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A Clinical and Echocardiographic Score for Assigning Risk of Major Events After Dobutamine Echocardiograms

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OBJECTIVES We sought to develop and validate a risk score combining both clinical and dobutamine echocardiographic (DbE) features in 4,890 patients who underwent DbE at three expert laboratories and were followed for death or myocardial infarction for up to five years.

BACKGROUND In contrast to exercise scores, no score exists to combine clinical, stress, and echocardiographic findings with DbE.

METHODS Dobutamine echocardiography was performed for evaluation of known or suspected coronary artery disease in 3,156 patients at two sites in the U.S. After exclusion of patients with incomplete follow-up, 1,456 DbEs were randomly selected to develop a multivariate model for prediction of events. After simplification of each model for clinical use, the models were internally validated in the remaining DbE patients in the same series and externally validated in 1,733 patients in an independent series.

RESULTS The following score was derived from regression models in the modeling group (160 events): DbE risk = (age · 0.02) + (heart failure + rate-pressure product <15,000) · 0.4 + (ischemia + scar) · 0.6. The presence of each variable was scored as 1 and its absence scored as 0, except for age (continuous variable). Using cutoff values of 1.2 and 2.6, patients were classified into groups with five-year event-free survivals >95%, 75% to 95%, and <75%. Application of the score in the internal validation group (265 events) gave equivalent results, as did its application in the external validation group (494 events, *C* index = 0.72).

CONCLUSIONS A risk score based on clinical and echocardiographic data may be used to quantify the risk of events in patients undergoing DbE. (J Am Coll Cardiol 2004;43:2102–7) © 2004 by the American College of Cardiology Foundation

The ability of functional testing to predict outcomes promises to guide the development of more cost-effective approaches to the treatment of coronary artery disease (CAD). Unlike the traditional binary approach to positive and negative test results, the development of multivariate scores permits the assessment of disease probability and outcome, using a spectrum of increasingly abnormal findings (1). The additional data provided by these functional testing approaches has led them to be recommended as part of the approach to stress testing in the recent American College of Cardiology/American Heart Association guidelines (2). Indeed, several studies of exercise testing scores have shown that their ability to predict outcome exceeds that of most physicians and is equal to that of experienced cardiologists (3). Other scores have added clinical data to the stress test findings, and these appear to have greater prognostic power than the exercise data alone (4). Such a score has been developed in patients followed after exercise echocardiography (5), but this study was small, the events included minor end points, and there was no validation in an external group.

Cardiac stress imaging combinations have been used widely in situations where exercise electrocardiography (ECG) is either not feasible because of an inability to exercise or suboptimal in situations where the ECG content of the test is nondiagnostic due to resting ST-segment changes (6). Dobutamine stress echocardiography has been shown to be an independent and incremental predictor of adverse outcome (7–10), and the findings of negative and positive stress responses have been shown to be associated with various levels of risk, with implications for subsequent management. However, no scores analogous to the treadmill score have been described using dobutamine echocardiography (DbE) techniques. We sought to develop and validate a prognostic score, taking into account both clinical and stress echocardiographic findings, that could facilitate the further investigation and management of patients undergoing DbE as their primary test.

METHODS

Patient selection. We studied consecutive patients undergoing DbE at two high-volume echocardiography laboratories in the U.S. (Cleveland Clinic Foundation and Indiana University Hospital) and validated the findings in a group of patients studied during the same era at the Thoraxcenter (Rotterdam, the Netherlands). All patients had either known or suspected CAD, and clinical data, stress test findings, and echocardiographic data were all gathered prospectively. The total group of 4,890 patients comprised

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Abbreviations and Acronyms

CAD = coronary artery disease
DbE = dobutamine echocardiography/echocardiogram
ECG = electrocardiogram/electrocardiographic
LV = left ventricular
MI = myocardial infarction

3,156 studied in the U.S. (from 1988 to 1994) and 1,734 studied in the Netherlands (from 1989 to 1997). At the American sites, the most common indication for testing was risk evaluation after infarction (23%) and before noncardiac surgery (37%); 544 (17%) had the test performed for the evaluation of chest pain. Known CAD was present in 941 patients (30%), reflecting a previous myocardial infarction (MI) in 23% and revascularization in 6%. In the Dutch group, the test was performed for diagnostic reasons in 707 patients (41%), for preoperative cardiac risk assessment in 722 (42%), and after infarction in 305 (21%). The relationship between stress echocardiographic findings and outcome in these series has been previously described (11,12).

Stress testing. Patients were prepared for dobutamine testing in the usual fashion: we followed a standard protocol of dose increments to a peak dose of 40 μg/kg/min (13). Clinical and ECG monitoring was performed throughout the test. Standard end points were used, with the test being stopped for severe ischemia (severe angina, >2-mm ST-segment depression), hypertension (systolic blood pressure >220 mm Hg), hypotension (decrement of systolic blood pressure to <100 mm Hg or with symptoms), or arrhythmias. The presence of angina, ST-segment depression, and magnitude of ST-segment depression were recorded.

Echocardiography. Standard two-dimensional echocardiography was obtained at rest and after stress. Images were interpreted independent of clinical, stress, or angiographic data, and the results were made available to the physicians responsible for the patient. Based on qualitative assessment, resting left ventricular (LV) function was evaluated as normal or abnormal. Regional dysfunction was required to designate the existence of "scar," which was defined on the basis of resting akinesia or severe hypokinesia. Abnormal scans were characterized as those showing abnormal regional function in one, two, or three coronary vascular territories. Ischemia was identified by new or worsening wall motion abnormalities. The extent of ischemia was also assessed based on the anticipated territories of the three coronary arteries.

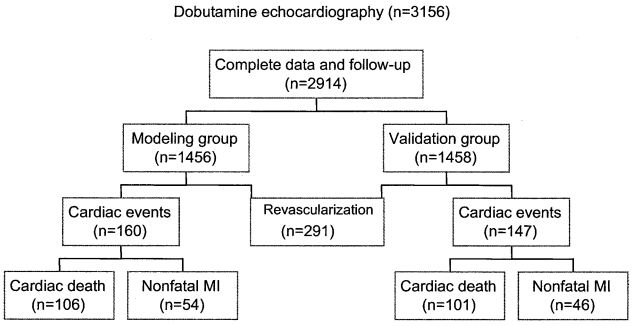

Figure 1. Distribution of patients and events into the modeling and internal validation groups for dobutamine echocardiography. MI = myocardial infarction.

Follow-up. The modeling and internal validation series (U.S. sites) were followed for 3.7 ± 1.8 years, and the external validation series (Dutch site) was followed for 3.0 ± 2.0 years. A composite end point of cardiac death or MI was used to maximize event rates in the modeling and validation groups. Those undergoing myocardial revascularization were censored at the time of this procedure. Follow-up was incomplete in 243 patients (5%), comprising 242 from the U.S. centers and one from the Dutch site.

Statistical analysis. Survival scores were developed by randomly separating the series into modeling and validation

Table 1. Clinical, Stress, and Echocardiographic Variables in the Dobutamine Echocardiography Groups

Parameter	Modeling Group (n = 1,456)	Internal Validation Group (n = 1,458)	External Validation Group (n = 1,733)
Age (yrs)	62 ± 12	62 ± 12	62 ± 12
Males (%)	856 (59%)	805 (55%)	1229 (71%)*
Diabetes (%)	298 (21%)	296 (20%)	144 (8%)*
Hypertension (>140/80 mm Hg) (%)	572 (39%)	560 (38%)	511 (29%)*
Beta-blocker (%)	275 (19%)	248 (17%)	380 (22%)
Calcium channel blocker (%)	527 (36%)	500 (34%)	347 (20%)*
Digoxin (%)	182 (13%)	187 (12%)	83 (10%)
Diuretics (%)	391 (27%)	415 (28%)	176 (10%)*
Angiotensin-converting enzyme inhibitors (%)	288 (20%)	276 (19%)	352 (20%)
Maximum heart rate (beats/min)	130 ± 19	131 ± 20	125 ± 21
Peak rate pressure product (×1,000)	19 ± 5	19 ± 5	17 ± 5†
Low rate pressure product (<15,000)	341 (23%)	340 (23%)	
Ischemia (with or without scar)	345 (24%)	351 (24%)	557 (32%)
Scar (with or without ischemia)	450 (31%)	490 (34%)	942 (54%)

There were no differences between the modeling and internal validation groups. The external validation group showed significantly fewer risk factors and a lower rate-pressure product, but more scar and ischemia (*$p = 0.01$, †$p < 0.001$). Data are presented as the mean value ± SD or number (%) of subjects.

Table 2. Independent Predictors of Events by Dobutamine Echocardiography in the Modeling Group

	Univariate Analysis		Multivariate Analysis	
	RR	p Value	RR (95% CI)	p Value
Age	1.03	0.001	1.02 (1.01–1.04)	0.008
Male gender	1.4	0.04		
Chest pain history	1.4	0.07		
Previous myocardial infarction	1.7	0.007		
History of heart failure	1.7	0.003	1.47 (1.06–2.04)	0.023
Previous myocardial infarction	1.7	0.003		
Diabetes mellitus	0.9	0.60		
Hypertension	1.7	0.03		
Beta-blocker	1.2	0.44		
Low workload	1.7	0.002	1.44 (1.03–2.02)	0.035
Peak heart rate	0.99	0.4		
Abnormal DbE	4.2	<0.0001		
Abnormality extent				
Single-vessel	2.7	<0.0001		
Two-vessel	3.2	<0.0001		
Three-vessel	3.8	<0.0001		
Ischemia	2.1	<0.0001	1.73 (1.24–2.43)	0.001
Ischemia extent				
Single-vessel	2.0	0.001		
Multivessel	2.6	<0.0001		
Scar	2.4	<0.0001	1.83 (1.32–2.55)	0.001
Scar extent				
Single-vessel	2.4	<0.0001		
Multivessel	2.9	<0.0001		
LV dysfunction	2.6	<0.0001		

CI = confidence interval; DbE = dobutamine echocardiogram; LV = left ventricular; RR = relative risk.

groups. The initial model for dobutamine stress was developed in 1,456 of 2,914 DbE patients studied at the U.S. sites and applied to validation in the remainder of the patients from these sites, as well as to the 1,733 patients with complete follow-up from the Dutch site.

The first step was identification of the univariate correlates of events using a Cox proportional hazards model. Variables showing an association with a value of $p < 0.10$ were entered into a multivariate model to identify the independent correlates with subsequent events. Rather than generate an equation where risk could be calculated as a continuous variable, but requiring calculation of exponentials (which are difficult to apply in the clinic), we used the odds ratios from this model to calculate a risk score, from which we classified low-, intermediate-, and high-risk groups with five-year event-free survival rates of >95%, 75% to 95%, and <75%, respectively, selected in order to be analogous with the classification of the Duke treadmill score. The equations were then applied in the internal and external validation groups, allowing a comparison of the outcomes between the modeling and validation groups.

RESULTS

Patient characteristics. The patient characteristics in the modeling and internal validation groups are compared in Table 1, which also shows equivalent data for the external validation group. These groups were generally well matched.

Outcomes. The outcomes of patients in the modeling and validation groups are summarized in Figure 1. The univariate risks associated with predictors of events are expressed in Table 2, which also summarizes the independent predictors of event-free survival from the best multivariate model. The simplification of these coefficients to single digits allowed the development of risk scores for DbE:

$$\text{Risk} = (\text{age} \cdot 0.02) + (\text{heart failure history} + \text{rate-pressure product} < 15{,}000) \cdot 0.4 + (\text{ischemia} + \text{scar}) \cdot 0.6$$

With the application of this score, the presence of each variable was scored as 1 and its absence scored as 0, except for age, which was entered as a continuous variable. The simplification of these parameters led to an underestimation of risk at higher levels of risk.

Patients were classified into low-, intermediate-, and high-risk groups with DbE (Fig. 3) using five-year event-free survival rates of >95%, 75% to 95%, and <75%, respectively. The relationship of stress and dobutamine scores with the three outcome categories is summarized in Table 3.

Outcomes in the validation group. Cardiac death or MI before revascularization occurred in 147 of 1,458 patients in the internal validation group and in 494 of 1,733 patients in the external validation group. The application of the risk scores to the validation groups is illustrated in Figures 2 and

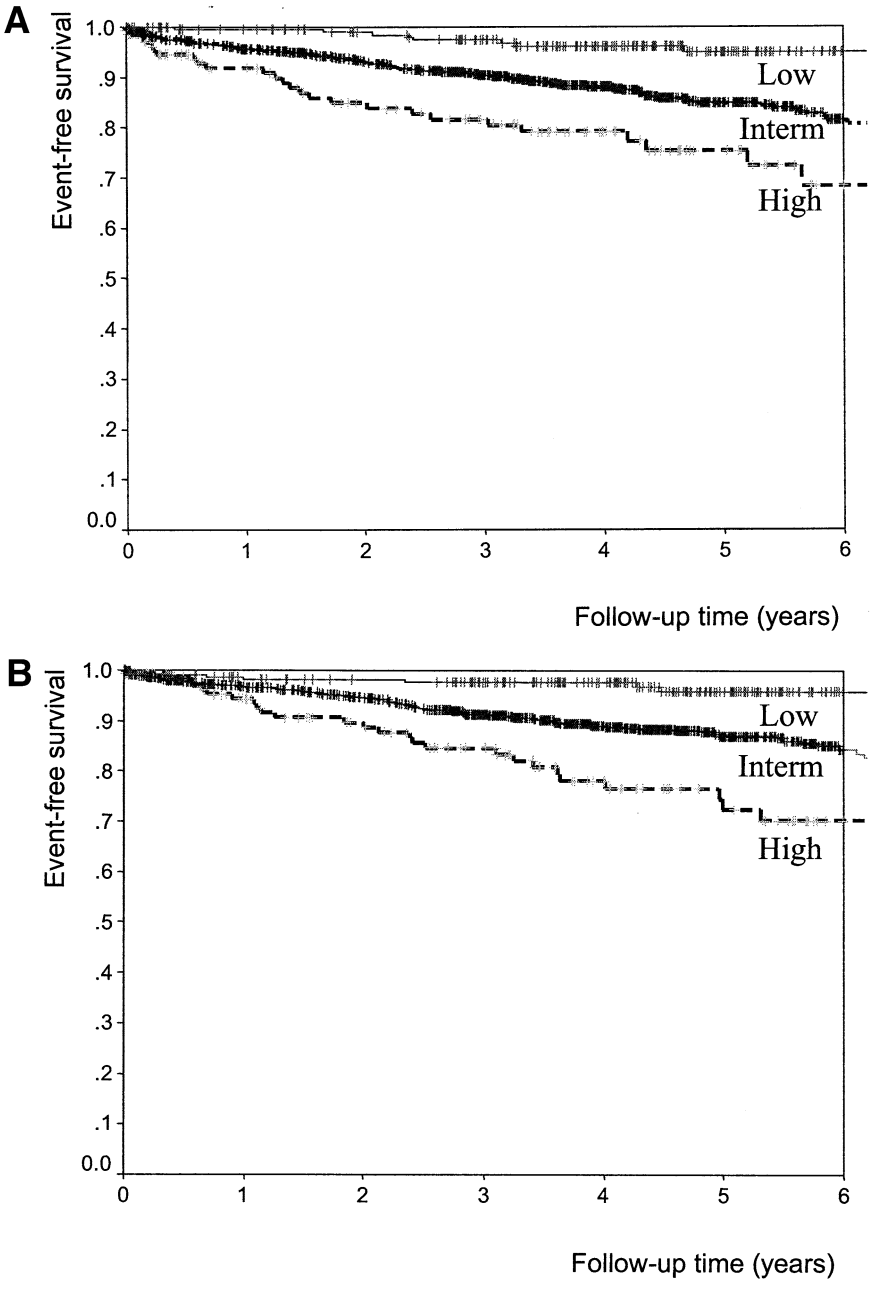

Figure 2. Outcomes of high-, intermediate-, and low-risk groups in the modeling **(A)** and internal validation **(B)** groups undergoing dobutamine echocardiography.

3. These outcomes are analogous to those in the modeling group (*C* index = 0.72).

DISCUSSION

The scores developed in this study can be used to classify patients into high-, low-, and intermediate-risk groups. Because many patients undergo DbE as their primary investigation rather than an exercise test, these tools may facilitate rational decision-making about medical management, based on the likelihood of an adverse outcome, rather than the current, more binary approach, based on a positive or negative stress result.

Prognostic implications of stress imaging tests. The performance of a negative stress test using either nuclear cardiology techniques (14) or stress echocardiography (11,12) has been shown to demonstrate low levels of risk (<1% per year). However, this risk is clearly modulated by clinical variables, including older age and diabetes (15). Moreover, if the test is positive, the level of risk is determined by the clinical setting, association with resting LV dysfunction, results of stress testing, ischemic threshold, and extent of ischemia (9,11,12), but there is no easy way of integrating these data.

A number of large databases have been used to develop prognostic scores with exercise testing. These account for not

Table 3. Relationship of Dobutamine Score With Outcome

Risk Category	Event-Free at 5 Yrs	Dobutamine Score
Low risk	>97%	<1.2
Intermediate risk	75%–97%	1.2–2.6
High risk	<75%	>2.6

only the development of ST-segment changes but also their degree, and in some instances include angina and uniformly include exercise capacity. The benefit of the scores is the incorporation of a number of prognostic variables that individually account for risk into a composite score where each of the variables is clearly represented. Although these variables are widely recognized, a number of studies have illustrated that physician estimates for both diagnosis and prognosis generally produce less favorable results than do the scores alone, certainly among noncardiologists (3). Some scores have incorporated clinical risk variables into the final score, and, as might be expected, these simple scores, despite involving a small number of variables, are more powerful than the scores based on stress testing alone (4). However, to date, no study has had a sufficient size to develop and validate a score for stress echocardiography within separate groups.

The parameters entering the scores developed in this study warrant some discussion. Notwithstanding the high risk of diabetes in those unable to exercise (16), diabetes did not appear as a major independent contributor to risk in patients undergoing DbE, probably because an inability to exercise is a marker of co-morbidities that contribute to poor outcomes. Increasing age was an important risk factor in patients undergoing DbE, perhaps reflecting the use of this test in an older group where age is more likely to be a predictor of adverse outcomes. Interestingly, the extent of abnormality did not show up as an independent marker of risk; this very likely reflects the low cardiovascular stress administered with dobutamine, as well as the tendency to stop the test at the onset of ischemia.

Clinical application of score results. The identification of low-risk patients has major management and thereby cost implications. A serious yearly event rate of <1% has been widely applied as a yardstick to identify patient groups that are unlikely to benefit prognostically from any form of mechanical coronary intervention, by percutaneous or surgical means. The development of a composite clinical and stress echocardiographic score enables the identification of such patients. For example, a 70-year-old patient with a history of heart failure has an intermediate risk score even with a negative DbE. Thus, the application of this composite score, rather than the results of stress echocardiography alone, may further streamline the allocation of low risk to individuals who do not require further investigation, while not compromising a few individuals without ischemia who are at risk and warrant further consideration.

The traditional angiographic criteria of risk readily address the extremes of high and low risk in patients with left main and triple-vessel disease with LV dysfunction (17), compared with no disease, but leaves individuals with multivessel disease at an intermediate risk. A high-risk stress echocardiographic score confers an event rate of ≥5% per year, analogous to that of patients with extensive CAD, in whom myocardial revascularization is indicated on prognostic grounds. The identification of high risk with dobutamine stress would be dependent on the identification of an abnormal stress test result. Nonetheless, the combination of

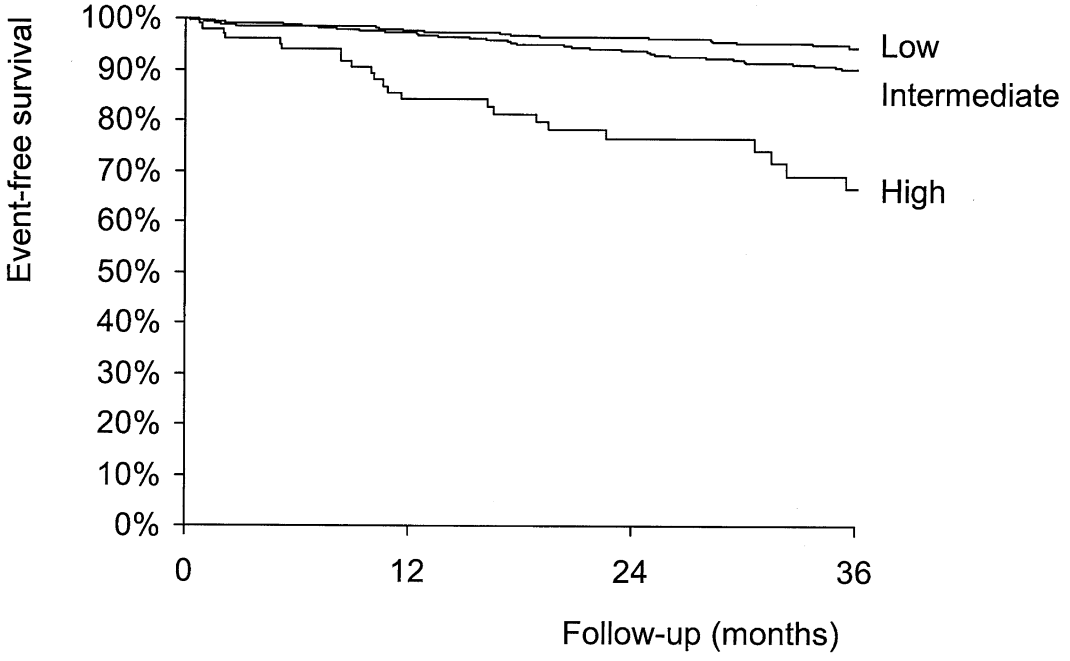

Figure 3. Outcomes of high-, intermediate-, and low-risk groups in the external validation group undergoing dobutamine echocardiography.

a patient's abnormal result with clinical markers of risk is an important predictor of high risk and may be useful in facilitating decision-making regarding revascularization.

Study limitations. The most important limitation of this study is that decision-making was likely colored by the test results. Although the original studies were performed early in the history of stress echocardiography, and prognostic data at that time would have been insufficient to directly justify decisions regarding revascularization, the test results would have influenced further investigation and thereby indirectly guided revascularization decisions. Consequently, the risk associated with a positive test result is likely underestimated, as the performance of revascularization may have reduced the risk in these patients. This limitation is inherent in such an observational study, and a large follow-up trial with the ordering physicians' results blinded to the final results is unlikely to be performed.

The selection of end points is frequently a matter of discussion in prognostic studies. Our selection of a composite end point of cardiac death or MI was used partly because of its wide usage in the prognostic literature and partly to maximize event rates in the modeling and validation groups. The relative risk with each of the variables is similar to that formerly reported using total mortality and cardiac mortality alone.

Finally, this study was performed at three large tertiary or quaternary referral centers—a feature it shares with most of the published data in this field. As such, its applicability to a general population of patients referred for DbE is not known.

Conclusions. The prognostic scores developed and validated in this study may be used to facilitate clinical decision-making in patients with known or suspected CAD, based on an individualized assessment of risk.

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