Exercise Stress Testing in Patients With Type 2 Diabetes: When Are Asymptomatic Patients Screened?

George D. Harris, MD, MS, and Russell D. White, MD

Patients are presenting to medical offices at younger ages than ever before with type 2 diabetes, obesity, hypertension, and dyslipidemia. Even in an asymptomatic state, these patients are at high risk for cardiovascular disease and significantly higher morbidity and mortality. The challenge for clinicians is to identify which of these diabetic patients will have significant coronary artery disease (CAD) as early as possible so they may benefit from medical or surgical intervention. This article provides clinicians with a review of recommendations and resources from the medical literature to assist in deciding which asymptomatic diabetic patients require exercise treadmill testing.

Although there has been a decreasing trend in mortality from CAD in the overall population,1 this condition remains the leading cause of death in patients with diabetes. Problems with prevention and diagnosis persist because 1) diabetes is an independent risk factor for heart disease, 2) the onset of diabetes produces coronary complications before the clinical diagnosis of diabetes is made, and 3) there may be atypical or absent symptoms of coronary disease in individuals with diabetes. Decreasing the mortality of patients with diabetes from CAD will necessitate improvement in the early diagnosis and aggressive treatment of diabetes, as well as careful screening for subclinical significant CAD.

There are no evidence-based guidelines for screening asymptomatic diabetic patients for coronary artery disease (CAD). One well-studied screening tool is exercise treadmill testing. Many diabetic patients with no symptoms of CAD have abnormal stress tests. For asymptomatic patients, identification of cardiovascular risk factors and risk stratification may help physicians justify the performance of treadmill evaluation. Patients considering moderate or vigorous exercise and those at highest risk can undergo exercise stress testing with referral for further evaluation as indicated. For patients with decreased exercise capacity, inability to reach target heart rates, or absence of chest pain during exercise, stress nuclear imaging may be more valuable than exercise electrocardiograph testing.

Table 1. Individual Risk Stratification

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<tr>
<th>Risk Level</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>Asymptomatic men &lt; 45 years of age or women &lt; 55 years of age with no more than one risk factor</td>
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<tr>
<td>Moderate risk</td>
<td>Men &gt; 45 years of age or women &gt; 55 years of age or individuals with &gt; 2 risk factors</td>
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<tr>
<td>High risk</td>
<td>Individuals who have ≥ 1 sign or symptom suggestive of cardiovascular disease or who have known cardiovascular disease, pulmonary disease, or metabolic disease (diabetes, thyroid disorders, renal disease, or liver disease)</td>
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Studies have demonstrated that a significant percentage of patients with diabetes who have no symptoms of CAD have abnormal stress tests, either by stress ECG, stress echocardiogram, or stress nuclear perfusion imaging. CAD in patients with diabetes is often silent, more advanced with significant coronary stenosis (noted on angiography), and associated with less favorable prognosis than those in the nondiabetic population. It has also been demonstrated that patients with silent myocardial ischemia have a poorer prognosis than
those with normal stress tests, and their risk is further accentuated if cardiac autonomic neuropathy coexists. As the number of individuals who develop diabetes increases, more patients will need to undergo further cardiovascular assessment.

Patients with diabetes may present with typical angina, but variant symptoms are often the earliest subtle manifestations of CAD. Unfortunately, patients with diabetes may present with an acute major cardiac event and remain asymptomatic until immediately before its onset. Thus, although diagnosing and treating patients with diabetes and associated CAD is important, the proper screening for disease and evaluation remains difficult.

According to the American Diabetes Association (ADA) and the American College of Cardiology (ACC), exercise stress testing (with or without imaging) is recommended in both symptomatic and asymptomatic patients with specific criteria (difficulty completing usual tasks, dizziness with activity, dyspnea with minimal exertion, easy fatigueability, lack of energy, neck or jaw discomfort, shoulder pain, or upper back pain). In addition, diabetic patients with microalbuminuria and patients > 35 years of age with evidence of autonomic neuropathy should undergo exercise stress testing because these two markers have been associated with a high risk of cardiovascular disease. If these initial tests are normal, repeat testing is recommended in 2 years.

Approximately 20–25% of asymptomatic patients with diabetes have perfusion defects consistent with CAD. The true prevalence of silent ischemia in patients with diabetes remains unknown. Candidates for a screening cardiac stress test include those with 1) a history of peripheral or carotid occlusive disease, 2) sedentary lifestyle, 3) age > 35 years, and 4) plans to begin a vigorous exercise program. It is important to qualify the intensity of exercise to be performed. There are no data to suggest that patients who initiate physical activity by walking or similar exercise increase their risk of a cardiovascular disease event. Therefore, they are unlikely to need a stress test. However, Sigal et al. note that exercise stress testing is indicated in individuals who will be exercising more than at the level of their activities of daily living or those who are at increased mortality risk based on the U.K. Prospective Diabetes Study (UKPDS) risk engine.

Identification of cardiovascular risk factors in asymptomatic patients with diabetes can assist physicians in justifying treadmill evaluation, the necessity for early treatment modalities, and the goal of reducing the occurrence of a cardiac event. For asymptomatic patients, exercise stress testing may provide valuable prognostic information and assist in risk stratifying men > 45 years of age who have risk factors. The higher the number of risk factors, the higher the pretest probability. Risk factors are strictly defined as the following: hyperlipidemia (total cholesterol > 240 mg/dl), hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure ≥ 90 mmHg), smoking, and history of myocardial infarction or sudden death in a first-degree relative < 60 years of age.

The Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects study suggested that conventional cardiac risk factors (Table 2) did not help to identify those patients with abnormal perfusion imaging. It is no longer recommended to routinely screen patients with diabetes with two or more additional risk factors. However, current evidence suggests that noninvasive tests can improve assessment of future coronary heart disease risk. There is no current evidence that such testing in asymptomatic patients with risk factors improves outcomes or leads to better utilization of treatments.

Approximately one in five patients with diabetes will have an abnormal treadmill test and approximately one in 15 will have a major abnormality. For prognosis and the value of early intervention (invasive or noninvasive), more information is needed before widespread screening is recommended. All patients irrespective of their CAD status should have aggressive risk factor modification, including control of glucose, lipids, and blood pressure and prophylactic aspirin therapy.

The ADA recommends coronary heart disease screening for asymptomatic patients initially through a risk factor evaluation to stratify patients by 10-year risk, treating the risk factors accordingly. In contrast, the American Heart Association (AHA) has recommended against routine testing in diabetic patients who are asymptomatic. Exercise testing in patients with diabetes is given a IIb evidence classification by the AHA and the ACC. This classification states that “usefulness or efficacy is less well established by evidence or opinion;” the guideline also states that exercise treadmill testing in general “might be useful in people with heightened pretest risk.” Exercise is recommended as one of the lifestyle interventions needed for cardiovascular prevention. In women, measuring exercise capacity can provide important

<table>
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<th>Table 2. Coronary Artery Risk Factors for Risk Stratification</th>
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<tr>
<td>• Hypertension</td>
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<td>• Dyslipidemia</td>
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<tr>
<td>• Impaired glucose tolerance</td>
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<tr>
<td>• Diabetes</td>
</tr>
<tr>
<td>• Cigarette smoking</td>
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<tr>
<td>• Obesity</td>
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<tr>
<td>• Sedentary lifestyle</td>
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<tr>
<td>• Family history</td>
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<tr>
<td>• Age</td>
</tr>
<tr>
<td>• Sex</td>
</tr>
<tr>
<td>• Poor exercise capacity on treadmill testing</td>
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<tr>
<td>• Personal history of vascular disease</td>
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<tr>
<td>• Sudden death in a first-degree relative</td>
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prognostic information concerning risk for a cardiovascular event or death.\textsuperscript{15,16}

Assessment of a patient’s exercise capacity, measured in metabolic equivalents (METs), can be performed with an exercise treadmill exam. Gulati et al.\textsuperscript{17} demonstrated that a woman’s inability to reach a MET level of 5 was associated with a 3.1-fold increase in the risk of death compared to MET levels > 8 and that asymptomatic women whose exercise capacity was < 85% of the age-predicted value had twice the risk of death from cardiac causes than those whose exercise capacity was ≥ 85% of the age-predicted value.

The American College of Sports Medicine (ACSM) has developed recommendations for exercise testing before beginning an exercise program.\textsuperscript{18} Patients are categorized according to low-, moderate-, and high-risk groups based on age, sex, presence of CAD risk factors, major symptoms of disease, or known heart disease (Table 3). Also, their level of activity is divided into moderate (3–6 METs), such as performing moderate housework and walking briskly, or vigorous exercise (> 6 METs), such as jumping rope or shoveling heavy snow.

There is no specific age for routine screening of individuals, but the ACSM recommends that high-risk individuals (including patients with diabetes) who will participate in moderate or vigorous exercise have routine screening.

The diagnostic utility of exercise treadmill testing is dependent on the prevalence of disease in the population to which the patient belongs. The most important factors in the analysis of these patients are the pretest prevalence of disease, the sensitivity and specificity of the test, the predictive value of the test, and the electrocardiogram criteria used to define a positive test.

Specific components known to predict CAD before testing include advanced age, male sex, and the presence of typical versus atypical anginal chest pain. It is known that various types of chest pain affect the probability of disease in each patient. By dividing the patients into one of four groups (typical angina, atypical angina, nonanginal pain or no chest pain), one can predict the pretest probability of heart disease in individuals.

The Duke Treadmill Score (DTS) has been recommended by the ACC and the AHA as a tool for posttest cardiac risk stratification. The use of multivariable statistical techniques to estimate probability of cardiac events or angiographic findings has led to several valid scores. The most universal of these tests is the DTS. It can be used both for prognosis and diagnosis.\textsuperscript{19} It consists of three variables: the amount of time of ST-segment deviation, exercise capacity or exercise time on the Bruce protocol, and whether angina occurred during the test (Table 4).

Considering the likelihood that a large number of diabetic patients will have obesity, hypertension, peripheral vascular disease, peripheral neuropathy, physical de-conditioning, and decreased functional capacity, all of these factors influence the ability of these patients to exercise long enough to achieve a low-risk DTS. Because the workload achieved may not be adequate to induce ischemia and its related symptoms and ECG findings, significant CAD may be present but remain undetected. As a result, these individuals may fall into the intermediate DTS range erroneously and be managed conservatively, similarly to their nondiabetic counterparts.

Realizing these limitations, DTS and exercise stress testing still can be used to provide prognostic information and functional capacity in a large number of patients with diabetes and remain the most common and preferred method of identifying patients with underlying CAD (Table 5). Lakkireddy et al.\textsuperscript{20} demonstrated the clinical value of the DTS in the risk stratification of nondiabetic and diabetic patients. They noted a strong association between DTS and the combined outcomes of cardiac death, nonfatal myocardial infarction, congestive heart failure, and revascularization in both nondiabetic and diabetic patients.

Various studies have suggested that patients with uncomplicated type 2 diabetes have an impaired peak exercise performance compared to healthy age-matched control subjects. Although it is known that the impairment is not associated with the degree of glycemic control, the mechanism leading to this impairment in exercise has not been identified. There is some evidence to suggest that measuring peak exercise oxygen consumption (VO2max), which determines exercise capacity, may be used to assess patients with diabetes for their risk of experiencing a future cardiovascular disease event.

Some physicians recommend patients with diabetes for exercise stress testing to determine if they have severe ischemic electrocardiogram changes present

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\hline
\textbf{Table 3. ACSM Guidelines for Exercise Testing Before Exercise} & \textbf{Low Risk} & \textbf{Moderate Risk} & \textbf{High Risk} \\
\hline
\textbf{Moderate Exercise} & No & No & Yes \\
\hline
\textbf{Vigorous Exercise} & No & Yes & Yes \\
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\textbf{Table 4. Duke Treadmill Score Formula}\textsuperscript{28} & \\
\hline
\textbf{Duke Treadmill Score:} & Exercise duration (minutes) − 5 × ST-segment deviation (millimeters) − 4 × treadmill angina index \\
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\textbf{Angina index:} & 0 = no exercise angina & 1 = exercise angina & 2 = exercise-limiting angina \\
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with exercise that are not present at rest, 2) clinical symptoms do occur with exercise but not during limited activity, or 3) significant arrhythmias occur with exercise. This testing process then prompts physicians to pursue further evaluation and management based on the results. However, this approach is not supported by evidence-based studies.

Other physicians use scoring systems for risk factor assessment. This usually involves either the Framingham Study scoring system (www.statcodec. com), the U.K. Prospective Diabetes Study (UKPDS) risk engine (www. dtu.ox.ac.uk/riskengine/download. htm), or the ADA Diabetes Personal Health Decisions program (http://www. diabetes.org/diabetesphd/default.jsp). Individuals with an increased score for CAD are studied further.

The Framingham Study has been adapted for people with diabetes and renders a cardiac risk score based on 15 risk factors. This score is limited by 1) a specific patient population, 2) older population data, and 3) limited risk factors.

The UKPDS risk engine renders a cardiovascular risk score based on multiple factors pertinent to people with type 2 diabetes. It considers duration of diabetes, hemoglobin A₁c, and ethnicity, in addition to the usual risk factors for future cardiovascular risk. Although this risk engine is limited to those diagnosed with type 2 diabetes, it is based on 4,540 patients and a total of 53,000 patient-years of data.

The Archimedes Diabetes Model used in the ADA Personal Health Decisions program includes 45 factors and markers for disease states associated with diabetes. This model can be used for all ethnic groups, all age-groups, both sexes, and all types of diabetes. The model calculates the 30-year risk for diabetes, myocardial infarction, stroke, renal failure, eye disease, and foot problems. It has been validated against clinical trials with excellent confirmation data (correlation coefficient \( r = 0.99 \) for all exercises).

As a test option, exercise ECG may be of limited value for patients with decreased exercise capacity, inability to reach target heart rates, or absence of chest pain during exercise. For these diabetic patients, stress nuclear imaging has been shown to have significant prognostic and risk-stratification value.

In addition, special situations may necessitate a myocardial perfusion imaging (MPI) study rather than an exercise stress test. These may include conduction abnormalities such as left bundle branch block and Wolf-Parkinson-White syndrome, medication effects (digoxin), and special clinical situations (unstable hypertension, aortic stenosis, marked exogenous obesity). Stress MPI studies should be considered for nondiagnostic ECG exercise stress testing and for patients with diabetes and those who are unable to exercise to an adequate end point.

For patients who are able to exercise, MPI is indicated for those patients with intermediate likelihood of CAD. Patients with an intermediate-risk treadmill score but with normal or near-normal exercise myocardial perfusion images and normal cardiac size are at low risk for subsequent cardiac death and can be safely managed medically until their symptoms warrant revascularization.

Alternatively, stress MPI can offer both perfusion (anatomic) and functional data to aid in the diagnosis and risk stratification of diabetic patients into low- and high-risk prognostic groups. However, studies have revealed that patients with diabetes and a normal MPI have a higher cardiac event rate than their nondiabetic counterparts. Also, the period of time the test can affirm no cardiac event potential is < 2 years.

Imaging techniques enhance the information gained from exercise testing; reduce the false-positive rate seen with exercise testing, which provides a better positive predictive value for risk stratification; allows for the identification of area of ischemia (subendocardial vs. transmural); and allows evaluation of ischemia in the presence of an abnormal resting ECG. However, all of these benefits come at a greatly increased cost.

Myocardial imaging studies are either MPI using either thallium (201Tl) or technitium (99mTc) or stress echocardiography. In each type of study, the myocardium can be stressed by either exercise or chemicals. The advantages of MPI over exercise stress testing are better sensitivity and specificity in the presence of inadequate workload, ability to localize area of ischemia, and the ability to detect graft closure. Studies corrected for referral bias show a sensitivity of 45–88% and a specificity of 59–91%. However, MPI is not a gold standard; it has false positives and negatives and requires clinical judgment when evaluating results.

**Summary**

Symptomatic patients benefit from diagnostic cardiac stress testing, whereas patients with known or suspected CAD obtain clinical value of a noninvasive prognostic test primarily through risk stratification into either low- or high-risk groups and interpretation of the results. However, for asymptomatic patients with diabetes, identification of cardiovascular risk factors and risk stratification may assist physicians in justifying the

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<th>Risk Group</th>
<th>Treadmill Score</th>
<th>Average Annual Cardiac Mortality (%)</th>
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<tr>
<td>Low</td>
<td>≥ +5</td>
<td>0.25–0.50</td>
</tr>
<tr>
<td>Moderate</td>
<td>−10 to +4</td>
<td>1.25–2.0</td>
</tr>
<tr>
<td>High</td>
<td>≤ −11</td>
<td>5.0–7.0</td>
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performance of treadmill evaluations. Patients considering exercise at a moderate or vigorous level or those in the highest-risk group can be immediately submitted to exercise stress testing and then referred for further evaluation as indicated. Patients with a normal exercise stress test may be reevaluated every 2 years.

Whatever type of patient is being evaluated, the overall goals are the same: to reduce the occurrence of a cardiac event and improve patients’ overall quality of life and survival. All patients deserve aggressive risk factor modification (smoking cessation and control of glucose, lipids, and blood pressure). Until evidence-based studies are available, there will be continued controversy regarding the proper CAD screening of asymptomatic patients with diabetes.

ACKNOWLEDGMENTS

The authors thank Gwen E. Sprague, clinical medical librarian at Truman Medical Center–Lakewood Medical and Dental Library, for her assistance in the literature review process.

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