Diabetes and Detection of CAD: Viewpoint

Should We Screen for Occult Coronary Artery Disease Among Asymptomatic Patients With Diabetes?

Marcelo F. Di Carli, MD, FACC,* Rory Hachamovitch, MD, MSc, FACC†
Boston, Massachusetts; and Los Angeles, California

Diabetes mellitus predisposes people to premature atherosclerotic coronary artery disease (CAD). The risk of a myocardial infarction in diabetics without overt evidence of obstructive CAD matches that of patients without diabetes who have had a previous myocardial infarction. The available data suggest that occult CAD is a common finding among asymptomatic diabetics, ranging from 20% to >50%. The diagnostic accuracy of myocardial perfusion single-photon emission computed tomography (SPECT) in diabetics appears to be comparable to that observed in nondiabetic individuals. As shown in other patient groups, the ischemic burden assessed by stress SPECT in subjects with diabetes is also linked to their increased risk of adverse cardiovascular events. Among patients with normal stress SPECT, however, those with diabetes are at significantly greater risk than non-diabetics. Testing diabetics with an abnormal resting electrocardiogram or with evidence of peripheral or carotid occlusive arterial disease appears to result in an excellent yield of abnormal SPECT findings, as does testing in the setting of dyspnea. However, recent evidence suggests that achieving an adequate yield in asymptomatic diabetics without overt evidence of CAD is a greater challenge. Further investigation of sequential testing strategies is needed in order to identify an efficient means for screening asymptomatic patients with diabetes. (J Am Coll Cardiol 2005;45:50–3) © 2005 by the American College of Cardiology Foundation

Diabetes mellitus is a major public health problem. It is estimated that 18.2 million Americans (6.3% of the population) have diabetes, of whom 5.2 million are not aware that they actually have the disease (1). A total of 95% of patients have type 2 diabetes. Further, nearly 1.3 million individuals in the U.S. are diagnosed with diabetes each year. This dramatic increase in diabetes prevalence is occurring in all age groups, especially in persons 20 to 59 years of age (1). In addition, approximately 25% of the U.S. population have the metabolic syndrome that greatly increases the risk of developing diabetes, and this prevalence rises to >40% in patients older than 60 years of age (2). Diabetes and its complications add $132 billion in health care and indirect (disability, work loss, and premature mortality) costs to society.

Diabetes is associated with a two- to four-fold increase in the risk of developing coronary artery disease (CAD). The risk of a myocardial infarction (MI) in patients with diabetes and no evidence of CAD matches that of patients without diabetes who have had a previous MI (3). In the recent report of the Adult Treatment Panel of the National Cholesterol Education Program, type 2 diabetes was accorded a CAD risk-equivalent (4). In patients with known CAD and diabetes, the rate of death is >70% over 10 years (3). Outcomes are worse in diabetic patients for each manifestation of CAD. After MI has occurred, the 30-day mortality rate increases in patients with diabetes by more than 50% (5). Of those who survive, approximately 50% die within five years after a MI, double the rate found in non-diabetic patients (6).

In addition, patients with diabetes have a high incidence of occult CAD, reflected by an increased incidence of silent MI (7) and ischemia (8–10). The lack of warning symptoms (i.e., angina) during infarction and ischemia in patients with diabetes has been linked to autonomic neuropathy involving afferent sympathetic fibers, which are considered a key component of the cardiac pain perception pathway. Clinical studies have confirmed an association between silent infarction and ischemia, and autonomic neuropathy (9,11,12). Recent evidence from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study suggests that more than one in five (22%) asymptomatic patients with type 2 diabetes show evidence of ischemia on stress myocardial perfusion imaging (9). However, other investigators have reported a substantially higher prevalence of occult CAD among asymptomatic diabetics. In a study of 1,427 asymptomatic diabetics without prior MI or revascularization undergoing nuclear stress testing, Rajagopalan et al. (10) reported that 826 patients (58%) had an abnormal stress single-photon emission computed tomography (SPECT) scan, and that 261 patients (18%) had a high-risk study as defined by the combined extent and severity of ischemia and/or scar on the nuclear scan. Likewise, a recent study from the Cedars-Sinai group (13) examining 1,737 diabetics without prior revascularization or MI—826 asymptomatic,
151 with dyspnea, and 760 with angina—reported an overall 42% abnormal SPECT rate with no differences between asymptomatic patients and those with angina. Patients with dyspnea, however, have a significantly higher abnormal SPECT rate (51%). Moreover, this high prevalence of occult CAD in asymptomatic diabetics was also similar to earlier smaller reports (14–16).

These large variations in prevalence and extent of obstructive CAD likely reflect important differences between the patient populations included in those studies. For example, compared with the DIAD trial, the study by Rajagopalan et al. (10) included a higher proportion of males (70% vs. 53%), with a longer duration of diabetes (10 vs. 8 years), poorer glycemic control (glycosylated hemoglobin >7%: 80% vs. 46%), higher prevalence of peripheral arterial disease reflecting more advanced atherosclerosis (31% vs. 9%), more patients with diabetic dyslipidemia (41% vs. 24%) with less patients on lipid-lowering treatment (19% vs. 47%), more patients with hypertension (71% vs. 31%), and a higher proportion of patients with abnormal Q waves on resting electrocardiogram (ECG) (9% vs. 0%). Moreover, patients in some of these studies had a clinical indication for stress SPECT imaging, and 50% of them underwent testing for preoperative evaluation, suggesting more advanced disease (10). Taken together, the available evidence suggests that occult CAD is a common finding among asymptomatic patients with diabetes, ranging from 20% in healthier subjects to >50% in patients with more complicated diabetes. This poses the challenge of how to efficiently identify these individuals and target them for appropriate therapy.

**Diagnosing and assessing the extent of CAD in patients with diabetes.** Few studies have reported on the diagnostic accuracy of noninvasive imaging methods for detecting and assessing the extent of CAD in patients with diabetes. Kang et al. (17) reported similar sensitivities and specificities of myocardial perfusion SPECT for detecting angiographic CAD in diabetic and non-diabetic patients. One relatively common finding in patients with diabetes is that the extent and severity of perfusion abnormalities on SPECT imaging frequently denotes more extensive and severe ischemia than predicted by coronary angiography. For example, the Mayo Clinic group reported that 51 of 127 patients (40%) with high-risk nuclear scans (reflecting extensive and severe ischemia and/or scar) undergoing coronary angiography showed relatively mild angiographic CAD (i.e., no epicardial disease, or one- to two-vessel disease excluding left main and proximal left anterior descending coronary artery stenoses). Likewise, 32 of 212 patients (15%) undergoing coronary angiography showed definite mild-to-severe ischemia on the nuclear scan without evidence of angiographically evident epicardial coronary artery obstructions. Although these discrepancies between function and anatomy have been frequently labeled as “false-positive” findings, they likely reflect severe underlying microvascular dysfunction in the diabetic heart that is underestimated by conventional coronary angiography. Indeed, there is growing, consistent evidence that diabetes causes important alterations in the regulation of coronary vasodilator function in both epicardial and resistance coronary vessels (18), which are present before the appearance of obstructive CAD within the epicardial coronary arteries. These disturbances are independent of diabetes-associated lipid abnormalities and hypertension, and have been linked to both hyperglycemia and insulin resistance (19,20). In addition, autonomic neuropathy, a common and well-recognized serious complication of diabetes mellitus, also modulates myocardial perfusion (21) and is frequently associated with perfusion abnormalities (9). Thus, functional imaging provides a more accurate assessment of the total ischemic burden, especially among diabetic patients with severe endothelial and smooth muscle cell dysfunction within the coronary microvasculature.

**Assessing risk in patients with diabetes.** The observed excess ischemic burden in subjects with diabetes is (likely) linked to their increased risk of adverse cardiovascular events. As has been the case with other patient populations, a shift has occurred toward the use of risk assessment and prognostication to guide patient management. To date, a number of studies have confirmed that stress SPECT provides incremental prognostic value and achieves adequate risk stratification in diabetic cohorts (13,22–24). Although a normal stress SPECT study is generally associated with a low risk (<1% annual risk of cardiac death or MI) (25), the challenge in a diabetic population is to define the elusive “low-risk” patient. To date, reports have consistently shown that normal stress SPECT in diabetic populations is not associated with this low level of risk and, in direct comparisons, patients with diabetes are at significantly greater risk than non-diabetics with normal SPECT (10,13,22–24,26). Similarly, in the setting of an abnormal SPECT, the risk conferred by any given extent and severity of perfusion abnormality is greater in patients with diabetes than in non-diabetics. Furthermore, the risk is greater for insulin-dependent versus non-insulin-dependent diabetes. Generally, it appears that clinical information adds incremental prognostic value over perfusion results and can further risk-stratify SPECT results. These factors include patient gender, age, presence of peripheral vascular disease or abnormal resting ECG, and the type of diabetes. The prognostic implications of symptoms are also important. Compared with asymptomatic patients, it is unclear if the presence of anginal symptoms is associated with increased risk in patients with diabetes. However, patients without angina presenting with dyspnea appear

**Abbreviations and Acronyms**

ADA — American Diabetes Association
CAD — coronary artery disease
DIAD — Detection of Ischemia in Asymptomatic Diabetics study
ECG — electrocardiogram
MI — myocardial infarction
SPECT — single-photon emission computed tomography

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to have a two- to three-fold greater risk than patients presenting with angina (13).

Our limited knowledge to date in this area indicates the need to address several issues. Is the greater risk in patients with diabetes one that can be reduced by intervention, medical or otherwise? Although post-SPECT risk is greater in patients with diabetes than in non-diabetics, patients with diabetes also appear to accrue greater survival benefit with revascularization over medical therapy in the setting of significant ischemia (27). Consequently, perhaps we should shift our focus from identification of risk to identification of benefit (27). Because we can improve outcomes in these patients, how should we go about identifying candidates for aggressive management? We must ask how to identify the diabetic patient in need of testing, and, once identified, decide which test and testing algorithm are optimal.

Which asymptomatic diabetics should be screened for occult CAD? The American Diabetes Association (ADA) consensus guidelines for CAD screening in people with diabetes recommend testing those patients under several circumstances. Testing is recommended in patients with an abnormal resting ECG or with evidence of peripheral or carotid occlusive arterial disease (28). The emerging evidence supports the appropriateness of testing in these patients (10). Indeed, the rate of high-risk scans in a study from the Mayo Clinic was 43% among patients with Q waves on the ECG, 26% among patients with an abnormal resting ECG, and 28% among those with peripheral arterial disease (10). The ADA guidelines also recommend testing in patients with symptoms suspicious of CAD (i.e., chest pain, dyspnea, fatigue). The data are less compelling for this indication. With respect to presenting symptoms, studies from both the Mayo Clinic (29) and Cedars-Sinai (13) groups report similar frequencies of stress SPECT abnormality in patients with and without anginal symptoms. The latter study identified dyspnea as the only symptom predictive of more frequent abnormal scans and greater risk (13).

In patients with no symptoms nor evidence of cardiac or peripheral vascular disease, the ADA guidelines recommend testing only for those individuals who have ≥2 risk factors (diabetic dyslipidemia, hypertension, active smoking, a family history of premature CAD, and albuminuria). In the DIAD study (9), 22% of patients with ≥2 risk factors (n = 306) had abnormal scans, a rate identical to that among those participants with fewer than two risk factors (n = 204). Indeed, 41% of all abnormal SPECT studies in the DIAD trial occurred in the group with fewer than two risk factors. The rate of high-risk scans was also similar in patients with ≥2 versus <2 risk factors. Similarly, Rajagopalan et al. (10) found that only 17% of patients with ≥2 risk factors had high-risk scans, a result no different from the overall cohort.

Hence, it appears that although testing diabetics with an abnormal resting ECG or with evidence of peripheral or carotid occlusive arterial disease results in an excellent yield, as does testing in the setting of dyspnea, achieving an adequate yield of abnormal SPECT in asymptomatic diabetics without overt evidence of CAD is a greater challenge. In order to augment this low yield, thereby enhancing the clinical- and cost-effectiveness of diagnostic evaluations, it is probably necessary to enrich the prevalence of disease in this asymptomatic diabetic population before the use of stress SPECT. Two approaches can potentially be used together or separately to achieve this end. First, the use of an aggregate score incorporating and weighting multiple risk factors is superior to an approach of counting the number of risk factors present (30,31). Indeed, some risk factors appear to be associated with higher frequencies of high-risk scans (e.g., male, > 65 years of age: 31%), whereas others have no significant associations with high-risk scan results (e.g., family history of CAD, insulin use, body mass index) (10). In addition, the ADA criteria may miss important predictors of risk in patients with diabetes, such as markers of autonomic function such as the Valsalva heart rate ratio, the strongest predictor of an abnormal scan in the DIAD study (9). This suggests that a substantial number of asymptomatic diabetic patients with few risk factors may have occult CAD, and may be missed on the basis of current ADA guidelines. Previous studies have shown that incorporating a clinical score into a testing strategy can enhance SPECT yield and improve cost-effectiveness (32–34). Indeed, a recent preliminary report extends some of these findings to the screening of a diabetic population (35).

A second approach that can be used in conjunction with or as an alternative to this approach is to utilize a test of atherosclerosis burden for the identification of asymptomatic diabetics with a higher likelihood of occult CAD. Previous studies have shown that the use of a calcium score threshold (e.g., 400) may identify those individuals with intermediate likelihood of SPECT abnormality (36,37). Although this threshold may need to be lowered in patients with diabetes, it may serve as a first-line test to better define which patients may benefit from referral to stress SPECT. Similarly, intima-medial thickness ratios or ankle-brachial indexes may also serve this role. Previous studies have shown that a sequential testing strategy combining clinical, low-cost noninvasive testing and stress SPECT improves both the clinical- and cost-effectiveness of testing (34).

Conclusions. The epidemic of diabetes has left us with the challenge of identifying those asymptomatic individuals with diabetes who have silent or occult CAD. Although the numbers of these patients are significant, not all are candidates for stress SPECT. The emerging evidence seems to confirm the potential role of stress SPECT in patients with greater likelihood of CAD (abnormal resting ECG, evidence of peripheral or carotid occlusive arterial disease, symptoms of dyspnea), as well as the low yield of SPECT in lower-risk asymptomatic diabetic patients. Further investigation of sequential testing strategies is needed in order to identify an efficient means for screening this population of patients.
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