REVIEW ARTICLE

Utility of Stress Testing and Coronary Calcification Measurement for Detection of Coronary Artery Disease in Women

Khurram Nasir, MD, MPH; Rita F. Redberg, MD, MSc; Matthew J. Budoff, MD; Elaine Hui, MBBS; Wendy S. Post, MD, MS; Roger S. Blumenthal, MD

Accurate and safe diagnostic testing provides the crucial link between detection and optimal management of coronary artery disease (CAD). Noninvasive diagnostic testing for CAD may be less accurate in women than in men. Many noninvasive diagnostic modalities are available for this purpose. An exercise tolerance test provides an assessment of functional capacity and has the advantages of wide availability and low initial cost. However, exercise echocardiography may be the most cost-effective method for the initial assessment of coronary artery disease in intermediate-risk women owing to its higher sensitivity and specificity. Recent studies with electron-beam computed tomography reveal that women with no coronary calcification are very unlikely to have obstructive CAD. In symptomatic women with an intermediate likelihood of CAD, either an exercise treadmill test or exercise echocardiography is appropriate for initial screening and can provide useful prognostic information. Alternatively, an electron-beam computed tomographic scan with a 0 calcium score may spare many women with atypical chest pain or equivocal findings on an exercise tolerance test from undergoing more expensive stress imaging studies or coronary angiography. For high-risk symptomatic women, a more aggressive approach involving coronary angiography appears to be the preferred initial diagnostic strategy.

Arch Intern Med. 2004;164:1610-1620

Noninvasive detection of coronary artery disease (CAD) in women is challenging but important because approximately 40% of deaths in American women are due to cardiovascular disease. The detection of CAD is potentially problematic in women for a variety of reasons.[1] Middle-aged women have a lower prevalence of manifest CAD than men and are more likely to have atypical symptoms. They are less likely to be promptly evaluated than men, which may also lead to delays in diagnostic testing.[2] Since women are often older at the time of diagnosis, age-related comorbidities and reduced exercise capacity contribute to a lower accuracy of exercise tests in women than in men. Hormonal and anatomic differences in women may alter the electrocardiography (ECG) or imaging results compared with those obtained in men. Therefore, optimal diagnostic tests for women may differ from those used for men.

When reviewing the literature on stress testing, one must note that sensitivity and specificity may vary from one study to another owing to different pretest probabilities of significant CAD or different reference standards (>50% vs >70% coronary obstruction in 1 or ≥2 vessels vs simply a positive radionuclide finding). In the present review, we discuss the efficacy of various noninvasive tests currently available for the diagnosis of CAD as well as methods to determine the risk of future cardiovascular events in women. Most of the women included in the following studies of stress testing were evaluated for the presence of obstructive CAD because they had a history of chest pain or dyspnea.

From the Divisions of Cardiology, Johns Hopkins Hospital, Baltimore, Md (Drs Nasir, Post, and Blumenthal), University of California San Francisco School of Medicine, San Francisco (Dr Redberg), and University of California Los Angeles School of Medicine, Los Angeles (Dr Budoff); and Guy's, King's, and St Thomas's School of Medicine, King's College, London, England (Dr Hui). *The authors have no relevant financial interest in this article.*

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

EXERCISE ECG

Exercise treadmill testing (ETT) is often used as the initial method for noninvasive assessment of CAD owing to its wide availability and relatively low cost. The 2002 joint report from the American College of Cardiology and the American Heart Association Task Force on exercise testing (ACC/AHA)[3] indicates that an exercise ECG is most useful as a diagnostic test in patients with an intermediate (25%-75%) pretest probability of CAD. Abnormal exercise stress test results in these patients are more likely to be true positives than in patients with lower pretest probabilities. The 2001 ACC/AHA guidelines for management of chronic stable angina also recommend that a standard ETT be used for diagnosis and risk stratification in patients who have not undergone revascularization if they have chest pain and an intermediate probability of CAD, provided that they (1) are able to exercise; (2) have a normal resting ECG; and (3) have no unstable symptoms that warrant urgent angiography. The guidelines acknowledge that the accuracy of ETT is lower in women.[4]

DUKE TREADMILL SCORE

A number of investigators have proposed methods to improve the accuracy of the standard ETT. Shaw et al[5] studied 2758 symptomatic patients (30% women) who underwent ETT and cardiac catheterization to evaluate the efficacy of using the Duke Treadmill Score (DTS) for risk stratification. The DTS was calculated as follows: DTS = exercise time − (5 × exercise-induced ST-segment deviation) − (4 × exercise angina index), where exercise time is measured in minutes of Bruce protocol; ST-segment depression is the largest stress-induced downward displacement; and angina index is assigned as follows: 0 = none, 1 = nonlimiting, and 2 = exercise-limiting. When compared with angiographic findings, DTS was found to be a reliable method of stratifying patients. In the study population, the odds of severe CAD (3-vessel coronary disease or ≥75% left main disease) was 4-fold and 26-fold higher for individuals with moderate-risk and high-risk DTSs, respectively, compared with those with low DTSs. The authors conclude that low-risk patients (DTS ≥+5) might be managed without further testing, whereas high-risk patients (DTS ≤−11) should be considered for cardiac catheterization, possible revascularization, and more aggressive risk-factor modification. Of the remaining moderate-risk patients (DTS between −10 and +4), use of an imaging modality is proposed for further risk stratification.[5]

In a study of 976 symptomatic women (mean age, 51 years), Alexander et al[6] demonstrated that the DTS could effectively stratify women into diagnostic and prognostic risk categories. In another study by Shaw et al,[7] 3620 symptomatic patients, stratified by DTS (42% women; mean age, 63 years), underwent exercise myocardial perfusion imaging (MPI) and were observed for 2.5 years for the development of subsequent cardiovascular events. The cardiac mortality rate was very low (0.3%-0.4% per year) among patients with a low DTS. The authors recommended that patients with a normal baseline ECG could undergo an exercise test initially without imaging and that further testing could be reserved for those patients with intermediate-risk or high-risk test results, consistent with the clinical guidelines published by the AHA and ACC.[3,4]

Although the DTS has been recommended by the AHA/ACC task force, its prognostic value in elderly persons is not as well established. Kwok et al[8] describe the results of a 7-year follow-up study of 247 elderly persons (mean age, 77 years; 44% women) and 2304 younger persons (mean age, 60 years; 42% women). These researchers found that although the DTS predicted cardiac outcomes in younger patients, it had a limited prognostic power in patients 75 years or older, which suggests that it has less of a role in the assessment of elderly patients. Clearly, however, more sex-specific studies are needed to confirm the role of the DTS in elderly women.

SEX DIFFERENCES IN ETT ACCURACY

The presence of greater than 2 mm of ST-segment depression has been shown in some studies to be equally predictive of cardiac death in women and men.[9] However, several older studies suggest that exercise-induced ST-segment changes are less accurate in women than in men and have a higher false-positive rate or lower positive predictive value.[10] Bayesian theory may explain some but not all of the higher false-positive rate in women because of a lower prevalence rate of CAD in the populations undergoing testing. In studies in which the prevalence of CAD was similar in men and women, there was still a lower specificity of ETT in women (64%-68%) than in men (74%-89%).[11,12] Other studies in women have also reported specificities in the same range (55%-75%).[13-15] However, in a follow-up of 3094 patients (men and women) who had ETT and coronary angiography for the evaluation of suspected CAD from 1969 to 1984, 1930 of them (20% women) were found to have CAD defined as stenosis of 75% or more.[16] In this study, there was no sex difference in the specificity (86% for women vs 83% for men),[16] while the sensitivity was different (57% for women vs 72% for men) ($P = .05$). Nevertheless, meta-analyses have shown that the overall sensitivity and specificity of ST-segment depression on ETTs is lower in women.[17]

IMPACT OF REFERRAL BIAS

By definition, true specificity should represent the percentage of negative responders in a population known to be free of disease confirmed by coronary angiography as the reference standard.[18] Unfortunately, such a design is difficult to achieve because it is rare for an individual with a negative stress test result to undergo a coronary angiogram. Thus, in stress testing, the test sensitivity and specificity are affected by referral bias (ie, the preferential selection of patients with positive exercise ECG results to undergo the confirmatory tests such as coronary angiography),[16] which results in an overestimation of the sensitivity and underestimation of the specificity with the ETT.[19]

A retrospective analysis of clinical and exercise ECG test data in 4467 patients (27% women) referred for the

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

evaluation of the presence of obstructive CAD in the exercise laboratories compared the accuracy of exercise ECG in biased and unbiased populations with possible coronary heart disease.[20] Within the cohort of women, the biased group represented a subset of patients who underwent coronary angiography (284 women), and the unbiased group was the entire cohort of 1643 women. In the unbiased group the accuracy of a positive ETT result was assessed with a method that used disease probability (derived with a logistic algorithm) rather than angiography results. Patients with a history of cardiovascular disease, those taking digitalis, and those with a noninterpretable ECG were excluded. The unbiased group had a higher mean ± SD specificity (89% ± 2% vs 73% ± 3%) and a lower mean ± SD sensitivity (33% ± 4% vs 47% ± 5%) than the biased group. These differences reflect the effect of posttest referral bias. Of note, the sensitivity and specificity were still significantly greater in men than in women in both groups.[20] In contrast, a single large angiographic study, the Coronary Artery Surgery Study,[21] matched subjects for age, prevalence, and severity of coronary disease and showed no significant difference in sensitivity between women and men (76% vs 78%).

Two studies using MPI as the reference point have reported better-than-expected specificities in women. Tavel[22] found no difference in stress ECG specificity between men (89%) and women (93%); of note, most of the study participants had a history of CAD. A Mayo Clinic study[23] reported that women had a higher specificity (78% vs 52%; $P<.001$) and a lower sensitivity (30% vs 42% $P<.001$) than men. However, interpretation of these studies is limited by the fact that they used MPI as the reference standard rather than the usual clinical and angiographic evaluation. Myocardial perfusion imaging may not always be accurate or reproducible enough to be an optimal reference standard.

POSSIBLE REASONS FOR THE APPARENT SEX DIFFERENCE

The vasodilator effect and the digitalislike structure of estrogen have been proposed as explanations for the lower accuracy of traditional ST-segment depression criteria in women than in men.[24] Other proposed mechanisms of the sex difference in stress test results include inappropriate catecholamine response to exercise, a higher incidence of mitral valve prolapse in women, a lower prevalence of obstructive multivessel disease, a higher incidence of underlying repolarization abnormalities, and the difference in the chest wall anatomy of women.[7,25,26]

ADDITIONAL CRITERIA TO IMPROVE THE INTERPRETATION OF ECG IN WOMEN

Integrating information from hemodynamic and functional parameters and ST-segment changes can improve the diagnostic and prognostic predictive accuracy of exercise ECG testing in women with suspected CAD. For instance, the degree of ST-segment displacement in relation to the increase in heart rate (HR) during exercise (ΔST/HR index),[27] a ΔST-segment depression of 0.5 mm or more and ΔR-wave amplitude depression of 1 mm or more in the same lead of any of the 12 leads,[28] QT dispersion,[29] and abnormal HR recovery[30] appear to enhance the accuracy for detecting the presence and severity of CAD in women. In a population involving 9454 patients who were specifically referred for stress ECG without imaging, Nishime et al[31] reported that HR recovery predicted risk above and beyond that estimated by the DTS. These studies indicate that additional criteria that can be obtained from the standard ETT support the ACC/AHA recommendation for exercise ECG to be the initial evaluation for women with low to intermediate likelihood for CAD and normal resting ECG (**Table 1**).[32]

STRESS MPI

Stress MPI with thallium Tl 201 (hereinafter "Tl 201") or technetium Tc 99m (hereinafter "Tc 99m") can provide incremental diagnostic and prognostic value in women above that provided by standard ETT.[33] A recent study of 7163 consecutive adults (mean age, 60 years; 25% women) demonstrated that myocardial perfusion defects detected by Tl 201 single-photon emission computed tomography (SPECT) is predictive of long-term all-cause mortality.[34] Pancholy et al[33] showed that SPECT added independent and incremental prognostic information to clinical, exercise, and coronary angiographic results in 212 women (using angiography as a reference) observed for 40 months, and the women with a large thallium abnormality (≥15% of the myocardium) had significantly worse event-free survival rates than women with no or small abnormalities.

Planar imaging and SPECT with Tl 201 have been associated with higher false-positive rates in some studies of women. This may be attributable to image attenuation artifacts predominantly caused by overlying breast tissue, to the smaller left ventricular chamber size in women, and to obesity.[35-37] Although breast attenuation with Tl 201 affects 8% to 30% of the images,[38] experienced readers usually can distinguish these artifacts from perfusion abnormalities secondary to inducible ischemia or myocardial scar.[37] In the meta-analysis by Kwok et al,[17] the exercise thallium test had a weighted mean sensitivity and specificity of 78% and 64%, respectively, lower than ETT alone in women. Nevertheless, the specificity was only 68% despite attempts at breast attenuation correction. Another meta-analysis, by Fleischmann et al,[39] reported similar diagnostic ability of stress MPI in identifying obstructive CAD (sensitivity, 87%; specificity, 64%), but the results were not sex-specific.

Newer radiotracers of Tc 99m compounds such as Tc 99m sestamibi and Tc 99m tetrofosmin have higher photon energy, which leads to less photon scatter and attenuation than with Tl 201 and may overcome some of the problems with soft tissue artifacts and obesity.[38,40] The diagnostic accuracy of Tc 99m MIBI SPECT appears similar in men and women when posttest selection bias is corrected.[41] There was no significant difference in sensitivity (87% vs 88%) or in specificity (91% vs 96%) in men and women, respectively.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

Table 1. Characteristics of Selected Major Studies Using Exercise Electrocardiography for Diagnosis of Coronary Artery Disease in Women

Source	Exercise Test(s)	No. of Women (% of Total No. Studied)	Prior CAD	Mean Age, y	Reference Standard*	Sensitivity	Specificity	PPV	NPV
Sketch et al,[10] 1975	ECG	56 (22)	–	50	a≥50%	NA	NA	0.67	0.15
Barolsky et al,[11] 1979	ECG†	92 (52)	–	50	a≥50%	0.60	0.68	NA	NA
Weiner et al,[12] 1979	ECG	580 (28)	+	NA	a≥70%	0.76	0.64	0.46	NA
Guiteras et al,[13] 1982	ECG	112 (100)	–	49	a≥70%	0.79	0.66	0.77	NA
Hlatky et al,[16] 1984	ECG	613 (27)	+	53	a≥70%	0.57	0.86	NA	NA
Hung et al,[14] 1984	ECG, Thal	92 (100)	–	51	a≥70%	0.75	0.59	NA	NA
Pratt et al,[15] 1989	ECG	200 (100)		51	a≥70%	0.69	0.56	NA	NA
Tavel,[18] 1992	ECG	228 (34)	+	62	Thal	NA	0.93	NA	NA
Morise and Diamond,[20] 1995									
Biased group	ECG	284 (100)	–	53	a≥50%	0.47	0.73	0.56	0.73
Unbiased group	ECG	1643 (37)	–	53	a≥50%	0.33	0.89	0.53	0.77
Okin et al,[27] 1995	ECG	91 (27)	+	NA	a≥50%	0.51	0.89	NA	NA
	ECG-ST/HR‡	91 (27)	+	NA	a≥50%	0.84	0.96	NA	NA
Marwick et al,[25] 1995	ECG	161 (100)	–	60	a≥50%	0.77	0.56	NA	NA
	Echo	161 (100)		60	a≥50%	0.80	0.81	0.71	0.87
Stoletniy et al,[29] 1997	ECG	64 (100)	NA	54	a≥50%	0.55	0.63	NA	NA
	ECG-QTD§	64 (100)	NA	54	a≥50%	0.70	0.95	NA	NA
Cheng et al,[28] 1999	ECG-ΔRdep§	74 (30)	–	60	a≥70%	0.76	0.83	0.91	NA
Miller et al,[23] 2001	ECG	205 (20)	–	60	CASS‖	0.53	0.69	0.88	0.50
	ECG	3213 (37)	–	60	MPI	0.30	0.82	0.34	0.78

Abbreviations: CAD, coronary artery disease; CASS, Coronary Artery Surgery Study criteria; ECG, electrocardiography; Echo, echocardiography; MPI, myocardial perfusion imaging; NA, results not available; NPV, negative predictive value; PPV, positive predictive value; QTD, QT dispersion; ΔRdep, R-wave changes; ST/HR, ST-segment depression/heart rate; Thal, thallium-201 perfusion imaging.

*Coronary angiography (a), with positive results defined as the percentage of narrowing of 1 or more coronary vessel(s).

†ECG positive results defined as ≥1 mm horizontal or downsloping ST-segment depression, unless specified.

‡Used as diagnostic criterion.

§Used as supplementary diagnostic criterion.

‖CASS criteria: stenosis ≥50% for left main or ≥70% for left anterior descending, left circumflex, or right coronary artery.

Taillefer et al,[42] in a prospective study of 115 women, compared the ability of Tl 201 and Tc 99m MIBI SPECT to detect CAD. They found that Tc 99m sestamibi SPECT perfusion and Tl 201 SPECT had a similar sensitivity (80% vs 84%, $P=.48$); however, Tc 99m sestamibi SPECT perfusions had a higher specificity (82% vs 59%, $P=.01$) for detecting stenosis of 70% or more.[42]

Exercise Tc 99m sestamibi perfusion imaging may provide greater prognostic value in women than in men.[43-45] The Economics of Noninvasive Diagnosis (END) Study Group[43] observed for a mean of 2.4 years 3402 symptomatic women who underwent MPI (mean ± SD age, 66 ± 11years). The investigators found that the number of abnormal territories in the 3 main coronary arteries remained the strongest correlate of mortality after adjustment for exercise variables. Boyne et al[46] showed that patients with abnormal scans have an approximately 7-fold increase in combined cardiac death and nonfatal infarction (5.4% per year in abnormal scans vs 0.8% per year in normal scans). Giri et al,[47] in a large cohort of diabetic (n=929) and nondiabetic women (n=3826) observed prospectively for a mean ± SD of 2.5 ± 1.5 years, found that SPECT MPI independently predicted cardiac death alone ($P=.007$). Hachamovitch et al[44,45] analyzed 3008 consecutive patients (35% women) who underwent exercise dual-isotope SPECT and found that this technique yielded incremental prognostic value and enhanced risk stratification in a cost-effective manner in both women and men with intermediate to high risk of prescan likelihood of CAD as determined by normal resting ECGs. However, the use of MPI as a routine first-line test in all women may not be practical owing to availability and cost. Women at low to moderate risk with a normal baseline ECG can probably undergo an exercise stress ECG alone as the initial diagnostic test.

In a recent study,[48] 2408 patients (48% women; mean age, 53 years) were randomly assigned to receive either the usual emergency department evaluation (n=1260) or the usual evaluation supplemented with results from acute resting MPI using SPECT. The results were interpreted in real time by local staff physicians and were provided to the emergency department physician for incorporation into clinical decision-making. Among patients with acute myocardial infarction and unstable angina, there were no differences in the hospitalization by the above strategies. However, among patients without acute cardiac ischemia (n=2146), hospitalization was 52% with usual care vs 42% with SPECT-enhanced care (relative risk [RR], 0.84; 95% confidence interval [CI], 0.77-0.92). In other words, the use of SPECT reduced unnecessary hospitalizations among patients without acute ischemia and did not reduce appropriate admission for patients with acute ischemia.[48] Recently, the American Society of Nuclear Cardiology,[49] in their consensus paper, stated that exercise stress radionuclide testing has higher diagnostic accuracy than exercise ECG in the diagnosis of CAD in women and is recommended for

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

Table 2. Weighted Mean Sensitivities and Specificities for Exercise Tests in Women*

Exercise Test	No. of Studies	No. of Women	Sensitivity, %		Specificity, %	
			Mean Weighted	95% CI	Mean Weighted	95% CI
Echo	3	296	86	75-96	79	72-86
Thallium imaging	5	842	78	72-83	64	51-77
ECG	19	3721	61	54-68	70	64-75

Abbreviations: CI, confidence interval; ECG, electrocardiography; Echo, echocardiography.
*Adapted from Kwok et al.[17]

the diagnosis of CAD in women with an intermediate to high pretest likelihood of CAD.

EXERCISE STRESS ECHOCARDIOGRAPHY

Exercise stress echocardiography can also provide incremental prognostic and diagnostic information in the noninvasive assessment of CAD risk.[17] Echocardiography combined with exercise or pharmacologic (dobutamine, dipyridamole, or adenosine) stress testing is widely used in the noninvasive assessment of CAD. Its capability to assess multiple parameters including global and regional ventricular function, chamber size, wall thickness, and valvular function renders echocardiography valuable for diagnosing CAD and other types of cardiovascular disease in women. A recent study[50] assessed 5798 consecutive patients (42% women; mean ± SD age, 62 ± 12 years) who underwent exercise echocardiography for evaluation of known or suspected CAD. Major cardiac events, including cardiac death and nonfatal myocardial infarction, occurred in 3% of women. The echocardiographic data provided incremental information in predicting cardiac events for women ($P = .046$). By multivariate analysis, exercise ECG and exercise echocardiographic predictors of cardiac events in men and women were workload and exercise wall motion score index. There was no significant interaction effect of rest echocardiography ($P = .79$), exercise ECG ($P = .38$), or exercise echocardiography ($P = .67$) with sex. Although cardiac events occurred more frequently in men, the incremental prognostic value of exercise echocardiography was comparable in both sexes.[50]

In studies of exercise echocardiography involving 384 women, the reported overall sensitivities ranged from 79% to 88%, while the specificities ranged from 81% to 86%.[19,51-53] The sensitivity was maintained for the subsets of women with single-vessel disease (88%) and with atypical chest pain (84%). The summarized positive predictive value, negative predictive value, and overall accuracy, weighted for sample size, were 72%, 84%, and 72%, respectively.[54] Studies using angiography as an end point have shown that stress echocardiography is superior in the detection of CAD and is somewhat better at stratifying women with intermediate pretest probability than standard ECG stress testing.[52,53] In a meta-analysis of 21 studies (N = 4113 women) published between 1966 and 1995, Kwok et al[17] looked at the ability to detect CAD in women using exercise ECG (19 studies, 3721 women), exercise Tl 201 imaging (5 studies, 842 women) and exercise echocardiography (3 studies, 296 women). Exercise ECG had a weighted mean sensitivity of 61% and a specificity of 70%. Exercise echocardiography had the highest sensitivity and specificity of 86% and 79%, respectively (**Table 2**). However, the available data are still limited owing to relatively small sample sizes and referral bias. In fact, the true unbiased sensitivity of stress echocardiography may be as low as 42%, while the specificity is reasonably good at 83%.[55]

In summary, exercise stress echocardiography is often helpful in providing diagnostic information in women presenting with chest pain and in those who have a baseline ECG abnormalities other than left bundle branch block. However, in women with a normal baseline ECG, an exercise ECG is a reasonable initial noninvasive test in women at low to intermediate risk because it has a high negative predictive value and lower cost vs stress MPI studies.[56] Nevertheless, many cardiologists prefer exercise stress echocardiography as the initial diagnostic test in women (even in the presence of a normal baseline ECG), because it allows evaluation of ventricular function at rest and stress, and it also provides an estimate of the severity, extent, and location of myocardial ischemia.

PHARMACOLOGIC STRESS TESTING

Pharmacologic stress testing such as dobutamine stress echocardiography (DSE) is an alternative to exercise stress testing in persons who cannot exercise adequately. Other studies have used a pharmacologic stress with an imaging method such as echocardiography or MPI.[56] The pharmacologic agent may be a vasodilator such as dipyridamole or adenosine or an inotrope such as dobutamine. As part of the Women's Ischemia Syndrome Evaluation (WISE) study,[57] DSE was assessed in low-risk symptomatic women (n = 92; mean age, 57.5 years) without a history of CAD: 14 women (15%) had abnormal ventricular wall motion during DSE, while in the same cohort of women, 25 (27%) had 50% or greater coronary stenosis. Dobutamine stress echocardiography had an overall sensitivity of 40%, and for detection of multivessel stenosis it was 60%. When women with inadequate HR response were excluded, the overall sensitivity was 50%, whereas it increased to 82% for detection of multivessel stenosis. This is similar to the findings in predominantly male cohort studies.[57]

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

Another study showed DSE findings to be normal in 54 of the 67 women with less than 50% coronary narrowing, yielding a specificity of 81%.[58] Although DSE reliably detects multivessel stenosis in women with suspected CAD, it may be less sensitive in detecting women with a low risk for inducible myocardial ischemia of sufficient severity to cause a wall motion abnormality. In addition, it is of limited value in women unable to achieve maximal age-predicted HR, sometimes as a consequence of premature termination of DSE owing to chest pain, dyspnea, and/or other cardiovascular symptoms.[58,59] This occurred in about 15% of all patients in the WISE study and in a study of more than 3000 patients undergoing DSE.[59]

A review of 9 studies of DSE found that the sensitivity ranged from 76% to 93%, with a specificity of 43% to 94%.[53] One study[60] evaluated the use of transesophageal DSE, which gave a higher specificity (100%) than ETT (68%) and thallium scintigraphy (80%) ($P<.001$), although all 3 tests had similar sensitivities for detection of CAD. Similar findings were cited in Ho et al[57] with a relatively lower specificity for exercise ECG testing. This may be partly explained by the fact that only 59% of the patients undergoing stress ECG attained more than 85% of maximum predicted HR, relating to the limited exercise tolerance in older women with other comorbidities.

A review of dobutamine stress MPI (DSMPI) looked at 20 studies with a total of 1014 patients; DSMPI was more sensitive, but less specific, than DSE. Patients with normal DSMPI findings had an annual hard event rate of less than 1%.[61] While the overall diagnostic accuracy of pharmacologic perfusion imaging is similar to that of exercise perfusion imaging, the latter technique provides prognostic information unavailable from the pharmacologic testing.[62,63] For example, an inability to walk for 6 minutes or longer on a Bruce protocol is by itself associated with an increased coronary heart disease event rate. Recently, Kim et al[63] reported that maximum sensitivity could be obtained by using a vasodilator combined with SPECT imaging, while maximum specificity was found in studies using a vasodilator with echocardiography. The best sensitivity/specificity combination appeared to be obtained with DSE. The mean sensitivity for DSE in women in this analysis was 76% (range, 69%-82%) with a specificity of 86% (range, 80%-91%).

INCREMENTAL DIAGNOSTIC VALUE OF STRESS ECHOCARDIOGRAPHY OVER ETT

To determine the additional prognostic value of exercise stress echocardiography in the presence of either a normal or abnormal ETT finding, a recent study[64] examined the outcomes of 1874 patients (mean±SD age, 64±10 years; 36% women) with known or suspected CAD who had at least fair exercise capacity (≥5 metabolic equivalents for women) but abnormal exercise echocardiograms and analyzed the potential association between clinical, exercise, and echocardiographic variables and subsequent cardiac events. An increase or no change in left ventricular end-systolic size in response to exercise was an independent predictor of cardiac death or nonfatal myocardial infarction (RR, 1.61; 95% CI, 1.1-2.5).[64] The percentage of left ventricular segments that were markedly abnormal (severely hypokinetic or worse) immediately after exercise added incremental information to clinical and ECG data. In another study, Mahenthiran et al[65] evaluated 95 patients (mean±SD age, 61±12 years; 47% women) with markedly abnormal ETT results (≥2-mm horizontal ST depression at peak stress) and stratified them according to results of the stress echocardiography. Patients with an abnormal stress echocardiogram had a significantly higher rate of cardiac events than individuals with normal stress test results (38% vs 4%; $P=.003$) during 2.6 years of follow-up. Incremental prognostic values of stress echocardiography to ETT findings have also been observed in higher-risk populations of diabetic[66] and hypertensive[67] women.

Recently, Palinkas et al[68] hypothesized that ST-segment depression on ETT may be a better marker of endothelial dysfunction ($P=.02$) than of obstructive CAD with 50% or greater stenosis ($P=.13$); on the other hand, angiographically documented CAD was predicted by the presence of stress-induced wall-motion abnormalities ($P<.001$). This might account for the previous findings that wall-motion abnormalities and ST changes may have additive, incremental prognostic value in risk stratification, possibly indicating that the 2 markers represent different physiologic variables. The authors concluded that "echocardiographic positivity is unrelated to endothelial dysfunction, while electrocardiographic positivity is an inaccurate predictor of coronary stenosis. An integration of ECG and functional markers is warranted in the stress-testing lab."[68]

ELECTRON-BEAM COMPUTED TOMOGRAPHY

The ACC/AHA/American College of Physicians–American Society of Internal Medicine guidelines for the management of chronic stable angina included electron-beam computed tomography (EBCT) as a potential modality to diagnose coronary atherosclerosis.[69] It allows detection and quantification of the amount of coronary artery calcium (CAC), which is a marker of coronary atherosclerosis. Shaw et al[70] recently reported that coronary calcium scores provide incremental prognostic information to the traditional CAD risk factors in predicting the risk of death. Several studies indicate that high EBCT coronary scores are comparable to exercise radionuclide testing in the detection of obstructive coronary atherosclerosis and are useful for predicting events in symptomatic women.[71-74] In a study of symptomatic patients by Kennedy et al,[75] EBCT-detected coronary calcium was a stronger independent predictor of disease and future events than a sum of all of the traditional risk factors combined.

A multicenter study of 491 patients (mean±SD age, 55±12 years;

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

36% women) who underwent coronary angiography and EBCT scanning found that higher calcium scores were associated with an increased risk of coronary events over the next 30 months.[72] This study found a 10-fold higher event rate increase in patients with calcium scores above the 75th percentile compared with those below the 25th percentile (odds ratio, 10.8; 95% CI, 1.4-85.6). Logistic regression including sex, age, calcium score, and angiographically diseased vessels showed that only EBCT calcium score predicted events.

Keelan et al[73] studied for a mean of 6.9 years 288 symptomatic persons (mean ± SD age, 56 ± 11 years; 23% women) who underwent angiography and EBCT calcium scanning. Event-free survival was significantly higher for patients with Agatston scores lower than 100 than it was for those with scores higher than 100 (RR, 3.2; 95% CI, 1.2-8.7) and above the median score (RR, 3.4; 95% CI, 1.3-8.7). In the final stepwise Cox proportional hazards model that included risk factors, CAD event history, CAC measures, and angiographic measures of disease, age, and log-transformed CAC score were the only independent predictors of future hard coronary events. Importantly, no conventional coronary risk factors other than age predicted events.[73] However, CAC scores in comparison with Framingham risk scores or ETT results were not reported.

A prospective observational study of 192 patients presenting to the hospital emergency department with chest pain (mean ± SD age, 56 ± 11 years; 47% women) demonstrated that the presence of coronary calcium (total calcium score > 0) and increasing score quartiles were strongly associated with hard cardiac events (death and myocardial infarction) ($P<.001$) and with all cardiovascular events ($P<.001$).[74] The absence of calcium implies a very low risk of coronary events (0.6% annual incidence), whereas the presence of coronary calcium was a strong independent predictor of future cardiac events. Multivariate logistic regression analysis demonstrated that CAC score and age- and sex-matched calcium percentiles were the strongest predictors of future events; of the traditional cardiac risk factors, only age and hypertension remained significant.[74]

The summary risk ratio for a combined coronary event (death, myocardial infarctions, or revascularization) was 9.3 in these 3 EBCT studies[72-74] of 971 symptomatic persons (38% women) observed for an average of 42 months. The EBCT appeared to outperform angiography and traditional risk factors in event prediction in each of these studies.

EBCT AS A DIAGNOSTIC TOOL

The presence of coronary calcium on EBCT is extremely sensitive for obstructive CAD (95%-99%), but it has low specificity for obstructive disease depending on the age of the patient and the amount of coronary calcification present (23%-57%).[73] This limits the use of this modality for older symptomatic persons because many such individuals with coronary calcium have nonobstructive disease. However, the exclusion of coronary calcium is a powerful tool to help rule out obstructive CAD, while a positive test does not always imply obstructive CAD.

A prospective study by Schmermund et al[76] assessed the use of EBCT for the detection of CAD in symptomatic patients who underwent exercise ECG and coronary angiography (n = 323; mean ± SD age, 55 ± 11 years; 23% women). In patients with equivocal exercise stress test findings, EBCT led to significantly improved classification of CAD (≥50% stenosis); 15% more patients were classified correctly when both tests were used in combination. Electron-beam computed tomography also improved classification in patients with normal stress test results, although the added value was of borderline statistical significance. However, EBCT offered no incremental predictive value in patients with clearly abnormal exercise stress test results.[76]

Lamont et al[77] demonstrated that in patients evaluated for chest pain, the mean ± SD CAC score for patients with angiographically documented CAD (≥50% stenosis) was 654 ± 838 compared with 50 ± 111 for those without it ($P<.001$). Sensitivity of presence of CAC tended to increase with advancing age (93%-100%); the overall specificity and negative predictive value was 66% and 93%, respectively. On the other hand, an abnormal ETT had an estimated sensitivity and specificity of 47% and 82%, respectively, for the diagnosis of CAD. Multiple logistic regressions demonstrated that presence of coronary calcification by EBCT was a stronger predictor of CAD than any individual cardiac risk factor.[77]

Atypical chest pain is more common in women than in men, perhaps because of the higher prevalence among women of mitral valve prolapse, coronary artery spasm, and syndrome X.[78] This leads physicians to perform more coronary angiograms on women with no obstructive disease than on men. Angiographic studies consistently demonstrate a low prevalence of significant obstructive disease among symptomatic women who are referred for cardiac catheterization.[79] A report of 9238 angiograms from 5 community hospitals demonstrated that 40% of women referred for angiography were found to have normal coronary arteries or nonsignificant disease, nearly twice the rate of men, despite there being no difference in the rate of positive functional tests in this cohort.[80] Another study of 1120 symptomatic patients (387 women referred for angiography for clinical indications) found that women were twice as likely as men to have normal coronary arteries or nonobstructive disease (59% vs 30%; $P<.001$).[81] Sharaf and colleagues[82] reported similar findings: 57% of women referred for angiography had normal findings or nonobstructive disease in the WISE study.

Thus, EBCT can be useful to rule out obstructive coronary disease, as demonstrated by several studies of symptomatic men and women who underwent both angiography and EBCT.[73,76,83,84] These studies of more than 5500 patients demonstrate a negative predictive value of coronary calcium levels greater than 95%, thus giving physicians a relatively high level of confidence that an individual with no coronary calcium (score of 0) has no obstructive angiographic disease. However, it is not as clear what the significance of a positive but low

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

Table 3. Diagnostic Accuracy of the Test for CAC>0 to Detect Obstructive Coronary Artery Disease in Symptomatic Women*

Source	No. of Women	Coronary Artery Diameter Obstruction, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Budoff et al[83]	387	≥50	96	57	55	96
Haberl et al[84]	539	≥50	100	40	66	100
Budoff et al[85]	682	≥50	96	46	55	95

Abbreviations: CAC, coronary artery calcium score; NPV, negative predictive value; PPV, positive predictive value.
*For details see text.

CAC score is in symptomatic women, although a calcium score greater than 0 can also be used in predicting posttest probability of the disease in women.[85] A recent multicenter study of 1851 patients (1169 men, 682 women) who underwent coronary angiography for clinical indications and EBCT found a sensitivity for coronary calcium detecting obstruction in women of 96% and a negative predictive power of 95% (**Table 3**).[85]

Data from Haberl et al[84] support the diagnostic significance of a 0 calcium score on EBCT. They performed an EBCT prior to angiography in persons with a history of chest pain or abnormal stress test results and found that 22% of these 539 women had an EBCT calcium score of 0, and none had a coronary artery diameter obstruction of 50% or more (negative predictive value, 100%). Thus, an EBCT calcium score of 0 may be used as a way to reduce the number of negative angiograms that are known to be more frequent in women than in men.

Budoff et al[81] studied 1120 symptomatic patients (387 women and 733 men) who underwent angiography and EBCT; there were no differences with regard to sensitivity of coronary calcification for obstructive disease (96% in men and women). However, women had a significantly higher specificity of coronary calcium predicting obstructive disease (46% in men vs 57% in women, $P=.01$). In this study, there were 135 women with no coronary calcification: 6 among those had single-vessel disease, and 129 had normal coronary arteries or nonobstructive disease only (negative predictive value, 96%). The negative predictive value for multivessel disease or left main disease was 100% (Table 3). In this study, elimination of symptomatic women with scores of 0 would have resulted in 135 fewer angiograms (35%).[81] The predictive value of EBCT is not limited by concurrent medication, the patient's ability to exercise, or baseline ECG abnormalities.

COST-EFFECTIVENESS OF STRESS TESTING IN WOMEN

There is a general consensus that coronary angiography without previous noninvasive testing is reasonably cost-effective for symptomatic men and women with a high pretest probability of CAD.[86,87] The value of noninvasive testing is highest in women with intermediate pretest risk, and most data support the use of testing in women who are symptomatic.[88] Exercise ECG and exercise echocardiography are the most widely used modalities in the present clinical settings and are often recommended as 2 of the initial assessments. Moreover, recent data also indicate that the HR at 1 or 2 minutes of recovery has been validated as a prognostic measurement and provides useful supplemental information to that provided by the DTS.[87] Myocardial perfusion imaging has also been shown to provide incremental diagnostic value to exercise ECG testing in a certain subset of patients.[26,30]

Marwick et al[43] analyzed various diagnostic strategies assuming no induced costs other than coronary angiography in the event of a positive screening test finding. Local Medicare reimbursement rates to compute costs were used ($63 for exercise ECG, $246 for exercise echocardiography, and $1424 for coronary angiography). The researchers found that the choice of exercise echocardiography as the initial test was less expensive than exercise ECG ($828 vs $1023 per patient). The lower total cost was due to the calculated higher specificity of exercise echocardiography, which resulted in a lower rate of inappropriate angiography (29% vs 56% for exercise ECG). The researchers concluded that stress echocardiography was equal or superior to stress ECG testing in terms of cost-effectiveness.[43]

Kim et al[89] performed an evidence-based analysis using simulations of 55-year-old ambulatory women with chest pain who underwent exercise ECG, exercise stress thallium imaging, exercise echocardiography, and angiography. The strategy using exercise echocardiography as a first-line diagnosis for CAD was more cost-effective in 55-year-old women with probable angina and nonspecific chest pain, whereas angiography was more cost-effective in women with definite angina. In this analysis, exercise stress echocardiography dominated because of lower cost and a higher accuracy than exercise thallium scan. The authors acknowledged that the cost-effectiveness of the initial diagnostic strategy depended on the pretest probability of CAD.[89]

In another analysis, Miller et al[23] used 3 cost strategies with the nontraditional reference standard of MPI: (1) exercise ECG followed by cardiac catheterization if the ECG findings were positive; (2) perfusion imaging followed by catheterization if the perfusion imaging findings were positive; (3) exercise ECG followed by perfusion imaging if the ECG findings were positive followed by cardiac catheterization if the perfusion imaging findings were positive. Interestingly, strategy 3 had a significantly lower cost than strategies 1 ($P<.001$) and 2 ($P<.001$) in women. The researchers pointed out that prior studies have likely underestimated the specificity of exercise ECG: an negative findings on and adequate stress test (≥6 minutes on the Bruce protocol) are associated with a good cardiovascular

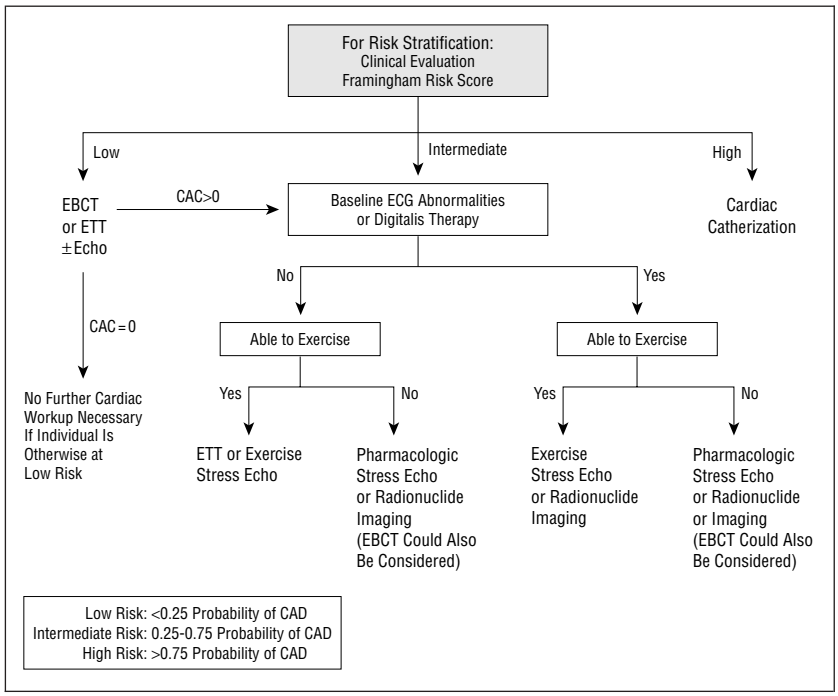
©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

prognosis.[23] However, Raggi et al[90] found that an algorithm using EBCT as the first-line test (rather than ETT) for evaluation of chest pain in patients with low to intermediate pretest probability of CAD actually resulted in significant cost savings of around 50%. Similarly, Rumberger et al[91] proposed that EBCT might be more cost-effective at diagnosing CAD than traditional noninvasive testing, especially in women.

SUMMARY

- An exercise ECG provides an assessment of functional capacity and has the advantages of wide availability and low initial cost in women with a normal baseline ECG findings with fair accuracy.
- Combining hemodynamic and functional information such as exercise capacity and HR changes with the standard diagnostic criteria of ST-segment changes can significantly improve the diagnostic accuracy of the treadmill stress ECG in women.
- Exercise echocardiography and gated Tc 99m sestamibi SPECT perfusion imaging appear to have the maximum diagnostic yield in detecting obstructive CAD in higher-risk or symptomatic women when compared with planar thallium imaging techniques.
- In decision-analysis simulated models, exercise echocardiography appeared to be the most cost-effective method for the initial assessment of CAD in women owing to a higher calculated specificity than exercise ECG and exercise radionuclide studies. However, larger comparative studies need to be done.
- If a woman has no coronary calcification on EBCT, it is very unlikely that she has obstructive CAD (≥50% diameter stenosis).



Clinical algorithm for the choice of noninvasive tests to detect coronary artery disease (CAD) in women. CAC indicates coronary artery calcium score; EBCT, electron-beam computed tomography; ECG, electrocardiography; Echo, echocardiography; and ETT, exercise treadmill testing.

RECOMMENDATIONS

A clinical algorithm for the choice of noninvasive tests to detect CAD in women is provided in the **Figure**.

If a woman (1) has a low to intermediate risk of CAD (25%-75%); (2) has a normal baseline ECG; and (3) is able to exercise, then either an ETT or treadmill stress echocardiography is an appropriate initial screening test and can provide useful prognostic information.

Alternatively, an EBCT scan with a calcium score of 0 can be used to help rule out obstructive CAD. This algorithm may potentially spare many otherwise low-risk women with atypical chest pain or equivocal standard ETT findings from undergoing more expensive stress imaging studies or coronary angiography. A calcium score greater than 0 can also be used in predicting posttest probability of the disease in women (**Table 4**).[85]

Exercise echocardiography or exercise radionuclide studies are preferred for women with an abnormal baseline ECG, underlying valvular disease, or those who have undergone revascularization.

Table 4. Posttest Probabilities for Obstructive Coronary Artery Disease for a Variety of Pretest and Total EBCT Scores in Women*

Pretest Probability	Age 40 y			Age 50 y			Age 60 y		
	CAC = 0	CAC = 100	CAC = 400	CAC = 0	CAC = 100	CAC = 400	CAC = 0	CAC = 100	CAC = 400
10	1	16	53	1	14	46	0.5	12	38
20	2	30	72	1.5	27	66	1	24	58
30	3	42	82	3	38.5	76.5	2	35	70
40	5	53	87	4	49	83.5	3	45	79
50	8	63	91	6	59	88	4	55	85
60	11	72	94	8	67	92	6	65	89
70	16	80	96	12	77	95	10	74	93
80	25	87	98	20	85	97	15	83	96
90	43	94	99	36	93	98	29	92	98

Abbreviations: CAC, coronary artery calcium score; EBCT, electron-beam computed tomography.
*Adapted from Budoff et al.[85] Data are percentages.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

For obese women or women unable to exercise owing to arthritis or neurologic disorders, pharmacologic stress testing is the recommended choice. The highest combination of sensitivity and specificity appears to be obtained with dobutamine echocardiography.[57-59,63] Electron-beam tomography is another choice for those patients who cannot exercise.

For high-risk symptomatic women, a more aggressive approach involving coronary angiography may be the preferred initial diagnostic strategy.

Accepted for publication August 18, 2003.

This work was supported by unrestricted educational grants by the Shoppers Food and Maryland Athletic Club Charitable Foundations, Timonium, Md.

Correspondence: Roger S. Blumenthal, MD, Ciccarone Preventive Cardiology Center, Blalock 524 C–Cardiology, Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21287 (rblument@jhmi.edu).

REFERENCES

1. Herlitz J, Bang A, Karlson BW, Hartford M. Is there a gender difference in the etiology of chest pain and symptoms associated with acute myocardial infarction? *Eur J Emerg Med*. 1999;6:311-315.
2. 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;120:559-566.
3. Gibbons RJ, Balady GJ, Timothy Bricker J, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol*. 2002;40:1531-1540.
4. Williams SV, Fihn S, Gibbons RJ. Guidelines for the management of patients with chronic stable angina: diagnosis and risk stratification. *Ann Intern Med*. 2001;135:530-547.
5. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation*. 1998; 98:1622-1630.
6. Alexander KP, Shaw LJ, Shaw LK, Delong ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. *J Am Coll Cardiol*. 1998;32:1657-1664.
7. Shaw LJ, Hachamovitch R, Peterson ED, et al. Using an outcomes-based approach to identify candidates for risk stratification after exercise treadmill testing. *J Gen Intern Med*. 1999;14:1-9.
8. Kwok JM, Miller TD, Hodge DO, Gibbons RJ. Prognostic value of the Duke treadmill score in the elderly. *J Am Coll Cardiol*. 2002;39:1475-1481.
9. 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;120:559-566.
10. Sketch MH, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol*. 1975; 36:169-173.
11. Barolsky SM, Gilbert CA, Faruqui A, Nutter DO, Schilant RC. Differences in electrocardiographic response to exercise of women and men: a non-Bayesian factor. *Circulation*. 1979;60:1021-1027.
12. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). *N Engl J Med*. 1979;301:230-235.
13. Guiteras P, Chaitman BR, Waters DD, et al. Diagnostic accuracy of exercise ECG lead systems in clinical subsets of women. *Circulation*. 1982;65: 1465-1474.
14. Hung J, Chaitman BR, Lam J, et al. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. *J Am Coll Cardiol*. 1984; 4:8-16.
15. Pratt CM, Francis MJ, Divine GW, Young JB. Exercise testing in women with chest pain: are there additional exercise characteristics that predict true positive test results? *Chest*. 1989;95:139-144.
16. 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.
17. 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; 83:660-666.
18. Tavel ME. Stress testing in cardiac evaluation: current concepts with emphasis on the ECG. *Chest*. 2001;119:907-925.
19. Roger VL, Pellikka PA, Bell MR, Chow CW, Bailey KR, Seward JB. Sex and test verification bias: impact on the diagnostic value of exercise echocardiography. *Circulation*. 1997;95:405-410.
20. Morise AP, Diamond GA. A comparison of the sensitivity and specificity of exercise electrocardiography in men and women using biased and unbiased populations of men and women. *Am Heart J*. 1995;130:741-747.
21. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). *N Engl J Med*. 1979;301:230-235.
22. Tavel ME. Specificity of electrocardiographic stress test in women versus men. *Am J Cardiol*. 1992; 70:545-547.
23. Miller TD, Roger VL, Milavetz JJ, et al. Assessment of the exercise electrocardiogram in women versus men using tomographic myocardial perfusion imaging as the reference standard. *Am J Cardiol*. 2001;87:868-873.
24. Rosano GMC, Sarrel PM, Poole-Wilson PA. Beneficial effect of estrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. *Lancet*. 1993;342:133-136.
25. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. *J Am Coll Cardiol*. 1995; 26:335-341.
26. Shaw LJ, Hachamovitch R, Redberg RF. Current evidence of diagnostic testing in women with suspected coronary artery disease: choosing the appropriate test. *Cardiol Rev*. 2000;8:65-74.
27. Okin PM, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. *Circulation*. 1995;92:1209-1216.
28. Cheng SL, Ellestad MH, Selvester RH. Significance of ST-segment depression with R-wave amplitude decrease on exercise. *Am J Cardiol*. 1999; 83:955-959, A9.
29. Stoletniy LN, Ramdas GP. Value of QT dispersion in the interpretation of exercise stress test in women. *Circulation*. 1997;96:904-910.
30. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediate after exercise as a predictor of mortality. *N Engl J Med*. 1999;341:1351-1357.
31. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*. 2000;284:1392-1398.
32. Morise AP. Are the American College of Cardiology/American Heart Association guidelines for exercise testing for suspected coronary artery disease correct? *Chest*. 2000;118:535-541.
33. 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;2:110-116.
34. Diaz LA, Brunken RC, Blackstone EH, Snader CE, Lauer MS. Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. *J Am Coll Cardiol*. 2001;37:1558-1564.
35. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation*. 2000;101: 1465-1478.
36. Hansen CL, Crabbe D, Rubin S. Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women: an effect of smaller chamber size. *J Am Coll Cardiol*. 1996;28:1214-1219.
37. Hansen CL, Woodhouse S, Kramer M. Effect of patient obesity on the accuracy of thallium-201 myocardial perfusion imaging. *Am J Cardiol*. 2000; 85:749-752.
38. Heller GV, Fossati AT. Detection of coronary artery disease in women. In: Zaret BL, Beller GA, eds. *Nuclear Cardiology: The State of Art and Future Directions*. 2nd ed. St Louis, Mo: Mosby–Year Book; 1998:298-311.
39. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? a meta-analysis of diagnostic test performance. *JAMA*. 1998;280:913-920.
40. Desmarais EL, Kaul S, Watson DD, Beller GA. Do false positive thallium-201 scans lead to unnecessary catheterization? outcome of patients with perfusion defects on quantitative planar thallium-201 scintigraphy. *J Am Coll Cardiol*. 1993;21: 1058-1063.
41. Santana-Boada 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;39:751-755.
42. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol*. 1997;29:69-77.
43. Marwick TH, Shaw LJ, Lauer MS, et al; Economics of Noninvasive Diagnosis (END) Study Group. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. *Am J Med*. 1999;106:172-178.
44. Hachamovitch R, Berman DS, Kiat H, 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.
45. Hachamovitch R, Berman DS, Kiat H, et al. Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms. *Circulation*. 2002; 105:823-829.
46. Boyne TS, Koplan BA, Parsons WJ, Smith WH, Watson DD, Beller GA. Predicting adverse outcome with exercise SPECT technetium-99m sestamibi imaging in patients with suspected or known

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015

coronary artery disease. *Am J Cardiol.* 1997;79: 270-274.
47. 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.
48. Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA.* 2002; 288:2693-2700.
49. Jennifer H, Mieres JH, Shaw LJ, et al. Consensus statement American Society of Nuclear Cardiology: task force on women and coronary artery disease. The role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women. Available at: www.asnc.org/resources/womencad.htm. Accessed January 4, 2003.
50. Arruda-Olson AM, Juracan EM, et al. Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference? *J Am Coll Cardiol.* 2002;39:625-631.
51. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation.* 1991;83: 1605-1614.
52. Williams MJ, Marwick TH, O'Gorman D, Foale RA. Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in women. *Am J Cardiol.* 1994;74:435-438.
53. Marwick TH. Current status of stress echocardiography in the diagnosis of coronary artery disease. *Cleve Clin J Med.* 1995;62:227-234.
54. Tong AT, Douglas PS. Stress echocardiography in women. *Cardiol Clin.* 1999;17:573-582.
55. Roger RL, Pellikka PA, Bell MR, Chow CW, Bailey KR, Seward JB. Sex and test verification bias: impact on the diagnostic value of exercise electrocardiography. *Circulation.* 1997;95:405-410.
56. Cortigiani L, Desideri A, Bigi R. Noninvasive assessment of coronary artery disease: the role of stress echocardiography. *Ital Heart J.* 2001;2: 250-255.
57. Ho YL, We CC, Huang PJ, et al. Assessment of coronary artery disease in women by dobutamine stress echocardiography: comparison with stress thallium-201 single-photon emission computed tomography and exercise electrocardiography. *Am Heart J.* 1998;135:655-662.
58. Beleslin BD, Ostojic M, Stepanovic J, et al. Stress echocardiography in the detection of myocardial ischemia: head-to-head comparison of exercise, dobutamine, and dipyridamole tests. *Circulation.* 1994;90:1168-1176.
59. Secknus MA, Marwick TH. Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. *J Am Coll Cardiol.* 1997;29:1234-1240.
60. Laurienzo J, Connon RO, Quyyumi AA, Vasken D, Panza JA. Improved specificity of transoesophageal dobutamine stress echocardiography compared to standard tests for evaluation of coronary artery disease in women presenting with chest pain. *Am J Cardiol.* 1997;80:1402-1407.
61. Geleijnse ML, Elhendy A, Fioretti PM, Roelandt JR. Dobutamine stress myocardial perfusion imaging. *J Am Coll Cardiol.* 2000;36:2017-2027.
62. Beller GA. Pharmacological stress imaging. *JAMA.* 1991;265:633-638.
63. Kim C, Kwok YS, Heagerty P, Redberg R. Pharmacologic stress testing for coronary disease testing: a meta-analysis. *Am Heart J.* 2001;142:934-944.
64. McCully RB, Roger VL, Mahoney DW, et al. Outcome after abnormal exercise echocardiography for patients with good exercise capacity: prognostic importance of the extent and severity of exercise-related left ventricular dysfunction. *J Am Coll Cardiol.* 2002;39:1345-1352.
65. Mahenthiran J, Singh BK, Yao SS, Chaudhry FA. Prognostic value of normal stress echocardiography in the presence of markedly positive stress echocardiogram [abstract]. *J Am Coll Cardiol.* 2002;39:351A.
66. Marwick TH, Case C, Sawada S, Vasey C, Short L, Lauer M. Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. *Diabetes Care.* 2002;25:1042-1048.
67. Marwick TH, Case C, Sawada S, Vasey C, Thomas JD. Prediction of outcomes in hypertensive patients with suspected coronary disease. *Hypertension.* 2002;39:1113-1118.
68. Palinkas A, Toth E, Amyot R, Rigo F, Venneri L, Picano E. The value of ECG and echocardiography during stress testing for identifying systemic endothelial dysfunction and epicardial artery stenosis. *Eur Heart J.* 2002;23:1587-1595.
69. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol.* 1999; 33:2092-2097.
70. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology.* 2003;228:826-833.
71. Shavelle DM, Budoff MJ, LaMont DH, Shavelle RM, Kennedy JM, Brundage BH. Exercise test and electron beam computed tomography in the evaluation of coronary artery disease. *J Am Coll Cardiol.* 2000;36:32-38.
72. Detrano R, Tzung H, Wang S, Puentes G, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. *J Am Coll Cardiol.* 1996;27: 285-290.
73. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation.* 2001;104:412-417.
74. Georgiou D, Budoff MJ, Kaufer E, Kennedy JM, Lu B, Brundage BH. Screening patients with chest pain in the emergency department using electron beam tomography: a follow-up study. *J Am Coll Cardiol.* 2001;38:105-110.
75. Kennedy J, Shavelle R, Wang S, Budoff M, Detrano RC. Coronary calcium and standard risk factors in symptomatic patients referred for coronary angiography. *Am Heart J.* 1998;135:696-702.
76. Schmermund A, Baumgart D, Sack S, et al. Assessment of coronary calcification by electron-beam computed tomography in symptomatic patients with normal, abnormal or equivocal exercise stress test. *Eur Heart J.* 2000;21:1674-1682.
77. Lamont DH, Budoff MJ, Shavelle DM, Shavelle R, Brundage BH, Hagar JM. Coronary calcium scanning adds incremental value to patients with positive stress tests. *Am Heart J.* 2002;143:861-867.
78. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med.* 1996;334:1311-1315.
79. Kaski JC, Rosano GM, Collins P, et al. Cardiac syndrome X: clinical characteristics and left ventricular function: long-term follow-up study. *J Am Coll Cardiol.* 1995;25:807-814.
80. Kugelmass AD, Houser F, Simon AW, et al. Diagnostic results: gender continues to make a difference [abstract]. *J Am Coll Cardiol.* 2001;37: 497A.
81. Budoff MJ, Shookooh S, Shavelle RM, Kim HT, French WJ. Electron beam tomography and angiography: gender differences. *Am Heart J.* 2002; 143:877-882.
82. Sharaf BL, Pepine CJ, Kerensky RA, et al; WISE Study Group. 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;87:937-941.
83. Budoff MJ, Georgiou D, Brody AS, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation.* 1996;93:898-904.
84. Haberl R, Becker A, Leber A, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol.* 2001;37:451-457.
85. Budoff MJ, Diamond GA, Raggi P, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. *Circulation.* 2002;105:1791-1796.
86. Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. *Ann Intern Med.* 1999; 130:709-718.
87. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodological issues. *J Am Coll Cardiol.* 2001;38:1980-1987.
88. Deaton C, Kunik CL, Hachamovitch R, Redberg RF, Shaw LJ. Diagnostic strategies for women with suspected coronary artery disease. *J Cardiovasc Nurs.* 2001;15:39-53.
89. Kim C, Kwok YS, Saha S, Redberg RF. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. *Am Heart J.* 1999; 137:1019-1027.
90. Raggi P, Callister TQ, Cooil B, Russo DJ, Lippolis NJ, Patterson RE. Evaluation of chest pain in patients with low to intermediate pretest probability of coronary artery disease by electron beam computed tomography. *Am J Cardiol.* 2000;85: 283-288.
91. Rumberger JA, Behrenbeck TR, Been JF. Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods. *J Am Coll Cardiol.* 1999; 33:453-462.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 10/04/2015