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FREE 1 CME CREDIT

Stress Nuclear Imaging for the Detection of Cardiovascular Disease in Diabetic Patients

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Obesity, Diabetes, Metabolic Syndrome, and Heart Disease

Diabetes mellitus is a well-recognized, growing health problem in the United States. However, metabolic syndrome, which can be a precursor to diabetes, is generally underrecognized in the primary care setting. Metabolic syndrome is a clustering of cardiovascular risk factors, including insulin resistance (which may be the primary underlying factor in this syndrome), abdominal obesity, atherogenic dyslipidemia, hypertension, and proinflammatory and prothrombotic states.[1] The dyslipidemia is characterized by low high-density lipoprotein (HDL) cholesterol, small low-density lipoprotein (LDL) particles, and elevated triglycerides.

The presence of metabolic syndrome is highly predictive of new-onset diabetes, and diabetes is a major risk factor for cardiovascular disease (CVD).[1] Therapeutic lifestyle changes, with emphasis on weight reduction and physical activity, are recommended by the National Cholesterol Education Program's Adult Treatment Panel III as first-line intervention for patients with metabolic syndrome.[2]

Practice Recommendations

- Diabetic patients are at high risk for adverse cardiovascular events; therefore, diabetes is considered a coronary risk equivalent.
- Patients with diabetes can have "silent ischemia," with no or atypical symptoms.
- Nuclear imaging has proven diagnostic and prognostic value in diabetic patients and should be considered as an option for cardiovascular disease assessment in this population.
- Many diabetic patients are unable to exercise to an adequate heart rate for stress nuclear imaging, so pharmacologic stress should be considered.

Both obesity and diabetes are independent risk factors for CVD.[3,4] In fact, diabetes is now considered a coronary risk equivalent and, from a risk factor management

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Learning objectives: Upon completion of this program, participants should be able to:

- Review the impact of obesity, diabetes, and the metabolic syndrome on the risk of coronary heart disease
- Assess the diagnostic and prognostic value of noninvasive cardiac imaging in patients with diabetes
- Discuss the use of exercise or pharmacologic stress MPI testing of diabetic patients

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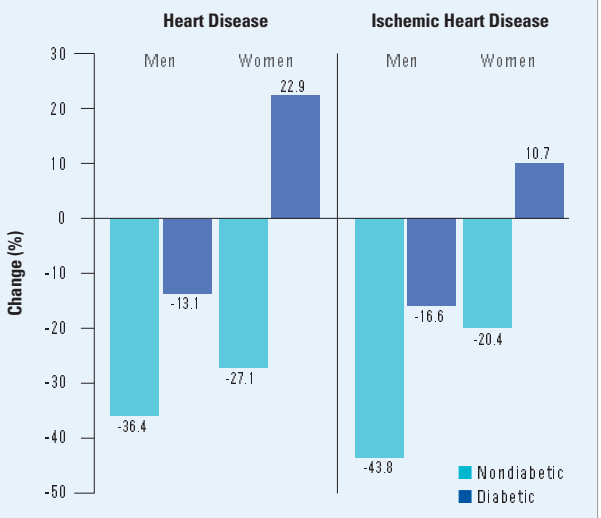
FIGURE 1

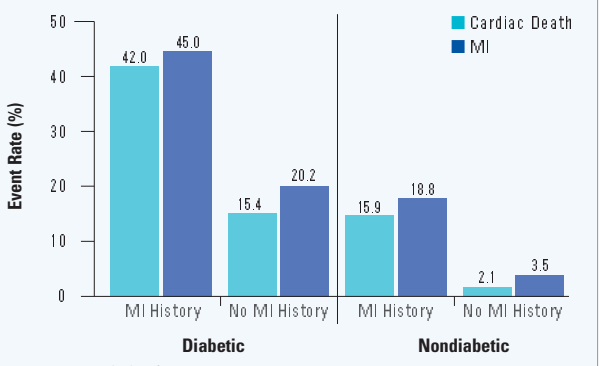
Change in Age-Adjusted Mortality*



*Changes reflect the difference between a cohort identified in 1971-1975 and a cohort identified in 1982-1984. Patients were followed for mortality for an average of 8-9 years.[6]

FIGURE 2

Cardiac Mortality and MI Rates in Diabetic and Nondiabetic Patients[8]



MI = myocardial infarction.

standpoint, diabetic patients should be managed as if they have coronary artery disease (CAD).[5]

Higher Heart Disease Mortality in Diabetic Patients

Coronary heart disease (CHD) mortality has declined substantially in the United States since the 1970s.[6] However, there is a large disparity between changes in cardiac mortality rates for diabetic vs nondiabetic patients. Although CHD mortality has decreased significantly in nondiabetic men, the decline in CHD mortality in diabetic men over the same time period was substantially smaller, and not statistically significant (FIGURE 1).[6] A decrease in CHD mortality was also observed in nondiabetic women, while CHD mortality rates in diabetic women showed a significant increase (FIGURE 1).

Coronary artery disease is the leading cause of death in diabetic women,[7] and Gu's data suggest that we are losing the battle in this patient population.[6]

Diabetic patients with or without a history of myocardial infarction (MI) have higher rates of cardiac death and MI than their nondiabetic counterparts. Additionally, the rates of cardiac death and MI in diabetic patients with no history of MI are almost identical to those in nondiabetic patients who have a history of MI (FIGURE 2).[8]

Later Diagnosis of CVD in Diabetics

Diabetic patients have been shown to have an increased likelihood of sudden cardiac death and unrecognized MI compared with nondiabetic patients.[9,10] At the time of diagnosis, CAD is usually more advanced in diabetic vs nondiabetic patients, and the prognosis is usually more unfavorable.[11,12]

The later diagnosis of CAD in diabetic patients may be explained by the presence of silent disease in these patients.[13] Typical cardiac symptoms, such as ischemia-induced chest pain, are often masked or blunted in diabetic patients, causing the diagnosis of MI in many cases to be missed or delayed.[10] Silent MI has been reported to occur in 10% to 20% of diabetic patients, compared with 1% to 4% of nondiabetic patients.[13] Silent myocardial ischemia occurs in more than 20% of asymptomatic diabetic patients.[14] Multivessel atherosclerosis is often present before ischemic symptoms appear in diabetic patients, and delayed recognition of CAD worsens the prognosis for survival for many diabetics.[13] As a result, more effective strategies for earlier detection of CVD in diabetic patients may reduce cardiac morbidity and mortality in this population.[13]

Diagnostic and Prognostic Value of Myocardial Perfusion Imaging (MPI)

Current radionuclide imaging guidelines have reported the average sensitivities and specificities of exercise and vasodilator stress perfusion single-photon emission computed tomography (SPECT) for detecting angiographically significant CAD.[15] Generally uncorrected for referral bias, the sensitivities average 87% for exercise and 89% for vasodilator stress, and the specificities average 73% for exercise and 75% for vasodilator stress.[15] The sensitivities and specificities of various stress testing methods in patients with an intermediate pretest risk of CHD are shown in TABLE 1.[16] Currently available data indicate that the sensitivity, specificity, and normalcy rates for the diagnosis of CAD with myocardial perfusion SPECT are comparable in diabetic and nondiabetic patients.[15]

Diabetic patients without a history of CVD may warrant stress testing to screen for CAD even in the absence of symptoms, according to the American Diabetes Association (ADA).[17] TABLE 2 lists the indications for stress testing in diabetic patients.

Because diabetic patients are less likely to be able to perform a standard treadmill test, an initial clinical assessment may determine that these patients will be better evaluated using pharmacologic stress imaging with either MPI or echocardiography, the choice of which may depend on local expertise. If expertise with both modalities is available, MPI would be preferred.[17]

The ADA has indicated that stress MPI is a clinically useful method of assessing heart disease in diabetic patients who have:[17,18]

- Inadequate exercise electrocardiographic results
- No symptoms but mildly or moderately positive exercise electrocardiograms (ECGs)
- Clear or suggestive evidence of ischemia or infarction on baseline ECG
- Mild angina and normal or near-normal ECGs
- Atypical angina and baseline ECG abnormalities, or
- Atypical chest pain and 2 or more cardiac risk factors (TABLE 2).

Patients who are asymptomatic, have a normal ECG, and no or 1 cardiac risk factor can be managed without stress testing.

Myocardial perfusion imaging has been suggested to have a lower specificity in women than echocardiography, and a meta-analysis of 21 studies indicated this.[19] However, many of the data included in the meta-analysis were derived from older studies, and no data from contemporary imaging techniques, such as gated SPECT, were included.[20] The reduced specificity reported with earlier MPI modalities may be related to attenuation from breast tissue. The simultaneous perfusion and function information obtained with gated SPECT can help achieve improved differentiation of attenuation artifact from infarct.[20] Studies using the more modern technique of gated SPECT with Tc-99m sestamibi, now widely used, demonstrated specificities of greater than 90% for the detection of CAD in women.[21,22]

For patients at low risk for cardiovascular events, a standard treadmill exercise test is often chosen. However, if a diabetic patient has typical angina or Q waves on a resting ECG, MPI should be performed to assess ventricular function and obtain quantitative information on the extent of the perfusion abnormality.[17]

Patients who undergo standard exercise ECG often require further assessment to accurately determine their cardiac risk. Approximately 50% of patients fall into the intermediate-risk category with the Duke Treadmill Score, which is the currently accepted standard for risk stratification on treadmill testing.[23,24] This intermediate-risk population can benefit from additional testing, including MPI.[15,25-27]

TABLE 1

Performance of Stress Testing Modalities for the Diagnosis of CHD: A Meta-analysis[16]

Test	Sensitivity (%)	Specificity (%)
Exercise ECG (n = 24,074)	68	77
SPECT MPI* (n = 628)	88	77
Echocardiography* (n = 1174)	76	88

*Includes both exercise and pharmacologic stress.
CHD = coronary heart disease, ECG = electrocardiography, SPECT = single-photo emission computed tomography, MPI = myocardial perfusion imaging.

TABLE 2

Criteria for Cardiac Testing With Standard Exercise ECG or Nuclear Imaging in Diabetic Patients[17]

1. Typical or atypical cardiac symptoms
2. Resting ECG suggesting ischemia or infarction
3. Peripheral or carotid occlusive arterial disease
4. Sedentary lifestyle, >35 years old, and plans to start a vigorous exercise program
5. Two or more of the following risk factors:
   - Total cholesterol >240 mg/dL, LDL cholesterol >160 mg/dL, or HDL cholesterol <35 mg/dL
   - Blood pressure >140/90 mm Hg
   - Smoking
   - Family history of premature CAD
   - Positive micro/macroalbuminuria test

ECG = electrocardiogram, LDL = low-density lipoprotein, HDL = high-density lipoprotein, CAD = coronary artery disease.

The utility of standard exercise ECG testing in patients with diabetes continues to be an area of concern and controversy. In addition to having decreased exercise capacity, diabetic patients often experience no chest pain during exercise,[17,20] and the standard exercise ECG may be less reliable for detecting significant CAD in diabetic patients.[20,25] Painless ST-segment depression during treadmill exercise is common in diabetic persons, and the diagnostic specificity of ST depression is often reduced in these patients.[10]

In a large study of 5183 patients, SPECT MPI was shown to provide incremental prognostic value in the prediction of cardiac death or MI.[28] Performed with either exercise or pharmacologic stress, SPECT MPI yielded clinically relevant risk-stratification information in intermediate- and high-risk groups. FIGURE 3 shows

CASE STUDY

Diabetic Woman Complains of Atypical Chest Pain

History of present illness and physical examination. A 68-year-old woman presented to our cardiology clinic with atypical chest pain. She had awakened 2 days earlier with a sharp, burning, "stabbing" discomfort beneath her breastbone that lasted approximately 10 minutes. In the emergency department of a local community hospital, she was found to be clinically stable. She was discharged with a diagnosis of suspected gastroesophageal reflux disease (GERD) and possible ischemic heart disease. She subsequently experienced occasional burning sensations in her chest but no exertional symptoms. Cardiovascular review of systems was otherwise negative. Results of cardiovascular physical examination were normal; her blood pressure was 120/60 mm Hg, her pulse 92 bpm, and her weight was 215 lb.

Personal and family medical history. She was a lifelong nonsmoker with a history of diabetes (receiving rosiglitazone 4 mg/d, glyburide 10 mg twice daily, and metformin 1000 mg twice daily), hypertension (lisinopril 30 mg/d and amlodipine 2.5 mg/d), hyperlipidemia (atorvastatin 10 mg/d), and GERD (pantoprazole 40 mg/d). Her brother had developed coronary disease at age 50, and her father had developed coronary disease at age 65 and died at age 81 from complications of stroke and heart disease.

Prior cardiovascular evaluation. Sixteen months earlier, the patient had experienced a similar episode of precordial chest discomfort that had wakened her and lasted approximately 5 to 10 minutes, with no subsequent pain. At that time, she was referred to a cardiologist, who performed treadmill stress echocardiography. After 3 minutes on the treadmill, she stopped exercising due to shortness of breath and fatigue (functional aerobic impairment was 33%). Her blood pressure increased from 125/80 to 165/80 mm Hg, and her heart rate increased from 79 to 135 bpm (88% of age-predicted maximum). She experienced no chest pain, and there were no diagnostic ECG changes with exercise.

Her echocardiographic images showed mild left ventricular hypertrophy and were otherwise normal, with no evidence of ischemia.

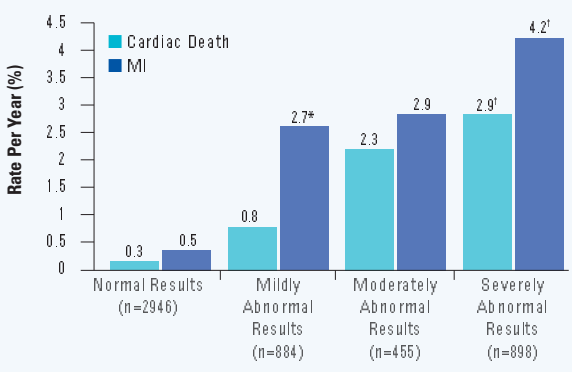
Clinical impression. The clinician believed that the patient's pain was likely due to GERD. However, because of her multiple cardiovascular risk factors, she was referred for stress myocardial perfusion imaging (MPI), and aspirin, 325 mg/d, was added to her medication regimen.

Myocardial perfusion imaging with pharmacologic stress. Because the patient's chart revealed previous limited exercise tolerance and because she was wary of treadmill exercise, pharmacologic stress with adenosine was used instead of exercise stress. She had an appropriate hemodynamic response to adenosine and experienced dizziness and chest pain during infusion, but there were no diagnostic ST changes.

Myocardial perfusion imaging revealed a severe, moderate-sized, reversible, anterolateral, and apical defect consistent with inducible ischemia. In addition, there was significant reversibility in the inferolateral wall. These findings were consistent with the presence of multivessel coronary disease. Gated images showed normal

FIGURE 3

Rates of Cardiac Death and MI in Patients Undergoing Myocardial Perfusion SPECT[28]



*Statistically significant increase in rate of MI vs cardiac death in patients with mildly abnormal results ($P < .05$).
†Statistically significant increase as a function of scan result ($P < .001$).
MI = myocardial infarction.

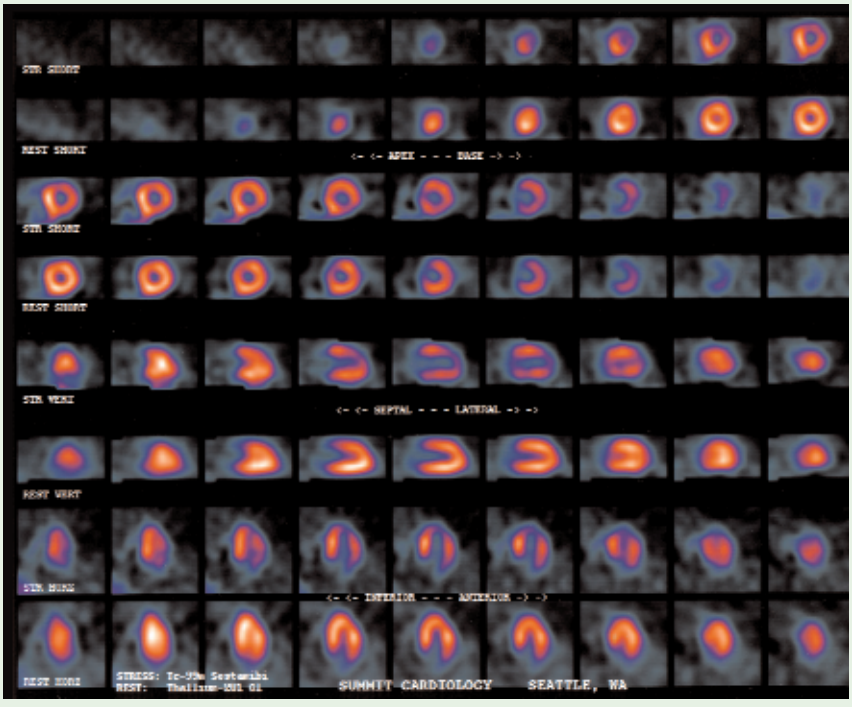
the rates of cardiac death and MI as a function of SPECT MPI scanning results.[28] The nuclear scan results in this study provided incremental risk-stratification information in each prescan likelihood-of-CAD category (ie, low, intermediate, and high).[28]

Revascularization rates show a pattern similar to the cardiac death and MI rates. However, outcomes research typically focuses on the cardiac death and MI events because they are not influenced by the study results in the way that revascularization is inevitably affected. These less-biased events (cardiac death and MI) are referred to as "hard events" in the nuclear cardiology literature.

SPECT MPI with exercise or pharmacologic stress has also specifically been shown to be useful for risk stratification and management of patients with diabetes.[29,30] In a study of 1271 diabetic and 5862 nondiabetic patients, nuclear imaging added incremental prognostic value over clinical information in patients with diabetes. Rates of cardiac death and MI increased as a

FIGURE 5

Severely Abnormal Myocardial Perfusion Images



Normal rest images (rows 2, 4, 6, and 8) indicative of healthy myocardial tissue with severely abnormal stress images (rows 1, 3, 5, and 7) demonstrating reversible ischemia in multiple vascular distributions.

left ventricular size and systolic function, with an ejection fraction of 69% (FIGURE 5).

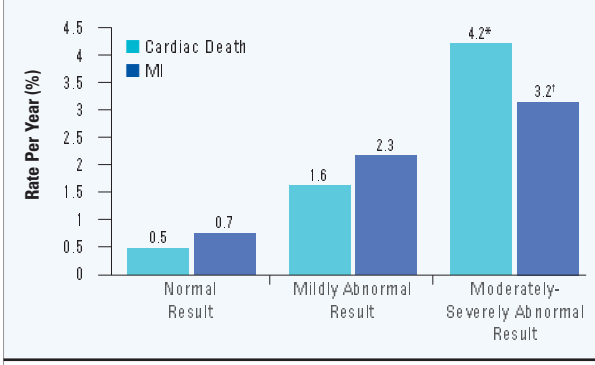
Clinical follow-up. Although the patient experienced no recurrent chest pain, she was referred for catheterization because the nuclear imaging results were consistent with the presence of multivessel coronary disease.

Catheterization. Coronary angiography revealed 90% distal left anterior descending (LAD) artery stenosis, 70% first diagonal stenosis, 80% ostial stenosis of a large circumflex marginal branch, and 80% proximal right coronary artery (RCA) stenosis. In light of the patient's multivessel disease, coronary artery bypass grafting was considered. However, normal left ventricular function and poor targets beyond the distal LAD artery and diagonal lesions favored percutaneous coronary intervention (PCI). A stent was placed in the mid-circumflex, extending into the stenosed origin of the circumflex marginal branch, and another stent was placed in the proximal RCA. Clopidogrel, 75 mg/day, and atenolol, 25 mg/day, were added to her medication regimen.

Clinical follow-up. At 1-month post-PCI, the patient had experienced no further chest pain, and she succeeded in losing 9 pounds. At 19 months post-PCI, the patient was stable, with class II dyspnea on exertion and no chest pain. There were no interval cardiovascular events.

FIGURE 4

Rates of Cardiac Death and MI in Diabetic Patients Undergoing Myocardial Perfusion SPECT[29]



*$P < .001$ †$P < .02$
MI = myocardial infarction.

function of stress-defect extent and severity, with diabetic patients with normal scan results having low cardiac event rates, and those with moderately to severely abnormal results having high cardiac event rates (FIGURE 4).[29]

The diabetic patients in this study had more significant perfusion defects and worse outcomes than the nondiabetic patients.[29] Diabetic patients who had moderately to severely abnormal scan results had a significantly higher rate of cardiac death or MI than nondiabetic patients with similar scan results ($P < .05$).

Another study of 2793 diabetic and 14,626 nondiabetic patients with suspected heart disease demonstrated the utility of SPECT MPI for noninvasive risk assessment in both diabetic and nondiabetic patients.[31] Once again, diabetic patients had worse outcomes than nondiabetic patients with regard to hard cardiac events over 18 months of follow-up (FIGURE 6).[31] The overall 18-month rates of cardiac death or MI were 5.4% for diabetic patients and 2.9% for nondiabetic patients ($P < .001$).[31]

FIGURE 6

Rates of Cardiac Death or MI in Diabetic and Nondiabetic Patients Undergoing Myocardial Perfusion SPECT[31]

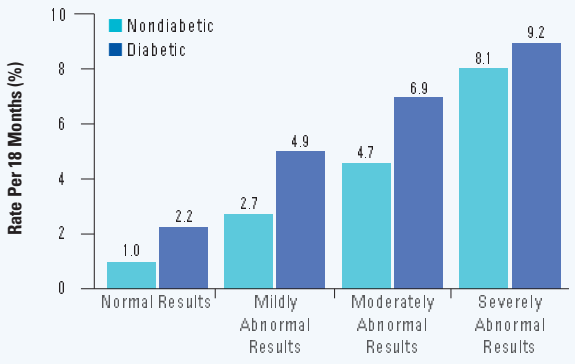
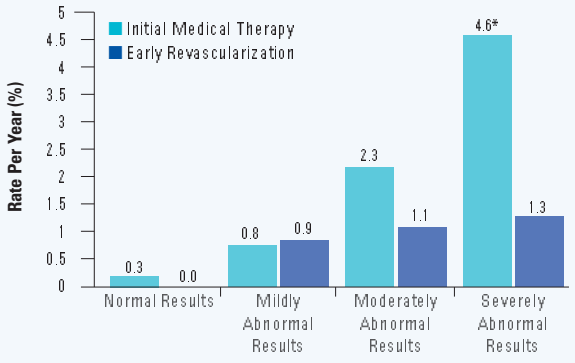


FIGURE 7

Rates of Cardiac Death in Patients Undergoing Early Revascularization or Medical Therapy After Nuclear Imaging[28]



*Statistically significant increase in rate of MI vs cardiac death in patients with mildly abnormal scan results ($P < .05$).

Exercise and Pharmacologic Stress

Treadmill exercise is the standard and generally preferred method of inducing stress for MPI. However, many patients are unable to exercise adequately (ie, reaching 85% of their maximal heart rate) to obtain accurate MPI results; this problem is encountered more often in female patients.[32] Diabetic patients may also be less able than nondiabetic ones to exercise adequately for stress MPI.[30]

In a study of 929 diabetic and 3826 nondiabetic patients undergoing MPI, 29.4% of the diabetic patients were unable to perform maximal exercise, compared with 17.1% of the nondiabetic patients ($P < .0001$).[30] Patients who were unable to exercise adequately underwent pharmacologic stress with either dipyridamole or adenosine. In diabetic patients, pharmacologic stress with adenosine has been validated as providing significant incremental value over historical and clinical data[33] as well as valuable risk stratification information.[29]

Revascularization in High-Risk Patients

The value of nuclear imaging in guiding patient treatment lies not only in its diagnostic utility but also in its utility as a risk-stratification tool. Patients who are categorized as being at low risk for cardiac death and MI can often be managed adequately with medical therapy. However, patients at high risk for hard events can potentially benefit from revascularization.

In Hachamovitch's study of 5183 patients, those with severely abnormal scans who underwent early revascularization (ie, < 60 days after imaging) experienced a significantly lower cardiac death rate than those treated initially with medical therapy (FIGURE 7).[28]

Conclusions

Diabetes is a growing health problem in the United States and is now considered a coronary risk equivalent. Cardiac event and mortality outcomes are generally worse in diabetic patients, especially women, than in nondiabetic patients. The diagnosis of CVD in diabetic patients is often delayed because of an atypical presentation due to physiologic mechanisms of diabetes.

Early detection of CVD may improve outcomes, and it is important to screen diabetic patients to avoid delaying diagnosis until advanced disease is present. Nuclear imaging, such as stress MPI, has proven value in the diagnosis and risk stratification of diabetic patients. At the discretion of the treating physician, patients who initially have compelling clinical symptoms may be sent directly for cardiac catheterization rather than for a noninvasive stress test. However, stress MPI is emerging as a valuable tool to improve CAD management in diabetic patients, with the potential not only to improve clinical outcomes but also to decrease the unnecessary use of other health care resources.[14]

Because many diabetic patients are unable to exercise adequately to obtain accurate nuclear imaging results, pharmacologic stress may be necessary for them. Several newer modalities may also have a role in cardiovascular assessment. Electron-beam computed tomography,[34] multislice computed tomographic angiography,[35] and cardiac magnetic resonance imaging[36] have all shown promise as noninvasive cardiovascular imaging tools. At this point in time, physicians are likely to encounter insurance payment issues with these newer modalities, as their roles in coronary disease assessment are still being defined. Even for nuclear cardiac imaging studies, reimbursement problems may arise with patients who are asymptomatic or do not yet have definite diagnoses.

Ongoing studies, such as the Detection of Ischemia in Asymptomatic Diabetics study, will continue to clarify the role of nuclear imaging in the diabetic population.[37]

In patients at high risk for cardiac events, such as MI and death, as demonstrated by severely abnormal nuclear imaging results, early revascularization (ie, <60 days after imaging) has been shown to result in a significantly lower rate of cardiac death than does initial medical therapy.[28] ■

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CME POSTTEST

For each of the following questions, please circle the best response.

1. **Which of these groups is at highest risk for cardiovascular mortality?**
   a. Nondiabetic men b. Nondiabetic women
   c. Diabetic men d. Diabetic women

2. **Which of the following is NOT a risk factor for both diabetes and coronary artery disease (CAD)?**
   a. Hypertension b. High body mass index
   c. Elevated high-density lipoprotein cholesterol level
   d. Central obesity

3. **Which of the following is an independent risk factor for cardiovascular disease?**
   a. Obesity b. Diabetes
   c. Alcohol consumption d. Both a and b

4. **Over the past 30 years, heart disease mortality has decreased for all of the following patient groups except:**
   a. Diabetic women b. Nondiabetic women
   c. Diabetic men d. Both a and c

5. **What is the leading cause of death in diabetic women?**
   a. Stroke b. Renal failure
   c. CAD d. Heart failure

6. **Silent myocardial ischemia occurs in approximately what proportion of asymptomatic diabetic patients?**
   a. 1 in 10 b. 1 in 5
   c. 2 in 5 d. 3 in 5

7. **Compared with their nondiabetic counterparts, diabetic patients with moderately to severely abnormal nuclear scan results have a:**
   a. Similar risk for cardiac death
   b. Significantly higher risk for cardiac death
   c. Significantly higher risk for myocardial infarction
   d. Both b and c

8. **What is the average sensitivity and specificity of stress (exercise and vasodilator) perfusion SPECT for detecting angiographically significant CAD?**
   a. 88% sensitivity; 74% specificity
   b. 75% sensitivity; 88% specificity
   c. 98% sensitivity; 75% specificity
   d. 74% sensitivity; 64% sensitivity

9. **Compared with exercise stress, pharmacologic stress with adenosine results in myocardial perfusion imaging studies that**
   a. Are more sensitive but less specific
   b. Are more specific but less sensitive
   c. Have comparable sensitivity but less specificity
   d. Have comparable sensitivity and specificity

10. **Compared with medical therapy, early revascularization has been shown to significantly improve outcomes in**

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Circle the number that best reflects your opinion of the following statements, using the following rating scale:

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