Curr Cardiol Rep (2010) 12:147–154
DOI 10.1007/s11886-010-0084-y

Noninvasive Assessment of Coronary Artery Disease in Women: What's Next?

Lawrence M. Phillips · Jennifer H. Mieres

Published online: 23 February 2010

Abstract Significant progress in research has been made in the areas of sex-specific aspects of cardiovascular disease. Despite these advances, coronary artery disease (CAD) is the leading cause of death of women in the Western world. Over the past decade, the focused research on women at risk for ischemic heart disease has helped to clarify our understanding of some of the sex-specific factors, which are important in detecting CAD. In women, the detection and evaluation of physiologically significant CAD is challenging, especially given that traditional tests designed to detect focal areas of coronary artery stenosis are less sensitive and specific in female patients who have a lower prevalence of obstructive coronary disease, greater burden of symptoms, and a high atherosclerotic burden. In this article, we review the available evidence on the role of contemporary cardiovascular imaging techniques in evaluating ischemic heart disease in women.

Keywords Sex-specific · Non-invasive imaging · Women

Introduction

Within the past two decades, significant progress in the identification and treatment of risk factors for coronary artery disease (CAD) as well as advances in diagnosis and treatment of ischemic heart disease (IHD) have resulted in a decline in mortality in the United States [1]. The recent National Health Statistics and Center for Disease Control data show a reduction in coronary heart disease (CHD) age-adjusted death rates for women by 26.9% since 1999 [1]. This decline in coronary deaths may be credited in part to a combination of reduction and treatment of major coronary risk factors as well as the application of evidence-based treatments for established CAD [2, 3]. Despite this dramatic improvement, CHD remains the leading cause of death of US women, claiming the lives of over 210,000 in 2005 [4]. Therefore, early identification of women at risk for CAD is crucial, especially given that sudden cardiac death is often the first manifestation of CAD in a high proportion of women (52%), compared with men (42%) [5].

The focus on sex-specific cardiovascular disease research has resulted in the development of a robust, multifactorial evidence base for the role of an assortment of diagnostic tests in women with suspected myocardial ischemia [6, 7]. Notable findings relevant to the practicing clinician include 1) the shift in focus from diagnostic accuracy in detecting CAD to risk assessment as a means to guiding therapy in women with symptoms suggestive of IHD; and 2) the observed paradoxical sex differences in which women with symptoms suggestive of IHD and documented ischemia on noninvasive imaging have less anatomic obstructive CAD but yet worse prognosis compared with age-matched men [6, 8, 9••]. Recently reviewed data demonstrated that symptomatic women with angiographically normal or nonobstructive coronary stenoses have increased rates of myocardial infarction (MI), stroke, hospitalization for congestive heart failure, and cardiac mortality compared with a similarly matched cohort of patients without symptoms [10••]. Therefore, the evolving evidence that "at-risk" women may have a high burden of atherosclerosis as evidenced by diffuse coronary atherosclerosis more often than focal lesions makes noninvasive evaluation increasingly challenging [6].

Based on recent insights on the complex pathophysiology of CHD including the spectrum of obstructive CAD, and

L. M. Phillips · J. H. Mieres (✉)
Division of Cardiology, Department of Medicine, New York University School of Medicine-Langone Medical Center,
550 First Avenue, TCH-2, Room 246,
New York, NY 10016, USA
e-mail: Jennifer.Mieres@nyumc.org

dysfunction of the coronary microvasculature and endothelium, Shaw et al. [9••] proposed the use of the term *ischemic heart disease* as a more appropriate term for the discussion specific to women, rather than CAD or CHD. Although, the evidence thus far indicates a high prevalence of obstructive CAD with flow-limiting stenosis in men and elderly women with acute coronary syndrome (ACS), in over 50% of women undergoing cardiac catheterization for ACS there is no evidence of obstructive CAD [9••]. These recent findings pave the way for an expanded role of cardiac imaging to investigate other parameters implicated in the spectrum of IHD in women—the coronary and noncoronary atherosclerotic burden and methods to detect dysfunction of the coronary endothelium, reserve, and microvasculature. We review the literature regarding the noninvasive assessment of CAD in symptomatic women, with a specific emphasis on the insights from recent publications with respect to the noninvasive assessment of IHD in women.

Role of the Exercise Electrocardiogram: Is It Sufficient to Assess Risk in Women?

As per the American College of Cardiology/American Heart Association guidelines, nonimaging treadmill exercise stress testing continues to be appropriate first-line test in symptomatic women with a normal resting 12-lead electrocardiogram (ECG) who are at intermediate risk for CHD based on risk factors and symptoms and are capable of maximal exercise stress [7, 11]. Recent evidence demonstrated the lower sensitivity and specificity of treadmill exercise testing for detecting obstructive CAD in women compared with men [12]. Coupled with the lower prevalence of obstructive CAD in women and lower exercise tolerance, the use of the traditional definition of an abnormal treadmill exercise stress test defined as reversible ST-segment depressions (≥1 mm horizontal or downsloping) leads to frequent underdiagnosis of obstructive CAD. In a meta-analysis of 3,721 women evaluated for detecting obstructive CAD with treadmill stress testing, ST-segment depression (≥1-mm horizontal or downsloping changes) during the test was shown to have a sensitivity and specificity in women of 61% and 70%, respectively [12]. This finding is compared with men whose treadmill stress test sensitivity and specificity has been found to be almost 10% higher [11]. Although several publications support a higher false-positive rate of exercise ECG in women compared with men, accuracy for detecting obstructive CAD is dependent on the morphology, magnitude, and duration of the ECG changes. Marked ST-segment changes (ie, ≥2-mm) horizontal or downsloping ST depression at low workloads and persisting into recovery are all sensitive markers for the presence of obstructive CAD in women and men [13]. False-positives are more often seen with exercise-induced upsloping ST changes in women. Variables felt to contribute to the false-positive stress-induced ECG changes noted in women include 1) low QRS voltage and 2) the digoxin-like effect of estrogen with resultant exercise-induced ST depression [7].

With regard to prognosis, the exercise ECG provides important data on risk of cardiac death or MI. The addition of variables such as functional capacity and calculation of the Duke treadmill score have been shown to enhance the prognostic ability of the treadmill ECG test in women [13]. The Duke treadmill score, defined as exercise time—(5× ST-segment deviation)−4×chest pain [1 = nonlimiting, 2 = limiting]—can accurately predict cardiac death [13]. Despite the inability of at-risk women to achieve maximum exercise stress, duration of exercise as manifested in metabolic equivalents (METs) is by far the strongest prognostic variable from treadmill exercise stress ECG [14, 15]. A sex-specific nomogram for predicting normative values of exercise for women has been devised based on age [16]. Limited functional capacity (<5 METs) has been shown to be a consistent marker of worsened prognosis. In the St. James WTH (Women Take Heart) Project, of the 5,721 asymptomatic women who underwent baseline symptom-limited stress ECG, those who achieved less than 5 METs had a greater than three times higher death rate than those who achieved more than 8 METs. At 20-year follow-up, nearly 20% of women achieving only less than 5.5 METs of exercise had died compared with 8% with peak METs of 9.3 [16].

For the clinician determining which women are capable of achieving maximum stress with the exercise ECG, the use of the Duke Activity Status Index (DASI) can help in predicting functional capacity. The DASI score, a weighted scoring system that uses a 12-question survey, has been validated in women to estimate the METs associated with the activities of daily living [17]. Using this scale, the investigators from the WISE (Women's Ischemia Syndrome Evaluation) study demonstrated an increased risk of cardiovascular death and nonfatal MI for women with a calculated DASI score of less than 5 METs (Table 1) [17].

Role of Stress Echocardiography

Stress echocardiography, with exercise or dobutamine pharmacologic stress, can be used to identify stress-induced ischemia. By providing information on the presence and location of wall-motion abnormalities related to a decrease in regional myocardial blood flow, the extent and location of ischemia can be defined.

The diagnostic role of stress echocardiography in women has been well established. Aggregate data analysis of over

Table 1 Duke activity status index

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

Scoring the Duke Activity Status Index (DASI): Add the point values for all questions checked in the Yes column and divide by 3.5 to calculate the estimated DASI metabolic equivalents

(*From* Shaw et al. [17]; with permission.)

1,000 women has shown a high accuracy for identifying physiologically significant CAD, with a mean sensitivity of 81% and a specificity of 86% [7, 18, 19]. In symptomatic women who are incapable of exercise, dobutamine stress echocardiography reliably detects multivessel disease, with reported sensitivities from 75% to 93% and specificities of 79% to 92% [7]. Based on recent studies, stress echocardiography with exercise or dobutamine stress is equally accurate for diagnosing physiologically significant CAD in women as in men. Stress echocardiography has been shown to be clinically useful for estimating cardiovascular prognosis in women [18, 20, 21]. In a study evaluating 5-year survival in 4,234 female patients undergoing exercise stress echocardiography, survival in patients with no evidence of ischemia was found to be 99.4%, 97.6% with evidence of single-vessel ischemia, and 95% in the setting of multiple-vessel ischemia [21]. Although an abnormal stress echocardiography correlates with a high cardiac event rate in women, a recent meta-analysis comparing dobutamine stress echocardiography to exercise single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) revealed a yearly rate of 0.75% of cardiovascular death and MI in the setting of a low-risk dobutamine echocardiography compared with 0.3% per year in low-risk exercise MPI [22]. The authors concluded that in the ischemic cascade, perfusion abnormalities detected by SPECT MPI precede the wall-motion abnormalities seen with stress echocardiography. Wall-motion abnormalities often occur in the setting of advanced stenosis and with less predictability in areas supplied by mild-to-moderate coronary artery stenoses. Given the fact that an acute MI often presents in areas subtended by a less critical stenosis, stress echocardiography may underestimate risk in women with less advanced CAD. Therefore, in women, a negative or low-risk stress echocardiography has a higher cardiac death or MI rate compared with a low-risk stress MPI [22].

Stress echocardiography in at-risk women has improved diagnostic and prognostic accuracy over exercise treadmill testing even when ECG stress interpretation is combined with the use of exercise capacity and hemodynamic data [19]. Compared with other noninvasive cardiac imaging modalities (eg, SPECT, cardiac CT, coronary artery calcium [CAC]), a specific benefit of stress echocardiography for evaluating at-risk women is the absence of radiation exposure.

Role of MPI with SPECT

SPECT with ECG gating, a nuclear-based technique, provides quantitative information on myocardial perfusion, regional and global left ventricular function, and end-systolic and end-diastolic volumes. The diagnostic and prognostic value of contemporary techniques of SPECT MPI in at-risk women has been supported by a growing body of evidence-based data [7, 23, 24]. Traditionally, SPECT MPI has been reported to have challenges that are specific to women. Technical limitations in women (including photon attenuation by breast tissue, lower prevalence of epicardial CAD, and small left ventricular chamber size) have accounted for past publications with decreased sensitivity and specificity [23, 25].

Advances in SPECT MPI have led to improvements of the limitations that are specific to women. Contemporary SPECT

MPI techniques that include ECG gating, attenuation artifact protocols, and the use of the higher-energy radioisotope technetium have resulted in enhanced diagnostic accuracy for evaluating physiologically significant CAD in women [7, 26–29].

SPECT MPI with pharmacologic stress is worth discussing because at-risk women are generally older and often have decreased exercise capacity when they present with symptoms of IHD [7, 30]. Vasodilator stress has been shown to be accurate in detecting physiologically significant CAD in women, with reported sensitivity of 91% and specificity of 86% for detecting a greater than 50% coronary artery stenosis [30].

A robust body of evidence supports the excellent prognostic accuracy of exercise and pharmacologic stress MPI in women. The prognostic value of MPI has been well established, with the size and severity of defects directly related to the annual risk of a cardiac event, independent of sex [24, 31, 32]. Pooled MPI data in over 7,000 women demonstrate a cardiac event rate of less than 0.7% with a normal study (and a 5% annual cardiac death rate for women with moderate-to-severe perfusion abnormalities) [32]. Vasodilator pharmacologic stress was shown to be effective in the risk assessment of diabetic women with suspected and known IHD. In a cohort of 2,656 women and 2,677 men who underwent adenosine SPECT, the annual CAD mortality rate in the setting of a moderately abnormal scan was roughly the same for nondiabetic men and women, 2.7% and 2.8%, respectively. Diabetic women with normal scans were at increased risk for CAD mortality at 1.6%, compared with diabetic men with a risk of 0.8% and nondiabetic women with a risk of 0.8% [33]. Diabetic women with severely abnormal MPI studies are at highest risk, with annual CAD mortality rates of 8.5% versus 6.1% in nondiabetic women. Of note, diabetic women with evidence of ischemia on MPI were at highest risk for cardiac event if insulin was used to manage their diabetes [33].

Future Directions in Noninvasive Imaging in Women

The growth in imaging modalities combined with the ability to define abnormalities specific to the coronary and vascular tree have provided insight into the pathogenesis of IHD in women. Clinical trials such as the WISE study have provided evidence to support the fact that several mechanisms contribute to the worse outcomes and continued symptoms in the cohort of women who have no evidence of obstructive CAD. In these women, microvascular dysfunction of the coronary tree may in part account for the paradoxical finding of a greater symptom burden and high cardiac mortality despite the lower burden of obstructive CAD. Although men and women have a similar amount of coronary plaque, data from recent trials and intravascular ultrasound and pathology studies underscore the limitations of traditional testing algorithms in estimating risk in these women. Notable findings include 1) a higher prevalence of "positive" or outward or negative coronary artery remodeling in women compared with men; 2) increased endothelial dysfunction with inability of the arteries and arterioles to dilate due to limited production of the vasodilator nitric oxide by the endothelium; and 3) smaller coronary arteries per body surface area compared with men, which might further magnify symptoms due to stenosis or endothelial dysfunction [34••]. The development of protocols and attention on methods to detect subclinical atherosclerosis and endothelial dysfunction promise to reveal a new model for heart disease in women [34••]. As we shift our focus from the detection of flow-limiting CAD lesions, cardiac imaging techniques with cardiac CT, positron emission tomography (PET), and cardiac magnetic resonance imaging (CMR) will play a future role as imaging is expanded to include methods to investigate other parameters implicated in the spectrum of IHD in women—the coronary and noncoronary atherosclerotic burden including methods to detect dysfunction of the coronary endothelium, reserve, and microvasculature.

Role of MPI with PET

MPI with PET provides higher spatial resolution than SPECT, and is a powerful noninvasive modality for the diagnosis and risk assessment of CAD [35, 36]. The ability to calculate absolute blood flow in coronary beds, assess wall motion at peak hyperemia with vasodilator stress, and evaluate coronary flow reserve enhances the diagnostic and prognostic accuracy of PET imaging [36, 37]. The intrinsic ability of PET to correct for photon attenuation provides enhanced specificity in evaluating IHD as it corrects for attenuation artifacts, such as breast tissue artifact and soft tissue attenuation in obese women [35, 36]. Although there is a paucity of sex-specific data with PET perfusion imaging, the identification of physiologically significant CAD has been shown to be high, with a sensitivity of 90%, specificity of 89%, and overall diagnostic accuracy of 90% [35]. Vasodilator stress MPI with PET, using rubidium-82 (Rb-82), offers several advantages for assessing IHD in at-risk obese women who are not capable of maximum exercise stress and in whom soft tissue attenuation can decrease the diagnostic accuracy of SPECT.

Emerging data on sex-specific prognosis support the role of PET in the risk assessment of women and men with known or suspected IHD. In a recent study on a cohort of over 1,400 patients followed up for 1 year, Rb-82 PET MPI with vasodilator stress was shown to provide incremental

prognostic value to historical/clinical variables and resting left ventricular ejection fraction (LVEF) to predict survival free of cardiac events and all-cause death. The addition of LVEF reserve was shown to provide significant independent and incremental value to Rb-82 MPI for predicting the risk of future adverse events [38]. Coronary flow reserve, a marker of endothelial dysfunction, was recently studied with PET [39]. In a small study of a cohort of 26 women and 16 men with complaints of chest pain and normal coronary angiography, PET perfusion with N-13 ammonia demonstrated reduced coronary flow reserve in women with symptoms of typical angina and no evidence of obstructive CAD. This method shows promise for the risk stratification and management of women with symptoms that may be due to endothelial dysfunction [40].

Role of CAC Scoring and CT Angiography

Cardiac CT, using electron beam tomography or multidetector CT, allows a noninvasive anatomic quantification of CAC, noncalcified coronary artery plaque, and degree of coronary artery stenosis. Although not specific for luminal obstruction, the CAC score provides an estimate of the total atherosclerotic plaque burden and thereby provides information regarding cardiac risk. The presence of calcification signifies the presence of atherosclerosis because calcification does not occur in a normal vessel wall. Recent data reveal an evolving role of cardiac CT in the identification and risk assessment of CAD in at-risk women [41]. Sex-specific data on the role of CAC in evaluating at-risk symptomatic women demonstrate a high negative predictive value when correlated with coronary angiography. In a cohort of 539 symptomatic women who underwent clinically indicated coronary angiography, 41% had a normal angiogram and no evidence of CAC, with a negative predictive value of 100%. There was a greater prevalence of obstructive CAD in women with CAC scores of more than 100 [41].

CAC detection adds incremental prognostic value to traditional risk factors in asymptomatic women at risk for IHD [42, 43]. In an asymptomatic cohort of 4,191 women and 6,186 men, CAC was associated with a higher risk of death in women than in men at each level of calcification. At 5-year follow-up, 80% of women with CAC scores of greater than 1,000, representing extensive coronary calcification, were alive compared with 98.4% of women with no evidence of CAC [41].

Cardiac CT angiography (CTA) allows the noninvasive anatomic evaluation of the coronary arteries. The introduction of updated software and 64-slice multidetector technology facilitates the noninvasive anatomic assessment of obstructive CAD with a high diagnostic accuracy with sensitivities and specificities in the ranges of 80% to 98% and 86% to 98%, respectively [43]. No sex-specific differences were noted with contemporary computed tomographic angiography (CTA) techniques [44]. In a recent study of 52 men and 51 women who were evaluated with 64-multislice CT and coronary angiography with segmental comparison, sensitivity and specificity were similar by gender at 85% and 99%, respectively [44]. Although the exposure to radiation with CTA remains a concern, the introduction of dual-source cameras and new protocols using techniques of retrospective ECG-gating show promise of decreasing the radiation dose while maintaining excellent image quality [45]. Cardiac CTA with its ability to facilitate visualization of the coronary lumen and vessel wall may be a useful noninvasive testing modality in the diagnosis and risk assessment of symptomatic women, in the setting of an abnormal or equivocal noninvasive stress imaging test.

Role of CMR

MRI is emerging as an important imaging modality for assessing CAD in women. In addition to the ability to evaluate anatomic obstruction by angiography and blood flow assessment, MR perfusion imaging allows functional assessment of pharmacologic vasodilator-induced ischemia and segmental wall-motion evaluation. Recent studies have shown that MRI with its superior spatial and temporal resolution can identify subendocardial ischemia and aid in detecting IHD in at-risk women [46]. In one small study, MRI was used to identify subendocardial ischemia in a cohort of women with symptoms but no evidence of obstructive CAD [46]. In a recent study of 204 women with suspected or known CAD who underwent conventional coronary angiography and dobutamine stress magnetic resonance, the sensitivity and specificity of MRI for detecting obstructive CAD in women was found to be 85% and 86%, respectively [47].

Prognostic data with MRI are limited. However, in a recent study of a cohort of 266 women followed up for a mean of 6.2 years, the identification of inducible wall-motion abnormalities with dobutamine stress CMR predicted cardiac death and MI [48]. Although additional sex-specific studies are needed, CMR is emerging as a clinically useful modality in the diagnostic and prognostic evaluation of women with suspected IHD. The absence of ionizing radiation in CMR may be an attractive technique for serial monitoring of women with known CAD.

Recommendations

For women with symptoms and risk factors for CAD, clinicians should first look at risk factors, symptoms, and the

baseline ECG to estimate pretest likelihood of CAD. This assessment should be followed by an estimation of functional capacity because this is strongly linked to prognosis and is useful in determining the appropriate noninvasive stress testing modality. Current evidence supports the use of the exercise ECG stress test as the initial test for the symptomatic woman with a normal resting ECG and good exercise tolerance (capable of >5 METs). The addition of nonexercise parameters, calculation of functional capacity, and clinical scores such as the Duke treadmill score to ST-segment depressions improves the ability for diagnosis and evaluation of prognosis in women [6, 7].

Cardiac imaging using contemporary SPECT MPI/stress echocardiography techniques provides excellent diagnostic accuracy and risk stratification in symptomatic women with known or suspected IHD. Stress MPI/stress echocardiography provides incremental value over clinical variables and the exercise ECG in women with suspected or known CAD. Local expertise should guide test selection. Of note, SPECT MPI provides validated quantitative data on the location, extent, and severity of stress-induced ischemia, whereas the interpretation of stress echocardiography is dependent on expertise and visual analysis. As per the recent American Heart Association consensus statement, symptomatic women with questionable exercise capacity, those with an abnormal baseline ECG, and those with diabetes mellitus, cardiac imaging with exercise or pharmacologic stress should be the first test of choice. Evolving evidence supports the use of cardiac CTA for the noninvasive evaluation of the coronary arteries in the setting of an abnormal or equivocal stress cardiac imaging study. CMR can be useful in evaluating symptomatic women with no evidence of obstructive CAD to evaluate the coronary microvasculature for evidence of subendocardial ischemia or abnormal coronary reserve. Figure 1 proposes a diagnostic pathway based on recent evidence for evaluating symptomatic women at risk for IHD.

Conclusions

Contemporary techniques for cardiac imaging with stress SPECT MPI and stress echocardiography are effective in the diagnosis and risk stratification of symptomatic women at risk for CAD. Insights from recent clinical trials have provided evidence that the etiology of IHD in women is multifactorial and includes obstructive CAD and dysfunction of the coronary microvasculature and endothelium.

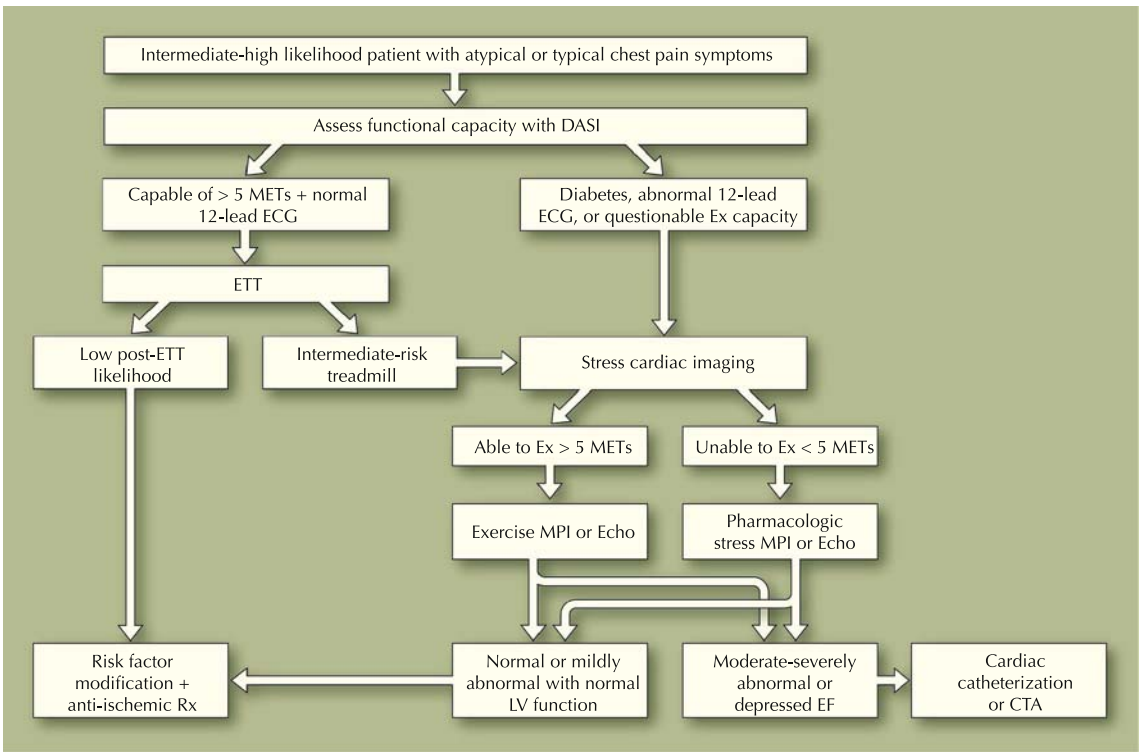

Fig. 1 Proposed algorithm for evaluating symptomatic women at intermediate risk for ischemic heart disease. Based on the recent evidence, an assessment of functional capacity (an important predictor of cardiac events in women) using the Duke Activity Status Index (DASI) is included in this algorithm to assist in the selection of the appropriate stress test. CTA—computed tomographic angiography; ECG—electrocardiogram; Echo—echocardiography; EF—ejection fraction; ETT—exercise treadmill test; Ex—exercise; LV—left ventricular; METs—metabolic equivalents; MPI—myocardial perfusion imaging; Rx—treatment. (*Adapted from* Shaw et al. [6] and Mieres et al. [7].)

Future imaging protocols that focus on measuring endothelial function and detecting subclinical atherosclerosis will be integrated into diagnostic and prognostic algorithms for at-risk women. Emerging technology and protocols using CMR, measurement of carotid intima-media thickness, and brachial artery flow–mediated dilatation will be useful in identifying endothelial dysfunction, microvascular disease, or abnormal coronary reactivity in symptomatic women with or without a normal stress echocardiography/SPECT MPI in the setting of nonobstructive CAD. Identification of these women is essential for the targeted prevention strategies because they are at intermediate risk for cardiac death and MI [10••].

Disclosure Dr. Lawrence M. Phillips is on the speakers' bureau of Astellas Pharma USA. Dr. Jennifer H. Mieres has received research support from Astellas Pharma USA and GE Healthcare.

References

Papers of particular interest, published recently, have been highlighted as follows:
•• Of major importance

1. Centers for Disease Control and Prevention: Deaths: *National Vital Statistics Reports—Deaths: Final Data for 2005*. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf. Accessed September 10, 2009.
2. Ford ES, Ajani UA, Croft JB, et al.: Explaining the decrease in U. S. deaths from coronary disease, 1980–2000. N Engl J Med 2007, 356:2388–2398.
3. Mosca L, Banka CL, Benjamin EJ, et al.: Evidence-based guidelines for cardiovascular disease prevention in women: 2007 Update. J Am Coll Cardiol 2007, 49:1230–1250.
4. Lloyd-Jones D, Adams R, Carnethon M, et al.: Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009, 119:480–486.
5. Murphy SL: Death: Final data for 1998. Natl Vital Stat Rep 2000, 48:1–105.
6. Shaw LJ, Bairey Merz CN, Pepine CJ, et al.: Insights From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. Part 1: gender differences in traditional an novel risk factors, symptom evaluation and gender optimized diagnostic strategies. J Am Coll Cardiol 2006, 47:4S–20S.
7. Mieres JH, Shaw LJ, Arai A, et al.: Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005, 111:682–696.
8. Bairey Merz CN, Shaw LJ, Reis SE, et al.: Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol 2006, 47(3 Suppl):S21–S29.
9. Shaw LJ, Bugiardini R, Bairey Merz CN: Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol 2009, 54:1561–1575. *In this state-of-the-art paper, the authors discuss the spectrum of etiologies involved in IHD in women. Dysfunction of the microvasculature is implicated as a cause of symptoms and worse prognosis in the absence of obstructive disease. An additional leading culprit is abnormal reactivity in the small heart arteries leading to poor blood flow (ischemia) to the heart muscle*
10. •• Gulati M, Cooper-DeHoff RM, McClure C, et al.: Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. Arch Intern Med 2009, 169:843–850. *This study reports on cardiovascular events (MI, death, stroke, heart failure) between the symptomatic cohort of women from the WISE study and the asymptomatic cohort of women from the St. James WTH Project. Women with symptoms and signs suggestive of ischemia but without obstructive CAD are at elevated risk for cardiovascular events compared with asymptomatic community-based women*.
11. Gibbons RJ, Balady GJ, Bricker JT, et al.: ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Available at http://www.americanheart.org/downloadable/heart/1032279013658exercise.pdf. Accessed December 2009.
12. Kwok YS, Kim C, Grady D, et al.: Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999, 83:660–666.
13. Alexander KP, Shaw LJ, Shaw LK, et al.: Value of exercise treadmill testing in women. J Am Coll Cardiol 1998, 32:1657–1664. (Published erratum appears in *J Am Coll Cardiol* 1999, 33:289.)
14. Gulati M, Pandey DK, Arnsdorf MF, et al.: Exercise capacity and the risk of death in women: the St. James Women Take Heart Project. Circulation 2003, 108:1554–1559.
15. Mora S, Redberg RF, Cui Y, et al.: Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women. JAMA 2003, 290:1600–1607.
16. Gulati M, Black HR, Shaw LJ, et al.: The prognostic value of a nomogram for exercise capacity in women. N Engl J Med 2005, 353:468–475.
17. Shaw LJ, Olson MB, Kip K, et al.: The value of estimated functional capacity in estimating outcome. J Am Coll Cardiol 2006, 47:36S–43S.
18. Cheitlin MD, Armstrong WF, Aurigemma GP, et al.: ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Coll Cardiol 2003, 42:954–970.
19. Williams MJ, Marwick TH, O'Gorman D, et al.: Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in women. Am J Cardiol 1994, 74:435–438.
20. Arruda-Olson AM, Jracan EM, Mahoney DW, et al.: Prognostic value of exercise echocardiography in 5,978 patients: is there a gender difference? J Am Coll Cardiol 2002, 39:625–631.
21. Shaw LJ, Vassey C, Sawada S, et al.: Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4,234 women and 6,898 men. Eur Heart J 2005, 26:447–456.
22. Metz LD, Beattie M, Hom R, et al.: The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007, 49:227–237.

23. Klocke FJ, Baird MG, Lorell BH, et al.: ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines of the Clinical Use of Cardiac Radionuclide Imaging). Circulation 2003, 108:1404–1418.
24. Mieres JH, Shaw LJ, Hendel RC, et al.: American Society of Nuclear Cardiology consensus statement: Task Force on Women and Coronary Artery Disease—the role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women. J Nucl Cardiol 2003, 10:95–101.
25. 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.
26. Taillefer R, DePuey EG, Udelson JE, et al.: Comparative diagnostic accuracy of Tl-201 and Tc-99 m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. J Am Coll Cardiol 1997, 29:69–77.
27. Santana-Boado C, Candell-Rivera J, Castell-Conesa J, et al.: Diagnostic accuracy of technetium-99 m-MIBI myocardial SPECT in women and men. J Nucl Med 1998, 39:751–755.
28. Mieres JH, Makaryus AN, Cacciabaudo JM, et al.: Value of electrocardiographically gated single-photon emission computed tomographic myocardial perfusion scintigraphy in a cohort of symptomatic postmenopausal women. Am J Cardiol 2007, 99:1096–1099.
29. Elhendy A, Schinkel AF, Bax JJ, et al.: Accuracy of stress Tc-99 m tetrofosmin myocardial perfusion tomography for the diagnosis and localization of coronary artery disease in women. J Nucl Cardiol 2006, 13:629–634.
30. Amanullah AM, Berman DS, Hachamovitch R, et al.: Identification of severe or extensive coronary artery disease in women by adenosine technetium-99 m sestamibi SPECT. Am J Cardiol 1997, 80:132–137.
31. Marwick TH, Shaw LJ, Lauer MS, et al.: The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Economics of Noninvasive Diagnosis (END) Study Group. Am J Med 1999, 106:172–178.
32. Shaw LJ, Iskandrian AE: Prognostic value of stress gated SPECT. J Nucl Cardiol 2004, 11:171–185.
33. Berman DS, Kang X, Hayes SW, et al.: Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 2003, 41:1125–1133
34. •• Bellasi A, Raggi P, Merz CN, Shaw LJ: New insights into ischemic heart disease in women. Cleve Clin J Med 2007, 74:585–594. *This paper discusses the recent evidence on sex differences in CAD and possible strategies for detecting and assessing coronary disease in women*.
35. Di Carli MF, Hachamovitch R: New technology for noninvasive evaluation of coronary artery disease. Circulation 2007, 115:1464–1480.
36. Heller GV, Calnon D, Dorbala S: Recent advances in cardiac PET and PET/CT myocardial perfusion imaging. J Nucl Cardiol 2009, 16:962–969.
37. Dorbala S, Vangala D, Samson U, et al.: Value of vasodilator left ventricular ejection fraction reserve in evaluation of the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: a 82 Rb PET/CT study. J Nucl Med 2007, 48:349–358.
38. Dorbala S, Hachamovitch R, Curillova Z, et al.: Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. JACC Cardiovasc Imaging 2009, 2:846–854.
39. Herzog BA, Husmann L, Valenta I, et al.: Long-term prognostic value of 13 N-ammonia myocardial perfusion Positron emission tomography added value of coronary flow reserve. JACC Cardiovasc Imaging 2009, 54:150–156.
40. de Vries J, DeJongste MJ, Jessurun GA, et al.: Myocardial perfusion quantification in patients suspected of cardiac syndrome X with positive and negative exercise testing: a [13-N] ammonia positron emission tomography study. Nucl Med Commun 2006, 27:791–794.
41. Raggi P, Shaw LJ, Berman DS, Callister TQ: Gender-based differences in the prognostic value of coronary calcification. J Womens Health (Larchmt) 2004, 13:273–283.
42. Budoff MJ, Achenbach S, Blumenthal RS, et al.: Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006, 114:1761–1791.
43. Greenland P, Bonow RO, Brundage BH, et al.: ACCF/AHA 2007 clinical expert consensus document on CAC scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007, 49:378–402.
44. Pundziute G, Schuijf JD, Jukema JW, et al.: Gender influence on the diagnostic accuracy of 64-slice multislice computed tomography coronary angiography for detection of obstructive coronary artery disease. Heart 2008, 94:48–52.
45. Pflederer T, Rudofsky L, Ropers D, et al.: Image quality in a low radiation exposure protocol for retrospectively ECG-gated coronary CT angiography. AJR Am J Roentgenol 2009, 192:1045–1050.
46. Panting JR, Gatehouse PD, Yang GZ, et al.: Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002, 346:1948–1953.
47. Gebker R, Jahnke C, Hucko T, et al.: Dobutamine stress magnetic resonance imaging for the detection of coronary artery disease in women. Heart 2009 August 16 (Epub ahead of print).
48. Wallace EL, Morgan TM, Walsh TF, et al.: Dobutamine cardiac magnetic resonance results, predict cardiac prognosis in women with known or suspected ischemic heart disease. JACC Cardiovasc Imaging 2009, 2:299–307.