Six-Minute Walk Test as a Prognostic Tool in Stable Coronary Heart Disease

Data From the Heart and Soul Study

Alexis L. Beatty, MD; Nelson B. Schiller, MD; Mary A. Whooley, MD

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

Methods: We measured 6MWT distance and treadmill exercise capacity in 556 outpatients with stable coronary heart disease from September 11, 2000, through December 20, 2002. Participants were followed up for a median of 8.0 years for cardiovascular events (heart failure, myocardial infarction, and death).

Results: Cardiovascular events occurred in 218 of 556 participants (39.2%). Patients in the lowest quartile of 6MWT distance (87-419 m) had 4 times the rate of events as those in the highest quartile (544-837 m) (unadjusted hazard ratio, 4.29; 95% CI, 2.83-6.53; $P < .001$). Each SD decrease in 6MWT distance (104 m) was associated with a 55% higher rate of cardiovascular events (age-adjusted hazard ratio, 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, amino-terminal portion of the prohormone of brain-type natriuretic peptide, and C-reactive protein), each SD decrease in 6MWT was associated with a 30% higher rate of cardiovascular events (hazard ratio, 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 the 6MWT was similar to that of treadmill exercise capacity for predicting cardiovascular events (C statistics both 0.72; $P = .29$).

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

Arch Intern Med. 2012;172(14):1096-1102.
Published online June 18, 2012.
doi:10.1001/archinternmed.2012.2198

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 patients with stable CHD,[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]

CME available online at www.jamaarchivescme.com and questions on page 1053

The 6-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 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 the 6MWT with other methods of risk assessment, including traditional risk factors and treadmill exercise capacity (in metabolic equivalents [METs]).

See Invited Commentary at end of article

METHODS

PARTICIPANTS

The Heart and Soul Study is a prospective cohort study designed to investigate the effects of psychosocial factors on health out-

Author Affiliations: Departments of Medicine (Drs Beatty, Schiller, and Whooley) and Epidemiology and Biostatistics (Dr Whooley), University of California, San Francisco, and Veterans Affairs Medical Center, San Francisco (Dr Whooley).

comes in patients with stable CHD. The 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 at least 50% stenosis in at least 1 coronary vessel, evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging, or a history of coronary revascularization. Patients were excluded if they were unable to walk 1 block, had an acute coronary syndrome within the previous 6 months, or were likely to move out of the area within 3 years. We mailed 15 438 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, leaving 1024 participants.

From September 11, 2000, through December 20, 2002, a total of 1024 participants were enrolled from 12 outpatient clinics in the San Francisco Bay Area, including 549 (53.6%) with a history of myocardial infarction, 237 (23.1%) with a history of revascularization but not myocardial infarction, and 238 (23.2%) with a diagnosis of CHD that was documented by their physician on the basis of outpatient *International Classification of Diseases, Ninth Revision* codes and review of medical records. 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 before the stress test.

A convenience sample of 769 participants was offered the 6MWT. We were not able to offer the 6MWT to all participants for logistical reasons (eg, not enough time during visit, obstruction of the 6MWT corridor, and study staff unavailable). Of the 769 participants who were offered the 6MWT, 186 were unable to complete the 6MWT (recently experienced unusual angina or chest pain or did not think they were capable of walking for 6 minutes owing to chest pain, shortness of breath, or musculoskeletal impediment), 6 refused, and 1 had incomplete data. Of the 576 participants who completed the 6MWT, a total of 18 were excluded because they did not complete the treadmill test and 2 were excluded 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 145.5 foot (44 m) hospital corridor, covering as much ground as they could during 6 minutes. Encouragement was given every minute in a standardized fashion. Total distance walked in 6 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 masked reviewers. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third masked 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; calculated as weight in kilograms divided by height in meters squared). 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 the drug database Epocrates Rx (Epocrates).

Total cholesterol, high-density lipoprotein cholesterol, hemoglobin, creatinine, and high-sensitivity C-reactive protein were determined from 12-hour fasting serum samples. Levels of the amino-terminal portion of the prohormone of brain-type natriuretic peptide (NT-proBNP) were determined using an electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics). The estimated glomerular filtration rate 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 METs achieved at peak exercise.[25] Before exercise, participants underwent complete resting 2-dimensional echocardiograms with all standard views using an Acuson Sequoia ultrasound system (Siemens Medical Solutions) with a 3.5-MHz transducer and Doppler ultrasound examination. Standard 2-dimensional parasternal short-axis and apical 2- and 4-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 2- and 4-chamber views were obtained to assess for wall motion abnormalities. We defined exercise-induced ischemia as the presence of 1 or more new wall motion abnormalities at peak exercise that were not present at rest. A single experienced cardiologist (N.B.S.), who was masked to the results of the 6MWT, treadmill exercise capacity, and clinical histories, interpreted all echocardiograms.

STATISTICAL ANALYSIS

Because there are no defined categories for the 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 for continuous variables, the χ^2 test for dichotomous variables, and the 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 distance as a continuous variable, per 1-SD decrease of 6MWT distance using Cox proportional hazards models adjusted for covariates associated with the 6MWT quartile at $P < .10$. For any covariates with more than 1% missing data, multiple imputa-

Table 1. Baseline Characteristics of 556 Participants With Stable Coronary Heart Disease by Quartile of 6MWT Distance[a]

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value
No. in quartile	139	139	139	139	. . .
6MWT distance, m	87-419	420-480	481-543	544-837	. . .
Demographic characteristic					
Age, mean (SD), y	72.8 (10.3)	68.2 (10.1)	67.3 (10.3)	62.2 (9.5)	<.001
Male sex, No. (%)	115 (83)	113 (81)	123 (88)	128 (92)	.03
White race, No. (%)	81 (58)	90 (65)	91 (65)	98 (71)	.20
Current smoking, No. (%)	27 (19)	33 (24)	20 (14)	11 (8)	.003
Medical history, No. (%)					
Hypertension	99 (71)	104 (75)	91 (65)	78 (56)	.005
Myocardial infarction	73 (53)	80 (58)	73 (53)	72 (52)	.72
Heart failure	27 (19)	21 (15)	22 (16)	14 (10)	.11
Dyslipidemia	83 (60)	100 (72)	97 (70)	103 (74)	.06
Diabetes mellitus	44 (32)	25 (18)	29 (21)	20 (14)	.003
Peripheral vascular disease	17 (12)	12 (9)	2 (1)	7 (5)	.001
Revascularization	83 (60)	77 (55)	88 (63)	98 (71)	.06
Chronic lung disease	26 (19)	31 (22)	20 (14)	16 (12)	.08
Depressive symptoms	18 (13)	18 (13)	18 (13)	18 (13)	>.99
Clinical measurement					
BMI, mean (SD)	28.4 (4.8)	28.1 (4.5)	26.8 (4.1)	27.6 (4.2)	.01
Systolic BP, mean (SD), mm Hg	134.1 (16.8)	130.3 (18.3)	129.6 (19.1)	127.0 (16.3)	.008
Diastolic BP, mean (SD), mm Hg	72.8 (10.0)	73.3 (9.6)	72.8 (10.6)	75.1 (10.1)	.16
Pulse, mean (SD), bpm	68.7 (12.4)	66.1 (10.6)	67.6 (11.6)	66.1 (11.7)	.18
Total cholesterol, mean (SD), mg/dL	172.2 (41.0)	177.7 (41.9)	179.1 (37.0)	175.1 (38.2)	.49
HDL cholesterol, mean (SD), mg/dL	45.6 (13.3)	47.0 (15.7)	47.0 (14.2)	48.0 (13.6)	.56
CKD-EPI eGFR, mean (SD), mL/min	65.2 (21.7)	74.5 (17.5)	71.8 (19.7)	78.6 (16.7)	<.001
Hemoglobin, mean (SD), g/dL	13.5 (1.3)	14.0 (1.2)	14.0 (1.3)	14.3 (1.1)	<.001
Medication, No. (%)					
Beta-blocker	83 (60)	85 (61)	81 (58)	75 (54)	.65
ACE inhibitor or ARB	75 (54)	72 (52)	76 (55)	54 (39)	.03
Statin	84 (60)	90 (65)	100 (72)	100 (72)	.11
Aspirin	101 (73)	113 (81)	113 (81)	112 (81)	.22
Diuretic	54 (39)	39 (28)	35 (25)	19 (14)	<.001
Biomarker					
C-reactive protein, median (IQR), mg/L	2.9 (1.4-7.1)	1.9 (0.8-3.9)	1.7 (0.9-3.6)	1.4 (0.5-3.2)	.10
NT-proBNP, median (IQR), pg/mL	281 (115-674)	162 (102-350)	138 (69-343)	97 (48-218)	<.001
Stress echocardiography					
Inducible ischemia, No. (%)	48 (35)	43 (31)	37 (27)	20 (14)	.001
Diastolic dysfunction, No. (%)	23 (17)	14 (10)	14 (10)	12 (9)	.09
LV ejection fraction, mean (SD), %	60.5 (10.7)	62.0 (10.1)	63.9 (9.5)	62.2 (9.0)	.045
Treadmill exercise capacity, mean (SD), METs	5.1 (2.0)	7.1 (2.5)	8.6 (2.4)	10.6 (3.3)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CKD-EPI eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation; HDL, high-density lipoprotein; IQR, interquartile range; LV, left ventricular; METs, metabolic equivalents; NT-proBNP, amino-terminal portion of the prohormone of brain-type natriuretic peptide; 6MWT, 6-minute walk test.

SI conversion factors: To convert cholesterol and HDL to millimoles per liter, multiply by 0.0259; hemoglobin to grams per liter, by 10.0.

[a] An explanation of the quartiles is given in the "Results" section.

tion was performed using iterative chained equations including history of hypertension (3.4% missing), dyslipidemia (5.6%), diabetes mellitus (3.8%), peripheral vascular disease (15.3%), and chronic lung disease (4.9%), as well as ejection fraction (3.4%), diastolic dysfunction (10.6%), log NT-proBNP (4.5%), and log C-reactive protein (4.5%). We tested for interactions between 6MWT distance and age, sex, current smoking, diabetes, BMI, systolic blood pressure, estimated glomerular filtration rate, hemoglobin, and left ventricular ejection fraction. Using a logistic regression model for predicting cardiovascular events on the basis of traditional risk factors (age, sex, current smoking, history of hypertension, history of dyslipidemia, history of diabetes, BMI, systolic blood pressure, diastolic blood pressure, and total cholesterol to high-density lipoprotein cholesterol ratio), we estimated the area under the receiver operating characteristic curve (C statistic), integrated discrimination improvement, and category-free net reclassification improvement for predicting cardiovascular events for the individual addition of continuous measures of the 6MWT, treadmill exercise capacity, NT-proBNP, C-reactive protein, and ejection fraction.[27-29] We compared treadmill exercise capacity to 6MWT distance using the Pearson correlation coefficient. Analyses were performed using Stata, version 12 (StataCorp).

RESULTS

Among the 556 participants, median (interquartile range) 6MWT distance was 481 (420-543) m. Compared with 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 angiotensin-converting enzyme inhibitors or angiotensin receptor blockers 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 estimated glomerular filtration rates 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 6MWT 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 (86.2% vs 79.3%; $P = .02$). 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 ($P = .63$ by log-rank test).

During a median (interquartile range) follow-up of 8.0 (4.2-9.0) years, there were 82 hospitalizations for heart failure, 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). The median (interquartile range) age at death was 79.0 (70.8-85.5) years. 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 4 times the rate of participants in the highest quartile (unadjusted hazard ratio [HR], 4.29; 95% CI, 2.83-6.53; $P < .001$).

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 (1.47; 1.15-1.89), a 54% higher rate of death (1.54; 1.32-1.80), and a 55% higher rate of any cardiovascular event (1.55; 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; $P = .002$). We found no evidence that the association between 6MWT distance and cardiovascular events varied by age, sex, current smoking, diabetes, BMI, systolic blood pressure, estimated glomerular filtration rate, hemoglobin, or left ventricular ejection fraction ($P > .10$ for all).

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 ($P = .04$), integrated discrimination improvement of 4.1% (95% CI, 1.0%-8.4%), and category-free net reclassification improvement of 39.3% (95% CI, 19.1%-59.9%) (**Table 3**).

The 6MWT was compared with treadmill exercise capacity (METs). There was significant correlation between 6MWT distance and treadmill exercise capacity ($r = 0.66$; $P < .001$) (**Figure 2**). The 6MWT distance and treadmill exercise capacity had similar discrimination for predicting cardiovascular events (C statistics both 0.72; $P = .29$), integrated discrimination improvement, and category-free net reclassification improvement (Table 3). Adding NT-proBNP and ejection fraction also improved risk prediction over traditional risk factors, and C-reactive protein provided no significant improvement in risk prediction. The addition of the 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; $P = .07$), resulted in an integrated discrimination improvement of 2.8% (0.4%-6.6%), and provided category-free net reclassification improvement of 35.3% (15.3%-59.2%).

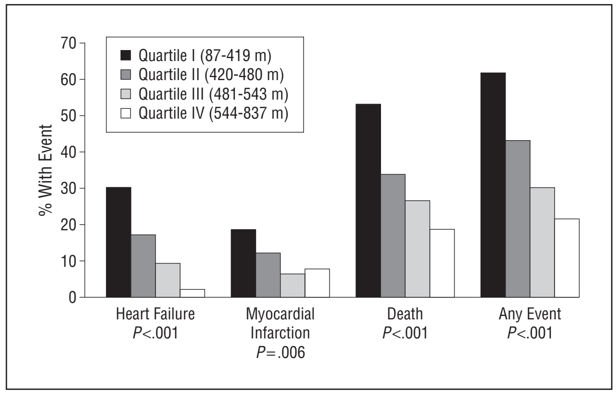

Figure 1. Cardiovascular events by quartile of 6-minute walk test distance.

COMMENT

In a cohort of patients with stable CHD, we found that shorter distance walked on the 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 that of treadmill exercise capacity (METs). These findings suggest that a simple 6MWT is a useful prognostic marker for identifying patients with CHD 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 the 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 the 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 the 6MWT still predicted hospitalizations for heart failure and death in patients with systolic heart failure.[13-16] In addition, a study of older adults with heart failure found that the 6MWT was associated with mortality

Table 2. Association Between 6MWT Distance and Cardiovascular Events

	Age Adjusted		Multivariate Adjusted[a]	
Event	HR (95% CI)[b]	*P* Value	HR (95% CI)[b]	*P* Value
Heart failure	1.86 (1.51-2.31)	<.001	1.38 (1.04-1.82)	.03
Myocardial infarction	1.47 (1.15-1.89)	.002	1.36 (1.00-1.85)	.047
Death	1.54 (1.32-1.80)	<.001	1.25 (1.04-1.50)	.02
Any event or death	1.55 (1.35-1.78)	<.001	1.30 (1.10-1.53)	.002

Abbreviations: HR, hazard ratio; 6MWT, 6-minute walk test.
[a]Multivariate model includes age, sex, smoking, hypertension,[c] dyslipidemia,[c] diabetes mellitus,[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 (amino-terminal portion of the prohormone of B-type natriuretic peptide),[c] and log C-reactive protein.[c]
[b]HR per 1-SD decrease in 6MWT distance (104 m).
[c]Multiple imputation performed for missing values.

Table 3. Prediction of Cardiovascular Events With the 6MWT and Traditional Risk Prediction Measures

	Point Estimate (95% CI)		
Risk Prediction Measure	C Statistic	IDI, %[a]	NRI, %[a]
TRF	0.69 (0.62 to 0.73)	. . .	. . .
TRF + 6MWT	0.72 (0.63 to 0.76)[b]	4.1 (1.0 to 8.4)	39.3 (19.1 to 59.9)
TRF + METs	0.72 (0.64 to 0.76)[c,d]	3.8 (1.0 to 7.9)	39.6 (18.6 to 61.7)
TRF + NT-proBNP	0.72 (0.66 to 0.76)	4.8 (1.6 to 9.5)	44.3 (26.6 to 67.2)
TRF + CRP	0.70 (0.63 to 0.74)	0.1 (−0.4 to 1.6)	12.6 (−23.4 to 33.3)
TRF + LVEF	0.72 (0.64 to 0.76)	5.4 (1.7 to 10.2)	47.7 (22.7 to 67.5)

Abbreviations: CRP, C-reactive protein; IDI, integrated discrimination improvement; LVEF, left ventricular ejection fraction; METs, metabolic equivalents (treadmill exercise capacity); NRI, net reclassification improvement; NT-proBNP, amino-terminal portion of the prohormone of B-type natriuretic peptide; TRF, traditional risk factors; 6MWT, 6-minute walk test.
[a]The improvement demonstrated by each of the risk prediction measures is in relation to the first model, TRF.
[b]$P = .04$ for comparison with TRF.
[c]$P = .02$ for comparison with TRF.
[d]$P = .29$ for comparison of C statistic of TRF + 6MWT vs TRF + METs.

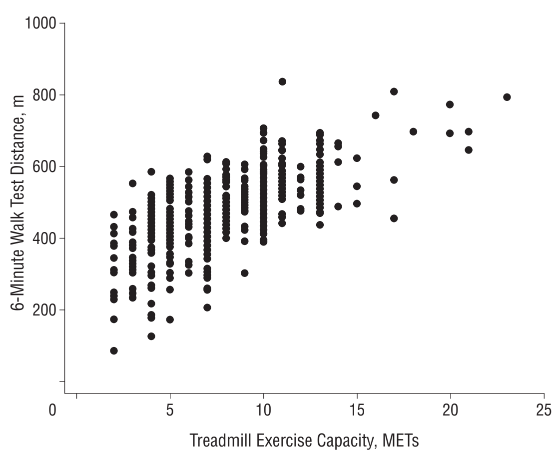

Figure 2. Six-minute walk test distance by treadmill exercise capacity in metabolic equivalents (METs). $r = 0.66$; $P < .001$.

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.

We found that the 6MWT performed comparably with 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 variables[34] 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, adverse events of chest pain, dyspnea, or musculoskeletal pain are usually mild; serious adverse events have not been described.[21] Furthermore, 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 Physician Fee schedule reports a payment for the 6MWT of $59.91 compared with 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. Although 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. Second, because our study comprised 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 1 block. Thus, the results may not extend to patients with significant angina or other limitations in walking. Participants in our study completed the 6MWT and the treadmill exercise test on the same day, which also could have affected 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 and those who have poor performance on the 6MWT are at increased risk of cardiovascular events.

In conclusion, we found that distance walked on the 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.

Accepted for Publication: April 10, 2012.
Published Online: June 18, 2012. doi:10.1001/archinternmed.2012.2198
Correspondence: Alexis L. Beatty, MD, Department of Medicine, University of California, 505 Parnassus Ave, PO Box 0124, San Francisco, CA 94143-0124 (alexis.beatty@ucsf.edu).
Author Contributions: Drs Beatty and Whooley had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Beatty. *Acquisition of data:* Whooley. *Analysis and interpretation of data:* Beatty and Schiller. *Drafting of the manuscript:* Beatty. *Critical revision of the manuscript for important intellectual content:* Beatty, Schiller, and Whooley. *Statistical analysis:* Beatty. *Study supervision:* Schiller and Whooley.
Financial Disclosure: Dr Whooley reports that she has received research support from Gilead Sciences, Inc, and Roche Diagnostics, Inc.
Funding/Support: Dr Beatty is supported by award F32 HL110518 from the National Heart, Lung, and Blood Institute. The Heart and Soul Study was supported by a grant from the Department of Veterans Affairs (Epidemiology Merit Review Program); grant R01 HL079235 from the National Heart, Lung, and Blood Institute; and grants from the Robert Wood Johnson Foundation (Generalist Physician Faculty Scholars Program), the American Federation for Aging Research (Paul Beeson Faculty Scholars in Aging Research Program), the Ischemia Research and Education Foundation, and Nancy Kirwan Heart Research Fund.
Role of the Sponsors: None of these funding sources had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

REFERENCES

1. D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study [published correction appears in *Am Heart J*. 2002;143(1):21]. *Am Heart J*. 2000;139(2 pt 1):272-281.
2. Vittinghoff E, Shlipak MG, Varosy PD, et al; Heart and Estrogen/Progestin Replacement Study Research Group. Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med*. 2003;138(2):81-89.
3. Shlipak MG, Ix JH, Bibbins-Domingo K, Lin F, Whooley MA. Biomarkers to predict recurrent cardiovascular disease: the Heart and Soul Study. *Am J Med*. 2008; 121(1):50-57.
4. Vanhees L, Fagard R, Thijs L, Staessen J, Amery A. Prognostic significance of peak exercise capacity in patients with coronary artery disease. *J Am Coll Cardiol*. 1994;23(2):358-363.
5. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002; 346(11):793-801.
6. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. 2002;106(6):666-671.
7. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol*. 2003; 42(12):2139-2143.
8. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol*. 1997;30(1):260-311.
9. Gibbons RJ, Balady GJ, Bricker JT, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*. 2002;106(14):1883-1892.
10. Douglas PS, Khandheria B, Stainback RF, et al; American College of Cardiology Foundation Appropriateness Criteria Task Force; American Society of Echocardiography; American College of Emergency Physicians; American Heart Association; American Society of Nuclear Cardiology; Society for Cardiovascular Angiography and Interventions; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance. ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance: endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. *Circulation*. 2008;117(11):1478-1497.
11. Hendel RC, Berman DS, Di Carli MF, et al; American College of Cardiology Foundation Appropriate Use Criteria Task Force; American Society of Nuclear Cardiology; American College of Radiology; American Heart Association; American Society of Echocardiography; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance; Society of Nuclear Medicine.

ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *Circulation*. 2009;119(22):e561-e587.
12. Shah BR, Cowper PA, O'Brien SM, et al. Association between physician billing and cardiac stress testing patterns following coronary revascularization. *JAMA*. 2011;306(18):1993-2000.
13. Rostagno C, Olivo G, Comeglio M, et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail*. 2003;5(3):247-252.
14. Bittner V, Weiner DH, Yusuf S, et al; SOLVD Investigators. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. *JAMA*. 1993;270(14):1702-1707.
15. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest*. 1996;110(2):325-332.
16. Shah MR, Hasselblad V, Gheorghiade M, et al. Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol*. 2001;88(9):987-993.
17. Ingle L, Shelton RJ, Rigby AS, Nabb S, Clark AL, Cleland JG. The reproducibility and sensitivity of the 6-min walk test in elderly patients with chronic heart failure. *Eur Heart J*. 2005;26(17):1742-1751.
18. Swiston JR, Johnson SR, Granton JT. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: a systematic review of the literature. *Respir Med*. 2010;104(11):1588-1607.
19. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Intern Med J*. 2009;39(8):495-501.
20. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;300(20):2379-2388.
21. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
22. Luepker RV, Apple FS, Christenson RH, et al; AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108(20):2543-2549.
23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
24. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
25. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000.
26. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2(5):358-367.
27. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172.
28. Pepe MS. Problems with risk reclassification methods for evaluating prediction models. *Am J Epidemiol*. 2011;173(11):1327-1335.
29. Pepe MS, Kerr KF, Longton GM, Wang Z. UW Biostatistics Working Paper Series: testing for improvement in prediction model performance. Collection of Biostatistics Research Archive. http://biostats.bepress.com/uwbiostat/paper379. Published 2011. Accessed March 18, 2012.
30. Cacciatore F, Abete P, Mazzella F, et al. Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting [published online September 20, 2011]. *Eur J Cardiovasc Prev Rehabil*. doi:10.1177/1741826711422991.
31. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circ Heart Fail*. 2009;2(6):549-555.
32. Pollentier B, Irons SL, Benedetto CM, et al. Examination of the six-minute walk test to determine functional capacity in people with chronic heart failure: a systematic review. *Cardiopulm Phys Ther J*. 2010;21(1):13-21.
33. Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail*. 2010;16(5):208-213.
34. Daly CA, De Stavola B, Sendon JL, et al; Euro Heart Survey Investigators. Predicting prognosis in stable angina: results from the Euro Heart Survey of stable angina: prospective observational study. *BMJ*. 2006;332(7536):262-267.
35. Blankenberg S, McQueen MJ, Smieja M, et al; HOPE Study Investigators. Comparative impact of multiple biomarkers and N-terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation*. 2006;114(3):201-208.
36. Omland T, de Lemos JA, Sabatine MS, et al; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361(26):2538-2547.
37. Centers for Medicare and Medicaid Services. Medicare Physician Fee schedule search. https://www.cms.gov/apps/physician-fee-schedule/overview.aspx. Published 2012. Accessed March 18, 2012.
38. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2011;(7):CD001800.
39. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116(10):682-692.
40. Smith SC Jr, Benjamin EJ, Bonow RO, et al; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458-2473.
41. Balady GJ, Ades PA, Bittner VA, et al; American Heart Association Science Advisory and Coordinating Committee. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association. *Circulation*. 2011;124(25):2951-2960.
42. Suaya JA, Shepard DS, Normand SL, Ades PA, Prottas J, Stason WB. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. *Circulation*. 2007;116(15):1653-1662.

INVITED COMMENTARY

Time for a 6-Minute Walk?

In this issue of the *Archives*, Beatty and colleagues[1] demonstrate that the 6-minute walk test (6MWT) provided, at low cost, very useful prognostic information in ambulatory patients with coronary heart disease. In 556 patients with stable coronary heart disease followed up for 8 years, cardiovascular events (eg, heart failure, myocardial infarction, and death) occurred in 218 (39.2%). Patients in the lowest quartile of 6MWT distance (87-419 m) had 4 times the rate of cardiovascular events as those in the highest quartile (544-837 m)