Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease

A Consensus Statement From the American Heart Association

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In recent decades, there has been an appropriate focus on ensuring gender equity in the quantity and quality of evidence to guide female-specific, optimal management strategies for suspected and known ischemic heart disease (IHD). The evolving evidence supports a multifactorial pathophysiology of coronary atherosclerosis that includes obstructive coronary artery disease (CAD) and dysfunction of the coronary microvasculature and endothelium, and therefore, the term IHD best encompasses this varied pathophysiology in women. An overwhelming body of evidence has documented undertreatment and undertesting of women, leading to higher case fatality rates and increased morbid complications among women.[1–3] Accordingly, to increase our knowledge base, women were given the status of a priority population, which resulted in federal policy to include proportional representation of females in clinical trials and registries.[4]

The past decade provided abundant evidence to guide clinical decision making regarding diagnostic testing for suspected IHD. In 2005, the American Heart Association (AHA) published an evidence synthesis on the use of CAD imaging for the evaluation of symptomatic women with suspected myocardial ischemia.[5] Numerous reports have since provided additional high-quality evidence, including data on coronary computed tomographic angiography (CCTA) and cardiac magnetic resonance imaging (CMR), which in 2005 were considered research techniques.[5] The present statement provides an update to the 2005 document and synthesizes contemporary evidence on appropriate symptomatic female candidates for diagnostic testing, as well as sex-specific data on the diagnostic and prognostic accuracy for exercise treadmill testing (ETT) with electrocardiography, stress echocardiography, stress myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) or positron emission tomography (PET), stress CMR, and CCTA.[5] Within this document, quality evidence is synthesized, and important gaps in knowledge about the assessment of IHD risk in women are identified. The 2005 document included sections on the evaluation of asymptomatic women, a topic that was updated recently in an American College of Cardiology (ACC) Foundation/AHA clinical practice guideline on detection of high-risk asymptomatic individuals.[6] The present statement will focus on the role of diagnostic testing in the identification of symptomatic women with no, nonobstructive, and obstructive CAD and the evolutionary changes resulting in a diagnostic paradigm based on female-specific evidence to identify women at an elevated IHD risk with and without obstructive CAD who require guideline-directed medical management tailored to their individual needs.

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Contemporary Diagnostic Evaluation of Women With Suspected IHD

Historically, the focus of the diagnostic evaluation for symptomatic women and men has been the detection of an obstructive coronary stenosis requiring revascularization (as appropriate). Two challenges to this approach have resulted in revision of this evaluation algorithm and provided added insight into the burden of atherosclerosis and overall hazard for IHD events in women. First, recent clinical trial data have revealed that prompt guideline-based medical management is safe and that revascularization may be deferred for women and men with stable IHD (SIHD).[7,8] Strategies of either revascularization with optimal medical therapy or optimal medical management alone are effective at reducing the burden of angina for SIHD patients.[9] Second, there is unfolding evidence of the clinical and prognostic significance of nonobstructive CAD, detected by intravascular ultrasound or CCTA.[10–18] Although it affects both women and men, the burden of nonobstructive CAD disproportionately disadvantages at-risk females, who have a higher prevalence of nonobstructive CAD (defined as 1%–49% stenosis) at coronary angiography.[19,20] There is a general pattern that women with stable ischemic symptoms, despite having a higher prevalence of nonobstructive CAD, have an elevated hazard for coronary events compared with the general population,[20–22] and this risk is particularly increased for women <75 years of age.[23] Moreover, myocardial ischemia is associated with higher IHD mortality among symptomatic women than among men.[23] The concept that symptoms in women are correlated with coronary vascular dysfunction in the setting of arterial expansive remodeling and nonobstructive plaque is a critical component for understanding female-specific patterns in symptom presentation and elevated IHD risk.[21,24,25] Thus, the contemporary perspective highlights the importance of documented myocardial ischemia and the burden of nonobstructive and obstructive CAD in women as being fundamental to determining IHD risk and guiding therapeutic decisions.

Accordingly, the present statement focuses on 2 general patterns of clinical presentation and correlative disease burden: (1) inducible ischemia caused by an obstructive CAD stenosis (ie, the diagnostic accuracy) and (2) the identification of the extent and severity of myocardial ischemia that results from coronary vascular dysfunction in the setting of nonobstructive CAD and the ensuing elevation of IHD risk (ie, prognostic accuracy for major adverse IHD events) in symptomatic women. Consequently, women with nonobstructive CAD and stress test abnormalities are no longer defined as having a false-positive test, but their test is classified as abnormal, and they are noted as being at an elevated IHD risk. Prognostic estimates relative to more extensive and severe wall-motion or perfusion abnormalities or CCTA-defined obstructive CAD are also addressed.

Table 1. Pretest CAD Likelihood in Women and Men Across Age Deciles

	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
Age, y	Women	Men	Women	Men	Women	Men
35	1–19	3–35	2–39	8–59	10–78	30–88
45	2–22	9–47	5–43	21–70	20–79	51–92
55	4–21	23–59	10–47	45–79	38–82	80–95
65	9–29	49–69	20–51	71–86	56–84	93–97

This table, taken from the recent guidelines on stable ischemic heart disease,[26] reports the significant overlap in the estimated CAD likelihood values for women and men with nonanginal chest pain, atypical angina, and typical angina, respectively. Values indicate percentage with significant CAD. The first value listed is the percentage for a low-risk, mid-decade patient without diabetes mellitus, smoking, or hyperlipidemia. The second is that of a patient of the same age with diabetes mellitus, smoking, and hyperlipidemia.

CAD indicates coronary artery disease.

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Typical Patterns of Symptom Presentation in Women

Both the 2005 document and previous reviews recognize that for women and men, the most common presentation of myocardial ischemia is chest pain or discomfort; however, along the spectrum of ischemic symptoms, women have a different pattern and distribution of non–chest-related pain symptoms. Compared with men, women's ischemic symptoms are more often precipitated by mental or emotional stress and less frequently by physical exertion. Studies that have systematically evaluated sex differences in presenting symptoms have not found a pattern of symptoms uniquely ascribed to male or female patients, but significant overlap in qualitative descriptors exists. Proportionately, women more often report epigastric discomfort and associated nausea; radiation of discomfort to the arms, neck, and interscapular areas; and dyspnea and fatigue.[1–3,5,21,24,25] Table 1, taken from the recent SIHD guidelines, reports the significant overlap in the estimated CAD likelihood values for women and men with nonanginal chest pain, atypical angina, and typical angina, respectively.[26] The National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE) registry collected detailed symptom descriptors to derive a typical female pattern of chest pain.[21] The evidence synthesis largely highlights that women experience a broad range of symptoms, frequently including rest and stress-related symptoms.[21,27] This nonspecific clinical presentation renders the evaluation of symptoms and the precision of an obstructive CAD likelihood in a female patient difficult.[28] The vast evidence on the typical presentation for chest pain symptoms as exertional and the associated prevalence of obstructive CAD was derived from largely male populations.[28–30]

The broader spectrum of presenting symptoms in women often leads to more frequent referral for diagnostic testing to improve the precision of the IHD likelihood estimate.[26] The present statement will emphasize value-based imaging strategies that incorporate effectiveness and efficiency within the IHD evaluation. Our aim is to limit the use of more expensive noninvasive and invasive imaging procedures, except when evidence clearly supports their benefit in improved diagnostic and prognostic accuracy. When comparative effectiveness evidence is available, in particular if it highlights a lower-cost procedure, this statement provides recommendations to curb the use of higher-cost procedures. The ensuing evidence tailored to the female patient can serve as a standard for value-based imaging that would be equally applicable to women and men alike.

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Pretest IHD Risk Assessment

Underlying Hazard for IHD Risk in Women: Selecting Optimal Candidates for Exercise Testing and CAD Imaging

Among asymptomatic women, risk assessment commonly involves the use of conventional global risk scores such as the Framingham risk score, and recent prevention guidelines have focused on the benefit of applying lifetime risk estimates in apparently healthy asymptomatic women.[31] However, for the symptomatic woman, use of risk scores weighted for the general population of asymptomatic individuals is not recommended. To date, there are no pretest risk scores that integrate the clinical and symptom parameters available for use in women and men presenting with suspected IHD. In general, the conventional terminology of pretest risk of likelihood was used to estimate CAD, but the estimates were based on decades-old data.[32] Cheng and colleagues[33] recently reported the prevalence of obstructive CAD by CCTA in a large cohort of women with chest pain symptoms (Figure 1).

In the present report, we will focus on pretest IHD risk as it relates to elevated risk of coronary events. Some general rules were synthesized from available evidence. IHD risk increases with age and is exacerbated in the woman with multiple risk factors or comorbidities.[18,20,21,23–25,33] The classification of IHD risk in women refers solely to women who present for evaluation of suspected IHD who have chest pain symptoms or some ischemic equivalent, including excessive dyspnea, with other cardiopulmonary comorbidities excluded.[5] Broadly characterized, premenopausal women with symptoms should be considered at low risk, excluding those with diabetes mellitus. With some exceptions, women at low IHD risk are not candidates for a diagnostic evaluation. When selective clinical judgment is used, a routine exercise ECG is the most appropriate test in women at low IHD risk. Symptomatic women in their fifth decade of life should be considered at low to intermediate IHD risk if they are capable of performing routine activities of daily living (ADL). If performance of routine ADL is compromised, then a woman is considered to be functionally limited. A symptomatic woman in her 50s who is functionally limited should be elevated to the intermediate IHD risk category. Symptomatic women in their 60s are also generally considered as being at intermediate IHD risk, whereas women ≥70 years old with ischemic symptoms are considered at high IHD risk. High-risk equivalent states, including peripheral arterial disease and long-standing or poorly controlled diabetes mellitus for women aged >40 years, categorize a woman at high IHD risk. Thus, the discrete categories of IHD risk for symptomatic women used throughout the present document include low, intermediate, and high IHD risk, respectively. Women may be categorized as low-intermediate IHD risk, which reflects their slightly elevated risk estimate. Importantly, these are general categorizations and do not replace clinical judgments, even for the woman with a low pretest IHD risk. Figure 2 provides a pictorial description of the above categorization of symptomatic women and their IHD risk estimates.

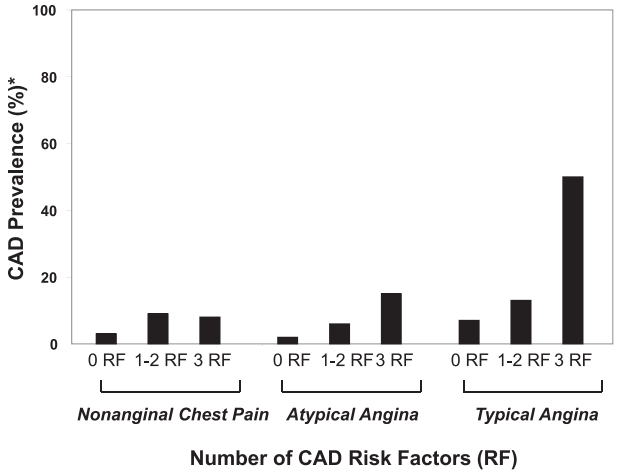

Figure 1. Prevalence of obstructive coronary artery disease (CAD) by coronary computed tomographic angiography in a large cohort of symptomatic women: results from CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry). RF indicates risk factors. *CAD prevalence defined as ≥70% stenosis. Reprinted from Cheng et al[33] with permission. Copyright © 2011, American Heart Association, Inc.

In the woman with extensive comorbidity, multiple risk factors, or functional disability, the IHD risk estimation may be elevated by 1 category. A compilation of these high-risk markers is reported in Table 2. For example, the woman with a high-risk marker who is otherwise classified as being at intermediate IHD risk should be reclassified as at high IHD risk.

This initial categorization of IHD risk should be used to define the index diagnostic procedure through which further assessment of IHD risk is ascertained. Low-risk women are generally not candidates for further diagnostic testing. The low-intermediate–risk or intermediate-risk woman is a candidate for an exercise ECG if she is functionally capable and has a normal or interpretable rest ECG. Women with intermediate-high IHD risk with an abnormal 12-lead rest ECG (ie, with resting ST-segment abnormalities) may be referred for stress imaging (MPI, echocardiography, or CMR) or CCTA. Women at high IHD risk with stable symptoms may be referred for a stress imaging modality for functional assessment of their ischemic burden and to guide posttest, anti-ischemic therapeutic decision making. Figure 3 provides a synopsis of this evaluation algorithm.

In each of the following sections, we highlight the evidence and provide a more detailed discussion on the appropriate candidates for each procedure.

Special Considerations in the Diagnostic Evaluation

Patient-Centered Care: Shared Decision Making

Input and guidance from the patient should play an integral role in clinical decision making for all testing and subsequent treatment decisions. Within the diagnostic evaluation, the point of referral is a prime opportunity for patient-physician shared decision making. Shared decision making at the point of testing is impractical for the patient to contemplate alternative testing (or no testing) options. All laboratories should provide an opportunity for discussion and educational materials tailored to the needs of female patients of varying ages, health literacy levels, and race/ethnicity to guide patient decision

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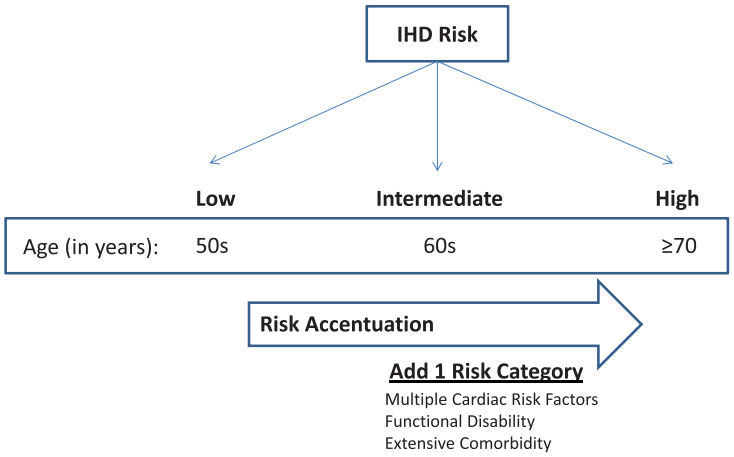

Figure 2. Pictorial description of the categorization of ischemic heart disease (IHD) risk in symptomatic women.

making. Minimum quality standards for an imaging laboratory include current laboratory accreditation and staff physicians with advanced certification in imaging. The ACC (http://www.cardiosmart.org) and AHA (http://www.heart.org or http://www.hearthub.org) have patient Web sites that feature information on diagnostic testing options.

Guiding Treatment With CAD Imaging Results

A critical aim of this document is not only optimal test decision making but also guidance of treatment of the symptomatic woman based on demonstrable stress-induced or anatomic abnormalities. Treatment decision-making components will be findings consistent with myocardial ischemia or scarred myocardium (that are not caused by technical artifact) and evidence of CCTA-defined nonobstructive and obstructive CAD. Treatment algorithms for the symptomatic woman are based on findings that meet diagnostic criteria (noted in each section below) and are not intended for the symptomatic woman with stress test results that fall within normal limits. Treatment of a symptomatic woman without corroborating diagnostic test abnormalities should be avoided. Definitive treatment algorithms for SIHD are provided in the "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease."[26]

Table 2. High IHD Clinical Risk Markers for Symptomatic Women

Peripheral arterial disease
Diabetes mellitus: 10-y history or poorly controlled in a woman >40 y of age
Chronic obstructive lung disease
Transient ischemic attacks or cerebrovascular accident
Chronic kidney disease
Functional disability: inability to perform activities of daily living or <5 estimated DASI METs

DASI METS indicates Duke Activity Status Index metabolic equivalents; and IHD, ischemic heart disease.

Diagnostic Procedures for IHD That Expose Women to Ionizing Radiation

Several diagnostic procedures discussed in this statement expose women to ionizing radiation, including stress MPI, CCTA, and invasive coronary angiography. Although it is beyond the scope of this statement to provide an in-depth review on this topic, any referring physician or imager should have adequate knowledge of a test's effective radiation dose and comprehend the relationship between patient exposure and projected cancer risk.[34–38] Estimation of cancer risk after exposure to ionizing radiation is based on the linear no-threshold hypothesis, which projects a cancer risk at low-dose exposure and has the projected cancer risk increasing proportionally with higher-dose exposures. The projected cancer risk based on the linear no-threshold hypothesis is extrapolated from higher-dose exposures (eg, atomic bomb exposure at Hiroshima, Japan). For medical imaging, the absolute increase in cancer risk is projected to be small, but even low-dose exposure has some small risk. The physicist and radiation biology communities agree that radiation-induced cancer risk is a concern even at low-dose exposure (such as that with CAD imaging techniques) and increases proportionally with higher-dose exposures. The goal of this section is to inform and prompt physicians to consider selection of optimal candidates for MPI, CCTA, or angiography in whom the benefit of IHD risk detection far exceeds the small projected cancer risk after exposure to ionizing radiation. When the benefit-risk ratio favors a high benefit of IHD risk detection, radiation exposure is not a major consideration in physician decision making.[39] However, in every case, the lowest dose should be used for all patients with an appropriate indication for testing. For low-risk premenopausal women, alternative tests without radiation exposure (eg, ECG) or a no-testing strategy should be strongly considered.[40]

Table 3 details the typical effective radiation dose for MPI, angiography, and CCTA.[35,41] Average background radiation exposure per year for a member of the US population is ≈3.1 mSv. CAD imaging modalities are associated with average exposures of ≈11 mSv for rest-stress myocardial perfusion

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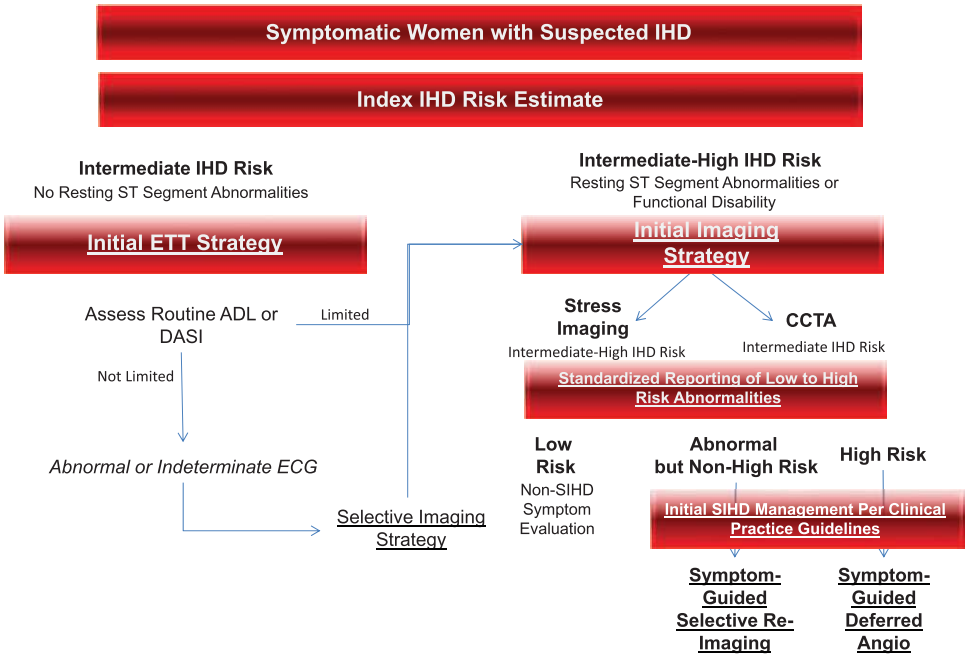

Figure 3. Diagnostic evaluation algorithm for women presenting with suspected ischemic heart disease (IHD) symptoms and intermediate IHD risk and intermediate-high IHD risk. ADL indicates activities of daily living; Angio, angiography; CCTA, coronary computed tomography angiography; DASI, Duke Activity Status Index; ETT, exercise treadmill testing; and SIHD, stable ischemic heart disease.

technetium Tc-99m SPECT and ≈10 mSv for CCTA.[42] Low-dose procedures should be applied preferentially, whenever possible. Dose-reduction techniques for CCTA result in substantially lower doses while maintaining image quality.[43] A prospectively triggered scan has a typical effective dose of 3 to 5 mSv, whereas a retrospectively gated scan has a typical effective dose from 12 to 25 mSv.[43] Higher doses may be needed for obese individuals.[43] Dual-isotope MPI (rest thallous chloride Tl 201, stress Tc-99m) generally should not be used for evaluation of SIHD patients, with an exception for the very elderly, for whom the shortened protocol time outweighs the minimal risk of exposure, or those requiring an assessment of myocardial viability.[44] Alternative SPECT camera technology allows for reduced radiation doses with SPECT imaging. Stress-only MPI (ie, eliminating the rest image portion of the study when the stress MPI is normal) should be encouraged whenever possible to decrease radiation exposure by one third.[45] The use of rest-stress rubidium Rb-82 PET results in a lower effective dose of ≈3 mSv.[46] Diagnostic invasive angiography results in an exposure of ≈7 mSv.[38]

The estimated cancer risk after CCTA[34,47] or MPI[37] is in the range of 3 to 8 affected people per 10 000 tested. Importantly, estimated cancer risk may be overestimated among symptomatic women with reduced life expectancy.[48] Similar estimates of incident breast cancer have been synthesized in a recent Institute of Medicine report.[49] These projections are broadly based across age groups and may not be precise for the symptomatic woman undergoing an IHD diagnostic evaluation (median age ≥60 years).[49] In-depth reviews of the subject have been published by the AHA, the Society of Cardiovascular Computed Tomography, and the American Society of Nuclear Cardiology.[39,43–45,50,51]

The National Council for Radiation Protection and Measurement has emphasized several key principles to guide referral of women to MPI, CCTA, and angiography. These principles include an emphasis on justification of use, dose-reduction optimization, and an adequate knowledge base to guide use.[52] With regard to justification of use, we propose to generally limit exposure to women who meet appropriate indications for testing based on the ACC's appropriate use criteria.[53–55] One approach for reducing population radiation exposure is to limit rarely appropriate imaging, as designated by the ACC appropriate use criteria.[53,54] Second, all laboratories should use readily available dose-reduction techniques. Finally, all clinicians should garner adequate knowledge

Table 3. Typical Radiation Exposure, as Measured by an Effective Dose, From Rest-Stress MPI, CCTA, and Angiography in Women

	Effective Dose, mSv
Annual background exposure	≈3
Invasive coronary angiography	≈7
Rest-stress MPI SPECT	
Technetium Tc 99m	≈11
Stress-only MPI SPECT	≈3
Dual-isotope MPI SPECT	22
Rest-stress MPI PET	
Rubidium Rb 82	≈3
Nitrogen N 13	≈2
CCTA	
Overall	≈10
With dose-reduction techniques	<2–5
Coronary artery calcium scoring	2

CCTA indicates coronary computed tomographic angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

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Table 4. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* COR III: No benefit — Procedure/Test: Not Helpful — Treatment: No Proven Benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful — Treatment: Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

about effective doses of CAD imaging, which exposes patients to ionizing radiation, with an emphasis on appropriate patient selection and the use of guidelines-accepted best practices for all patients.

Diagnostic Accuracy and Risk Stratification Statistics

Evidence Rating and Recommendation Procedures for Level of Evidence

Subcommittees were organized by noninvasive testing modality and were charged with preparation of summary evidence tables for each testing modality based on the updated literature review. These tables were then reviewed, after which the subcommittee modified or retained the current recommendation on the basis of the writing group comments. Each recommendation was assigned both a strength of recommendation (Class I, IIa, IIb, or III) and a Level of Evidence (A, B, or C) as outlined in Table 4. The updated recommendations were voted on by the writing group by individual ballot to determine by a majority vote the final rating of evidence, the strength of the recommendation, and its wording. Further minor modifications to text and clinical recommendations were based on peer review comments. The recommendations were then finalized and approved by the writing group.

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Evidence Synthesis in Functional Stress Testing

Index Evaluation of Symptomatic Women at Low-Intermediate and Intermediate IHD Risk

Role of the Exercise ECG in Women

ETT with ECG is one of the oldest forms of stress testing for assessment of myocardial ischemia and the most commonly used method of diagnosing CAD in women.[56–58] On the basis of the "ACC/AHA 2002 Guideline Update for Exercise Testing"[59] and the 2005 AHA expert consensus statement on the "Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Coronary Artery Disease,"[5] the exercise ECG is the recommended initial noninvasive test of choice among symptomatic, intermediate IHD risk women with a normal baseline ECG who are able to exercise. Common reasons for using an exercise ECG without imaging as the index diagnostic procedure include the following: (1) the assessment of physical work capacity in the functionally capable woman; (2) the high negative predictive value of the exercise ECG; and (3) recent evidence of similar 2-year clinical outcomes for women randomized to exercise ECG compared with stress MPI.[5,60]

The 2005 statement on the role of noninvasive testing in the clinical evaluation of women with suspected CAD made the same recommendation[5] but further recommended that a pretest evaluation be made to determine whether a woman can exercise to a reasonable level (ie, maximal heart rate and peak exercise greater than stage I of the Bruce protocol [ie, >5 metabolic equivalents, or METs]) at which ischemia may be detected using such tools as the validated Duke Activity Status Index (DASI). The DASI is a self-administered, 12-question form designed to provide an estimate of physical exercise capacity (in milliliters per kilogram per minute; dividing by 3.5 can provide estimated METs). Routine ADL require ≈4 to 5 METs of work; women who indicate difficulties in performing daily activities should be considered to have functional limitations. An inability to achieve an exercise capacity of <5 METs based on the evaluation of a woman's capability in ADL, through the DASI or on the ETT, is rationale for referral to pharmacological stress testing given that such a low exercise capacity may be insufficient to adequately induce ischemia.[61,62] Thus, the index evaluation favors the ETT for women whose physical functioning is sufficient to achieve adequate levels of exercise and for those with a normal rest ECG on which ST segments may be interpreted reliably.

Cardiorespiratory Fitness

Cardiorespiratory fitness, also known as exercise capacity or functional capacity, is one of the most important risk markers in cardiovascular medicine that can be easily assessed with an ETT or with knowledge of the patient's abilities during ADL. Exercise capacity is an independent predictor of the presence of CAD in women.[63–66] A nomogram of exercise capacity in women across various age groups is detailed in Figure 4.[67] In a study that examined the relationship between cardiorespiratory fitness and prevalence of myocardial ischemia, women and men who achieved ≥10 METs had a very low prevalence of myocardial ischemia, but those who achieved <7 METs were more likely to have provocative ischemia (0.4% versus 7.1%, $P<0.001$).[68] The threshold for functional disability is noted as peak exercise capacity of <5 METs or inability to exercise beyond stage I of the Bruce protocol.[5,69,70]

The Bruce protocol is commonly applied in US ETT laboratories but requires initial workloads of 4.7 METs and graded increases of 2 to 3 METs per stage, which may precipitate early fatigue in women with less muscle mass than men, particularly for less physically fit women. Adaptive protocols that use small increases or start at lower workloads are preferable for most symptomatic women, such as the

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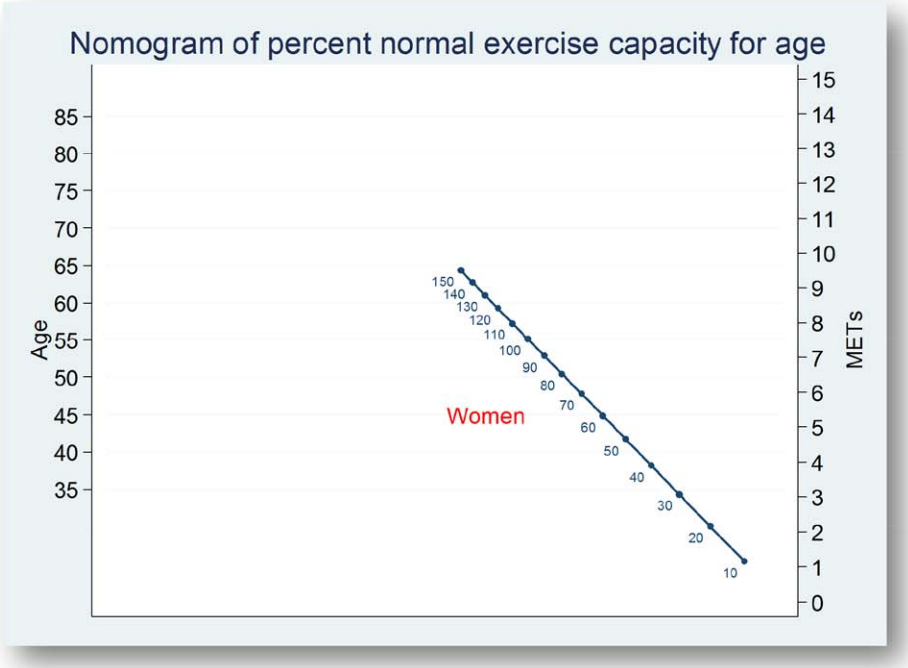

Figure 4. Nomogram of the percentage of predicted exercise capacity for age in asymptomatic women. A line drawn from the patient's age on the left-hand scale to the metabolic equivalent (MET) value on the right-hand scale will cross the percentage line at the point that corresponds to the patient's percentage of predicted exercise capacity for age. From Gulati et al,[67] copyright © 2005, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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Asymptomatic Cardiac Ischemia Pilot,[71] modified Bruce,[72] or Balke[73] protocols.

Chronotropic Response

The inability to achieve 85% of the maximum age-predicted heart rate with exercise is associated with an increased risk of obstructive CAD in women. In an older study of 200 symptomatic women with abnormal ECGs who were undergoing ETT, an inability to reach target heart rate was associated with a higher likelihood of CAD.[74] Recently, the calculation of a woman's age-predicted heart rate has been revised as 206−(0.88×age).[75] Kaplan-Meier survival with the female-specific measure of chronotropic incompetence with an index <0.80 identifies worse overall survival than for women who have a chronotropic index ≥0.80.[75] Achievement of 85% of age-predicted heart rate should not be used as the reason for ETT protocol termination.[59,76] All exercise tests should be continued to the point of volitional fatigue, unless significant ischemia or symptoms prompt otherwise.

ST-Segment Response

Significant ST-segment depression (defined as ≥1.0 mm of horizontal or downsloping depression or ≥1.5 mm of upsloping depression at 60 ms after the J point) with ETT is considered diagnostic for ischemia. This threshold parameter is generally considered to be less accurate for the detection of obstructive CAD in women.[5] The sensitivity and specificity of ST-segment depression with an exercise ECG in symptomatic women vary widely, but often, a lower sensitivity than specificity is reported in women. The sensitivity and specificity for the diagnosis of obstructive CAD in women range from 31% to 71% and from 66% to 86%, respectively.[77–84] In a meta-analysis of 19 exercise ECG studies, the mean sensitivity and specificity, respectively, were 61% and 70% among women and 72% and 77% among 1977 men.[80] In a recent Agency for Healthcare Research and Quality (AHRQ) meta-analysis, 29 studies that included 3392 women were synthesized, with a reported diagnostic sensitivity and specificity, respectively, of 62% (95% confidence interval [CI], 55%–68%) and 68% (95% CI, 63%–73%) for detection of obstructive CAD.[85] Although the AHRQ review did not compare diagnostic accuracy by sex, it did report that the overall accuracy statistics in women were similar to a mixed population of men and women. Several reports have noted that the diminished accuracy of the ECG response to exercise in women has been attributed to 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.[86–89] Although the positive predictive value of ST-segment depression with ETT among women is significantly lower than in men (47% versus 77%, $P<0.05$), the negative predictive value of ST-segment depression among symptomatic women was similar to men (78% versus 81%).[86] A negative exercise ECG in the setting of maximal exercise is useful in effectively ruling out a diagnosis of obstructive CAD and predicting excellent event-free survival. The diagnostic performance of the exercise ECG is diminished in the setting of resting ST-segment changes (>0.5 mm), and these women should be referred to stress imaging, as discussed in the following sections.

Importantly, in studies comparing the exercise ECG with angiography, it is the minority of patients who undergo invasive angiography. Therefore, posttest referral bias contributes to artificial elevation of diagnostic sensitivity and may reduce specificity[90]; this bias is operational for all diagnostic test modalities.

The exercise ECG has a diminished diagnostic accuracy for detection of obstructive CAD compared with other imaging modalities; however, this should not lead clinicians to ignore the presence and severity of inducible ECG changes or other ischemic equivalents in women. A markedly positive ST-segment response during exercise testing (ie, ≥2 mm of ST-segment depression or ≥1 mm of ST-segment elevation in a non–q-wave lead, excluding aVR) that occurs at a low workload (<5 METs) or persists into recovery for >5 minutes is considered a high-risk ETT for both women and men.[5]

ETT Risk Scores

The integration of multiple parameters from an ETT has been shown to improve accuracy in women compared with a single variable.[91] The Duke Treadmill Score (DTS) is the most widely used of all risk scores in ETT and has diagnostic and prognostic value in both women and men.[92,93] The DTS incorporates exercise time (which is a measure of exercise capacity), ST-segment changes, and the presence of angina:

$$\text{DTS} = \text{Exercise time} - (5 \times \text{ST-segment deviation}) - (4 \times \text{angina score index})$$

Exercise time is measured (in minutes) on the commonly used standard Bruce protocol. ST-segment deviation is the greatest net ST-segment deviation in any lead (other than aVR), and the angina score index is scored from 0 to 2 (where 0 is no angina, 1 is nonlimiting angina with exercise, and 2 is exercise-limiting angina). Recognized categories for the calculated DTS are low risk (DTS ≥5), moderate risk (DTS −10 to 4), and high risk (DTS −11 or less).[94] In a cohort of 976 symptomatic women referred for ETT followed by coronary angiography from 1984 to 1994, significant coronary stenosis (≥75%) was present in 19%, 35%, and 89% of low-, moderate-, and high-risk women, respectively, based on the DTS risk categories.[91] Women with an intermediate DTS should, in general, be referred for additional risk stratification with a stress imaging study.[5] Exertional chest pain symptoms were less accurate for detection of obstructive CAD.[91] Given that this was an angiographic cohort, the application of these data to the index diagnostic evaluation is unclear.

Risk Assessment With ETT

Cardiorespiratory Fitness

Cardiorespiratory fitness is one of the strongest predictors of outcomes for women,[67,69,70,95–97] and as such, the maximal exercise capacity (measured as exercise METs or time) achieved with an ETT should be an integral component of the test interpretation. Women who achieve <5 METs are at an increased risk of death and related IHD events, independent of traditional cardiac risk factors.[69,70] Age-predicted cardiorespiratory fitness can be used to assess prognosis in women (Figure 4). Age-predicted maximal fitness was defined in a cohort of 5721 asymptomatic women[67] as predicted METS=14.7−(0.13×age).

Compared with asymptomatic women who achieved ≥85% age-predicted cardiorespiratory fitness level, those who achieved <85% of their age-predicted cardiorespiratory

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fitness level had approximately twice the risk of death of any cause (hazard ratio, 2.0; $P<0.001$) and a greater risk of death of CAD (hazard ratio, 2.4; $P<0.001$).[67] When validated in 4421 symptomatic women, those who achieved <85% of their age-predicted cardiorespiratory fitness level had at least twice the risk of death of any cause and of CAD causes as women who achieved ≥85% of their age-predicted cardiorespiratory fitness level (hazard ratio, 2.4 [$P<0.001$] and hazard ratio, 2.0 [$P<0.001$], respectively).[67] For prognostic purposes, information related to cardiorespiratory fitness level should be incorporated into the interpretation of every ETT.

Chronotropic Response

A normal chronotropic response to exercise is based on the heart rate response to an increase in cardiac output. An attenuated heart rate response to exercise is defined as chronotropic incompetence.[79,98] An abnormal chronotropic response is associated with a poorer prognosis among women than a normal heart rate response.[75,99,100] The majority of these reports excluded patients taking β-blockers, and thus, the prognostic meaning of an impaired heart rate response to exercise should be viewed in light of onboard medications. It is standard practice to discontinue β-blockers within 24 to 48 hours of testing.

Heart Rate Recovery

Heart rate recovery is another important prognostic marker that is easily obtained with ETT and has substantial prognostic value. An abnormal heart rate recovery can be defined as a decrease in the heart rate of <12 beats per minute at 1 minute of recovery compared with the peak heart rate. In a study of 720 women who underwent ETT and subsequent angiography, abnormal heart rate recovery was an independent predictor for all-cause mortality (hazard ratio, 1.5; $P=0.0002$).[101] An abnormal heart rate recovery is also a possible sign of autonomic dysfunction and has been correlated with insulin resistance in otherwise healthy adults.[102] For these reasons, the heart rate response should be incorporated into the ETT results.

Blood Pressure Response

In symptomatic populations, the relationship between a hypertensive response and future risk of developing hypertension remains unknown. In addition, in symptomatic cohorts, the evidence is conflicting as to whether a hypertensive response (≥190 mm Hg in women, ≥210 mm Hg in men) to exercise is associated with future IHD events. A study from the Mayo Clinic showed that a hypertensive response to an ETT was significantly associated with an increased risk of cardiovascular events during a mean follow-up of 7.7 years ($P<0.03$).[103] In contrast, a study from the Cleveland Clinic failed to show such a relationship and in fact noted a lower prevalence of severe obstructive CAD ($P=0.004$) in addition to a lower risk of death over the next 2 years ($P=0.03$) than in those with a normotensive response to exercise.[104]

ST-Segment Response

In contrast to men, ST-segment depression with ETT does not appear to provide strong prognostic value among women, with the exception of the markedly abnormal ST-segment changes discussed in the subsection on "ST-Segment Response" in the section "Evidence Synthesis in Functional Stress Testing."[69,105] However, combining exercise markers into a risk score improves prognostication among women.[91]

A recent comparative effectiveness trial, the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial, randomized 824 symptomatic women with suspected CAD to exercise ECG versus exercise MPI. Women were followed up for 2 years for major adverse CAD outcomes.[60] The eligibility criteria included functionally capable women who reported a DASI of ≥5 METs. Functionally capable women who sought evaluation of ischemic symptoms had similar 2-year outcomes whether randomized to exercise ECG or MPI ($P=0.59$; Figure 5). Importantly, an initial exercise ECG prompted a follow-up evaluation with stress MPI in nearly 1 in 5 women; to that end, this trial put forth the recommendation that an initial ECG strategy with follow-up stress imaging be limited to women with indeterminate or abnormal ECG findings (Figure 5).

Risk Scores From ETT

The DTS is an excellent prognostic tool in symptomatic women, with a low DTS being associated with an annual mortality rate of ≈0.25% in contrast to an annual mortality rate of ≈5% in those with a high-risk DTS, with lower mortality rates among women than men.[91,92,94] The quoted mortality rates are derived from earlier patient cohorts; contemporary

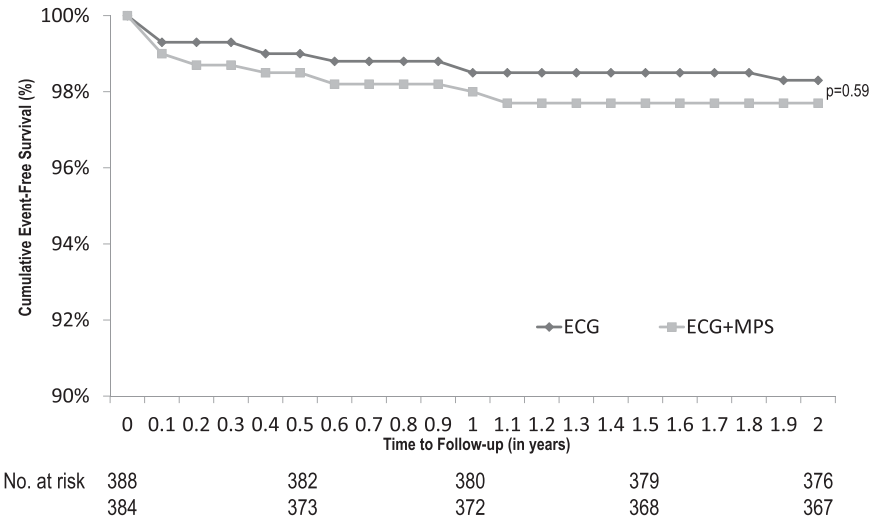

Figure 5. Coronary artery disease event-free survival from the WOMEN (What Is the Optimal Method for Ischemia Evaluation in Women) trial comparing 2-year effectiveness of an exercise ECG with exercise myocardial perfusion imaging in women at low-intermediate risk for ischemic heart disease with suspected coronary artery disease who are capable of performing ≥5 metabolic equivalents of exercise. MPS indicates myocardial perfusion scintigraphy. Based on the Duke Activity Status Index.[60]

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cohorts would be unlikely to have the same high-risk mortality rates. Despite this limitation, the DTS is a valuable tool to predict the risk of future myocardial infarction (MI), revascularization, and IHD event-free and all-cause survival among women, but it may be less effective at predicting prognosis in elderly women (aged ≥75 years).[106]

A nomogram for integration of ETT risk parameters is detailed in Figure 6.[107]

Summary

The ETT provides important diagnostic and prognostic information, far beyond the ST-segment response alone. Table 5 highlights the high-risk markers that should be interpreted and reported from the exercise ECG for women. The diagnostic and prognostic accuracy of ETT in women can be improved by incorporating parameters such as exercise capacity, chronotropic response, heart rate recovery, blood pressure response, and the DTS, in addition to ST-segment changes with exercise. Regardless of whether imaging is used, these important prognostic and diagnostic variables should be assessed and reported when one interprets a stress test.

Future Directions of Research in Exercise ECG

Compared with what has been assessed in men, the implications, interpretation, and application of ETT data among women remain limited. We need to evaluate sex-specific patterns from the ETT. Questions that remain unanswered are related to the concept of increased false-positive results (based on ST-segment depression interpretation) in women. Given the evidence of a higher prevalence of nonobstructive CAD in women, it remains unknown whether ST-segment depression is most likely the result of myocardial ischemia caused by vascular dysfunction and nonobstructive atherosclerosis. Moreover, given the low cost of the exercise ECG and the frequent bypassing of this test for CAD imaging, comparative effectiveness evidence on the exercise ECG compared with higher-cost imaging options may help to guide clinical decision making as to the optimal and cost-efficient test choice

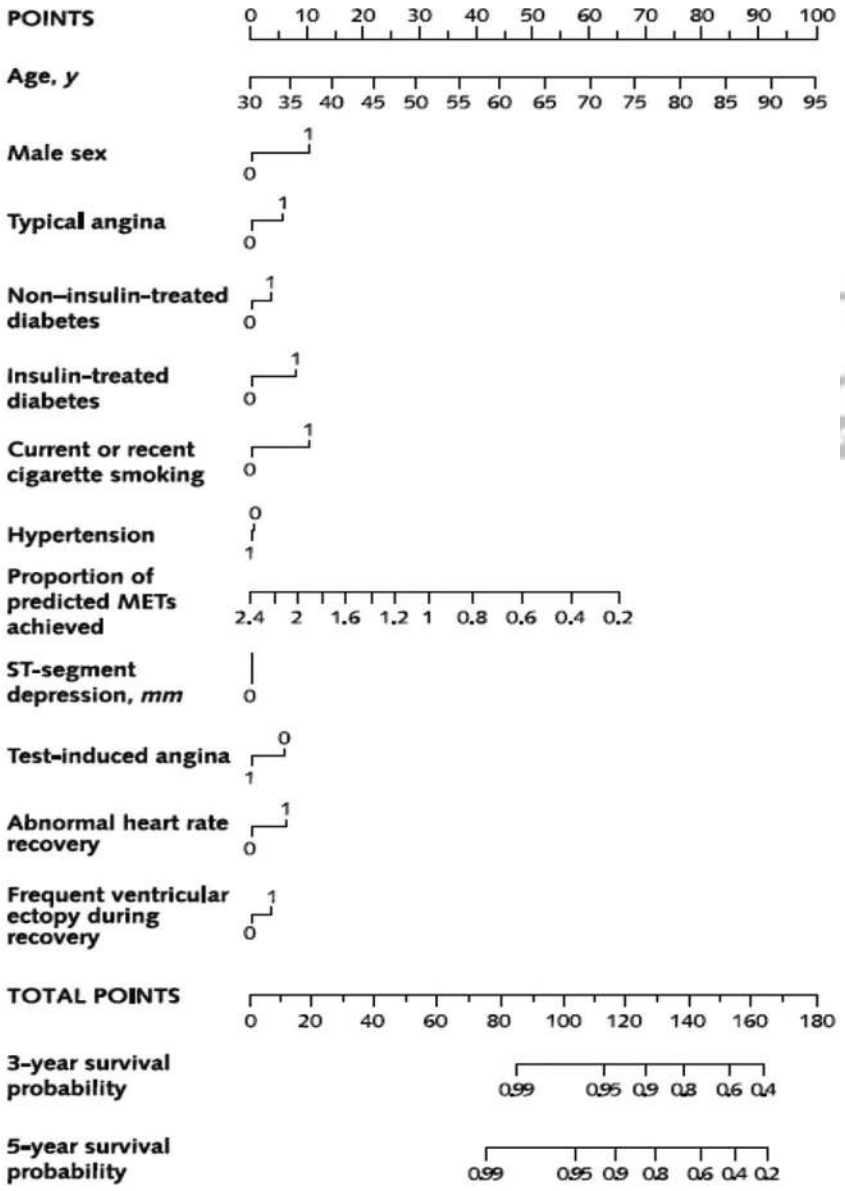

Figure 6. A nomogram for integration of exercise treadmill test risk parameters estimating 3- and 5-year survival. This nomogram integrates clinical and exercise treadmill test parameters into an estimate of survival. To determine risk, draw a vertical line from each risk marker to the top line, labeled *POINTS*, to calculate points for each risk marker. The sum of all these points is then marked on the line labeled *TOTAL POINTS*. Drop vertical lines from there to yield the 3- and 5-year survival probabilities. For binary variables, 1 means yes and 0 means no. MET indicates metabolic equivalent. Reprinted from Lauer et al[107] with permission of the publisher. Copyright © 2007, American College of Physicians.

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Table 5. ECG and Non-ECG Variables Associated With an Elevated IHD Risk From Exercise Testing in Women

Stress Testing Variables	Method of Assessment	High-Risk Value
Exercise capacity	Estimated by ETT protocol (speed and grade)	<5 METs <100% Age-predicted METs=14.7–(0.13×age)
HR recovery	Difference between peak HR and HR at 1 min of recovery	≤12 bpm after 1 min recovery (upright cooldown period)
ST-segment changes	Difference in ST segment Δs (at 60 ms after the J point) between peak exercise (or recovery) and rest ECG	ST-segment depression ≥2 mm ST-segment depression ≥1 mm at <5 METs or >5 min into recovery ST-segment elevation ≥2 mm (not in q-wave lead or aVR)
DTS	DTS=exercise time–(5×STΔ)–(4×angina index)	High-risk DTS less than or equal to –11
BP response	Assessment of BP response to exercise, change in SBP from rest to peak exercise	Decrease in SBP >10 mm Hg from rest
Ventricular arrhythmias		Persistent ventricular tachycardia/fibrillation

BP indicates blood pressure; DTS, Duke Treadmill Score; ETT, exercise treadmill testing; HR, heart rate; IHD, ischemic heart disease; METs, metabolic equivalents; and SBP, systolic blood pressure.

for symptomatic women and may be similarly helpful in the evaluation of symptomatic men.

Recommendations

1. **For a symptomatic woman with intermediate IHD risk who is capable of exercising at >5 METs and who has a normal rest ECG, the ETT is recommended as the initial test of choice, with imaging reserved for those women with resting ST-segment abnormalities or those unable to exercise adequately *(Class I; Level of Evidence B)*.**
2. **As per standardized reporting, the ETT interpretation should include not only the ST-segment response and risk score measurements but also exercise capacity, chronotropic response, heart rate recovery, and the blood pressure response to exercise *(Class I; Level of Evidence B)*.**
3. **If an ETT is indeterminate (eg, negative ECG in the setting of submaximal exercise [below age-predicted level or failure to achieve >85% predicted maximal heart rate]) or abnormal, the next step should be additional diagnostic testing with stress imaging. Individualized decision making and targeted anti-ischemic therapies after the ETT should consider the woman's ongoing symptom burden and the degree of abnormalities noted during the ETT *(Class I; Level of Evidence C)*.**

Index Evaluation of Symptomatic Women With an Abnormal Rest ECG or With Functional Disability

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

Stress echocardiography combines ultrasound imaging of the heart with stress testing for the detection of CAD and IHD risk among symptomatic women. Exercise echocardiography is usually combined with treadmill exercise but can be performed with supine or upright bicycle exercise. ETT is preferred for patients who are able to exercise because of the additional prognostic information provided by the patient's exercise capacity.[95] For patients who are unable to exercise, pharmacological stress testing may be performed, most commonly with dobutamine. Vasodilator stress echocardiography, with dipyridamole or adenosine, has been reported to have a slightly lower sensitivity.[108]

Stress echocardiography provides information about left ventricular (LV) global and regional systolic function, as well as the extent of scarred myocardium and stress-induced myocardial ischemia.[109] The ability to obtain diagnostic-quality images with use of intravenous contrast (if >2 segments cannot be visualized adequately at rest) exceeds 97%. Echocardiography can also identify other causes of chest pain or dyspnea, such as valvular heart disease, pericardial disease, pulmonary hypertension, and aortic dissection. Additionally, diastolic function, LV filling pressure, and tricuspid regurgitation velocity (as an indicator of right ventricular systolic pressure) can be estimated at rest and with stress to identify patients with exertional symptoms unexplained by IHD.

Exercise echocardiography has an improved diagnostic sensitivity and specificity compared with the exercise ECG alone in women.[80,110,111] The accuracy of stress echocardiography in detecting CAD in women is also superior to combined scores that include exercise ECG interpretation, exercise capacity, and hemodynamics.[112] In a recent meta-analysis published by the AHRQ, the diagnostic sensitivity and specificity for detection of obstructive CAD in women from 14 reports were 79% (95% CI, 74%–83%) and 83% (95% CI, 74%–89%), respectively.[85] Dobutamine stress echocardiography accurately detects CAD among women with suspected IHD.[108] The majority of dobutamine stress echocardiography studies in women have reported sensitivities ranging from 75% to 93% and specificities from 79% to 92%.[113–117] A meta-analysis of dobutamine stress echocardiography found an overall sensitivity of 80% (95% CI, 77%–83%) and specificity of 84% (95% CI, 80%–86%).[108]

For exercise and dobutamine stress echocardiography, the diagnostic accuracy is generally comparable among women and men, although the prevalence of CAD by angiography is generally lower for women. As noted previously, in studies comparing stress echocardiography with angiography, it is the minority

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of stress-testing patients who undergo invasive angiography. Therefore, posttest referral bias contributes to artificial elevation of the diagnostic sensitivity and may reduce specificity,[90] and this bias is operational for all diagnostic test modalities.

Risk Assessment

The prognostic value of stress echocardiography has been demonstrated in numerous single-center and multicenter observational studies comprising >40 000 men and women[109] and appears comparable among men and women,[97,110] although IHD event rates were higher in men. The prognostic accuracy of stress echocardiography has been assessed in various subgroups, including patients of varying ages[118] and those with symptoms including chest pain and dyspnea[114,119–122]; with known, obstructive CAD or coronary revascularization[123]; and with chronic kidney disease,[124] peripheral arterial disease,[125] or diabetes mellitus.[126,127] The information provided by stress echocardiography wall-motion assessment adds incremental prognostic value to clinical, rest echocardiography, and exercise ETT variables.[123,128,129] The IHD event rate (IHD death, MI, or revascularization) after a normal exercise echocardiography is <1% per year but would be higher for patients with greater degrees of comorbidity and for women with diabetes mellitus.[130] For patients with an abnormal stress echocardiogram, not only the presence of an abnormality but the extent and severity of that abnormality are associated with a higher rate of IHD events (Figure 7).[97,131] Markers of high IHD event rates include not only the inability to perform an ETT but also numerous echocardiographic markers (Table 5). Among these are the number of abnormal segments at rest, the number of segments that become ischemic, the stress wall-motion score index, the change in wall-motion score index from rest to stress, an increase in systolic size with stress, LV ischemia that extends into the right ventricle,[132] an increase in end-systolic size, and a decrease in LV ejection fraction (LVEF) with stress.[109] Both short- and long-term follow-up studies show that stress echocardiography is predictive of subsequent MI, need for coronary revascularization, IHD death, and all-cause mortality.[97,119,131] Abnormal stress echocardiography is associated with subsequent IHD events, even in the absence of obstructive CAD by angiography.[133] The typical IHD event rates for patients undergoing dobutamine stress echocardiography are decidedly higher than for those undergoing exercise testing.[134]

Overall, reports have compared stress echocardiography with stress MPI in meta-analyses[135] or in the same group of patients.[136] The diagnostic accuracy of the tests is comparable,[135] and their prognostic value appears similar.[136] Although published evidence shows comparable accuracy, local expertise has an impact on test performance. The issue of local expertise guides test performance and selection for all of the imaging modalities.

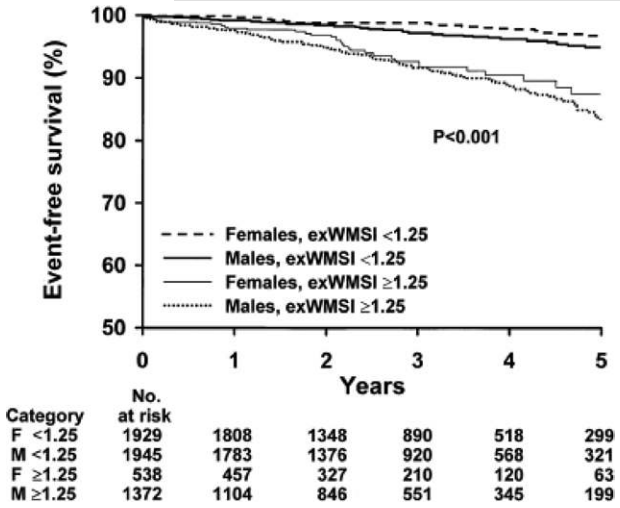

Figure 7. Survival free of ischemic heart disease events, including myocardial infarction or coronary artery disease death, for women and men according to the exercise wall-motion score index (exWMSI). An exercise wall-motion score ≥1.25 corresponds to hypokinesis in ≥4 left ventricular segments, or more severe abnormalities (akinesis or dyskinesis) in fewer segments. F indicates female; and M, male. Reprinted from Arruda-Olson et al,[97] copyright © 2002, with permission from the American College of Cardiology.

Summary

Stress echocardiography with exercise or dobutamine stress is an accurate, noninvasive technique for the detection of obstructive CAD and risk among symptomatic women with intermediate to high IHD risk. Exercise stress testing is recommended for patients able to achieve maximal exercise capacity/heart rate levels. Stress echocardiography provides incremental information beyond that which can be ascertained from clinical symptoms, the ETT, and rest echocardiography data. The information provided by a stress echocardiogram appears comparable to that of stress MPI and is predictive of short- and long-term IHD events. Nonischemic causes of cardiac symptoms can also be recognized with relevant echocardiographic techniques. Table 6 highlights the evidence on high-risk markers from stress echocardiography for women.

Table 6. Markers of High IHD Risk in Women for Stress Imaging and CCTA

Stress Imaging	
Stress echocardiography	Rest LVEF ≤40% Extensive rest wall-motion abnormalities or extensive ischemia (≥4–5 LV segments) Right ventricular ischemia Increase in end-systolic size with stress Right ventricular ischemia LVEF decrease with stress
Stress MPI	Summed stress score >8 ≥10% of the abnormal myocardium at stress ≥10% of the ischemic myocardium LV dilation Peak stress or poststress LVEF ≤45%
Stress CMR	Rest or stress LVEF ≤40% ≥3 Abnormal or ischemic CMR MPI segments ≥3 Abnormal or ischemic CMR wall-motion segments
CCTA	CAC ≥400 Proximal LAD stenosis ≥70% 2- Or 3-vessel CAD Left main stenosis ≥50% 3-Vessel nonobstructive CAD

CAC indicates coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; IHD, ischemic heart disease; LAD, left anterior descending coronary artery; LV, left ventricle; LVEF, left ventricular ejection fraction; and MPI, myocardial perfusion imaging.

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Future Directions of Research in Stress Echocardiography

Three-dimensional echocardiography offers the potential for rapid visualization of all myocardial segments in tomographic planes. Strain rate imaging, combined with stress echocardiography, permits quantification of regional systolic and diastolic function. Echocardiographic contrast for MPI appears useful as an adjunct to wall-motion assessment but is awaiting approval from the US Food and Drug Administration.

Recommendations

1. **Stress echocardiography is recommended for identification of obstructive CAD and estimation of prognosis for symptomatic women at intermediate-high IHD risk and with any of the following: (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate-risk stress ECG *(Class I; Level of Evidence B)*.**
2. **Additional assessment of diastolic function and pulmonary artery pressures may be reasonable in the echocardiographic evaluation of women presenting with dyspnea *(Class IIb; Level of Evidence C)*.**
3. **For the premenopausal woman with functional disability, pharmacological stress echocardiography is recommended for identification of obstructive CAD and estimation of prognosis *(Class I; Level of Evidence C)*.**
4. **As per standardized reporting, markers of high IHD event rates reported in Table 6 for stress echocardiography should be detailed in each woman's stress echocardiography final report (*Class I; Level of Evidence C*).**

Role of Stress MPI in the Diagnosis and Risk Assessment of Women

Similar to echocardiography, stress MPI can be used within the diagnostic evaluation of symptomatic women with an intermediate-high IHD risk who also have abnormal rest ST-segment changes or functional disability. Stress MPI with SPECT or PET provides information on the extent and severity of myocardial perfusion and wall-motion abnormalities, as well as LVEF assessment at rest and after stress. For rest and stress SPECT, the lower-exposure radioisotope Tc-99m should be used. Dual-isotope (rest Tl 201/stress Tc-99m) MPI generally should not be performed in women because of the higher radiation exposure (see exceptions for the very elderly or for assessment of myocardial viability in Diagnostic Procedures for IHD That Expose Women to Ionizing Radiation). Women capable of maximal exercise should have an exercise MPI, whereas those who are functionally incapable should undergo a pharmacological stress test with 1 of several vasodilator agents (ie, dipyridamole, adenosine, or regadenoson). When using Rb-82 or [^{13}N]ammonia (N-13 ammonia) PET, absolute blood flow at rest and stress may be ascertained to provide measurements of myocardial flow reserve (MFR).[137]

MPI With SPECT

Diagnosis

The diagnostic accuracy of contemporary MPI techniques in the evaluation of symptomatic women at intermediate-high IHD risk is supported by an extensive evidence base on the diagnostic accuracy of stress MPI. As is the case for other stress imaging modalities, the overall sensitivity of exercise MPI is significantly higher than ETT findings for detection of obstructive CAD.[138] For the diagnosis of obstructive CAD in symptomatic women, the sensitivity and specificity of exercise MPI range from 78% to 88% and from 64% to 91%, respectively.[5,139,140] Pharmacological stress MPI has a diagnostic sensitivity and specificity in women of 91% and 86%, respectively.[5] In a recent meta-analysis published by the AHRQ, the diagnostic sensitivity and specificity for detection of obstructive CAD among women from 14 reports were 81% (95% CI, 76%–86%) and 78% (95% CI, 69%–84%), respectively.[85] Breast tissue artifact has been shown to decrease the specificity of the MPI SPECT among women compared with men (94% for men and 74% for women, $P<0.01$).[138] Existing MPI techniques improve diagnostic accuracy in women, including examination of LVEF, wall motion, and thickening. Reports have also noted improved diagnostic accuracy with prone imaging and attenuation correction techniques, although these techniques are frequently underused.[60,141–148] As noted previously, in studies comparing stress MPI with invasive angiography, it is the minority of patients who undergo invasive angiography, and posttest referral bias elevates diagnostic sensitivity and may reduce specificity.[90]

Risk Assessment

A large body of evidence supports the prognostic accuracy of exercise and pharmacological stress MPI among women, with the extent and severity of rest and stress perfusion abnormalities exhibiting a graded relationship with the risk of IHD events; in particular, data are available in ethnically diverse cohorts of women (Figure 8).[139,149–154] The American Society of Nuclear Cardiology published an information statement on the use of stress MPI in women,[155] and a detailed review of the prognostic evidence base with stress MPI was published recently.[139] Data support that stress myocardial perfusion and ventricular function measurements provide independent and incremental information over and above clinical history and ECG data.[156] In one recent report, the net reclassification improvement was calculated from a multicenter registry cohort of 4575 patients, with more than one third being women.[156] The net reclassification improvement for stress MPI data was ≈36% over and above clinical and DTS results, which suggests that new IHD risk information was available to guide management for nearly 1 in 3 patients.[156]

The evidence published in the past several decades on prognostication based on the extent and severity of inducible perfusion abnormalities and extent of LV dysfunction is replete with a generally high representation of women. A normal or low risk study (defined as having <5% of abnormal myocardium or equivalent to a summed stress score of <4) is associated with a <1% annual risk of CAD death or nonfatal MI.[157] A meta-analysis by Metz and colleagues[158] reported that the annual CAD death or MI rate was 0.3% for 1443 women and 0.8% for 1457 men for those with a normal or low-risk exercise MPI. Typical IHD event rates for patients undergoing pharmacological stress MPI are ≈2-fold higher than for those undergoing exercise testing.[60,139,157,159,160]

IHD event risk increases in a gradient from low, mildly abnormal, to moderately to severely abnormal studies, such

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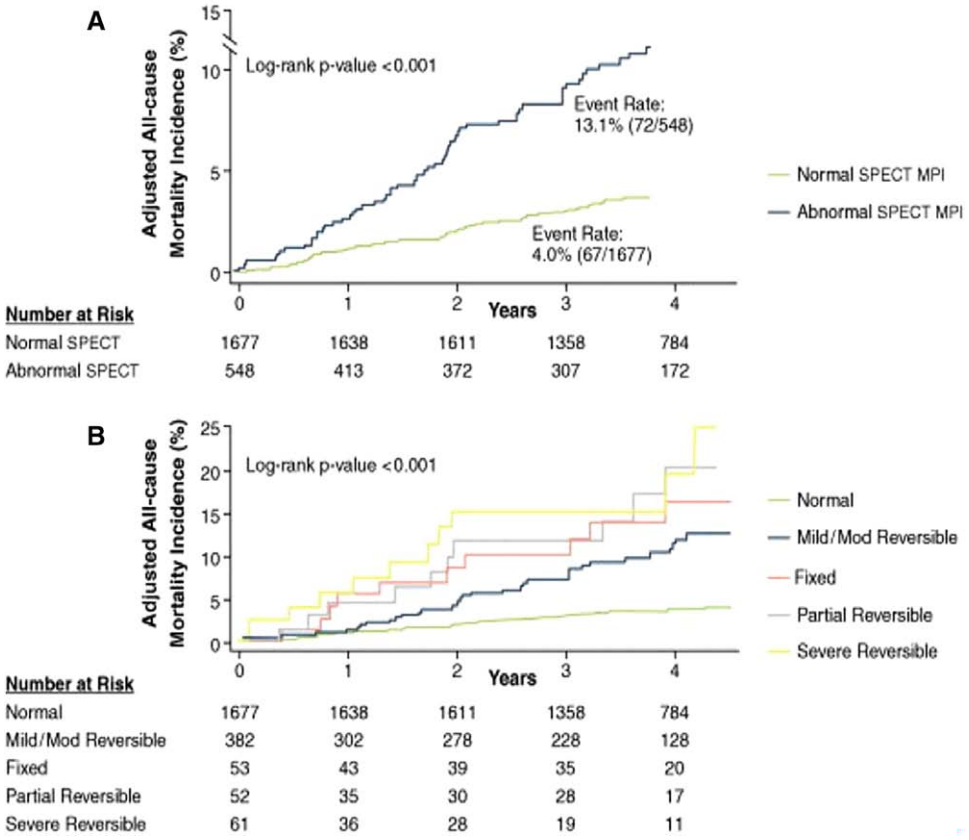

Figure 8. Four-year ischemic heart disease event-free survival in 2225 Hispanic women referred for stress myocardial perfusion imaging (MPI). The 4-year ischemic heart disease event rate was 13.1% for Hispanic women with abnormal results on stress MPI compared with 4.0% for those with normal results on stress MPI. Mod indicates moderate; and SPECT, single-photon emission computed tomography. Reprinted from Cerci et al,[153] copyright © 2011, with permission from the American College of Cardiology Foundation.

that for a high-risk or moderately to severely abnormal MPI result, the annual IHD death or MI rate among women is ≈6% or greater.[157] These rates are higher among patients with an LVEF measurement of <45%.[160] Nomograms have been published that examine the interrelationship between IHD prognosis and measures of LVEF and percentage of ischemic myocardium.[160] Moreover, clinical subsets of women with extensive comorbidity (including those with long-standing or poorly controlled diabetes mellitus) or those requiring pharmacological stress would have higher IHD event rates.[159] In a recent meta-analysis that included elderly patients >65 years of age, the summary odds for an IHD event were elevated nearly 12-fold for an abnormal compared with a normal stress MPI test (95% CI, 7.5–18.7).[161] In addition to clinical risk markers (Table 2), there are additional high-risk markers that accentuate IHD risk estimates, including LV dilation, rest and stress LV dysfunction, and a decrease in LVEF with stress LV dilation (Table 6).

MPI With PET

Stress MPI PET, with superior spatial resolution, has been reported to improve image quality and diagnostic accuracy statistics for women, particularly for those who are obese.[162] Rb-82 (≈3 mSv) is the more commonly used radioisotope, but N-13 ammonia (≈2 mSv) MPI is also used in some laboratories. In a recent meta-analysis, the diagnostic sensitivity and specificity from 19 studies using stress MPI PET were 92% and 85%, respectively.[163] One report noted a modest improvement in diagnostic sensitivity between stress MPI PET and SPECT among women, with the greatest improvement reported for diagnostic specificity for the exclusion of obstructive CAD.[162] For women, the overall improvement in diagnostic accuracy was ≈20% for stress MPI PET compared with SPECT MPI (88% versus 67%, respectively; P=0.009).[162] PET improves detection of severe, multivessel obstructive CAD, which can be challenging with SPECT because of a balanced reduction in perfusion.[164] An abnormal LVEF reserve, defined as a diminished increase or decrease on the peak stress LVEF with PET, also improves detection of left main or 3-vessel CAD.[165]

One distinct advantage of stress PET MPI is the ability to calculate absolute blood flow across the coronary vessels, which leads to the calculation of PET MFR.[137,166] Damped PET MFR can augment MPI findings, particularly for those with normal or low-risk findings.[167] Evidence of diminished MFR (defined as <1.9–2.0) suggests underlying vascular dysfunction and may aid in the detection of microvascular CAD, which may be particularly helpful in the evaluation of women with more prevalent nonobstructive CAD.[20,139] The addition of hybrid PET/computed tomography (CT) may prove useful to assess the presence and magnitude of coronary artery calcium (CAC) or anatomic obstructive CAD, although few reports in women have been published.[139] The combination of CCTA and stress MPI PET adds radiation burden, but the use of CAC with MPI findings may help to define the underlying obstructive CAD burden in the setting of perfusion abnormalities while adding minimally to the radiation burden (≈2 mSv with CAC). At this time, hybrid PET/CT imaging has a limited evidence base and is under investigation.

As noted previously, in studies comparing stress MPI with invasive angiography, it is the minority of patients who

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undergo invasive angiography, and posttest referral bias elevates diagnostic sensitivity and may reduce specificity.[90]

Risk Assessment

As with SPECT, an increase in the extent and severity of perfusion defects seen on stress PET is associated with an increasing frequency of IHD events. The data for stress MPI PET are less robust but show similar prognostic findings concerning the extent and severity of myocardial perfusion abnormalities at rest and stress, with an incremental ability to stratify IHD event risk with peak stress LVEF.[139,168] A recent meta-analysis reported that the summary relative risk ratio for an abnormal stress Rb-82 MPI PET examination was elevated 5.1-fold (95% CI, 2.8–9.3; $P<0.0001$).[139] This report also included pooled IHD event data, with a normal stress Rb-82 PET scan having an annual event rate of 0.4% (n=2947), which increased to 11.5% (n=1445) with moderately to severely abnormal stress Rb-82 MPI PET findings.[139] In a recent report on 457 women, the annual rate of death or MI was 0.47% per year with a normal stress Rb-82 MPI PET examination.[169]

Summary

Stress MPI SPECT and PET imaging performed with contemporary techniques have a high diagnostic accuracy in the evaluation of symptomatic women with intermediate and intermediate-high IHD risk. Risk stratification based on the extent and severity of stress MPI abnormalities is effective at improving delineation of symptomatic women at low to high risk of IHD events, providing incremental and improved risk reclassification over and above clinical and ETT parameters. Rest-stress MFR with MPI PET may further delineate risk in women. Table 6 highlights the evidence on high-risk markers from the stress MPI for women.

Future Directions of Research in Stress MPI

The evolution of clinical research in MPI should be oriented toward the development and application of low-dose radiation SPECT and PET protocols. Moreover, integration of rest and stress MPI data with MFR data in the evaluation of vascular function remains an intriguing area for the detection of IHD risk in women. Additional data on prognosis with PET are indicated. There is also a new fludeoxyglucose F 18 PET agent, currently in phase 3 clinical trials, with an improved defect contrast that should improve diagnostic and prognostic accuracy.[170] Specific trials should be planned to define accuracy by sex. Comparative effectiveness research, particularly as it relates to new testing options or the use of tests without ionizing radiation, is an important patient-centered goal for the evaluation of symptomatic women.

Recommendations

1. **For symptomatic women at intermediate-high IHD risk and with (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate-risk stress ECG, stress MPI with SPECT or PET is recommended for identification of obstructive CAD and estimation of prognosis *(Class I; Level of Evidence B)*.**
2. **Radiation dose-reduction techniques should be used in all women undergoing clinically necessary (or appropriate) stress MPI whenever possible *(Class I; Level of Evidence C)*.**
3. **For the premenopausal woman with functional disability, alternative tests, such as stress echocardiography or CMR, are encouraged; MPI may be considered when radiation exposure levels are ≤3 mSv *(Class IIb; Level of Evidence C)*.**
4. **In younger women, the choice of a test should be based on concerns about radiation exposure and increased projected cancer risk and not higher reported accuracy[35,37,171] *(Class IIb; Level of Evidence C)*.**
5. **As per standardized reporting, markers of high IHD event rates reported in Table 6 for stress MPI should be detailed in each woman's stress MPI final report *(Class I; Level of Evidence C)*.**

Role of CMR in the Diagnosis and Risk Assessment of Women

Diagnosis

CMR has developed considerably during the past decade and is increasingly accepted for the evaluation of suspected myocardial ischemia in symptomatic women at intermediate-high IHD risk. A growing number of CMR studies have evaluated provocative ischemia in symptomatic women. The vast majority of studies used pharmacological stress because of requirements of a magnetic resonance–compatible treadmill to perform treadmill exercise in the scanner room,[172] an area of ongoing study. CMR with use of a contrast agent (gadolinium) for MPI may be performed safely in most patients, with the exclusion of patients with stage 4 or 5 chronic kidney disease. The safety of CMR was shown in a study of >1000 patients (24% women).[173]

Initial studies in patients of both sexes validated the use of dobutamine stress CMR wall-motion imaging against invasive angiography and demonstrated a high diagnostic accuracy.[174,175] The safety of this approach was clearly shown in a study of >1000 individuals.[173] A meta-analysis of stress functional CMR studies reported a sensitivity of 83% and specificity of 86% for the diagnosis of CAD.[176]

Vasodilator (adenosine or regadenoson) stress perfusion CMR has been used for more than a decade as an alternative to dobutamine stress because it offers a shorter period of stress and uses gadolinium contrast, which facilitates late gadolinium enhancement imaging for detection of MI. Vasodilator stress perfusion CMR was validated initially against PET[177] and invasive angiography.[177,178] A study combining qualitative analysis of CMR perfusion images with late gadolinium enhancement yielded an overall accuracy of 88% compared with angiography.[179] One meta-analysis of stress CMR perfusion studies demonstrated a sensitivity and specificity of 89% and 80% (median of 30% of subjects were women).[180] Another meta-analysis demonstrated a sensitivity of 91% and specificity of 81% for the diagnosis of CAD on a per-patient level (median of 22% of subjects were women).[176] More recently, stress CMR has been investigated among women. In a multicenter registry of 147 symptomatic women who underwent vasodilator stress MPI and late gadolinium enhancement,

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diagnostic sensitivity and specificity were 84% and 88%, respectively.[181] Another study compared the accuracy of CMR among 77 women and 179 men and demonstrated a higher diagnostic specificity among women (91% versus 82%), with a similar sensitivity for the detection of obstructive CAD.[182]

Stress CMR perfusion allows for the assessment of subendocardial perfusion because of its high spatial resolution. In a small study of 20 patients (80% of whom were female) with abnormal stress tests and normal coronary arteries, subendocardial ischemia was frequently present compared with control subjects when adenosine CMR was performed.[183] This was later validated in additional studies (46 women among 73 patients and 22 women among 34 patients).[184,185] In women with acute coronary syndrome and normal coronary arteries, subendocardial ischemia on CMR was a common finding.[186]

As noted previously, in studies comparing CMR with invasive angiography, it is the minority of patients who undergo invasive angiography, and posttest referral bias elevates diagnostic sensitivity and may reduce specificity.[90]

Prognosis

Evidence for the prognostic accuracy of stress CMR has been increasing steadily. A study of 1493 patients showed that either a positive study using dobutamine stress wall motion or MPI was associated with a hazard ratio of >5 for subsequent MI and CAD death over a 2-year follow-up period.[187] In a cohort of 279 patients (including 124 women) who were referred for dobutamine stress CMR for the detection of ischemia, the presence of inducible ischemia or an LVEF ≤40% was a predictor of CAD death or MI at an average follow-up of 2.5 years.[188] Similar prognostic information as for dobutamine stress wall motion is available with dobutamine stress MPI, as demonstrated in a study of 513 patients who underwent both types of imaging[189]; those with a normal CMR had an excellent 3-year survival.

Although the sample sizes for CMR studies are much smaller than those for echocardiography or MPI, women have featured prominently in several recent prognostic studies. In a study with >6 years of follow-up, women with an abnormal dobutamine stress CMR had a hazard ratio of 4.1 for subsequent MI or CAD death compared with those with normal findings.[190] In a study of 208 women who underwent both dobutamine stress wall motion and MPI with CMR, event-free survival was 100% over 4 years among women with a negative result.[191] The presence of ischemia on vasodilator stress MPI in another study of 168 women was associated with an annual major cardiovascular event rate of 15% compared with 0.3% among those without ischemia (Figure 9).[192]

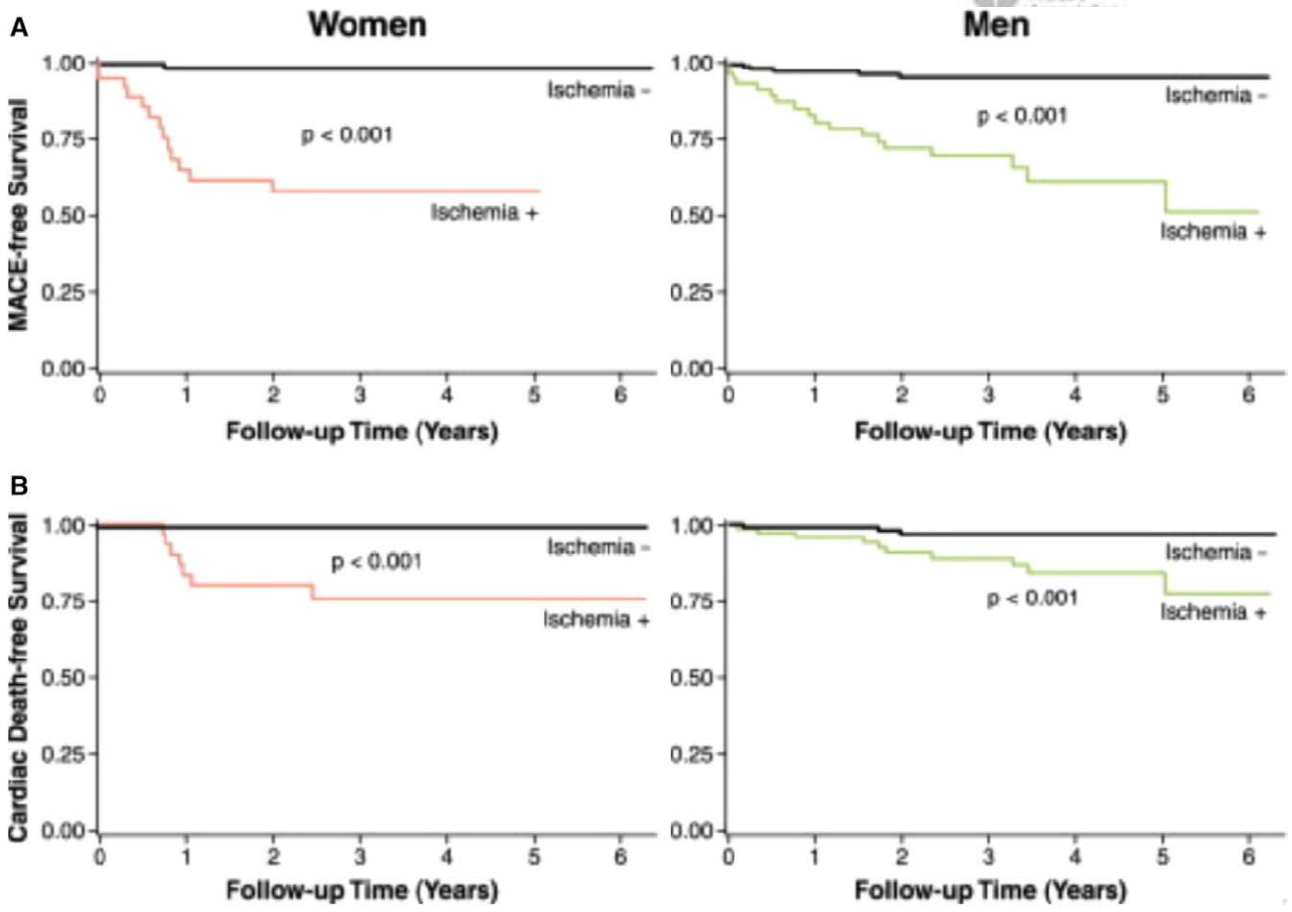

Figure 9. Similar ischemic heart disease event-free survival in women and men based on stress cardiac magnetic resonance perfusion ischemia. Ischemic heart disease risk stratification for women and men with and without ischemia was similar at 5 years of follow-up. **A** and **B**, Kaplan-Meier survival curves for major adverse cardiac events (MACE; **A**) and death of ischemic heart disease (**B**), stratified by evidence of ischemia by sex. Reprinted from Coelho-Filho et al,[192] copyright © 2011, with permission from the American College of Cardiology Foundation.

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There is limited information regarding IHD prognosis related to stress-induced CMR perfusion abnormalities in women with nonobstructive CAD. In a small substudy from the WISE registry, women with nonobstructive CAD and abnormal stress-induced CMR perfusion abnormalities had an elevated risk of IHD events.[193]

Summary

The evidence regarding the utility of stress wall motion and perfusion CMR for the identification of obstructive CAD and determination of IHD prognosis has expanded greatly over the past several years. Pharmacological stress CMR should be considered a useful modality for stress testing in women who are unable to perform exercise, as noted above in the ETT sections. Table 6 highlights the evidence on high-risk markers from the stress CMR for women.

Future Directions of Research in Stress CMR

Comparative effectiveness research comparing stress CMR with other pharmacological stress imaging approaches should be performed. Newer research with CMR (including ETT CMR)[172,194,195] is being evaluated, and CMR may be useful to detect ischemia, particularly subendocardial ischemia in women with nonobstructive CAD.[183] In addition, studies of quantitative stress MPI should be undertaken to understand the potential additive value of quantitation over qualitative interpretation and to consider various thresholds of risk and therapeutic benefit. The addition of strain imaging by CMR could add to the utility of dobutamine stress functional CMR in women. For women with signs and symptoms of ischemia but nonobstructive CAD, further work is needed to determine whether stress CMR detection of limited MFR attributable to microvascular coronary disease improves IHD risk assessment.

Recommendations

1. **For symptomatic women at intermediate-high IHD risk and with (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate risk, it may be reasonable to use stress CMR, especially vasodilator stress perfusion CMR, as the index procedure within the diagnostic evaluation *(Class IIb; Level of Evidence B)*.**
2. **For the premenopausal woman with functional disability, stress CMR may be reasonable for the identification of obstructive CAD and estimation of prognosis *(Class IIb; Level of Evidence B)*.**
3. **As per standardized reporting, markers of high IHD event rates reported in Table 6 for stress CMR should be detailed in the woman's stress CMR final report *(Class I; Level of Evidence C)*.**

Evidence Synthesis in Noninvasive Coronary Angiography

Cardiac CT has undergone rapid development during the past decade, with solid evidence about its diagnostic and prognostic accuracy.[196] CCTA provides information on the presence, extent, and severity of both obstructive and nonobstructive CAD. Furthermore, CCTA provides measures of other important atherosclerotic plaque features, including arterial remodeling and plaque composition (eg, noncalcified or calcified plaque burden, low attenuation plaque).[196] In comparison, the non–contrast-requiring CAC score, commonly reported as an Agatston score, provides a quantitative measurement of CAC extent and is derived by multiplying the density of the plaque (in Hounsfield units) by the area of the plaque. More recent studies have demonstrated the potential of contrast-enhanced CCTA to quantify coronary artery flow[197] and fractional flow reserve,[198–200] myocardial perfusion,[201–206] and scarred myocardium via delayed enhancement imaging.[207–216] Because these newer applications of cardiac CT have not amassed sufficient evidence to allow definition of their role in the evaluation of women with suspected IHD, this update will focus on CAC scoring and CCTA.

Role of Cardiac CT: Coronary Calcium Scoring and CCTA in the Diagnosis and Risk Assessment of Women

Diagnosis

Measurement of CAC provides a direct marker of the burden of atherosclerosis.[217,218] Sex and age distributions of the presence and quantity of CAC in symptomatic cohorts have been published.[219–221] These data consistently show that the prevalence and severity of CAC increase with age and male sex, with women demonstrating less prevalent and less severe CAC than men.[219–221] For premenopausal women, the prevalence of CAC is low (similar to angiographic rates of obstructive CAD); CAC prevalence lags by ≈10 years compared with men.[222]

Data specific to symptomatic women come from multiple large cohort studies that included >1200 women and have demonstrated that the presence of detectable CAC for the diagnosis of obstructive CAD possesses a sensitivity in the range of 96% to 100% and a specificity in the range of 40% to 66% for the detection of obstructive CAD compared with invasive angiography.[223–225] Although diagnostic performance was similar in women and men, the specificity of the criterion of any CAC (ie, >0) for detection of obstructive CAD was significantly better in women than in men (40%–66% for women and 23%–36% for men).[224,225] Importantly, the presence of CAC is not site-specific for luminal obstruction. Use of a higher cutoff value of CAC ≥100, reflective of a greater burden of atherosclerosis, improved the specificity to 76% at a minimally reduced sensitivity of 82%.[224]

Coronary CT Angiography

Diagnosis

For CCTA, referral of symptomatic women with intermediate IHD risk may be reasonable, including those with indeterminate or submaximal stress test results.[226] Several meta-analyses (comprising approximately one third female enrollees) have reported the accuracy of 64-slice (and higher) CCTA, with mean sensitivity and specificity values in the range of 97% to 99% and 88% to 91%, respectively, based on per-patient analyses.[227–232] Controlled clinical trial data reveal that CCTA has a high diagnostic sensitivity (range, 85%–99%) and specificity (range, 64%–90%) for the detection of obstructive CAD compared with invasive angiography.[233–235] Five published studies specifically evaluated the diagnostic performance of CCTA in women compared with men[236–240] and included a total of 679

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women and 1173 men (1 of the studies[238] included patients from a previous study[236]). The diagnostic performance of CCTA was not significantly different between women and men, as analyzed on a per-patient level. In a recent secondary analysis of the Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY) trial, the diagnostic sensitivity and specificity in women were 90% and 88%, respectively.[240] In general, women included in these cohorts tended to be significantly older than men, with a lower prevalence of obstructive CAD.[236–238,240] In a recent meta-analysis published by the AHRQ, the diagnostic sensitivity and specificity for detection of obstructive CAD in women from 5 reports were 93% (95% CI, 81%–98%) and 77% (95% CI, 68%–96%), respectively.[85]

As noted previously, in studies comparing CCTA with invasive angiography, it is the minority of patients who undergo invasive angiography, and posttest referral bias elevates diagnostic sensitivity and may reduce specificity.[90] For CCTA, a low rate of invasive angiography has been reported for patients with nonobstructive CAD.[241]

Risk Assessment

Several meta-analyses[242,243] and large multicenter registries[244] have evaluated the prognostic accuracy of CCTA for both all-cause mortality and IHD events. Women represented 38% to 50% of participants in these cohorts. These studies revealed a low IHD event rate for patients without evidence of obstructive CAD on CCTA, with a mortality rate of 0.15% to 0.4% per year.[242–244] Patients with evidence of obstructive CAD (>50% stenosis) demonstrated a high IHD event rate of 8.8% to 11.9% per year,[242,243] including end points of death or MI and revascularization. When women were matched to men by CAD extent and severity, no sex differences in mortality were observed.[245]

Recently, the Coronary CT Angiography Evaluation for Clinical Outcomes International Multicenter (CONFIRM) registry reported on sex differences in the prognostic value of CCTA for all-cause mortality in 23 854 symptomatic patients (12 128 women) without known CAD.[16] Analyses from the CONFIRM registry demonstrated a significantly increased death rate that increased proportionally with the extent (number of vessels involved) and severity (degree of luminal stenosis) of CAD (adjusted hazard ratios of 1.6, 2.0, 2.9, and 3.7, respectively, for nonobstructive, 1-vessel, 2-vessel, and 3-vessel obstructive [>50% stenosis] CAD compared with no CAD).[244] The CONFIRM registry demonstrated a significantly elevated risk-adjusted mortality for nonobstructive and obstructive CAD in women, but only for extent of obstructive CAD in men.[16] When stratified by age and sex, differences in multivariable risk-adjusted hazards for mortality were observed for the presence of nonobstructive CAD and extent of CAD in all individuals aged ≥65 years and for the presence of 2- and 3-vessel obstructive CAD in individuals aged <65 years (Figure 10).[16] Similarly, in a recent cohort study that included 1070 women, CCTA was predictive of the composite end point of IHD death or nonfatal MI, with an annualized event rate of 0.2%, 1.2%, and 2.1%, respectively, for women with normal coronaries, nonobstructive CAD, and obstructive CAD.[246] In a related observational registry led by Lin and colleagues,[17] the prognostic value of nonobstructive plaque for estimating all-cause mortality was explored in a cohort of 2583 patients with ≤50% stenosis. The relative hazard for death was 1.9, 2.7, and 6.1, respectively, for 1-, 2-, and 3-vessel nonobstructive CAD compared with no CAD (P<0.0001). An exploratory study of the prognostic value of CCTA in 646 women with suspected CAD (mean age 60±10 years) demonstrated that the estimation of all-cause mortality was associated with adjusted hazard ratios of 2.1 per vessel with obstructive CAD and 1.3 per nonobstructive lesion, whereas in 481 men, the extent of nonobstructive CAD was not independently predictive of all-cause mortality in a model that also contained the extent of obstructive CAD.[18]

Summary

The current evidence base with CCTA has grown substantively since the 2005 expert consensus statement.[5] Although women lag by ≈10 years in the development of obstructive CAD, consistent with findings at invasive angiography, the diagnostic accuracy data from several clinical trials and numerous observational series report similar diagnostic performance characteristics by sex. CCTA can be used to identify symptomatic women with obstructive CAD who may benefit from SIHD management, as per recent clinical practice guidelines.[26] Considerable data now exist on the prognostic value of CCTA in the risk stratification and estimation of IHD in women based on the extent of both obstructive and nonobstructive CAD.[55]

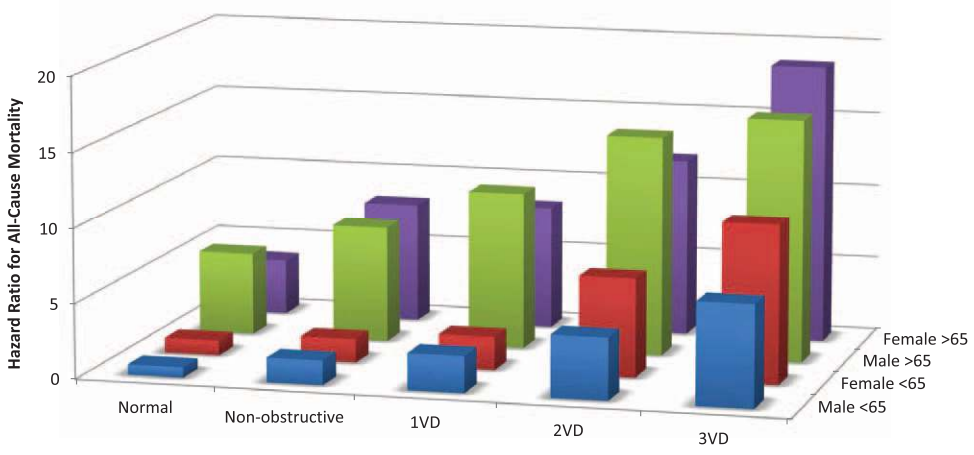

Figure 10. Relative hazard for all-cause mortality from CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) in younger (aged <65 years) and older (aged ≥65 years) women (n=12 128) and men (n=11 726). The relative hazard for death increased with age and the prevalence of more extensive coronary artery disease. 1VD indicates 1-vessel disease; 2VD, 2-vessel disease; and 3VD, 3-vessel disease. Modified with permission from Min et al.[16] Copyright © 2011, the American College of Cardiology Foundation.

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CCTA can also be used to identify women with nonobstructive CAD with increased risk of IHD events who may benefit from risk factor modification and medical therapy. Table 6 highlights the evidence on high-risk markers from the CCTA for women.

Future Directions of Research in CCTA

Although the CCTA evidence base has grown since 2005, focused research among larger, diverse cohorts of women is needed to assess IHD risk according to various degrees of atherosclerotic plaque composition and extent, as well as extent and severity of obstructive CAD. Moreover, the development of CCTA strategies of care to assess CCTA-guided management and intervention on IHD outcomes in women and men is also needed. The development of comparative effectiveness research on the use of CCTA compared with no testing or functional testing assessments remains a valuable aim for future research. Additional research is also needed on newer cardiac CT applications, including assessment of coronary artery flow and fractional flow reserve, myocardial perfusion, and scarred myocardium, with specific focus on women.

Recommendations

1. **For symptomatic women at intermediate IHD risk and with (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate-risk stress ECG, it may be reasonable to use CCTA as the index procedure within the diagnostic evaluation *(Class IIb; Level of Evidence C)*.**
2. **Radiation dose-reduction techniques should be used in all women undergoing CCTA whenever possible *(Class I; Level of Evidence C)*.**
3. **For the premenopausal woman with functional disability, alternative tests, such as stress echocardiography or CMR, are encouraged; CCTA may be considered when radiation exposure levels can be ≤3 mSv *(Class IIb; Level of Evidence C)*.**
4. **In younger women, the choice of a test should be based on concerns about radiation exposure and increased projected cancer risk and not higher reported accuracy[35,37,171] *(Class I; Level of Evidence C)*.**
5. **As per standardized reporting, markers of high IHD event rates reported in Table 6 for CCTA should be detailed in each woman's CCTA final report *(Class I; Level of Evidence C)*.**

Development of Clinical Strategies That Incorporate Diagnostic Testing in Women

In the 2005 expert consensus statement, the diagnostic and prognostic evidence for ETT, stress imaging, and CCTA in women was synthesized.[5] In the present statement, we have provided updated evidence and have highlighted the importance of guiding posttest medical management based on demonstrable evidence of stress abnormalities or CCTA-defined nonobstructive or obstructive CAD. Comparative effectiveness research is lacking in this area, and the current recommendations are based on evidence synthesis combined with expert opinion that is considered reasonable care for at-risk women. At-risk women are those defined as having ongoing CAD symptoms and demonstrable ischemia (in which all forms of artifact have been reasonably excluded) or nonobstructive or obstructive CAD. Moderate to severe stress or ischemic abnormalities or nonobstructive to obstructive CAD is associated with a significantly elevated risk of IHD events among women. For these women, intensive medical management that includes anti-ischemic therapy with the goal of symptom control and risk factor modification should be undertaken. Referral to angiography may be considered an option (Figure 3). For the woman with indeterminate or abnormal exercise ECG findings, additional stress imaging or CCTA may be used to further refine risk-based management.

Two randomized clinical trials are under way or in the planning phases and will further define medical management and provide more information to aid the decision to refer women to invasive angiography for stable IHD. The National Heart, Lung, and Blood Institute–sponsored International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) will enroll a total of 8000 SIHD patients with moderate to severe ischemia; patients will be randomized to a management strategy of invasive angiography or medical management alone (with angiography recommended for patients with refractory symptoms). A second trial, the ISCHEMIA-WISE (Will Intensive Strategies Reduce Events) study, is currently under evaluation at the National Heart, Lung, and Blood Institute and proposes to compare the effectiveness of intensive medical management for 2200 women and men with demonstrable ischemia in the setting of nonobstructive CAD. Both of these trials, successors to the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)[7] and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)[8] trials, expand our current management approaches to higher-risk subsets with moderate to severe ischemia, and in the case of ISCHEMIA-WISE, explore optimal management of patients with nonobstructive CAD.

Diagnostic Strategies for Women With Nonobstructive CAD

A frequent dilemma facing clinicians is what to do about the woman with nonobstructive CAD with evidence of demonstrable ischemia. As noted above, the WISE-ISCHEMIA trial in patients with nonobstructive CAD is proposed to provide more definitive guidance on optimal management strategies for women with demonstrable ischemia and nonobstructive CAD. However, in lieu of trial evidence, it remains reasonable to consider initiation of anti-ischemic regimens for women with IHD symptoms and demonstrable ischemia in the setting of mild but not obstructive CAD (ie, >0% but <50% stenosis), including women with significant CAC (eg, score ≥100). The standard approach of treating IHD symptoms is consistent with current clinical practice guidelines and antianginal medication labeling (ie, angina treatment is not angiography based). The goal is to tailor anti-ischemic and risk factor–modifying therapy toward the goal of symptom resolution in women with a sizeable burden of myocardial ischemia.

A few reports evaluated anti-ischemic therapy to induce myocardial ischemia resolution on a follow-up stress test.[247–250] Applying a paired or serial testing algorithm, anti-ischemic therapy is initiated (consistent with guideline-accepted best practices), and a second study is performed after a time period sufficient for deployment of standard medical titration. For a paired stress imaging study, the second study would test the patient

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Table 7. Summary Table for Indications to Stress Testing/Imaging or CCTA in Women With Ischemic Symptoms

	Exercise Status		ECG Interpretable		Pretest Probability of IHD		
Test	Able	Unable	Yes	No	Low	Intermediate	High
Exercise ECG	X		X			X	
Exercise MPI	X			X		X	X
Exercise echocardiography	X			X		X	X
CCTA	X			X		X	
Pharmacological stress MPI		X	Any			X	X
Pharmacological stress echocardiography		X	Any			X	X
Pharmacological stress CMR		X	Any			X	X
CCTA		X		X		X	

CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; IHD, ischemic heart disease; and MPI, myocardial perfusion imaging.

while the patient was taking all anti-ischemic and preventive medications, with the aim of demonstrating a significant resolution of pretreatment ischemia. A paired testing strategy remains exploratory because of the limited evidence base and cannot be recommended at this time, but it may prove useful for women with nonobstructive CAD and demonstrable ischemia. Given that repeat testing is common in current clinical practice despite minimal evidence of benefit, serial testing should be a focus of future research. These investigations should not only assess optimal timing of the repeat evaluation to allow for treatment titration or disease progression but also consider the interplay with the stability and frequency patterns of clinical symptoms.

Sex-Based Patient-Centered Imaging

The evaluation algorithm created in the present report for the symptomatic woman was guided by initial IHD risk estimates to tailor the choice of diagnostic testing. Women at low IHD risk most often require no testing. Women at low-intermediate or intermediate IHD risk who can exercise adequately should be referred to an ETT-first strategy. CAD imaging is indicated for intermediate-risk or high IHD risk women with functional disability or an abnormal rest ECG. Choosing the right test for the right woman is the central principle of patient-centered imaging. For the imager, another principle is timely interpretation and the use of standardized reporting to guide a consistent and optimal image interpretation for all women. Finally, for the interpreting and referring physician, diagnostic test findings form the basis for creating a treatment plan tailored to each woman based on the extent and severity of stress-induced abnormalities or identified nonobstructive or obstructive CAD.

Quality of the Published Evidence and the Need for Sex-Based Comparative Effectiveness Research

Although there is abundant high-quality evidence on each of the ETT and imaging techniques and emerging evidence on the prognostic significance of nonobstructive CAD in women, significant gaps in research remain. A recent publication by Murthy et al[251] adds to the existing literature by confirming the link with adverse outcomes for both women and men with nonobstructive coronary atherosclerosis as documented by reduced MFR on cardiac PET. Therefore, comparative effectiveness registries and trials to optimally guide the diagnostic evaluation and improved treatment evidence for symptomatic women should be a high priority. The goal of this requisite evidence would be to ascertain long-term effectiveness data comparing stress testing or anatomic testing with no testing or alternative approaches for the diagnostic evaluation of women with ischemic symptoms. Limited comparative evidence hinders the present report, because statements contrasting one modality with another have significant limitations and biases that diminish the reliability of any single recommendation. Consideration of radiation exposure and cumulative costs of care are important secondary aims of these registries and trials. The National Heart, Lung, and Blood Institute–sponsored Prospective Multicenter Imaging Study for Evaluation of Chest Pain is an ongoing comparative effectiveness trial of functional stress testing (with exercise ECG, stress echocardiography, or stress MPI) compared with CCTA for the evaluation of >8000 patients presenting for a diagnostic evaluation. It remains vital for the provision of care to women presenting with ischemic symptoms that current and future trials enroll sufficiently large samples of women such that secondary analysis may establish a definitive statement with regard to the generalizability of trial findings to female patients.

Summary

The present statement includes an evidence synthesis on the abundant diagnostic and prognostic accuracy data for the diagnostic evaluation of women with ischemic symptoms. There is a greater degree of gender equity in the availability and quality of evidence across the various diagnostic testing modalities in the present report than in the prior 2005 statement,[5] which allows for evidence-based recommendations for testing that are tailored to female-specific IHD risk. First, low-risk women, with some exceptions, are not candidates for diagnostic testing. Second, the present statement recommends an initial exercise ECG–first strategy for women at low and intermediate IHD risk. Third, for symptomatic women with functional disability, an indeterminate ETT, or an abnormal rest ECG, echocardiography or MPI is recommended or CMR may be considered a reasonable test option. CCTA may also be considered reasonable for women at intermediate IHD risk. Premenopausal women at intermediate IHD risk who are functionally disabled generally should undergo echocardiography or CMR but may undergo MPI or CCTA if an effective radiation dose of <3 mSv is possible. Risk stratification is based on the extent and severity of inducible abnormalities noted on the stress examination. Moreover, evidence supports CMR and CCTA as being accurate in the detection of obstructive CAD and for IHD risk assessment of symptomatic women, whereas these modalities were considered research techniques in 2005.[5] CCTA can uniquely provide information on the obstructive and nonobstructive burden of CAD, which may be reasonable to guide posttest management approaches for women. A summary of recommendations for IHD imaging in women is detailed in Table 7. Acquisition of additional comparative effectiveness evidence remains essential to further improve and guide testing and the treatment of women presenting with ischemic symptoms and is an important aim for future research.

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Disclosures

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Daniel S. Berman	Cedars-Sinai Medical Center	Astellas Healthcare†; Cardium Therapeutics†; GE Healthcare†; Lantheus Medical Imaging†; Siemens†	None	Astellas Healthcare*; IBA Molecular*	None	Patent royalties for software for Cedars Sinai Medical Center†; equity interest in Spectrum Dynamics†	Lantheus Medical Imaging*	On Boards for ASNC and SCCT*
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Sharonne N. Hayes	Mayo Clinic	None	None	None	None	None	None	None
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L. Kristin Newby	Duke University Medical Center	None	None	None	None	None	None	None
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Patricia A. Pellikka	Mayo Clinic	None	None	None	None	None	None	On BOD for ASE from 2012 through June 2014*
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Nanette K. Wenger	Emory University School of Medicine	None	None	None	None	None	None	Member UA/NSTEMI ACC/AHA writing group (diagnostic part)*; Chair of IOM Committee to Advise the Social Security Administration on Revision of the Disability Listings (some content involves noninvasive testing)*

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

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Raymond J. Gibbons	Mayo Clinic	None	None	AstraZeneca*	None	None	Lantheus Medical Imaging*	None
W. Gregory Hundley	Wake Forest University	Prova Images*; Bracco*; NIH†	None	None	None	Prova Images*	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease: A Consensus Statement From the American Heart Association

Jennifer H. Mieres, Martha Gulati, Noel Bairey Merz, Daniel S. Berman, Thomas C. Gerber, Sharonne N. Hayes, Christopher M. Kramer, James K. Min, L. Kristin Newby, J.V. (Ian) Nixon, Monvadi B. Srichai, Patricia A. Pellikka, Rita F. Redberg, Nanette K. Wenger and Leslee J. Shaw

on behalf of the American Heart Association Cardiac Imaging Committee of the Council on Clinical Cardiology and the Cardiovascular Imaging and Intervention Committee of the Council on Cardiovascular Radiology and Intervention

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