Prognostic Value of Dobutamine-Atropine Stress Myocardial Perfusion Imaging in Patients With Diabetes

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OBJECTIVE — Exercise tolerance in patients with diabetes is frequently impaired due to noncardiac disease such as claudication and polyneuropathy. This study assesses the prognostic value of dobutamine stress myocardial perfusion imaging in patients with diabetes.

RESEARCH DESIGN AND METHODS — A total of 207 consecutive diabetic patients who were unable to undergo exercise stress testing underwent dobutamine-atropine stress myocardial perfusion imaging. Follow-up was successful in 206 of 207 (99.5%) patients. A total of 12 patients underwent early (<60 days) revascularization and were excluded from the analysis. End points during follow-up were hard cardiac events, defined as cardiac death and nonfatal myocardial infarction.

RESULTS — Abnormal myocardial perfusion was detected in 125 (64%) patients. During 4.1 ± 2.4 years of follow-up, 73 (38%) deaths occurred, 36 (49%) of which were due to cardiac causes. Nonfatal myocardial infarction occurred in 7 (4%) patients, and 45 (23%) patients underwent late coronary revascularization. Cardiac death occurred in 2 of 69 (3%) patients with normal myocardial perfusion and in 34 of 125 (27%) patients with perfusion abnormalities ($P < 0.0001$). A multivariable Cox proportional hazard model demonstrated that, in addition to clinical and stress test data, an abnormal scan had an incremental prognostic value for prediction of cardiac death (hazard ratio 7.2, 95% CI 1.7–30). The summed stress score was an important predictor of cardiac death; the hazard ratio was 1.2 (95% CI 1.07–1.34) per one-unit increment.

CONCLUSIONS — Dobutamine-atropine stress myocardial perfusion imaging provides additional prognostic information incremental to clinical data in patients with diabetes who are unable to undergo exercise stress testing.

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Diabetes is considered a major risk factor for cardiovascular disease (1–4). Coronary artery disease is a major cause of morbidity and mortality in patients with diabetes. When clinical coronary heart disease develops in patients with diabetes, the clinical outcome is worse than in patients with coronary heart disease without diabetes (5,6). Diabetic patients have higher cardiac event rates, more silent ischemia, and a higher morbidity after acute myocardial infarction than nondiabetic patients (7–10). Myocardial revascularization procedures in diabetic patients are associated with higher morbidity and mortality rates than nondiabetic patients. However, coronary artery bypass grafting may substantially improve long-term outcome in selected diabetic patients (11,12). Therefore, it is clinically important to determine the risk of cardiac events in patients with diabetes in order to select the appropriate management strategy.

Several techniques have been proposed for the prognostic stratification of diabetic patients, such as exercise stress testing, in conjunction with thallium scintigraphy or echocardiography (13–17). However, many diabetic patients are unable to undergo an exercise stress test due to the higher prevalence of stroke, peripheral vascular disease, and neuropathy (18–20). Such patients generally represent a higher risk population than patients who are able to undergo exercise stress testing, and therefore, pharmacologic stress testing may predict a greater number of cardiac events in these patients. Dobutamine-atropine stress myocardial perfusion imaging may be a useful alternative in these high-risk patients (21,22). However, the value of dobutamine-atropine stress myocardial perfusion imaging in the prognostic stratification of diabetic patients has not been previously studied. The aim of this study was to assess the incremental prognostic value of dobutamine-atropine stress myocardial perfusion imaging relative to clinical data in diabetic patients who are unable to undergo an exercise test.

RESEARCH DESIGN AND METHODS

Patient population

The study population consisted of 207 consecutive patients with diabetes who were unable to undergo an exercise test and underwent dobutamine-atropine stress myocardial perfusion imaging. These patients were included in an electronic registry that accumulated in the course of daily clinical care. The test was requested for evaluation of myocardial ischemia in all patients; 91 patients had

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Abbreviations: ^{99m}Tc, technetium-99m; SPECT, single-photon emission computed tomography; SSS, summed stress score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics*

N	194
Age (years)	61 ± 10
Male sex	116 (60)
Hypertension	110 (57)
Smoking	48 (25)
Hypercholesterolemia	64 (33)
Heart failure	51 (26)
History of myocardial infarction	82 (42)
History of myocardial revascularization	52 (27)
β-blockers	66 (34)
Calcium channel blockers	102 (53)
Type 1 diabetes	58 (30)
Duration of diabetes (years)	9 ± 10
Complications of diabetes	
Nephropathy	37 (19)
Neuropathy	31 (16)
Retinopathy	37 (19)
Peripheral atherosclerosis	34 (18)
Stroke	17 (9)

Data are means ± SE or *n* (%).

known or suspected coronary artery disease, 63 had atypical angina, and 53 had typical angina. Diabetes was defined as a fasting blood glucose level >140 mg/dl or the need for insulin or oral hypoglycemic agents. Follow-up was successful in 206 of 207 patients (99.5%). A total of 12 patients who underwent coronary revascularization within 60 days of the test were excluded from the analysis. This exclusion was based on previously published data indicating that referral to coronary revascularization in the first 60 days after nuclear testing tends to be based on the results of the scan and that referral to revascularization >60 days after nuclear testing tends to be based on worsening of the patient's clinical status (23). Data from the remaining 194 patients are reported. All patients gave informed consent before testing. The medical ethics committee of the hospital approved the study protocol.

Clinical data

Before the test, a structured interview was performed and a clinical history was obtained, including assessment of cardiac risk factors. Hypertension was defined as blood pressure ≥140/90 mmHg or need for antihypertensive medication. Hypercholesterolemia was defined as total cholesterol level ≥6.4 mmol/l or need for lipid-lowering medication.

The type and duration of diabetes, as well as the presence of diabetic complications at baseline, including nephropathy, neuropathy, stroke, retinopathy, and peripheral atherosclerosis, were assessed by review of hospital records or contacting the patient's treating physician. Nephropathy was defined as a serum creatinine concentration >250 μmol/l, urinary albumin excretion rate in an overnight specimen >200 μg/min on more than one consecutive occasion, or the need for dialysis or renal transplantation. Stroke was defined as a sudden neurologic deficit that persisted for >24 h and was evidenced by a lesion in the expected site of injury by computed tomography or magnetic resonance imaging when available. Diabetic retinopathy was assessed by experienced ophthalmologists via ophthalmoscopy with pupil dilatation and/or retinal photography. Peripheral atherosclerosis was defined as the need for peripheral bypass surgery or amputation of at least one digit.

Dobutamine stress protocol

Dobutamine-atropine stress testing was performed according to a standard protocol as previously reported (24). Dobutamine was administered intravenously, starting at a dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min, increasing by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 3 min, up to a maximum dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If the test end point was not reached at a dobutamine dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, atropine (≤1 mg) was administered intravenously. Blood pressure and heart rate were monitored and electrocardiography was performed constantly. Test end points included the following: achievement of target heart rate (85% of maximum age- and sex-predicted heart rate), horizontal or downsloping ST-segment depression >2 mm at an interval of 80 ms after the J-point compared with baseline, ST-segment elevation >1 mm in patients without previous myocardial infarction, severe angina, decrease in systolic blood pressure >40 mmHg, blood pressure >240/120 mmHg, or significant cardiac arrhythmia. Metoprolol was available for administration to reverse the adverse effects of dobutamine/atropine.

Myocardial perfusion imaging

Approximately 1 min before the termination of the dobutamine-atropine stress test, an intravenous dose of 370 MBq of technetium-99m (^{99m}Tc)-sestamibi (in 69 patients) or ^{99m}Tc-tetrofosmin (in 125 patients) was injected. For resting studies, 370 MBq of the same tracer was injected at least 24 h after the stress test. Image acquisition was performed with a commercially available single-photon emission computed tomography (SPECT) camera system (Orbiter camera; Siemens, Iselin, NJ; or Picker Prism 3000XP camera; Picker, Cleveland, OH). For each study, six oblique (short axis) slices from the apex to the base and three sagittal (vertical long axis) slices were defined. Each of the six short-axis slices was divided into eight equal segments. The septal part of the two basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. Therefore, a total of 47 segments were identified (3 long-axis and 44 short-axis). The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side-by-side by two experienced observers who were unaware of the patients' clinical data. In case of disagreement, a majority decision was achieved by a third observer. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥2 contiguous segments or slices in the 47-segment model. A fixed perfusion defect was defined as a perfusion defect on stress images in two or more contiguous segments or slices that persisted on rest images in the 47-segment model. An abnormal study was considered in the presence of a fixed and/or reversible perfusion defect. To assess the severity of perfusion abnormalities, the left ventricular myocardium was divided into six segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical. Each of the six major left ventricular segments was scored using a four-point scoring system (0 = normal, 1 = slightly reduced, 2 = moderately reduced, and 3 = severely reduced or absent uptake). The perfusion defect score was derived by the summation of the score of the six myocardial segments at stress (summed stress score [SSS]).

Data collection and end points

Follow-up data were obtained by reviewing hospital records and/or by contacting

Table 2—*Predictors of cardiac death*

	Univariate	Multivariate analysis		
		Clinical data	Model I	Model II
Clinical characteristics				
Age*	1.07 (1.03–1.12)	1.08 (1.03–1.12)	1.08 (1.03–1.13)	1.08 (1.04–1.13)
Male sex	0.8 (0.4–1.6)	NS	NS	NS
Previous myocardial infarction	1.8 (0.9–3.5)	NS	NS	NS
Hypertension	0.6 (0.3–1.2)	NS	NS	NS
Hypercholesterolemia	1.1 (0.6–2.2)	NS	NS	NS
Smoking	1.2 (0.6–2.5)	NS	NS	NS
Heart failure	3.8 (2.0–7.4)	3.1 (1.6–6.0)	2.5 (1.3–4.9)	2.2 (1.1–4.4)
Type 1 diabetes	1.8 (0.8–3.9)	NS	NS	NS
Duration of diabetes (years)*	1.05 (1.01–1.08)	NS	NS	NS
Diabetic complications				
Nephropathy	1.9 (0.8–4.3)	NS	NS	NS
Neuropathy	0.8 (0.3–2.3)	NS	NS	NS
Retinopathy	1.3 (0.5–3.1)	NS	NS	NS
Peripheral atherosclerosis	3.7 (1.6–8.4)	3.2 (1.6–6.5)	3.1 (1.5–6.2)	3.4 (1.7–6.9)
Stroke	2.7 (0.9–7.8)	NS	NS	NS
Stress test results				
Typical angina	0.8 (0.3–1.7)	—	NS	NS
ST-segment changes	1.1 (0.5–2.2)	—	NS	NS
Scan parameters				
Abnormal scan	9.7 (2.3–40)	—	7.2 (1.7–30)	—
SSS*	1.21 (1.10–1.34)	—	—	1.20 (1.07–1.34)

Data are Cox proportional hazard ratio (95% CI). In model I, the variable entered was the presence of an abnormal scan; in model II, the SSS was included. *Per one-unit increment; —, variable excluded; NS, not statistically significant.

the patient's general practitioner. The date of the last review or consultation was used to determine follow-up time. The mean follow-up period was 4.1 ± 2.4 years (range 6 months to 10 years). End points comprised overall death, cardiac death, nonfatal myocardial infarction, and late (>60 days) coronary revascularization. Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death. Nonfatal myocardial infarction was defined by elevated cardiac enzyme levels and typical changes on electrocardiography.

Statistical analysis

Values were expressed as mean value ± SD or number and were compared using the Student's *t* test or χ^2 test. Univariate and multivariate Cox proportional hazard regression models (BMDP statistical software, Los Angeles, CA) were used to identify independent predictors of late cardiac events (25). Variables were selected in a stepwise forward-selection manner with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with corresponding 95% CI. The incremental value of myocardial perfusion scintigraphy over the clinical variables in the prediction of events was determined according to two models. In model I, the variable entered was the presence of an abnormal scan; in model II, the SSS was entered. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics and dobutamine stress test

Baseline data from the 194 patients (116 men and 78 women aged 61 ± 10 years) are summarized in Table 1. During the dobutamine-atropine stress test, heart rate increased from 77 ± 17 to 136 ± 17 bpm ($P < 0.0001$), and systolic blood pressure increased from 144 ± 26 to 158 ± 33 mmHg ($P < 0.001$). The peak dobutamine dose was 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 5 patients (3%), 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 24 patients (12%), 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 35 patients (18%), and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 130 patients (67%). In 78 patients (40%), atropine was added. Atropine was more frequently administered in patients using β-blocker therapy (41 of 66 patients, 62%) than in those not taking β-blockers (37 of 128, 29%, $P < 0.0001$). Adverse effects during the test were ventricular tachycardia (>10 beats) in 1 patient (0.5%), short ventricular tachycardia (<10 beats) in 7 patients (3.6%), atrial fibrillation in 2 patients (1.0%), severe hypotension (decrease in systolic blood pressure >40 mmHg) in 3 patients (1.5%), nausea in 11 patients (5.7%), and headache in 12 patients (6.2%). No patient experienced a myocardial infarction or fatal complication. Typical angina occurred in 53 patients (27%), whereas 54 patients (28%) exhibited ST-segment changes.

Myocardial perfusion images and follow-up

Abnormal myocardial perfusion was detected in 125 patients (64%). A total of 17 patients (9%) had reversible perfusion de-

Table 3—*Predictors of hard cardiac events (cardiac death or myocardial infarction)*

		Multivariate analysis		
	Univariate	Clinical data	Model I	Model II
Clinical characteristics				
Age*	1.06 (1.03–1.12)	1.06 (1.03–1.11)	1.07 (1.03–1.11)	1.06 (1.03–1.10)
Male sex	0.7 (0.4–1.3)	NS	NS	0.5 (0.3–0.9)
Previous myocardial infarction	1.6 (0.9–2.9)	NS	NS	NS
Hypertension	0.9 (0.5–1.6)	NS	NS	NS
Hypercholesterolemia	1.0 (0.5–1.9)	NS	NS	NS
Smoking	1.4 (0.7–2.6)	NS	NS	NS
Heart failure	3.2 (1.7–5.9)	2.7 (1.5–5.0)	2.5 (1.4–4.7)	2.1 (1.1–4.0)
Type 1 diabetes	2.0 (0.9–4.2)	NS	NS	NS
Duration of diabetes (years)*	1.04 (1.01–1.08)	1.04 (1.01–1.07)	1.04 (1.01–1.07)	1.04 (1.01–1.07)
Diabetic complications				
Nephropathy	1.7 (0.7–3.7)	NS	NS	NS
Neuropathy	0.8 (0.3–2.1)	NS	NS	NS
Retinopathy	1.2 (0.7–1.4)	NS	NS	NS
Peripheral atherosclerosis	3.2 (1.4–7.0)	3.0 (1.6–5.8)	3.3 (1.6–5.9)	3.1 (1.6–6.0)
Stroke	NS	NS	NS	
Stress test results				
Typical angina	0.8 (0.4–1.7)	—	NS	NS
ST-segment changes	1.1 (0.6–2.0)	—	NS	NS
Scan parameters				
Abnormal scan	3.4 (1.4–8.1)	—	2.8 (1.2–6.8)	—
SSS*	1.16 (1.06–1.27)	—	—	1.13 (1.02–1.25)

Data are Cox proportional hazard ratio (95% CI). In model I, the variable entered was the presence of an abnormal scan; in model II, the SSS was included. *Per one-unit increment; —, variable excluded.

fects, 61 patients (31%) had fixed defects, and 47 patients (24%) had fixed plus reversible defects. During the follow-up period of 4.1 ± 2.4 years, 73 patients (38%) died; 36 of these patients (19%) died of cardiac causes. Nonfatal myocardial infarction occurred in 15 patients (8%), and 18 patients (9%) underwent late coronary revascularization (coronary artery bypass grafting in 6 patients and percutaneous transluminal coronary angiography in 12 patients). Of the remaining 46 patients with reversible perfusion defects or fixed and reversible perfusion defects, most (43 patients) had limited perfusion defects and received medical treatment; one patient was accepted for coronary revascularization but died of noncardiac cause before coronary revascularization, one patient refused coronary revascularization and received medical treatment, and one patient had normal results of coronary angiography.

Predictive value of clinical data and test results

During a follow-up period of 4.1 ± 2.4 years, cardiac death occurred in 2 (3%) of 69 patients with normal myocardial perfusion and 34 (27%) of 125 patients with abnormal perfusion ($P < 0.0001$). Univariate and multivariate predictors of cardiac events are shown in Tables 2 and 3. Among clinical variables, age, heart failure, and peripheral atherosclerosis were independent predictors of cardiac death and hard cardiac events (cardiac death/nonfatal infarction). The duration of diabetes was a clinical predictor of hard cardiac events as well. An abnormal scan provided incremental prognostic information over these clinical variables. Kaplan-Meier survival curves for the end points cardiac death and cardiac death/nonfatal infarction are presented in Figs. 1 and 2, respectively. Event-free survival was significantly better for patients with normal perfusion than for those with abnormal perfusion. In patients with a normal scan, there was no cardiac mortality ≤2.5 years after the myocardial perfusion study. The SSS provided incremental prognostic information as well (see Tables 2 and 3). Cumulative event rates according to the SSS are depicted in Fig. 3. Cumulative event rates increased as a function of defect extent and severity.

CONCLUSIONS — This study assessed the incremental value of dobutamine-atropine stress myocardial perfusion imaging in the prediction of cardiac events in diabetic patients with limited exercise capacity. Follow-up end points were cardiac death and nonfatal myocardial infarction. During the follow-up period of 4.1 ± 2.4 years, 73 patients (38%) died; 36 of these patients (27%) died of cardiac causes. Nonfatal myocardial infarction occurred in 15 patients (8%), and 18 patients (9%) underwent late coronary revascularization. Clinical predictors of cardiac death alone and hard cardiac events (cardiac death and myocardial infarction) were age, heart failure, and peripheral atherosclerosis. The duration of diabetes (years) was a clinical predictor of hard cardiac events as well. Dobutamine-atropine stress myocardial perfusion imaging provided incremental prognostic information for the prediction of cardiac death and hard cardiac events relative to clinical and stress test data. Cardiac death occurred in 3% of the patients with normal myocardial perfusion and in 27% of the patients with abnormal perfusion ($P < 0.0001$). The

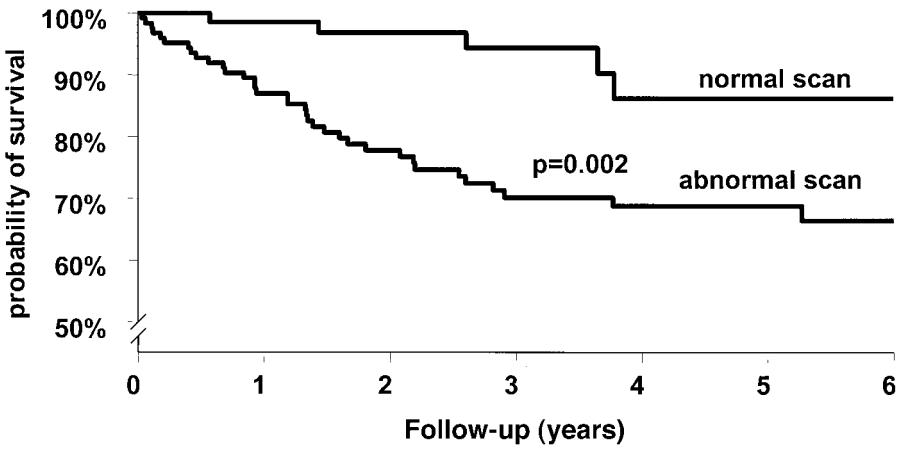

Figure 1—*Kaplan-Meier survival curves for cardiac death as a function of dobutamine stress ^{99m}Tc-sestamibi SPECT results. Event-free survival is much better in patients with normal test results compared with those with abnormal test results.*

SSS also provided powerful prognostic information on both end points. These findings demonstrate that the evaluation of severity of functional abnormalities as a consequence of coronary artery disease by dobutamine-atropine stress myocardial perfusion imaging provides clinically useful information in diabetic patients.

Previous studies

Currently, there are no clinical outcome data to define the role of dobutamine-atropine stress myocardial perfusion imaging as a prognostic tool in patients with diabetes (26). Data on the prognostic value of myocardial perfusion imaging in diabetic patients are limited. Felsher et al. (13) demonstrated that exercise planar thallium imaging was useful for the risk stratification of 123 diabetic patients. Four cardiac deaths and eight nonfatal infarctions occurred during the follow-up period of 1.8 ± 0.9 years. Vanzetto et al. (14) evaluated the prognostic value of exercise thallium imaging in 158 diabetic patients. During the follow-up period of 1.9 ± 1.4 years, cardiac death occurred in 8 patients and nonfatal infarction occurred in 14 patients. The authors concluded that inability to exercise was associated with a high risk of events and suggested that, for the assessment of prognosis in these patients, pharmacologic stress myocardial perfusion imaging be performed. Cohen et al. (15) demonstrated that abnormal dipyridamole stress thallium images were important adverse indictors of long-term prognosis in 101 diabetic patients undergoing peripheral vascular surgery. Kang et al. (16) evaluated the prognostic value of rest thallium/stress ^{99m}Tc-sestamibi myocardial perfusion imaging in diabetic patients. During the follow-up period of 2.0 ± 0.6 years, 50 cardiac deaths and 42 nonfatal infarctions occurred in 1,080 patients with diabetes. Most of these patients had undergone exercise stress testing, whereas the others had undergone adenosine stress testing. As in the present study, an abnormal scan and the SSS provided incremental prognostic information over clinical data. Recently, Giri et al. (27) studied 929 diabetic patients after exercise or vasodilator stress myocardial perfusion imaging. During a follow-up period of 2.5 ± 1.5 years, 39 deaths and 41 nonfatal infarctions occurred. The presence and the extent of abnormal stress myocardial perfusion imaging independently predicted subsequent cardiac events. Although exercise is the most physiological stress method and provides useful prognostic information by studying hemodynamic response and exercise tolerance, many diabetic patients are unable to exercise adequately due to peripheral vascular disease, neuropathy, and degenerative joint disease (18–20). Therefore, studies of the prognostic value of pharmacological stress testing are important in these patients. Cardiac death rate in this study is much higher (4.5%) than in previous studies of diabetic patients, in which cardiac death rate ranged between 1.8 and 2.7%. This demonstrates the importance of noninvasive imaging in this high-risk population with limited exercise capacity. Previous studies of the general population showed that dobutamine-atropine stress myocardial perfusion imaging is an alternative in patients who are unable to undergo exercise stress testing (21,22,26), particularly in patients with relative contraindications to vasodilator stress agents (patients with obstructive airway disease) or in those who have ingested caffeine or aminophylline shortly before stress myocardial perfusion imaging. The present study is the first to demonstrate that dobutamine-atropine stress myocardial perfusion imaging forms a safe and useful substitute to exer-

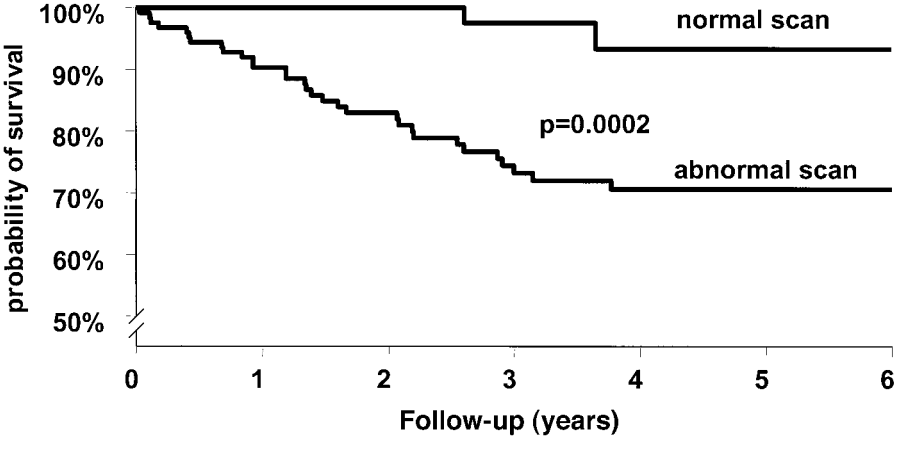

Figure 2—*Kaplan-Meier survival curves for hard cardiac events (cardiac death/nonfatal infarction) as a function of dobutamine stress ^{99m}Tc-sestamibi SPECT results. A significant difference in event-free survival exists between patients with normal test results and those in whom test results are abnormal.*

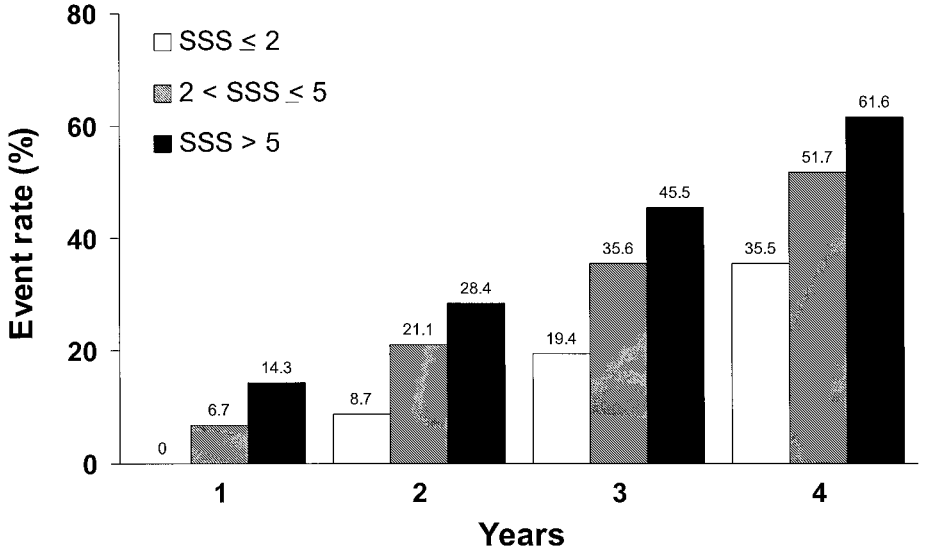

Figure 3—*Cumulative cardiac event rates (cardiac death/nonfatal infarction/revascularization) according to SSS.*

cise stress imaging in patients with diabetes as well.

In summary, dobutamine-atropine stress myocardial perfusion imaging is a clinically useful method for the prognostic stratification of patients with diabetes who were unable to undergo exercise stress testing. The test provides incremental prognostic information relative to clinical parameters. Patients with normal perfusion have a good prognosis, whereas patients with an abnormal test are at a high risk for cardiac events. Both an abnormal myocardial perfusion and the SSS are important determinants of prognosis.

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References

1. Kannel WB, McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 2:120–126, 1979
2. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR: Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 100:1134–1146, 1999
3. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
4. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP: Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med* 159: 1450–1456, 1999
5. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilehto J: Impact of diabetes on mortality after the first myocardial infarction. *Diabetes Care* 21:69–75, 1998
6. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, Turi ZG, Strauss HW, Willerson JT, Robertson T, Braunwald E, Jaffe AS: The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary artery disease and diastolic left ventricular dysfunction to the adverse prognosis: the MILIS Study Group. *J Am Coll Cardiol* 14:49–57, 1989
7. Chiariello M, Indolfi C: Silent myocardial ischemia in patients with diabetes mellitus. *Circulation* 93:2089–2091, 1996
8. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V: Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care* 22: 1396–1400, 1999
9. Smith JW, Marcus FI, Serokman R: Prognosis of patients with diabetes mellitus after acute myocardial infarction. *Am J Cardiol* 54:718–721, 1984
10. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ: Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction: GUSTO-I Investigators: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol* 30:171–179, 1997
11. The Bypass Angioplasty Revascularization Investigation (BARI) investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 335:217–225, 1996
12. Detre KM, Lombardero MS, Brooks MM, Hardison RM, Holubkov R, Sopko G, Frye RL, Chaitman BR, for the Bypass Angioplasty Revascularization Investigation Investigators: The effect of previous coronary artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. *N Engl J Med* 342:989–997, 2000
13. Felsher J, Meissner MD, Hakki AH, Heo J, Kane-March S, Iskandrian AS: Exercise thallium imaging in patients with diabetes mellitus. *Arch Intern Med* 147:313–317, 1987
14. Vanzetto G, Halimi S, Hammoud T, Fagret D, Benhamou PY, Cordonnier D, Denis B, Machecourt J: Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. *Diabetes Care* 22:19–26, 1999
15. Cohen MC, Curran PJ, L'Italien GJ, Mittleman MA, Zarich SW: Long-term prognostic value of preoperative dipyridamole thallium imaging and clinical indexes in patients with diabetes mellitus undergoing peripheral vascular surgery. *Am J Cardiol* 83:1038–1042, 1999
16. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, Hachamovitch R, Shaw LJ: Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J* 138:1025–1032, 1999
17. Elhendy A, Arruda AM, Mohoney DW, Pellikka PA: Prognostic stratification of diabetic patients by exercise echocardiography. *J Am Coll Cardiol* 37:1551–1557, 2001
18. Jorgensen H, Nakayama H, Raaschou HO, Olsen TS: Stroke in patients with diabetes: the Copenhagen Stroke Study. *Stroke* 25:1977–1984, 1994
19. Akbari CM, LoGerfo FW: Diabetes and peripheral vascular disease. *J Vasc Surg* 30:373–384, 1999
20. May O, Arildsen H, Damsgaard EM, Mickley H: Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated risk of coronary heart disease in the general population. *J Intern Med* 248:483–491, 2000
21. Geleijnse ML, Elhendy A, Van Domburg RT, Cornel JH, Reijs AEM, Roelandt JRTC, Krenning EP, Fioretti PM: Prognos-

tic value of dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain. *J Am Coll Cardiol* 28:447–454, 1996
22. Senior R, Raval U, Lahiri A: Prognostic value of stress dobutamine technetium-99m sestamibi single-photon emission computed tomography (SPECT) in patients with suspected coronary disease. *Am J Cardiol* 78:1092–1096, 1996
23. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA: Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation* 93:905–914, 1996
24. Elhendy A, Valkema R, van Domburg RT, Bax JJ, Nierop PR, Cornel JH, Geleijnse ML, Reijs AE, Krenning EP, Roelandt JRTC: Safety of dobutamine-atropine stress myocardial perfusion scintigraphy. *J Nucl Med* 39:1662–1666, 1998
25. Cox DR: Regression models and life-tables. *J R Stat Soc (B)* 34:187–202, 1972
26. Geleijnse ML, Elhendy A, Fioretti PM, Roelandt JRTC: Dobutamine stress myocardial perfusion imaging. *J Am Coll Cardiol* 36:2017–2027, 2000
27. Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R, Borges-Neto S, Berman DS, Waters DD, Heller GV: Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation* 105:32–40, 2002