The WOMEN study: What is the optimal method for ischemia evaluation in women? A multi-center, prospective, randomized study to establish the optimal method for detection of coronary artery disease (CAD) risk in women at an intermediate-high pretest likelihood of CAD: study design

Jennifer H. Mieres, MD,[a] Leslee J. Shaw, PhD,[b] Robert C. Hendel, MD,[c] and Gary V. Heller, MD, PhD[d]

Background. **Coronary artery disease remains the leading cause of morbidity and mortality in women. The optimal non-invasive test for evaluation of ischemic heart disease in women is unknown. Although current guidelines support the choice of the exercise tolerance test (ETT) as a first line test for women with a normal baseline ECG and adequate exercise capabilities, supportive data for this recommendation are controversial.**

Objective. **The what is the optimal method for ischemia evaluation in women? (WOMEN) study was designed to determine the optimal non-invasive strategy for CAD risk detection of intermediate and high risk women presenting with chest pain or equivalent symptoms suggestive of ischemic heart disease. The study will prospectively compare the 2-year event rates in women capable of performing exercise treadmill testing or Tc-99 m tetrofosmin SPECT myocardial perfusion imaging (MPI).**

Methods/study design. **The study will enroll women presenting for the evaluation of chest pain or anginal equivalent symptoms who are capable of performing >5 METs of exercise while at intermediate-high pretest risk for ischemic heart disease who will be randomized to either ETT testing alone or with Tc-99 m tetrofosmin SPECT MPI. The null hypothesis for this project is that the exercise ECG has the same negative predictive value for risk detection as gated myocardial perfusion SPECT in women. The primary aim is to compare 2-year cardiac event rates in women randomized to SPECT MPI to those randomized to ETT.**

Conclusions. **The WOMEN study seeks to provide objective information for guidelines for the evaluation of symptomatic women with an intermediate-high likelihood for CAD. (J Nucl Cardiol 2009;16:105–12)**

From the Department of Medicine,[a] New York University School of Medicine, New York, NY; Emory University School of Medicine,[b] Atlanta, GA; Midwest Heart Specialists,[c] Fox River Grove, IL; Hartford Hospital,[d] Hartford CT and the University of Connecticut School of Medicine, Farmington, CT.

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Reprint requests: Jennifer H. Mieres, MD, Department of Medicine, New York University School of Medicine, 550 First Ave, TCH-2; Rm 246, New York, NY 10016; *Jennifer.Mieres@nyumc.org; Jennifer.Mieres@med.nyu.edu.*

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Coronary artery disease (CAD) remains the leading cause of morbidity and mortality among women, accounting for approximately 220,000 deaths per year.[1] Although cardiac mortality has declined on average 3% per year, the rates have substantially decreased for men with little change noted for women.[1] In addition to the lack of risk reduction in women, there is a paucity of evidence from clinical trials which have traditionally focused on predominately male cohorts.[2,3] The lack of improvement in morbidity and mortality for women in the US is in part related to a lack of effective, evidence-based diagnostic testing strategies. Thus, there is a need for specific diagnostic testing algorithms for the early identification of at-risk women.[4,5]

Despite evidence in support of electrocardiographic gated myocardial perfusion single photon emission computed tomography (SPECT MPI) [3] as an effective tool for risk stratification of women with stable chest pain syndromes, current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for exercise testing and stable angina recommend the exercise tolerance test (ETT) as the initial diagnostic test for symptomatic women with suspected CAD.[6] Although exercise tolerance testing (ETT) is recommended as an initial diagnostic test by current guidelines, no randomized trials support this strategy in women with suspected CAD.[2,7,8]

A recent meta-analysis of 3,874 women reported only a modest sensitivity (62%) and specificity (69%) for ECG stress testing.[8] Furthermore, there is an ensuing high rate of false positives that limits the clinical application of ETT for female patients presenting for the evaluation of chest pain. However, there are data to support the prognostic accuracy of the parameters, exercise duration, heart rate, and marked ECG changes for the identification of at-risk women. [6]

Research studies in large cohorts of women undergoing SPECT MPI demonstrate an independent and incremental value for both diagnostic and prognostic applications.[8-10] The ability of SPECT MPI to define low to high risk women has been reported in several reports that include >1,000 women.[11-17] A recent consensus paper from the American Society of Nuclear Cardiology suggested a strategy employing this technology, although it provided little supportive clinical trial evidence.[2]

The what is the optimal method for ischemia evaluation in women? (WOMEN) study was designed to determine the optimal non-invasive strategy for CAD risk detection of intermediate and high risk women presenting with chest pain or equivalent symptoms suggestive of ischemic heart disease. The focus of this ongoing clinical trial is to enroll symptomatic women with an intermediate or high clinical risk for CAD and randomize them to either ETT alone or ETT with SPECT MPI. The primary endpoint for this randomized trial is a comparison of the negative predictive accuracy of these two techniques in 824 women.

The WOMEN study utilizes the Duke Activity Status Index (DASI) as a screening test to identify women capable of perfusion treadmill exercise, a new application for this index and potentially a strategy to determine the suitability of exercise testing in women. The DASI which was developed using graded exercise testing with the measurement of peak oxygen uptake, is a 12-item questionnaire that estimates self-reported physical work capacity and is converted to an estimate of peak metabolic equivalents (METs).[18,19] Each question is assigned a numerical value based on the estimated peak oxygen uptake. The patient's DASI score is the sum of all the "yes" responses. DASI scores range from 0, which represent an inability to carry out any of the activities to 58.2 mL/kg/minute which represents the ability to carry out all listed activities. METs are calculated by dividing the DASI by 3.5. (Figure 1).[18,19] Women enrolled in this study must be capable of achieving >5 METs of physical work; as defined by DASI.

STUDY DESIGN

This prospective, multi-center randomized trial will enroll women who are referred for the evaluation of chest pain or anginal equivalent symptoms at intermediate to high pretest risk for CAD, as defined by AHA/ACC guidelines for chronic stable angina and exercise testing (Table 1).[20-22] Qualified women must be capable of performing >5 METs of exercise (as determined by the DASI questionnaire). Once informed consent is obtained, patients are randomized to either ETT alone or in conjunction with Tc–99 m tetrofosmin SPECT MPI. All patients will be followed for a 2-year time period for the occurrence of subsequent cardiac events.

STUDY OBJECTIVES

This study will analyze the 2-year cardiac event rates for women capable of performing maximal

Duke Activity Status Index (DASI) [18,19]

	Can you:	Yes	No	Weight
1	Take care of self, that is ,eating dressing , bathing, or using the toilet?			2.75
2	Walk indoors, such as around the house?			1.75
3	Walk a block or two on level ground?			2.75
4	Climb a flight of stairs or walk uphill?			5.50
5	Run a short distance?			8.00
6	Do light work around the house like dusting or washing dishes?			2.70
7	Do Moderate work around the house like vacuuming, sweeping floors or carrying in groceries?			3.50
8	Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?			8.00
9	Do yard work around the house like raking leaves, weeding, or pushing a power mower?			4.50
10	Have sexual relations?			5.25
11	Participate in moderate recreational activities like golf, bowling, dancing, double tennis or throwing a baseball or football?			6.00
12	Participate in strenuous sports like swimming, single tennis, football, basketball, or skiing?			7.50

Scoring the DASI: Add the point values for all questions checked in the Yes column and divide by 3.5 to calculate the estimated DASI METs

Figure 1. Duke Activity Status Index (DASI) for the determination of METs.

Table 1. Pretest probability of coronary artery disease by age, gender and symptoms* (modified from the ACC/AHA practice guidelines on exercise testing)[22]

Age(years)	Typical/definite angina pectoris	Atypical/probable angina pectoris	Non-anginal chest pain	Asymptomatic
50-59	Intermediate	Intermediate	Low	Very low
60-69	High	Intermediate	Intermediate	Low
≥70	High	Intermediate	Intermediate	Low

*High indicates >90%; intermediate, 10-90%; and very low, <5%.

exercise (as defined by a DASI score >5 METs) who have normal SPECT MPI using Tc-99 m tetrofosmin (i.e., defined as a summed stress score <4) compared with women who have a negative stress ECG (defined as <1.0 mm of horizontal or downsloping ST segment depression). The study's null hypothesis is that the ETT is equally as accurate at risk detection as SPECT MPI in women. The current study seeks to establish the optimal method for exclusion of CAD risk in symptomatic women who are at an intermediate-high pretest likelihood of the disease and are capable of exercising to >5 METs.

The key objectives of this trial are:

- To evaluate the differential prognostic accuracy of normal exercise Tc-99 m tetrofosmin SPECT MPI compared with a normal ETT.
- To evaluate the predictive accuracy and ensuing 2-year clinical outcomes in women with low, intermediate, and high risk test results; either with the ETT (e.g., Duke treadmill score) or Tc-99 m tetrofosmin SPECT MPI.
- To compare the diagnostic sensitivity and specificity in women undergoing coronary angiography who were randomized to ETT vs Tc-99 m tetrofosmin SPECT MPI and who undergo an elective cardiac catheterization.
- To determine the utility of the DASI questionnaire in determining which women are able to achieve predicted maximal heart rate response with ETT.
- A secondary evaluation will be changes in quality of life following each randomized strategy.

The primary endpoint for this trial is a composite of cardiac events including: cardiac death; non-fatal myocardial infarction; unstable angina leading to revascularization; unstable angina with objective evidence of ischemia (positive cardiac biomarkers; ECG ST-segment deviation and/or T wave inversion) requiring hospitalization, hospitalization for heart failure, or

the performance of revascularization (consistent with ACC/AHA class I indications).Secondary endpoints will include quality of life measures assessed serially with a comparison of the relative improvement or worsening changes noting within each diagnostic strategy. Serial measurements of symptoms and functional capacity will be assessed using the Seattle Angina Questionnaire (SAQ) and the DASI questionnaire, respectively.

Eligibility Criteria

Inclusion criteria. The patient populations eligible for inclusion in this study will be any one of the following three groups of women:

1. Women 50 years of age and older or women who have had surgical menopause and are 30 years of age or older, presenting for the evaluation of chest pain symptoms meeting an intermediate to high pretest likelihood for ischemic heart disease, as defined by AHA/ACC guidelines for chronic stable angina OR
2. Diabetic women of any age presenting for the evaluation of chest pain symptoms or equivalent OR
3. Women with the metabolic syndrome of any age presenting for the evaluation of chest pain symptoms. The metabolic syndrome is defined by the presence of $\geq$3 of the following factors[23]:
   a. Waist circumference >88 cm (35 inches)
   b. Fasting triglycerides >150 mg/dL
   c. HDL-cholesterol <50 mg/dL
   d. Hypertension (systolic blood pressure $\geq$130 mm Hg, diastolic blood pressure $\geq$85 mm Hg or use of anti-hypertensive drug therapy), and
   e. Fasting glucose $\geq$110 mg/dL.

Exclusion criteria. Women with known CAD defined as a history of myocardial infarction or catheterization results revealing a >50% lesion in one or more coronary arteries are excluded. In addition, women scoring $\leq$5 METs on the DASI, those nursing or pregnant females, as well as those having a nuclear medicine study within the preceding 10 days will be excluded from the WOMEN trial. Electrocardiographic abnormalities excluded will be: left bundle branch block, electronic ventricular pacemaker, left ventricular hypertrophy, and resting ST-T wave changes. Other exclusion criteria: women with significant valvular heart disease (i.e., severe aortic stenosis or regurgitation, or severe mitral insufficiency), uncontrolled hypertension (blood pressure >210/110 mL Hg) hypotension (<90/60 mm/Hg), history of heart failure, left ventricular ejection fraction <50%, women receiving digoxin therapy, or inability or unwillingness to complete long-term follow-up.

Data Safety Monitoring Board (DSMB) and Quality Control

A DSMB has been established and will periodically evaluate safety and clinical outcomes data. Additionally, quality assurance measures have been included, such as the use of a blinded nuclear cardiologist to review image quality, and a clinical events committee (CEC) to adjudicate potential/reported cardiac events. Data from sample ECG's will also be evaluated on the quality of the ECG recording including motion artifact, baseline wander, and muscle interference. This quality evaluation will be performed by an independent study investigator. A medical monitor has also been assigned to answer medical questions regarding patient eligibility and queries related to the study protocol.

STUDY PROCEDURES

The study consists of (1) a screening (day 1) time period that includes randomization, (2) the performance of the stress test, and (3) follow-up telephone interviews at the 6, 12, 18, and 24 month time points. The follow-up calls are conducted by an independent call center (Cardiovascular Clinical Studies, Boston, MA).

Randomization

Screening (Figures 1 and 2). Following informed consent, all subjects will complete the DASI questionnaire and the Seattle Angina Questionnaire (SAQ). The DASI will be scored by the site staff. Patients having a DASI score of $\leq$5 METs will be considered as screening failures and excluded from study entry. If a woman qualifies, a comprehensive medical history will be obtained. As depicted in Figure 2, women having estimated >5 METs on the DASI will be eligible for study enrollment. Given an adequate DASI score, the study coordinator will begin the randomization process by contacting the centralized phone center to receive the subject's testing assignment for either routine (non-imaging) ETT OR exercise Tc-99 m tetrofosmin SPECT MPI. Within 15 business days from the date of randomization, the following information will be recorded: (a) Completion of the post-randomization diagnostic procedure and (b) Completion of other clinical information as required by the protocol and case report forms.

Clinical course. Following the performance of the stress testing procedures, the care of patients will be at the discretion of the primary physician; while no management strategies will be suggested by the study protocol, the post-test recommendations of the ACC practice guidelines will be provided to all sites. Follow-up data will be reviewed for compliance with ACC

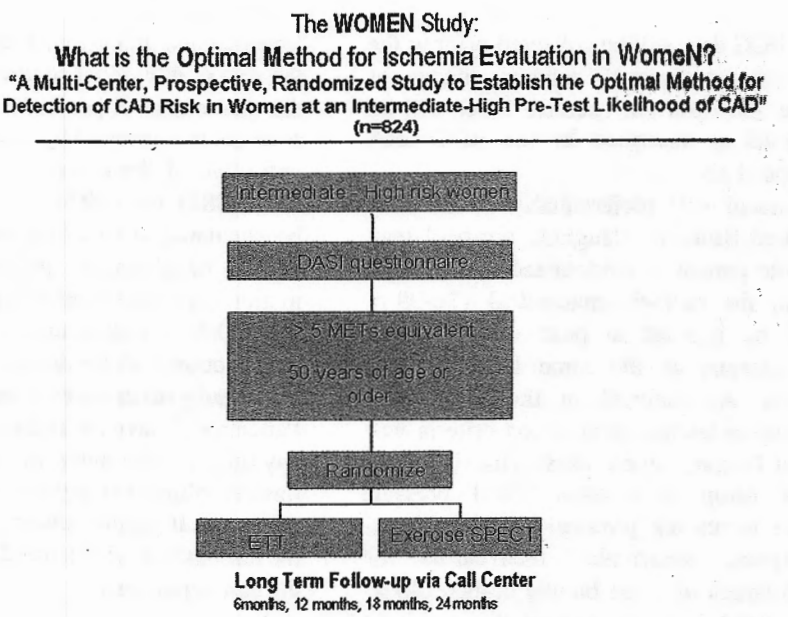

Figure 2. Inclusion and randomization Schema based on pretest risk of CAD and Duke Activity Status Index score.

guideline recommendations regarding treatment of symptomatic ischemic heart disease.

Angiographic data will be collected and used in the assessment of diagnostic accuracy for the detection of physiologically significant CAD (defined as stenosis ≥50% in a major coronary artery). ETT and SPECT MPI data will be compared to angiographic data if the cardiac catheterization is performed within 12 months of patient enrollment and no intervening events (i.e. myocardial infarction, heart failure) have occurred. In the cases where cardiac catheterization is performed later than 12 months post-enrollment, data will be collected on the CAD disease extent (i.e., 0, 1, 2, or 3 vessel disease).

Follow-up at 6, 12, and 24 month contact (±5 days). All patients will be contacted by telephone at 6, 12, 18, and 24 months following randomization to determine the occurrence of the study's primary and secondary endpoints. Experienced research personnel will utilize a scripted interview for ascertainment of clinical events. Repeat DASI and SAQ questionnaires will be completed. All events will be evaluated by the CEC.

Clinical Assessments

History and physical examination. A medical history, including tobacco and alcohol use will be taken at screening. An abbreviated physical exam including body weight, vital signs, and heart and lung sounds will be performed and documented. The site investigator or qualified designee will perform the physical examination.

Women's health baseline data. The onset of CAD is influenced by menopausal status in women presenting for evaluation of suspected cardiac symptoms. As such, data related to a women's menopausal history will be collected. This will include epidemiologic factors that uniquely affect disease risk and prevalence in women such as history of menopausal hormone therapy use and prior hysterectomy.

ECG interpretation. ECG analysis will be performed in the standard fashion by the site. As per ACC/AHA guidelines[6,22], an exercise ECG will be considered abnormal if there is ≥1 mm of horizontal (occurring 60 ms past the J-point) or downsloping ST-segment depression, or if there is a change of ≥1 mm in a segment with a baseline abnormality of ≤0.5 mm deviation from the isoelectric line. A threshold of 1.5 mm ST segment depression will also be considered when upsloping ST-segment depression is noted.

Stress testing protocols. All exercise stress testing will be performed in accordance with the most recent ACC/AHA guidelines[6,22,24] which stipulates that continuous ECG monitoring be employed. Blood pressure and 12-lead ECG's will be monitored continuously every 3 minutes during the protocol, at peak stress, and at 1, 2, 3, and 5 minutes post-exercise, or until the heart rate and blood pressure have returned to baseline levels. In the case of exercise-induced ECG changes, 12-lead ECG's will be obtained in recovery until ST-segments return to baseline.

Twelve-lead ECG data will be collected prior to the procedure and at any maximum ST segment change, or if normal, at peak exercise. An exercise ECG will be considered abnormal as described by the ACC/AHA guidelines as outlined above.

A Bruce protocol will preferentially be utilized, although a modified Bruce or Naughton protocol may also be used. If the patient is randomized to the exercise SPECT arm, the radiopharmaceutical (Tc-99 m tetrofosmin) will be injected at peak exercise with continuation of exercise at the same level for 1-2 additional minutes. As outlined in the ACC/AHA guidelines for exercise testing, termination criteria will include: volitional fatigue, severe chest pain, hemodynamic instability (drop in systolic blood pressure >20 mm Hg with increasing physical work), chronotropic incompetence, ventricular tachycardia or fibrillation, development of a left bundle branch block, ST elevation (≥1 mm) in leads without diagnostic Q waves (other than V1 or aVR),ST or QRS changes such as excessive ST depression (>2 mm of horizontal or down-sloping ST-segment depression), or marked axis shift.[6]

SPECT MPI Image Acquisition

Imaging for the SPECT study will begin 15-60 minutes after the administration of the radiopharmaceutical (Tc-99 m tetrofosmin). SPECT images will be obtained in the usual manner for each laboratory, following ASNC imaging guidelines.[23,25,26] The resting images will be obtained either before or after the stress images and may be done in a manner consistent with the laboratory protocol and ASNC guidelines. Acceptable acquisition protocols include a dual isotope protocol (rest thallium/stress tetrofosmin), a 2-day Tc-99 m tetrofosmin protocol or a 1-day Tc-99 m tetrofosmin (rest/stress sequence) protocol. All studies will be acquired in a gated mode (8-16 frames per cycle) when possible. Attenuation correction is advised, but optional. The expected doses for tetrofosmin will be 10 mCi rest and 30 mCi stress for a 1-day protocol. Gray scale hard copy (paper) of SPECT images using ACC/ASNC format will be submitted for each patient for the purposes of quality assurance.

Image interpretation. SPECT MPI images will be interpreted locally by visual analysis, with the aid of quantitative programs. The myocardium will be divided into 17 segments and each segment will be scored in a semi-quantitative fashion using a five point scoring system (0 = normal, 1 = mildly abnormal, 2 = moderately abnormal, 3 = severely abnormal, 4 = absent perfusion). The summed stress score (SSS) is obtained by adding the individual segment scores on the stress study and is indicative of the combined extent of myocardial ischemia and infarction. The summed rest score (SRS) is the sum of individual segment scores at rest, and reflects the total extent of previous MI. The summed difference score (SDS), obtained by subtracting SRS from the SSS, is indicative of the extent of ischemia.[24-26] The summed stress (SSS), rest (SRS), and difference (SDS) scores will be calculated and used for the clinical determination of a normal or abnormal perfusion study. Regional wall motion will be assessed using the same 17-segment model (score 0-5) as well as the calculated left ventricular ejection fraction at stress and at rest (when available).

Study termination and withdrawal criteria. Patients will have the right to withdraw from the study at any time. Additionally, the site investigator may discontinue enrollment at any time if he/she feels it is medically necessary. If patient consent is withdrawn from the study, the reasons will be recorded on source documents and on the case report form.

STATISTICAL ANALYSES

Sample Size Determination

The primary goal of this study is to test the null hypothesis that the hazard rate, which is assumed to be constant across all study intervals, is identical in the two groups (exercise ECG vs stress SPECT). Computation of power is based on a hazard rate of 0.20 and was derived based upon women enrolled in the recent Myoview prognosis registry.[27] It is equivalent to a cumulative survival at 36 months of 95.8% for the negative exercise ECG group vs 99.0% for the SPECT MPI group.[27] This was selected as the smallest effect that would be important to detect, as smaller effect would be unlikely to have clinical or substantive significance.

For this study, the necessary and sufficient sample size is 412 patients per group, standard ECG OR SPECT MPI (2-tailed $\alpha = 0.05$, $\beta = 0.80$); given an expected loss to follow-up of 2% per group. This sample size calculation has also been adjusted for two interim analyses. For this study design, sample size, attrition rate, alpha and tails, and the population effect size described above, the study will have power ≥80% to yield a statistically significant result.

Primary Endpoint

The primary endpoint for this study is time to major adverse cardiac events, defined as cardiac death, nonfatal myocardial infarction, unstable angina leading to revascularization, unstable angina with objective evidence of ischemia requiring hospitalization, and hospitalization for heart failure in women with a negative ETT as compared with a normal exercise Tc-99 m

tetrofosmin SPECT MPI study. Cumulative survival as a function of time to event will be calculated using a Cox proportional hazards model. For the estimation of major adverse cardiac events, univariable and multi-variable Cox proportional hazards models will be calculated. Individual models estimating the relationship between SPECT imaging parameters and cardiac events will be risk-adjusted and include covariates for important clinical and baseline historical measures (e.g., age, diabetes, hypertension, smoking status, and angina). Thus, a comparison of the primary endpoint will be performed using unadjusted and risk-adjusted Cox models. Finally, cumulative survival as a function of time to cardiac catheterization and coronary revascularization will also be calculated. From this latter analysis, hospitalization rates at 180-days and 2-years will be calculated.

DISCUSSION

The goal of the WOMEN study is to provide sufficient objective data to support current guidelines or alternatively to refute these recommendations by providing evidence that SPECT MPI should be the test of choice for symptomatic women at risk for CAD.[25,28] This trial will add to existing data for risk stratification using SPECT MPI that has included more than 15,000 women.[28-30]

One recent report demonstrated that coronary angiography was performed in 8% of patients with a low risk or negative exercise ECG, suggesting that physicians may distrust its accuracy.[16] Furthermore, in this large cohort study (N = 3,796, some with known CAD) that included 425 patients with a low risk exercise ECG, the annual cardiac death or non-fatal myocardial infarction rate was 1.8%.[16] It remains possible that a failure to provoke ECG changes may result in suboptimal risk stratification for the exercise ECG in women.

Within the ischemic cascade, myocardial perfusion abnormalities are elicited early and may be more sensitive for detecting intermediate-severe coronary stenosis, while demonstration of marked ST segment changes signifies significant luminal stenosis. A normal stress SPECT MPI may then exclude the likelihood of an intermediate stenosis that remains more likely to progress and rupture.[16]

Data comparing the predictive value of SPECT MPI to the ETT are currently not available. In fact, few randomized trials are available for diagnostic procedures. Thus, the WOMEN study represents a landmark in the diagnostic testing literature, providing a multicenter, large scale randomized evaluation of non-invasive testing options. We anticipate that this trial will serve as a standard for the development of further gender-specific guidelines and appropriateness criteria.

In summary, the WOMEN study will provide clinical insight as how best to evaluate symptomatic women at an intermediate or high likelihood of CAD. Enrollment and randomization was completed in December of 2007 with a total of 825 women. We believe this trial has the potential to exert a profound impact on existing diagnostic strategies and will lead to the development of critical criteria for effective risk stratification of symptomatic women at risk for ischemic heart disease. Moreover, a direct outcome of the WOMEN study may be the development of an efficient and timely diagnostic pathway optimized for women being evaluated with suspected myocardial ischemia.

References

1. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69-171.
2. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005;111:682-96.
3. Shaw LJ, Miller DD, Romeis JC, Kargl D, Younis LT, Chaitman BR. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120:559-66.
4. Mosca L, Banka CL, Benjamin EJ. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007;115:1481-501.
5. Holdright DR, Fox KM. Characterization and identification of women with angina pectoris. Eur Heart J 1996;17:510-7.
6. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, et al. ACC/AHA guidelines for exercise testing: Executive summary. Circulation 1997;96:345-54.
7. Hlatky MA, Pryor DB, Harrel FE Jr, et al. Factors affecting sensitivity and specificity of exercise electrocardiography: Multivariable analysis. Am J Med 1984;77:64-71.
8. 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 1999;83:660-6.
9. Iskandrian AE, Heo J, Nallamothu N. Detection of coronary artery disease in women with use of stress single-photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 1997;4:329-35.
10. Santana-Boado C, Candell-Riera J, Castell-Conesa J, et al. Diagnostic accuracy of technetium-99m-MIBI myocardial SPECT in women and men. J Nucl Med 1998;39:751-5.
11. Hachamovitch R, Berman DS, Kiat H, Bairey CN, Cohen I, Cabico A, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. J Am Coll Cardiol 1996;28:34-44.
12. Pancholy SB, Fattah AA, Kamal AM, Ghods M, Heo J, Iskandrian AS. Independent and incremental prognostic value of exercise thallium single-photon emission computed tomographic imaging in women. J Nucl Cardiol 1995;2:110-6.

13. Hachamovitch R, Berman DS, Kiat H, et al. Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms. An evaluation of incremental prognostic value and cost-effectiveness. Circulation 2002;105:823-9.
14. Galassi AR, Azzarelli S, Tomaselli A, et al. Incremental prognostic value of technetium-99m-tetrofosmin exercise myocardial perfusion imaging for predicting outcomes in patients with suspected of known coronary artery disease. Am J Cardiol 2001;88:101-6.
15. Shaw LJ, Hendel R, Borges-Neto S, et al. Prognostic value of normal exercise and adenosine Tc-99m tetrofosmin SPECT imaging: Results from the multicenter registry of 4, 728 patients. J Nucl Med 2003;44:134-9.
16. Marwick T, Shaw L, Lauer M, Kesler K, Hachamovitch R, Heller G, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease: Economics of Noninvasive Diagnosis (END) Study Group. Am J Med 1999;106:172-8.
17. Shaw LJ, Heller GV, Travin MI, Lauer M, Marwick T, Hachamovitch R, et al. Cost analysis of diagnostic testing for coronary disease in women with stable chest pain. J Nucl Cardiol 1999;6:559-69.
18. Shaw LJ, Olson MB, Kip K, Kelsey SF, Johnson BD, Mark DB, et al. The value of estimated functional capacity in estimating outcome: Results from the NHLBI-sponsored women's ischemia syndrome evaluation. J Am Coll Cardiol 2006;47:S36-43.
19. Hltaky MA, Boineau RE, et al. A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 1989;64:651-4.
20. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: Executive summary and recommendations. Circulation 1999;99:2829-48.
21. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350-8.
22. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee of Exercise Testing). 2002 American College of Cardiology website. Available at: www.acc.org/clinical/guidelines/exercise/dirIndex.htm.
23. Grundy SM, Brewer HB, Cleeman JL, et al. Definition of metabolic syndrome. Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-8.
24. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to revise the 1995 guidelines for the clinical use of cardiac radionuclide imaging). Circulation 2003;108:1404-18.
25. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-42.
26. DePuey EG, et al. Imaging guidelines for nuclear cardiology procedures. J Nucl Cardiol 2006;13:21-171.
27. Shaw LJ, Hendel R, Borges-Neto S, For the Myoview Multicenter Registry, et al. Prognostic value of normal exercise and adenosine 99mTc-tetrofosmin SPECT imaging: Results from the multi-center registry of 4,728 patients. J Nucl Med 2003;44:1-6.
28. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: A meta-analysis. J Am Coll Cardiol 2007;49:227-37.
29. Berman DS, Kang X, Hayes SW, et al. Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 2003;41:1125-33.
30. Giri S, Shaw LJ, Murthy DR, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 2002;105:32-40.