

Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease

Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial

Leslee J. Shaw, PhD; Jennifer H. Mieres, MD; Robert H. Hendel, MD; William E. Boden, MD; Martha Gulati, MD; Emir Veledar, PhD; Rory Hachamovitch, MD; James A. Arrighi, MD; C. Noel Bairey Merz, MD; Raymond J. Gibbons, MD; Nanette K. Wenger, MD; Gary V. Heller, MD, PhD; for the WOMEN Trial Investigators

Background—There is a paucity of randomized trials regarding diagnostic testing in women with suspected coronary artery disease (CAD). It remains unclear whether the addition of myocardial perfusion imaging (MPI) to the standard ECG exercise treadmill test (ETT) provides incremental information to improve clinical decision making in women with suspected CAD.

Methods and Results—We randomized symptomatic women with suspected CAD, an interpretable ECG, and ≥ 5 metabolic equivalents on the Duke Activity Status Index to 1 of 2 diagnostic strategies: ETT or exercise MPI. The primary end point was 2-year incidence of major adverse cardiac events, defined as CAD death or hospitalization for an acute coronary syndrome or heart failure. A total of 824 women were randomized to ETT or exercise MPI. For women randomized to ETT, ECG results were normal in 64%, indeterminate in 16%, and abnormal in 20%. By comparison, the exercise MPI results were normal in 91%, mildly abnormal in 3%, and moderate to severely abnormal in 6%. At 2 years, there was no difference in major adverse cardiac events (98.0% for ETT and 97.7% for MPI; $P=0.59$). Compared with ETT, index testing costs were higher for exercise MPI ($P<0.001$), whereas downstream procedural costs were slightly lower ($P=0.0008$). Overall, the cumulative diagnostic cost savings was 48% for ETT compared with exercise MPI ($P<0.001$).

Conclusions—In low-risk, exercising women, a diagnostic strategy that uses ETT versus exercise MPI yields similar 2-year posttest outcomes while providing significant diagnostic cost savings. The ETT with selective follow-up testing should be considered as the initial diagnostic strategy in symptomatic women with suspected CAD.

Clinical Trial Registration—<http://www.clinicaltrials.gov>. Unique identifier: NCT00282711. (*Circulation*. 2011;124:1239-1249.)

Key Words: clinical trials ■ diagnostic testing ■ exercise testing ■ physical capacity ■ women

Diagnostic testing for detection of obstructive coronary artery disease (CAD) is commonly performed each year in nearly 20 million patients.¹ Two common options for testing include the use of the standard exercise treadmill test (ETT), the use of ETT combined with single photon emission computed tomographic myocardial perfusion imaging (MPI), or, in patients unable to exercise, the use of MPI with pharmacological vasodilator stress. Despite its commonplace use, there is a limited

evidence base with no randomized trials comparing the effectiveness of the standard ETT compared with an imaging-guided strategy as an initial diagnostic approach in symptomatic women.¹ Clinical practice guidelines recommend an ETT as the preferred procedure for the initial evaluation of women with suspected myocardial ischemia.² However, frequent reports detail limitations of the accuracy of the ECG in women, including a high false-positive rate.² As a result, current practice

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received March 2, 2011; accepted June 29, 2011.

From Emory University, Atlanta, GA (L.J.S., E.V., N.K.W.); North Shore–Long Island Jewish Hospital, Manhasset, NY (J.H.M.); University of Miami, Miami, FL (R.H.H.); University of Buffalo, Buffalo, NY (W.E.B.); Ohio State University, Columbus (M.G.); Cleveland Clinic Foundation, Cleveland, OH (R.H.); Brown University, Providence, RI (J.A.A.); Cedars-Sinai Heart Institute, Los Angeles, CA (C.N.B.M.); Mayo Clinic, Rochester, MN (R.J.G.); and Hartford Hospital, Hartford, CT (G.V.H.).

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.029660/-DC1>.

Correspondence to Leslee J. Shaw, PhD, 1462 Clifton Rd NE, Emory University, Atlanta, GA 30324. E-mail lshaw3@emory.edu

© 2011 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.029660

patterns are variable and include direct referrals of women to higher-cost procedures, such as MPI.

Editorial see p 1207
Clinical Perspective on p 1249

A major challenge with the available evidence is that it is largely derived from observational data in which selection bias and other factors affect test selection and, in turn, may affect clinical outcomes. A compelling need exists for higher levels of scientific evidence, including more randomized trials, and this has resulted in increased attention toward developing targeted, prospective, comparative effectiveness research to more rigorously address the outpatient diagnostic evaluation of patients with suspected CAD.^{1,3} In particular, the evaluation of women with suspected CAD remains a conundrum because of their atypical symptom presentation, which often results in varied diagnostic practice patterns. The What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial was designed to evaluate whether a diagnostic strategy using ETT versus exercise MPI in women with an intermediate pretest likelihood of CAD affects 2-year posttest outcomes for major adverse cardiovascular events (MACE).⁴

Methods

The trial design was published previously.⁴ A total of 43 cardiology practices (Appendix in the online-only Data Supplement) participating in this trial enrolled 824 women presenting for evaluation of suspected CAD. Women were eligible for the trial if they (1) had typical/atypical chest pain or ischemic equivalents (eg, dyspnea); (2) had an interpretable baseline ECG (ie, no significant resting ST-segment changes ≥ 0.5 mm); (3) were aged ≥ 40 years or postmenopausal; (4) were capable of performing ≥ 5 metabolic equivalents (METs) on the Duke Activity Status Index (DASI) questionnaire⁵; and (5) were at intermediate pretest CAD likelihood.⁶ Each site was provided with calculation of intermediate pretest CAD likelihood tables based on age and typicality of symptoms.⁶ Women with an intermediate CAD likelihood were (1) aged ≥ 50 years with typical or atypical angina or (2) aged ≥ 60 years with nonanginal symptoms. Eligible women were judged to be at intermediate pretest CAD likelihood by the enrolling physician. Representative enrollment was blocked by age, with one half of the women required to be aged ≥ 50 years and one quarter aged ≥ 65 years. A site screening log recorded 2859 consecutively eligible women, of whom 29% were randomized.

Randomization

Telephone randomization occurred at the data coordinating center (Cardiovascular Clinical Specialists, Boston, MA), with baseline documentation of symptoms. A medical monitor supervised the eligibility and randomization process.

Clinical History Case Report Form

The baseline case report form was sent to the data coordinating center within 2 weeks of randomization and detailed clinical history, presenting symptoms, and cardiac risk factors. Menopausal status and baseline physical examination measurements were ascertained and entered on the case report form.

Health Status Measurements

The DASI is a 12-item questionnaire in which patients detail their activities of daily living and has been reported to be valid,

reliable, and prognostic of subsequent cardiac events.⁵ The DASI provides an estimate of peak exercise METs.⁵

The Seattle Angina Questionnaire (SAQ) is a 19-item questionnaire that quantifies patients' symptoms, function, treatment satisfaction, and quality of life.^{7,8} It has been demonstrated to be valid, reliable, and prognostic of subsequent cardiac events.⁹ SAQ subscales include physical limitation, angina frequency, angina stability, treatment satisfaction, and quality of life. Scores are scaled 0 to 100, with 100 denoting the best outcome (eg, fewest limitations, no angina).

The DASI and SAQ were collected at baseline and during follow-up.

Exercise Treadmill Test Procedures

Routine ETT was performed with the use of the standard or modified Bruce protocol. The ETT was continued until the occurrence of marked ST-segment changes, worsening chest pain, sustained ventricular arrhythmias, or excessive fatigue. Throughout testing, ST-segment changes, heart rate, and blood pressure measurements were recorded. Exertional chest pain or excessive dyspnea was also documented.

A normal ETT was defined as the lack of significant ST-segment changes with adequate exercise tolerance. An indeterminate ETT was defined as 0.5 to 1.0 mm of ST-segment changes, exertional chest pain, and/or submaximal exercise tolerance. An abnormal ETT was defined as ≥ 1 mm of ST-segment changes generally occurring in ≥ 2 leads. The ECG was interpreted by site investigators.

Myocardial Perfusion Imaging Procedures

MPI procedures were standardized across centers and consistent with published guidelines.^{10–12} Before trial initiation, sites were required to send representative MPI scans to the quality control laboratory for approval. All MPI scans were interpreted with the use of a 17-segment model in which each segment was scored with a 5-point scoring system (0=normal perfusion to 4=no uptake).¹³ Data on rest/stress myocardial perfusion and poststress left ventricular ejection fraction were recorded.

Average rest and stress doses of Tc-99m tetrofosmin were 11.6 ± 5 and 31.2 ± 6 mCi. MPI was performed as same-day rest/stress imaging. In 94 women, dual-isotope imaging was performed; average rest dose of Tl-201 was 3.9 ± 3 mCi. Rest and stress images were motion corrected in 5% and 15% of patients. Attenuation correction was employed in 14% of images. During MPI, women were exposed to an average of 14 mSv of ionizing radiation, including 10 mSv for rest and stress Tc-99m and 24 mSv for dual-isotope MPI.

A normal, mildly abnormal, and moderate to severely abnormal MPI was defined as a summed stress score of < 4 , 4 to 8, and > 8 , respectively. The MPI interpretation was provided by site investigators.

Quality Control Laboratory

After completion of the index procedure, a copy of the rest and peak exercise ECG was sent to the quality control laboratory for review of data quality. Good to excellent data quality was defined as minimal baseline wander or motion artifact on the peak exercise ECG. Good to excellent quality and satisfactory quality were reported in 94% and 6% of ECGs, respectively. The rest and stress MPI scans were also sent to the quality control laboratory. A good to excellent quality MPI scan was defined as one with adequate radioactive count density and minimal image distortion due to attenuation or patient motion.¹⁴ These criteria were met in 96% of women.

Follow-Up Procedures

Patients were contacted at 6, 12, and 24 months for ascertainment of trial end points and health status measurements. Follow-up contact was made by a central telephone center employing trained nursing staff using a scripted interview. The occurrence of downstream procedures (ETT, MPI, coronary angiography, and

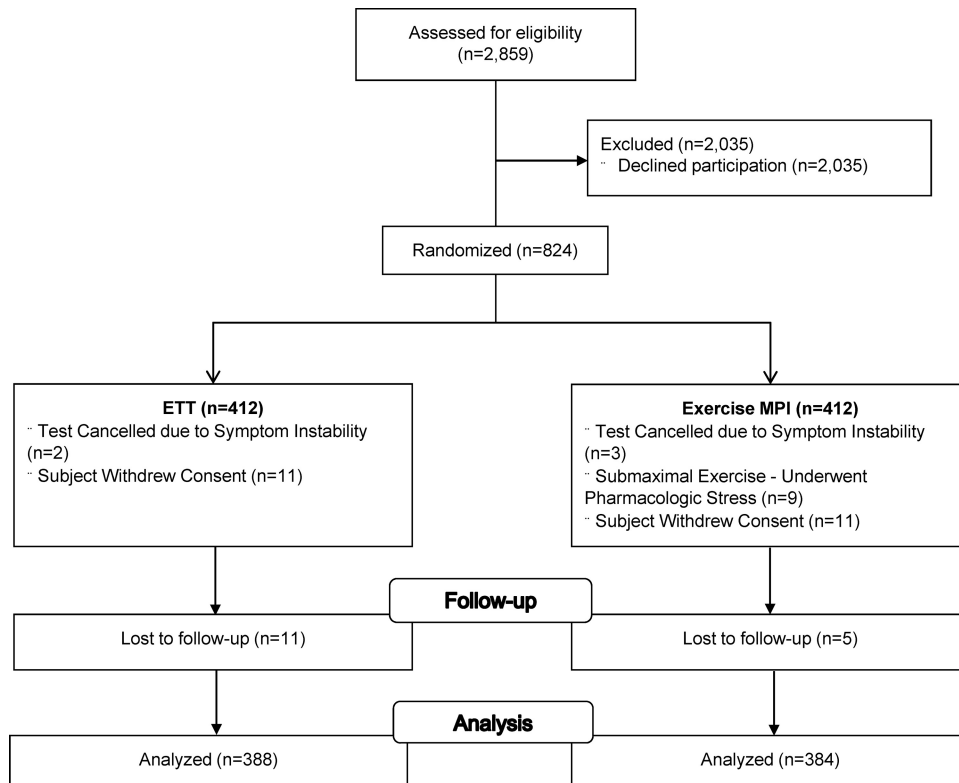


Figure 1. Flow diagram of eligible and randomized patients including disposition by randomized testing arm. ETT indicates exercise treadmill test; MPI, myocardial perfusion imaging.

revascularization) was collected during follow-up. All diagnostic procedures were confirmed by site personnel. Coronary angiography and revascularization procedures were confirmed through review of the patients' medical records.

Five patients had testing cancelled because of symptom instability or marked ECG abnormalities (n=2 in the ETT arm, with failure to complete MPI in 3 patients) (Figure 1). Nine patients randomized to MPI had submaximal exercise, underwent pharmacological stress MPI, and, on an "intention to treat" basis, were excluded. Physician or patient withdrawal of consent was reported in 22 patients because of a preferred testing or no testing approach, with no difference by randomization ($P=0.66$). Women withdrawing consent agreed to a final survival assessment, with no deaths recorded during follow-up. A total of 16 patients (1.9%) were lost during follow-up.

Primary and Secondary End Points

The primary MACE was a composite of cardiac death, nonfatal myocardial infarction (MI), or hospital admission for an acute coronary syndrome or heart failure. Cardiac death was defined as (1) confirmed enzymatic evidence of acute MI with death ensuing within 24 hours; (2) sudden cardiac death defined as a witnessed or unwitnessed sudden death of suspected cardiac etiology defined as the primary cause of death on the death certificate; or (3) death related to an ischemic cardiomyopathy defined as end-stage CAD in a patient with a prior diagnosis of heart failure or defined as primary cause of death on death certificate review. Nonfatal MI was defined by hospitalization records noting biomarker elevations concordant with myocardial necrosis. For a nonfatal MI, the discharge summary diagnosis of acute MI was needed for defining this event. A heart failure admission was confirmed by review of the patient's hospital discharge summary with heart failure listed as a primary or secondary diagnosis. An acute coronary syndrome admission was confirmed as presentation of acute-onset chest pain co-occurring with ECG changes and documented as the primary diagnosis on the hospital discharge summary.

Secondary end points included hospitalization for any chest pain, follow-up worsening SAQ measurements, and all-cause death. SAQ subscales of angina frequency or stability scores of <50 were used to define worsening chest pain.⁹

Site-identified end points were reviewed by an external clinical end points committee blinded to randomization. For each suspected end point, the site provided a hospital discharge summary or physician narrative to the clinical end points committee to classify primary end point occurrence. Clinical end points committee rules included review of each suspected end point by 2 reviewers. Discordance was resolved with a third reviewer for classification of end point status.

Sample Size Estimate

This trial was designed as a superiority trial of exercise MPI versus ETT for MACE-free survival. The sample size calculation was based on observational, nonadjudicated event data noting a higher rate of unstable angina and combined MACE in women undergoing ETT.^{15,16} The projected 2-year MACE rate was 3.2% for ETT and 1.0% for exercise MPI. This modeling resulted in a projected sample size of 412 patients per trial arm ($\alpha=0.05$, $\beta\geq 0.80$), calculated with the use of SamplePower (<http://www.SPSS.com>).

Procedural Cost

Diagnostic costs were a tertiary end point and were estimated by applying a nationwide reimbursement rate derived from the Center for Medicare and Medicaid Services' outpatient PC pricer database from 2004 to 2009 for each Healthcare Common Procedure Code (http://www.cms.hhs.gov/PCPricer/08_OPPTS.asp#TopOfPage;www.cms.hhs.gov/pfslookup/). Costs were inflation adjusted with the medical care component of the consumer price index and discounted at 3%/y.

Statistical Analyses

Categorical variables were compared with the use of a χ^2 likelihood ratio statistic. Continuous measurements were com-

pared with the Wilcoxon statistic. Continuous data were presented as mean (SD) or median (interquartile range).

The probability of MACE-free survival was estimated with the use of Kaplan-Meier survival analysis with comparisons performed with the log-rank statistic. A Cox proportional hazards model was employed to estimate the relative hazard of MACE by randomized test strategy, deriving hazard ratios and 95% confidence intervals (CIs). Prespecified subset analyses by DASI, age, and site were not significant and are not reported herein. Additional Cox models were employed to evaluate risk stratification with ECG and MPI results.

Follow-up angina status was compared with a χ^2 likelihood ratio statistic. Follow-up procedures were plotted with a Kaplan-Meier survival analysis. The estimated survival functions for first follow-up downstream procedure were compared with the log-rank statistic.

Index and follow-up procedural costs were summarized as mean (SD) and quartiles and compared with the Wilcoxon statistic. Nominal *P* values <0.05 were considered significant.

Results

Clinical Characteristics of the Enrolled Women

Trial participants were predominantly middle-aged (median=62 years), with the majority being postmenopausal (Table 1).

Functional Capabilities

Women reported median METs of ≈ 12 on the DASI, with no difference by randomization (*P*=0.71) (Table 2). From the DASI, women reported limitations in 0 (17%), 1 to 2 (35%), 3 to 4 (24%), and ≥ 5 activities of daily living (24%), respectively.

Exercise Test Results

Women exercised to an average 8.4 METs or into stage III of the Bruce protocol, indicating intact effort tolerance (Table 2). Observed exercise METs were significantly lower than predicted METs by the DASI. Nearly one third of women exhibited ≥ 1 mm of ST-segment changes during exercise. Exertional chest pain occurred in 13% and 12% of women randomized to ETT and exercise MPI, respectively (*P*=0.51).

For women randomized to ETT, the test results were normal in 64%, indeterminate in 16%, and abnormal in 20% (Figure 2). For the exercise MPI arm, the ECG results were similar.

Myocardial Perfusion Imaging Results

The MPI results were normal in 91%, mildly abnormal in 3%, and moderate to severely abnormal in 6% of women (Figure 2). In women randomized to exercise MPI with an indeterminate or abnormal ECG, the rate of abnormal MPI findings was 28%. The median postexercise left ventricular ejection fraction was 68% (interquartile range, 62%, 76%), with only 4% having a postexercise left ventricular ejection fraction $\leq 50\%$.

Two-Year Major Adverse Cardiovascular Events -Free Survival

A total of 17 primary end points were confirmed, including 3 nonfatal MIs, 1 heart failure hospitalization, 12 acute coronary syndrome hospitalizations, and only 1 sudden cardiac death reported in 772 women (Figure 3). At 2 years, MACE-free survival was identical (98%) for women

Table 1. Clinical Characteristics of Women Randomized to Exercise Treadmill Test vs Exercise Myocardial Perfusion Imaging

	ETT (n=388)	Exercise MPI (n=384)	<i>P</i>
Age, median (25th,75th percentile), y	63 (60, 69)	62 (58, 68)	0.15
Postmenopausal, %	78.2	76.8	0.65
Systolic/diastolic blood pressure, mm Hg	130/80	130/78	0.47/0.15
Body mass index, median (25th,75th percentile), kg/m ²	27.4 (24.2, 30.9)	27.4 (24.6, 31.8)	0.57
Cardiac risk factors, %			
Family history of CHD	47.3	45.8	0.74
Current/past smoker	48.8	42.4	0.19
Hypertension	55.2	52.0	0.66
Hyperlipidemia	50.0	53.7	0.57
Diabetes mellitus	12.6	14.2	0.41
Presenting symptoms, %			
Chest pain	89.4	90.0	0.76
Typical angina	61.2	59.8	
Atypical angina	9.1	9.3	
Nonspecific chest pain	27.0	27.8	
Dyspnea	53.5	48.3	0.14
Chest pain within 4 weeks, %			0.29
Almost daily episodes	16.3	18.5	
≥ 3 episodes per week	29.3	25.9	
No rest ST-segment changes <0.5 mm, %	92.2	95.7	0.12
Comorbidity, %			
Depression	18.8	18.7	0.50
COPD	4.7	2.8	0.26
Esophageal reflux	36.9	40.1	0.52
Mitral valve prolapse	6.4	7.5	0.77
Baseline medications, %			
ACE inhibitor	15.6	18.4	0.14
Angiotensin receptor blocker	10.9	10.9	0.50
β -Blocker	18.3	19.7	0.44
Calcium channel blocker	9.9	11.2	0.55
Aspirin	33.2	37.1	0.25
Gastrointestinal	25.5	28.4	0.36
Antidepressant	16.6	18.7	0.44
Anxiolytic	5.2	6.4	0.49
Nitrates	3.5	2.5	0.36
Statins	31.7	33.1	0.67
NSAIDs	14.9	16.9	0.36

ETT indicates exercise treadmill test; MPI, myocardial perfusion imaging; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; and NSAIDs, nonsteroidal antiinflammatory drugs.

Table 2. Exercise Test and Index Duke Activity Status Index Results by Randomized Test Strategy: Exercise Treadmill Test vs Exercise Myocardial Perfusion Imaging

	ETT (n=388)	Exercise MPI (n=384)	P
DASI METs	11.7 (8.2, 14.5)	12.2 (8.3, 14.5)	0.71
Resting			
Heart rate, bpm	76 (68, 86)	72 (65, 81)	<0.001
Blood pressure, mm Hg	132/78	132/78	0.59/0.80
Peak exercise			
Heart rate, bpm	149 (137, 160)	149 (139, 158)	0.99
Blood pressure, mm Hg	176/82	170/80	0.09/0.10
Heart rate recovery at 1 min, bpm	23 (16, 32)	23 (15, 33)	0.65
% with ≤12 bpm	20.4	17.2	0.32
≥85% predicted maximal heart rate, %	88.1	88.4	0.88
Peak exercise METs	8.2 (7.0, 10.1)	8.5 (7.0, 10.1)	0.50
Maximum ST-segment Δ	-0.5 (0.0, -1.1)	-0.4 (0.0, -1.0)	0.38
Maximum ST-segment Δ, if abnormal	-1.5 (-1.0, -1.9)	-1.4 (-1.0, -1.9)	0.72
% with ≥1 mm ST-segment Δ	35.9	32.5	0.32
No. of abnormal leads	3 (2, 5)	4 (3, 6)	0.18
Time to ≥1 mm ST-segment Δs, min	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	0.79
Recovery time to ST segment <1 mm, min	2.0 (1.0, 3.0)	1.2 (1.0, 4.8)	0.94
Exertional symptoms, %			
Chest pain	13.2	11.6	0.51
Dyspnea	37.0	42.2	0.14
Fatigue	51.4	52.8	0.71

Values are median (25th,75th percentile) unless indicated otherwise. ETT indicates exercise treadmill test; MPI, myocardial perfusion imaging; DASI, Duke Activity Status Index; and METs, metabolic equivalents. Exercise test results exclude early dropouts. Median blood pressure measurements are presented to include both systolic and diastolic values.

randomized to the ETT or exercise MPI arm ($P=0.59$). The observed 2-year MACE rate was 1.7% for ETT and 2.3% for exercise MPI. The relative hazard for MACE was 1.3 (95% CI, 0.5 to 3.5) for the exercise MPI arm compared with the ETT-only arm ($P=0.59$).

For secondary end points, the overall rate of hospitalization for chest pain was 3%. By randomization, the 2-year rate of hospitalization for chest pain symptoms was 3% for women in the ETT arm and 4% for those in the exercise MPI arm ($P=0.39$). An additional 6 women died from noncardiac causes (ETT arm, 0.5%; exercise MPI arm, 1%; $P=0.39$).

MACE-free survival was 99%, 97%, and 96%, respectively, for normal, indeterminate, and abnormal exercise ECG results ($P=0.016$), indicating that this was a group with an observed event rate lower than one that might have been predicted on the basis of pretest CAD probability or anginal symptoms. For the ECG results, the results were similar for both randomized groups and are reported combined. We then devised separate Cox models for estimation of the relative hazard for MACE based on ECG and MPI results. In the ECG model, for women with an indeterminate ECG, the hazard ratio for MACE was 3.7 (95% CI, 0.99 to 13.79; $P=0.051$), and for women with an abnormal exercise ECG, the hazard ratio was 4.5 (95% CI, 1.4 to 14.9; $P=0.012$) compared with those with a negative exercise ECG (model $\chi^2=8$, $P=0.016$). In the MPI model, MACE-free survival was 99%, 91%, and 88%, respectively, for normal, mildly abnormal, and moderate to severely abnormal scans ($P<0.0001$). For women with a mildly abnormal exercise MPI, the hazard ratio for MACE was 16.5 (95% CI, 1.5 to 182.5; $P=0.022$), and for women with a moderate to severely abnormal MPI scan, the hazard ratio was 21.8 (95% CI, 3.6 to 130.4; $P=0.001$) compared with those with a negative exercise MPI (model $\chi^2=25$, $P<0.001$). When women with a normal ECG versus normal MPI findings were compared, the 2-year primary end point rate was similar (Figure 4; ETT, 0.4%; MPI, 1.2%; $P=0.40$). For women with abnormal findings, the 2-year primary end point rate was similar (ETT, 5.1%; MPI, 13.1%; $P=0.19$).

Follow-Up Health Status Measures

By 6 months, half of enrolled women were symptom free (Figure 5). By 2 years, 60% and 65% of women randomized to the ETT and exercise MPI arms were asymptomatic, respectively ($P=0.25$). All SAQ subscales were similar by randomized groups during follow-up (data not shown). Women reported a high level of physical functioning with few angina episodes per week. As well, mild angina and some reductions in quality of life were observed similarly in both groups. Women noted a consistently high level of treatment satisfaction throughout follow-up, regardless of strategy assignment. Cumulative incidence of worsening SAQ angina frequency or stability was 5% for both the ETT and exercise MPI arms ($P=0.75$).

Downstream Procedural Use

Only 3 women had follow-up exercise ECG testing (exercise MPI=1 and ETT=2) (Figure 6). Crossover to MPI was observed in 18% of women undergoing index ETT (Figure 6). Among women randomized to ETT, the rate of crossover to MPI was 8%, 25%, and 43%, respectively, for those with normal, indeterminate, and abnormal ECG results ($P<0.0001$). Repeat MPI was reported in 9% of women randomized to exercise MPI. Among this group, repeat MPI was observed in 9%, 8%, and 15% for women with normal, mildly abnormal, and moderate to severely abnormal results ($P=0.52$).

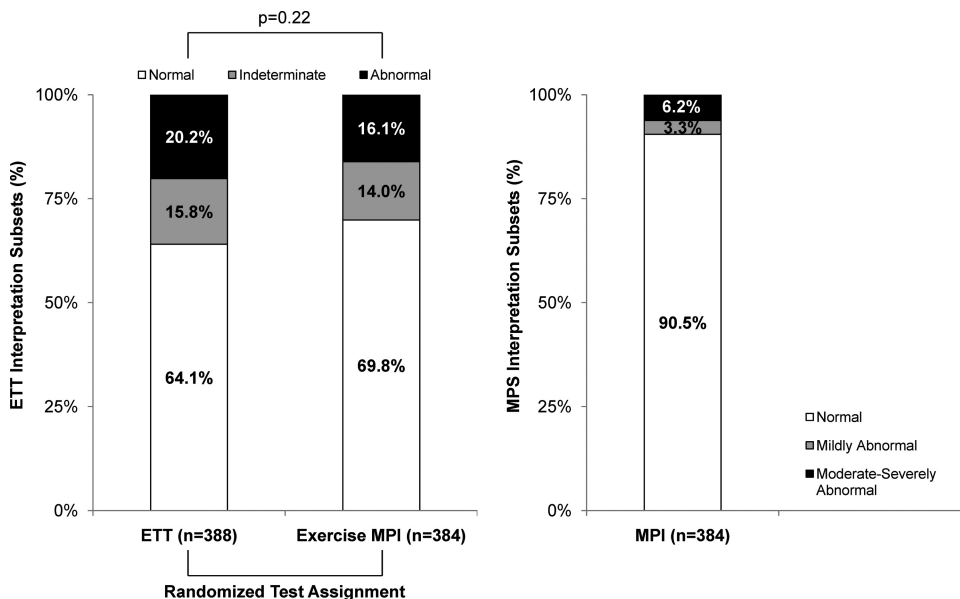


Figure 2. ECG interpretation (left) based on randomized test assignment to exercise ECG vs exercise ECG plus myocardial perfusion imaging (MPI). The figure on the right includes myocardial perfusion imaging (MPI) interpretation of stress-induced myocardial perfusion abnormalities. ETT indicates exercise treadmill test.

Overall, 6% of women who were randomized to either ETT alone or exercise MPI proceeded to coronary angiography, with nearly half of this referral to angiography occurring within 2 months of follow-up ($P=0.98$). Referral to angiography differed by randomized testing assignment; for those who underwent ETT alone, the rates were 3%, 7%, and 18%, respectively, for women with normal, indeterminate, and abnormal ECG findings ($P<0.0001$). In the exercise MPI arm, referral to angiography was 4%, 0%, and 29% in women with normal, mildly abnormal, and moderate to severely abnormal results ($P<0.0001$). Of the 10 women referred to coronary angiography with normal MPI, 6 had indeterminate or abnormal ECG findings.

Postrandomization Differences in Therapeutic Intervention

In the 6 months after randomization, changes in anti-ischemic therapy were similar by testing arm. No difference

in the use or discontinuation of nitrates, β -blockers, statins, and antidepressant therapies was observed through 2 years of follow-up ($P>0.20$). Follow-up coronary revascularization occurred in 1.0% and 2.2% of women randomized to ETT and exercise MPI, respectively ($P=0.16$). Of these, only 0.5% of women in the exercise MPI arm had an urgent revascularization after an acute coronary syndrome.

Diagnostic Testing Costs

Although index testing costs were higher for exercise MPI, downstream procedural costs were minimally higher for the ETT group ($P=0.0008$) (Table 3). During follow-up, 81% and 89% of women randomized to ETT and MPI, respectively, had no additional diagnostic testing, respectively ($P<0.0001$). Overall diagnostic costs were 48% lower for the ETT compared with the exercise MPI group ($P<0.001$).

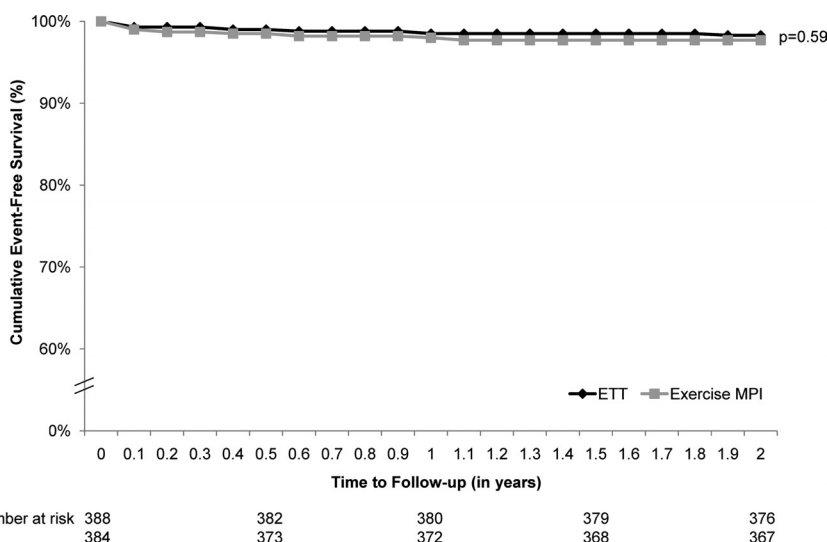


Figure 3. Kaplan-Meier major adverse cardiovascular event-free survival by randomized test assignment to an exercise treadmill test (ETT) vs exercise myocardial perfusion imaging (MPI.)

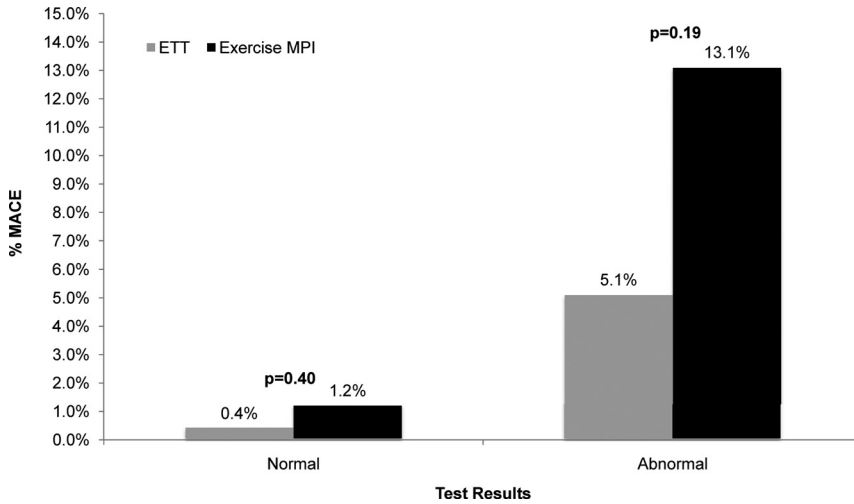


Figure 4. Differences in 2-year primary end points by randomized test assignment in patients with normal and abnormal test results. ETT indicates exercise treadmill test; MPI, myocardial perfusion imaging; and MACE, major adverse cardiovascular events.

Discussion

The principal finding of the WOMEN trial is that there was no incremental benefit of an initial diagnostic strategy of exercise MPI compared with standard ETT in symptomatic women with suspected CAD and preserved functional capacity who were able to exercise. We could not demonstrate an incremental prognostic benefit of exercise MPI in predicting clinical outcomes at 2 years compared with an ETT-only strategy. These findings represent the first randomized trial evidence comparing the effectiveness of standard treadmill exercise ECG compared with combined ETT and radionuclide imaging for women presenting for evaluation of suspected CAD. There has been a paucity of comparative effectiveness research to guide this common diagnostic decision.^{17–21} The preponderance of evidence has been derived from observational registries supporting the superiority of exercise MPI over standard ETT alone, particularly for women.^{2,22–27} As a consequence, the lack of randomized trial evidence has resulted in significant variability in utilization patterns and perhaps contributed to the frequent application of MPI approaches over the last decade.^{1,28,29}

The results of the current trial represent an important step forward in the development of prospectively derived

scientific evidence to guide clinical decision making in the use of a diagnostic procedure and to provide both clinical effectiveness and cost efficiency data to address the appropriateness for stress testing in women with suspected CAD. We demonstrated that near-term clinical outcomes were similar for exercising women randomized to the ETT compared with the exercise MPI ($P=0.59$). Thus, we failed to demonstrate the superiority of an exercise MPI compared with an ETT strategy. Despite enrolling women who were largely postmenopausal or aged ≥ 65 years, women presenting for a de novo chest pain evaluation had an observed event rate that was lower than one that might have been predicted on the basis of pretest CAD probability and anginal symptoms. Moreover, our MACE rate was lower than our a priori assumptions of a 1% rate for exercise MPI and a 3.2% rate for ETT. In a recent retrospective series of 516 patients with high exercise capacity, a similarly low cardiac event rate was reported, supporting the notion that differentiation of risk is ineffective in low-risk cohorts.³⁰ We applied the DASI as a pretesting decision node whereby patients were allowed trial entry after successful notation of ≥ 5 METs on the DASI. Such a threshold signifies that enrolled woman were similarly capable of performing activities of daily living,

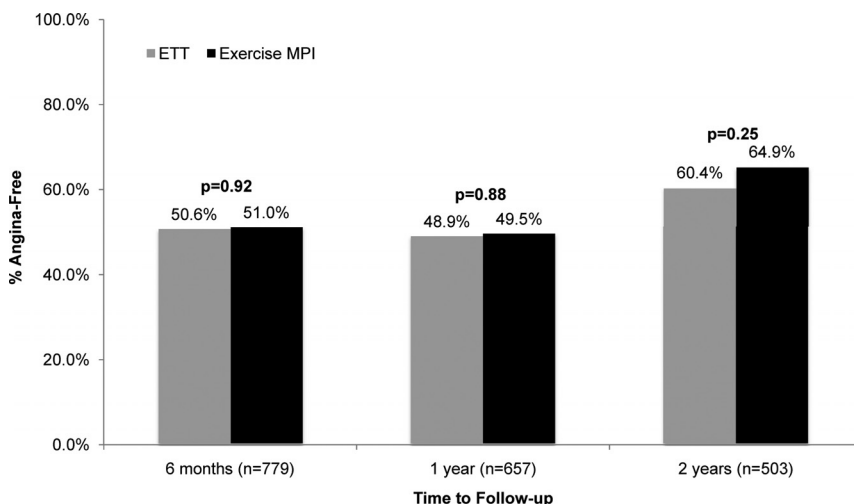


Figure 5. Angina-free status during follow-up by randomization to an exercise treadmill test (ETT) vs exercise myocardial perfusion imaging (MPI).

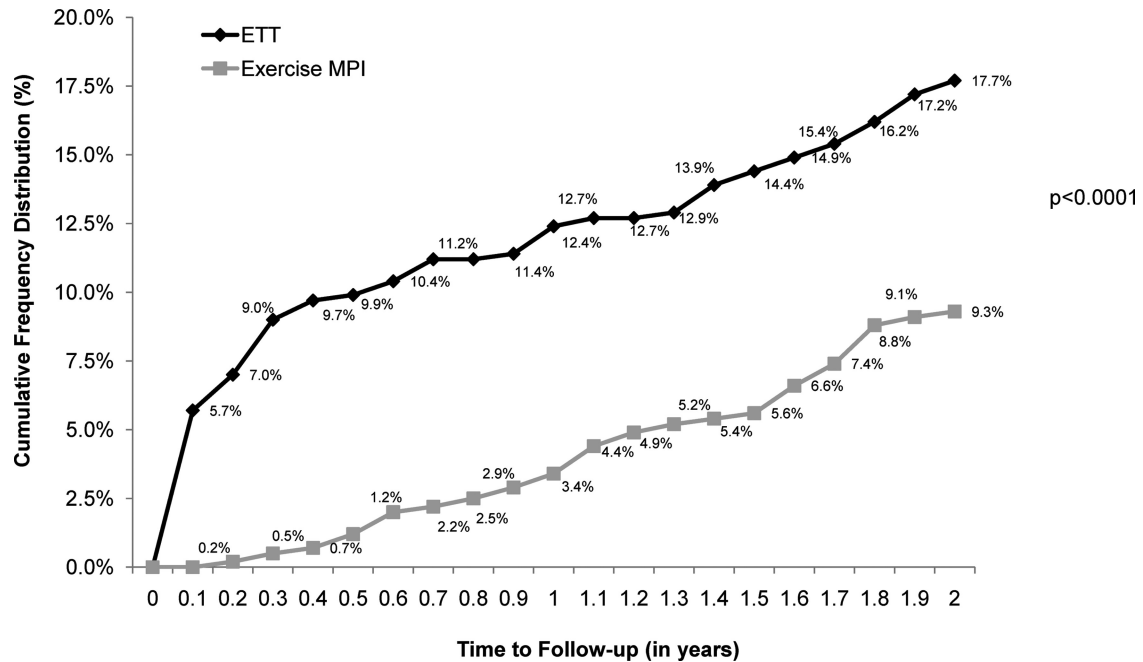


Figure 6. Cumulative frequency of crossover or repeat stress myocardial perfusion imaging (MPI) after randomization to an exercise treadmill test (ETT) vs exercise MPI.

and hence this may be an important factor in explaining the observed findings. Similar negative trial results were also reported recently in low-risk diabetics.³¹

The clinical implications of this trial results are noteworthy. For low-risk women capable of performing exercise, routine ETT without imaging appears a reasonable (and justifiable) first-line test resulting in 2-year outcomes equivalent to those achieved with exercise MPI. These results could have implications for the estimated 2 to 3 million women undergoing exercise MPI annually and would likely result in sizable cost savings within the noninvasive diagnostic evaluation (ie, 48%), leading to reductions in the societal economic burden of medical imaging and reducing unnecessary radiation exposure for a large sector of women presenting with suspected CAD. A trend toward higher overall costs with radionuclide imaging was similarly reported in a randomized trial of ETT versus stress MPI in 457 men and women.³⁰ In this report, diagnostic costs at ≈ 2 years were 9.4% higher with stress MPI compared with ETT ($P=0.062$).³²

The patients enrolled in the WOMEN trial may have included lower-risk women than are widely encountered in routine clinical practice. Accordingly, it is difficult to generalize these results to a broader population of women at higher risk who might be appropriate candidates for MPI. The hazard ratio for MACE was higher for a moderate to severely abnormal MPI (21.8) compared with the abnormal ECG (4.5), suggesting a greater ability to detect risk for MPI versus the ECG results. However, with overlapping CIs on the hazard ratio for the abnormal ECG and moderate to severe MPI, definitive statements about improved risk detection cannot be made. Our sample size estimate was based on observational database evidence.³³ The lower rate of adjudicated end points has important implications for the design of future trials that are guided by observational evidence.³³ A post hoc sample size calculation revealed power of 15%, at a 0.05 significance level, on the basis of our observed primary end point results (PASS 2008).^{34,35} Thus, our study was underpowered to reliably detect a significant difference between these 2 testing strategies.

Table 3. Diagnostic Workup Costs for Exercise ECG Compared With Single Photon Emission Computed Tomographic Myocardial Perfusion Imaging

Randomized Test Strategy	Index Testing	Follow-Up Testing	Total Costs
ETT			
Mean (SD)	\$154.28 (\$30.42)	\$179.97 (\$413.64)	\$337.80 (\$416.26)
Median (25th, 75th percentile)	\$169.86 (\$111.57, \$178.22)	\$0 (\$0, \$0)	\$174.14 (\$169.86, \$182.29)
Exercise MPI			
Mean (SD)	\$495.24 (\$8.54)	\$144.77 (\$407.75)	\$643.24 (\$411.51)
Median (25th, 75th percentile)	\$492.67 (\$87.95, \$508.68)	\$0 (\$0, \$0)	\$492.67 (\$487.95, \$508.68)
Wilcoxon <i>P</i>	<0.001	0.0008	<0.001

ETT indicates exercise treadmill test; MPI, myocardial perfusion imaging.

The conundrum frequently facing physicians who refer women to diagnostic ETT is the high rate of ECG abnormalities, which is greater than that documented with MPI or other imaging modalities (ie, ECG versus perfusion abnormalities).^{36,37} In the WOMEN trial, nearly one third of women had indeterminate or abnormal ECG findings, whereas only 9% of MPI results were abnormal. Current clinical practice patterns often rely on direct imaging strategies for women. In fact, use of MPI has been one of the fastest growing Medicare procedures.¹ However, despite this higher rate of normal findings in women randomized to exercise MPI, no differences were noted in clinical outcomes and, importantly, health status measures. Thus, despite differences in the intensity of resources expended, both strategies appeared equally effective in clinical and patient-centered outcomes.

Although there was a trend toward higher use of downstream diagnostic procedures with the ETT strategy, the upfront exercise MPI costs were nearly 3-fold higher, and this difference was not offset during 2 years of follow-up. In general, there was a low rate of follow-up testing that occurred in ≈ 1 in 10 women. Thus, the index testing costs associated with exercise MPI exceeded any rate of selective follow-up testing with the ETT strategy. The result was significant fractional diagnostic cost savings (ie, 48%) for women randomized to ETT compared with the exercise MPI arm ($P < 0.001$).

The WOMEN trial was designed as a pragmatic trial. Physicians were educated on accepted standards for ETT and MPI interpretation, but posttest management was left to the discretion of the patient's care management team. In some cases, the ECG-guided strategy served as a gatekeeper and led to selective, additional diagnostic testing, such as a crossover to MPI, with a graded downstream utilization ranging from 4% to 19% for women with normal to abnormal ECG results. The use of a noninvasive test as a gatekeeper has been frequently touted as a means to promote cost efficiency.^{38–42} Nearly one third of women with indeterminate or abnormal ECG results had MPI abnormalities, which was a rate higher than that noted for all women randomized to exercise MPI (10% abnormal). This higher rate of abnormalities supports a selective approach to testing whereby MPI would be recommended for women with abnormal ECG results or for those with exertional chest pain symptoms during exercise.

Trial Limitations

We observed few MACE during limited follow-up of 2 years likely because of the high exercise capacity of enrolled women. Longer follow-up and larger sample size are necessary to discern differences in low-risk patients. The limited number of events hampered our ability to perform traditional cost-effectiveness analysis. Selection bias was operational, with only 29% of eligible women enrolled. Detailed clinical data on unenrolled but eligible women are lacking and could help to clarify the generalizability of our trial findings to relevant female cohorts. It remains likely that the enrolled women were a biased cohort with site physicians less likely to randomize higher-

risk women. Early dropouts were surprising, given that both ETT and MPI are commonly performed diagnostic procedures.¹ We performed multiple analyses in this report, which may result in the possibility of an inflated type I error rate; many of the subset analyses were inadequately powered.

Our trial hypothesis was that test findings would guide clinical practice patterns, leading to improved patient outcomes, and, specifically, that the choice of a diagnostic procedure would affect patient outcomes. This type of trial design may be more aptly applied to therapeutic intervention trials. The optimal comparative effectiveness trial for a diagnostic test may require novel designs linking test results with targeted therapeutic outcomes with an established clinical benefit for a given patient cohort. Our trial was designed to reflect “real world” diagnostic testing practices, and we did not employ a more detailed test interpretation, including non-ECG parameters. We relied on on-site interpretation of test findings and implementation of initiated treatment decisions based on exercise findings. The lack of clinical practice guideline-accepted best practices (eg, the observed low rate of coronary angiography) may have contributed to our null findings.

Conclusion

To date, the evidence base for diagnostic testing in women with suspected CAD has been limited, with no randomized trials to guide appropriate clinical decision making in the choice of noninvasive testing strategies. The aim of the WOMEN trial was to provide comparative effectiveness data for women capable of performing exercise testing in regard to whether the addition of imaging to standard ETT provided incremental clinical benefit over index ETT alone. The results of this trial demonstrated that an initial diagnostic strategy employing ETT only resulted in 2-year outcomes similar to those obtained with exercise MPI in low-risk women. The ETT-guided strategy resulted more often in selective follow-up testing compared with exercise MPI yet provided significant diagnostic cost savings (ie, 48%). Accordingly, among women who are capable of exercise at the time of planned diagnostic testing, our data support an initial ETT-alone testing strategy compared with an initial exercise MPI testing strategy. However, because our observed event rates were lower than those that would have been otherwise predicted on the basis of symptoms and pretest CAD likelihood, we cannot be certain that we missed a potential benefit of MPI that might have been discerned in a higher-risk cohort. Accordingly, future prospective trials are needed to clarify this further. Nevertheless, both the clinical and health economic implications of this trial are potentially profound and may help to further inform clinical practice guideline development and potentially healthcare coverage decisions.

Sources of Funding

This trial was supported by an investigator-initiated grant from GE Healthcare.

Disclosures

No authors are consultants or are on the speaker's bureau for GE Healthcare. Drs Hendel and Heller served previously on an advisory board for GE Healthcare.

References

- Shaw LJ, Min JK, Hachamovitch R, Peterson ED, Hendel RC, Woodard PK, Berman DS, Douglas PS. Cardiovascular imaging research at the crossroads. *J Am Coll Cardiol Cardiovasc Imaging*. 2010;3:316–324.
- Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease. *Circulation*. 2005;111:682–696.
- Douglas PS, Chen J, Gillam L, Hendel R, Hundley WG, Masoudi F, Patel MR, Peterson E. Achieving quality in cardiovascular imaging. *J Am Coll Cardiol Cardiovasc Imaging*. 2009;2:231–240.
- Mieres JH, Shaw LJ, Hendel RC, Heller GV. The WOMEN study: what is the optimal method for ischemia evaluation in women? *J Nucl Cardiol*. 2009;16:105–112.
- Shaw LJ, Olson MB, Kip K, Kelsey SF, Johnson BD, Mark DB, Reis SE, Mankad S, Rogers WJ, Pohost GM, Arant CB, Wessel TR, Chaitman BR, Sopko G, Handberg E, Pepine CJ, Bairey Merz CN. The value of estimated functional capacity in estimating outcome. *J Am Coll Cardiol*. 2006;47:S36–S43.
- Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC. ACC/AHA 2002 guideline update for exercise testing. *J Am Coll Cardiol*. 2002;40:1531–1540.
- Spertus J. Evolving applications for patient-centered health status measures. *Circulation*. 2008;118:2103–2110.
- Spertus JA WJ, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire. *J Am Coll Cardiol*. 1995;25:333–341.
- Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. *Circulation*. 2002;106:43–49.
- Hansen CL, Goldstein RA, Akinboboye OO, Berman DS, Botvinick EH, Churchwell KB, Cooke CD, Corbett JR, Cullom SJ, Dahlberg ST, Druz RS, Ficaro EP, Galt JR, Garg RK, Germano G, Heller GV, Henzlava MJ, Hyun MC, Johnson LL, Mann A, McCallister BD Jr, Quaipe RA, Ruddy TD, Sundaram SN, Taillefer R, Ward RP, Mahmarian JJ. Myocardial perfusion and function. *J Nucl Cardiol*. 2007;14:e39–e60.
- Hendel RC, Wackers FJ, Berman DS, Ficaro E, Depuey EG, Klein L, Cerqueira M. ASNC consensus statement. *J Nucl Cardiol*. 2003;10:705–708.
- Hendel RC, Wackers FJ, Berman DS, Ficaro E, DePuey EG, Klein L, Cerqueira M. ASNC consensus statement. *J Nucl Cardiol*. 2006;13:e152–e156.
- Douglas PS, Hendel RC, Cummings JE, Dent JM, Hodgson JM, Hoffmann U, Horn RJ III, Hundley WG, Kahn CE Jr, Martin GR, Masoudi FA, Peterson ED, Rosenthal GL, Solomon H, Stillman AE, Teague SD, Thomas JD, Tilkemeier PL, Guy Weigold W. ACCF/ACR/AHA/ASE/ASNC/HRS/NASCI/RSNA/SAIP/SCAI/SCCT/SCMR 2008 health policy statement on structured reporting in cardiovascular imaging. *J Am Coll Cardiol*. 2009;53:76–90.
- Nichols KJ, Bacharach SL, Bergmann SR. ASNC imaging guidelines for nuclear cardiology procedures. *J Nucl Cardiol*. 2007;14:e61–e78.
- Shaw LJ, Marwick TH, Berman DS, Sawada S, Heller GV, Vasey C, Miller DD. Incremental cost-effectiveness of exercise echocardiography vs. SPECT imaging for the evaluation of stable chest pain. *Eur Heart J*. 2006;27:2448–2458.
- Marwick TH, Shaw L, Case C, Vasey C, Thomas JD. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. *Eur Heart J*. 2003;24:1153–1163.
- Douglas PS, Taylor A, Bild D, Bonow R, Greenland P, Lauer M, Peacock F, Udelson J. Outcomes research in cardiovascular imaging. *J Am Coll Cardiol Cardiovasc Imaging*. 2009;2:897–907.
- Lauer MS. Can the ST segment be saved? *J Nucl Cardiol*. 2005;12:622–624.
- Chen MS, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery and impact of myocardial revascularization on long-term mortality. *Circulation*. 2004;110:2851–2857.
- Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. *JAMA*. 2004;292:1462–1468.
- Gulati M, Shaw LJ, Thisted RA, Black HR, Merz CN, Arnsdorf MF. Heart rate response to exercise stress testing in asymptomatic women. *Circulation*. 2010;122:130–137.
- Berman DS, Kang X, Hayes SW, Friedman JD, Cohen I, Abidov A, Shaw LJ, Amanullah AM, Germano G, Hachamovitch R. Adenosine myocardial perfusion SPECT in women compared with men. *J Am Coll Cardiol*. 2003;41:1125–1133.
- Hachamovitch R, Berman DS, Kiat H, Bairey-Merz N, Cohen I, Cabico JA, Friedman JD, Germano G, Van Train KF, Diamond GA. Gender-related differences in clinical management after exercise nuclear testing. *J Am Coll Cardiol*. 1995;26:1457–1464.
- Amanullah AM, Berman DS, Hachamovitch R, Kiat H, Kang X, Friedman JD. Identification of severe or extensive coronary artery disease in women by adenosine technetium-99m sestamibi SPECT. *Am J Cardiol*. 1997;80:132–137.
- Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion SPECT for the prediction of cardiac death. *Circulation*. 1998;97:535–543.
- Marwick TH, Shaw LJ, Lauer MS, Kesler K, Hachamovitch R, Heller GV, Travin MI, Borges-Neto S, Berman DS, Miller DD. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. *Am J Med*. 1999;106:172–178.
- Gibbons RJ, Hodge DO, Berman DS, Akinboboye OO, Heo J, Hachamovitch R, Bailey KR, Iskandrian AE. Long-term outcome of patients with intermediate-risk exercise electrocardiograms who do not have myocardial perfusion defects on radionuclide imaging. *Circulation*. 1999;100:2140–2145.
- Lucas FL, DeLorenzo MA, Siewers AE, Wennberg DE. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the US. *Circulation*. 2006;113:374–379.
- Lucas FL, Sirovich BE, Gallagher PM, Siewers AE, Wennberg DE. Variation in cardiologists' propensity to test and treat. *Circ Cardiovasc Qual Outcomes*. 2010;3:253–260.
- Marshall AJ, Hutchings F, James AJ, Kelion AD. Prognostic value of a nine-minute treadmill test in patients undergoing myocardial perfusion scintigraphy. *Am J Cardiol*. 2010;106:1423–1428.
- Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Heller GV, Iskandrian AE, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes. *JAMA*. 2009;301:1547–1555.
- Sabharwal NK, Stoykova B, Taneja AK, Lahiri A. A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD. *J Nucl Cardiol*. 2007;14:174–186.
- Shah BR, Drozda J, Peterson ED. Leveraging observational registries to inform comparative effectiveness research. *Am Heart J*. 2010;160:8–15.
- Lakatos E. Designing complex group sequential survival trials. *Stat Med*. 2002;21:1969–1989.
- Lakatos E. Sample sizes based on the log-rank statistic in complex clinical trials. *Biometrics*. 1988;44:229–241.
- Shaw LJ, Vasey C, Sawada S, Rimmerman C, Marwick TH. Impact of gender on risk stratification by exercise and dobutamine stress echocardiography. *Eur Heart J*. 2005;26:447–456.
- Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography. *J Am Coll Cardiol*. 2007;49:227–237.
- Shaw LJ, Hachamovitch R, Berman DS, Marwick TH, Lauer MS, Heller GV, Iskandrian AE, Kesler KL, Travin MI, Lewin HC, Hendel RC, Borges-Neto S, Miller DD. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients. *J Am Coll Cardiol*. 1999;33:661–669.
- Shaw LJ, Heller GV, Travin MI, Lauer M, Marwick T, Hachamovitch R, Berman DS, Miller DD. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. *J Nucl Cardiol*. 1999;6:559–569.
- van der Wall EE, Siebelink HM, Bax JJ, Schalij MJ. Cardiac magnetic resonance imaging: gatekeeper in suspected CAD? *Int J Cardiovasc Imaging*. 2011;27:123–126.

41. Budoff MJ, Karwasky R, Ahmadi N, Nasserian C, Pratt F, Stephens J, Chang WW, Flores FR, Rizzo JA, Gunnarsson CL, McKay CR. Cost-effectiveness of multidetector computed tomography compared with myocardial perfusion imaging as gatekeeper to invasive coronary angiography in asymptomatic firefighters with positive treadmill tests. *J Cardiovasc Comput Tomogr*. 2009;3:323–330.
42. Yao SS, Chaudhry FA. Assessment of myocardial viability. *Future Cardiol*. 2008;4:443–447.

CLINICAL PERSPECTIVE

There is a paucity of prospective, randomized trials as well as a compelling need for higher levels of scientific evidence, including targeted, prospective comparative effectiveness research, to more rigorously address the outpatient diagnostic evaluation of patients with suspected coronary artery disease. In particular, the evaluation of women with suspected coronary artery disease remains a conundrum because of their atypical symptom presentation, which often results in varied diagnostic practice patterns. The What Is the Optimal Method for Ischemia Evaluation in Women trial was designed to compare the effectiveness of the standard exercise tolerance test (ETT) versus exercise myocardial perfusion imaging (MPI) for predicting 2-year event-free survival for women with suspected coronary artery disease at intermediate pretest coronary artery disease likelihood who are capable of performing exercise. A total of 824 women were randomized to a standard ETT or exercise MPI. At 2 years, there was no difference in major adverse cardiovascular events (ETT, 98.0%; MPI, 97.7%; $P=0.59$). Compared with ETT alone, index testing costs were higher for the exercise MPI group ($P<0.001$), whereas downstream procedural costs were slightly lower ($P=0.008$). Overall, the cumulative diagnostic cost saving was 48% for the ETT compared with the exercise MPI group ($P<0.001$). In conclusion, in low-risk, symptomatic women capable of exercise, a nonimaging strategy employing standard ETT was as effective in predicting clinical outcomes and more cost efficient than a strategy of initial exercise MPI.

Go to <http://cme.ahajournals.org> to take the CME quiz for this article.