



## CONSENSUS STATEMENT

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### A Report of the American Society of Nuclear Cardiology Task Force on Women and Heart Disease (Writing Group on Perfusion Imaging in Women)

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#### PREAMBLE

The American Society of Nuclear Cardiology (ASNC), founded in 1993, is a professional medical society whose mission is to foster optimal delivery of nuclear cardiology services through professional education and leadership in the establishment of standards and guidelines for the practice of nuclear cardiology. ASNC will from time to time publish position, policy, or consensus statements that reflect a body of knowledge and clinical evidence for an application of radionuclide imaging techniques in the clinical care of patients with known or suspected heart disease. Position, policy, or consensus statements are approved by the ASNC Board of Directors before publication.

This consensus statement will examine the role of myocardial perfusion imaging studies in the diagnosis, risk assessment, and treatment of women with known or suspected coronary artery disease.

#### BACKGROUND

Cardiovascular disease is the leading cause of death among women in the United States. Despite advances in its diagnosis and management, coronary artery disease continues to claim the lives of more than 230,000 American women each year.<sup>1</sup> The lifetime risk of cardiovascular disease and its ensuing complications is 25% for a 40-year-old woman but increases to nearly 50% for older women.<sup>2</sup> Before the last decade, under-representation of women in clinical trials and observational studies led to a lack of available evidence and a generalized misperception that coronary artery disease was a “man’s disease.”<sup>3-11</sup> As a result of the paucity of clinical evidence on diagnosis and treatment of coronary artery

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disease, the ensuing management patterns for women have been exceedingly inefficient. There is an abundance of evidence on under-recognition, under-diagnosis, and under-treatment of coronary disease in women contributing to a higher cardiovascular mortality rate.<sup>3-11</sup> Increased mortality has been repeatedly noted in women after myocardial infarction: 38% of women will die within 1 year after hospitalization, as compared with 25% of men.<sup>1</sup> These data support a worse prognosis for women with coronary artery disease compared with men.

We believe that one key to effecting significant changes in the cardiovascular mortality rate for women is the appropriate use of a highly accurate diagnostic test, such as gated myocardial perfusion single photon emission computed tomography (SPECT), that results in early and effective treatment and improved outcome for at-risk women. The current document aims to put forth a synopsis of available evidence on the role of myocardial perfusion imaging studies in women.

### **GENDER DIFFERENCES IN NONINVASIVE DIAGNOSTIC TESTING FOR CORONARY ARTERY DISEASE**

There are several challenges for the noninvasive diagnosis of coronary artery disease in women. Under-representation of women in the major trials of coronary artery diagnosis has contributed to the paucity of gender-specific data on the test performance characteristics and diagnostic accuracy of the most commonly used noninvasive tests. Since the 1990 congressional mandate that women be included in all federally funded cardiovascular trials, a growing body of data continues to support the fact that diagnostic accuracy of noninvasive cardiac tests is different in women than in men.

Several early reports have suggested that women are less often referred to undergo invasive cardiac procedures, even in the presence of multiple clinical variables or abnormal noninvasive test results.<sup>3-5</sup> This reduced utilization of cardiac catheterization for women may result in part from the lower pre- and post-testing noninvasive estimates of coronary artery disease. Although recent studies have reported the absence of gender-related differences with regard to referral for coronary angiography, controversy still exists as to the significance of gender bias in clinical practice.<sup>6-11</sup>

### **CHALLENGES IN DIAGNOSIS OF CORONARY ARTERY DISEASE WITH EXERCISE ELECTROCARDIOGRAPHY**

Numerous reports have demonstrated a lower diagnostic accuracy for exercise electrocardiography in women, in particular, the occurrence of 1 mm of ST-

segment depression or greater.<sup>12-14</sup> The mean sensitivity and specificity for the exercise electrocardiogram (ECG) are 61% and 69%, respectively.<sup>13,14</sup>

The increased age at presentation by women, coincident with functional impairment, is associated with lower exercise capacity and an inability to attain maximal stress. Additional critical factors that have been reported to affect test accuracy in women include resting ST-T-wave changes in hypertensive women, lower electrocardiographic voltage, and hormonal factors.<sup>15-20</sup> For the premenopausal woman, endogenous estrogen has a digoxin-like effect that may precipitate ST-segment depression, resulting in a false-positive test result.<sup>15</sup> Physicians who test premenopausal women with chest pain or established coronary disease should caution against the use of exercise stress testing in a woman's mid cycle, during which estrogen levels are highest. Reports have noted a reduced frequency of ischemic episodes and chest pain during this phase of the menstrual cycle.<sup>16</sup>

The accuracy of the exercise ECG in women is highly variable and influenced by multiple factors, including exercise capacity and hormonal status. The current American College of Cardiology/American Heart association guidelines for exercise testing recommend it as a first-line test for those with a normal resting 12-lead ECG and for those capable of performing maximal stress.<sup>18</sup> Although maximal stress may be defined as achieving at least 85% of predicted maximal heart rate, care should be taken when a woman's heart rate response is being interpreted. For deconditioned patients, a hyper-exaggerated response to physical work may result in marked increases in heart rate. Thus the test should be continued until maximal symptom-limited exercise capacity is reached. Women incapable of performing a minimum of 5 metabolic equivalents of exercise should be considered candidates for myocardial perfusion imaging with pharmacologic stress.

Women with diabetes mellitus are a special population worthy of mention. They are at an increased risk for premature atherosclerosis and significant risk for myocardial infarction and cardiac death.<sup>1</sup> The unique pathophysiology of diabetes makes traditional symptoms less reliable and diagnosis of coronary artery disease more challenging. The ECG is often a less reliable indicator of significant coronary artery disease in the patient with diabetes.<sup>1</sup> Myocardial perfusion imaging has been shown to be accurate in the risk assessment and prediction of future cardiac events in the woman with diabetes. In a cohort of 2086 women, stress myocardial perfusion imaging independently predicted future cardiac events in the 451 women with diabetes enrolled in the study.<sup>22</sup> The presence and extent of perfusion defects were the strongest predictor of future cardiac events among women with diabetes.<sup>22</sup> Therefore, given the challenge of diag-

nosing coronary artery disease in patients with diabetes, myocardial perfusion imaging should be considered instead of exercise electrocardiography in diabetic women with suspected coronary artery disease.

A major key to the accurate diagnosis of coronary artery disease based on the exercise ECG in women is to include factors other than ST-segment depression in interpreting the test.<sup>19,20</sup> The integration of parameters such as the  $\Delta$ ST/heart rate index and the Duke treadmill score may improve the diagnostic and prognostic accuracy of testing in women.<sup>19,20</sup> Women with a normal baseline ECG and an intermediate-to-high pretest likelihood of coronary artery disease should be considered for exercise combined with myocardial perfusion imaging, because myocardial perfusion imaging provides added diagnostic accuracy and incremental prognostic value in this group.<sup>14,23</sup>

### Consensus

Exercise electrocardiography is useful in women with a good exercise capacity and a normal baseline resting ECG.<sup>18</sup> In the group of women with an intermediate-to-high pretest likelihood of coronary artery disease, combining exercise with myocardial perfusion imaging has added diagnostic and prognostic value over the exercise ECG.<sup>14,23</sup> For those women incapable of maximal exercise, those with diabetes, and those with an abnormal baseline ECG, myocardial perfusion imaging adds substantial incremental diagnostic and prognostic value over the exercise ECG.<sup>13,22-29</sup>

### DIAGNOSIS OF CORONARY ARTERY DISEASE WITH MYOCARDIAL PERFUSION STUDIES

A growing body of evidence supports the diagnostic value of stress myocardial perfusion imaging in the detection of coronary artery disease in women. Data have shown that stress myocardial perfusion imaging consistently has a significantly higher diagnostic accuracy than exercise testing alone.<sup>13,28,30-34</sup> In addition, exercise SPECT myocardial perfusion imaging is more accurate in diagnosing coronary artery disease than planar imaging.<sup>31</sup> Limited data regarding diagnostic accuracy with pharmacologic stress imaging suggest improvement over exercise electrocardiography alone.<sup>32-34</sup>

It is well appreciated that diagnostic accuracy in women is adversely affected by gender-specific factors such as breast attenuation, small left ventricular chamber size, and a high prevalence of single-vessel coronary artery disease.<sup>31,35</sup> A study using thallium 201 imaging demonstrated a lower sensitivity for single-vessel disease in women than men.<sup>25</sup> This lower sensitivity for single-vessel disease in women may be related to a chamber

size that is generally smaller in female patients than in male patients.<sup>35</sup> One study using technetium 99m sestamibi and pharmacologic stress has demonstrated a high sensitivity but a moderate specificity.<sup>34</sup> The reduced specificity may be related to soft-tissue attenuation from breasts.

A recent meta-analysis (21 studies with a total of 4113 women) comparing exercise electrocardiography, stress myocardial perfusion imaging, and stress echocardiography also suggested a reduced specificity for myocardial perfusion imaging compared with echocardiographic techniques.<sup>14</sup> However, the perfusion imaging studies included in that analysis incorporated substantial data from older literature, and no studies that incorporated contemporary imaging techniques such as gated SPECT imaging were included. With the use of gated SPECT, the simultaneously derived information on perfusion and function can assist in better differentiation of attenuation artifact from infarct.

In two recent studies involving over 170 women, gated SPECT imaging with Tc-99m sestamibi improved the previously reported specificity for detection of coronary artery disease in cohorts of women with suspected coronary artery disease.<sup>28,36</sup> The specificities in these two studies, 92% and 91%, were both higher than the upper limits of the confidence intervals on specificity in the meta-analysis of exercise electrocardiography, perfusion imaging, or echocardiographic studies.<sup>14,28,36</sup> Therefore contemporary myocardial perfusion imaging techniques with gated SPECT imaging and technetium-99m-based agents are of considerable importance in enhancing the diagnostic accuracy of myocardial perfusion imaging studies in women. These studies suggest that the specificity for ruling out disease when such techniques are used equals or possibly exceeds that of other techniques.

In summary, although some limitations are recognized, stress myocardial perfusion imaging plays an important role in the diagnosis of coronary artery disease in women and is clearly superior to exercise testing alone.

### Consensus

Stress myocardial gated perfusion SPECT imaging is an effective noninvasive means of evaluating women with an intermediate-to-high pretest likelihood of suspected coronary artery disease.

### PHARMACOLOGIC SPECT MYOCARDIAL PERFUSION IMAGING IN WOMEN

Because women are generally older when they present with coronary artery disease and have a higher

**Table 1.** Key indications for referral to gated myocardial perfusion SPECT imaging with exercise or pharmacologic stress in women: A synthesis of the supportive evidence

	<b>Key indications</b>	<b>Supportive evidence for referral</b>
Pretest likelihood of coronary artery disease	Intermediate-to-high risk undergoing testing for symptom evaluation with the following:  (1) Abnormal Rest ECG  (2) Poor exercise capacity (<5 METs) (3) Intermediate Duke treadmill score or indeterminate exercise ECG	(1) ACC/AHA Guidelines for exercise testing and stable angina <sup>18,58</sup>  (2) Effective risk stratification using exercise myocardial perfusion SPECT in women: Gender-related differences in prognostic nuclear testing <sup>29</sup>
Special populations		
Women with stable chest pain	Candidates for pharmacologic stress of abnormal rest ECG	ACC/AHA guidelines for stable angina <sup>58</sup>
Women with diabetes	Preoperative risk assessment for vascular surgery or kidney or pancreas transplant	Single-site and multicenter registry data <sup>22</sup>

ACC/AHA, American College of Cardiology/American Heart Association, METs, metabolic equivalents.

incidence of decreased exercise capacity, many with known or suspected coronary artery disease are not able to complete a symptom-limited exercise protocol and are therefore candidates for pharmacologic stress testing. Approximately 40% of women who are referred for myocardial perfusion studies for the evaluation of known or suspected coronary artery disease are candidates for pharmacologic stress testing. Although several studies have demonstrated a similar diagnostic accuracy of pharmacologic stress and exercise myocardial perfusion imaging, there are few data specific for women undergoing myocardial perfusion imaging with the pharmacologic stressors dipyridamole, adenosine, or dobutamine.<sup>26,27,32-34</sup>

Limited data comparing pharmacologic stress perfusion imaging with exercise electrocardiography support its higher diagnostic accuracy,<sup>13</sup> although it is controversial as to which pharmacologic stress protocol is ideal for women with known or suspected coronary artery disease who are incapable of maximal stress with exercise. One study demonstrated a lower sensitivity of pharmacologic stress with Tl-201 in women compared with men, especially in the setting of 1-vessel disease.<sup>25</sup> The accuracy of pharmacologic stress with dipyridamole Tc-99m sestamibi SPECT was shown to be similar for detecting multivessel disease for men and women, with a higher sensitivity for detecting disease of the left anterior descending coronary artery in women.<sup>28,37</sup> Pharmacologic stress with adenosine that used a dual-isotope SPECT protocol was shown to have a sensitivity of 93%, specificity of 78%, and diagnostic accuracy of 88% in a

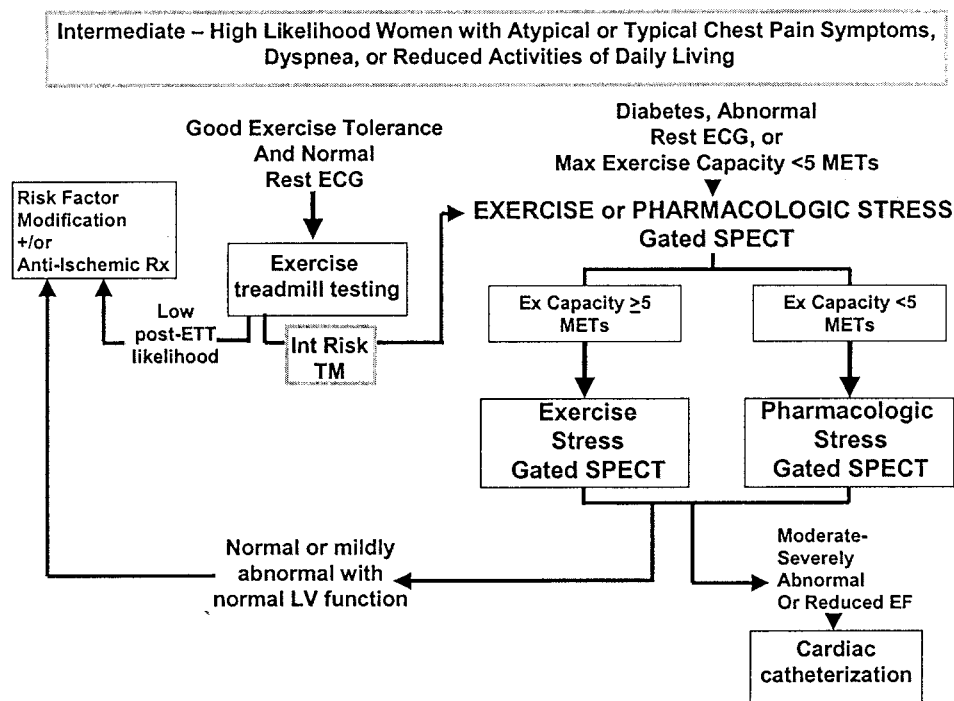
cohort of women with suspected coronary artery disease who underwent cardiac catheterization.<sup>32</sup>

### Consensus

Data thus far confirm the higher diagnostic accuracy of pharmacologic stress compared with exercise electrocardiography in the diagnosis of coronary artery disease in women. Pharmacologic stress myocardial perfusion imaging is recommended for the diagnosis of coronary artery disease in women with an intermediate-to-high pretest likelihood of coronary artery disease who are incapable of achieving maximal stress with exercise.

### ROLE OF MYOCARDIAL PERFUSION IMAGING IN RISK STRATIFICATION OF WOMEN WITH SUSPECTED CORONARY ARTERY DISEASE

Myocardial perfusion imaging has been shown in a multitude of clinical investigations, which have included over 20,000 patients, to have powerful predictive value with regard to the development of subsequent cardiac events or need for revascularization.<sup>22,29,39-56</sup> This prognostic value has also been documented specifically for women. Pooled data from over 7500 women demonstrated an annual cardiac event rate of less than 1% in the setting of a normal myocardial perfusion study.<sup>27,38,41-56</sup> Conversely, data from over 5000 women demonstrated a substantially increased risk for cardiac events if they had an abnormal perfusion study.<sup>26,29,40,43,44,46-54</sup> Even when a high pretest likelihood of coronary disease is present, a



**Figure 1.** Recommended algorithm for evaluation of women with suspected or known coronary artery disease.<sup>57,58</sup> ETT, Exercise treadmill test; TM, treadmill; Max, maximal; METs, metabolic equivalents; LV, left ventricular; EF, ejection fraction.

very low cardiac event rate and performance of revascularization have been documented after a normal stress perfusion study.<sup>29</sup> As the extent of the perfusion defect increases, so do the rates for both myocardial infarction and cardiac death (4- to 6-fold increase),<sup>26-29</sup> and the odds ratio for an event with an abnormal scan has been found to be substantially higher for women than for men.<sup>29</sup>

Even when other clinical risk factors are present, the severity and extent of the perfusion defect independently predict future cardiovascular events.<sup>26,29,39,40</sup> An abnormal SPECT study is therefore independently valuable beyond any clinical or stress test parameter.<sup>26,29,39,40</sup> Myocardial perfusion imaging has also demonstrated prognostic value for women with regard to specific applications, such as in the assessment of perioperative risk before major noncardiac surgery.<sup>27</sup>

### Consensus

On the basis of a substantial body of evidence, including 3402 women with chest pain in the Economics of Noninvasive Diagnosis multicenter registry of stable chest pain,<sup>26</sup> myocardial perfusion imaging with exercise or pharmacologic stress is valuable and is recommended for the risk stratification of women with known or suspected coronary artery disease.

### RECOMMENDATIONS FOR MYOCARDIAL PERFUSION IMAGING IN WOMEN

The early and accurate detection of flow-limiting coronary artery disease in women is of crucial importance in the selection of patients for referral for invasive procedures, coronary artery revascularization with percutaneous coronary intervention, or coronary artery bypass graft surgery. The diagnostic and prognostic value of stress myocardial perfusion imaging for the detection of coronary artery disease in women is firmly established.<sup>57,58</sup> The use of gated SPECT imaging adds significantly to the diagnostic accuracy of imaging in women, by improving specificity to more than 90%. Myocardial perfusion imaging adds incremental value to the use of clinical variables or exercise stress testing alone in the risk assessment of women with known or suspected coronary artery disease. On the basis of the clinical evidence, myocardial perfusion SPECT imaging with electrocardiographic gating, therefore, continues to be the cornerstone of the noninvasive evaluation of women with an intermediate pretest likelihood of coronary artery disease.

Table 1 details the appropriate candidates for referral to gated myocardial perfusion SPECT imaging. In general, the current evidence supports the use of gated myocardial perfusion SPECT imaging for symptomatic

women who are at an intermediate pretest likelihood for coronary artery disease. Although the data are not as strong for women with a high pretest likelihood of coronary artery disease, myocardial perfusion imaging adds incremental prognostic value over resting ECG and clinical variables in this group.<sup>29</sup> In women, normal scan is associated with an annual cardiac event rate of lower than 1% even when a high pretest likelihood of coronary artery disease is present.<sup>29</sup> Additional candidates for imaging include women with diabetes<sup>22</sup> and those who should undergo pharmacologic stress testing because they are incapable of maximal exercise. A recommended approach for the evaluation of women based upon the current clinical evidence is detailed in Figure 1.

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