The combination of clinical coronary artery disease and diabetes mellitus is a harbinger of adverse outcome. Recently, in a jointly issued statement, the American Diabetes Association, the National Heart, Lung, and Blood Institute, the Juvenile Diabetes Foundation International, the National Institute of Diabetes and Digestive and Kidney Diseases, and the American Heart Association indicated the importance of diabetes mellitus as a major risk factor for cardiovascular disease.\textsuperscript{1,2} Patients with diabetes mellitus often have premature coronary artery disease; the disease is often asymptomatic and in an advanced stage when detected.\textsuperscript{3} In general, the outcome of patients with diabetes mellitus is poorer than those without diabetes, and coronary artery disease in the diabetic patient may be less amenable to favorable interventional treatment compared with the nondiabetic population.\textsuperscript{4–6} Moreover, it seems that in women with diabetes mellitus and coronary artery disease, overall outcome has not improved to the extent observed in men, despite aggressive medical or interventional treatment.\textsuperscript{7} Such observations have led to the need for more aggressive approaches to preventive, diagnostic, and therapeutic strategies in patients with diabetes mellitus.

Stress radionuclide myocardial perfusion imaging (MPI) is used widely to evaluate patients with suspected or known coronary artery disease. A large body of evidence attests to the high diagnostic yield of stress MPI and its important incremental prognostic value over both clinical and angiographic variables for the prediction of major acute coronary events.\textsuperscript{8,9} The degree and extent of myocardial perfusion abnormalities observed on stress MPI are related directly to outcome. The greater the myocardial perfusion abnormality, the greater the likelihood of future cardiac events. On the other hand, unequivocally normal stress MPI is associated with an excellent outcome and a cardiac event rate of \textless 1\% per year.\textsuperscript{8,10} Several investigators have reported that single-photon emission computed tomography (SPECT) MPI had similar prognostic value in patients with diabetes mellitus.\textsuperscript{11,12}

In the present issue of \textit{Circulation}, Giri et al\textsuperscript{13} evaluate stress SPECT MPI for risk stratification of patients with diabetes mellitus who had been referred to the nuclear cardiology stress laboratory for cardiac evaluation. In this retrospective, multicenter, database analysis involving a large number of patients, patients with diabetes mellitus had a significantly higher cardiac event rate (death and myocardial infarction) than that of the nondiabetic patient cohort. When adjustment was made for clinical variables and SPECT MPI results, however, cardiac survival was comparable, indicating that MPI prognostic categorization supersedes the adverse predictive value of diabetes mellitus as an unvariable parameter. Interestingly, women had a worse outcome for any given extent of myocardial perfusion abnormality than did men.

Of substantial clinical interest was the observation that after the index study, patients with diabetes mellitus and normal stress SPECT images had a significantly higher 2-year cardiac event rate than that of patients without diabetes. This prognostic finding is in marked contrast to the experience in the nondiabetic population, in whom the association of normal MPI and excellent outcome has been demonstrated repeatedly.\textsuperscript{8,10} Defining those factors responsible for this altered prognostic value of normal MPI in diabetic patients will require further study. However, patients with diabetes mellitus and normal stress images may require more frequent follow-up testing.

Although the study by Giri et al\textsuperscript{13} provides clinically important information about the predictive power of stress SPECT MPI in this population, several issues should be emphasized: The patients with diabetes mellitus in this analysis were highly selected; they were specifically referred for stress testing because of suspected or established coronary artery disease. It is not stated how many patients were truly asymptomatic at the time of referral. There is no detailed information about the duration of diabetes, mode of treatment, or degree of diabetic control. The extent of secondary organ involvement and autonomic dysfunction, variables that have been found to be associated with the presence of subclinical coronary artery disease, are not specified. The typical diabetic patient population frequently has multiple risk factors for coronary artery disease, as well as other comorbidities that can affect outcomes.\textsuperscript{14–17}

Although it confirmed the potent prognostic value of MPI, the study by Giri et al\textsuperscript{13} did not address some key questions in the management of patients with diabetes mellitus: What is the value of stress MPI for detecting coronary artery disease in asymptomatic patients with diabetes mellitus? When, how, and which asymptomatic patients with diabetes mellitus should be screened? A clinical analogy may be found in the approach toward preoperative testing of patients with periph-
eral arterial disease before vascular surgery. In this patient population, which has a relatively high prevalence of subclinical coronary artery disease and a substantial perioperative cardiac event rate, vasodilator radionuclide MPI has been extremely useful in identifying high-risk operative patients.\textsuperscript{18}

It was soon obvious, however, that not all patients scheduled for surgical procedures needed preoperative testing. Evidence-based guidelines that took multiple clinical variables into consideration were developed to determine in which subpopulations preoperative MPI was beneficial.\textsuperscript{19} A similar scenario can be envisioned for patients with diabetes mellitus.

Giri et al\textsuperscript{13} demonstrated that radionuclide stress MPI is a particularly appropriate noninvasive means of evaluating patients with diabetes mellitus in whom coronary artery disease is suspected. However, the challenge of detecting asymptomatic but substantial coronary artery disease is a formidable one in patients with diabetes mellitus. There are \(\approx 16\) million patients with known diabetes mellitus in the United States alone.\textsuperscript{20} Of these, \(\approx 20\%\) (3.5 million) are known to have coronary artery disease. One can expect coronary artery disease to become clinically manifest in an additional \(15\%\) (1.8 million) of these patients within 1 year.\textsuperscript{20} Clinical manifestations of heart disease may be sudden death, acute myocardial infarction, stroke, congestive heart failure, or angina, but the disease may remain asymptomatic in many patients.

Which of the 12.5 million asymptomatic diabetic patients should be screened and evaluated for subclinical coronary artery disease is a crucial question. Screening all patients with diabetes mellitus is not practical, either economically or clinically. In February 1998, the American Diabetes Association published a consensus statement on the diagnosis of coronary artery disease in people with diabetes mellitus.\textsuperscript{21} It was recommended that those asymptomatic diabetic patients with \(\geq 2\) risk factors for coronary artery disease or those beginning an exercise program should have exercise stress testing. It was stated that asymptomatic diabetic patients with \(\leq 1\) risk factor do not require cardiac testing. However, these recommendations were based on the clinical judgment of a panel of experts rather than on data.

There is a clear need for evidence-based guidelines for the early detection of coronary artery disease in the population with diabetes mellitus. We are presently conducting the Detection of Ischemia in Asymptomatic Ischemia (DIAD) trial, which is designed to address this question. In this multicenter study, 1000 asymptomatic type-2 diabetic patients are being evaluated. The primary end point of the study is the observed prevalence of myocardial perfusion abnormalities on SPECT imaging. By analysis of the data, a clinical/biochemical profile of patients at high risk for subclinical coronary artery disease should be possible. On the basis of Bayesian principles, the definition of a high-risk population is of practical importance. If the prevalence of asymptomatic coronary disease is relatively low in the general diabetes population, screening will not be of much use because of the number of false-positive test results that can be anticipated. Stress MPI has its greatest diagnostic yield in a patient population with a moderate-to-intermediate likelihood of coronary artery disease. Is it hoped that the DIAD study will define such an “enriched” population of patients with diabetes mellitus and a relatively high prevalence of disease for whom MPI screening will be both efficacious and cost-effective.

After clarification of the diagnostic issues, the next important question involves the appropriate treatment of patients in whom subclinical coronary artery disease is detected. Several studies have revealed that percutaneous coronary interventions may not have the same favorable results in patients with diabetes as they do in the general population.\textsuperscript{5,22–25} However, a recent registry data analysis challenged this finding.\textsuperscript{26} In the presently ongoing Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2) trial, patients with moderate angiographic coronary artery disease are being randomized to interventional or medical treatment to answer this question in a selected population.

Clearly, the question of evaluation and treatment of coronary disease, symptomatic and asymptomatic, in patients with diabetes mellitus remains complex and in need of further study. The report by Giri et al\textsuperscript{13} indicates the important role stress MPI can play in this patient population. As the knowledge base is extended to the asymptomatic diabetic patient, it is anticipated that stress MPI will have an increasingly relevant role.

References


**Key Words:** Editorials • diabetes mellitus • ischemia • radioisotopes • imaging
Detection of Myocardial Ischemia in Patients With Diabetes Mellitus
Frans J. Th. Wackers and Barry L. Zaret

Circulation. 2002;105:5-7
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/1/5

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/