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Diabetes and coronary artery disease: The role of stress myocardial perfusion imaging

■ ABSTRACT

Stress myocardial perfusion imaging (MPI) has the potential not only to improve clinical outcomes in diabetic patients, but also to decrease unnecessary use of health care resources. However, before routine screening can be recommended, cost-effectiveness analyses are required to identify patients in whom such testing is appropriate. Nevertheless, MPI is clearly emerging as a valuable tool for improving management of coronary artery disease in all patients with diabetes mellitus.

■ KEY POINTS

Medical complications of diabetes have substantial impact on survival and quality of life, particularly as a result of associated cardiovascular disease, the leading cause of morbidity and mortality in diabetic patients.

The prognostic value of stress MPI has been validated only in patients with diabetes referred for stress testing for a variety of reasons. No published data exist on truly asymptomatic patients with diabetes.

The results of MPI with gated single-photon emission computed tomography can be used in conjunction with other prognostic variables (eg, clinical risk factors) to further improve risk stratification of these patients.

DIABETES SIGNIFICANTLY INCREASES a person's risk of cardiovascular events. In diabetic patients compared with people without diabetes, coronary artery disease (CAD) is often silent, more advanced at diagnosis, and associated with an unfavorable prognosis.

Early intervention may prevent progression of disease and decrease the risk of clinical events. This requires the ability to stratify patients according to their risk of future clinical events.

The most common noninvasive testing options include exercise tolerance testing, stress echocardiography, and stress myocardial perfusion imaging (MPI) with or without gated single-photon emission computed tomography (SPECT). Recent studies have demonstrated that stress MPI with gated SPECT is more sensitive and specific than the other tests in patients with diabetes, and this technique can provide additional prognostic information beyond that obtained by clinical history alone or clinical history combined with exercise tolerance testing.

In this article I review the risk of CAD in patients with diabetes mellitus and discuss the role of noninvasive testing in the diagnosis and risk stratification of these patients.

To produce this article, I conducted a MEDLINE search to identify published clinical studies, specifically large comparative studies, that assess the risk of CAD in diabetic patients and the diagnostic and prognostic

capabilities of various noninvasive testing methods. Consensus guidelines were also identified.

■ THE SCOPE OF CAD AND DIABETES

CAD is the leading cause of death in people with diabetes mellitus. According to data from the US Centers for Disease Control and Prevention, the prevalence of diabetes increased from 4.9% in 1990 to 6.5% in 1998,[1] with a further increase to 6.9% in 1999.[2] This increase closely parallels the increase in the prevalence of obesity. In addition, because the incidence of diabetes increases with age, the overall aging of the population is expected to contribute to more cases in the future.

Medical complications of diabetes have substantial impact on survival and quality of life, particularly as a result of associated cardiovascular disease, the leading cause of morbidity and mortality in diabetic patients[3]: an estimated 80% die from cardiovascular disease, 75% of which is attributed to CAD.[4]

Since the risk for complications due to CAD can be modified by appropriate interventions, early detection is important.

■ HOW CAD MANIFESTS ITSELF IN DIABETES

Using a range of diagnostic methods, the overall prevalence of CAD is reported to be as high as 55% in patients with diabetes, compared with 2% to 4% in the general population.[5] Notably, asymptomatic CAD has been observed in 10% to 20% of patients with diabetes.[3–8] Compared with nondiabetic patients, CAD in diabetic patients is often more advanced (including multivessel disease) at the time of diagnosis and is characterized by more extensive atherosclerosis, a greater incidence of left ventricular dysfunction, and higher rates of cardiac events.[4]

Silent ischemia
Silent ischemia is a particular concern in patients with diabetes.[9,10] The pain response to ischemia is often absent or blunted in these patients (possibly related to diabetic neuropa-

thy), resulting in a lack of symptoms or an atypical presentation.[11] Thus, the first sign of CAD may be acute myocardial infarction or cardiac death.[4] This late presentation probably contributes to the higher mortality rate in diabetic patients.[9]

CAD in diabetic vs nondiabetic patients
Several factors are known to differentiate CAD in patients with diabetes from CAD in nondiabetic patients. These factors may provide clues to the differences in prognosis for patients with diabetes, as well as suggest limitations of available testing methods.

For example, although atherosclerotic plaque appears to be morphologically similar among patients with or without diabetes, pathologic studies have demonstrated that coronary arteries in patients with diabetes and CAD show diffuse disease, in contrast to the more localized involvement often seen in the absence of diabetes.[4] Diabetes also is associated with generalized endothelial dysfunction and small-vessel abnormalities, in addition to the larger-vessel abnormalities seen in nondiabetic patients with CAD.[4,12]

Risk factors for coronary artery disease
Major risk factors for CAD include hypertension, dyslipidemia, smoking, family history of premature atherosclerotic disease, obesity, and a sedentary lifestyle.[3,4] Although patients with diabetes have a higher prevalence of these traditional risk factors, these factors account for less than half of the excess mortality seen in patients with diabetes. Therefore, diabetes itself appears to be an independent risk factor for CAD and related clinical events.[4]

Diabetes is also a risk factor for the development of congestive heart failure.[13,14] In the Framingham study, the presence of diabetes (after adjusting for age, blood pressure, cholesterol level, obesity, and history of CAD) produced a fourfold to fivefold increase in the risk of congestive heart failure.[13]

The overall population of the United States has enjoyed impressive declines in heart disease mortality over the last few decades. However, the drop in cardiovascular mortality in diabetic men and women has lagged well behind that of the general popula-

> **The risk of CAD events can be reduced by interventions, so early detection is important**

tion.[15] In addition, evidence from a recent study suggests that women with diabetes have a significantly poorer clinical outcome than men with diabetes for any given level of ischemia.[16] In this study, in diabetic patients with one ischemic vessel, the 3-year rate of survival free of death or myocardial infarction was 72.5% in women vs 77% in men (*P* < .05). In patients with two or more ischemic vessels, the rate was 60% in women and 79% in men (*P* < .05).

Increased risk of cardiac events associated with diabetes

The combination of diabetes and CAD is associated with a higher rate of cardiac events and a poorer prognosis. Evidence for this includes increased risk of recurrent infarction and congestive heart failure, as well as increased morbidity and mortality associated with myocardial infarction.[4] Haffner et al[17] found that the 7-year risk of myocardial infarction among those with diabetes with and without a prior myocardial infarction at baseline was 45.0% and 20.2%, respectively.[17] The corresponding values for nondiabetic subjects were 18.8% and 3.5%, suggesting that patients with diabetes who have not had a myocardial infarction have a risk of a subsequent myocardial infarction similar to that of patients without diabetes who have already had a myocardial infarction.

Moreover, the rate of mortality after myocardial infarction is higher for patients with diabetes. In a study based on the Finnish Contribution to the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease, also called the FINMONICA project, the 1-year mortality rate after a first myocardial infarction among diabetic patients was 44.2% for men and 36.9% for women, compared with 32.6% and 20.2% for nondiabetic men and women, respectively.[18]

The effect of diabetes and the benefit of aggressive treatment on the incidence of major cardiac events were evaluated in a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S).[19] In this study, 202 patients with diabetes mellitus and 4,242 patients without diabetes were followed for more than 5 years for major cardiac events.

Patients with diabetes had a greater incidence of major cardiac events and a lower survival rate than patients without it.

Among placebo recipients, diabetic patients were more likely than nondiabetic patients to experience a definite myocardial infarction (24.7% vs 11.6%), a nonfatal major coronary heart disease event (36.1% vs 21.9%), death from coronary heart disease (17.5% vs 8.1%), or death from any cause (24.7% vs 10.9%).

Although simvastatin decreased the relative risk similarly in all patients, the absolute risk reduction was greater among those with diabetes, due to a higher absolute risk of heart disease and other atherosclerotic events. For example, among patients without diabetes, the Kaplan-Meier 6-year probability of survival was 91.6% for those receiving simvastatin vs 88.4% for placebo-treated patients (absolute risk reduction 3.2%). In diabetic patients, the values were 84.0% for simvastatin and 68.8% for placebo (15.2% absolute risk reduction). Similarly, the absolute risk reduction for a major coronary heart disease event was 8.5% for those without diabetes vs 24.4% for those with diabetes.

■ BENEFITS OF EARLY SCREENING IN DIABETIC PATIENTS WITH KNOWN OR SUSPECTED CAD

Given the prevalence of CAD in patients with type 2 diabetes, the American Diabetes Association (ADA) recommends performing a cardiovascular risk assessment at least yearly.[3] In addition, the ADA recommends exercise stress testing in all asymptomatic patients with diabetes.

The optimal frequency of stress testing is unknown, although it has been suggested that stress testing should be considered every 3 to 5 years for asymptomatic patients with no new risk factors.[9] For patients with multiple or new risk factors, testing should be increased to every 1 to 2 years.

For patients with type 1 diabetes, testing should generally begin after age 30, since this is the age at which significant CAD usually begins to manifest.

Electron-beam CT can be used to measure calcification of coronary arteries, an early

CAD in diabetic patients tends to be more advanced at diagnosis

marker for CAD.[20] This technique has substantial potential for risk assessment.[21] Still, although it can detect the presence of atherosclerosis, it cannot measure the severity of obstruction. In addition, a low calcium score does not rule out CAD. Because this technique has low specificity, the American College of Cardiology does not recommend its routine use in the diagnosis of CAD.[21]

Identification of diabetic patients with early CAD allows for risk stratification at a point where the disease process is more likely to be modifiable. An approach based on risk factors is recommended as part of the initial diagnostic evaluation to detect CAD in asymptomatic patients with diabetes.[3] Patients at low risk can be managed medically without additional testing, while patients with advanced disease may require revascularization procedures that could prolong life. Once asymptomatic CAD is diagnosed, physicians should recommend patients' adherence to risk factor intervention and treatment regimens.[22] This is important, since the aggressive use of secondary interventions has been proven to reduce morbidity and mortality.[17,23]

Cardiovascular mortality is declining in general, but not as much for diabetic patients

Because diabetes confers a risk for clinical events similar to that of established CAD, it has been suggested that all patients with diabetes be treated as if they have established coronary disease.[17,23] However, patients who are asymptomatic and yet have severe disease could be discovered with a more thorough assessment. The importance of early intervention for patients with diabetes was underscored in the FINMONICA project, which assessed mortality among patients with and without diabetes who had already had a myocardial infarction.[18] The case mortality rate was significantly higher for patients with diabetes. Of those who died, approximately 50% of men and 25% of women died before they reached the hospital.

Despite the potential benefits of early diagnosis and treatment in patients with diabetes, the clinical role of early screening is not precisely defined due to the lack of outcome-based studies. Studies currently under way will better define the role of screening and determine its clinical and economic benefits.

When to do cardiac screening in patients with diabetes

The ADA recommends annual evaluation of patients with diabetes. Exercise electrocardiography (ECG) is recommended as the initial screening tool to help identify patients who would be considered at higher-than-average risk of cardiac events.[3] Candidates for exercise ECG include patients with:
- Typical or atypical signs or symptoms of CAD
- An abnormal resting ECG
- Peripheral or carotid occlusive disease
- Age over 35, a sedentary lifestyle, and plans to initiate an exercise program
- Two or more of the following, in addition to diabetes: elevated total and low-density lipoprotein cholesterol or low high-density lipoprotein cholesterol; elevated blood pressure; smoking; family history of premature CAD; or positive microalbuminuria or macroalbuminuria.

Those with symptomatic disease require evaluation by a cardiologist. Since the incidence of asymptomatic CAD in patients with diabetes is high (10%–20%), exercise stress testing should be performed in all patients who meet the criteria listed above. Those with an abnormal exercise ECG should also be referred to a cardiologist.

■ NONINVASIVE TESTING OPTIONS

Exercise tolerance testing
An exercise tolerance test with ECG alone can be performed for screening purposes in patients with diabetes who test normal on resting ECG. A completely negative test result suggests a favorable prognosis,[4] although it does not always exclude CAD.[3,24] In particular, those with single-vessel disease may not be identified.[9]

In addition, an exercise tolerance test alone may not be able to reliably assess the severity of CAD or the risk of future clinical events.[9,24] Further, there are no studies specifically evaluating the diagnostic accuracy of exercise tolerance testing in patients with diabetes.[9]

The sensitivity of exercise tolerance testing for detecting CAD may be decreased if the patient is unable to achieve 85% of the maxi-

mal predicted heart rate response to stress.[4,24] In one study, as many as 51% of patients were unable to perform adequate physical exercise. In such situations, other tests should be considered.[4]

Stress echocardiography

Stress echocardiography is a noninvasive test that detects regional wall motion abnormalities induced by myocardial ischemia. Recent advances in echocardiographic machines and contrast agents have substantially improved the value of this technique.

Drawbacks. Despite the widespread use and reported accuracy of stress echocardiography, it is technically challenging, and reproducibility is still somewhat limited due to high interobserver variability.[25] Standard echocardiographic examinations may be suboptimal in quality and frequently do not yield sufficient diagnostic information. In diabetic patients, many of whom are overweight, the increased weight contributes to a poor echocardiographic image. In addition, many diabetic patients cannot exercise adequately because of increased weight and neuropathic complications. Finally, the sensitivity and specificity of exercise stress testing are reduced in certain subgroups of patients, such as women, patients with single-vessel disease, and those with extensive anterior wall myocardial infarction.[26]

Pharmacologically induced stress is an alternative to exercise-induced stress for the detection of CAD in patients with diabetes.[27,28] In one study, the sensitivity and specificity of dobutamine stress echocardiography for predicting hard clinical events were lower in diabetic patients (59% and 44%, respectively) than in nondiabetic patients (83% and 47%, respectively), although the differences did not reach statistical significance.[27] In the other study, the specificity of stress echocardiography in diabetic patients was also found to be low (54%).[28]

Stress perfusion imaging

During the past two decades, MPI has become an established and validated method for assessing myocardial ischemia, viability, and function. Stress MPI is a flexible, noninvasive imaging procedure in widespread use. In the United States alone, 5 to 7 million MPI studies are performed annually.

To perform stress MPI, a radiolabeled agent such as thallium-201 (Tl-201) or one based on technetium-99m (Tc-99m sestamibi or Tc-99m tetrofosmin) is injected intravenously at peak physical exercise or during maximum pharmacologic arteriolar vasodilatation.[9] The accuracy of Tc-99m sestamibi stress MPI has been validated in numerous clinical studies in a wide range of populations and stress protocols.[16,29,30] When performed by experienced readers, artifacts that could potentially lead to false-positive results can be recognized and managed.[31] Furthermore, recent advances in SPECT and software, including attenuation and scatter correction, have improved the diagnostic accuracy of MPI.[32–35]

Stress protocols utilizing exercise, pharmacologic, or combined approaches essentially provide equivalent results.[36,37] Pharmacologic stress imaging is an important noninvasive approach for detecting CAD and determining prognosis in patients who are unable to adequately exercise.[38] Since many patients with diabetes cannot perform adequate exercise for a number of reasons, vasodilator stress (eg, dipyridamole, adenosine, dobutamine) may be the only means of stress testing in these patients.

Stress MPI with gated SPECT

Gated SPECT adds prognostic value beyond risk factor assessment, clinical history, or exercise tolerance testing as a predictor of cardiac death.[39] It provides information on perfusion and function, including wall motion, ejection fraction, and myocardial viability.[40]

The left ventricular ejection fraction data that can be obtained through gated Tc-99m sestamibi imaging are particularly useful in risk stratification.[41] The left ventricular ejection fraction is the most important measure of cardiac function and is also an excellent prognostic indicator.[42] Ejection fraction data obtained through gated SPECT have shown excellent correlation with values obtained using other methods.[41,43] In addition, gated SPECT has been shown to differentiate between ischemic and nonischemic cardiomyopathy.[39]

Stress echocardiography: widely used, considered accurate, but limited by interobserver variability

Risk-based approach to treating patients with coronary artery disease

IMAGING RESULT	ANNUALIZED RISK OF CARDIAC EVENTS	TREATMENT IMPLICATIONS
Normal	Less than 1%	Risk factor modification
Mildly abnormal	Low risk of cardiac death Intermediate risk of myocardial infarction	Aggressive risk factor modification and medical treatment
Moderately to severely abnormal	Intermediate to high risk of both cardiac death and myocardial infarction	Catheterization with possible revascularization Risk factor modification

Numerous clinical studies have confirmed the diagnostic accuracy and prognostic importance of Tc-99m sestamibi MPI with gated SPECT for the evaluation of patients with known or suspected CAD.[16,29,30,41,44] Iskander and Iskandrian performed a meta-analysis of 14 studies of risk assessment using Tc-99m sestamibi in more than 12,000 patients with stable symptoms.[30] The annual risk of nonfatal myocardial infarction or death was 7.4% among patients with an abnormal study vs 0.6% for those with a normal study.

Based on clinical studies assessing the prognostic value of MPI, a risk-based approach to the treatment of patients with CAD has been developed (**TABLE 1**).[29] This assessment allows treatment intensity to be determined by the absolute risk of cardiovascular events.

■ THE VALUE OF STRESS MPI IN PATIENTS WITH DIABETES

Important differences in the appearance of CAD in diabetic patients may affect the diagnostic accuracy and prognostic applicability of tests used for CAD. Most importantly, the greater incidence of silent ischemia in diabetic patients means that they are less likely to experience exertional angina or chest pain with exercise testing, thereby making the diagnosis of CAD more difficult.

Nevertheless, several studies have demonstrated that the use of stress MPI produces comparable diagnostic results in patients with and without diabetes.[45–47] More recently, the diagnostic accuracy, prognostic value, and risk stratification with the use of stress MPI have been validated in patients with diabetes.[16,48,49]

Gated SPECT MPI in patients with diabetes

Kang et al[49] compared the diagnostic value of dual-isotope (Tl-201 at rest vs Tc-99m sestamibi during stress) MPI in patients with and without diabetes and with known or suspected CAD. Patients were followed for 1 year. A total of 138 patients with diabetes and 188 patients without diabetes had coronary angiography within 6 months. Overall, the sensitivity, specificity, and normalcy rates of gated SPECT MPI in diabetic patients were not significantly different from those seen in nondiabetic patients (**FIGURE 1**).[49]

These same investigators also defined the risk of "hard" events (ie, cardiac death or nonfatal myocardial infarction) for diabetic patients on the basis of scan results.[48] For those with normal scans, the event rate was low (1%–2% per year). For patients with mildly abnormal scans, the event rate was 3% to 4%, while for those with moderately to severely abnormal scans the event rate was greater than 7%. Although diabetic patients tended to have slightly higher event rates than nondiabetic patients in all stress-score categories, only those diabetic patients with moderate to severe abnormalities had significantly higher event rates than nondiabetic patients.

Giri et al[16] evaluated 4,755 patients (929 with diabetes) with symptoms of CAD who were undergoing stress MPI with Tl-201 or Tc-99m sestamibi for the occurrence of cardiac death, myocardial infarction, and revascular-

Stress MPI produces comparable diagnostic results in patients with and without diabetes

SPECT myocardial perfusion imaging in diabetes: Sensitivity and specificity
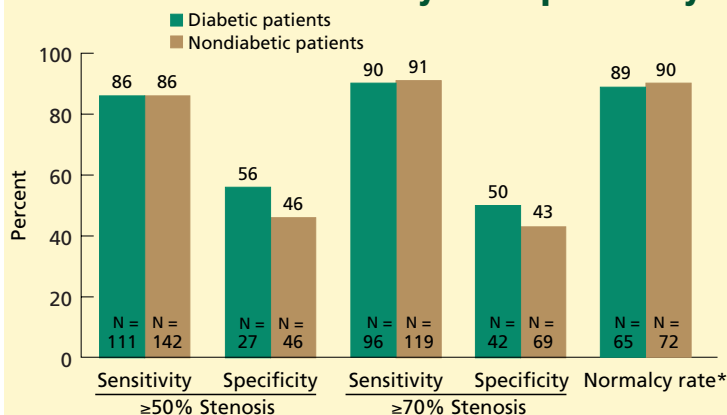

FIGURE 1. Overall, the sensitivity, specificity, and normalcy rates of myocardial perfusion imaging with gated single-photon emission computed tomography (SPECT) in patients with diabetes did not differ significantly from those in nondiabetic patients when compared with results from angiography, the gold standard.

*The normalcy rate is the percentage of low-likelihood patients (normals) who have a normal test

REPRINTED FROM KANG X, BERMAN DS, LEWIN H, ET AL. COMPARATIVE ABILITY OF MYOCARDIAL PERFUSION SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY TO DETECT CORONARY ARTERY DISEASE IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS. AM HEART J 1999; 137:949–957, WITH PERMISSION FROM ELSEVIER

ization. Patients were followed for 2.5 years. Those with diabetes consistently had higher event and procedure rates than nondiabetic patients (**FIGURE 2**). The overall 3-year survival was 91% for patients with diabetes and 97% for patients without diabetes. In this study, an abnormal stress MPI was an independent predictor of myocardial infarction and cardiac death in patients with and without diabetes. Patients with diabetes who had ischemic defects had a significantly increased number of cardiac events, with the highest myocardial infarction rate (17.1%) observed with three-vessel ischemia. A multivessel fixed defect was associated with the highest rate of cardiac death (13.6%) among these patients. In addition, the incremental predictive value of nuclear imaging in patients with diabetes was considerable. An abnormal stress MPI result was a greater predictor of the risk for cardiac death or myocardial infarction than either the pretest clinical risk or the presence of diabetes

(**FIGURE 3**).

Lewin et al[50] evaluated outcomes from 17,419 patients undergoing stress MPI. Eighteen-month Kaplan-Meier cardiac death rates were low (< 3%) for those with normal or mildly abnormal MPI results. However, among those with moderate to severely abnormal MPI results, cardiac death rates were 5.6% to 6.1%, and death or myocardial infarction rates were 6.9% to 9.2% in patients with diabetes. In a multivariate model, there was a 29% increased risk of death and a 20% increase in death or myocardial infarction for each five-unit increase in the stress-scan score.

Overall, these data demonstrate that stress MPI provides quantifiable data and identifies patients with diabetes who are at low and high risk for future adverse cardiovascular events. These risk stratification data are useful in planning appropriate treatment strategies for patients with diabetes.

Ongoing trial of Tc-99m sestamibi in diabetic patients

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial is a prospective, multicenter study in totally asymptomatic patients with type 2 diabetes. Patients in the DIAD trial are randomized to either "testing" with adenosine-Tc-99m sestamibi MPI or "no testing."

The primary objective of the trial is to determine the prevalence and severity of myocardial ischemia and clinical outcome in asymptomatic patients with diabetes and to define a profile for patients at high risk for asymptomatic CAD. Patient recruitment was completed in August 2002. This study found that 22% of patients in the "testing" group had abnormalities indicative of silent ischemia, including 5% who had major perfusion abnormalities.[51] The clinical outcome of patients with and without silent myocardial ischemia on MPI will be evaluated during 5 years of follow-up.

■ RECOMMENDATIONS BASED ON THE EVIDENCE

CAD in patients with diabetes is often silent, more advanced at diagnosis, and associated with an unfavorable prognosis compared with

CAD in patients without diabetes. Early intervention may prevent progression of disease and decrease the risk of clinical events. This requires the ability to stratify patients according to their risk of future clinical events.

A number of noninvasive stress tests are available for assessing CAD, including ECG exercise tolerance testing, stress echocardiography, and stress SPECT MPI. MPI appears to have advantages over other methods, including a higher incremental value than exercise tolerance testing for risk stratification, particularly if ECG-gated SPECT is included. Stress echocardiography can be technically difficult to perform, potentially resulting in insufficient diagnostic information and decreased sensitivity.

Prognostic value of stress MPI

Stress MPI has emerged as an established and well-validated method for assessing myocardial ischemia, viability, and function. The diagnostic accuracy and prognostic importance of SPECT MPI for the evaluation of patients with known or suspected CAD have been confirmed in numerous clinical studies. By offering data on both perfusion and function, MPI with gated SPECT has proven to be a valuable diagnostic and risk stratification management tool.

Patients with diabetes often have significant functional abnormalities that may alter the clinical prognosis. The prognostic value of stress MPI has been validated thus far only in selected patients with diabetes who were referred for stress testing for a variety of reasons. No published data exist on truly asymptomatic patients with diabetes. In other patient populations studied, the presence and extent of an abnormal stress MPI test independently predict cardiac events in diabetic patients. Thus, the results of MPI with gated SPECT can be used in conjunction with other prognostic variables (eg, clinical risk factors) to further improve risk stratification for these patients. For example, patients with a low risk of events may be managed with risk factor modification. As the degree of risk increases, medical therapy may be added or intensified. Those with the highest degree of risk require more aggressive management that may include catheterization and revascularization.

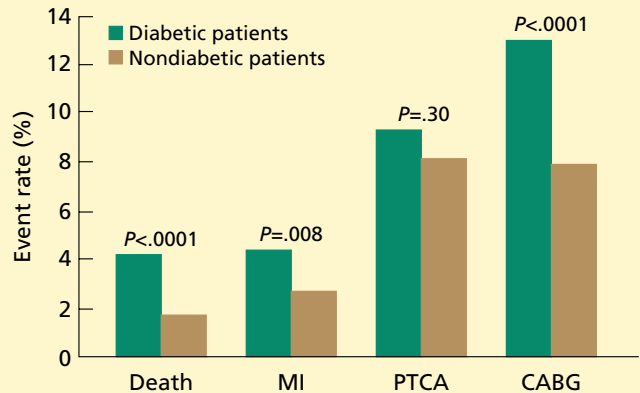## Outcomes of diabetic and nondiabetic patients undergoing stress testing

FIGURE 2. Of 4,755 patients undergoing stress myocardial perfusion imaging and followed for 2.5 years, diabetic patients underwent more revascularization procedures than nondiabetic patients, and yet they had higher event rates.

USED BY PERMISSION. GIRI S, SHAW LJ, MURTHY DR, ET AL. IMPACT OF DIABETES ON THE RISK STRATIFICATION USING STRESS SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY MYOCARDIAL PERFUSION IMAGING IN PATIENTS WITH SYMPTOMS SUGGESTIVE OF CORONARY ARTERY DISEASE. CIRCULATION 2002; 105:32–40.

Added value of nuclear imaging for risk stratification in diabetic patients
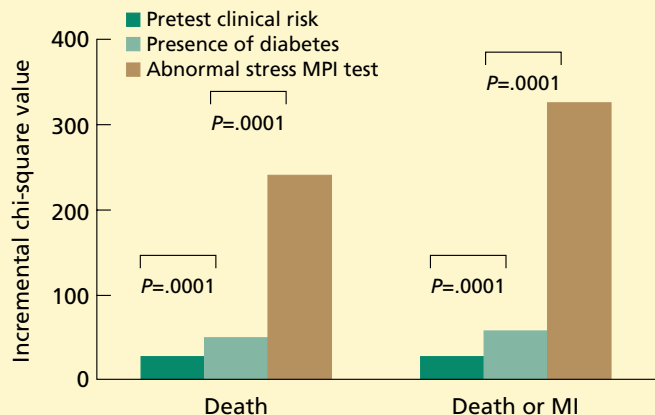

FIGURE 3. An abnormal stress myocardial perfusion imaging test was a much stronger predictor of cardiac death or myocardial infarction than was either pretest clinical risk or diabetes.

USED BY PERMISSION. GIRI S, SHAW LJ, MURTHY DR, ET AL. IMPACT OF DIABETES ON THE RISK STRATIFICATION USING STRESS SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY MYOCARDIAL PERFUSION IMAGING IN PATIENTS WITH SYMPTOMS SUGGESTIVE OF CORONARY ARTERY DISEASE. CIRCULATION 2002; 105:32–40.

The improved diagnostic certainty associated with MPI has the potential not only to improve clinical outcomes in diabetic patients, but also to decrease unnecessary use of resources. However, before routine screening is recommended, cost-effectiveness analyses are required to identify those for whom such testing is most appropriate. Nevertheless, MPI is clearly emerging as a valuable tool for improving management in all diabetic patients. ✷

■ REFERENCES

1. **Mokdad AH, Ford ES, Bowman BA, et al.** Diabetes trends in the United States. 1990–1998. Diabetes Care 2000; 23:1278–1283.
2. **Mokdad AH, Ford ES, Bowman BA, et al.** The continuing increase in diabetes in the US [letter]. Diabetes Care 2001; 24:412.
3. **American Diabetes Association.** Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002; 25:S33–S49.
4. **American Diabetes Association.** Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes: 10–11 February 1998, Miami, Florida. Diabetes Care 1998; 21:1551–1559.
5. **Hammoud T, Tanguay J-F, Bourassa MG.** Management of coronary artery disease: therapeutic options in patients with diabetes. J Am Coll Cardiol 2000; 36:355–365.
6. **Janand-Dellene B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V.** Silent myocardial ischemia in patients with diabetes. Diabetes Care 1999; 22:1396–1400.
7. **Koistinen MJ.** Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. Br Med J 1990; 301:92–95.
8. **Naka M, Hiramatsu K, Aizawa T, et al.** Silent myocardial ischemia in patients with noninsulin-dependent diabetes mellitus as judged by treadmill exercise testing and coronary angiography. Am Heart J 1992; 123:46–53.
9. **Cooper S, Caldwell JH.** Coronary artery disease in people with diabetes: diagnostic and risk factor evaluation. Clin Diabetes 1999; 17:58–70.
10. **Nesto RW, Philips RT, Kett KG, et al.** Angina and exertional myocardial ischemia in diabetic and nondiabetic patients: assessment by exercise thallium scintigraphy. Ann Intern Med 1988; 108:170–175.
11. **Jacoby RM, Nesto RW.** Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course, and prognosis. J Am Coll Cardiol 1992; 20:736–744.
12. **Clarkson P, Celermajer DS, Donald AE, et al.** Impaired vascular reactivity in insulin-dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels. J Am Coll Cardiol 1996; 28:573–579.
13. **Kannel WB, Hjortland M, Castelli WP.** Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974; 34:29–34.
14. **Coughlin SS, Tefft MC.** The epidemiology of idiopathic dilated cardiomyopathy in women: The Washington DC Dilated Cardiomyopathy Study. Epidemiology 1994; 5:449–455.
15. **Gu K, Cowie CC, Harris MI.** Diabetes and decline in heart disease mortality in US adults. JAMA 1999; 281:1291–1297.
16. **Giri S, Shaw LJ, Murthy DR, et al.** Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 2002; 105:32–40.
17. **Haffner SM, Lehto S, Ronnemma J, Pyorala K, Laakso M.** Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339:229–234.
18. **Miettinen H, Lehto S, Salomaa V, et al.** Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care 1998; 21:69–75.
19. **Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G.** Cholesterol lowering with simvastatin improved prognosis of diabetic patients with coronary heart disease. Diabetes Care 1997; 20:614–620.
20. **Starkman HS, Cable G, Hala V, Hecht H, Donnelly CM.** Delineation of prevalence and risk factors for early coronary artery disease by electron beam computed tomography in young adults with type 1 diabetes. Diabetes Care 2003; 26:433–436.
21. **O'Rourke RA, Brundage BH, Froelicher VF, et al.** American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol 2000; 36:326–340.
22. **Nesto RW.** Screening for asymptomatic coronary artery disease in diabetes. Diabetes Care 1999; 22:1393–1395.
23. **Haffner SM.** Coronary heart disease in patients with diabetes. N Engl J Med 2000; 342:1040–1042.
24. **Vanzetto G, Halimi S, Hammoud T, et al.** Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. Prognostic value of exercise stress test and thallium-201 single-photon emission computed tomography. Diabetes Care 1999; 22:19–26.
25. **Leischik R, Kuhlman C, Bruch C, Joremias A, Buck T, Erbel R.** Reproducibility of stress echocardiography using intravenous injection of ultrasound contrast agent (BY 963). Int J Card Imaging 1997; 13:387–394.
26. **Chaitman BR.** Exercise stress testing. In: Braunwald E, Zipes DP, Libby P, eds. Heart Disease: A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia: W.B. Saunders; 2001:129–155.
27. **Hung M-J, Wang C-H, Cherng W-J.** Can dobutamine stress echocardiography predict cardiac events in nonrevascularized diabetic patients following acute myocardial infarction? Chest 1999; 116:1224–1232.
28. **Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD.** Evaluation of patients with diabetes mellitus for coronary artery disease using dobutamine stress echocardiography. Coron Artery Dis 1997; 8:171–174.
29. **Hachamovitch R, Shaw LJ, Berman DS.** The ongoing evaluation of risk stratification using myocardial perfusion imaging in patients with known or suspected coronary disease. ACC Curr J Rev 1999; 8:66–71.
30. **Iskander S, Iskandrian AE.** Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. J Am Coll Cardiol 1998; 32:57–62.
31. **Desmarais RL, Kaul S, Watson DD, Beller GA.** Do false positive thallium-201 scans lead to unnecessary catheterization? Outcome of patients with perfusion defects on quantitative planar thallium-201 scintigraphy. J Am Coll Cardiol 1993; 21:1058–1063.
32. **Williams KA, Schuster RA, Williams KA Jr, Schneider CM, Pokharna R.** Correct spatial normalization of myocardial perfusion SPECT improves detection of multivessel coronary artery disease. J Nucl Cardiol 2003; 10:353–360.
33. **Cachin F, Lipiecki J, Mestas D, et al.** Preliminary evaluation of a fuzzy logic-based automatic quantitative analysis in myocardial SPECT. J Nucl Med 2003; 44:1625–1632.
34. **Kjaer A, Cortsen A, Rahbek B, Hasseldam H, Hesse B.** Attenuation and scatter correction in myocardial SPECT: improves diagnostic accuracy in patients with suspected coronary artery disease. Eur J Nucl Med Mol Imaging 2002; 29:1438–1442.
35. **Narayanan MV, King MA, Pretorius PH, et al.** Human-observer receiver-operating-characteristic evaluation of attenuation, scatter, and resolution compensation strategies for (99m)tc myocardial perfusion imaging. J Nucl Med 2003; 44:1725–1734.
36. **Leppo JA.** Comparison of pharmacologic stress agents. J Nucl Cardiol 1996; 3:S22–S26.

37. **Heller GV, Shehata AR.** Pharmacological stress testing with technetium-99m single-photon emission computerized tomography imaging in the preoperative assessment of patients undergoing noncardiac surgery. Am J Card Imaging 1997; 10:120–127.

38. **Beller GA, Zaret BL.** Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000; 101:1465–1478.

39. **Danias PG, Ahlberg AW, Clark BA 3rd, et al.** Combined assessment of myocardial perfusion and left ventricular function with exercise technetium-99m sestamibi gated single-photon emission computed tomography can differentiate between ischemic and nonischemic dilated cardiomyopathy. Am J Cardiol 1998; 82:1253–1258.

40. **Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F.** Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. J Am Coll Cardiol 1997; 29:69–77.

41. **Sharir T, Germano G, Kavanagh PB, et al.** Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999; 100:1035–1042.

42. **Lee KL, Prior DB, Pieper KS, et al.** Prognostic value of radionuclide angiography in medically treated patients with coronary artery disease: a comparison with clinical and catheterization variable. Circulation 1990; 82:1705–1717.

43. **DePuey EG, Rozanski A.** Using gated technetium-99m sestamibi SPECT to characterize fixed myocardial defects as infarct or artifact. J Nucl Med 1995; 36:952–955.

44. **Shaw LJ, Hachamovitch R, Heller GV, et al.** Noninvasive strategies for the estimation of cardiac risk in stable chest pain patients. Am J Cardiol 2000; 86:1–7.

45. **Paillole C. Ruiz J, Juliard JM, Leblanc H, Gourgon R, Passa PH.** Detection of coronary artery disease in diabetic patients. Diabetologia 1995; 38:726–731.

46. **Boudreau RJ, Strony JT, du Cret RP, et al.** Perfusion thallium imaging of type 1 diabetes patients with end-stage renal disease: comparison of oral and intravenous dipyridamole administration. Radiology 1990; 175:103–105.

47. **Bell DSH, Yumuk VD.** Low incidence of false-positive exercise thallium 201 scintigraphy in a diabetic population [letter]. Diabetes Care 1996; 19:185–186.

48. **Kang X, Berman DS, Lewin HC, et al.** Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. Am Heart J 1999; 138:1025–1032.

49. **Kang X, Berman DS, Lewin H, et al.** Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. Am Heart J 1999; 137:949–957.

50. **Lewin HC, Berman DS, Shaw LJ, et al.** Noninvasive risk assessment of diabetic and nondiabetic patients with suspected ischemic heart disease [abstract]. J Am Coll Cardiol 1999; 33:447A.

51. **Wackers FJTh, Young LY, Inzucchi SE, et al, for the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators.** Detection of silent myocardial ischemia in asymptomatic diabetic subjects. Diabetes Care 2004; 27:1954–1961.

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