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Dobutamine Stress Echocardiography in Patients With Diabetes Mellitus

Enhanced Prognostic Prediction Using a Simple Risk Score

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OBJECTIVES	We sought to determine the prognostic value of dobutamine stress echocardiography (DSE) for predicting long-term outcomes in a large cohort with diabetes mellitus and to develop a simple risk score using clinical and echocardiographic data.
BACKGROUND	Neither risk scores nor long-term prognostic value of DSE has been described in a large diabetic population.
METHODS	We studied 2,349 patients with diabetes mellitus (1,338 men, 67 ± 11 years of age) during a follow-up of 5.4 ± 2.2 years.
RESULTS	Mortality and morbidity (myocardial infarction and late coronary revascularization) occurred in 1,044 (44%) and 309 (13%) patients, respectively. Addition of stress echocardiographic variables to the clinical and rest echocardiographic model provided incremental prognostic information for predicting mortality (chi-square = 243 to 270, $p < 0.0001$) and morbidity (chi-square = 38 to 78, $p < 0.0001$). For each end point, a simple risk score was derived according to the estimated values of beta coefficients of multivariate predictors (insulin therapy, smoking, failure to achieve target heart rate, percentage of ischemic segments, and impaired left ventricular systolic function) and resulted in an assessment of risk among all age groups. The C-statistic values were 0.60 to 0.64, indicating modest discrimination. The estimated five-year event-free survivals of patients in three risk categories were 94%, 86%, and 80% for morbidity ($p < 0.00001$) and 69%, 60%, and 47% for mortality ($p < 0.0001$).
CONCLUSIONS	In patients with diabetes mellitus, a simple and practical risk score using clinical variables and results of DSE stratified patients into three risk groups for mortality and cardiovascular morbidity. (J Am Coll Cardiol 2006;47:1029–36) © 2006 by the American College of Cardiology Foundation

Patients with diabetes mellitus are at increased risk of mortality and cardiovascular morbidity (1,2). Individuals with diabetes mellitus are more likely have clinical coronary artery disease (CAD), concomitant risk factors for CAD, an asymptomatic presentation, and a worse prognosis (3–7). As a result, multivessel CAD may not be recognized early, contributing to a worse prognosis (8). Early identification and risk stratification of CAD in patients with diabetes mellitus is particularly essential in identifying those requiring prompt and appropriate therapeutic intervention.

Clinical assessment of cardiac risk may be insufficient in asymptomatic patients with diabetes. Furthermore, inability to exercise and failure to achieve an adequate workload may limit the applicability of exercise stress testing in patients with diabetes mellitus (9). Dobutamine stress echocardiography (DSE) is an accurate and reliable noninvasive technique used for the diagnostic and prognostic assessment of CAD (10–14). However, fewer data exist regarding the long-term prognostic role of DSE in a large cohort with diabetes mellitus. The purposes of this study were to determine the prognostic value of DSE for predicting the

long-term outcome in a large cohort with diabetes mellitus, regardless of the presence of known or suspected CAD, and to develop a simple model for risk stratification using clinical and stress echocardiographic data.

METHODS

Study population. Of 10,650 patients referred for clinically indicated DSE from January 1990 through December 2000, we identified 2,618 (25%) patients with diabetes mellitus. From 1990 to 1997, diabetes mellitus was defined as fasting plasma glucose level ≥ 140 mg/dl on at least two occasions and/or requirement for insulin or oral hypoglycemic agents (15). Patients who underwent DSE from 1998 to 2000 were diagnosed as having diabetes mellitus according to the criteria by the American Diabetes Association (16), including fasting plasma glucose level ≥ 126 mg/dl. Two hundred sixty-nine patients were excluded: 137 had inadequate echocardiographic images, 128 international patients and prisoners were lost to follow-up, and 4 patients refused research authorization. The remaining 2,349 (90%) patients constituted the study population.

Clinical characteristics and results of stress echocardiography were recorded at the time of DSE. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medication. Patients were considered to have hyperlipid-

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Abbreviations and Acronyms

CAD	= coronary artery disease
DSE	= dobutamine stress echocardiography
LVESV	= left ventricular end-systolic volume
MI	= myocardial infarction
WMA	= wall motion abnormality

emia if their total cholesterol was ≥ 200 mg/dl or if they were receiving lipid-lowering medication. Age as a cardiovascular risk factor was defined as ≥ 45 years for men and ≥ 55 years for women.

Dobutamine stress echocardiography. Dobutamine stress echocardiography was performed according to a previously described protocol using 3-min stages, a peak dose of 40 $\mu\text{g}/\text{kg}/\text{min}$ and atropine, to a total dose of 2 mg, as needed to augment the heart rate (12). Contrast was used for endocardial border detection when two or more segments could not be adequately visualized. Ejection fraction was evaluated as previously described (17) or by visual estimation. Impaired left ventricular systolic function was defined as ejection fraction $< 50\%$. Wall motion was assessed and scored 1 through 5 in each of 16 segments, and left ventricular wall motion score index was calculated at rest and peak stress (12,18). The development of new or worsening wall motion abnormality (WMA), including a deterioration of wall motion after an improvement at low-dose dobutamine, was considered inducible ischemia. A resting WMA unchanged with dobutamine infusion or an akinetic segment that became dyskinetic was defined as fixed (19,20). The percentage of abnormal segments (rest or stress-induced abnormalities) was calculated at rest and stress as the number of abnormal segments divided by the number of visualized segments, multiplied by 100. The percentage of ischemic segments was similarly derived. Normal DSE was defined if there was no WMA at rest or stress. Target heart rate was defined as 85% of age-predicted maximal heart rate ($220 - \text{age}$). The dose of dobutamine and heart rate at which the deterioration of wall motion first occurred were recorded. Ischemic threshold was defined as the heart rate at which new or worsening WMA occurred, divided by the age-predicted maximal heart rate, multiplied by 100%. The change in left ventricular end-systolic volume (LVESV) from rest to peak stress was recorded as normal (decrease in LVESV) or abnormal (increase or absence of a decrease). The stress electrocardiogram was positive for ischemia if there were horizontal or downsloping ST-segment depression of ≥ 1 mm at 80 ms after the J-point in the absence of baseline ST-segment deviation.

Follow-up. Follow-up information was obtained from medical records, telephone interviews, mailed questionnaires, and the Social Security Death Index. End points were all-cause mortality and cardiovascular morbidity, defined as myocardial infarction (MI) and late (more than three months) coronary revascularization. For the analysis of morbidity, patients who underwent coronary revascularization within three months

after DSE were censored at the time of revascularization. For patients who experienced both MI and late coronary revascularization, only the first event was included for the analysis of morbidity. The statistical analyses of all-cause mortality and morbidity were performed separately.

Statistical analysis. Characteristics were summarized as percentages for categorical variables and as mean \pm standard deviation for continuous variables. Comparisons between groups were based on Wilcoxon rank-sum test for continuous variables and the Pearson chi-square test for categorical variables. Cumulative probabilities of overall survival or freedom from morbidity were estimated by the Kaplan-Meier method. For the event-free survival analysis, patients were censored at the time of non-cardiac death and at early revascularization. Univariable and multivariable associations of clinical and echocardiographic variables with the end points were assessed using the Cox proportional hazards model. All clinical variables and representative DSE variables were considered in the model, regardless of their univariate significance. The proportional hazards assumption was tested by retaining the model-based risk score and performing a time-dependent proportional hazards analysis in which the risk score was entered along with its interaction both with time and with log (time). Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. Results of these analyses were summarized as hazard ratios with 95% confidence intervals. To determine the incremental value of DSE, models of: 1) clinical variables alone; 2) clinical and rest echocardiographic variables; and 3) clinical, rest, and stress echocardiographic variables were compared via their log likelihood ratio chi-square statistics. For each end point, a simple integer risk score was derived according to the estimated values of beta coefficients of multivariable predictors. The fitted model included age only for the purpose of adjustment; all other models were based on the variables selected in the stepwise algorithm, which were replaced by dichotomous versions to facilitate ease of clinical use. This integer risk score was then divided into three categories, based on choosing the split that maximized the three-group log rank chi-square statistic, as well as the model chi-squared statistic when age and the three risk categories were included in a proportional hazards model. Patients were classified as being at low, intermediate, and high risk according to this categorization. The estimated five-year event survivals of each risk category were derived from the Kaplan-Meier method. In addition, the best model for each end point using the original clinical and echocardiographic variables was summarized by way of its prediction of the one-, three-, five-, or eight-year probability of survival or morbidity-free status, as a function of the respective model variables. This is included in the Appendix for users wishing a more accurate prediction model. Finally, the accuracy (calibration) of prediction models was assessed by dividing the patient population into deciles of estimated risk, calculating the average proportional hazards model-based probabilities of

Table 1. Clinical Characteristics

Variables	Ischemic DSE n = 1,007	Non-Ischemic DSE n = 1,342	p Value
Age (yrs)	68 ± 10	67 ± 12	0.006
Male gender	634 (63)	704 (52)	<0.0001
Hypertension	758 (75)	952 (71)	0.02
Insulin therapy	503 (50)	612 (46)	0.04
Smoking	648 (64)	817 (61)	0.09
Family history of CAD	435 (43)	496 (37)	0.002
Prior MI	356 (35)	289 (22)	<0.0001
Prior revascularization	355 (35)	298 (22)	<0.0001
Indication for testing			0.48
Preoperative assessment	491 (49)	675 (50)	
Evaluation of known or suspected CAD	474 (47)	602 (45)	
Other	42 (4)	65 (5)	
Reasons for test termination			<0.0001
Achieving target heart rate	666 (66)	983 (73)	
Ischemia	128 (13)	14 (1)	
Completion of protocol	101 (10)	186 (14)	
Adverse effects	112 (11)	159 (12)	

Results are expressed as number (%) of patients or as mean ± standard deviation.
 CAD = coronary artery disease; DSE = dobutamine stress echocardiography; MI = myocardial infarction.

survival or morbidity-free status at each time point within these deciles, and comparing them with the corresponding Kaplan-Meier (model-free) estimates of the probabilities within the same deciles of risk. To assess the predictive power of each model, the C-statistic for censored data was calculated and reported for each model. Analyses were carried out using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Study population. Of 2,349 patients, 1,338 (57%) were men; age was 67 ± 11 years. Indications for DSE were for preoperative cardiac risk assessment in 1,166 (50%), evaluation of known or suspected CAD in 1,076 (46%), and other in 106 (4%) patients. Reasons for inability to exercise

were peripheral vascular disease in 711 (30%), orthopedic limitations in 603 (26%), debility in 214 (9%), pulmonary disease in 112 (5%), and other in 709 (30%) patients. Of 2,349 patients, 1,115 (47%) were receiving insulin (with or without concomitant oral hypoglycemic agents), whereas 740 (32%) and 494 (21%) patients were receiving oral hypoglycemic agents and diet control only, respectively. Cardiovascular risk factors included age in 91% (60% men, 40% women), hypertension in 73%, smoking in 62%, hyperlipidemia in 56%, and family history of CAD in 40%. History of CAD, prior MI, and prior revascularization were present in 47%, 27%, and 28%, respectively. Clinical characteristics, according to results of DSE, are shown in Table 1.

Rest and DSE data. The peak dose of dobutamine infusion was 34 ± 9 µg/kg/min. Atropine, 0.84 ± 0.61 mg, was administered to 910 (41%) patients. Six hundred three (26%) patients did not achieve target heart rate; among these, 262 (43%) were on beta-blockers. Heart rate increased from 73 ± 13 beats/min to 128 ± 16 beats/min. The stress electrocardiogram was positive in 233 (10%) patients. At rest, the ejection fraction was 54 ± 14% and systolic function was impaired in 589 (25%) patients. Resting WMA was present in 1,238 (53%) patients; among these, 414 (33%) reported no history of CAD. Ejection fraction increased from 54 ± 14% at rest to 64 ± 17% at peak stress. The DSE was abnormal in 1,505 (64%) patients. Inducible ischemia developed in 1,007 (43%) patients. Of 1,111 patients with no resting WMA, inducible ischemia developed in 267 (24%) patients. Ischemic threshold was 74 ± 13%, detected at a heart rate of 111 ± 19 beats/min and a dobutamine infusion rate of 30 ± 10 µg/kg/min. An abnormal LVESV response was noted in 334 (14%) patients.

Outcomes. Follow-up periods for all-cause mortality and cardiovascular morbidity were 5.4 ± 2.2 (maximum, 13.2) years and 3.9 ± 2.7 (maximum, 13.2) years, respectively. Death occurred in 1,044 (44%) patients. Survival probabil-

Table 2. Dobutamine Stress Echocardiographic Data

Variables	All-Cause Mortality			Cardiovascular Morbidity		
	Event n = 1,044	No Event n = 1,305	p Value	Event n = 309	No Event n = 2,040	p Value
Rest heart rate (beats/min)	73 ± 13	73 ± 13	0.8	72 ± 13	74 ± 13	0.007
Peak heart rate (beats/min)	126 ± 17	131 ± 16	<0.0001	127 ± 15	129 ± 17	0.001
Ejection fraction (%)	51 ± 15	56 ± 12	<0.0001	53 ± 12	54 ± 14	0.16
Target heart rate achieved	726 (70)	1,020 (78)	<0.0001	216 (70)	1,530 (75)	0.055
Positive stress ECG	112 (11)	121 (9)	0.2	30 (10)	203 (10)	0.88
Abnormal LVESV response	205 (20)	129 (10)	<0.0001	61 (20)	283 (13)	<0.003
Abnormal DSE	765 (73)	740 (57)	<0.0001	204 (73)	1,301 (63)	<0.0001
Ischemic DSE	502 (48)	505 (39)	<0.0001	150 (54)	857 (41)	<0.0001
Percent ischemic segments	14 ± 19	10 ± 17	<0.0001	16 ± 21	11 ± 17	<0.0001
Rest percent abnormal segments	32 ± 35	19 ± 29	<0.0001	25 ± 30	25 ± 33	0.087
Peak percent abnormal segments	38 ± 34	24 ± 30	<0.0001	35 ± 32	30 ± 33	<0.0001
Rest WMSI	1.5 ± 0.6	1.3 ± 0.4	<0.0001	1.4 ± 0.5	1.4 ± 0.5	0.08
Peak WMSI	1.6 ± 0.6	1.4 ± 0.5	<0.0001	1.5 ± 0.5	1.5 ± 0.5	<0.0001

Results are expressed as number (%) of patients and mean ± standard deviation.
 DSE = dobutamine stress echocardiography; ECG = electrocardiogram; LVESV = left ventricular end-systolic volume; WMSI = wall motion score index.

Table 3. Predictors of All-Cause Mortality

Variables	Univariate Analysis				Multivariate Analysis				Risk Score
	HR	95% CI	Chi-Square	p Value	HR	95% CI	Chi-Square	p Value	
Age*	1.39	1.30–1.48	114	<0.0001	1.45	1.35–1.55	125	<0.0001	
Insulin therapy	1.16	1.02–1.31	5	0.02	1.28	1.13–1.45	14	0.0001	1
Prior MI	1.47	1.30–1.67	34	<0.0001					
Prior revascularization	1.25	1.10–1.37	11	0.001					
Smoking	1.22	1.08–1.39	10	0.002	1.30	1.13–1.49	13	0.0003	1
Rest ejection fraction†	0.80	0.77–0.83	104	<0.0001	0.85	0.78–0.93	14	0.0002	3§
Abnormal stress LVESV	1.79	1.53–2.08	49	<0.0001					
Failure to achieve target heart rate	1.29	1.13–1.47	14	0.0002	1.29	1.12–1.48	13	0.0004	1
Percent ischemic segments†	1.08	1.05–1.12	22	<0.0001	1.10	1.04–1.15	12	0.0005	2
Rest percent abnormal segments†	1.09	1.07–1.11	91	<0.0001					
Peak percent abnormal segments†	1.10	1.08–1.12	105	<0.0001					
Rest WMSI‡	1.15	1.12–1.18	90	<0.0001					
Peak WMSI‡	1.15	1.12–1.18	105	<0.0001					

Overall chi-square value for multivariate analysis = 273; p < 0.0001. *Per decade; †per 10% increment; ‡per 0.25-U increment; §if ejection fraction <50%; ||if percentage of ischemic segments >25%

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1 and 2.

ities at 1, 3, 5, and 8 years were 89%, 74%, 60%, and 44%, respectively. The cumulative mortality rate was higher in patients with abnormal compared with patients with normal DSE at 1 year (13% vs. 7%), 3 years (30% vs. 19%), 5 years (45% vs. 31%), and 8 years (61% vs. 48%) (p < 0.0001). Patients on insulin had lower survival probabilities compared with patients who were on oral agents or diet alone (87% vs. 90% at 1 year, 71% vs. 76% at 3 years, 57% vs. 62% at 5 years, 42% vs. 46% at 8 years; p = 0.005).

Cardiovascular morbidity occurred in 309 (13%) patients; 193 had MI and 116 had late coronary revascularization. Early coronary revascularization (with no intervening event) was performed in 148 patients. Patients with inducible ischemia were more likely to undergo coronary revascularization than those with nonischemic DSE (19% vs. 9%, p < 0.0001). The DSE data of patients with and without mortality and cardiovascular morbidity are shown in Table 2.

Predictors of outcomes. Variables associated with an increased risk of mortality and cardiovascular morbidity in univariate and multivariate analysis are listed in Tables 3 and 4, respectively. All variables from Table 1 and repre-

sentative variables from Table 2 were considered in the multivariate analysis. In multivariate analysis, age, failure to achieve target heart rate, and the percentage of ischemic segments were important predictors of both mortality and morbidity. Table 5 shows the incremental prognostic value of DSE over clinical and rest echocardiographic variables for predicting mortality and morbidity. The Kaplan-Meier curves for overall survival according to the test result and extent of inducible ischemia are illustrated in Figure 1. Patients with inducible ischemia were at an increased risk of mortality; risk was higher in those with more extensive ischemia. When the proportional hazards assumption was tested, there was no evidence for lack of proportionality for either end point based on the models in Tables 3 and 4.

A simple risk score for risk stratification. ALL-CAUSE MORTALITY. Multivariate predictors of mortality were used to develop a risk score. The continuous variables, rest ejection fraction and percentage of ischemic segments, were dichotomized using cut points of 50% and 25%, respectively. Age group was used to further classify patients in each risk category. The risk score was based on assigning

Table 4. Predictors of Cardiovascular Morbidity

Variables	Univariate Analysis				Multivariate Analysis				Risk Score
	HR	95% CI	Chi-Square	p Value	HR	95% CI	Chi-Square	p Value	
Age*	1.24	1.11–1.14	14.7	<0.0001	1.26	1.13–1.42	16.8	<.0001	
Hypertension	1.49	1.13–1.96	7.9	0.005	1.33	1.01–1.76	4.1	0.042	1
Prior MI	1.49	1.18–1.89	10	0.001	1.27	1.00–1.62	3.9	0.047	1
Prior revascularization	1.54	1.19–1.90	11.7	0.001					
Rest ejection fraction†	0.89	0.82–0.96	7.86	0.005					
Abnormal stress LVESV	2.11	1.40–2.57	27.2	<0.0001					
Failure to achieve target heart rate	1.49	1.15–1.87	9.57	0.002	1.49	1.16–1.91	9.8	0.001	2
Percent ischemic segments†	1.20	1.14–1.26	44.5	<0.0001	1.19	1.12–1.25	37.9	<0.0001	3§
Rest percent abnormal segments†	1.00	1.00–1.01	6.57	0.010					
Peak percent abnormal segments†	1.01	1.01–1.02	31.28	<0.0001					
Rest WMSI‡	1.07	1.02–1.33	6.55	0.011					
Peak WMSI‡	1.14	1.11–1.20	26.84	<0.0001					

Overall chi-square value for a multivariate analysis = 57; p < 0.0001. *Per decade; †per 10% increment; ‡per 0.25-U increment; §if percentage of ischemia segments >25%. Abbreviations as in Table 3.

Table 5. Independent Predictors of All-Cause Mortality and Cardiovascular Morbidity Using a Three-Step Model

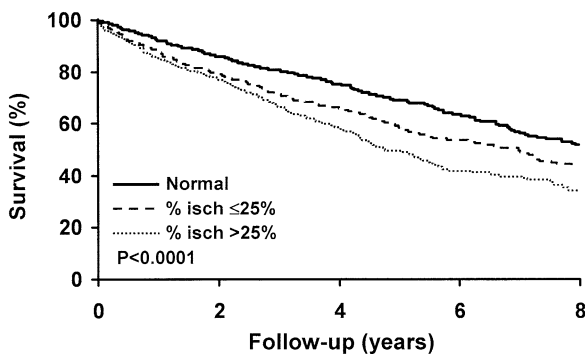
Models	Variables	HR	95% CI	p Value	Model Chi-Square	
All-cause mortality	Clinical	Age*	1.43	1.34-1.53	<0.0001	174
		Male gender	1.01	0.89-1.16	0.8	
		Hypertension	1.05	0.92-1.21	0.5	
		Insulin therapy	1.30	1.15-1.47	<0.0001	
		Smoking	1.30	1.13-1.50	0.0002	
		Prior MI	1.36	1.20-1.55	<0.0001	
	Clinical + rest echo	Rest ejection fraction†	0.82	0.78-0.86	<0.0001	243
	Clinical, rest echo + stress echocardiography	Failure to achieve target heart rate	1.29	1.13-1.48	0.0003	270
		Percent ischemic segments†	1.06	1.03-1.10	0.0003	
	Cardiovascular morbidity	Clinical	Age*	1.24	1.01-1.39	0.0002
Male gender			1.18	0.87-1.43	0.38	
Hypertension			1.44	1.09-1.90	0.01	
Insulin therapy			1.19	0.95-1.50	0.13	
Smoking			1.14	0.88-1.46	0.32	
Prior MI			1.37	1.08-1.75	0.009	
Clinical + rest echo		Rest ejection fraction†	0.94	0.86-1.03	0.16	38
Clinical, rest echo + stress echocardiography		Percent ischemic segments†	1.18	1.12-1.25	0.0001	78
		Failure to achieve target heart rate	1.48	1.15-1.90	0.002	

*Per decade; †per 10% increment.
 Abbreviations as in Table 3.

weights to each variable according to their parameter estimates from the Cox proportional hazard model, including: 1 point each for insulin therapy, smoking, or failure to achieve target heart rate; 2 points if the percentage of ischemic segments was >25%, and 3 points for impaired left ventricular systolic function (Table 3). Patients were then classified into three risk categories according to their summed risk score (0 to 1, 2 to 3, and ≥4, respectively). The coefficient of the risk score for mortality was similar in patients with or without known CAD (hazard ratio, 1.2 and 1.2; p < 0.0001 for each). The C-statistic of this simple risk score model was 0.60. The corresponding mortality rates per person-year of follow-up were 7%, 10%, and 16%, respectively. The estimated five-year survivals of patients in the three risk categories were 69%, 60%, and 47% (p < 0.0001). The Kaplan-Meier survival curves of patients in these three risk categories are shown in Figure 2. The predictive value

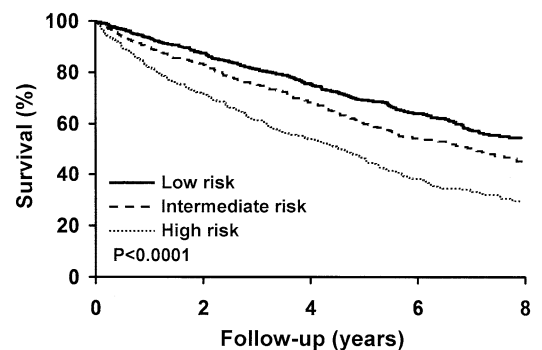
of this mortality risk score was independent of age (p < 0.0001). Figure 3 shows the estimated five-year mortality in the subsets of patients according to age group and risk category.

CARDIOVASCULAR MORBIDITY. We assigned 1 point each for prior MI and hypertension, 2 points for failure to achieve target heart rate, and 3 points if the percentage of ischemic segments was ≥25% (Table 4). The coefficient of the risk score for morbidity was similar in patients both with and without coronary artery disease (hazard ratio, 1.2, p = 0.0002; and 1.3, p < 0.0001; respectively). A risk score of 0, 1 to 2, or ≥3 permitted classification of patients into three risk categories. This C-statistic of this model was 0.62. The event rates per person-year of follow-up of patients in the three risk categories were 2%, 3%, and 6%. The estimated five-year probability of remaining free of an ischemic event



No. at risk	0	2	4	6	8
Normal	844	723	421	184	83
% isch ≤25%	596	469	307	153	71
% isch >25%	411	317	187	83	31

Figure 1. Kaplan-Meier survival curves for patients with diabetes mellitus according to the test result and extent of inducible ischemia. % isch = the percentage of ischemic segments.



No. at risk	0	2	4	6	8
Low risk	910	795	480	228	102
Intermediate risk	773	637	386	178	91
High risk	666	474	270	121	50

Figure 2. Kaplan-Meier survival curves for patients with diabetes mellitus according to the risk category.

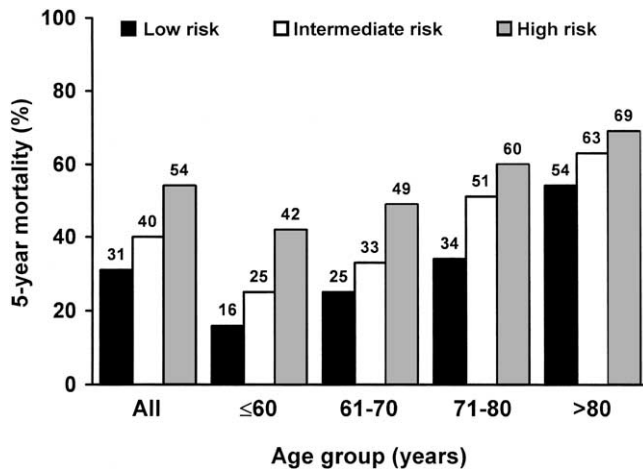


Figure 3. The estimated five-year mortality, derived from the Kaplan-Meier method, for patients with diabetes mellitus according to age group and risk category.

(excluding early revascularization) of patients in the three risk categories were 94%, 86%, and 80% ($p < 0.0001$).

An exact model-based prediction for each end point using the continuous risk models of Tables 3 and 4 is described in the Appendix. The C-statistic for each model was 0.64. When these model-based probabilities were averaged within model-based deciles of risk and compared directly with the Kaplan-Meier based probabilities for the same time points and deciles, the 40 discrepancies were within 3% more than 80% of the time for both end points. There was no systematic overestimation or underestimation of risk among the groups.

DISCUSSION

Although the diagnostic and prognostic role of DSE in evaluation of CAD is well established, less is known about its incremental value for predicting long-term outcomes in a large cohort of diabetic patients. This study shows the prognostic value of DSE in 2,349 patients with diabetes mellitus during a follow-up of up to 13 years. The mortality and cardiovascular morbidity were significantly higher in patients with abnormal or ischemic test results. Also, failure to achieve target heart rate and percentage of ischemic segments, an indicator of the extent of inducible ischemia, were independent predictors and incremental to clinical and rest echocardiographic variables for predicting adverse long-term outcomes. Simple, practical risk scores for risk stratification were developed. These models should be applied to improve treatment strategies for patients who are at high risk.

Clinical importance of a high mortality rate in patients with diabetes mellitus. In the present study, the mortality rate of patients with diabetes mellitus was higher than that in a recent study by Sozzi *et al.* (44% vs. 24%) (21). Several population-based studies of patients with diabetes mellitus, which showed mortality rates of 20% to 48% during follow-up of 5 to 10 years (22–24), provide evidence for the

adverse impact of diabetes mellitus on mortality. Cardiovascular mortality has been shown to account for the majority of deaths in diabetic patients. Although direct comparisons across these studies are problematic because of differences in baseline characteristics and follow-up duration, the mortality rate is substantial in patients with diabetes mellitus. Therefore, accurate risk stratification is important for optimal patient management.

The present study develops the prognostic information from DSE in patients with diabetes mellitus using a risk score that combines both echocardiographic and clinical variables. This score, which divides patients into three categories, is sufficiently simple for use in clinical practice.

In our study, patients with diabetes mellitus had a high prevalence of CAD risk factors and prior MI, reflecting a high-risk population. Furthermore, inability to exercise in patients with diabetes mellitus, the reason for DSE rather than exercise testing, is a marker not only of a high pretest probability of CAD but also of a poorer prognosis (25,26). Even patients in the lowest risk group had substantial mortality. As a consequence of a long duration of follow-up, the progression of non-obstructive coronary lesions and the development of new obstructive lesions may also contribute to high event rates. The present study also found that survival probabilities were lower in patients on insulin. However, this may be related to the severity of diabetes mellitus rather than to an effect of therapy.

Role of DSE in the diabetic population. Myocardial perfusion scintigraphy has been recommended by the American Diabetes Association and the American College of Cardiology for the evaluation of CAD in patients with diabetes mellitus (27). Because of the paucity of outcome data, the prognostic role of stress echocardiography in patients with diabetes mellitus was not established. Since then, more information regarding the role of stress echocardiography (exercise, dobutamine, dipyridamole, or combination) in patients with diabetes has become available (21,22,28–32). Our findings validate the prognostic significance of DSE in predicting long-term outcomes in a large cohort with diabetes mellitus and provide a simple approach for clinical risk stratification.

Study limitations. Data regarding types, duration, complications of diabetes mellitus, degree of glycemic control, and changes in medications after the DSE were not available. Also, criteria for diagnosis of diabetes mellitus evolved during the time period of the study (16). To avoid inaccuracy in defining causes of death, all-cause mortality was selected as an unbiased, objective end point (33). Data on cancer or history of congestive heart failure, important contributors to mortality, were not available in this study. To focus on the prognostic significance of DSE on cardiac outcomes, we regarded MI and coronary revascularization as cardiovascular morbidity, which was analyzed separately. It is possible, especially in this population with diabetes mellitus, that some patients may have had myocardial infarction that was not clinically recognized. Post-test re-

ferral bias likely influenced the decision to perform coronary revascularization. Although we excluded early revascularization for this reason, it is possible that test results influenced the decision for late revascularization. Nevertheless, DSE provided similar incremental value in predicting both all-cause mortality and cardiovascular morbidity. The present study provides simple risk scores for risk stratification in patients with diabetes mellitus. However, the C-statistic values of 0.60 to 0.64 for the various models presented indicate modest discrimination. External validity testing with independent samples, ideally from different institutions, would be desirable.

CONCLUSIONS

The present data verify the prognostic significance of DSE in predicting mortality and cardiovascular morbidity during a long follow-up period in a large cohort of patients with diabetes mellitus. The extent of inducible ischemia and inadequate chronotropic response showed a strong association with worse outcomes, independent and incremental to clinical and rest echocardiographic data. The simple risk scores developed in this study may be applied to the assessment of risk category in patients with diabetes mellitus.

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REFERENCES

1. Saydah S, Eberhardt M, Loria C, Brancati F. Age and the burden of death attributable to diabetes in the United States. *Am J Epidemiol* 2002;156:714–9.
2. Thomas R, Palumbo P, Melton L. Trends in the mortality burden associated with diabetes mellitus: a population-based study in Rochester, Minn 1970–1994. *Arch Intern Med* 2003;163:445–51.
3. Nesto R, Phillips R. Asymptomatic myocardial ischemia in diabetic patients. *Am J Med* 1986;80:40–7.
4. Wingard D, Barrett-Connor E, Scheidt-Nave C, McPhillips J. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study. *Diabetes Care* 1993;16:1022–5.
5. Stone P, Muller J, Hartwell T. The effect of diabetes mellitus on prognosis and serial left ventricular 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* 1989;14:49–57.
6. Smith J, Marcus F, Serokman R. Prognosis of patients with diabetes mellitus after acute myocardial infarction. *Am J Cardiol* 1984;54:718–21.
7. Koistinen M, Huikuri H, Pirttiaho H, Linnaluoto M, Takkinen J. Prevalence of asymptomatic myocardial ischemia in diabetic subjects. *BMJ* 1990;301:92–5.
8. Grundy S, IJ B, Burke G. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100:1134–46.
9. Bacci S, Villella M, Villella A. Screening for silent myocardial ischemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol* 2002;147:649–54.
10. Chuah S, Pellikka P, Roger V, McCully R, Seward J. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. *Circulation* 1998;97:1474–80.

11. Das M, Pellikka P, Mahoney D, et al. Assessment of cardiac risk before nonvascular surgery: dobutamine stress echocardiography in 530 patients. *J Am Coll Cardiol* 2000;35:1647–53.
12. Pellikka P, Roger V, Oh J, Miller F Jr., Seward J, Tajik A. Stress echocardiography. Part II. Dobutamine stress echocardiography: techniques, implementation, clinical applications, and correlations. *Mayo Clin Proc* 1995;70:16–27.
13. Poldermans D, Fioretti P, Boersma E. Dobutamine-atropine stress echocardiography and clinical data for predicting late cardiac events in patients with suspected coronary artery disease. *Am J Med* 1994;97:119–25.
14. Segar D, Brown S, Sawada S, Ryan T, Feigenbaum H. Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. *J Am Coll Cardiol* 1992;19:1197–202.
15. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039–57.
16. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–97.
17. Quinones M, Waggoner A, Reduto L, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981;64:744–53.
18. Schiller N, Shah P, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *Am Soc Echocardiogr* 1989;2:358–67.
19. Arnese M, Fioretti P, Cornel J, Postma-Tjoa J, Reijs A, Roelandt J. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J Cardiol* 1994;73:896–99.
20. Armstrong W, Pellikka P, Ryan T, Crouse L, Zoghbi W. Stress echocardiography: recommendations for performance and interpretation of stress echocardiography. Stress Echocardiography Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 1998;11:97–104.
21. Sozzi F, Elhendy A, Roelandt J. Prognostic value of dobutamine stress echocardiography in patients with diabetes. *Diabetes Care* 2003;26:1074–8.
22. Bigi R, Desideri A, Cortigiani L, Baxx J, Celegon L, Fiorentini C. Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. *Diabetes Care* 2001;24:1596–601.
23. de Fine Olivarius N, Andreasen A. Five-year all-cause mortality of 1,323 newly diagnosed middle-aged and elderly diabetic patients. Data from the population-based study, diabetes care in general practice, Denmark. *J Diabetes Complications* 1997;11:83–9.
24. Shenfield G, Elton R, Bhalla I, Duncan L. Diabetic mortality in Edinburgh. *Diabetes Metab* 1979;5:149–58.
25. Florkowski C, Scott R, Coope P, Moir C. Predictors of mortality from type 2 diabetes mellitus in Canterbury, New Zealand; a ten-year cohort study. *Diabetes Res Clin Pract* 2001;53:113–20.
26. Rubler S, Gerber D, Reitano J, Chokshi V, Fisher V. Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. *Am J Cardiol* 1987;59:1310–3.
27. Consensus development conference on the diagnosis of coronary artery disease in people with diabetes: 10–11 February 1998, Miami, Florida. American Diabetes Association. *Diabetes Care* 1998;21:1551–9.
28. Elhendy A, Arruda A, Mahoney D, Pellikka P. Prognostic stratification of diabetic patients by exercise echocardiography. *J Am Coll Cardiol* 2001;37:1551–7.
29. Elhendy A, van Domburg R, Poldermans D. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. *Diabetes Care* 1998;21:1797–802.
30. D'Andrea A, Severino S, Caso P. Prognostic value of pharmacological stress echocardiography in diabetic patients. *Eur J Echocardiogr* 2003;4:202–8.
31. Hennessy T, Cood M, Kane G, McCarthy C, McCann H, Sugrue D. Evaluation of patients with diabetes mellitus for coronary artery disease

- using dobutamine stress echocardiography. *Coron Artery Dis* 1997;8:171–4.
32. Marwick T, Case C, Sawada S, Vasey C, Short L, Lauer M. Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. *Diabetes Care* 2002;25:1042–8.
 33. Lauer M, Blackstone E, Young J, Topol E. Cause of death in clinical research: time for reassessment? *J Am Coll Cardiol* 1999;34:618–20.

APPENDIX

For the proportional hazards model-based probability of surviving one, three, five, and eight years, as well as the probability of avoiding a cardiac morbidity event, please see the online version of this article.

**Dobutamine Stress Echocardiography in Patients With Diabetes Mellitus:
Enhanced Prognostic Prediction Using a Simple Risk Score**

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