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Impact of Exercise on the Relationship Between CAC Scores and All-Cause Mortality

Yoav Arnson, MD,[a,b] Alan Rozanski, MD,[c] Heidi Gransar, MS,[a,b] Sean W. Hayes, MD,[a,b] John D. Friedman, MD,[a,b] Louise E.J. Thomson, MBChB,[a,b] Daniel S. Berman, MD[a,b]

ABSTRACT

OBJECTIVES This study aims to assess the correlations among coronary artery calcium (CAC), self-reported exercise, and mortality in asymptomatic patients.

BACKGROUND The interaction between reported exercise habits and CAC scores for predicting clinical risk is not yet well known.

METHODS We followed 10,690 asymptomatic patients who underwent CAC scanning. Patients were divided into 4 groups based on a single-item self-reported exercise. Mean follow-up was 8.9 ± 3.5 years for the occurrence of all-cause mortality (ACM).

RESULTS Annualized ACM progressively increased with increasing CAC score ($p < 0.001$) and decreasing exercise ($p < 0.001$). Among patients with CAC scores of 0, ACM was low regardless of the amount of exercise. Among patients with CAC scores from 1 to 399, there was a stepwise increase in ACM for each reported decrement in exercise, and this difference was markedly more pronounced among patients with CAC scores ≥400. Compared with highly active patients with a CAC score of 0, highly sedentary patients with CAC scores ≥400 had a 3.1-fold increase (95% confidence interval: 1.35 to 7.11) in adjusted ACM risk. Our single-item physical activity questionnaire was also predictive of risk factors and clinical and lipid profile measurements.

CONCLUSIONS In asymptomatic patients, self-reported exercise is a significant predictor of long-term outcomes. Prognostic value of the reported exercise is additive to the increasing degree of underlying atherosclerosis. Among patients with high CAC scores, exercise may play a protective role, whereas reported minimal or no exercise substantially increases clinical risk. Our results suggest there is clinical utility for the use of a simple single-item exercise questionnaire for such assessments. (J Am Coll Cardiol Img 2017;10:1461–8) © 2017 by the American College of Cardiology Foundation.

Coronary artery calcium (CAC) scanning is a sensitive means for detecting and indirectly quantifying the magnitude of underlying atherosclerosis within the coronary vasculature. For this reason, CAC scanning is commonly used as a screening test for coronary artery disease (CAD). In addition, various lines of evidence suggest that CAC scanning may also be useful for other clinical purposes, such as triaging patients for cardiac stress testing and improving Bayesian estimates of CAD likelihood (1–3). Whereas CAC scores are a potent predictor of long-term clinical risk, combining CAC scores with assessment of myocardial ischemia, as evaluated by stress-rest myocardial perfusion imaging, provides synergistic information with respect to patient outcomes (4). Based on this observation, it is reasonable to postulate that combining CAC scores with other clinical or physiological variables might also be synergistic in predicting patient outcomes. To date, however, there has been little study in this

From the [a]Department of Imaging, Burns and Allen Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; [b]Department of Medicine, Burns and Allen Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; and the [c]Division of Cardiology, Mount Sinai St. Luke's Hospital, Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, New York. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACM = all-cause mortality

CAC = coronary artery calcium

CAD = coronary artery disease

CI = confidence interval

HR = hazard ratio

regard. A readily available clinical variable that provides risk prediction is the query of patients' exercise habits. Accordingly, we undertook the present study to compare the additive prognostic information provided by combining CAC scan results with a simple single-item question regarding patients' exercise habits.

METHODS

Our study population consisted of 19,249 patients referred for CAC scanning between 1998 and 2012. All followed patients signed a consent form. The study was approved by the Cedars-Sinai Medical Center Institutional Review Board. We excluded patients with known CAD (1,333), symptomatic patients (chest pain or exertional shortness of breath) within the year preceding the scan (2,691), patients with incomplete questionnaires (1,202), and patients with <1 year of follow-up (2,240), resulting in a study cohort of 11,912 patients. Of the latter, 1,094 (9.28%) were lost to follow-up, resulting in a cohort of 10,690 patients.

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Before CAC scanning, patients completed a questionnaire regarding pertinent demographic information, cardiac risk factors, and medication use. Resting heart rate, blood pressure, height, and weight were recorded, and patients had blood drawn to assess serum lipid and fasting glucose. Premature familial CAD history was defined as a primary relative diagnosed for CAD or cardiac event, <55 years for male family member or <65 for female family member. Smoking was defined as either currently smoking or having stopped for <1 year. Hypertension was defined as previously diagnosed hypertension or systolic blood pressure >140 mm Hg. Diabetes was defined as having been previously diagnosed with diabetes or fasting blood glucose >126 mg/dl (7.0 mmol/l). Dyslipidemia was defined as previously diagnosed dyslipidemia, treatment with lipid-lowering agents, low-density lipoprotein >130 mg/dl, high-density lipoprotein <40 mg/dl for men and <50 mg/dl for women, or total cholesterol ≥230 mg/dl (5).

Exercise habits were assessed according to a single-item question that was incorporated into our standard questionnaire, as follows: "On a scale of 0 to 10, how much do you exercise (0 - none, 10 - always)?"

CORONARY ARTERY CALCIUM SCANNING. Scanning was performed using electron beam (GE-Imatron Inc., San Francisco, California) or a multislice computed tomography scanner (Siemens Medical Systems, Erlangen, Germany; or Philips, Cleveland, Ohio). During a single breath-hold, 30 to 40 images were acquired from the carina to the diaphragm at 3.0- or 2.5-mm thickness at 50% to 80% of the cardiac cycle based on heart rate. Foci of CAC were identified by detection of at least 3 contiguous pixels (voxel size = 1.03 mm^3) of peak density ≥130 Hounsfield units within a coronary artery using semiautomatic commercial software (NetraMD, ScImage, Los Altos, California) and were verified by an imaging cardiologist. Density-weighted lesion-specific scores were calculated as the product of the area of each calcified focus as a density factor, according to the Agatston method (6). Lesion scores were summed to provide the total CAC score.

FOLLOW-UP DATA COLLECTION. The primary endpoint of this study was death from all causes, determined by query of the Social Security Death Index. Outcomes were only assessed for individuals who had at least 1 year of follow-up after CAC scanning.

STATISTICAL METHODS. Subjects were categorized into 4 groups on the basis of their self-reported exercise: scores of 0 and 1 were classified as no exercise; scores of 2 to 5 were classified as low exercise; scores of 6 to 8 were moderately active; and scores of 9 and 10 were classified as highly active. Continuous measures are presented as mean ± SD, and discrete data are presented as numbers or proportions. Baseline characteristics were tested across the exercise groups using chi-square test for categorical variables and analysis of variance for continuous variables. A two-tailed p value <0.05 was considered statistically significant. Time to death and mortality risk were estimated with a Cox proportional hazards model. Logistic regression analysis was used to assess the relation among patients' CAC scores, reported exercise, and the identified cardiac risk factors, including hazard ratios (HR) with 95% confidence intervals (CI). The associations between CAC and exercise were analyzed with multivariate logistic regression models. All statistical analyses were performed with Stata Statistical Software release 11.0 (Stata Corporation, College Station, Texas) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The clinical characteristics of the study population are shown in Table 1. Mean age was 55.7 ± 11.0 years and 66% were men. As exercise amount decreased, most CAD risk factors increased proportionally, including hypertension, diabetes, smoking, and family history of premature CAD. Lipid measurements also varied according to reported exercise. Statin use rose with progressively less exercise, and

TABLE 1 Study Population Characteristics

	Highly Active (n = 1,329)	Moderately Active (n = 3,467)	Low Exercise (n = 4,912)	No Exercise (n = 982)	p Values
Age, yrs	55.7 ± 10.1	54.9 ± 10.4	54.9 ± 11.0	55.3 ± 11.6	0.019
Male	71.6	67.4	64.7	58.8	<0.001
Cardiovascular risk factors					
Hypertension	33.2	37.0	43.0	48.0	<0.001
Dyslipidemia	63.7	67.0	70.6	65.9	<0.001
Diabetes	4.5	5.7	8.4	13.5	<0.001
Smoking	6.1	7.4	9.8	14.0	<0.001
Family history of CVD	32.9	34.7	36.3	36.7	<0.001
Resting heart rate, beats/min	61.9 ± 10.4	64.9 ± 10.2	68.0 ± 10.9	769.6 ± 10.8	<0.001
Systolic BP, mm Hg	125.8 ± 18.0	125.8 ± 19.0	127.0 ± 19.0	128.9 ± 19.0	<0.001
Diastolic BP, mm Hg	72.9 ± 10.0	73.3 ± 10.7	73.8 ± 10.7	74.2 ± 11.5	0.019
BMI, kg/m^2	24.9 ± 3.7	25.5 ± 4.0	27.1 ± 5.0	28.1 ± 5.7	<0.001
Glucose and lipid profile					
Total cholesterol	197.0 ± 38.0	201.2 ± 42.0	203.4 ± 42.0	200.7 ± 72.0	<0.001
Triglycerides	101.0 ± 63.0	114.0 ± 76.0	135.0 ± 86.0	145.9 ± 93.0	<0.001
VLDL cholesterol	21.0 ± 11.9	23.0 ± 12.2	26.0 ± 14.0	28.0 ± 15.0	<0.001
LDL cholesterol	118.9 ± 33.0	122.9 ± 36.0	124.9 ± 38.0	122.8 ± 55.0	<0.001
HDL cholesterol	57.5 ± 18.0	54.2 ± 18.0	50.9 ± 17.0	49.7 ± 18.0	<0.001
Fasting glucose, mg/dl	94.2 ± 18.0	95.6 ± 19.6	98.0 ± 23.9	103.6 ± 32.8	<0.001
Medications					
Aspirin	42.2	39.7	38.5	35.8	0.004
Statins	24.7	26.2	28.1	28.7	0.009
ACE inhibitors	8.8	9.3	11.0	11.3	0.005
ARB	6.6	10.4	14.0	14.3	<0.001
Beta-blocker	6.2	7.0	10.0	14.3	<0.001
Calcium-channel blocker	3.7	4.4	5.1	6.0	0.015
Coronary calcium scores					
CAC score	153.7 ± 459.0	134.3 ± 404.0	132.1 ± 404.0	165.5 ± 459.0	0.017
CAC score = 0	45.3	49.5	51.2	49.1	<0.001
CAC score >400	10.5	8.8	9.3	11.2	<0.001
CAC plaques, n	5.1 ± 7.7	4.8 ± 7.8	5.1 ± 8.4	6.2 ± 10.1	<0.001

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

the highly active group had higher high-density lipoprotein and lower low-density lipoprotein, very low-density lipoprotein, and triglyceride values. The more active groups also had lower blood pressure measurements, body mass index, fasting blood glucose levels, and resting heart rate, all rising progressively in the less active groups.

The median CAC scores were highest among the lowest reported exercise group, but the frequency of CAC scores of 0 was relatively similar in all 4 exercise groups. The odds ratio for having any CAC in the lowest exercise activity group compared with in the highest exercise activity, unadjusted for other covariates was 0.95 (95% CI: 0.82 to 1.07; p = 0.43). The frequency of CAC scores ≥400 and mean number of CAC plaques were highest in the no-exercise group. The odds ratio for having a CAC score ≥400 was 1.25 (95% CI: 1.04 to 1.50; p = 0.02) for the no-exercise group compared with the highly active group. Following adjustment for age, and cardiac risk factors, the odds ratio based on exercise groups for having a CAC score ≥400 became nonsignificant (HR: 1.10; 95% CI: 0.87 to 1.39; p = 0.41).

EXERCISE, CAC SCORES, AND MORTALITY. Patients were followed for a mean of 8.9 ± 3.5 years. During this time, 439 patients (4.12%) died. Table 2 shows mortality rates according to both CAC score groups and reported exercise. There was a progressive increase in crude mortality rates with both parameters. Compared with a CAC score of 0, the annualized mortality rate was increased by 8.9-fold (95% CI: 7.92 to 12.52) among those with a CAC score ≥400. Compared with those reporting high exercise, patients with no exercise had a 2.3-fold (95% CI: 1.6 to 3.5) increase in mortality. Figure 1 shows the

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TABLE 2 Total and Annual ACM Rates for Each Individual Exercise Group and for CAC Score Groups (n = 10,690)

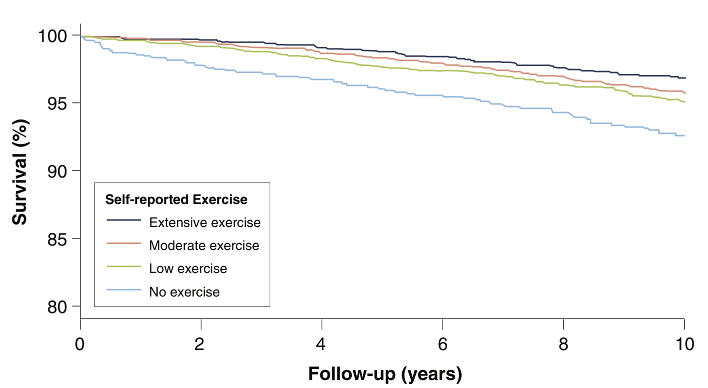
	Frequency of ACM (%)	ACM Rate (Mortality/1,000 Patient-Years)
CAC score		
CAC = 0	2.02	2.21
CAC 1-400	5.93	6.58
CAC >400	17.91	22.23
Reported exercise activity		
Highly active	2.86	3.08
Moderately active	3.63	3.99
Low exercise	4.27	4.76
No exercise	6.62	7.26

ACM = all-cause mortality; CAC = coronary artery calcium.

Kaplan-Meier survival curves by reported exercise groups. There was a progressive temporal widening in the survival curves from highest to lowest reported exercise.

COMBINED CAC AND EXERCISE INFORMATION. Table 3 shows both unadjusted and adjusted HR for all-cause mortality (ACM) according to CAC score and reported exercise. Compared with highly active individuals with CAC scores of 0, those who did not exercise and had CAC scores ≥400 had an overall adjusted 3.1-fold (95% CI: 1.35 to 7.11) increased risk for ACM. Figure 2 shows the Kaplan-Meier survival curves divided by both CAC score and reported exercise. Among patients with a CAC score of 0, there was no significant difference in survival according to reported exercise. Among those with a CAC score of 1 to 399, those who reported being highly sedentary had a significant reduction in survival. Among those with CAC scores ≥400, there was a progressive diminution in survival with each level of decreasing physical activity, and there was very early separation of survival curves of those with no exercise from those of the other exercise groups.

FIGURE 1 Event-Free Survival by Exercise Category



Kaplan-Meier survival curves for all-cause mortality among the entire cohort, divided according to patients' reported exercise.

MULTIVARIABLE PREDICTION OF ACM. Table 4 shows the results of the multivariable analysis to assess the predictors of ACM in the patient population. CAC score and reported exercise were significant predictors as were age, smoking, and hypertension. The standardized coefficients show that the strongest predictor relative to the others was age, followed by CAC score, followed by being in the no-exercise group.

DISCUSSION

CAC represents a potent means for predicting future clinical events and is highly useful for cardiovascular risk stratification, especially in the intermediate-risk population without known CAD (7–10). Our results in a large patient cohort confirm the strong relationship between the magnitude of CAC and mortality risk, with annualized mortality increasing in stepwise fashion with each increment of CAC.

This application of the CAC score for risk assessment is based on a proportional relationship between CAC and the overall burden of coronary atherosclerosis (11). CAC score scanning represents an anatomic test, and its utility in risk prediction may be enhanced by the consideration of functional information. For instance, it has been proposed that combining CAC scanning with treadmill exercise testing might provide added clinical utility (12). Thus, in this study, we evaluated a practical approach for assessing risk by combining CAC scanning with exercise information derived from patients' subjective reports of exercise habits.

SELF-REPORTED EXERCISE AND MORTALITY. Employing a single-item question regarding exercise according to a 0 to 10 scale, we assessed 4 groups, ranging from highly active patients (scores 9 and 10) to highly inactive patients (scores 0 and 1). Among these groups, we observed a stepwise inverse relationship between the amount of patients' reported exercise and annualized mortality. Those reporting no exercise had a mortality rate 2.3-fold higher than did patients who reported being highly active. These results are consistent with strong published data demonstrating increasing clinical events among individuals with low physical activity during daily life activity (13–17).

CORRELATION BETWEEN CAC SCORES AND REPORTED EXERCISE ACTIVITY. In our study, there was only a modest relationship between reported exercise activity and CAC scores. This modest relationship became insignificant after adjustment for covariates. The relationships among CAC scores, exercise habits, or cardiorespiratory fitness have been assessed by a variety of measures in prior studies, but the findings have been inconsistent (18–24). Of note, however, it is been observed that many clinical and psychosocial variables that are long-term predictors of adverse clinical outcomes do not correlate with concurrent CAC scores, including such factors as cholesterol measurements (25). This lack of association is believed to be due to the multifactorial nature of atherosclerosis.

CAC SCORES, REPORTED EXERCISE ACTIVITY AND OUTCOMES. A central finding of our results was the association between CAC scores and patients' reported exercise in predicting patient outcomes. As CAC score increased, so did the importance of reported exercise. Among patients with a CAC score of 0, there was no significant difference in mortality rate among patients according to reported exercise. Among patients with a CAC score of 1 to 399, the subgroup who reported very low exercise activity had substantially increased mortality risk. The separation in mortality risk according to reported exercise activity was most pronounced in patients with a CAC score ≥400. Those with CAC scores ≥400 and reporting no exercise activity had a 3.1-fold increased ACM risk. It is notable that this increase was observed in a low-risk asymptomatic population undergoing CAC scanning for screening purposes. It remains to be determined whether the differentiation of risk according to CAC score and reported exercise is further accentuated when these parameters are assessed in higher risk symptomatic populations.

COMPARISON TO PRIOR PUBLISHED DATA. Although both CAC scanning and exercise habits are commonly assessed, there has been a dearth of studies to evaluate whether combined assessment of CAC and physical activity provides significant incremental information in risk prediction. One relevant study involves data from the AGES (Age, Gene/Environment Susceptibility)-Reykjavik Study (26). In this study, 4,074 individuals with a mean age of 76 years had CAC scans along with assessment of gait speed. The individuals were followed for a mean of 5.4 years. Cardiac mortality risk increased in an additive fashion when both high CAC scores and slow gait speed were present. In another study, LaMonte et al. (27) found that high exercise duration was associated with a significant decreased risk of events with patients presenting with intermediate CAC scores at baseline.

TABLE 3 HR of ACM According to CAC Score and Reported Exercise Activity

	Highly Active	Moderately Active	Low Exercise	No Exercise
Unadjusted ACM risk				
CAC = 0	1.0 (ref)	0.78 (0.38–1.57)	1.02 (0.53–1.96)	1.12 (0.47–2.63)
CAC 1–400	1.7 (0.81–3.58)	2.43 (1.28–4.61)	2.63 (1.41–4.93)	3.81 (1.89–7.68)
CAC >400	3.06 (1.23–7.6)	6.72 (3.43–13.1)	9.51 (5.04–17.9)	14.6 (7.3–29.30)
Adjusted ACM risk*				
CAC = 0	1 (ref)	0.69 (0.32–1.50)	0.89 (0.44–1.78)	1.1 (0.43–2.79)
CAC 1–399	0.76 (0.34–1.75)	1.36 (0.68–2.69)	1.26 (0.64–2.48)	2.48 (1.18–5.22)
CAC ≥400	1.23 (0.47–3.23)	1.59 (0.72–3.48)	2.62 (1.27–5.44)	3.1 (1.35–7.11)

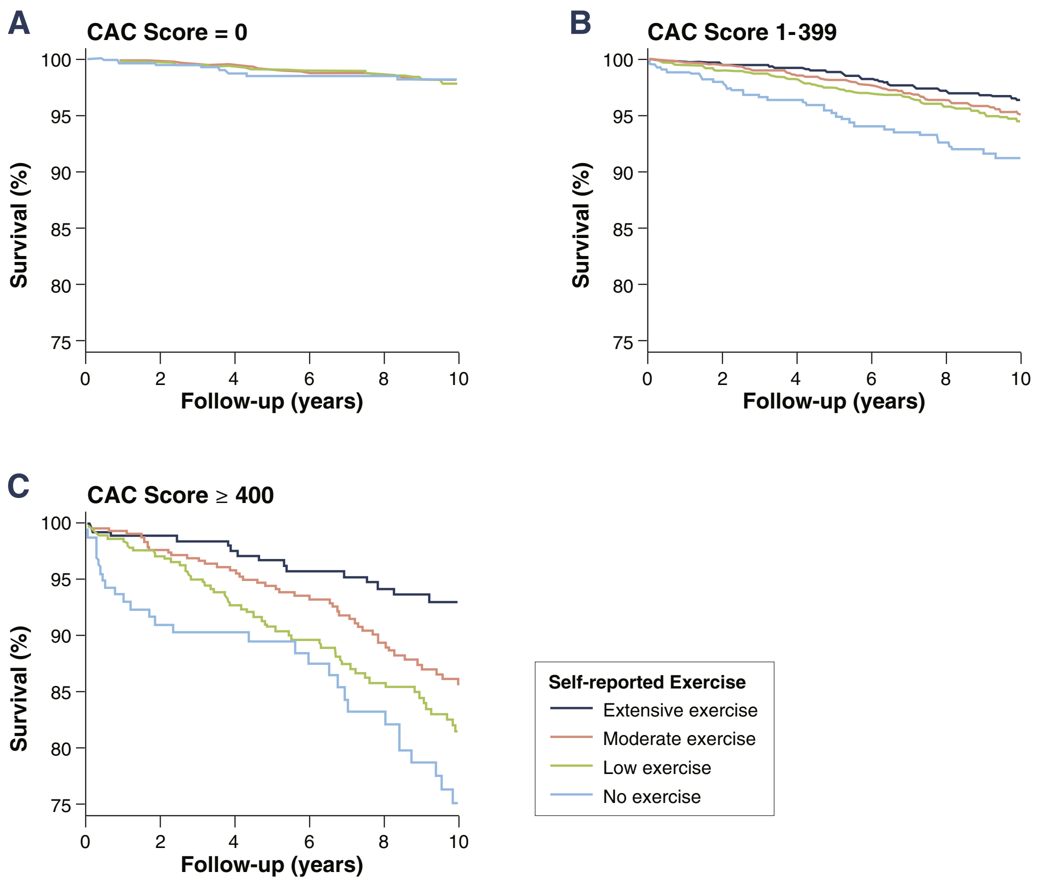
Values are HR (95% CI). *HR for ACM adjusted for age, sex, diabetes, hypertension, dyslipidemia, family history of CAD, and smoking.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

These previous reports are consistent with the observations of our study.

SINGLE-ITEM OR SHORT ASSESSMENTS OF EXERCISE ACTIVITY. The use of a single-item questionnaire to assess exercise activity, as employed in our study, is not without precedent. The general thrust of such single-item questionnaires is to provide practical information as to who is and is not participating in regular physical exercise. A variety of single or short items to assess physical activity have been employed previously and found to correlate with various clinical outcomes. For example, Hamilton et al. (28) found moderate to strong correlations between their single-item measurement of physical activity and both 7-day recall of physical activity and measurement of physical activity using pedometers. In another study, comparable correlations were found among a single-item physical activity survey, a more standard detailed physical activity survey, and accelerometer readings (29). In a general review of 14 prior studies using single-item physical activity surveys, Milton et al. (30) reported a moderate correlation with longer self-report physical activity surveys and a weaker correlation with objective measures of physical activity, such as the use of accelerometers. In our study, our single-item exercise question was found to be associated with multiple clinical measures. We observed a stepwise increase in a variety of CAD risk factors, adverse lipid measurements, fasting glucose, blood pressure, and resting heart rate in accordance with patients' reported physical activity. Similar associations regarding clinical parameters and a single-item exercise question was previously reported by Schechtman et al. (31).

STUDY LIMITATIONS. First, for this cohort, we used an arbitrarily developed physical activity question and we did not compare our measurement for

FIGURE 2 Event-Free Survival by Exercise Category and CAC Group



Kaplan-Meier survival curves for all-cause mortality according to patients' reported exercise and coronary artery calcium (CAC) category. Patients with CAC scores of 0 **(A),** 1 to 399 **(B)**, and ≥400 **(C)**.

concurrent validity against more standard physical activity questionnaires or objective measurements of physical fitness or physical activity. Second, our question most likely represented patients' exercise at the time of scanning and not their lifetime assessment of exercise. Third, our question cannot assess the differences among overall sedentary behavior, amount of daily physical activity, and amount of exercise. Fourth, although we assessed ACM, cardiac outcomes were not assessed.

CLINICAL IMPLICATIONS. Our findings suggest that very short physical activity questionnaires and potentially even single-item questionnaires might be useful for clinical purposes to augment the prognostic utility of anatomic tests such as CAC scanning and coronary computed tomography angiography. Similarly, physical activity questionnaires could be used

TABLE 4 Cox Proportional Hazard Regression Examining the Association of CAD Risk Factors and CAC Scores With Mortality

	HR (95% CI)	p Value
Age, for every 10 yrs	2.19 (1.87–2.36)	<0.001
Male	0.82 (0.64–1.03)	0.098
Dyslipidemia	0.80 (0.65–1.00)	0.06
Diabetes	0.92 (0.64–1.30)	0.62
Hypertension	1.40 (1.12–1.76)	0.003
Smoking	1.62 (1.16–2.26)	0.004
Family history of CAD	0.82 (0.64–1.04)	0.10
Log, CAC score + 1	1.47 (1.31–1.65)	<0.001
Level of exercise activity		
Highly active	1.00 (ref)	
Moderately active	1.29 (0.86–1.95)	0.21
Low exercise	1.56 (1.06–2.30)	0.024
No exercise	2.35 (1.49–3.70)	0.002

CAD = coronary artery disease; other abbreviations as in Tables 1 and 3.

to complement risk assessment in a wide variety of other medical settings, ranging from ambulatory settings to the in-hospital assessment of patients. One large medical group, for example, has incorporated a two-item exercise questionnaire as a routine "vital sign" within their electronic medical records (32). Our findings suggest that physical inactivity poses particularly accentuated risk among patients who also have a high burden of atherosclerosis, as identified by CAC scanning, and have not yet sustained a cardiac event.

As shown in a recent meta-analysis of 63 studies, cardiac rehabilitation is associated with substantial reduction in cardiovascular mortality, reduced hospital admissions, improved quality of life (33,34) and national health expenditures (35). Currently, however, cardiac rehabilitation is only an intervention for "secondary" CAD prevention, reserved for patients who have sustained cardiac events, had recent myocardial revascularization, or who have heart failure. Thus, if confirmed by further study, our results suggest that assessment of exercise habits might identify patients manifesting sedentary lifestyles and high CAC scores as a primary CAD prevention group for whom cardiac rehabilitation may also be of benefit.

ADDRESS FOR CORRESPONDENCE: Dr. Daniel S. Berman, Department of Imaging, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 1258, Los Angeles, California 90048. E-mail: bermand@cshs.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Exercise is known to have positive prognostic impact with respect to cardiovascular events. CAC scanning is in common use in asymptomatic patients for assessing cardiovascular risk. The use of a simple question about patients' exercise habits can be additive to CAC screening in long-term risk assessment.

TRANSLATIONAL OUTLOOK: The role of exercise habits in progression of coronary atherosclerosis and in modulation of acute coronary events is well documented. The degree of benefit from exercise according to extent of subclinical atherosclerosis is unknown. In a large population of asymptomatic patients undergoing CAC scanning, ACM increased as self-reported degree of exercise decreased in patients with evidence of subclinical atherosclerosis and was most marked in the patients with extensive CAC.

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