Impact of inducible ischemia by stress SPECT in cardiac risk assessment in diabetic patients: Rationale and design of a prospective, multicenter trial

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Background. **A prospective, multicenter trial has been designed to evaluate the impact of inducible ischemia by stress single photon emission computed tomography (SPECT) in diabetic patients and to define the role of SPECT in assessing the cardiac risk in such patients. This report presents the details and implications of the Impact of Inducible Ischemia by Stress SPECT (IDIS) trial design.**

Methods and Results. **Between January 2002 and September 2005, 1006 consecutive patients (649 men and 357 women; mean age, 63 ± 9 years) with at least a 5-year history of type 2 diabetes mellitus were enrolled. All patients underwent stress-rest sestamibi SPECT imaging with physical exercise (n = 573) or dipyridamole (n = 433). SPECT studies will be analyzed by use of a 17-segment scoring system to calculate left ventricular ejection fraction, summed stress score, summed rest score, and summed difference score. The SPECT study will be considered abnormal if the summed stress score is 3 or greater. Patients with abnormal studies will be considered to have ischemia if the summed difference score is 2 or greater.**

Conclusion. **The results of this trial should help to define the role of SPECT in assessing cardiac risk in diabetic patients. Furthermore, this trial will prospectively evaluate subsequent patient outcome during long-term follow-up. (J Nucl Cardiol 2008;15:100-4.)**

Key Words: Inducible ischemia • diabetes mellitus • single photon emission computed tomography imaging

Coronary artery disease (CAD) is the leading cause of morbidity and death in patients with diabetes mellitus.[1] Furthermore, diabetic patients have a high prevalence of silent myocardial ischemia that is associated with poor outcome.[2,3] The frequent occurrence of silent events in diabetic patients provides support for disease detection in its preclinical stages. The introduction of atherosclerosis imaging modalities, such as computed tomography for coronary artery calcium, may enhance risk stratification, particularly in patients with uncomplicated diabetes and those who are asymptomatic.[4,5] The value of myocardial perfusion imaging with single photon emission computed tomography (SPECT) in the evaluation of diabetic patients has been extensively investigated.[6-9] Although the prognostic value of inducible myocardial ischemia in diabetic patients with known CAD and the prevalence of occult disease in an asymptomatic diabetic population have been evaluated,[10-13] how to correctly identify the diabetic patients in need of testing remains to be defined.[14] The American Diabetes Association guidelines recommend testing of patients with symptoms suspicious for CAD and those with no symptoms and 2 or more risk factors.[15] However, it has recently been demonstrated by the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study that the rate of high-risk SPECT scans is similar in patients with 2 or more risk factors and those with less than 2 risk factors.[13] Therefore in the DIAD study selecting only patients who met the American Diabetes Association guidelines would have failed to identify 41% of patients with silent

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ischemia.[13] The DIAD study assessed the prevalence and clinical predictors of silent myocardial ischemia in asymptomatic patients with type 2 diabetes mellitus.[13] To date, several well-powered studies have demonstrated that stress myocardial perfusion SPECT yields incremental prognostic value over pre-SPECT data, enhances risk stratification, and when applied to appropriate patient populations, reduces costs, in part by decreasing the need for additional invasive evaluation.[16-21] We hypothesized that a Bayesian approach could be more effective in identifying which diabetic patients should undergo myocardial perfusion imaging. Thus in patients with diabetes the use of an aggregate score incorporating and weighting multiple risk factors could be superior to an approach based on the number of risk factors to define the patients' risk.[21,22] To classify patients in different risk subsets, the likelihood of CAD can be calculated by CADENZA (Advanced Heuristics, Bainbridge Island, Wash).[23] In addition, evaluating how the risk changes over time as a function of the patients' characteristics and test results might help to guide therapeutic decision making and to determine the timing for retesting patients during follow-up.[24]

It is within this context that the Impact of Inducible Ischemia by Stress SPECT (IDIS) trial was conceived. IDIS is a prospective, multicenter trial designed (1) to evaluate the prevalence of inducible ischemia by technetium 99m sestamibi SPECT in symptomatic and asymptomatic diabetic patients with different prescan likelihoods of ischemia, (2) to determine the number of patients who were reclassified with respect to their risk of adverse outcomes by the addition of SPECT data to pre-SPECT information, and (3) to prospectively evaluate subsequent patient outcome during long-term follow-up. In particular, the temporal characteristics of cardiac risk in diabetic patients undergoing stress SPECT will be assessed by use of a parametric survival model, estimating time to predefined risk and level of risk at specific time intervals during follow-up. These times might represent the warranty period before retesting diabetic patients. The purpose of this report is to discuss the details and implications of the IDIS trial design.

METHODS

The organizational structure of the IDIS trial, including principal investigators and co-investigators at participating centers and by-center recruitment, is contained in the Appendix.

Study Population

The study population includes consecutive patients with at least a 5-year history of type 2 diabetes mellitus referred for myocardial stress perfusion imaging. Patients have been excluded from study enrollment for the following: (1) recurrent chest pain unresponsive to anti-ischemic medications; (2) recent acute coronary syndrome, stroke, or transient ischemic attack (in the last 3 months); (3) uncompensated congestive heart failure (New York Heart Association class III or IV) or recent admission for decompensated heart failure (in the last 3 months); (4) recent myocardial revascularization procedures (in the last 3 months); (5) an absolute contraindication to dipyridamole in patients unable to exercise, defined as ongoing wheezing, greater than first-degree atrioventricular block without a pacemaker, systolic blood pressure lower than 90 mm Hg, or recent (<24 hours) use of dipyridamole or xanthines (eg, aminophylline and caffeine); and (6) a concomitant noncardiac illness that would limit follow-up for at least 1 year. Also excluded were premenopausal women, unless it could be documented that they were not pregnant or lactating, and any patients unable to provide signed informed consent. The ethics committees of the different institutions approved the protocol, and all patients provided informed consent.

Study Protocol

Stress test. All patients underwent stress-rest cardiac gated SPECT imaging by physical exercise or dipyridamole stress test. In all patients β-blocking medications and calcium antagonists were withheld for 48 hours and long-acting nitrates were withheld for 12 hours before testing. For patients undergoing exercise testing, symptom-limited treadmill standardized protocols were performed, with monitoring of heart rate and rhythm, blood pressure, and electrocardiography. Test endpoints were as follows: achievement of 85% of the maximal predicted heart rate, horizontal or downsloping ST-segment depression greater than 2 mm, ST-segment elevation greater than 1 mm, moderate to severe angina, decrease in systolic blood pressure by greater than 20 mm Hg, blood pressure greater than 230 mm Hg/120 mm Hg, dizziness, or clinically important cardiac arrhythmia. For dipyridamole stress testing, patients were instructed not to consume products containing caffeine for 24 hours before the test. Dipyridamole was infused intravenously at a dose of 0.56 $mg \cdot kg^{-1}$ body weight given in a period of 4 minutes. A dose of 100 mg of aminophylline was administered intravenously in the event of chest pain or other symptoms or after significant ST depression.

At peak exercise or at 4 minutes after completion of the dipyridamole infusion, a bolus of 370 MBq Tc-99m sestamibi was intravenously injected. Patients continued to exercise for an additional 60 seconds after tracer injection. For both types of stress, heart rate, blood pressure, and 12-lead electrocardiographic (ECG) data were recorded at rest, at the end of each stress stage, at peak stress, and in the delay phases at rest. The maximal degree of ST-segment change at 80 milliseconds after the J point on the electrocardiogram was measured and classified as horizontal, downsloping, or upsloping. Four hours after the conclusion of stress testing, 1110 MBq Tc-99m sestamibi was injected at rest. SPECT was performed 60 minutes after tracer injection for both stress and rest studies.

Image acquisition. Gated SPECT acquisition was performed according to the recommendations of the American