 (14.7)
Exertional angina	978 (13.8)	253 (8.2)	433 (21.7)	1664 (13.7)
Exertional hypotension*	208 (3.0)	64 (2.1)	60 (3.0)	332 (2.7)†
Ectopy at CPXT (Lown grade 3, 4, 5)	2061 (29)	1257 (41)	518 (26)	3836 (31.5)

Values are mean±SD for continuous variables and n (%) for categorical variables. CPXT indicates cardiopulmonary exercise test; BP, blood pressure.

\*Systolic BP falls or rises <10 mm Hg from resting.

†n=12 083.

have also demonstrated that a 1-MET (3.5 mL/kg per minute) advantage in  $\dot{V}O_{2peak}$  (7 versus 6 METs) is associated with a halving of mortality rate (1.5% to 0.75%) over an 8-year follow-up.<sup>14</sup> Moreover, a similar benefit is seen if an unfit but otherwise healthy group of adults is persuaded to become fit.<sup>15</sup>

In chronic heart failure patients, a  $\dot{V}O_{2peak}$  of 14 mL/kg per minute has been recognized as a cutoff below which the risk of death is significant and cardiac transplantation becomes a preferred option.<sup>16–18</sup> Myers and Gullestad,<sup>19</sup> on the other hand, noted that whereas patients who achieved >14 mL/kg per minute had an 82% survival rate and those with 14 mL/kg per minute or less had a survival rate of 60%, this 20% difference was similar when using any cutoff value between

10 and 17 mL/kg per minute. Chomsky et al<sup>20</sup> found a poorer prognosis only in those with an aerobic power of <10 mL/kg per minute. The  $\dot{V}O_{2peak}$  cutoff points selected for our patient categorization were determined by the characteristics of our sample (mean  $\dot{V}O_{2peak}$ , 20.2±5.1 mL/kg per minute) and the levels customarily used in prognostic stratification of patients referred for cardiac rehabilitation (<4, 4 to 6, and >6 METS).<sup>21,22</sup>

In our sample, the estimated 15-year prognosis dropped substantially from the least-fit group (average  $\dot{V}O_{2peak}$ , 13.0 mL/kg per minute, 35% mortality) to the middle group (average  $\dot{V}O_{2peak}$ , 18.6 mL/kg per minute, 19% mortality). In an average (not median) 6-year follow-up of a smaller sample, Vanhees et al<sup>13</sup> found a progressive decline in

**TABLE 2. Cox Proportional Hazards Model for Cardiac Deaths (All Diagnostic Categories) at Entry to Study**

Variable	Hazard Ratio	Confidence Interval	P
$\dot{V}O_{2peak} < 15$ mL/kg per minute	1.00	...	...
$\dot{V}O_{2peak}$ 15–22 mL/kg per minute	0.62	0.54–0.71	<0.0001
$\dot{V}O_{2peak} > 22$ mL/kg per minute	0.39	0.33–0.47	<0.0001
Age per year	1.01	1.00–1.01	0.0019
Current smokers	1.65	1.45–1.88	<0.0001
Diabetes	1.86	1.51–2.28	<0.0001
$\beta$ -Blockers	0.87	0.77–0.98	0.0313
Platelet inhibitors	0.69	0.60–0.79	<0.0001
Diuretics	1.43	1.24–1.66	<0.0001
Digoxin	1.97	1.70–2.28	<0.0001
Antiarrhythmics	1.33	1.10–1.60	0.0030
Antihypertensives	1.45	1.19–1.75	0.0001
Vasodilators	1.17	1.03–1.31	0.0094
ST-segment depression $\geq 0.2$ mv	1.22	1.06–1.40	0.0038
Exertional hypotension	1.50	1.16–1.93	0.0020

all-cause mortality with aerobic power from a group with a  $\dot{V}O_{2peak}$  of 15.5 mL/kg per minute to the quintile with the highest aerobic fitness (32.3 mL/kg per minute). In their sample, the largest difference in prognosis was seen between the 2 highest quintiles of fitness.

Dorn et al,<sup>23</sup> reporting on a long-term follow-up of post-myocardial infarction patients who completed an exercise program, found a reduction of 8% to 14% in all-cause death for every 1 MET increment in work capacity. The 9% improvement in prognosis associated with a 1 mL/kg per minute advantage of  $\dot{V}O_{2peak}$  in our cohort suggests that cardiac rehabilitation patients who make only modest gains in cardiorespiratory fitness could nevertheless obtain significant prognostic and functional benefits. Such gains may be particularly relevant for patients in the lowest of our 3 categories, ie,  $\dot{V}O_{2peak} < 15$  mL/kg per minute.

The  $\dot{V}O_{2peak}$  may be serving in part as a measure of residual pump function.<sup>20</sup> However, others have suggested that prognosis bears little relationship to more direct measures of cardiac performance.<sup>16,19,24</sup> We thus suspect that over a long-term follow-up, those with a low initial aerobic power progress more quickly to the point where pump function becomes inadequate. Another possibility is that an individual's peak  $\dot{V}O_2$  influences the proportion of aerobic power used

**TABLE 4. Cox Proportional Hazards Model for All-Cause Death (All Diagnostic Categories) at Entry to Study**

Variable	Hazard Ratio	Confidence Interval	P
$\dot{V}O_{2peak} < 15$ mL/kg per minute	1.00	...	...
$\dot{V}O_{2peak}$ 15–22 mL/kg per minute	0.66	0.59–0.73	<0.0001
$\dot{V}O_{2peak} > 22$ mL/kg per minute	0.48	0.42–0.55	<0.0001
Age per year	1.04	1.03–1.04	<0.0001
Body mass index $\geq 30$ kg/m <sup>2</sup>	1.25	1.11–1.42	0.0003
Current smokers	1.72	1.56–1.90	<0.0001
Diabetes	1.86	1.59–2.17	<0.0001
$\beta$ -Blockers	0.85	0.77–0.93	0.0004
Platelet inhibitors	0.79	0.72–0.87	<0.0001
Diuretics	1.36	1.22–1.52	<0.0001
Digoxin	1.79	1.60–2.00	<0.0001
Antiarrhythmics	1.23	1.06–1.42	0.0065
Antihypertensives	1.32	1.04–1.53	0.0147
Vasodilators	1.12	1.02–1.23	0.0124
Exertional angina	1.17	1.13–1.53	0.0003
Exertional hypotension	1.27	1.03–1.56	0.0024

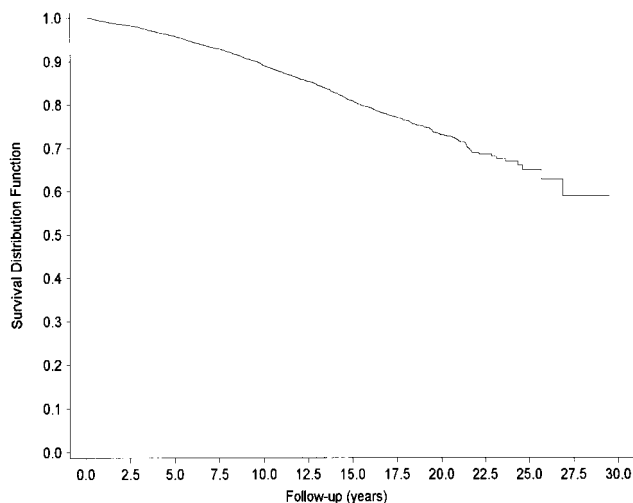
during heavy activities and thus the vulnerability to catecholamine-induced arrhythmias. Exertional hypotension is also a significant factor in prognosis<sup>25</sup> and again an indication of impaired pump function, although here we are looking at the ability of the individual to augment stroke volume during exercise in the face of a poorly perfused myocardium.

For the exercise test laboratories that do not have the facilities for collecting and analyzing respiratory gases, our finding that on receiver operating curve analysis the predicted  $\dot{V}O_{2peak}$  has the same prognostic power as measured  $\dot{V}O_{2peak}$  seems reassuring. However, others have shown that predicted values overestimate  $\dot{V}O_2$ , particularly in cardiac patients,<sup>26</sup> and this is confirmed in our data. For instance, 55% of patients whose measured  $\dot{V}O_{2peak}$  was  $< 15$  mL/kg per minute had a predicted measure of 15 to 22 mL/kg per minute, whereas only 19% of those with a predicted value of  $< 15$  mL/kg per minute had a measured  $\dot{V}O_{2peak}$  of 15 to 22 mL/kg per minute. Similarly, 33% of patients with a measured  $\dot{V}O_{2peak}$  ranging from 15 to 22 mL/kg per minute were predicted to have their measurements in the range of  $> 22$  mL/kg per minute, whereas only 7% of those with a predicted value of 15 to 22 mL/kg per minute had their measured  $\dot{V}O_{2peak}$  in the higher category of  $> 22$  mL/kg per minute.

**TABLE 3. Cox Proportional Hazards Model for Cardiac Death According to Diagnostic Category and Common Variables**

Variable	MI		CABG		IHD	
	HR	P	HR	P	HR	P
$\dot{V}O_{2peak}$ 15–22 mL/kg per minute	0.67	<0.0001	0.57	0.0003	0.38	<0.0001
$\dot{V}O_{2peak} > 22$ mL/kg per minute	0.40	<0.0001	0.40	0.0001	0.27	<0.0001
Current smokers	1.53	<0.0001	2.38	<0.0001	1.77	<0.0027
Digoxin	1.97	<0.0001	2.53	<0.0001	2.15	<0.0022

HR indicates hazard ratio.

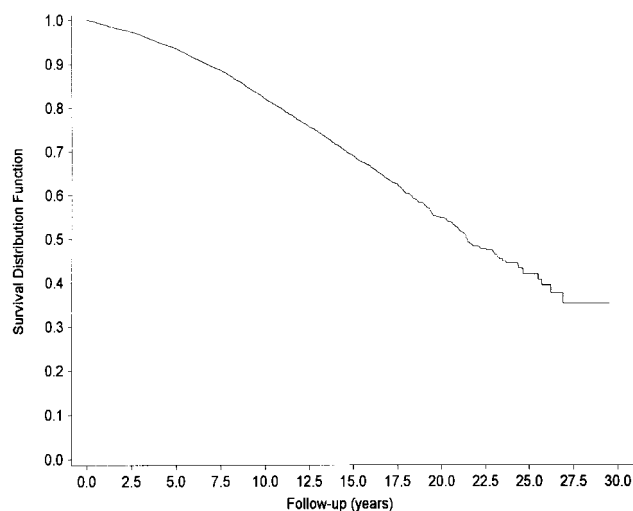


**Figure 1.** Overall Kaplan-Meier survival curve for cardiac deaths.

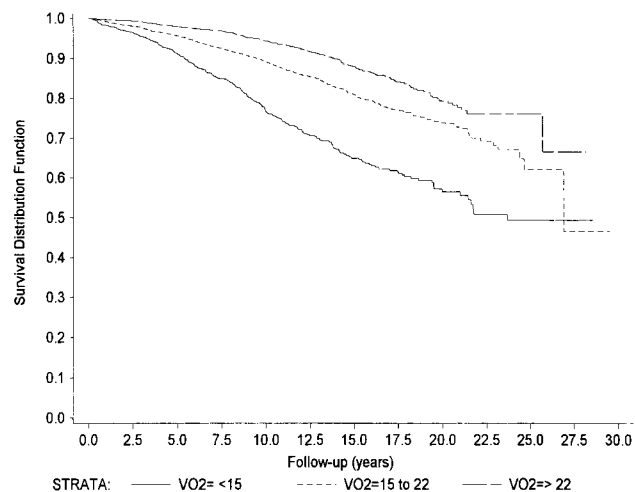
Caution is urged, therefore, in the use of predicted values for risk stratification. Obviously, our findings need to be evaluated using other data, particularly from the chronic heart failure population.

For interest, we have derived a simple multivariate risk score using the coefficients from the Cox model and the 4 highest performing variables in Table 3, as follows:  $\dot{V}O_2$  (in mL/kg per minute)  $<15=2$ ,  $15$  to  $22=1$ ,  $>22=0$ ; digoxin, yes=2, no=0; and smoking, yes=2, no=0. Low risk is defined as  $<2$ , moderate risk as 3 or 4, and high risk as  $>5$ . We used this grouping to predict 5-, 10-, and 15-year survival probabilities as well as to calculate Kaplan-Meier survival curves (Figure 4). We note that the patient who has a low level of fitness and is a smoker is at much greater risk of cardiac death than one who is free from these risk factors. Because both factors are amenable to exercise rehabilitation, this emphasizes its value. However, the cumulative risk score needs to be validated on a separate data set.

Our follow-up lacks studies in women, and, although risk factors in women resemble those in men (although some



**Figure 2.** Overall Kaplan-Meier survival curve for all-cause deaths.

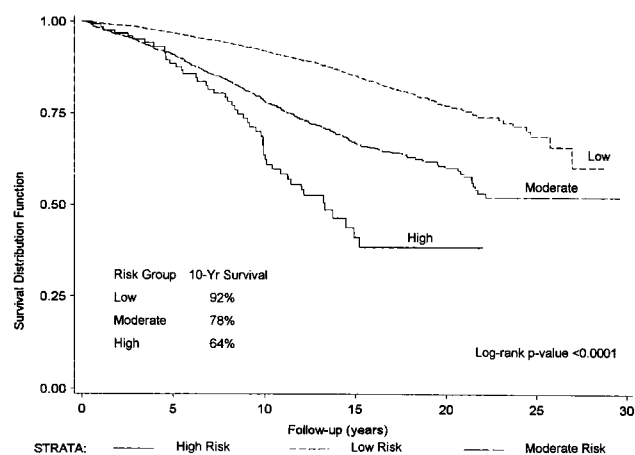


**Figure 3.** Kaplan-Meier survival curves for cardiac deaths, based on  $\dot{V}O_{2peak}$  at referral.

differ in magnitude of effect),<sup>27</sup> it nevertheless remains important to determine whether peak aerobic power carries similar prognostic weight in women, given that they seem less vulnerable to exercise-induced sudden death.<sup>28,29</sup> We also have a preponderance of white professional or managerial-class patients. Thus, our findings need replication in samples of differing ethnic and socioeconomic status. Finally, the length of the follow-up, although a unique and desirable feature of our study, also exposes the observations to potential contamination from secular trends in behavior and environmental factors; these may have influenced the shape of the mortality curves. For instance, during the period from 1968 to 1994, the average life expectancy of the Canadian male has increased substantially.<sup>30</sup>

## Conclusions

Whether a cardiac patient is referred for rehabilitation after MI, CABG, or the onset of IHD, the most important single predictor of both cardiac and all-cause deaths is the  $\dot{V}O_{2peak}$  as measured by cardiorespiratory testing. Even a small exercise-induced gain in aerobic power should thus make a major



**Figure 4.** Kaplan-Meier survival curves for cardiac deaths, based on risk score group.



difference not only in functional capacity but also in survival prospects.

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