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Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the Heart and Soul Study

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Abstract

Background—The prognostic value of the six-minute walk test (6MWT) in patients with stable coronary heart disease (CHD) is unknown. We sought to determine whether the 6MWT predicted cardiovascular events in ambulatory patients with CHD.

Methods—We measured 6MWT distance and treadmill exercise capacity in 556 outpatients with stable CHD between September 2000 and December 2002. Participants were followed for a median of 8.0 years for cardiovascular events (heart failure, myocardial infarction, and death).

Results—Cardiovascular events occurred in 39% (218/556) of participants. Patients in the lowest quartile of 6MWT distance (87–419 meters) had 4 times the rate of events as those in the highest quartile (544–837 meters) (unadjusted HR 4.29, 95%CI 2.83–6.53, $p < 0.0001$). Each standard deviation (SD) decrease in 6MWT distance (104 meters) was associated with a 55% higher rate of cardiovascular events (age-adjusted HR 1.55, 95%CI 1.35–1.78). After adjustment for traditional risk factors and cardiac disease severity measures (ejection fraction, inducible ischemia, diastolic dysfunction, NT-proBNP, and CRP), each SD decrease in 6MWT was associated with a 30% higher rate of cardiovascular events (HR 1.30, 95%CI 1.10–1.53). When added to traditional risk factors, the 6MWT resulted in category-free net reclassification improvement of 39% (95%CI 19%–60%). The discriminative ability of 6MWT was similar to treadmill exercise capacity for predicting cardiovascular events (c-statistics both 0.72, $p = 0.29$).

Conclusions—Distance walked on 6MWT predicted cardiovascular events in patients with stable CHD. The addition of a simple 6MWT to traditional risk factors improved risk prediction and was comparable to treadmill exercise capacity.

INTRODUCTION

For patients with stable coronary heart disease (CHD), prognostic models based on traditional cardiovascular disease risk factors do not fully explain the risk of future cardiovascular events.^{1–3} Exercise treadmill testing provides information regarding prognosis in stable CHD patients,^{4–9} but testing can be costly and time-consuming, especially if testing is bundled with imaging studies that may be unnecessary in stable patients.^{10–12}

The six-minute walk test (6MWT) is a simple, easy-to-perform, commonly used test of functional exercise capacity. Its ability to predict outcomes has been established in patients

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with heart failure,^{13–17} pulmonary hypertension,¹⁸ and pulmonary disease.¹⁹ However, there is no evidence regarding the ability of the 6MWT to predict outcomes in patients with stable CHD.

In the present study, we evaluated the ability of the 6MWT to predict heart failure, myocardial infarction, and death in a sample of 556 patients with stable CHD enrolled in the Heart and Soul Study. We compared the predictive ability of 6MWT to other methods of risk assessment including traditional risk factors and treadmill exercise capacity (METs).

METHODS

Participants

The Heart and Soul Study is a prospective cohort study designed to investigate the effects of psychosocial factors on health outcomes in patients with stable CHD. Methods have been previously described.²⁰ Patients were eligible if they had at least 1 of the following: history of myocardial infarction, angiographic evidence of 50% stenosis in 1 coronary vessels, evidence of exercise-induced ischemia by treadmill ECG or stress nuclear perfusion imaging, or a history of coronary revascularization. Patients were excluded if they were unable to walk one block, had an acute coronary syndrome within the previous six months, or were likely to move out of the area within three years. We mailed 15438 potentially eligible participants an invitation to participate, and 2495 responded with interest. Of those responding, 505 could not be reached for scheduling, 596 declined, and 370 met exclusion criteria.

Between September 2000 and December 2002, 1024 subjects were enrolled from 12 outpatient clinics in the San Francisco Bay Area, including 549 (54%) with a history of myocardial infarction, 237 (23%) with a history of revascularization but not myocardial infarction, and 238 (23%) with a diagnosis of coronary disease that was documented by their physician, based on a positive angiogram or treadmill test in over 98% of cases. All study participants completed a full-day study including medical history, extensive questionnaires, and an exercise treadmill test with baseline and stress echocardiograms. Twelve hour fasting serum samples were obtained in the morning prior to stress test.

A convenience sample of 769 participants was offered the 6-minute walk test. We were not able to offer the 6MWT to all participants for logistical reasons (e.g., not enough time during visit, obstruction of the 6MWT corridor, study staff unavailable). Of the 769 participants who were offered the 6MWT, 186 were unable to complete the 6MWT (recently experiencing unusual angina or chest pain, or did not think they were capable of walking for 6 minutes due to chest pain, shortness of breath, or musculoskeletal impediment), 6 refused, and 1 had incomplete data. Of the 576 participants who completed the 6-minute walk test, 18 were excluded from this analysis because they did not complete the treadmill test and 2 because they were lost to follow-up, leaving 556 participants for this analysis.

Six-Minute Walk Test

The 6MWT was administered according to standard guidelines.²¹ A single walk test without practice was administered. Participants were instructed to walk continuously on a hospital corridor 145.5 feet (44m) in length, covering as much ground as they could during six minutes. Encouragement was given every minute in a standardized fashion. Total distance walked in six minutes was recorded.

Outcome Ascertainment

Annual telephone interviews were conducted with participants or their proxy to inquire about interval emergency department visit, hospitalization, or death. For any reported event, medical records, electrocardiograms, death certificates, autopsy, and coroner's reports were obtained. Each event was adjudicated by 2 independent and blinded reviewers. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator, if needed.

The primary outcome was a composite of cardiovascular events of heart failure, myocardial infarction, or death from any cause. Secondary outcomes were the individual components of heart failure, myocardial infarction, and death from any cause. Myocardial infarction was defined using standard diagnostic criteria.²² Heart failure was defined as hospitalization or emergency department visit for signs and symptoms of heart failure. Death was verified by death certificates.

Other Patient Characteristics

Demographic characteristics, medical history, and smoking status were assessed by self-report questionnaire. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire, a self-report instrument that measures the frequency of depressive symptoms, with a score of 10 or higher being classified as having depressive symptoms.²³ We measured weight and height and calculated the body mass index (BMI) (kg/m²). Resting blood pressure and heart rate were measured. Participants were asked to bring their medication bottles to the study appointment, and research personnel recorded all current medications. Medications were categorized using Epocrates Rx (San Mateo, CA).

Total cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin, creatinine, and high sensitivity C-reactive protein (CRP) were determined from 12-h fasting serum samples. Levels of the amino terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) were determined using Roche Diagnostics Elecsys NT-proBNP electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, IN). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.²⁴

Participants underwent symptom-limited exercise stress testing according to a standard Bruce protocol (those unable to complete the standard protocol were converted to a manual protocol) with continuous 12-lead electrocardiogram monitoring, and exercise capacity was estimated as the total metabolic equivalents (METs) achieved at peak exercise.²⁵ Prior to exercise, participants underwent complete resting two-dimensional echocardiograms with all standard views using an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, CA) with a 3.5-MHz transducer and Doppler ultrasound examination. Standard two-dimensional parasternal short-axis and apical two- and four-chamber views were obtained during held inspiration and were used to calculate the left ventricular ejection fraction.²⁶ Diastolic dysfunction was defined as pseudonormal or restrictive filling on mitral inflow.²⁰ At peak exercise, precordial long- and short-axis and apical two- and four-chamber views were obtained to assess for wall motion abnormalities. We defined exercise-induced ischemia as the presence of one or more new wall motion abnormalities at peak exercise that were not present at rest. A single experienced cardiologist (NBS), who was blinded to the results of the 6MWT, treadmill exercise capacity, and clinical histories, interpreted all echocardiograms.

Statistical Analysis

Since there are no defined categories for 6MWT in patients with CHD, participants were divided into quartiles on the basis of 6MWT distance. Baseline participant characteristics across quartiles were compared using analysis of variance (ANOVA) for continuous variables, χ^2 test for dichotomous variables, and Fisher exact test for dichotomous variables with fewer than 5 participants in a category. We compared unadjusted rates of cardiovascular events by quartile using Cox-proportional hazards models and the log-rank test. We compared adjusted rates of cardiovascular events, analyzing 6MWT as a continuous variable, per one standard deviation decrease of 6MWT distance using Cox-proportional hazards models adjusted for covariates associated with 6MWT quartile at $p < 0.1$. For any covariates with more than 1% missing data, multiple imputation was performed using iterative chained equations including history of hypertension (3% missing), dyslipidemia (6%), diabetes (4%), peripheral vascular disease (15%), and chronic lung disease (5%), as well as ejection fraction (3%), diastolic dysfunction (11%), log NT-proBNP (4%), and log CRP (4%). We tested for interactions between 6MWT distance and age, gender, current smoking, diabetes, BMI, systolic blood pressure, estimated GFR, hemoglobin, and left ventricular ejection fraction. Using a logistic regression model for predicting cardiovascular events based on traditional risk factors (age, sex, current smoking, history of hypertension, history of dyslipidemia, history of diabetes, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol to HDL cholesterol ratio), we estimated the area under the receiver operating curve (c-statistic), integrated discrimination index (IDI), and category-free net reclassification improvement (NRI) for predicting cardiovascular events for the individual addition of continuous measures of 6MWT, treadmill exercise capacity, NT-proBNP, CRP, and ejection fraction.^{27–29} We compared treadmill exercise capacity to 6MWT using the Pearson correlation coefficient. Analyses were performed using Stata (version 12; StataCorp, College Station, TX).

RESULTS

Among the 556 participants, median 6MWT distance was 481 meters (interquartile range 420–543 m). Compared to participants in the highest quartile of 6MWT distance (544–837 m), participants in the lowest quartile of 6MWT distance (87–419 m) were older, less likely to be male, and more likely to be current smokers (Table 1). Participants in the lowest quartile were more likely to have clinical risk factors of hypertension, dyslipidemia, diabetes, peripheral vascular disease, and higher BMI. A higher proportion of participants in the lowest quartile were taking ACE-inhibitors or ARBs and diuretics than participants in the highest quartile. Participants in the lowest quartile had more inducible ischemia on stress echocardiography, slightly lower left ventricular ejection fraction, and higher NT-proBNP. In addition, participants in the lowest quartile had lower eGFR and lower hemoglobin levels. Treadmill exercise capacity (METs) was worse in participants in the lowest quartile.

Comparing the 556 participants who completed the 6MWT with the 213 participants who were offered the 6-minute walk test but excluded from this analysis, the 556 participants included in the analysis were similar in age and left ventricular ejection fraction, but more likely to be male (86% vs. 79%, $p = 0.02$). Cardiovascular event-free survival of the participants who were offered the 6MWT but not included in this analysis was similar to participants in the lowest quartile of 6MWT distance ($p = 0.63$ by log-rank test).

During a median follow-up of 8.0 years (interquartile range 4.2–9.0 years) there were 82 heart failure hospitalizations, 63 myocardial infarctions, and 184 deaths from any cause, with 218 participants experiencing the primary outcome of heart failure, myocardial infarction, or death (cardiovascular events). Median age at death was 79.0 (interquartile range 70.8–85.5). Participants in the lowest quartile of 6MWT distance experienced more

events than those in the other quartiles of 6MWT distance (Figure 1). Participants in the lowest quartile of 6MWT distance experienced cardiovascular events at four times the rate of participants in the highest quartile (unadjusted HR 4.29, 95% CI 2.83–6.53, $p < 0.0001$).

We evaluated continuous 6MWT distance and found that each SD decrease in 6MWT distance (104 m) was associated with an 86% higher rate of heart failure (age-adjusted HR 1.86, 95% CI 1.51–2.31), a 47% higher rate of myocardial infarction (age-adjusted HR 1.47, 95% CI 1.15–1.89), a 54% higher rate of death (age-adjusted HR 1.54, 95% CI 1.32–1.80), and a 55% higher rate of any cardiovascular event (age-adjusted HR 1.55, 95% CI 1.35–1.78) (Table 2). After adjusting for baseline characteristics and markers of cardiac disease severity, 6MWT distance remained independently associated with cardiovascular events (HR 1.30, 95% CI 1.10–1.53, $p = 0.002$). We found no evidence that the association between 6MWT distance and cardiovascular events varied by age, gender, current smoking, diabetes, BMI, systolic blood pressure, estimated GFR, hemoglobin, or left ventricular ejection fraction (all p -values for interaction > 0.10).

When considered alongside traditional risk factors, the addition of the 6MWT to traditional risk factors resulted in an increase in the c-statistic from 0.69 to 0.72 ($p = 0.04$), IDI of 4.1% (95% CI 1.0%–8.4%), and category-free NRI of 39.3% (95% CI 19.1%–59.9%) (Table 3).

Six-minute walk test was compared with treadmill exercise capacity (METs). There was significant correlation between 6MWT distance and treadmill exercise capacity ($r = 0.66$, $p < 0.0001$) (Figure 2). 6MWT distance and treadmill exercise capacity had similar discrimination for predicting cardiovascular events (c-statistics 0.72 and 0.72, $p = 0.29$ for comparison), IDI, and category-free NRI (Table 3). NT-proBNP and ejection fraction also improved risk prediction over traditional risk factors, and CRP provided no significant improvement in risk prediction. The addition of 6MWT to a model including traditional risk factors and NT-proBNP increased the c-statistic from 0.72 to 0.74 (95% CI 0.67–0.78; $p = 0.07$), resulted in IDI of 2.8% (95% CI 0.4%–6.6%), and provided category-free NRI of 35.3% (95% CI 15.3%–59.2%).

DISCUSSION

In a cohort of patients with stable CHD, we found that shorter distance walked on 6MWT was associated with higher rates of heart failure, myocardial infarction, and death, independent of traditional cardiovascular disease risk factors and markers of cardiac disease severity. The 6MWT provided additional predictive information beyond traditional risk factors. The ability of the 6MWT to predict cardiovascular events was similar to treadmill exercise capacity (METs). These findings suggest that a simple 6MWT is a useful prognostic marker for identifying CHD patients at high risk of cardiovascular events.

There has been limited evidence regarding the prognostic ability of the 6MWT in patients with chronic CHD. One study evaluated patients with recent coronary artery bypass surgery undergoing cardiac rehabilitation, and found 6MWT to be a predictor of mortality.³⁰ Our findings extend the evidence that the 6MWT predicts cardiovascular events to a general population of patients with stable CHD. The results of this study also expand beyond previous studies that have investigated 6MWT in patients with heart failure.^{13–17,31} Although 6MWT distance did not reliably correlate with cardiopulmonary exercise testing measures in previous studies,^{31,32} most studies found that 6MWT still predicted heart failure hospitalizations and death in patients with systolic heart failure.^{13–16} In addition, a study of older adults with heart failure found that 6MWT was associated with mortality and highly correlated with frailty.³³ Our study reveals that the 6MWT predicts cardiovascular events in

a broader population of patients with stable CHD, independent of traditional risk factors and markers of cardiac disease severity.

Comparing the 6MWT to other prognostic tools, we found that the 6MWT performed comparably to other tools for predicting future cardiovascular events. Methods of risk assessment based on traditional risk factors do not adequately predict risk of subsequent cardiovascular events in patients with existing CHD.¹ Revised methods using additional clinical variables³⁴ or biomarkers^{3,35,36} have demonstrated only modest improvement in risk discrimination. Cardiopulmonary exercise testing and treadmill exercise capacity can identify patients at high risk of future events and can be used to aid in physical activity and cardiac rehabilitation recommendations.⁴⁻⁷ Our study suggests a potential alternative to treadmill exercise testing for assessment of prognosis in patients with stable CHD.

Treadmill exercise testing will remain the preferred modality for evaluating patients with suspected ischemia. However, for stable outpatients undergoing testing for prognosis, the 6MWT offers potential advantages. The 6MWT can be conducted with little equipment other than a hallway marked for distance and a stopwatch. Due to the self-paced nature of the test, side effects of chest pain, dyspnea, or musculoskeletal pain are usually mild; serious adverse events have not been described.²¹ Further, the 6MWT is less expensive than treadmill exercise testing, especially if stress testing is bundled with imaging that may be unnecessary.¹² The 2012 Medicare National Physician Fee schedule reports a payment for 6MWT of \$59.91, compared to cardiovascular stress testing at \$88.50 (plus \$208–\$503 for imaging).³⁷

The ability of the 6MWT, a simple office-based test of functional exercise capacity, to predict outcomes in patients with stable CHD is especially relevant because the 6MWT addresses physical activity, a modifiable risk factor for secondary prevention of CHD. Despite evidence demonstrating the efficacy of exercise-based rehabilitation in patients with CHD for reducing mortality,^{38,39} most patients do not participate in cardiac rehabilitation or achieve recommended levels of physical activity.⁴⁰⁻⁴² There is a need for improved strategies to identify patients at the greatest risk of cardiovascular events and to motivate patients and physicians to address physical activity as a modifiable risk factor.⁴¹ Repeated measurement of the 6MWT could be used as a simple office-based tool to monitor exercise capacity and motivate patients to achieve appropriate levels of physical activity. While we demonstrated that the 6MWT can predict cardiovascular events in stable CHD, its use for improving prognosis merits further study.

Our study has several limitations. First, we cannot exclude the possibility of selection bias in the main cohort of participants, since many invited participants did not enroll in the study. Additionally, since our study was comprised of predominantly male participants, the results may not generalize to women. Third, participants were excluded from the Heart and Soul study if they were unable to walk one block. Thus, the results may not extend to patients with significant angina or other limitations in walking. Participants in our study completed both the 6MWT and the treadmill exercise test on the same day, which also could have impacted these measurements. Finally, not all study participants were able to complete the 6MWT, and participants who could not complete the 6MWT had similar event rates to participants in the lowest quartile of 6MWT performance. This suggests that patients with CHD who cannot perform the 6MWT or who have poor performance on the 6MWT are both at increased risk of cardiovascular events.

In conclusion, we found that distance walked on 6MWT predicted subsequent cardiovascular events in patients with stable CHD, and its predictive ability was similar to treadmill exercise capacity. The 6MWT may be a useful tool for measuring functional

exercise capacity in patients with stable CHD to help target secondary prevention goals for physical activity.

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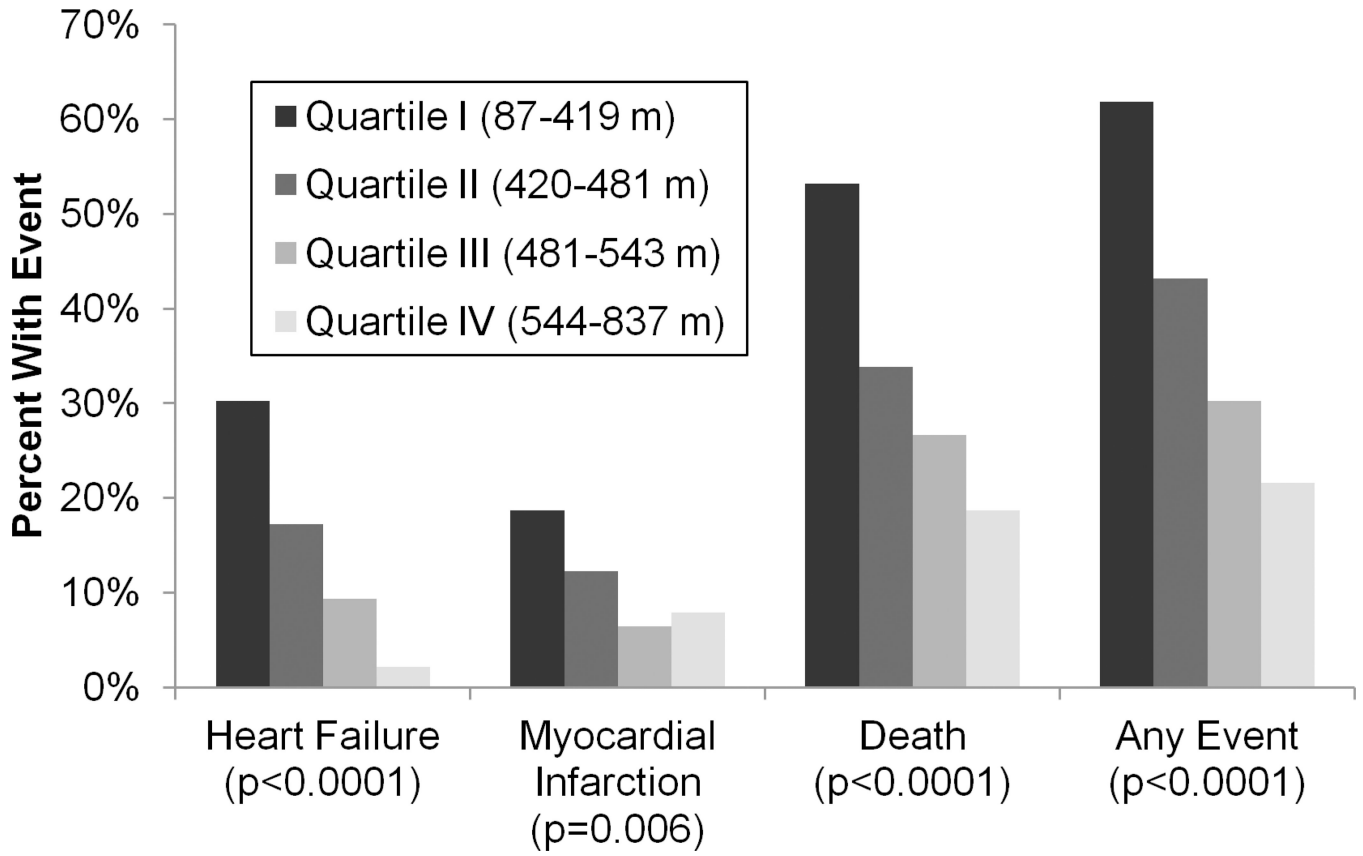


Figure 1. Cardiovascular events by quartile of six-minute walk test distance.

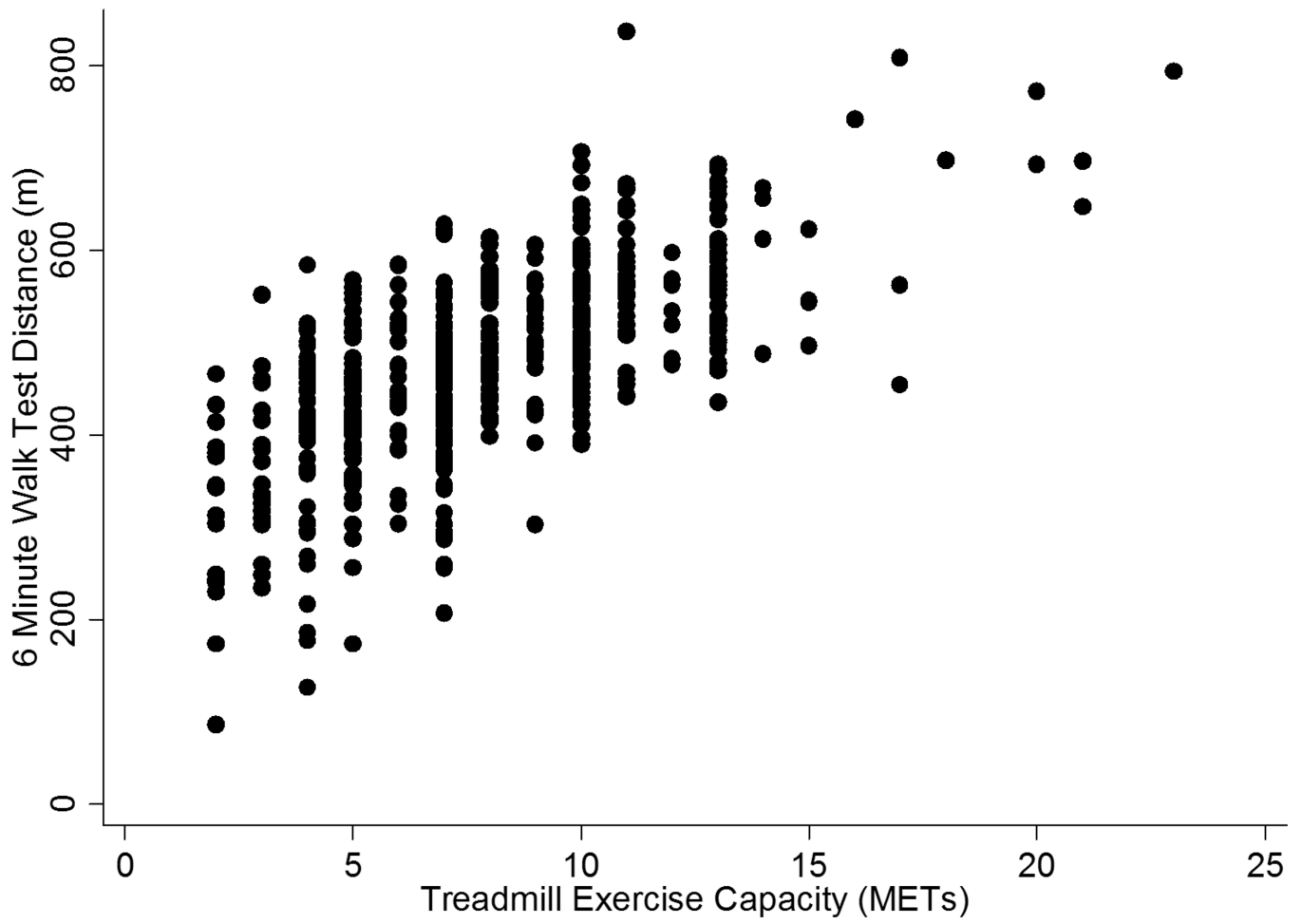


Figure 2.
Six-minute walk test distance by treadmill exercise capacity.
Correlation coefficient $r=0.66$, $p<0.0001$.

Table 1

Baseline characteristics of 556 participants with stable coronary heart disease by quartile of six-minute walk test distance.

Number in quartile	Quartile I			Quartile II			Quartile III			Quartile IV			p value
	139	139	139	139	139	139	139	139	139	139	139	139	
6MWT distance (m)	87–419	420–481	481–543	544–837									
	72.8 (10.3)	68.2 (10.1)	67.3 (10.3)	62.2 (9.5)									<0.0001
Demographics													
Age (years)	115 (83)	113 (81)	123 (88)	128 (92)									0.03
Male sex	81 (58)	90 (65)	91 (65)	98 (71)									0.20
Caucasian	27 (19)	33 (24)	20 (14)	11 (8)									0.003
Current Smoking													
Medical History													
Hypertension	99 (71)	104 (75)	91 (65)	78 (56)									0.005
Myocardial Infarction	73 (53)	80 (58)	73 (53)	72 (52)									0.72
Heart Failure	27 (19)	21 (15)	22 (16)	14 (10)									0.11
Dyslipidemia	83 (60)	100 (72)	97 (70)	103 (74)									0.06
Diabetes	44 (32)	25 (18)	29 (21)	20 (14)									0.003
Peripheral Vascular Disease	17 (12)	12 (9)	2 (1)	7 (5)									0.001
Revascularization	83 (60)	77 (55)	88 (63)	98 (71)									0.06
Chronic Lung Disease	26 (19)	31 (22)	20 (14)	16 (12)									0.08
Depressive Symptoms	18 (13)	18 (13)	18 (13)	18 (13)									>0.99
Clinical Measurements													
Body Mass Index (kg/m ²)	28.4 (4.8)	28.1 (4.5)	26.8 (4.1)	27.6 (4.2)									0.01
Systolic Blood Pressure (mmHg)	134.1 (16.8)	130.3 (18.3)	129.6 (19.1)	127.0 (16.3)									0.008
Diastolic Blood Pressure (mmHg)	72.8 (10.0)	73.3 (9.6)	72.8 (10.6)	75.1 (10.1)									0.16
Pulse (bpm)	68.7 (12.4)	66.1 (10.6)	67.6 (11.6)	66.1 (11.7)									0.18
Total Cholesterol (mg/dL)	172.2 (41.0)	177.7 (41.9)	179.1 (37.0)	175.1 (38.2)									0.49
HDL Cholesterol (mg/dL)	45.6 (13.3)	47.0 (15.7)	47.0 (14.2)	48.0 (13.6)									0.56
CKD-EPI eGFR (ml/min)	65.2 (21.7)	74.5 (17.5)	71.8 (19.7)	78.6 (16.7)									<0.0001
Hemoglobin (g/dL)	13.5 (1.3)	14.0 (1.2)	14.0 (1.3)	14.3 (1.1)									<0.0001
Medications													
Beta-Blockers	83 (60)	85 (61)	81 (58)	75 (54)									0.65

	Quartile I	Quartile II	Quartile III	Quartile IV	p value
Number in quartile	139	139	139	139	
6MWT distance (m)	87–419	420–481	481–543	544–837	
ACE-inhibitor or ARB	75 (54)	72 (52)	76 (55)	54 (39)	0.03
Statin	84 (60)	90 (65)	100 (72)	100 (72)	0.11
Aspirin	101 (73)	113 (81)	113 (81)	112 (81)	0.22
Diuretics	54 (39)	39 (28)	35 (25)	19 (14)	<0.0001
Biomarkers					
C-reactive Protein (mg/L) ^a	2.9 (1.4–7.1)	1.9 (0.8–3.9)	1.7 (0.9–3.6)	1.4 (0.5–3.2)	0.099
NT-proBNP (pg/mL) ^a	281 (115–674)	162 (102–350)	138 (69–343)	97 (48–218)	0.0009
Stress Echocardiography					
Inducible Ischemia	48 (35)	43 (31)	37 (27)	20 (14)	0.001
Diastolic Dysfunction	23 (17)	14 (10)	14 (10)	12 (9)	0.09
LV Ejection Fraction (%)	60.5 (10.7)	62.0 (10.1)	63.9 (9.5)	62.2 (9.0)	0.045
Treadmill Exercise Capacity (METs)	5.1 (2.0)	7.1 (2.5)	8.6 (2.4)	10.6 (3.3)	<0.0001

Values are expressed as mean (SD) or number (%).

^aValues expressed as median (interquartile range).

Abbreviations: 6MWT: Six-minute walk test; eGFR: estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation; HDL: high-density lipoprotein; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; LV: left ventricular; NT-proBNP: amino-terminal portion of the prohormone of B-type natriuretic peptide; METs: metabolic equivalents.

Table 2

Association between six-minute walk test distance and cardiovascular events.

	Age Adjusted		Multivariate Adjusted ^b	
	HR ^a	95% CI	HR ^a	95% CI
Heart Failure	1.86	1.51–2.31	1.38	1.04–1.82
Myocardial Infarction	1.47	1.15–1.89	1.36	1.00–1.85
Death	1.54	1.32–1.80	1.25	1.04–1.50
Any Event or Death	1.55	1.35–1.78	1.30	1.10–1.53

^aHazard Ratios (HR) per 1-standard deviation decrease in Six Minute Walk Test distance (104m).

^bMultivariate Model includes: age, gender, smoking, hypertension^c, dyslipidemia^c, diabetes^c, peripheral vascular disease^c, revascularization, chronic lung disease^c, body mass index, systolic blood pressure, estimated glomerular filtration rate, hemoglobin, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, diuretic use, inducible ischemia, ejection fraction^c, diastolic dysfunction^c, log NT-proBNP^c (amino terminal fragment of the prohormone of B-type natriuretic peptide), log C-reactive protein^c.

^cMultiple imputation performed for missing values.

Table 3

Prediction of cardiovascular events with six-minute walk test and traditional risk prediction measures.

	c-statistic	IDI (%)	NRI (%)
Traditional Risk Factors (TRF)	0.69 (0.62 – 0.73)	Reference	Reference
TRF + 6MWT	0.72 (0.63 – 0.76) ^a	4.1 (1.0 – 8.4)	39.3 (19.1 – 59.9)
TRF + METs	0.72 (0.64 – 0.76) ^{ab}	3.8 (1.0 – 7.9)	39.6 (18.6 – 61.7)
TRF + NT-proBNP	0.72 (0.66 – 0.76)	4.8 (1.6 – 9.5)	44.3 (26.6 – 67.2)
TRF + CRP	0.70 (0.63 – 0.74)	0.1 (–0.4 – 1.6)	12.6 (–23.4 – 33.3)
TRF + LVEF	0.72 (0.64 – 0.76)	5.4 (1.7 – 10.2)	47.7 (22.7 – 67.5)

Values are expressed as point estimate (95% CI).

^a p-value for comparison with TRF p<0.05

^b p-value for comparison of c-statistic of TRF + 6MWT vs. TRF + METs p=0.29

Abbreviations: TRF: Traditional Risk Factors; IDI: integrated discrimination improvement; NRI: net reclassification improvement; 6MWT: six-minute walk test; METs: treadmill exercise capacity in metabolic equivalents; NT-proBNP: amino-terminal portion of the prohormone of B-type natriuretic peptide; CRP: C-reactive protein; LVEF: left ventricular ejection fraction.