

Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Coronary Artery Disease: Consensus Statement From the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association

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Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Coronary Artery Disease

Consensus Statement From the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association

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Abstract—Cardiovascular disease is the leading cause of mortality for women in the United States. Coronary heart disease, which includes coronary atherosclerotic disease, myocardial infarction, acute coronary syndromes, and angina, is the largest subset of this mortality, with >240 000 women dying annually from the disease. Atherosclerotic coronary artery disease (CAD) is the focus of this consensus statement. Research continues to report underrecognition and underdiagnosis of CAD as contributory to high mortality rates in women. Timely and accurate diagnosis can significantly reduce CAD mortality for women; indeed, once the diagnosis is made, it does appear that current treatments are equally effective at reducing risk in both women and men. As such, noninvasive diagnostic and prognostic testing offers the potential to identify women at increased CAD risk as the basis for instituting preventive and therapeutic interventions. Nevertheless, the recent evidence-based practice program report from the Agency for Healthcare Research and Quality noted the paucity of women enrolled in diagnostic research studies. Consequently, much of the evidence supporting contemporary recommendations for noninvasive diagnostic studies in women is extrapolated from studies conducted predominantly in cohorts of middle-aged men. The majority of diagnostic and prognostic evidence in cardiac imaging in women and men has been derived from observational registries and referral populations that are affected by selection and other biases. Thus, a better understanding of the potential impact of sex differences on noninvasive cardiac testing in women may greatly improve clinical decision making. This consensus statement provides a synopsis of available evidence on the role of the exercise ECG and cardiac imaging modalities, both those in common use as well as developing technologies that may add clinical value to the diagnosis and risk assessment of the symptomatic and asymptomatic woman with suspected CAD. (*Circulation*. 2005;111:682-696.)

Key Words: AHA Scientific Statements ■ women ■ coronary disease ■ imaging ■ exercise testing

Cardiovascular disease is the leading cause of mortality for women in the United States. Coronary heart disease, which includes coronary atherosclerotic disease, myocardial infarction (MI), acute coronary syndromes, and angina, is the largest subset of this mortality. Atherosclerotic coronary artery disease (CAD) is the focus of this consensus document. Although US men have experienced a decline in CAD deaths,

the number of coronary deaths in women, >240 000 annually, has remained stable or has increased, depending on the study referenced.^{1,2} CAD, which increases with advancing age, also is a substantial cause of morbidity and disability for US women.³ Women, in particular young women (<55 years), have a worse prognosis from acute MI than their male counterparts, with a greater recurrence of MI and higher

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mortality.^{4–6} Furthermore, women have less favorable near-term outcomes after myocardial revascularization procedures than do their male peers.^{7–10} An effective diagnostic strategy is critical in women at risk because up to 40% of initial cardiac events are fatal.¹¹

The diagnosis of CAD and assessment of potential risk of cardiovascular disease are crucial steps toward improving outcomes. Thus, noninvasive diagnostic and prognostic testing offers the potential to identify women at increased CAD risk and establish the basis for instituting preventive and therapeutic interventions. Women with abnormal noninvasive tests also are more likely to be referred to coronary arteriography as compared with a decade ago, and in contrast to previous years, objective testing is currently undertaken earlier in women with chest pain who are suspected of having CAD.^{12,13} Because the contemporary use of myocardial revascularization procedures is almost “sex neutral” and is based on the severity of coronary arterial obstruction at coronary arteriography,^{14,15} the appropriate application of noninvasive testing is pivotal.

A consistent body of evidence documents that women are less likely than age-matched men to have obstructive CAD; in particular, triple-vessel or left main CAD is more common in men, even though more women than men die from CAD.¹⁴ The high prevalence of nonobstructive CAD and single-vessel disease in women results in an observed decreased diagnostic accuracy and higher false-positive rate for noninvasive testing in women versus men.¹⁶ The substantial underrepresentation of women in studies of noninvasive testing further limits the evidence-based information on which to base clinical decision making.¹⁶ Physicians may choose from a wide range of diagnostic modalities, but the accuracy and limitations of stress testing in women patients remains an area of significant confusion. Thus, the present review provides a synopsis of available evidence about noninvasive cardiac testing modalities in the diagnosis and risk assessment of both the symptomatic and asymptomatic woman patient with suspected CAD.

Sex-Specific Challenges in Diagnostic and Prognostic Testing for CAD: Importance of Pretest Probability and Referral Bias

One of the greatest challenges in diagnostic testing is the selection of appropriate diagnostic testing candidates, a challenge further exacerbated in populations with a lower prevalence of disease.^{17,18} CAD is less prevalent in premenopausal women, and its incidence tends to lag 10 to 15 years behind that of men until approximately the seventh decade of life.¹⁹ Thus, a woman’s risk factors and chest pain history play an important role in determining the probability of CAD. Risk prediction charts are available for both asymptomatic and symptomatic women.^{20–27} Calculating global risk or pretest CAD likelihood from the risk scores has been advocated as an aid to choosing the appropriate next step in clinical evaluation, including cardiovascular imaging.

Asymptomatic Women

For the asymptomatic woman, the goal of risk assessment is to identify those at risk for developing CAD. The Framing-

ham risk score (FRS) is one global risk score that includes traditional risk factors for CAD, including age, smoking, blood pressure, and cholesterol values.²⁴ From the FRS, women with low-, intermediate-, and high-risk scores have expected annual rates of CAD death or MI of <0.6% (low risk), 0.6% to 2.0% (intermediate risk), and >2.0% (high risk), respectively. This and other studies confirm that the risk of disease and events is low in premenopausal women and that screening will be, in general, of lesser value in this cohort, with the important exception of women with diabetes, known vascular disease, and, perhaps in the future, chronic kidney disease.¹⁹ At present, individuals with diabetes and peripheral arterial disease are considered to be at high risk because both diabetes and peripheral arterial disease are considered CAD risk equivalents. Patients with these conditions have risk levels similar to those of patients with an established CAD diagnosis, and thus treatment is recommended to established secondary prevention goals. As detailed in recent publications, support is growing for the use of cardiovascular risk screening (including imaging of subclinical atherosclerotic disease) in asymptomatic women with an intermediate FRS,^{26,28} although definitive randomized trial evidence is still forthcoming. A recent report incorporating the Framingham offspring and cohort revealed that 4%, 13%, and 47% of asymptomatic women ages 50 to 59, 60 to 69, and 70 to 79, respectively, were at intermediate or high risk, with an annual risk of CAD death or MI of $\geq 0.6\%$.²⁸ Recently, the National Cholesterol Education Program III further defined risk as those with ≥ 2 risk factors with a 10-year risk <10% (moderate risk) and with a 10-year risk 10% to 20% (moderately high risk). As noted, current evidence does not support the use of imaging in low-risk asymptomatic women, and conversely, women at high risk should be subject to secondary prevention goals.

Symptomatic Women

For the symptomatic woman, imaging is recommended for those at intermediate risk of having CAD. Key parameters from the clinical history that are important in determining a woman’s pretest probability of CAD include traditional coronary risk factors as well as symptoms. Although chest pain can be classified as typical angina, atypical angina, or nonanginal chest pain, these definitions were largely derived from male populations.^{17,18,20–22} From the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for exercise testing, women at intermediate to high pretest likelihood for CAD (based on symptoms) may be crudely defined as those with typical or atypical chest pain at ≥ 50 years of age and those <50 years of age with typical angina (Table).²⁹ Women with symptoms, diabetes, or multiple risk factors (ie, the metabolic syndrome) are at increased CAD risk and should be considered for testing.

As defined by Bayesian theory, the posttest likelihood of disease is heavily influenced by a patient’s pretest risk estimate.³⁰ Stress testing with exercise ECG or cardiac imaging has the greatest incremental value in women with a pretest intermediate risk for CAD (Table), in which a maximal shift in pre- to posttest CAD probabilities may occur. As few women with a low pretest likelihood of CAD have the

ACC/AHA Practice Guidelines on Exercise Testing: Pretest Probability of CAD by Age, Sex, and Symptoms

Age, y	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Intermediate	Very low	Very low	Very low
40–49	Intermediate	Low	Very low	Very low
50–59	Intermediate	Intermediate	Low	Very low
60–69	High	Intermediate	Intermediate	Low
≥70	High	Intermediate	Intermediate	Low

Adapted with permission from Gibbons et al (*Circulation*. 2002;106:1883–1892).²⁹

disease, testing results in a minimal shift from pre- to posttest assessment.^{31–33} Thus, referral of low-likelihood women (eg, premenopausal women with ≤1 risk factor and nonanginal/atypical symptoms) will be associated with a high rate of false-positives.

Imaging symptomatic women at high risk for CAD, however, has demonstrated value in guiding management decision making and therapeutic risk-reduction strategies according to the extent and severity of ischemia. Thus, current guidelines²⁹ support imaging for symptomatic intermediate- to high-risk women.

Work-Up Bias and Prognostication

The aim of the diagnostic work-up is to diagnose CAD with optimal accuracy. In the diagnostic evaluation of patients, however, calculating diagnostic sensitivity and specificity is hampered by verification or work-up bias in which women with abnormal test results are referred to cardiac catheterization, resulting in enhanced diagnostic sensitivity and diminished specificity.^{31–36} Recent data on the assessment of long-term prognosis based on the results of imaging tests to define false-negative and false-positive results have been shown to be reliable and helpful in predicting the risk of cardiac events. The availability of prognostic information promotes a change from an anatomy-based to a risk-based treatment strategy on the basis of the interpretation of the noninvasive test results.²¹ This shift is valuable in symptomatic women in whom nonobstructive coronary disease is prevalent. In daily clinical practice, the assessment of risk allows for the identification of subsets of women who are at increased risk for a cardiac event (CAD death or MI) and should be referred for testing and more intensive treatment. Assessment also identifies women at low risk for cardiac events whose risk can be managed with medical therapy, risk-factor modification, and no testing.

Summary

The diagnosis of CAD in women presents challenges not seen in testing men. Differences in the epidemiology of CAD between men and women render women at generally lower risk than their male counterparts until the seventh decade of life. For both asymptomatic and symptomatic women, initial test choice is guided by classifying women into low, intermediate, or high pretest risk categories. It remains controversial whether selective screening of asymptomatic women at intermediate risk for CAD should be routine. Although asymptomatic intermediate-risk women have decidedly lower event rates, support is growing for selective screening of women with an intermediate FRS. In symptomatic women,

noninvasive diagnostic studies (exercise ECG and cardiac imaging studies) are recommended for those who are at an intermediate to high pretest likelihood of coronary artery disease²⁹ (Table). Therapeutic decision making is guided by the extent and severity of inducible ischemia, and as such, imaging also is supported by recent guidelines documents in women at high pretest risk.

Role of Exercise ECG in the Diagnosis and Risk Assessment of Symptomatic Women With Suspected CAD

Diagnosis

Treadmill testing with exercise ECG is the oldest and most commonly used form of stress testing and the one that has been frequently evaluated in women. The wealth of published data on the exercise ECG includes numerous reports and several meta-analyses in women.^{29,37–39} According to the ACC/AHA exercise testing guidelines, women should undergo exercise testing if they are at an intermediate pretest risk of CAD on the basis of symptoms and risk factors, have a normal resting ECG, and are capable of maximal exercise.²⁹ ECG changes during exercise have been reported to be of diminished accuracy in women as a result of more frequent resting ST-T-wave changes, lower ECG voltage, and hormonal factors such as endogenous estrogen in premenopausal women and hormone replacement therapy in postmenopausal women.^{40–55} In a published meta-analysis that included 19 exercise ECG studies with 3721 women, sensitivity and specificity were 61% and 70%,³⁷ as compared with a mean sensitivity and specificity of 72% and 77% for 1977 men.²⁹ Despite these diminished accuracy statistics for the ECG alone, integrating multiple parameters (eg, simple Δ ST/heart rate index or the Duke treadmill score, defined as exercise time – (5 × ST deviation) – (4 × chest pain [1=nonlimiting, 2=limiting]) into risk scores has been reported to improve the accuracy of testing in populations of women.^{29,56,57} From a cohort of 976 symptomatic women who were referred for exercise treadmill testing followed by coronary arteriography, significant coronary stenosis (ie, ≥75%) was present in 19%, 35%, and 89% of low-, moderate-, and high-risk women, respectively, as based on the Duke treadmill score risk categories.⁵⁶ Thus, obstructive disease is more prevalent in women with a high Duke treadmill score, and these women may benefit from referral to coronary angiography. Women with an intermediate Duke treadmill score should, in general, be referred for additional risk stratification with a cardiac imaging study.

Risk Assessment

Although many clinicians rely solely on ECG changes in their interpretations of the exercise test, ST-segment depression alone does not provide adequate prognostication. Additional factors that improve the accuracy of the exercise treadmill test include chronotropic and hemodynamic responses to exercise. The presence of cardiac symptoms (limiting or nonlimiting chest pain) is of limited predictive value in women.^{29,58–63} All test interpretations should include a description of maximal exercise capacity measurements, as well as integrative test scores (eg, Duke treadmill score); these test scores are readily available on most commercial equipment.^{29,56,58–63} The Duke treadmill score also has sex-specific prognostic data. In a cohort of 976 women, the 5-year CAD death rates ranged from 5% to $\geq 10\%$ for women with a low- to high-risk Duke treadmill score. By comparison, men ($n=2249$) have higher CAD mortality rates that range from $\leq 9\%$ to $\geq 25\%$ for low- to high-risk scores, respectively.⁵⁶

Maximal exercise capacity and heart rate recovery measurements can aid in the estimation of near- and long-term outcome in large cohorts of women.^{62,63} Recent reports have noted that a simple measure such as heart rate recovery (at 1 or 2 minutes after exercise) have substantial prognostic value.^{58–63} Heart rate recovery has been directly related to heart rate variability and correlates with insulin resistance.^{60,61} Functional capacity is one of the strongest predictors of cardiovascular outcomes and should be an integral component of a test's interpretation.^{62,63} Given the large body of evidence, the inclusion of heart rate recovery measurement data may be a valuable addition to the interpretation of a test.

Women engage less often in physical exercise programs, have lower functional capacity, and have more functional decline during their menopausal years. Their lower work capacity on exercise tests (on average 5 to 7 minutes) challenges the ability to provoke myocardial ischemia as a result of premature peripheral fatigue.^{56,64} Women who exercise < 5 metabolic equivalents (METs) are at increased risk of death.^{65,66} An aid to the identification of women who are incapable of performing a minimum of 5 METs of exercise is the Duke Activity Status Index (DASI).^{65,66} From the DASI, women expected to perform < 5 METs may be better evaluated with pharmacological stress imaging. However, women who have inducible ischemia at low workloads (ie, < 5 METs) have a high likelihood of obstructive coronary disease and may be referred to coronary angiography.

Summary

Despite sex-specific limitations in the accuracy of the exercise ECG (false-positive ST-segment responses and the influence of submaximal stress on sensitivity), existing guidelines have proposed that evidence is insufficient to remove the stress exercise ECG test as the initial test for the symptomatic woman at intermediate risk for CAD who has a normal resting ECG and is capable of exercise.²⁹ The exercise ECG test does have a high negative predictive value in women with a low pretest probability of CAD and a low-risk Duke treadmill score. Emerging evidence on the role of heart rate recovery, functional capacity, and integrative test scores specifically applied in large cohorts of women have not been

fully incorporated into the most recent ACC/AHA guidelines for exercise testing.²⁹ These data indicate that the diagnostic and prognostic accuracy of the exercise ECG stress test in symptomatic women with suspected CAD is enhanced by the inclusion of additional parameters (eg, functional capacity, treadmill scores) to the interpretation of the ST-segment response to exercise.

Cardiovascular Imaging in Intermediate-Risk Symptomatic Women for Diagnostic and Risk Assessment of CAD

Role of Stress Echocardiography in the Diagnosis and Risk Assessment of Symptomatic Women With Suspected CAD

Diagnosis

Stress echocardiography can provide information about the presence of left ventricular systolic or diastolic dysfunction, valvular heart disease, and the extent of infarction and stress-induced ischemia. Exercise echocardiography may be performed via treadmill or via supine or upright bicycle exercise. In patients who cannot exercise, dobutamine is the most commonly used pharmacological stress agent; vasodilator stress echocardiography (with dipyridamole or adenosine) has been reported to have a lower diagnostic sensitivity for single-vessel disease.⁶⁷ Although the majority of stress echocardiography studies have predominantly included men, existing data indicate that this modality provides significantly higher specificity and accuracy than does standard exercise ECG testing in women.^{37,68,69} Because, in general, the onset of CAD is delayed in women as compared with men, women referred for stress testing may be older and less likely to reach an adequate heart rate with exercise testing without imaging. Moreover, in the exercise ECG data among women, even the use of combined scores that encompass exercise ECG interpretation, exercise capacity, and hemodynamics is less accurate than stress echocardiography.⁷⁰

On the basis of the aggregate data available in studies of nearly 1000 women with suspected CAD, stress echocardiography has demonstrated good diagnostic accuracy for detecting or excluding significant CAD, with a mean sensitivity of 81% (89% in women with multivessel disease), a specificity of 86%, and overall accuracy of 84%.^{27,33–35,37–39,67,69,71–78} There appears to be no significant sex effect on the diagnostic accuracy of exercise echocardiography; thus, interpretation is sex neutral and equally accurate for women and men. Most stress echocardiography studies have not corrected for posttest referral bias, however; the few studies that have attempted to correct for posttest verification bias^{33–35,71} demonstrate decreased sensitivity and increased specificity in identifying coronary artery disease as compared with unadjusted data.^{38,71,72}

Dobutamine stress echocardiography (DSE) reliably detects multivessel stenoses in women with suspected CAD who cannot exercise.^{67,69} The majority of DSE studies in women have reported sensitivities ranging from 75% to 93% and specificities from 79% to 92%, with an overall accuracy of 82% to 88%.^{67,69,70,73,74,78} A meta-analysis of DSE found an overall sensitivity of 80% (95% CI 77% to 83%) and specificity of 84% (95% CI 80% to 86%)⁶⁷; however, these

estimates were not corrected for posttest referral bias. DSE had a higher sensitivity but a lower specificity than those of stress echocardiography performed with dipyridamole or adenosine.^{75,76} Similar to the results for exercise stress echocardiography in women, the diagnostic accuracy of DSE to detect CAD in women appears to be similar to that in men.

Risk Assessment

The prognostic information provided by DSE and exercise stress echocardiography in evaluating suspected and known CAD also appears to be comparable in women and men. The presence of an abnormal exercise or DSE is associated with an increased risk of future cardiac events in women, whereas a normal study is associated with a low risk of cardiac events.^{27,72,79–81} A number of studies have demonstrated that stress echocardiography in women offers additional prognostic data beyond that provided by clinical or exercise treadmill variables alone.^{72,80,81} From a recent report of 4234 women, ≈ 1 in 1000 women with a negative exercise test and 1 in 100 women with a negative DSE will experience cardiac death within 5 years of testing.⁸¹ By comparison, 1 to 3 in 100 women with exercise and DSE multivessel ischemia will die within 5 years of follow-up, which are rates ≈ 10 -fold higher than for women with a negative study.⁸¹

In addition, the results of several studies indicate that stress echocardiography may be a cost-efficient tool in diagnosing suspected CAD in women with an intermediate pretest likelihood of CAD.^{72,82–85} The low specificity of exercise ECG testing in women, especially in young and middle-aged women, may lead to a higher rate of unnecessary angiography and expense, particularly if stress imaging is not used before coronary angiography in a sequential testing strategy. Hence, data indicate that stress echocardiography may be a cost-efficient approach, particularly in women at intermediate risk for coronary heart disease.^{82–85} Observational data from a multicenter registry found that stress echocardiography was more cost-effective than exercise ECG.⁸³

Summary

Stress echocardiography with exercise or dobutamine is an effective and highly accurate noninvasive means of detecting ischemic heart disease and risk-stratifying symptomatic women with an intermediate to high pretest likelihood of CAD. Stress echocardiography provides incremental value over the exercise ECG and clinical variables in women with suspected or known coronary heart disease. Exercise stress echocardiography is recommended for the symptomatic woman with an intermediate to high pretest probability of CAD (for women with suspected CAD, they must also have an abnormal resting ECG), and dobutamine stress echocardiography is recommended for women with a normal or abnormal ECG who are incapable of exercise.

Role of Cardiac Radionuclide Imaging: Myocardial Perfusion and Ventricular Function Imaging in the Diagnosis and Risk Assessment of Symptomatic Women With Suspected CAD

Diagnosis

Gated myocardial perfusion single-photon emission computed tomography (SPECT) is a nuclear-based technique that

provides a combination of test elements that are used to diagnose and risk-stratify women. These parameters include perfusion defects, global and regional left ventricular function, and left ventricular volumes.⁸⁶ Of the imaging modalities, SPECT imaging is the most commonly performed stress imaging test in the United States. Of the estimated 7.8 million patients who underwent perfusion imaging in 2002, $\approx 40\%$ were women.⁸⁷ Myocardial perfusion imaging, however, has been reported to have technical limitations in women, including false-positive results due to breast attenuation and small left ventricular chamber size.⁸⁸ The accuracy of ²⁰¹Tl SPECT imaging, for example, is reduced in patients with small hearts, and these patients are more likely to be women than men.⁸⁸ When ²⁰¹Tl is used as the radioisotope in women, false-positive test results may be the result of soft tissue (ie, breast) attenuation in the anterior and anterolateral segments.⁸⁸

During the past decade, innovations in myocardial perfusion imaging have resulted in substantial improvements in its accuracy.⁸⁶ For women, the lower-energy isotope ²⁰¹Tl has been largely supplanted by technetium-based imaging agents that improve accuracy, particularly with gated SPECT imaging in which poststress wall motion and ejection fraction are evaluated.^{86–91} In a small randomized trial comparing the diagnostic accuracy of ²⁰¹Tl with gated ^{99m}Tc sestamibi SPECT in women, the sensitivity for detecting CAD was 80%, and test specificity improved dramatically from 67% for ²⁰¹Tl to 92% for gated ^{99m}Tc sestamibi SPECT.⁸⁹ This improvement is derived from the higher-count profile obtained with the ^{99m}Tc radioisotope enhancing image quality.⁸⁸ In an additional study, bias-corrected accuracy results were evaluated in a cohort of 63 women and 100 men with suspected CAD who underwent stress myocardial perfusion imaging with exercise or dipyridamole SPECT.⁹² From the above report on 163 women and men, the referral bias-adjusted sensitivity and specificity were 87% and 91%, respectively, for women and 88% and 96%, respectively, for men.⁹² Bias-corrected sensitivity and specificity in a series of 14 273 patients were considerably lower.⁹³

Pharmacological stress SPECT also merits consideration, given the higher incidence of decreased exercise capacity and advanced age for women, as previously discussed.^{27,86,88} With the growing prevalence of obesity in the United States, the proportion of women and men requiring the use of pharmacological stress procedures is expected to increase substantially. In a study on vasodilator stress in a cohort of 130 women who underwent adenosine ^{99m}Tc sestamibi imaging, there was a reported 91% sensitivity and 86% specificity for detecting significant coronary artery stenoses $>50\%$.⁹⁰ In a later publication, the same authors⁹⁴ found that a moderate to severely abnormal perfusion scan (ie, summed stress score >8) was associated with a sensitivity and specificity of 91% and 70%, respectively, for the detection of multivessel coronary disease in women; however, these estimates were not corrected for posttest referral bias. Vasodilator pharmacological stress perfusion imaging has been shown to be more accurate than exercise perfusion imaging in the identification of CAD in both men and women with left bundle-branch block.⁸⁶

Risk Assessment

Myocardial perfusion imaging has been shown in a multitude of clinical studies including 15 000 women to have powerful predictive value with regard to the development of subsequent cardiac death or MI or the need for coronary revascularization.^{95–116} A number of large observational studies have demonstrated that both ^{99m}Tc (rest and stress) and dual isotope myocardial perfusion SPECT add incremental prognostic value to clinical and exercise variables in women.^{95–116} For example, a recent multicenter registry of 5009 men and 3402 women with stable chest pain symptoms undergoing perfusion imaging demonstrated that myocardial perfusion imaging had a similar prognostic ability regardless of sex.⁶⁴ Pooled myocardial perfusion data from >7500 women demonstrated an annual cardiac event rate of <1% in the setting of a normal study.¹¹⁵ Data from >5000 women demonstrated a significantly increased risk for cardiac events in the setting of an abnormal perfusion study.^{95–116} Simplistically stated, prognosis worsens commensurate with the number of vascular territories involved, with 3-year survival rates ranging from 99% for women without ischemia to 85% with 3-vessel territories with ischemia⁶⁴; however, by assessing the extent and severity of defect size and its degree of reversibility, myocardial perfusion imaging can provide a continuum of risk (ie, low risk, mildly abnormal, moderately abnormal, and severely abnormal, which correlated with ever-increasing CAD event rates) rather than simply a positive-versus-negative result.^{95–97}

Pharmacological stress recently was also shown to be effective in the risk stratification of diabetic women with suspected and known CAD. In a recent report in which adenosine SPECT was used, the annual CAD mortality rate increased from 0.8% to 1.6% for nondiabetic as compared with diabetic women with a normal SPECT study. In this cohort, the CAD mortality for nondiabetic women with a moderately abnormal scan was 2.8% as compared with 4.1% in diabetic women.⁹⁷ The annual CAD mortality rates are highest for women with severely abnormal SPECT scans (ie, 6.1% and 8.5% for the nondiabetic and diabetic women). Of particular importance, diabetic women (especially those requiring insulin) with ischemia are at the highest risk for cardiac events^{97,115}; thus, they require aggressive posttest antiischemic and risk factor management and consideration of coronary angiography. It may be expected that the overall event rates are at least 50% higher for diabetic than for nondiabetic women.^{97,115} Additional high-risk markers from the SPECT study include poststress ejection fraction <45%, end-systolic volume >70 mL, transient ischemic dilation, and increased lung uptake of ²⁰¹Tl.^{96,115}

Summary

Stress myocardial gated perfusion SPECT imaging performed with contemporary techniques has high diagnostic and prognostic accuracy in the evaluation of symptomatic women with an intermediate to high risk of CAD. Stress myocardial perfusion imaging provides incremental value over clinical variables and the exercise ECG in women with suspected or known ischemic heart disease. Stress myocardial perfusion imaging is recom-

mended for the symptomatic woman with an intermediate to high pretest likelihood of CAD (for the woman with suspected CAD, an additional criterion includes those with an abnormal baseline ECG). Pharmacological stress is recommended for the symptomatic woman with a normal or abnormal baseline ECG who is incapable of maximal exercise. With the abundant risk assessment data, clinicians should integrate the concepts of low- to high-risk imaging results to guide and improve clinical decision making in women.

Emerging Imaging Modalities and Their Role in the Evaluation of Women at Risk for CAD

Three relatively new and rapidly developing imaging technologies—computed tomography (CT), magnetic resonance imaging (MRI), and carotid intima-media thickness (IMT) in the detection of subclinical CAD—have not amassed the wealth of evidence that would clearly define their role in the clinical evaluation of women with suspected CAD. For CT, the available data on coronary artery calcification comes largely from referral populations and cannot be compared with population-based studies (eg, Multi-Ethnic Study of Atherosclerosis). Similarly for MRI, the prognostic evidence is sparse; however, recent small reports from expert centers, specifically from the Women's Ischemic Syndrome Evaluation (WISE), and other studies including women with less extensive disease have been reported. As the evidence base on the clinical role of CT and MRI is evolving rapidly, a synthesis of sex-specific evidence is worthwhile. A short section on the role of carotid IMT in the evaluation of women with suspected CAD is included below because an emerging body of evidence suggests its usefulness in the estimation of cardiovascular risk.

Role of CT Measurements of Coronary Calcification in the Diagnosis and Risk Assessment of Women With Suspected CAD

Coronary CT detects and quantifies the amount of coronary artery calcium (CAC), a marker of atherosclerotic disease burden, via either electron beam tomography (EBT) or multidetector CT (MDCT). Although some limitations remain for MDCT (including slower speed of the acquisition [EBT 50 to 100 ms, MDCT 200 to 330 ms], higher radiation dose [EBT dose 0.7 mSv, MDCT dose 1.5 to 1.8 mSv], and possibly greater interscan variability of measurement [EBT 11% to 16%, MDCT 23% to 35%]), it does appear that CAC measurements are comparable with either technique.¹¹⁷

Calcification does not occur in a normal vessel wall, thus signifying the presence of atherosclerosis; however, it is not specific for luminal obstruction. CAC scores approximate the total atherosclerotic plaque burden. Data specific to symptomatic women include a report on a cohort including 539 women (mean age 60 ± 16 years) undergoing clinically indicated angiography. Among the 220 (41%) women with a normal coronary arteriogram, none had detectable CAC, yielding a negative predictive value of 100%. In contrast, women with moderate (≥100) or higher (≥400) CAC scores had a greater prevalence of obstructive coronary disease.¹¹⁸ Although these findings are consistent with the concept that calcified plaque burden

parallels overall plaque burden, CAC testing is not appropriate as a surrogate for angiographic disease detection because of the modest relationship between CAC and obstructive coronary artery disease. On the basis of this modest relationship, calcium testing was not recommended in the 2000 ACC/AHA expert consensus document to diagnose obstructive CAD because of its low specificity.¹¹⁹

Sex and age distributions of the presence and severity of CAC have been published.¹²⁰ Although derived largely from referred populations, these data consistently show that the prevalence and severity of CAC is strongly related to increasing age and to sex (ie, women have less prevalent and less severe CAC than do men). For women, the prevalence of CAC is low premenopausally, but in general, across age deciles, prevalence lags by ≈ 10 years when compared with their male counterparts. Such distributions have been developed largely in white women and should not be applied to nonwhite women until ethnicity-specific data are developed.

Risk Assessment

The greatest potential for CAC detection could be as a marker for CAD prognosis in asymptomatic women, beyond the prognostic information supplied by conventional coronary risk factors. Since the 2000 ACC/AHA expert consensus document on EBT noted inconclusive risk-stratification evidence on CAC scanning,¹¹⁹ a number of studies primarily composed of men have reported that the presence and severity of CAC has independent and incremental value when added to clinical or historical data in the estimation of death or nonfatal MI.^{121–126} Included among these is one study estimating total mortality that is notable for the inclusion of a large number of women. In a cohort of 10 377 asymptomatic individuals (including >4000 women¹²⁷) undergoing CAC measurement with EBT (with a mean follow-up of 5.0 years), the extent of CAC was an independent and incremental estimator of all-cause mortality over and above an estimate of the FRS determined by patient history without measurement of lipids or glucose. For women, risk-adjusted relative risk ratios for all-cause mortality were elevated 2.5-, 3.7-, 6.3-, and 12.3-fold for calcium scores of 11 to 100, 101 to 400, 401 to 1000, and >1000, respectively ($P < 0.0001$), as compared with a score of ≤ 10 . Similar data examining the relationship of CAC to CAD outcomes (MI and coronary death) in women also are needed. Importantly, for a given CAC score, mortality rates in this study were 3- to 5-fold higher for women than they were for men. Thus, this study makes clear the need for data on female-specific cut points for determination of a “high-risk” CAC score for various CAD outcomes, as the relationships between CAC and outcomes are different than for men. **Beyond this single study, however, no other study has included sufficient numbers of women to make confident statements about the incremental value of CAC testing.** Ongoing studies are addressing these important questions.

Among the available studies on CAC and CAD outcomes, a number of methodological differences have contributed to discordance among studies with regard to

the strength and magnitude of independent prognostication with CAC scanning. These study differences, some of which were highlighted in a recent meta-analysis,¹²⁸ include the use of referred populations, the admixture of outcomes including “soft end points” (ie, revascularization), the manner of outcome adjudication, the use of historical versus measured coronary risk factors, and the inclusion of men and women together in predictive models. Concurrent with these challenges are concerns about potential adverse effects of screening (eg, unnecessary invasive procedures, overtreatment, disease labeling,¹²⁹ induced testing, and cost), the absence of reimbursement strategies, and an absence of data showing that screening leads to improved health outcomes. These concerns have created considerable controversy about the role of CAC testing for CAD risk screening. Thus, in 2000, the ACC/AHA issued a joint statement¹¹⁹ that noted a lack of supportive evidence for the use of CAC testing as a screening procedure for CAD risk except in selected clinically referred individuals with intermediate clinical risk. Since then, on the basis of the evolving literature, other guidelines and expert consensus documents have extended this recommendation to suggest its use, or the use of other tests of atherosclerosis burden, in clinically selected intermediate–CAD risk patients (eg, those with a 10% to 20% Framingham 10-year risk estimate) to refine clinical risk prediction^{130,131} and to select patients for altered targets for lipid-lowering therapies.¹³² Consistent with these statements, the recent US Preventive Services Task Force recommends against EBT scanning for either the presence of severe coronary artery stenosis or for prediction of CAD events in adults at low risk for CAD events.¹²⁹

Summary

For the clinical indication of risk stratification in asymptomatic women, the available data are limited to a few reports. Given the evolving literature since the last ACC/AHA Expert Consensus statement,¹¹⁹ current data indicate that CAD risk stratification is possible in women. Specifically, low CAC scores are associated with a low adverse event risk, and high CAC scores are associated with a worse event-free survival.^{119,127} Additional high-quality data are needed from larger cohorts that specifically address CAD outcomes in women to more precisely establish female-specific CAC risk cut points and to more precisely quantify the incremental prognostic value beyond the measurement of conventional coronary risk factors. Until then, consistent with recent consensus statements, CAC testing for CAD risk detection should be limited to clinically selected women at intermediate risk.

Role of Cardiovascular Magnetic Resonance Imaging in the Diagnosis and Risk Assessment of Women With Suspected CAD

Diagnosis

Cardiovascular magnetic resonance imaging (CMR) has undergone rapid development during the past decade, and with an emerging body of evidence, this cardiovascular imaging modality is likely to become an accepted tech-

nique for the evaluation of suspected myocardial ischemia. As a result of its enhanced spatial and temporal resolution, CMR has the potential to evaluate the presence of CAD by multiple techniques including direct visualization of coronary stenoses¹³³ and determination of flow within the coronary arteries (analogous to conventional catheter-driven coronary angiography)¹³⁴; evaluation of myocardial perfusion^{135,136} and metabolism¹³⁷ (similar to SPECT imaging); assessment of abnormal wall motion during stress^{138,139} (similar to echocardiography); and identification of infarcted myocardium via delayed hyperenhancement imaging.¹⁴⁰ Of these, the evaluation of perfusion and left ventricular function and the determination of infarcted myocardium are in the furthest stage of development. This section focuses on the role of CMR in the evaluation of ischemic heart disease. To date, few CMR studies have evaluated ischemia provocation in women,^{137,141–143} although 2 recent studies^{137,141} used CMR spectroscopy and myocardial perfusion techniques to demonstrate abnormalities of myocardial metabolism and perfusion in women with syndrome X (ie, chest pain in the absence of significant epicardial CAD). In another study, CMR myocardial perfusion reserve was found to be comparable to standard gated SPECT techniques.¹⁴² Most recently, in a series of 1000 examinations (including 257 women) for high-dose dobutamine stress, CMR was found to have a safety profile comparable to that of high-dose dobutamine echocardiography.¹⁴⁴ Previous data in 208 patients (including 61 women) suggested greater accuracy of high-dose dobutamine CMR as compared with high-dose dobutamine echocardiography with quantitative coronary angiography as the reference standard,¹⁴⁵ which supports its use as a measure of inducible myocardial ischemia.

Although initial data are limited, this early work suggests a potential role for CMR in the diagnostic evaluation of symptomatic women. The absence of ionizing radiation in CMR may be attractive when monitoring women with established CAD. The lion's share of the evidence has been reported from expert centers, however, and as such the generalizability of their findings has not been established. Other than stress echocardiography, all other imaging techniques—SPECT, CT, and conventional angiography—require the use of ionizing radiation. Thus, patient preferences may play a role in the decision to use CMR rather than other techniques. A closed bore magnet is associated with claustrophobia for certain patients and remains a challenge for this modality.

Risk Assessment

Prognostic data with CMR are just becoming available (in small patient samples) and suggest that this technique is accurate for estimating risk through an array of markers. For example, in a cohort of 279 patients (including 124 women) who were referred for dobutamine/atropine cardiac MRI for the detection of ischemia, the presence of inducible ischemia or a left ventricular ejection fraction of <40% were predictors of CAD death or MI at an average follow-up period of 20 months.¹⁴⁶ Patients in this study with no evidence of ischemia and a left ventricular ejection

fraction of $\geq 40\%$ had an excellent prognosis in the 2 years after stress cardiac MRI. In an update from the WISE trial, the prognostic value of ³¹P magnetic resonance spectroscopy¹⁴³ revealed that a reduced adenosine triphosphate/phosphocreatine ratio, a marker for metabolic ischemia, was associated with a poorer event-free survival, although the higher event rate was primarily the result of hospitalization for unstable angina.

Summary

Limited data support the use of CMR in the detection of coronary heart disease in symptomatic women. The available data from expert centers suggest a possible future role for CMR in the diagnosis and risk assessment of symptomatic women with an intermediate pretest likelihood of CAD.

Role of Carotid IMT in the Detection of CAD in Women

Subclinical atherosclerosis in the carotid artery, including the presence of focal plaque and the thickness of the combined intima and medial layer in the far wall of the carotid artery (IMT) detected by using high-frequency B-mode carotid ultrasonography, has been extensively studied as a marker of coronary heart disease risk in women. Carotid IMT is most commonly examined in the distal common carotid artery where it is most simply and reproducibly measured via manual or automated techniques. The advantages of carotid ultrasonography as a test for subclinical atherosclerosis include the wide availability of ultrasound technology, absence of ionizing radiation or incidental scan findings, and well-validated nature of the test results. The limitations of this technique include the lack of accepted technical standards for IMT testing and the absence of published population distributions of IMT.

Carotid IMT measurements are slightly lower in women than in men at a given age.¹⁴⁶ Minor ethnic differences in carotid IMT are present, but their magnitudes are small enough not to affect risk stratification.¹⁴⁶ Threshold values for definition of an abnormal IMT (eg, upper quartile population value) require age adjustment. Upper-quartile carotid IMT values for a 40-year-old woman are ≈ 0.5 mm and increase by ≈ 0.10 to 0.15 mm per decade of age.^{146,147} More precise definitions of an "abnormal" level of IMT via standardized imaging and measurement guidelines are needed.

Common carotid IMT has been demonstrated to have an independent relationship to cardiovascular outcomes in women >45 years old to an extent that equals or exceeds that seen in men.^{148,149} Observational epidemiological data have shown that, after adjustment for conventional risk factors, carotid IMT is strongly associated with the risk of cardiovascular events. In the Cardiovascular Health Study, older women in the highest quintile of IMT were >3-fold more likely to suffer a cardiovascular event than were younger women. The relationship between IMT and events is continuous, with an $\approx 40\%$ increase in relative risk per 0.15- to 0.20-mm increase in IMT.^{148,150} Similar to other techniques for the noninvasive measurement of atherosclerosis burden for CAD risk stratification in asymptomatic women, the clinical use of carotid IMT has not been shown to result in improved outcomes.

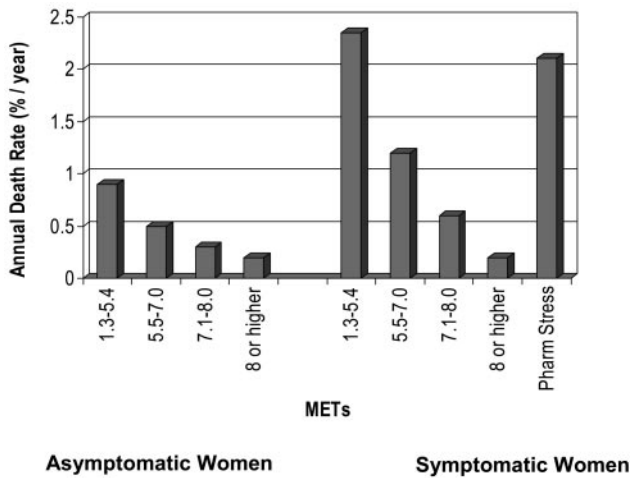


Figure 1. Prognostic value of functional capacity in asymptomatic (n=8715) and symptomatic (n=8214) women as synthesized from published reports and available data. Pharm Stress indicates women referred for adenosine or dipyridamole SPECT or dobutamine stress echocardiography. Adapted with permission from Gulati et al (*Circulation*. 2003;108:1554–1559),⁶² Mora et al (*JAMA*. 2003;290:1600–1607),⁶³ Marwick et al (*Am J Med*. 1999;106:172–178),⁶⁴ and Marwick et al (*Circulation*. 2001;105:2566–2571).¹⁶⁸

Future Developments in Cardiovascular Imaging

Evidence increasingly suggests that the risk of CAD in women is multifactorial. In general, imaging markers have not been adequately integrated with clinical parameters. Given the complexity of the diagnosis and evaluation of risk in women with known or suspected CAD, new imaging research must integrate hormonal, traditional, historical, and emerging risk markers in the assessment of major adverse cardiac outcomes in large cohorts of asymptomatic and symptomatic women at risk for CAD.¹⁵¹

One emerging risk marker of atherosclerosis is the identification of coronary artery endothelial dysfunction. Coronary vascular dysfunction has been documented to be a precursor for atherosclerosis and is linked to CAD progression and an increasing incidence of major adverse cardiac events.^{152–154} The connection between endothelial dysfunction in women with chest

pain and the future development of CAD was demonstrated in 2 recent publications.^{155,156} An impaired vasomotor response to acetylcholine has been independently linked to adverse cardiovascular outcomes regardless of CAD severity in a cohort of 163 women with chest pain from the WISE trial.¹⁵⁵ In a recent study of 42 women with angina, reversible perfusion defects on SPECT myocardial perfusion imaging and normal coronary angiograms showed that coronary artery endothelial dysfunction (as identified by vasoconstriction with acetylcholine) was a marker for the future development of coronary atherosclerosis.¹⁵⁶ Additional research must therefore focus on the frequency and resulting prognosis of women with evidence of microvascular disease or endothelial dysfunction with or without concomitant chest pain symptoms. This latter point would include the utility of brachial artery reactivity testing or coronary flow reserve testing (invasively by catheterization or noninvasively with echocardiography, magnetic resonance, or positron emission tomography techniques) in the determination of endothelial dysfunction or evidence of microvascular disease by retinal photography or carotid IMT.^{157,158}

Recommendations for Noninvasive Testing in Women With Suspected CAD

For women with a normal resting ECG and good exercise tolerance, evidence supports the recommendation from the ACC/AHA guidelines for a routine exercise treadmill test as the initial test for the evaluation of suspected CAD.²⁹ Combining parameters such as exercise capacity and heart rate changes with the traditional evaluation of ST-segment changes improves the prognostic accuracy of the exercise treadmill test, making it a cost-efficient modality to use in this group of women (Figure 1).

The indications for cardiac imaging in symptomatic cohorts of women are summarized in Figure 2. Cardiac imaging is recommended for symptomatic women with established CAD. Current evidence and practice guidelines recommend cardiac imaging for women with suspected CAD with an abnormal resting 12-lead ECG. More widespread use may be justified, but data are insufficient to support the primary use of imaging tests in all female patients. Cardiac imaging is recommended for women

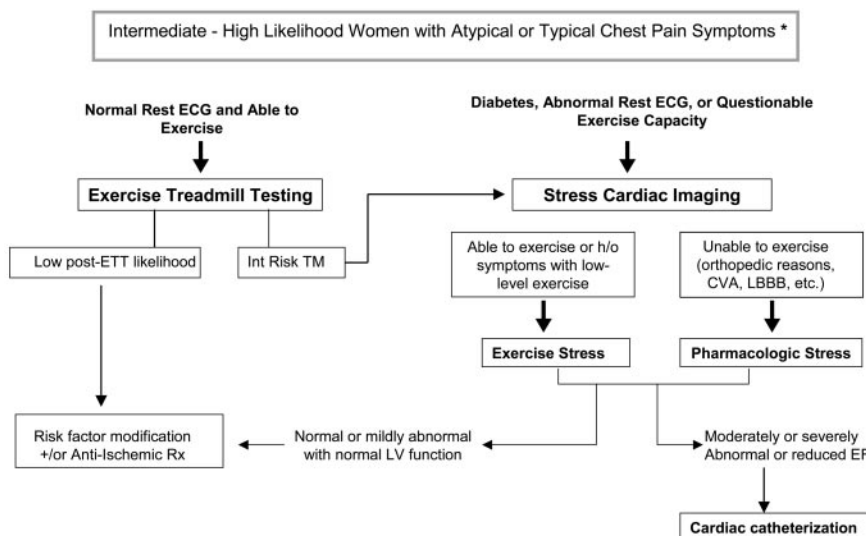


Figure 2. Algorithm for evaluation of symptomatic women using exercise ECG or cardiac imaging. Refer to the Table for further information on asterisk (*).

with an indeterminate or intermediate-risk exercise ECG test, as well as those with an intermediate-risk Duke treadmill score.

Although not considered in the current ACC/AHA guidelines, diabetic women merit special consideration and are included in the present statement as candidates for cardiac imaging because they have a risk of cardiovascular death that is up to 8-fold higher than that of nondiabetic women. As outlined in Figure 2, additional candidates for cardiac imaging include other intermediate- to high-risk groups with functional impairment that are suitable for pharmacological stress. On the basis of a growing body of evidence, cardiac imaging via contemporary techniques of stress echocardiography or gated SPECT myocardial perfusion imaging provides accurate diagnostic and prognostic information for women with suspected ischemic symptoms. Additional special populations of women who also may be at risk include women with the metabolic syndrome and those with polycystic ovary syndrome, although definitive imaging evidence is not available.

On the basis of existing evidence, the asymptomatic woman with a calcium score ≥ 400 has an annualized risk of CAD death or MI of $\approx 2\%$ and should be considered at high cardiac risk. This recommendation is supported by the recently published AHA

guidelines on CAD prevention in women, which noted that a 2% risk of major adverse cardiac events places a patient at high risk.¹⁵⁹ Thus, many experts advocate that women with significant subclinical atherosclerosis should be treated with secondary prevention goals, although definitive randomized trial evidence is not available.

Conclusion

A review of the data suggests that as in men, women with suspected and known CAD can be accurately diagnosed and risk-stratified via contemporary cardiac imaging techniques. Despite this, an abundance of evidence still suggests that women at risk for CAD are less often referred for the appropriate diagnostic test than are men.^{160–168} The present approaches to diagnostic testing may require some variation when applied to women, and ongoing investigation is needed to fully appreciate the multifactorial role of reproductive hormones on the vascular system and diagnostic testing. Additional work also is needed to fully assimilate sex-specific issues into clinical guidelines and everyday clinical practice when appropriate. The data reviewed here, however, suggest that

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Nanette K. Wenger	Emory University School of Medicine	Eli Lilly; Astra-Zeneca; Pfizer	None	None	Pfizer, Novartis, Merck, Bristol-Myers Squibb, Eli Lilly	Eli Lilly Raloxifene Advisory Committee; Heart Disease in Women, Med-ED, Pfizer; Cardiology/Lipidology Advisory Board, Merck; Cardiology Consultant, Bristol-Myers Squibb; Ranolazine Advisory Board, CV Therapeutics; Sanofi-Adventis, Kos Pharmaceuticals	None

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women benefit from risk stratification with commonly used noninvasive cardiac tests. Local expertise and availability should guide the selection of cardiac imaging techniques in women with suspected and known CAD who are candidates for cardiovascular screening.

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