The Potential of Myocardial Perfusion Scintigraphy for Risk Stratification of Asymptomatic Patients With Type 2 Diabetes

Jeroen J. Bax, MD,* Robert O. Bonow, MD,† Diethelm Tschöpe, MD,‡ Silvio E. Inzucchi, MD,§ Eugene Barrett, MD,|| on behalf of the Global Dialogue Group for the Evaluation of Cardiovascular Risk in Patients With Diabetes

Leiden, the Netherlands; Bad Oeynhausen, Germany; Chicago, Illinois; New Haven, Connecticut; and Charlottesville, Virginia

Patients with diabetes, in particular patients with type 2 diabetes, are at a 2- to 4-fold higher risk of cardiovascular mortality compared with their nondiabetic peers. Patients with diabetes are also more likely to have silent ischemia and less likely to survive a myocardial infarction than nondiabetic patients. Recent studies with electron beam computed tomography (EBCT) have shown that subclinical atherosclerosis is common in patients with diabetes, and studies with myocardial perfusion scintigraphy (with single-photon emission computed tomography) or stress echocardiography have demonstrated that between 25% and 50% of asymptomatic diabetic patients have ischemia during exercise or pharmacological stress and that a substantial proportion of these patients go on to develop major cardiovascular events within several years. Clearly, asymptomatic diabetic patients include a subset of individuals at high risk of cardiovascular disease who would benefit from improved risk stratification beyond that possible with risk factor scoring systems alone. Single-photon emission computed tomography, stress echocardiography, and possibly EBCT or multi-slice computed tomography, are emerging as valuable diagnostic tools for identifying asymptomatic diabetic patients who might require early and aggressive intervention to manage their cardiovascular risk. (J Am Coll Cardiol 2006;48:754–60) © 2006 by the American College of Cardiology Foundation

Management guidelines in Europe (1) and the U.S. (2) consider type 2 diabetes to be a cardiovascular disease equivalent. Patients with type 2 diabetes have a 2- to 4-fold higher risk of a cardiovascular event than nondiabetic patients (3), and Haffner et al. (3) have shown that the risk of myocardial infarction (MI) in a diabetic patient is comparable to the risk of recurrent infarction in a nondiabetic patient with a previous MI (Fig. 1). However, other studies suggested a lower prevalence of MI in diabetic patients, and the exact prevalence of cardiovascular events in asymptomatic diabetic patients remains unclear (4–6).

Still, cardiovascular disease is the principal cause of death in patients with type 2 diabetes (1,2). The relationship between cardiovascular risk and cardiovascular outcomes differs importantly between type 2 diabetic and nondiabetic patients. Silent myocardial ischemia is more common among diabetic patients compared with nondiabetic patients (7), and diabetic patients are less likely to survive a first MI than their nondiabetic peers (8).

An increasing prevalence of obesity and sedentary lifestyles is expected to drive the number of individuals with diabetes worldwide to more than 330 million by the year 2025 (9). The burden of cardiovascular disease and premature mortality associated with diabetes will also increase steeply in the coming years, reflecting the increased numbers of younger adults and adolescents with type 2 diabetes. Cardiologists will be at the forefront of dealing with this therapeutic challenge. There is a clear need to identify patients with type 2 diabetes who are at risk of cardiovascular events before the onset of symptoms. Accordingly, early identification of atherosclerosis and ischemia is needed. In addition, evidence is accumulating that myocardial perfusion scintigraphy (MPS) is a particularly promising approach for risk stratification within the population of diabetic patients who do not have symptoms of coronary artery disease (CAD). A group of physicians from Europe and the U.S. (the Global Dialogue Group for the Evaluation of Cardiovascular Risk in Patients With Diabetes) recently met to consider the problem of detecting CAD and silent ischemia in asymptomatic diabetic patients. This viewpoint summarizes the evidence supporting MPS as a diagnostic tool for identification of CAD and silent ischemia in asymptomatic diabetic patients. Moreover, a rec-
Abbreviations and Acronyms

- CAD = coronary artery disease
- DIAD = Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics study
- EBCT = electron beam computed tomography
- ECG = electrocardiography/electrocardiogram
- MI = myocardial infarction
- MPS = myocardial perfusion scintigraphy
- MSCT = multi-slice computed tomography
- SPECT = single-photon emission computed tomography

ommmation for the place of MPS in management algorithms for this vulnerable patient population is discussed.

DETECTION OF CAD WITH MYOCARDIAL PERFUSION IMAGING IN PATIENTS WITH TYPE 2 DIABETES

Prevalence. The recently-published initial data from the DIAD (Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics) study (10) have highlighted the scale of the problem of CAD and silent ischemia in a population of 1,123 asymptomatic diabetic patients. A middle-aged or elderly patient population (mean age 61 years) and high proportions of patients with dyslipidemia (58%), hypertension (65%), a history of smoking (58%), or at least 2 cardiovascular risk factors (60%) indicated a population at substantial risk of CAD. Patients were randomized to undergo adenosine electrophysiology (ECG)-gated technetium-99m sestamibi single-photon emission computed tomography (SPECT) plus follow-up (n = 561, with 522 patients having evaluable scans) or to clinical follow-up only (n = 562). Studies were abnormal in 22% of the MPS group, and 16% showed evidence of myocardial perfusion abnormalities, whereas the remainder revealed stress-induced ECG abnormalities or left ventricular function abnormalities indicating ischemia (Fig. 2). Perfusion abnormalities were reversible in 88% of these patients (indicating ischemia), although 4% demonstrated irreversible abnormalities (indicating scar tissue), and 8% demonstrated both reversible and irreversible perfusion defects (Fig. 2). The perfusion defect involved more than 5% of the left ventricle in 40% of patients with an abnormal SPECT study (Fig. 2). Importantly, assessment of most established and emerging clinical and biochemical risk factors for cardiovascular disease did not predict which the DIAD study patients would exhibit abnormal perfusion. However, cardiac neuropathy was an independent predictor of abnormal MPS. This issue might be of clinical value to identify high-risk diabetic patients and might have implications for aggressive medical therapy (e.g., additional beta-blocking therapy).

The results of the DIAD study (in terms of prevalence of abnormal MPS) are consistent with other studies in populations of diabetic patients who were asymptomatic for CAD (Table 1), in which the prevalence of abnormal perfusion scans ranged from 21% to 59% (10–24). Moreover, 1 of these studies reported that the prevalence of perfusion abnormalities was comparable between asymptomatic diabetic patients and patients presenting with symptoms suggesting CAD (angina pectoris and/or dyspnea) (14). On the basis of these observations, it is clear that silent ischemia is common among type 2 diabetic patients who have yet to develop symptoms of CAD. It should, however, also be emphasized that the prevalence of ischemia varied significantly between these different reports and that not much is known about the extent to which ischemia is clinically (and prognostically) meaningful. These differences can (at least partially) be attributed to the differences in study populations. The majority of the studies have included small numbers of patients, and even the largest studies (with more than 500 patients undergoing MPS) that are currently available (10,13,14,16,24) have important differences in characteristics of study populations. The DIAD trial is the only prospective trial, whereas the other studies are retrospective analyses. Patients with abnormal ECGs were excluded in the DIAD trial (10) but were included in the other studies. Also, 1 study included a substantial percentage of patients who needed pre-operative evaluation (16).

Association with adverse clinical outcomes. Several of the aforementioned studies followed up asymptomatic diabetic patients to establish the relationships between abnormal MPS scans and adverse cardiovascular outcomes. The study that enrolled 3 subsets of patients (without symptoms, with angina, and with dyspnea) reported that the annual critical event rates (MI or cardiac death) were about 3-fold higher in patients with abnormal SPECT results (5.4% in patients with perfusion abnormalities on SPECT vs. 1.9% in patients with normal SPECT) in the overall study population (14). Importantly, the risk of these events did not differ significantly between asymptomatic patients and patients with angina.

The available data in asymptomatic diabetic patients confirm the results in the general population in that patients with a high-risk MPS have an elevated risk for adverse events, whereas patients with a normal MPS are at low risk.
Still, in the general population, the annual hard event rate (death or MI) is \(<1\%\) (25), whereas the event rate in diabetic patients with a normal MPS might be higher, as emphasized recently (26).

Still, various studies reported significant associations between the incidence of major cardiovascular events, defined as cardiac death or nonfatal MI (odds ratio 5.7, \(p = 0.03\)) or nonfatal MI (odds ratio 2.9, \(p = 0.04\)) (15), a higher likelihood of 3-vessel CAD in diabetic versus non-diabetic subjects (13), or higher rates of revascularization in patients with abnormal SPECT scans (12,13). Overall, these studies showed that SPECT added important prognostic information to that provided by standard risk factor assessment alone and also provided valuable guidance for selecting therapy for these patients.

**PLACE OF MPS IN RISK STRATIFICATION FOR TYPE 2 DIABETES PATIENTS WITHOUT SYMPTOMS OF CAD**

Comparison with other noninvasive modalities. Single-photon emission computed tomography has important advantages over other noninvasive modalities for detecting myocardial ischemia. Exercise testing is well-established and well-validated in patients with known CAD, but its sensitivity is low in patients with early atherosclerotic changes, and this method is less well studied in the asymptomatic diabetic population (27). In addition, many patients with diabetes, especially those with obesity, peripheral vascular disease, or neuropathy, are unable to perform adequate exercise to provide useful end points. The sensitivity and specificity of stress (exercise or pharmacological) echocardiography seem similar to SPECT (28), and recent data obtained in patients undergoing contrast echocardiography are promising (29), although reproducibility and quantification of echocardiographic approaches might be less developed than with SPECT. The value of other noninvasive imaging modalities (such as magnetic resonance imaging, electron beam computed tomography [EBCT], and multi-slice computed tomography [MSCT]) has not been explored extensively in asymptomatic diabetic patients.

Proposed algorithm for risk stratification in asymptomatic diabetic patients. Current guidelines and reports from European and U.S. expert societies in cardiovascular medicine recognize the potential utility of MPS in risk stratification of diabetic patients but do not widely recommend its use in patients without symptoms of CAD (1,2,30–32). Rather, these documents tend to concentrate on patients presenting with evidence of CAD. Given the rapid advances in the understanding of the extent and prognostic importance of the problem of silent ischemia in the diabetic population, extension of these guidelines to address these developments might be considered.

On the basis of the emerging evidence in published reports, a potential algorithm for risk stratification of asymptomatic diabetic patients could be proposed (Fig. 3), although much more data are needed before a definitive algorithm can be developed and implemented in the clinical setting. Cardiovascular risk scoring (e.g., with the well-known risk engines derived from the Framingham Study or the UK Prospective Diabetes Study) is used to identify asymptomatic diabetic patients at low risk, who could be followed up conservatively with risk factor modification. Of note, patients with an abnormal ECG indicating previous infarction or ischemia should be referred for stress testing according to the Guidelines of the American Diabetes Association (32). Indeed, it was recently demonstrated that the presence of Q waves on the ECG was highly predictive of a severely abnormal MPS (16).

![Figure 2](756 Bax et al. Diagnosing Silent Ischemia in Type 2 Diabetes JACC Vol. 48, No. 4, 2006 August 15, 2006:754–60)

**Figure 2.** Prevalence and characteristics of abnormal single-photon emission computed tomography scans in diabetic patients without evidence of coronary artery disease: data from the DIAD (Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics) study. On the basis of data presented by Wackers et al. (10).
ISSUES OF FUTURE RESEARCH

Many issues are currently unclear in the evaluation of asymptomatic diabetic patients for CAD. In this viewpoint,

Patients with moderate to high risk (on the basis of cardiovascular risk scoring) might be referred for MPS. On the basis of the extent and severity of perfusion abnormalities, additional evaluation, treatment, and follow-up could be planned. Patients with mild perfusion abnormalities could be treated conservatively with risk factor modification, aggressive medical therapy, and follow-up MPS. It is currently unclear how frequent follow-up MPS should be performed, but the available data suggest that the warranty period of a normal MPS in patients with diabetes is in the range of 1 to 3 years; a follow-up MPS could be proposed at 2-year intervals, but more data are needed before a definitive interval can be pointed out. Patients with moderate to severe perfusion abnormalities might need to be referred for invasive coronary angiography with intervention if needed. Another issue that is unclear at present is the precise definitions of the extent and severity of perfusion abnormalities enabling the categorization of the patients as indicated in the preceding section.

Table 1. Evidence for Silent Ischemia in Diabetic Patients Without Symptoms of CAD

<table>
<thead>
<tr>
<th>Reference</th>
<th>n*</th>
<th>Patient Characteristics</th>
<th>MPS Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>10†</td>
<td>1,123</td>
<td>Type 2 DM without clinically apparent CAD</td>
<td>Gated 99mTc sestamibi SPECT + exercise or dipyridamole (n = 158, 100%)</td>
<td>Abnormal MPS scans in 21% (16% of perfusion abnormalities involved &gt;5% of the left ventricle)</td>
</tr>
<tr>
<td>11</td>
<td>56</td>
<td>Type 1 or 2 DM with ≥3 CV risk factors</td>
<td>201TI SPECT + exercise (n = 56, 100%)</td>
<td>Abnormal MPS scans in 21% (significant coronary lesions in 16%)</td>
</tr>
<tr>
<td>12</td>
<td>180</td>
<td>DM patients with multiple CV risk factors</td>
<td>99mTc sestamibi SPECT + exercise or dipyridamole (n = 180, 100%)</td>
<td>Abnormal MPS scans in 26%</td>
</tr>
<tr>
<td>13</td>
<td>1,738</td>
<td>DM patients without clinically apparent CAD</td>
<td>201TI or 99mTc sestamibi SPECT + exercise or dipyridamole (n = 1,738, 100%)</td>
<td>Abnormal MPS scans in 59% (20% were considered to represent high CV risk)</td>
</tr>
<tr>
<td>14</td>
<td>1,737</td>
<td>826 were asymptomatic, 151 had shortness of breath, 760 had angina pectoris</td>
<td>Rest 201TI SPECT + exercise or adenosine (n = 1,737, 100%)</td>
<td>Abnormal MPS scans in 39% of the asymptomatic group; 51% of patients short of breath; 44% of the angina group</td>
</tr>
<tr>
<td>15</td>
<td>158</td>
<td>DM patients mostly asymptomatic for CAD (78%) with ≥2 CV risk factors</td>
<td>201TI SPECT + exercise or dipyridamole (n = 158, 100%)</td>
<td>Abnormal MPS scans in 56%</td>
</tr>
<tr>
<td>16</td>
<td>1,427</td>
<td>DM patients without clinically apparent CAD</td>
<td>201TI or 99mTc sestamibi SPECT + exercise, adenosine, dobutamine, or dipyridamole (n = 1,427, 100%)</td>
<td>Abnormal MPS scans in 58% (20% were considered to represent high CV risk)</td>
</tr>
<tr>
<td>17</td>
<td>1,323</td>
<td>DM patients without clinically apparent CAD</td>
<td>Stress exercise 201TI scintigraphy in patients with positive exercise tests (n = 91, 9%)</td>
<td>Positive MPS in 95 of 91 (93%) patients with positive exercise test; 9.1% had evidence of SMI overall (exercise or MPS)</td>
</tr>
<tr>
<td>18</td>
<td>120</td>
<td>No history of MI or angina</td>
<td>Dipyridamole stress 201TI scintigraphy (n = 75, 63%)</td>
<td>Evidence of silent myocardial ischemia in 30.7%</td>
</tr>
<tr>
<td>19</td>
<td>203</td>
<td>DM patients without clinically apparent CAD</td>
<td>Stress exercise or dipyridamole 201TI scintigraphy in patients with a positive exercise test (n = 105, 52%)</td>
<td>Evidence of SMI in 15.7% (exercise or MPS)</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>DM patients with peripheral vascular disease but no evidence of CAD</td>
<td>Dipyridamole 201TI scintigraphy (n = 30, 100%)</td>
<td>Abnormal scans suggesting SMI were found in 47%, 37% displayed evidence of prior silent MI</td>
</tr>
<tr>
<td>21</td>
<td>136</td>
<td>DM asymptomatic for CAD or age- and gender-matched control subjects</td>
<td>201TI scintigraphy (n = 136, 100%)</td>
<td>23% reported positive MPS scan</td>
</tr>
<tr>
<td>22</td>
<td>58</td>
<td>DM patients without clinically apparent CAD</td>
<td>Exercise 201TI scintigraphy (n = 58, 100%)</td>
<td>17% displayed evidence of SMI on scintigraphy</td>
</tr>
<tr>
<td>23</td>
<td>925</td>
<td>DM patients without clinically apparent CAD</td>
<td>Exercise 201TI scintigraphy (n = 112, 12%)</td>
<td>Abnormal MPS scan found in 59 of 112 (53%) patients with abnormal or unequivocal exercise stress tests (patients with negative stress tests did not receive MPS)</td>
</tr>
<tr>
<td>24</td>
<td>826</td>
<td>DM asymptomatic for CAD</td>
<td>201TI or 99mTc sestamibi SPECT + exercise, adenosine, dobutamine, or dipyridamole (n = 826, 100%)</td>
<td>All had abnormal MPS by inclusion, and 32% had high-risk MPS</td>
</tr>
</tbody>
</table>

*Overall study populations (the number of patients undergoing myocardial perfusion scintigraphy [MPS] is indicated in column 4); †Detection of Silent Myocardial Ischemia in Asymptomatic Diabetes (DIAD) study (see text).

CAD = coronary artery disease; CV = cardiovascular; DM = diabetes mellitus; MI = myocardial infarction; SMI = silent myocardial ischemia; SPECT = single photon emission computed tomography.
MPS is proposed for screening for asymptomatic patients with diabetes. However, frequently patients with atherosclerosis might not necessarily have already developed ischemia. At present, atherosclerosis can be assessed noninvasively by EBCT. This technique permits accurate detection of calcifications in the coronary arteries, reflecting atherosclerotic degeneration (33). In the general population (including patients with diabetes), various studies have shown that (cardiovascular) mortality is related to the severity of the extent of coronary artery calcium (34). The relationship between atherosclerosis on EBCT and perfusion abnormalities on MPS was highlighted recently by Berman et al. (35). The authors demonstrated on the one hand that ischemia on MPS increased in parallel to increasing coronary artery calcium scores but on the other hand that patients with a normal MPS frequently already have extensive atherosclerosis according to EBCT (35). Alternatively, patients with minimal coronary artery calcium (scores <400) infrequently have ischemia on MPS.

Not much information is currently available on the value of EBCT for evaluation of asymptomatic diabetic patients. Because EBCT (or MSCT) provides identification of CAD at an earlier stage than MPS, it might be of particular interest to consider screening for CAD in asymptomatic diabetic patients with EBCT and MPS sequentially, as recently proposed by Anand et al. (36). The authors performed a stepwise screening: patients were first screened for atherosclerosis by EBCT, followed by screening for ischemia by MPS in patients with extensive coronary artery calcium. With this approach, Anand et al. (36) demonstrated that MPS was virtually never abnormal in patients without substantial atherosclerosis on EBCT, whereas 48% of patients with substantial atherosclerosis on EBCT had an abnormal MPS. This stepwise evaluation could potentially further refine management of asymptomatic patients. In patients with atherosclerosis on EBCT who do not (yet) have ischemia on MPS risk factor modification, medical therapy and monitoring might be indicated, whereas patients with atherosclerosis on EBCT and ischemia should be referred for invasive coronary angiography and intervention if needed. Before implementation of this approach, several issues need to be resolved. First, the stepwise approach might be of interest, particularly from a cost-effectiveness point-of-view, and might avoid the use of MPS in all patients but rather allow a pre-selection for MPS by a relatively inexpensive technique (EBCT). In that case, the algorithm proposed in Figure 3 could be adapted, and an entrance criterion in addition to age ≥40 years could be the presence of atherosclerosis on EBCT (or MSCT). However, what cutoff level on EBCT or MSCT (which calcium score?) should be used to refer patients for SPECT? Second, what extent of ischemia is needed on MPS to refer a patient for invasive evaluation?

In asymptomatic diabetic patients, information on this issue is not available. However, Hachamovitch et al. (37) have demonstrated in the general population that patients with 10% of the myocardium-exhibiting ischemia benefit more from revascularization as compared with medical therapy in terms of short-term survival.

Third, if a patient is managed conservatively, when is repeat testing indicated? The issue of repeat testing is an important one. It is well known that a normal MPS study has an excellent prognosis and that this prognostic value is maintained over many years (25). However, it has also been shown that in patients with diabetes and a normal MPS, events occur after 1 to 3 years (38,39). It has been suggested that in patients with diabetes the process of atherosclerosis is characterized by a faster progress as compared with nondiabetic patients. At present, the warranty period of a normal scan in patients with diabetes might be 1 to 3 years, but further research is needed to define the optimal warranty period of a normal MPS, both in symptomatic and asymptomatic patients. This will eventually allow for a precise definition of how frequently follow-up MPS is needed in these patients.

The next issue that needs to be addressed is the following: the clinical benefit from screening on patient outcome remains to be proven. At present, no solid outcome studies have been presented demonstrating that implementation of screening for ischemia will alter patient outcome. This information will eventually be provided by the DIAD study (10). However, recent data from the Mayo Clinic provide some evidence concerning the value of SPECT in relation to outcome in asymptomatic diabetic patients. Sorajja et al. (24) evaluated 826 asymptomatic diabetic patients without known CAD with abnormal MPS (261, or 32%, had a high-risk SPECT study). Revascularization (either coronary artery bypass surgery or percutaneous coronary intervention) was performed in 54 of 261 patients with a high-risk SPECT study and was independently associated with improved survival. These are the first (nonrandomized) data indicating that SPECT findings in asymptomatic patients influence outcome, but data from large randomized trials (e.g., the DIAD study) are needed to confirm these findings.
Finally, considering the large population of asymptomatic diabetic patients, the cost-effectiveness of screening is an important issue; before implementation of any form of screening, large outcome studies are needed, followed by analyses on the cost/benefit ratio.

CONCLUSIONS

Recent studies highlight the prevalence of CAD and silent ischemia in asymptomatic diabetic patients. Considering the high cardiovascular event rate and mortality in diabetic patients, risk stratification should be optimized in this exponentially expanding population. Noninvasive imaging might be of particular value in this regard, as emerging studies with MPS have recently indicated. In particular, the DIAD trial has demonstrated the potential of MPS for evaluation of asymptomatic diabetic patients. Management guidelines in cardiovascular medicine might be updated to reflect the recent advances in this field, with potential use of MPS for risk stratification of asymptomatic diabetic patients. Still, many issues need to be resolved before screening of asymptomatic diabetic patients for CAD and silent ischemia can be implemented in clinical management.

Reprint requests and correspondence: Dr. Jeroen J. Bax, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: jbax@knoware.nl.

REFERENCES


APPENDIX

For a list of the contributors to the Global Dialogue on the Evaluation of Cardiovascular Risk in Patients With Diabetes, please see the online version of this article.