Detection of Silent Coronary Artery Disease in Asymptomatic Patients with Type 2 Diabetes Mellitus

a report by

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Diabetes—A Coronary Artery Disease Equivalent

Diabetes mellitus is an important risk factor for cardiovascular disease. Moreover, cardiovascular diseases are the leading causes of morbidity and mortality in patients with type 2 diabetes mellitus. The high mortality rate is partly due to the diabetic state per se, above and beyond the clustering of other risk factors such as hypertension, dyslipidemia, and obesity. Over the last decade, the overall mortality from cardiovascular disease in the general population has decreased by about 20%. In contrast, mortality in patients with diabetes has increased with a similar percentage. As mentioned above, cardiovascular events account for the majority of the deaths.

Diabetes is considered a ‘coronary artery disease (CAD) equivalent’ because patients with diabetes without known CAD have a similar cardiac event rate to patients without diabetes who had a prior myocardial infarction (MI). In the US, the direct medical cost of diabetes mellitus to society is about US$92 billion per year. Most of these costs are due to cardiovascular complications of diabetes.

The conundrum of CAD in conjunction with type 2 diabetes is that it is often silent and when it becomes clinically manifest the disease is often in an advanced stage. Thus, there is justification to consider appropriate means of screening for CAD in asymptomatic patients with diabetes in order to detect the disease before it strikes.

Prevalence of Silent CAD

In 1998, the American Diabetes Association (ADA) proposed guidelines for screening of asymptomatic patients with diabetes (see Table 1). It should be realized that these guidelines represented the best medical judgment of an expert panel and were not based on evidence in the literature.

For example, no credible data existed on the prevalence of silent CAD in asymptomatic diabetic patients. The prevalence of silent myocardial ischemia, as evidenced by abnormal stress myocardial perfusion imaging, was reported to be as high as 58% and as low as 7%. Most studies in the literature were flawed by selection bias.

Three types of studies existed.

- Retrospective database analyses of patients who were referred for stress testing because of typical or atypical symptoms – in general, these studies had no reliable data about clinical aspects of diabetes, such as duration and treatment. These analyses

Table 1: ADA Consensus Guidelines for Cardiac Stress Testing in Diabetic Patients

Testing for CAD is warranted in patients with the following:
- Typical or atypical cardiac symptoms
- Resting electrocardiogram (ECG) suggestive of ischemia or infarction
- Peripheral or carotid occlusive arterial disease
- Sedentary lifestyle, age ≥35 years, and plans to begin vigorous exercise program

Asymptomatic individuals:
- Two or more of the risk factors listed below (a–e) in addition to diabetes:
  a) Total cholesterol ≥240mg/dl, LDL cholesterol ≥160mg/dl, or HDL cholesterol ≤35mg/dl
  b) Blood pressure >140/90mmHg
  c) Smoking
  d) Family history of premature CAD
  e) Positive micro/macroproteinuria

Table 2: Inclusion Criteria for the DIAD Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Age</td>
<td>50–75 years</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>No history of infection</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>No history of infection</td>
</tr>
<tr>
<td>Clinical indication for stress testing</td>
<td>No clinical indication for stress testing</td>
</tr>
<tr>
<td>Cardiac stress testing or coronary angiography</td>
<td>No cardiac stress testing or coronary angiography in three years before enrollment</td>
</tr>
<tr>
<td>Normal resting electrocardiogram (ECG)</td>
<td>Normal resting electrocardiogram (ECG)</td>
</tr>
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</table>

Type 2 diabetes mellitus, onset ≥30yrs, no history of ketoacidosis
Age 50–75 years
No history of coronary artery disease, no angina pectoris
No history of congestive heart failure
No clinical indication for stress testing
No cardiac stress testing or coronary angiography in three years before enrollment
Normal resting electrocardiogram (ECG)

usually revealed a high (~58%) prevalence of myocardial ischemia.
- Retrospective database analyses of patients who were likely asymptomatic and mostly referred for pre-operative risk stratification – this category generally showed a lower prevalence of ischemia in the range of 26% to 36%.11-13
- Prospectively designed studies in truly asymptomatic patients with diabetes14-15 – these studies revealed the lowest prevalence of silent ischemia but with a relatively wide range from 21% to 7%. The latter studies were often open to critique because of inconsistencies in stress testing methodology, which potentially resulted in underestimation of disease.

The Detection of Ischemia in Asymptomatic Diabetics Study

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study was designed to prospectively determine the prevalence of silent myocardial ischemia in truly asymptomatic patients.14 Precise determination of the prevalence of silent ischemia in asymptomatic diabetics is of clinical relevance. It is generally agreed that screening is not justified in patient cohorts with low (e.g. <10%) prevalence of disease. If the overall prevalence of disease is low, a relatively high number of false positive results can be anticipated. Screening yields optimal results in populations with an intermediate pre-test likelihood of disease, ranging from 20% to 80%. In the DIAD study, special attention was given to ensuring that enrolled patients were truly asymptomatic (see Table 2). All patients completed the Rose Questionnaire to exclude angina or angina-like symptoms. A total of 1,123 patients were enrolled in the DIAD study between 2000 and 2002 in 14 clinical centers in the US and Canada. Patients were randomized to testing (n=561) or no-testing (n=562). Testing consisted of adenosine pharmacologic vasodilator stress in conjunction with Te-99m Sestamibi single-photon-emission computed tomography (SPECT) imaging, which was ultimately performed in 522 of randomized patients. Pharmacological stress was chosen because it could be anticipated that many patients with diabetes would not be able to perform adequate physical exercise. Indeed, only about half of the patients in the

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DIAD study could not even perform low-level exercise in conjunction with adenosine infusion. As mentioned, enrollment was completed in 2002, and all 1,123 patients will be followed for five years for the occurrence of cardiac events. Follow-up will be complete in September 2007. Patients who were randomized to 'no testing' will also have five-year follow-up and represent a 'natural history' arm.

Of the 522 patients randomized to testing with adenosine-Tc-99m Sestamibi SPECT, 113 (22%) had abnormal results suggestive of silent CAD. Of these, 73 patients (16% of the entire cohort) had regional myocardial perfusion abnormalities on SPECT imaging. The remaining patients (6%) had non-perfusion abnormalities, predominantly consisting of ischemic ST segment changes during the adenosine infusion. Of the patients with regional myocardial perfusion defects, 44% (6% of the screened cohort) were moderate to large in size, abnormalities that would warrant further evaluation by a cardiologist and consideration of coronary angiography.

**Predictors of Silent CAD**

Thus, the DIAD study, which is the first large prospective study in asymptomatic patients with diabetes, revealed a prevalence of silent myocardial ischemia of 22%. This intermediate prevalence would justify systematic screening of asymptomatic patients with diabetes. However, as there are more than 18 million persons with diabetes in the US alone, the costs of such screening would be prohibitive. It was therefore important to explore multivariate predictors for abnormal SPECT imaging. In multivariate logistic regression, the main predictors for moderate to large myocardial perfusion abnormalities were evidence of cardiac autonomic dysfunction (blunted heart rate response to the Valsalva maneuver) (OR 5.6), diabetes duration (OR 5.2), and male gender (OR 2.5). Traditional risk factors for CAD, such as hypertension, dyslipidemia, smoking, and family history for CAD, were not predictive for myocardial perfusion abnormalities. In fact, if the ADA consensus statement guidelines for testing had been followed, i.e. testing only asymptomatic diabetic patients with >2 additional risk factors, 41% of abnormal SPECT studies would have been missed. Other demographic characteristics, diabetes complications, and clinical and laboratory values were not predictive of abnormal studies. Specifically, C-reactive protein, hyperhomocysteinemia, plasminogen activator inhibitor-1, hemoglobin A1C, and retinopathy were not statistically associated with evidence for silent CAD. Of note, the strongest statistical predictor, blunted heart rate response to Valsalva maneuver, had a positive predictive value of only 19%, which makes it of limited practical value (even though the negative predictive value was high at 95%). Ischemic ST-segment depression during adenosine infusion was significantly associated with female gender (OR 3.4). The key conclusions of the DIAD study are listed below.

- More than one in five of asymptomatic patients with type 2 diabetes have evidence of silent myocardial ischemia.
- In approximately one in 16 patients, perfusion defects are sufficiently large to warrant further cardiologic evaluation.
- Emerging and traditional risk factors do not help the clinician in determining which patients are at greatest risk for an abnormal SPECT study.
- The presence of cardiac autonomic dysfunction increases the risk of silent ischemia.

It is important to consider the general applicability of the findings of the DIAD study. The DIAD findings apply to truly asymptomatic patients. Patients with abnormal resting electrocardiogram (ECG) were excluded from the DIAD study. As in any larger randomized trial, unintended selection bias may occur: because of the process of targeted recruitment and informed consent, generally ‘healthier’ patients are enrolled and their outcome may be better than that of patients not enrolled. In the ‘real world’ of clinical practice the prevalence of silent ischemia may be somewhat higher.

**Coronary Artery Calcium Scoring for Detecting Patients at Higher Risk**

The true practical implications of the findings of the DIAD will become apparent when five-year follow-up is complete in 2007. Nevertheless, it will be important to explore other ways for identifying higher risk asymptomatic diabetic patients in whom the yield of screening (i.e. number of abnormal test results) will be more (cost-) effective. One method was recently proposed by Anand et al.\(^{15}\) These investigators also evaluated the presence of silent myocardial ischemia in asymptomatic patients with type 2 diabetes. However, they applied a prescreening step involving coronary calcium scoring (CAC) with electron beam CT scanners. Previous studies have shown that if CAC is

<100 Agatston units (AU), the likelihood of abnormal myocardial perfusion imaging is low. Accordingly, Anand et al. performed stress myocardial perfusion imaging SPECT only in asymptomatic diabetic patients with CAC >100 AU. The overall prevalence of silent myocardial ischemia in this selected cohort was 39%. (Extrapolated to their total initial population the overall prevalence would amount to about 13%.) Importantly, they observed an increasing incidence of abnormal myocardial perfusion images (i.e. silent ischemia) with increasing CAC scores: 60% in patients with >400 AU and 71% in patients with >1,000 AU. Whereas in DIAD only 6% of the cohort had moderate to large myocardial perfusion abnormalities, this occurred in 31.5% of the patients in the study by Anand et al. after prescreening with electron beam computed tomography (EBCT).

**Summary**

The literature until recently was ambiguous concerning the true prevalence of silent CAD in asymptomatic patients with type 2 diabetes mellitus. Recent prospective studies suggested that the overall prevalence is about 20% in patients aged 50 to 75 years. Abnormal SPECT studies were not reliably predicted by clinical and biochemical variables, nor traditional clinical risk factors. The observed prevalence was not as high as initially reported, but high enough to justify systematic screening for CAD. Because of the large number of patients with diabetes it is important to identify patients at greatest risk. Prescreening for CAC by CT scanning, followed by stress myocardial perfusion imaging has the promise for the effective detection of silent CAD before it strikes patients with diabetes (see Figure 1).