Journal of the American College of Cardiology Vol. 47, No. 3 Suppl S

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.03.080

CLINICAL RESEARCH

The Value of Estimated Functional Capacity in Estimating Outcome

Results From the NHBLI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study

Leslee J. Shaw, PHD* Marian B. Olson, MS,† Kevin Kip, PHD,† Sheryl F. Kelsey, PHD† B. Delia Johnson, PHD,† Daniel B. Mark, MD,‡ Steven E. Reis, MD,* Sunil Mankad, MD,§ William J. Rogers, MD,‖ Gerald M. Pohost, MD,¶ Christopher B. Arant, MD,# Timothy R. Wessel, MD,# Bernard R. Chaitman, MD,** George Sopko, MD,†† Eileen Handberg, PHD,# Carl J. Pepine, MD,# C. Noel Bairey Merz, MD*

Los Angeles, California; Pittsburgh, Pennsylvania; Birmingham, Alabama; Gainesville, Florida; Durham, North Carolina; St. Louis, Missouri; and Bethesda, Maryland

OBJECTIVES Our objective was to determine the prognostic value of estimated metabolic equivalents (METs) based on self-reported functional capacity by the Duke Activity Status Index (DASI) in symptomatic women.

BACKGROUND Functional capacity is an important component affecting the predictive value of exercise testing, yet current guidelines offer limited assistance regarding identification of functional impairment and choice of pharmacologic stress testing.

METHODS A total of 914 women underwent clinically indicated coronary angiography and completed the 12-item DASI questionnaire; a subgroup of 251 women also underwent exercise testing. Cox proportional hazards modeling was used to estimate five-year death or myocardial infarction by DASI scores. In a secondary analysis, additional events included unstable angina, heart failure, or stroke at five years.

RESULTS Average DASI-estimated functional capacity was 5.7 ± 4.2 METs and, for exercising women, 6.0 ± 2.6 METs. In the 914 women, event-free survival ranged from 83% to 95% in subgroups with ≤4.7 to >9.9 METs ($p = 0.009$); 67% of the events occurred in women scoring ≤4.7 METs ($p = 0.003$). Event rates were similar by exercise and DASI MET values. In women with DASI-estimated METs ≤4.7 ($n = 75$), ischemia occurred less (39% vs. 64%, $p < 0.0001$), and exercise testing results were more often indeterminate (<85% predicted maximum heart rate = 37% vs. 6%, $p = 0.001$) as compared to women achieving >4.7 METs.

CONCLUSIONS Among women with suspected myocardial ischemia, functional impairment estimated by the DASI correlates with indeterminate exercise test results and is associated with an adverse prognosis. Use of the DASI before exercise testing can risk stratify symptomatic women and may improve the identification of higher-risk, functionally impaired subjects that would benefit from pharmacologic stress imaging and targeted risk management. (J Am Coll Cardiol 2006;47:36S–43S) © 2006 by the American College of Cardiology Foundation

The exercise electrocardiogram has been reported to have a lower diagnostic accuracy in women (1,2). While a number of factors may contribute to this, the lower diagnostic accuracy of the exercise electrocardiogram is, in part, related to the fact that women have higher rates of functional impairment leading to a diminished exercise capacity, an inability to attain maximal stress, and to provoke ischemia (3). Women incapable of performing maximal exercise testing are candidates for pharmacologic stress testing, although current guidelines offer limited assistance with regard to the methods of recognition and identification of functionally impaired subsets of the population (4).

Maximal predicted heart rate, oxygen consumption, and, more commonly, metabolic equivalents (METs) are mea-

From the *Division of Cardiology, Department of Medicine, Cedars-Sinai Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; †Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; ‡Duke Clinical Research Institute, Duke University, Durham, North Carolina; §Division of Cardiology, Department of Medicine, Allegheny University of Health Sciences, Pittsburgh, Pennsylvania; ‖Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; ¶Division of Cardiology, University of Southern California, Los Angeles, California; #Division of Cardiology, Department of Medicine, University of Florida, Gainesville, Florida; **St. Louis University Medical Center, St. Louis, Missouri; and the ††National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

This work was supported by contracts from the National Heart, Lung, and Blood Institute, nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants U0164829, U01 HL649141, U01 HL649241, a GCRC grant M01-RR00425 from the National Center for Research Resources, and grants from the Gustavus and Louis Pfeiffer Research Foundation, Denville, New Jersey, Women's Guild of Cedars-Sinai Medical Center, Los Angeles, California, Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, Pennsylvania, and QMED Inc., Laurence Harbor, New Jersey. Preliminary results have been presented at the 52nd Annual Scientific Sessions of the American College of Cardiology in Chicago, Illinois, March 30 to April 2, 2003.

Manuscript received September 9, 2004; revised manuscript received March 4, 2005, accepted March 10, 2005.

Abbreviations and Acronyms
DASI = Duke Activity Status Index
METs = metabolic equivalents
WISE = Women's Ischemia Syndrome Evaluation

sures used to estimate physical work capacity. Recent studies demonstrate that the estimation of MET capacity may be used for prognostication in women (5,6). The Duke Activity Status Index (DASI) is a simple 12-item questionnaire that computes functional capabilities based upon activities of daily living and recreational activities and is a validated estimator of maximal oxygen consumption (7). Despite the ease with which the questionnaire can be measured and its validation specifically in women (8), the DASI has not been evaluated with regards to prognosis or compared to exercise testing results in a large cohort of women.

The purpose of the current analysis was to evaluate and compare the prognostic value of estimated METs as determined from the DASI in a cohort of 914 women with suspected myocardial ischemia and angiographically defined coronary disease, a subset of whom also underwent exercise stress testing (n = 251).

METHODS

Patient entry criteria. The Women's Ischemia Syndrome Evaluation (WISE) is a four-center study aiming to improve diagnostic testing strategies and advance new hypotheses related to the pathophysiology of cardiovascular disease in women (9). The study cohort consisted of 914 women (of 7,603 women screened) presenting with suspected myocardial ischemia that underwent diagnostic coronary angiography and were enrolled in the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored WISE study. Before enrollment, all women were referred for a clinically indicated coronary angiogram with diagnostic testing being performed after catheterization. Women enrolled in the WISE study underwent a battery of noninvasive and invasive diagnostic tests in order to identify an improved strategy for the detection of coronary artery disease. Exercise stress testing was performed only at the University of Florida and, as such, MET values and their associated prognosis could be compared in a subset of 251 women that also underwent graded treadmill stress testing.

Baseline evaluations. Initial evaluation included the collection of demographic, medical history, and symptom data. Subjects also underwent a physical examination that included blood pressure and physical measurements. The complete design and methodology of the WISE study are described elsewhere (9). However, in brief, in response to the National Institutes of Health proposal, each individual center devised its own diagnostic armamentarium, but a core of historical (e.g., vascular disease history), angiographic (i.e., ≥50% stenosis), symptom (e.g., typical angina) profile, and quality-of-life parameters were collected at baseline (Table 1). The DASI was part of the quality-of-life measurements that were collected on all women.

Coronary angiography core laboratory. All angiograms were quantitatively evaluated by an independent WISE angiographic core laboratory (10). Angiograms were interpreted blinded to the patient's clinical history. Obstructive coronary disease was defined quantitatively as ≥50% stenosis in ≥1 epicardial coronary artery (10). The number of diseased vessels was then scored.

Exercise testing procedures. Treadmill exercise testing was performed using the modified or Bruce (n = 165) or Asymptomatic Cardiac Ischemia Pilot (n = 86) protocols. Standards for the conductance of testing and termination of exercise were consistent with the current American College of Cardiology/American Heart Association guidelines for exercise testing (4). Generally, patients exercised until the point of volitional fatigue unless marked electrocardiographic abnormalities, hemodynamic instability, chronotropic incompetence, ventricular tachycardia or fibrillation, or disabling chest pain symptoms occurred.

Functional status measures. Patients completed the DASI at baseline before exercise testing (7). The DASI is a simple, easily administered, 12-item quality-of-life instrument that provides a patient's self-assessment of her functional capabilities. Original development of the DASI was correlated and validated to estimate maximal oxygen consumption measurements at peak exercise (7). Using an estimation of maximal oxygen consumption, METs were calculated by dividing by 3.5. We categorized the DASI based upon MET values for stages of the commonly applied Bruce protocol including 1 to 4.7, 4.8 to 7.4, 7.5 to 9.9, and >9.9 METs. (See the Appendix for a copy of the DASI questionnaire and scoring, in METs.) We have previously validated the DASI in the WISE study population for the estimation of exercise stress test METs (8).

Follow-up procedures. Each patient gave informed consent and was enrolled in the follow-up portion of this study. Each center had institutional review board approval for the inclusion of patients in this registry as well as for the collection of follow-up data. Patients were contacted at six weeks and at one-year intervals after their initial enrollment. During the telephone contact, an experienced nurse or physician completed a scripted interview. At the time of this interview, each patient or a family member was queried for the occurrence of major adverse cardiac events or hospitalizations.

The primary end point for this analysis was five-year death or non-fatal myocardial infarction. Due to the smaller sample size of the exercising cohort (n = 251), a secondary analysis included other major adverse events including hospitalization for congestive heart failure or unstable angina. In the event that a major adverse cardiac event was identified, the referring investigator was contacted for formation dates and documentation of the occurrence. In the event of death, a death certificate was requested. An experienced investigator blinded to the clinical and stress

JACC Vol. 47, No. 3 Suppl S
February 7, 2006:36S–43S

Table 1. Clinical Characteristics* of the 914 Patient Study Cohort Enrolled in the Women's Ischemia Syndrome Evaluation (WISE)

% or Mean ± SD Values (Where Indicated)	Women Undergoing Exercise Testing and DASI (n = 251)	Women With DASI Measurement (n = 914)
Age (yrs)	56.3 ± 10	58.2 ± 12
Postmenopausal	70%	72%
Body mass index	30 ± 7	30 ± 7
>30 kg/m^2	43%	40%
Chest pain		
Nonanginal	35%	34%
Atypical	29%	36%
Typical	36%	30%
Cardiac risk factors		
Hypertension	48%	59%
Current smoker	22%	20%
Diabetes	17%	25%
Insulin-dependent	8%	12%
Hypercholesterolemia	43%	50%
Coronary disease extent		
No stenosis ≥50%	68%	60%
1-vessel coronary disease	12%	16%
2-vessel coronary disease	12%	10%
3-vessel coronary disease	8%	14%
Exercise test results		
Total exercise time (min)	5.7 ± 3	n/a
Peak METs	6.0 ± 3	
≤4.7 METs	30%	
4.8–7.4 METs	45%	
7.5–9.9 METs	14%	
>9.9 METs	12%	
Peak heart rate (beats/min)	144 ± 21	
≥85% predicted maximum heart rate	64%	
Peak systolic blood pressure (mm Hg)	168 ± 27	
Exertional chest pain	27%	
ST-segment depression >1.0 mm	41%	
Number of abnormal leads	1.9 ± 3	
Maximal ST-segment depression (mm)	−0.7 ± 0.9	
DASI score		
1–4.7 METs	43%	52%
4.8–7.4 METs	20%	18%
7.5–9.9 METs	17%	11%
>9.9 METs	20%	19%

*All values are % except where indicated as mean ± SD for age, body mass index, total exercise time, peak metabolic equivalents, peak heart rate, peak systolic blood pressure, number of abnormal leads, and maximal ST-segment depression.
DASI = Duke Activity Status Index; METs = metabolic equivalents; n/a = not applicable.

test data collected this confirmation. Follow-up was complete in >95% of patients.

Statistical analysis. Continuous variables were expressed as means ± SD. General linear models or analysis of variance techniques were used to compare continuous measures by DASI and exercise MET categories. Categorical variables were recorded as frequencies and compared by chi-square statistic or Fisher exact test. A Fisher exact test was computed for tables containing cells with an expected frequency of <5. A value of $p < 0.05$ was considered statistically significant.

The primary end point for this prognostic analysis was time to death or non-fatal myocardial infarction for the 914 patients. Using a post-hoc sample size calculation, (alpha = 0.05, two-tailed), statistical power exceeded 0.80 for a comparison of differences in event-free survival based on a sample size of 914 women. For validation of the DASI's prognostic value, a secondary analysis in a smaller cohort of 251 exercising women evaluated time to death, stroke, congestive heart failure, myocardial infarction, or unstable angina. Cox proportional hazards models were used to assess time to cardiac events by the DASI and exercise MET estimates using subsets of 1 to 4.7, 4.8 to 7.4, 7.5 to 9.9, and >9.9; as noted previously, these MET groupings were chosen to correlate with the standard Bruce protocol exercise stress testing stages. From the Cox model, five-year event-free survival was calculated for each of the DASI subsets. From the Cox proportional hazards model, the relative risk ratio and 95% confidence intervals were calculated. Additionally, in the exercising subset of patients, predicted event rates were calculated from two separate univariable Cox mod-

Table 2. Clinical Characteristics of the 251 Women by Exercise Testing Measures of METs

% or Mean ± SD Values (Where Indicated)	1–4.7 METs (n = 75)	4.8–7.4 METs (n = 113)	7.5–9.9 METs (n = 34)	>9.9 METs (n = 29)
Age (yrs)*	60 ± 10	58 ± 10	51 ± 10	49 ± 9
Postmenopausal*	81%	77%	56%	41%
Body mass index	32 ± 7	29 ± 7	29 ± 6	28 ± 6
≥30 kg/m^2	56%	40%	38%	31%
Chest pain†				
Nonanginal	27%	31%	59%	45%
Atypical	37%	36%	29%	38%
Typical	36%	33%	12%	17%
Cardiac risk factors				
Hypertension*	68%	43%	38%	24%
Current smoker	20%	20%	32%	21%
Diabetes†	29%	14%	12%	7%
Insulin-dependent	17%	5%	6%	3%
Hypercholesterolemia	53%	46%	44%	32%
Coronary disease extent‡				
No stenosis ≥50%	59%	70%	65%	90%
1-vessel coronary disease	11%	12%	18%	3%
2-vessel coronary disease	17%	11%	15%	3%
3-vessel coronary disease	13%	7%	2%	0%
Exercise test results				
Peak heart rate (beats/min)*	131 ± 22	148 ± 18	152 ± 17	160 ± 16
≥85% predicted max heart rate*	54%	59%	90%	98%
Peak systolic blood pressure (mm Hg)	169 ± 27	168 ± 28	170 ± 23	174 ± 24
Exertional chest pain	34%	40%	13%	12%
ST-segment depression ≥1.0 mm‡	18%	55%	19%	8%
Number of abnormal leads‡	1.0 ± 2	2.3 ± 3	2.6 ± 3	1.4 ± 3
Max ST-segment depression‡ (mm)	−0.4 ± 0.7	−0.9 ± 1	−1.0 ± 1.1	−0.6 ± 0.9

*$p < 0.001$; †$p < 0.05$; ‡$p < 0.01$.
METs = metabolic equivalents.

els for DASI and exercise METs and annualized throughout follow-up. A p value was calculated based upon the predictive value of each univariable Cox model. Finally, a risk-adjusted model was devised to evaluate the independent contribution of the DASI MET values when controlling for important clinical characteristics including age, body mass index, diabetes, hypertension, hyperlipidemia, history of coronary disease, and the extent of coronary disease at angiography.

RESULTS

Clinical characteristics of the WISE study cohort. Women completing the DASI questionnaire were largely post-menopausal with 40% of them being obese (defined with a body mass index ≥30 kg/m^2) (Table 1). Cardiac risk factors were prevalent with more than half of women being hypertensive and hyperlipidemic. A majority of the 914 women had <50% stenosis at coronary angiography. The subset undergoing exercise stress testing was similar in terms of risk factors and coronary disease extent, although they were slightly younger with an average age of 56 ± 10 years as compared to the overall group.

DASI and exercise testing MET results. On average, women exercised for 5.7 ± 3 min or 6 ± 3 METs (Table 1). Only 12% of women achieved >9.9 METs during treadmill exercise while nearly two-thirds of women achieved >85% predicted maximal heart rate. During exercise testing, 27% of women reported chest pain symptoms. Myocardial ischemia, documented by ST-segment depression ≥1.0 mm, was reported in 41% of women.

Women who had lower peak METs were generally older, postmenopausal, obese, had more typical angina, hypertensive, diabetic, hypercholesterolemic, and had a greater prevalence of obstructive coronary disease at coronary angiography (Table 2). As expected, higher peak heart rates and a greater frequency of ≥85% predicted maximum heart rate were observed in women with higher MET capacity during treadmill exercise.

When compared with the entire cohort of 914 women (Table 3), exercising patients were younger with a generally lower cardiac risk factor profile. However, a similar pattern across the MET categories was observed when compared with the exercising subset. That is, patients with higher DASI scores were younger, with a lower body mass index, more likely to have atypical or non-anginal chest pain, less likely to have cardiac risk factors, and to have more prevalent non-obstructive coronary disease at angiography.

DASI scores. Self-reported DASI scores revealed that 52%, 18%, 11%, and 19% women estimated their MET capacity at 1 to 4.7, 4.8 to 7.4, 7.5 to 9.9, and >9.9, respectively (Table 1). Of the women who reported capabilities of performing ≤4.7 METs of work during household chores and recreational activities, they more often had typical angina, more often were current smok-

JACC Vol. 47, No. 3 Suppl S
February 7, 2006:36S–43S

Table 3. Clinical Characteristics of the 914 Women by Duke Activity Status Index Estimated METs

% or Mean ± SD Values (Where Indicated)	1–4.7 METs (n = 472)	4.8–7.4 METs (n = 168)	7.5–9.9 METs (n = 103)	>9.9 METs (n = 171)
Age*	59 ± 12	59 ± 12	60 ± 11	55 ± 10
Postmenopausal	76%	78%	81%	66%
Body mass index*	31 ± 7	29 ± 6	29 ± 7	28 ± 5
≥30 kg/m^2	47%	41%	41%	34%
Chest pain*				
Nonanginal	28%	38%	43%	43%
Atypical	38%	32%	32%	36%
Typical	34%	30%	25%	21%
Cardiac risk factors				
Hypertension*	65%	57%	50%	51%
Current smoker	22%	19%	18%	15%
Diabetes†	32%	21%	15%	14%
Insulin-dependent*	14%	13%	6%	6%
Hypercholesterolemia†	62%	56%	44%	41%
Coronary disease extent*				
No stenosis ≥50%	57%	57%	70%	78%
1-vessel coronary disease	18%	20%	15%	11%
2-vessel coronary disease	12%	17%	5%	5%
3-vessel coronary disease	13%	6%	10%	7%

*$p < 0.01$; †$p < 0.001$,
METs = metabolic equivalents.

ers, diabetic, hypercholesterolemic, or had a family history of premature coronary disease. Additionally, women who reported higher DASI-estimated METs were less likely to have obstructive coronary disease at coronary angiography.

DASI-estimated prognosis. A total of 92 of the 914 women experienced death or non-fatal myocardial infarction during five years of follow-up (Fig. 1). Overall, event-free survival was significantly different by the extent of coronary disease at angiography. Five-year rates of death or myocardial infarction were 7%, 18%, 27%, and 34% for zero-, one-, two-, and three-vessel coronary disease, respectively ($p < 0.0001$).

Cox proportional hazard event-free survival analysis revealed that DASI-estimated METs was independently predictive of death or myocardial infarction ($p = 0.009$).

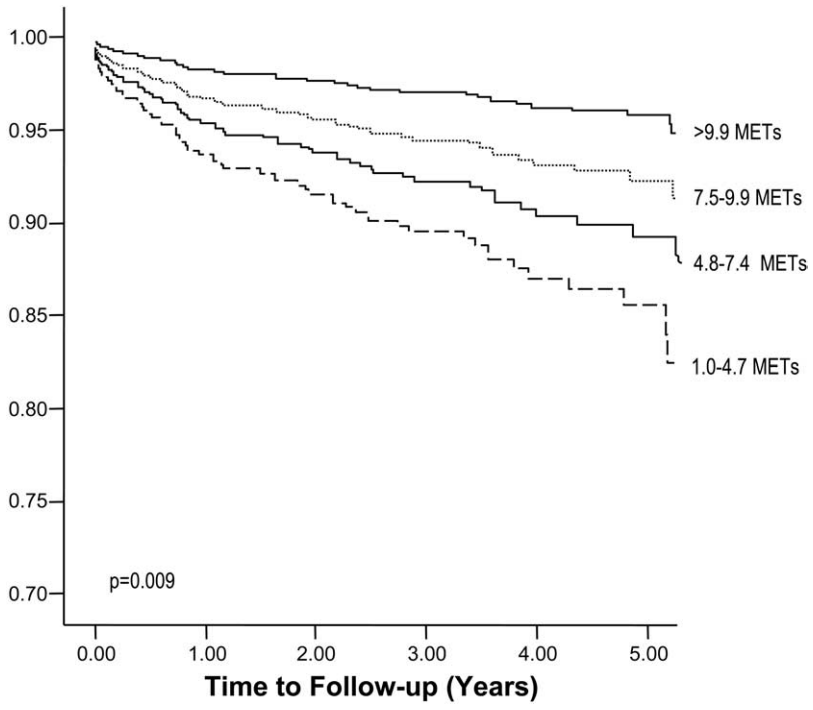

Figure 1. Death or myocardial infarction-free survival by Duke Activity Status Index measurements of metabolic equivalents (METs), using Bruce protocol stage cutpoints (n = 914). Five-year survival corresponds to 95%, 92%, 88%, and 85% for >9.9, 7.5 to 9.9, 4.8 to 7.4, and 1 to 4.7 METs, respectively ($p = 0.009$).

Table 4. Rates of Ischemia and Indeterminate Test Results (i.e., <85% Predicted Maximum Heart Rate) by DASI Measurements of METs

MET Category	No Ischemia (n = 70)	Ischemia (n = 142)	Indeterminate Results (n = 39)	p Value
≤3 METs (n = 62)	28%	40%	32%	0.001
>3 METs (n = 189)	27%	63%	10%	
≤4.7 METs (n = 108)	24%	39%	37%	<0.0001
>4.7 METs (n = 143)	30%	64%	6%	
≤6 METs (n = 141)	21%	59%	20%	0.021
>6 METs (n = 110)	34%	56%	10%	

DASI = Duke Activity Status Index; METs = metabolic equivalents.

Event-free survival was 95%, 92%, 88%, and 83% for METs of >9.9, 7.5 to 9.9, 4.8 to 7.4, and 1 to 4.7, respectively ($p = 0.009$). Relative risk ratios were elevated 1.9-, 2.1-, and 3.7-fold for women with estimated DASI MET scores of 7.5 to 9.9, 4.8 to 7.4, and 1 to 4.7, respectively, when compared with those scoring >9.9 METs ($p = 0.009$). Overall 67% of all deaths or myocardial infarction occurred in women whose DASI METs were ≤4.7 ($p = 0.003$).

In a risk-adjusted analysis, the DASI remained an independent estimator of death or myocardial infarction ($p = 0.015$), even after controlling for age, body mass index, diabetes, hypertension, hyperlipidemia, history of coronary disease, and the extent of coronary disease at angiography. Specifically, in this risk-adjusted model, every unit increase in the DASI MET subsets of 4.8 to 7.4, 7.4 to 9.9, and >9.9 was associated with a 25% (95% confidence interval 5% to 40%) decrease in death or myocardial infarction when compared to women with DASI MET values <4.7 ($p = 0.015$).

Incidence of indeterminate exercise testing results by DASI scores. Of the women who reported an estimated DASI of ≤4.7 METs (n = 108), an inability to achieve predicted maximal heart rate was noted in 37%, and stress-induced ischemia was observed in 39% ($p < 0.0001$) (Table 4). For women with DASI estimates of >4.7 METs (n = 143), only 6% failed to achieve peak maximal stress levels, and 30% did not exhibit electrocardiographic ischemia ($p < 0.0001$). Similar results were noted using a cutpoint of ≤6 and >6 or ≤3 and >3 METs ($p = 0.021$ and $p = 0.001$).

Prognosis by exercise and DASI METs. Of the 251 women that had both exercise test and DASI MET measurements, there were a total of 73 cardiac events observed over five years of follow-up (Fig. 2). This included 54 admissions for unstable angina, 4 myocardial infarctions, 11 admissions for heart failure, 9 strokes, and 13 deaths. From the exercise test, estimated METs levels from ≤4.7 to >9.9 were associated with annualized risk-adjusted event rates ranging from 7.2% to 1.8% ($p = 0.007$) (Fig. 2). These results were similar to the event rates noted with estimated DASI MET levels ($p < 0.0001$).

Of the 40 women who failed to achieve ≥85% predicted maximum heart rate, five-year event-free survival was 52% as compared to 77% for the 220 women achieving adequate heart rate levels ($p = 0.005$). Approximately 63% of the events occurred in women with ≤4.7 METs on DASI ($p < 0.0001$), compared to only 28% of women with significant ST-segment depression ($p = 0.011$).

DISCUSSION

The current results support the value of the DASI-estimated MET functional capacity as an added guide to diagnostic decision making in women presenting with signs and symptoms suggestive of myocardial ischemia. The DASI is a short, easily administered questionnaire of self-reported activities of daily living used to estimate maximal oxygen consumption and, in this case, to provide insight into their likelihood of major adverse cardiac events (7,11–20). Although recent work has documented the prognostic value of exercise capacity in women (5,6), the current results suggest that application of the DASI might be used alternatively to easily and economically identify at-risk symptomatic women (20–23). The use of the DASI may be particularly helpful, as a pre-test risk assessment tool, for the large subset of women less capable of performing maximal levels of exercise stress, including those with

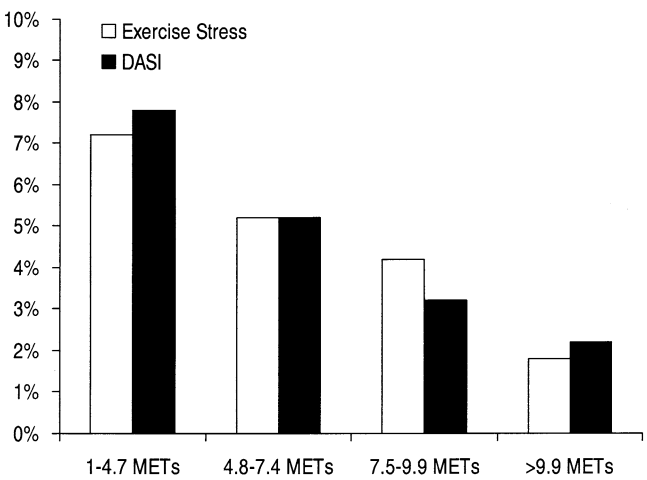

Figure 2. Annualized total cardiovascular event rates by exercise stress testing and Duke Activity Status Index (DASI)-estimated metabolic equivalents (METs) in 251 symptomatic women. $p = 0.007$ for exercise and $p < 0.0001$ for DASI based upon the univariable Cox model for exercise and DASI METs.

JACC Vol. 47, No. 3 Suppl S
February 7, 2006:36S–43S

advanced comorbidity, obesity, or the elderly, by providing further insight into their event risk (20–23).

From the WISE study, women who report functional impairment on the DASI (i.e., ≤4.7 METs) were less likely to exhibit myocardial ischemia and more likely to have indeterminate stress test results (i.e., failure to achieve 85% predicted maximum heart rate). As these women with inadequate heart rate responses to exercise have worsening event-free survival, including more hospitalizations for acute myocardial infarction or death, when compared to women achieving adequate stress levels, the current results suggest that the DASI could be used before exercise stress testing in symptomatic women to improve identification of higher-risk, functionally impaired subjects that might benefit from pharmacologic as opposed to exercise stress testing. This strategy could foster reduced evaluation costs and improve time to diagnosis for women presenting for the evaluation of chest pain symptoms. It should also be noted that the current exercise testing guidelines support referral to pharmacologic stress testing in patients with submaximal exercise capacity (4).

The impact of functional capacity on prognosis in women. Functional capacity is one of the strongest and most consistent estimators of cardiac prognosis in women and men (4). Exercise capacity is also strongly associated with all-cause mortality for both genders (18,19). In the recent American College of Cardiology/American Heart Association guidelines for exercise testing, treadmill stage, exercise duration, exercise capacity, peak watts, and METs were all significant independent predictors of an adverse outcome (4). In particular, failure to achieve 5 METs during treadmill exercise is associated with worsening prognosis in multiple reports (3–6). In two recent cohorts of asymptomatic women, all-cause survival was 98% at 9 years (5) but decreased to 65% at 20 years (6) among the women who achieved <5.5 METs on exercise testing. From the current series of symptomatic women, event-free survival at five years ranged from 83% to 95% for estimated METs ranging from ≤4.7 to >9.9 using the self-reported DASI. Similarly, in a report comprising 147 post-myocardial infarction and 159 coronary bypass surgery patients, functional status at three months was one of the main determinants of recovery at one year (16). In our subset of 251 women undergoing exercise stress testing, a similar ability to risk stratify was noted for exercise and DASI MET measurements.

Snader and colleagues (24) examined the prognostic value of estimated functional capacity and thallium-201 single-photon emission computed tomography findings. Based upon these findings in 3,400 patients, 57% of the deaths occurred in patients achieving <6 METs ($p < 0.0001$). From the current series of 914 women, 67% of all deaths or myocardial infarctions occurred in women with ≤4.7 METs on DASI. Even when controlling for other factors, fair or poor functional capacity was associated with a 4.4-fold (95% confidence interval: 1.6 to 12.0) higher rate of cardiac mortality ($p = 0.004$). In the current series, a reduced DASI score of ≤4.7 METs was associated with a 3.7-fold higher relative risk of cardiac events when compared to women with higher functional capabilities. Consistent with the current study examining electrocardiographic stress results, the presence of single-photon emission computed tomography perfusion defects in the Cleveland Clinic series (24) was a less powerful estimator of death (adjusted relative risk [for each two defects] 1.2, 95% confidence interval: 1.03 to 1.4, $p = 0.02$) as compared with functional capacity.

Exercise testing in women. For women undergoing exercise testing, it appears from our experience base and interactions with many clinicians that the short duration of treadmill exercise for women is often questioned as to whether a sufficient observational period transpired for the ascertainment of coronary disease likelihood. Prior reports (25–29) and the current study results demonstrate that the average woman has an estimated MET capacity of 5.5 to 6.0 METs. For many women, undergoing common exercise stress testing protocols, such as the Bruce (or modified) protocol, where the first few minutes of exercise require 3 to 4.7 METs of work, premature peripheral fatigue may preempt achievement of an adequate level of stress. This supposition is supported by our results revealing a higher rate of indeterminate results and less inducible ischemia for women with self-reported low DASI scores. Nearly one-third of our women who exhibited functional impairment (i.e., ≤4.7 DASI METs) failed to achieve target heart rates during exercise stress testing.

The recent American College of Cardiology/American Heart Association stable angina guidelines delineate decisions regarding the use of exercise or pharmacologic stress testing as determined by a patient's ability to exercise (26). As most household chores require approximately 4 METs of work (4), the self-reported DASI results could be used to more precisely guide optimal test choice in women and men. Specifically, women with impaired (i.e., ≤4.7 METs) aerobic capacity should be considered for pharmacologic stress imaging. Nearly two-thirds of cardiovascular events occurred in women whose DASI MET level was ≤4.7 as METs compared to only 28% of poor outcomes occurring in women with an abnormal ST-segment response, suggesting that the DASI could be used as an indicator of global risk status for targeted risk management. The DASI could also provide complementary prognostic information for the more than two million women who undergo pharmacologic stress testing every year (27).

Study limitations. Although we present data prospectively collected from a multicenter registry, additional validation of the current study results is needed; validation of these results will be important in non-catheterized populations. However, the included patient series appears typical for at-risk women evaluated with suspected myocardial ischemia, and the results should be generally applicable to typical stress laboratory populations (25). In addition to the prognostic value of functional capacity, recent data suggest

that measures of heart rate recovery could further risk stratify female cohorts (30). However, at the time of design for the WISE study, these data were not available, and, therefore, heart rate recovery measurements were not collected.

Conclusions. The current results support prior evidence reporting that women with suspected myocardial ischemia often have impaired functional capacity and are at increased risk of cardiac events. The DASI, a simple and inexpensive questionnaire that takes 5 to 8 min to administer and score, correlates with a woman's capabilities to perform adequate levels of exercise stress testing and predicts prognosis to a similar degree. Based upon the current results, if applied prospectively, administration of the DASI may improve identification of higher-risk women for diagnostic pharmacologic stress testing and targeted risk management to improve prognosis.

Reprint requests and correspondence: Dr. Leslee J. Shaw, 8700 Beverly Boulevard, Taper Building, Room 125, Cedars-Sinai Medical Center, Los Angeles, California 90048. E-mail: leslee.shaw@cshs.org.

REFERENCES

1. Hlatky MA, Pryor DB, Harrell FE Jr., Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. Am J Med 1984;77:64–71.
2. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1991;83:660–6.
3. Alexander KP, Shaw LJ, Shaw LK, Delong ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. J Am Coll Cardiol 1998;32:1657–64.
4. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing—summary article. J Am Coll Cardiol 2002;106:1883–92.
5. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St. James Women Take Heart project. Circulation 2003;108:1554–9.
6. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. JAMA 2003;290:1600–7.
7. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke activity status index). Am J Cardiol 1989;64:651–44.
8. Bairey Merz CN, Olson M, McGorray S, et al. Physical activity and functional capacity measurements in women: a report from the NHLBI-sponsored WISE study. J Wom Health Gend Based Med 2000;9:769–77.
9. Bairey Merz CN, Kelsey SF, Pepine CJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. J Am Coll Cardiol 1999;33:1453–61.
10. Sharaf BL, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] study angiographic core laboratory). Am J Cardiol 2001;87:937–41.
11. McGlade DP, Poon AB, Davies MJ. The use of a questionnaire and simple exercise test in the preoperative assessment of vascular surgery patients. Anaesth Intensive Care 2001;29:520–6.
12. Nelson CL, Herndon JE, Mark DB, Pryor DB, Califf RM, Hlatky MA. Relation of clinical and angiographic factors to functional capacity as measured by the Duke activity status index. Am J Cardiol 1991;68:973–5.
13. Carter R, Holiday DB, Grothues C, Nwasuruba C, Stocks J, Tiep B. Criterion validity of the Duke activity status index for assessing functional capacity in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2002;22:298–308.
14. Nease RF, Whitcup SM, Ellwein LB, Fox G, Littenberg B. Utility-based estimates of the relative morbidity of visual impairment and angina. Ophthalmic Epidemiol 2000;7:169–85.
15. Hamilton DM, Haennel RG. Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardiopulm Rehabil 2000;20:156–64.
16. Hamalainen H, Smith R, Puukka P, et al. Social support and physical and psychological recovery one year after myocardial infarction or coronary artery bypass surgery. Scand J Public Health 2000;28:62–70.
17. Lin A, Lenert LA, Hlatky MA, McDonaldd KM, Olshen RA, Hornberger J. Clustering and the design of preference-assessment surveys in healthcare. Health Serv Res 1999;34:1033–45.
18. Von Dras DD, Siegler IC, Williams RB, Clapp-Channing N, Haney TL, Mark DB. Surrogate assessment of coronary artery disease patients' functional capacity. Soc Sci Med 1997;44:1491–502.
19. Alonso J, Permanyer-Miralda G, Cascant P, Brotons C, Prieto L, Soler-Soler J. Measuring functional status of chronic coronary patients. Reliability, validity and responsiveness to clinical change of the reduced version of the Duke Activity Status Index (DASI). Eur Heart J 1997;18:414–9.
20. Nichol G, Llewellyn-Thomas HA, Thiel EC, Naylor CD. The relationship between cardiac functional capacity and patients' symptom-specific utilities for angina: some findings and methodologic lessons. Med Decis Making 1996;16:78–85.
21. Vaccarino V, Chen YT, Wang Y, Radford MJ, Krumholz HM. Sex differences in the clinical care and outcomes of congestive heart failure in the elderly. Am Heart J 1999;138:835–42.
22. Ghali WA, Faris PD, Galbraith PD, et al., Albera Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Sex differences in access to coronary revascularization after cardiac catheterization: importance of detailed clinical data. Ann Intern Med 2002;136:723–32.
23. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. Circulation 2002;105:1176–81.
24. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. J Am Coll Cardiol 1997;30:641–8.
25. Marwick TH, Shaw LJ, Lauer MS, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Am J Med 1999;106:172–8.
26. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article. J Am Coll Cardiol 2003;41:159–68.
27. Shaw LJ, Hendel R, Lauer MS, et al. Prognostic value of normal exercise and adenosine Tc-99m tetrofosmin SPECT imaging: results from the multicenter registry in 4,728 patients. J Nucl Med 2003;44:134–9.
28. Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailery KR, Gersh BJ. Gender differences in use of stress testing and coronary heart disease mortality: a population-based study in Olmsted County, Minnesota. J Am Coll Cardiol 1998;32:345–52.
29. Brach JS, Fitzgerald S, Newman AB, et al. Physical activity and functional status in community-dwelling older women. Arch Int Med 2003;163:2565–71.
30. Mieres JH, Shaw LJ, Arai A, et al., for the Cardiovascular Imaging Committee. American Heart Association—cardiac imaging committee consensus statement: the role of cardiac imaging in the clinical evaluation of women with known or suspected coronary artery disease. Circulation 2005;111:682–96.

APPENDIX

For the DASI questionnaire and scoring, please see the online version of this article.