

Assessing Cardiovascular Risk in Asymptomatic Diabetes: The DIAD Study

Reviewed by Elizabeth Anne Fasy, MD, CDE

STUDY

Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE, the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators: Detection of silent myocardial ischemia in asymptomatic diabetic subjects. *Diabetes Care* 27:1954–1961, 2004

SUMMARY

Objective. To determine the prevalence and severity of inducible myocardial ischemia in asymptomatic patients with type 2 diabetes, aged 50–75 years, with normal electrocardiograms (ECGs), using adenosine-stress single photon emission-computed tomography (SPECT) myocardial perfusion imaging along with clinical and laboratory predictors of abnormal test results.

Design. A randomized, open, prospective, clinical trial following patients for a period of 5 years to determine the prevalence and predictors of silent myocardial ischemia (SMI) in people with type 2 diabetes with no history of known coronary artery disease (CAD) and no cardiac symptoms. Approximately half of the subjects were randomized to adenosine-stress perfusion imaging at baseline and follow-up, and half were randomized to follow-up without imaging screening.

End points. Prevalence, severity, and predictors of patients with SMI as defined by perfusion abnormalities on pharmacological stress perfusion imaging (adenosine-sestamibi SPECT).

Results. Of 1,123 patients with type 2 diabetes aged 50–75 years without known or suspected CAD, 113 (22%) had silent ischemia. Eighty-three had regional myocardial perfusion abnormalities, and 30 had normal perfusion with other abnormalities. Moderate and large perfusion defects were present in 33 patients (6% of the screened cohort). Of those with perfusion abnormalities, 96% had some degree of reversibility indicative of ischemia. The strongest predictors for abnormal tests were abnormal Valsalva, male sex, and diabetes duration. Traditional cardiovascular risk factors, such as hypertension, hyperlipidemia, tobacco use, family history of premature CAD, and micro- or macroalbuminuria, as well as emerging cardiovascular risk factors such as C-reactive protein, plasminogen activator inhibitor-1, and homocysteine were not found to be predictors.

Conclusions. Silent ischemia occurs in > 20% of asymptomatic people with type 2 diabetes. Traditional and emerging risk factors were not predictors of abnormal stress tests. Cardiac autonomic dysfunction was found to be a strong predictor of abnormal stress tests, suggesting that patients with cardiac autonomic neuropathy deserve close attention. The relationship between abnormal perfusion imaging and cardiac events in asymptomatic patients should be further elucidated at the 5-year follow-up evaluation.

COMMENTARY

Diabetes has been demonstrated to increase the risk of CAD by a factor of

two to four.¹ Myocardial ischemia is a major complication in the course of diabetes, causing 75% of diabetes-related deaths. Moreover, patients with diabetes have a higher rate of sudden death and poorer outcomes after myocardial infarction.²

Because of the significant correlation between diabetes and heart disease and the higher likelihood of initial poor outcomes, it would be beneficial to know the true prevalence of CAD in this population and other associated risk factors to stratify patients with diabetes. It would also be helpful to know who, when, and with which test to screen such patients to achieve the most effective primary prevention of cardiovascular disease in this high-risk population.

Several large screening studies for SMI in diabetes have been performed demonstrating variable prevalence rates from 6.4 to 58%.^{3–5} The higher prevalence estimates are likely the result of both retrospective data in patients with documented angiographic evidence of CAD⁴ and the inclusion of individuals with abnormal ECGs and those with a high suspicion of CAD.⁵ Lower prevalence rates are likely related to the exclusion of patients with microvascular disease or the use of insulin therapy.³

In contrast, the DIAD study is a prospective trial assessing the prevalence rate of SMI using a single standardized imaging study in a population of patients with type 2 diabetes excluded only if they had any history of CAD, any symptoms that would warrant immediate stress testing, or an ECG suggestive of ischemia. Subjects in the DIAD study appear to be representative of American

middle-aged diabetic patients: 20% are from ethnic minority groups, 63% are on oral agents, 22% are on insulin or insulin plus oral agents, 56% are treated for hypertension, 47% are on cholesterol-lowering drugs, 44% are on aspirin therapy, and the average hemoglobin A_{1c} is 7.1%.

Thus, the prevalence rate of myocardial ischemia in 22% or just over one in five patients with diabetes is noteworthy. For care providers of people with diabetes, consideration of earlier screening appears tempting. However, we await outcomes data reflecting the impact of screening on cardiovascular event reduction in this asymptomatic population.

The finding that traditional risk factors were not predictive of cardiovascular disease is important because this provides data that could result in modification of the 1998 American Diabetes Association (ADA) consensus statement on CAD screening guidelines in people with diabetes.⁶ The current recommendations call for screening only those asymptomatic individuals who:

- Have evidence of peripheral or carotid occlusive arterial disease,
- Have a sedentary lifestyle, are > 35 years of age, and plan to begin a vigorous exercise program,
- Have two or more risk factors, including hyperlipidemia, hypertension, smoking, family history of premature CAD, or micro- or macroalbuminuria.

The DIAD study authors note that if this screening strategy had been used in their study population, 40% of the individuals with abnormal test results would not have been screened.⁷ This reinforces the importance of implementing intensive risk factor management in patients with diabetes and continuing to consider them at the same high risk as nondiabetic individuals with known CAD.

Although traditional risk factors and emerging risk factors were not found to be reliable predictors, evidence of car-

diac autonomic neuropathy, as defined as a lower Valsalva heart rate ratio, was associated with an abnormal stress test and moderate or large perfusion abnormalities. Cardiac autonomic neuropathy has been shown to be highly correlated with a high risk of cardiovascular events and death, but this has not always been shown to be associated with SMI.⁸ Because of this lack of a clear causal relationship between autonomic neuropathy and SMI, the recommendation to screen for cardiac autonomic neuropathy as a predictor for SMI cannot be made. We must await outcomes data to help us consider whether in-office autonomic testing will be helpful in predicting higher-risk individuals and ultimately preventing cardiac events through earlier screening.

The preliminary findings of this ongoing study enlighten caregivers of people with type 2 diabetes that SMI is present in 1 in 5 asymptomatic patients and that 1 in 16 has significant perfusion abnormalities that should warrant further evaluation with coronary angiography. The threshold to consider perfusion imaging may need to be re-evaluated, although as of yet, there are no data to suggest that expensive cardiac screening leads to better long-term outcomes. The conclusion of the DIAD study may help to elucidate this issue by comparing the outcomes of individuals in the screened versus the unscreened cohort. However, the incidence of cardiac events could potentially be too small over this 5-year time frame to give us conclusive information. Based on current clinical data, the recommendations of the American Heart Association and the ADA are to continue intensifying risk factor identification and intervention in all asymptomatic patients with diabetes.⁹

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Elizabeth Anne Fasy, MD, CDE, is an assistant professor in the Division of Endocrinology and Metabolism at the University of North Carolina School of Medicine in Chapel Hill.

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