Marked reductions in cardiovascular mortality in women have occurred for the first time this decade as a result of advances in medical treatment, improvement in medical technology, and a greater focus on women and their cardiovascular risk. Nonetheless, cardiovascular disease remains the No. 1 cause of death for women in the United States, and more women die from cardiovascular disease than men every year. In addition, women with coronary artery disease (CAD) are more likely to have a poorer prognosis than men. Women who have an acute myocardial infarction have a higher mortality than their male counterparts, and women who have symptoms of angina or an abnormal stress test are less likely to be referred for further diagnostic testing.

Given these gender differences in the evaluation of possible CAD symptoms and the higher mortality due to CAD in women, critical steps should be taken to identify women at the earliest stage of presentation so that appropriate therapeutic strategies can be implemented. Nonetheless, identifying women with coronary disease can be a diagnostic challenge. The prevalence of CAD in younger women is low, and women tend to present with symptoms and CAD at older ages as compared with men. In addition, women may present with more atypical symptoms. Women also have a lower prevalence of obstructive coronary disease, making diagnostic testing designed to detect focal areas of coronary stenosis less sensitive and specific in this population.

Currently, exercise stress testing is the most commonly used method of diagnosing CAD in women, and the exercise stress ECG is the initial noninvasive study of choice in the diagnosis of CAD. Both the 2002 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for Exercise Testing and the 2005 Guidelines for the Role of Noninvasive Testing in the Clinical Evaluation of Women with Suspected Coronary Artery Disease recommend the exercise ECG as the first diagnostic test of choice in symptomatic, intermediate-risk women with a normal baseline ECG. Historically, exercise stress testing in women has been thought to have a decreased diagnostic accuracy because of a lower prevalence of CAD in women, but most early studies evaluating stress testing as a diagnostic tool were performed in almost exclusively male cohorts. Until recently, the representation of women in published studies was too small to determine any gender differences in test accuracy. The underrepresentation of women, as well as the bias in selection of women when included, may be the reason for the misconceptions regarding the value of exercise stress testing in women. Nonetheless, research on exercise stress testing in women has increased in the past decade, improving our understanding of the diagnostic and prognostic value of this modality in women.

The purpose of this article is to review the literature regarding exercise stress testing in women, with a focus beyond ST-segment depression alone. It addition to interpretation of ECG changes with exercise, evaluation of exercise capacity, chronotropic index, heart rate (HR) recovery (HRR), blood pressure response, and Duke Treadmill Score (DTS) can be used to enhance the utility of exercise testing. The diagnostic and prognostic value of these non-ECG variables in women is reviewed, with a goal of highlighting the importance of exercise stress testing in women on the basis of the research available to date.

ST-Segment Depression

**Diagnostic Value**

ST-segment depression that occurs with exercise stress testing reflects ischemia, which may indicate the presence of obstructive CAD. ST-segment depression that occurs with exercise stress testing is thought to be less accurate in identifying CAD in women than in men. The sensitivity and specificity of ST-segment depression with an exercise ECG in symptomatic women vary widely depending on the study, with the sensitivity generally being worse than the specificity. The sensitivity and specificity for the diagnosis of CAD in women range from 31% to 71% and 66% to 86%, respectively. In a meta-analysis of exercise testing in women, the sensitivity and specificity for ST-segment depression in symptomatic, intermediate-risk women were 61% and 70%, respectively. This is compared with a sensitivity and specificity of 68% and 77%, respectively, in a meta-analysis of predominantly male participants. In a study of symptomatic men and women undergoing exercise ECG and subsequent angiography, the positive predictive value of ST-segment depression with exercise testing in women was significantly lower than in men.
(47% versus 77%, respectively; *P*<0.05).35 However, the negative predictive value (NPV) of ST-segment depression in symptomatic women was similar to that of men (78% versus 81%, respectively). Although women are more likely to have a “false-positive” exercise ECG, a negative exercise stress test is useful in effectively ruling out a diagnosis of CAD.

Differences in the accuracy of ST-segment depression for men and women may be explained by several factors. First, women are more likely than men to have baseline ST- and T-wave changes, making interpretation of ECG changes with exercise difficult.36,37 Second, it has been thought that women have more ST-segment depression with exercise testing.32 In an early study that included both asymptomatic men and women, women were more likely than men to have ST-segment depression after 3 minutes of exercise (16% of women, women were more likely than men to have ST-segment depression with exercise testing.32 In an early study that included both asymptomatic men and women, women were more likely than men to have ST-segment depression after 3 minutes of exercise (16% of women versus 3% of men).38 However, in larger and more recent studies of asymptomatic women, ST-segment depression appears far less common than noted in prior reports.39,40 ST-segment depression with exercise stress testing occurred in 6.2% of the 5721 women in the St James Women Take Heart Project cohort39 and in 4.7% of the 2994 women in the Lipid Research Clinics study.40 Third, it has been hypothesized that estrogen (natural or otherwise) may cause a digoxin-like effect on ST segments with exercise, which may account for the difference in accuracy in ST-segment depression in women compared with men. In premenopausal women with no CAD, the presence of ST-segment depression during exercise appears to vary with the menstrual cycle.41 Furthermore, postmenopausal women receiving oral estrogen therapy are more likely to have exercise-induced ST-segment depression with normal coronary angiograms than postmenopausal women not on estrogen replacement.42 Finally, women are generally older when they present for stress testing and may have a decreased exercise tolerance, decreasing the ability of the test to induce ischemia and ST-segment depression and limiting the ability to accurately identify women with CAD.14

**Prognostic Value**

Although ST-segment depression with exercise provides some diagnostic information in women, these same ECG changes do not appear to provide strong prognostic value in women. In the large cohort of >5000 asymptomatic women from the St James Women Take Heart Project, there was no relationship between ST-segment depression with exercise stress testing and cardiovascular mortality or all-cause mortality.39,43 The frequency of ST-segment depression was the same in women who died and those who survived (6.2% versus 6.4%; *P*=0.99). A similar relationship between ST-segment depression with exercise testing and cardiovascular and all-cause mortality was described among the asymptomatic women from the Lipid Research Clinics,40 in contrast to the relationship seen between ST-segment depression with exercise testing and cardiovascular and all-cause mortality in asymptomatic men.44

**Exercise Capacity**

Exercise capacity, also known as functional capacity or cardiorespiratory fitness, has emerged as one of the most important diagnostic and prognostic markers that can be easily assessed with exercise stress testing.44–49 Exercise capacity is an estimate of the maximal oxygen uptake for a given workload and can be expressed in metabolic equivalents (METs).50 One MET is a unit of basal oxygen consumption, which equals 3.5 mL of oxygen consumption per kilogram of body weight per minute for an average adult. The exercise capacity can be estimated for any exercise stress protocol with the use of the speed and grade of the treadmill at peak exercise or the workload achieved on a bicycle ergometer.51

**Diagnostic Value**

Exercise capacity has been shown to be an independent predictor of the presence of CAD in women. In a study of 135 symptomatic women undergoing exercise stress testing and subsequent angiography, maximal exercise capacity achieved was among the best stress testing variables for predicting the presence of CAD and improved the sensitivity and specificity of exercise stress testing when added to ST-segment depression.49 This finding was confirmed in a group of 419 women and 555 men who underwent maximal exercise stress testing for symptom evaluation with the use of the Bruce protocol with single photon emission computed tomography (SPECT) imaging. Those who achieved ≥10 METs had a very low prevalence of significant ischemia (defined as ≥10% of the left ventricle on myocardial perfusion imaging), but those who achieved <7 METs were more likely to have significant ischemia (0.4% versus 7.1%; *P*<0.001).52 No (0%) significant ischemia was observed in participants who achieved >10 METs and had no ST-segment depression with exercise.

**Prognostic Value**

Exercise capacity has strong prognostic implications in asymptomatic and symptomatic women.39,40,53–55 In a retrospective study of exercise stress testing in a symptomatic referral population that included 741 women, exercise capacity was the only exercise stress testing variable that was an independent predictor of mortality.53 For every 1-MET increase in exercise capacity, there was a 25% reduction in risk of all-cause mortality and a 23% reduction in risk of cardiac events for women.53

Exercise capacity has also been shown to be a strong independent predictor of all-cause mortality in asymptomatic women, beyond traditional cardiac risk factors.39,40,56 In the St James Women Take Heart Project, those asymptomatic women who were unable to achieve 5 METs on a Bruce protocol had a 3-fold increased risk of death compared with women who achieved >8 METs.39 For each additional MET achieved on the exercise stress test, there was a 17% reduction in mortality, after controlling for traditional cardiac risk factors. These results were confirmed in the asymptomatic women from the Lipid Research Clinics study as well.40

In addition to absolute exercise capacity achieved, age-predicted exercise capacity can be determined after exercise stress testing and used for prognosis in women. Age-predicted exercise capacity was defined with the use of the large cohort of asymptomatic women from the St James Women Take Heart Project,57 who underwent a symptom-limited, maximal stress test with the use of the Bruce protocol. There was a linear and inverse relationship between
age and exercise capacity. On the basis of the linear regression analysis of exercise capacity for age, the following equation was developed:57

\[
P_{\text{age}} = 14.7 - (0.13 \times \text{age})
\]

A nomogram was constructed for simplicity of use of this calculation, in which age and achieved fitness level can be used to determine a woman’s percentage of age-predicted fitness level achieved (Figure 1).57 This relationship between age and exercise capacity and the ability to achieve a woman’s age-predicted fitness level was shown to be a predictor of both all-cause and cardiovascular mortality in asymptomatic women. Compared with asymptomatic women who achieved ≥85% of their age-predicted exercise capacity, those who achieved an exercise capacity <85% of their age-predicted value had approximately twice the risk of death from any cause (hazard ratio = 2.0; \( P < 0.001 \)) and a slightly greater risk of death from cardiac causes (hazard ratio = 2.4; \( P < 0.001 \)).

Furthermore, age-predicted exercise capacity for women was validated as a prognostic indicator in 4421 symptomatic women from the Economics of Noninvasive Diagnosis (END) study. These women also underwent a symptom-limited exercise stress test with the use of the Bruce protocol and were followed for events. Those symptomatic women who achieved <85% of their age-predicted exercise capacity also had at least twice the risk of death from any cause and cardiac causes compared with women who achieved ≥85% of their age-predicted exercise capacity (hazard ratio = 2.4; \( P < 0.001 \), and hazard ratio = 2.0; \( P < 0.001 \), respectively). In this study, asymptomatic and symptomatic women whose observed exercise capacity exceeded their age-predicted exercise capacity by at least 3 METs had a lower risk of death from any cause than their less-fit counterparts.57

**Figure 1.** 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 MET value on the right-hand scale will cross the percentage line at the point corresponding to the patient’s percentage of predicted exercise capacity for age. Adapted from Gulati et al, *N Engl J Med.* 2005;353:468–475.57

**Chronotropic Response**

The normal chronotropic response to exercise is based on the physiological requirement of the body to increase its cardiac output. This requires augmentation of both the HR and stroke volume. However, after the HR increases to >110 to 120 bpm, stroke volume ceases to increase, at which point HR alone contributes to the increase in cardiac output.58 The peak HR achieved with maximal exercise testing is influenced by both age and gender.59,60 An attenuated HR response to exercise (or an abnormal chronotropic response) is defined as chronotropic incompetence21,61 and has been associated with poorer prognosis60,62–64 Measures of chronotropic response include the following: (1) peak HR achieved with maximal exercise stress testing; (2) HR reserve or change in HR with exercise (peak HR with exercise minus resting HR); (3) ability to achieve at least 85% of the maximum age-predicted HR; and (4) chronotropic index. The latter 2 parameters have been the most studied in women.

**Ability to Reach 85% of Maximum Age-Predicted HR**

In the diagnosis of CAD, the ability to reach 85% of the maximum age-predicted HR with exercise can be used to determine the likelihood of CAD. In a small study of 200 symptomatic women undergoing exercise testing, inability to reach target HR was associated with higher likelihood of CAD.65 The ability to reach target HR also has prognostic value in women. Lauer et al63 demonstrated that the inability to achieve 85% of maximum age-predicted HR (defined as 220–age) was associated with decreased survival in both men and women. More recently, on the basis of the St James Women Take Heart cohort, the peak HR for age in women was redefined as 206–0.88(age).60 In this cohort of women, for every 1-bpm increase in peak HR with exercise achieved, there was a 3% reduction in all-cause mortality (\( P < 0.001 \)), and for every 1-bpm increase in HRR, there was 2% reduction in mortality (\( P < 0.001 \)), after controlling for traditional cardiac risk factors and exercise capacity. The inability to achieve 85% of age-predicted HR (with the use of the traditional estimate for age or the new equation for women) was not an independent predictor of mortality in these asymptomatic women. This new equation has not been validated, as of yet, in a symptomatic cohort of women.

Despite its possible diagnostic value, achievement of 85% of age-predicted HR was never intended to be an end point of any stress test protocol,13,66 and terminating exercise before symptoms occur may result in an inadequate exercise stress test.39,40,56

**Chronotropic Index**

Chronotropic index, defined as the ratio between HRR and metabolic reserve, is another measure of chronotropic response that has substantial prognostic value.64,67 In a healthy subject, HRR and metabolic reserve are equal, and therefore a normal chronotropic index should be =1.0. An abnormal chronotropic index is defined as <0.80. Chronotropic index can account for differences in baseline resting HR and functional capacity.64 In a cohort of symptomatic women and men referred for exercise testing, a low chronotropic index (<0.80) was shown to be an independent predictor of mortality (hazard ratio = 2.19; \( P < 0.001 \)).63 Chronotropic index was also shown to be a superior measure compared with
the ability to achieve 85% of the maximum age-predicted HR in the prediction of cardiac death and all-cause mortality.62

In the asymptomatic women from the St James Women Take Heart Project, when the chronotropic index was calculated, the newer estimate of peak HR for age in women was used. On the basis of the new value of age-predicted HR, chronotropic index was a better predictor of all-cause mortality compared with either the ability to achieve 85% of maximal age-predicted HR or the chronotropic index calculated with the use of the traditional age-predicted peak HR estimate (220—age). A chronotropic index of <0.80 was associated with a 30% increase in mortality from any cause (P<0.023) in asymptomatic women, after adjustment for cardiac risk factors and exercise capacity.60

**HR Recovery**

**Prognostic Value**

HRR, defined as peak HR achieved minus HR 1 minute into recovery, has been shown to have independent prognostic value in women as well as men.69–70 In a study that included 720 women who underwent exercise stress testing and subsequent angiography, 25% had an abnormal HRR (defined as a decrease in the HR of <12 bpm in the first minute of recovery). An abnormal HRR was found to be an independent predictor for all-cause mortality (hazard ratio=1.5; P=0.0002).70 This finding was confirmed in the asymptomatic women in the Lipid Research Clinics study, in which abnormal HRR was found to be an independent predictor of all-cause mortality and cardiovascular death.40

**HR-Adjusted Measures of ST Depression:**

**ΔST/ΔHR Index and ST/HR Slope**

Diagnostic Value

HR-adjusted measures of ST-segment depression have been developed to improve the diagnostic accuracy of ST depression with exercise stress testing. One such measure is the ΔST/ΔHR index, which is HR-adjusted ST-segment depression. The ΔST/ΔHR index during exercise stress testing can increase the specificity (94%) and sensitivity (94%) of exercise testing in women, with greater test sensitivity in women compared with men.67 The use of the ΔST/ΔHR index has been shown to improve the sensitivity to detect significant 3-vessel CAD by 33% to 35%. The ST/HR slope, or the rate of ST-segment depression with respect to increase in HR, has also been shown to increase the diagnostic value of the exercise ECG.71 For women particularly, the use of the ST/HR slope may improve the sensitivity of the exercise ECG.67 Despite the improved diagnostic accuracy of these measures, neither is used routinely in the interpretation of exercise stress testing in women. Some have argued that the ΔST/ΔHR index is statistically flawed because the respective weight given to both ST-segment depression and the change in HR response to exercise by the formula may be inaccurate.72,73 Because of the possible flaws in this technique and the technical difficulty in doing the calculation, neither are commonly used in clinical practice.74

**Blood Pressure Response to Exercise**

Exercise is associated with an increase in sympathetic tone and skeletal blood flow but a decrease in peripheral resistance.75 With exercise, a rise in systolic blood pressure is expected (to a maximum of 230 mm Hg), whereas the change in diastolic blood pressure can vary (10-mm Hg increase or decrease). Abnormal changes in blood pressure response with exercise have both diagnostic and prognostic value.

**Diagnostic Value**

A hypotensive response to exercise, defined as a fall in systolic blood pressure >10 mm Hg, may reflect acute left ventricular dysfunction due to ischemia. Studies that include predominantly male participants suggest that this drop in systolic blood pressure with exercise may be a very specific marker of the presence of left main or severe triple-vessel CAD,76–78 particularly if ST-segment depression occurs as well.79 However, the diagnostic value of a drop in systolic blood pressure with exercise in women is unclear. One study suggested that the specificity was lower in women because the hypotensive response appeared to occur more frequently in women in the absence of CAD,79 but other studies were unable to demonstrate its occurrence in women with normal coronary angiograms.78

**Prognostic Value**

An abnormal rise in blood pressure with exercise stress testing and during recovery has been shown to be associated with an increased risk of developing hypertension in both women and men.80,81 In asymptomatic men and women undergoing exercise stress testing in the Coronary Artery Risk Development in Young Adults (CARDIA) study, participants who had an exaggerated blood pressure response (defined as ≥210 mm Hg in men or ≥190 mm Hg in women) were 1.7 times more likely to have hypertension at the 5-year follow-up visit compared with those with a normal blood pressure response.80 The pattern of exaggerated blood pressure response between men and women may differ. In the Framingham Offspring Study, which included asymptomatic men (n=1026) and women (n=1284), an exaggerated diastolic blood pressure response with exercise was predictive of hypertension in both genders, but an elevated systolic blood pressure in recovery was only predictive of the development of hypertension in men.81

**Duke Treadmill Score**

Multiple risk scores have been developed that incorporate specific exercise stress testing and clinical variables, and they have been shown to be more useful than single variables in the diagnosis of CAD, in addition to improving the prognostic capabilities of exercise stress testing.49,82,83 The DTS, which was developed in 1987 by Mark et al,82 is the most widely used of all risk scores in exercise stress testing and has diagnostic and prognostic value in both women and men. The use of the DTS in the interpretation of exercise stress testing is recommended in the current ACC/AHA guidelines for exercise stress testing.13 This score was originally developed with the use of data from 2842 patients, including 30% women, with known or possible CAD who underwent exer-
cise testing before diagnostic angiography and had no prior revascularization or recent myocardial infarction.82

The DTS incorporates exercise time (which is also a measure of exercise capacity), ST-segment depression, and the presence or absence of angina, as follows:

\[
\text{DTS} = \text{exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{angina score index})
\]

Exercise time is measured in minutes on the Bruce protocol. ST deviation is 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).84

### Diagnostic Value

The DTS has been shown to have diagnostic value in both women and men.82,84–86 The diagnostic value of the DTS was shown in a study of 2758 symptomatic patients (30% women) who underwent exercise stress testing with subsequent angiography.86 Patients with a high-risk DTS were 376-fold more likely to have significant CAD than those with a low-risk DTS.

Similar results for the diagnostic value of DTS have also been demonstrated in symptomatic women.85 In a series of 976 symptomatic women referred for exercise testing and coronary angiography, the presence of CAD correlated with category of DTS risk: 19.1% of low-risk DTS, 34.9% of moderate-risk DTS, and 89.2% of high-risk DTS had at least 1-vessel CAD with 75% stenosis. Although women had less coronary disease compared with their male counterparts at every level of DTS, the relationship between DTS and presence of CAD was similar. Eighty-one percent of low-risk DTS women had no coronary stenosis >75%, whereas 46% of women with a high-risk DTS had 3-vessel or left main disease. In symptomatic men, 52.6% with a low-risk DTS had no coronary stenosis, and 71.5% with a high-risk DTS had 3-vessel or left main disease.

### Prognostic Value

The DTS has been shown to be an excellent prognostic tool in symptomatic women as well as men. A low-risk DTS is associated with a lower mortality rate.82,84,85 In both genders, a low-risk DTS was associated with an annual mortality rate of ~0.25%, in contrast with an annual mortality rate of 5% in those with a high-risk DTS.84 The prognostic ability of the DTS has been confirmed in a number of studies that followed.82,84,85 Overall, survival for women appears to be better at all levels of the DTS compared with men.82,85 The DTS is a valuable tool to predict the risk of future myocardial infarction, revascularization, cardiac survival, and all-cause mortality in both genders, but it does not appear effective at assessing prognosis in the elderly (those aged ≥75 years).87

The prognostic value of the DTS has been demonstrated in asymptomatic women. In the Women Take Heart Project, the DTS was an independent predictor of all-cause and cardiac mortality in asymptomatic women.43 Those women with a moderate- or high-risk DTS had a hazard ratio for all-cause mortality that was twice that of women with a low-risk DTS (P<0.001). The hazard ratio for cardiac death was 2.5 times greater in those with a high-risk DTS than those with a low-risk DTS (P<0.001). Because of the rare occurrence of symptoms and infrequency of ST-segment depression with exercise stress testing in asymptomatic women, the predictive value of the DTS was equal to that of exercise capacity in this cohort of women.43

### Exercise Stress Testing With Imaging

The addition of imaging to exercise, with either SPECT or echocardiography, is recommended by the AHA Consensus Statement in the evaluation of intermediate-risk women who have an abnormal exercise ECG or an abnormal baseline ECG that would preclude the interpretation of ST-segment depression with exercise.14

Both exercise stress echocardiography and SPECT techniques have limitations that are specific to women and must be taken into consideration.88 In exercise SPECT imaging, a false-positive test result can occur because of soft tissue attenuation due to either breast tissue or body habitus.89–91 Other gender differences in exercise SPECT may be explained by reduced left ventricular cavity size and smaller coronary arteries in women.90 Stress echocardiography may be limited by the variability in acoustic windows and the ability to capture images at the point of maximal stress. Despite these limitations, both the diagnostic accuracy and prognostic value of stress SPECT and stress echocardiography exceed those of exercise ECG alone, with no significant differences between men and women.

### Diagnostic Value

Exercise stress echocardiography has a higher specificity and sensitivity than exercise ECG alone, increasing the specificity and sensitivity to 81% to 86% and 80% to 88%, respectively, for diagnosis of obstructive coronary disease in symptomatic women.33,92–94 These values are similar to the sensitivity and specificity of these tests in men.95 In 161 symptomatic women undergoing exercise echocardiography and subsequent angiography, ST-segment depression with exercise and exercise-induced wall motion abnormalities had similar sensitivity, but the echocardiogram had a much higher specificity in the detection of coronary disease (80% for exercise echocardiography versus 56% for exercise ECG in this study).92 The positive predictive value of exercise echocardiography in this same population was 74%, and the NPV was 86%.

Similar to exercise echocardiography, the diagnostic accuracy of exercise SPECT exceeds that of exercise ECG alone in women.96,97 In a study of symptomatic postmenopausal women undergoing exercise SPECT, the accuracy of exercise testing was improved by the addition of nuclear imaging.97 The sensitivity and specificity of exercise ECG alone in this population were 67% and 69%, respectively, but with SPECT, the sensitivity and specificity rose to ~88% for both. In the diagnosis of CAD in symptomatic women, the sensitivity of exercise SPECT ranges from 78% to 88%, with a specificity of 64% to 91%,97–99 and there appear to be no
significant differences in diagnostic accuracy between men and women.98–101

There has been no direct comparison of the diagnostic ability of exercise SPECT and exercise echocardiography. In a systematic review of the literature of exercise testing with imaging that included women, the results of 10 studies in which SPECT was used and 4 studies in which echocardiography was used were combined. There was no difference between exercise SPECT and exercise echocardiography in the sensitivity (77% and 81%, respectively) and specificity (63% and 73%, respectively) for the diagnosis of CAD in women.102

Prognostic Value
Exercise echocardiography and SPECT both provide incremental prognostic information in women beyond the exercise ECG when one relies on ST-segment depression alone. Women with no ECG or echocardiographic evidence of ischemia had an excellent (96%) cardiac event–free survival over >3 years of follow-up, in contrast to a much higher cardiac event rate in those women with ECG and echocardiographic findings consistent with ischemia (cardiac event–free survival of 55%).103 In the same study, women with positive ECG findings and negative echocardiographic findings with stress had a longer event-free survival than women with negative ECG findings but echocardiographic findings consistent with ischemia.103 The prognostic value of exercise echocardiography appears to be similar in men and women.55,104 Similarly, exercise SPECT provides more prognostic value than ST-segment depression alone in women. In a study of men and women undergoing exercise SPECT, the imaging results provided 37% more prognostic information than exercise ECG variables, any woman who is able to exercise and have a normal baseline ECG.

Algorithm for Stress Testing in Women

Asymptomatic Women
As described above, exercise stress testing appears to provide important prognostic information in asymptomatic women, beyond traditional risk factors.99,100 However, there are no studies to date demonstrating that an intervention to improve exercise parameters changes outcomes.47 As such, although exercise stress testing information may better risk stratify women beyond traditional cardiac risk factor assessment, exercise stress testing in asymptomatic women for this purpose is not currently recommended.13,107

Table 1. ACC/AHA Practice Guidelines on Exercise Testing: Pretest Probability of CAD by Age and Symptoms in Women

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Typical/Definite Angina Pectoris</th>
<th>Atypical/Probable Angina Pectoris</th>
<th>Nonanginal Chest Pain</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>Intermediate</td>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>40–49</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>50–59</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>60–69</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>≥70</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
</tbody>
</table>

High indicates >90%; intermediate, 10–90%; low, <10%; and very low, <5%. Source: American Heart Association, Inc.

Table 2. Diagnostic Value of Various Stress Testing Modalities in Women

<table>
<thead>
<tr>
<th>Stress Testing Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG</td>
<td>31–71</td>
<td>66–78</td>
<td>78</td>
<td>47</td>
</tr>
<tr>
<td>Exercise echocardiography</td>
<td>80–88</td>
<td>79–86</td>
<td>98</td>
<td>74</td>
</tr>
<tr>
<td>Exercise SPECT</td>
<td>78–88</td>
<td>64–91</td>
<td>99</td>
<td>87</td>
</tr>
<tr>
<td>Pharmacological echocardiography</td>
<td>76–90</td>
<td>85–94</td>
<td>68</td>
<td>94</td>
</tr>
<tr>
<td>Pharmacological SPECT</td>
<td>80–91</td>
<td>65–75</td>
<td>90</td>
<td>68</td>
</tr>
</tbody>
</table>

Values are percentages. PPV indicates positive predictive value.
self-administered 12-question form designed to provide an assessment of exercise capacity, and an estimated exercise capacity of <5 METs may be a reason to undergo a pharmacological stress test rather than an exercise stress test, given that such a low exercise capacity may not adequately induce ischemia.\textsuperscript{109,110}

The diagnostic and prognostic accuracy of exercise testing in women can be improved by incorporating parameters such as exercise capacity, chronotropic response, HRR, blood pressure response, and the DTS, in addition to ST-segment depression with exercise (Table 3).\textsuperscript{111} A negative stress ECG has a high NPV, which in combination with its low cost and wide availability make it the recommended first step in the evaluation of a symptomatic woman with chest pain. A positive or inconclusive exercise ECG should be followed by stress testing with imaging or angiography if the exercise ECG appears particularly high risk. Similar to the stress ECG alone, negative stress testing with imaging effectively rules out CAD in a symptomatic woman.

**Conclusion**

The standard exercise stress test is recommended by the AHA, the ACC, and the American Society of Nuclear Cardiology as the initial stress test of choice in most patients who can exercise, including women.\textsuperscript{13,14} Use of the exercise stress test with imaging is recommended when an ECG cannot be interpreted (with the noted exception of women with a left bundle branch block, who will require a pharmacological stress test), if a patient is on digoxin, or if the exercise stress test is abnormal.\textsuperscript{13} Nonetheless, exercise stress testing with imaging or pharmacological testing is often the immediate choice for many physicians without regard for the recommendation of the guidelines and without regard for the important diagnostic and prognostic information that can be retrieved from the exercise ECG.\textsuperscript{52,112,113}

In the current climate of rising healthcare costs, it is important to critically evaluate the manner in which to appropriately use exercise stress testing in women to make accurate diagnostic assessments, reduce radiation exposure, and ensure appropriate allocation of medical resources.
Although the focus of stress exercise ECG has centered mainly on ST-segment depression as a method of diagnosing CAD, the use of additional exercise parameters in women improves the diagnostic accuracy of the exercise stress test, as well as the prognostic assessment. In women, exercise capacity, percentage of age-predicted exercise capacity, chronotropic response, HRR, blood pressure response, and the DTS can all be used to enhance the diagnostic and prognostic value of exercise ECG. Standardization of exercise stress test reporting should include this information, in addition to information regarding ST-segment depression. An assessment of risk stratification should be described in the report in such a way that the ordering physician may make use of this information. By providing the important diagnostic and prognostic data, physicians may adequately assess their risk of ischemia/detection of CAD in asymptomatic and symptomatic women; in symptomatic women, moderate- and low-risk DTS indicate more severe CAD.

Table 3. Non-ECG Exercise Test Variables of Diagnostic and Prognostic Value in Women

<table>
<thead>
<tr>
<th>Exercise Variable</th>
<th>Method of Assessment</th>
<th>High-Risk Values</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise capacity</td>
<td>Estimated by the stress protocol (in METs)</td>
<td>&lt;5 METs; &lt;85% of predicted value (predicted METs=14.7−(0.13×age))</td>
<td>Predictive of mortality and cardiovascular events in both asymptomatic and symptomatic women</td>
</tr>
<tr>
<td>Chronotropic response</td>
<td>Achievement of age-predicted HR</td>
<td>&lt;85% of age-predicted HR</td>
<td>Predictive of survival in symptomatic women</td>
</tr>
<tr>
<td>Chronotropic index: chronotropic index=HR/age×(100%−age-predicted peak HR−HRrest); metabolic reserve=(METpeak−1)/(METstage−1); HRR=(HRpeak−HRrest)/HRrest</td>
<td>Chronotropic index ≤0.80</td>
<td>Predictive of mortality and cardiovascular events in asymptomatic and symptomatic women</td>
<td></td>
</tr>
<tr>
<td>HRR</td>
<td>Difference between HR at peak exercise and HR after 1-minute recovery</td>
<td>≤12 bpm after 1-minute recovery (upright cool-down period)</td>
<td>Predictive of mortality in asymptomatic and symptomatic women</td>
</tr>
<tr>
<td>DTS</td>
<td>DTS=exercise time−(5×ST deviation)−(4×angina score index)</td>
<td>Low-risk DTS, ≤5; moderate-risk DTS, &gt;−11, &lt;5; high-risk DTS, ≥11</td>
<td>Predictive of all-cause mortality and cardiac mortality in asymptomatic and symptomatic women; in symptomatic women, moderate- and high-risk DTS indicate more severe CAD</td>
</tr>
<tr>
<td>∆ST/∆HR index</td>
<td>Maximum change in ST-segment depression/change in HR</td>
<td>Abnormal, &gt;1.6 μV/bpm</td>
<td>Increased the sensitivity for detection of CAD in asymptomatic women</td>
</tr>
<tr>
<td>ST/HR slope</td>
<td>Greatest statistically significant slope by linear regression relating ST-segment depression to HR during exercise</td>
<td>Abnormal, &gt;2.4 μV/bpm; markedly abnormal, &gt;6.0 μV/bpm</td>
<td>Increases the sensitivity for detection of CAD in asymptomatic women</td>
</tr>
<tr>
<td>BP response</td>
<td>Assessment of BP response to exercise, change in SBP and DBP from rest with maximal stress</td>
<td>Decrease in SBP &gt;10 mm Hg from baseline</td>
<td>High likelihood of ischemia/detection of CAD in left main coronary artery and/or 3-vascular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SBP &gt;190 mm Hg with exercise testing</td>
<td>Increased risk of developing hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exaggerated DBP response to exercise</td>
<td>Increased risk of developing hypertension</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Source: American Heart Association, Inc.

*Using peak age-predicted HR=206−0.88 (age) in asymptomatic women for chronotropic index calculation.

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References


