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# Prediction of Mortality Using Dobutamine Echocardiography

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**OBJECTIVES** We sought to find out whether dobutamine echocardiography (DbE) could provide independent prediction of total and cardiac mortality, incremental to clinical and angiographic variables.

**BACKGROUND** Existing outcome studies with DbE have examined composite end points, rather than death, over a relatively short follow-up.

**METHODS** Clinical and stress data were collected in 3,156 patients (age 63 ± 12 years, 1,801 men) undergoing DbE. Significant stenoses (>50% diameter) were identified in 70% of 1,073 patients undergoing coronary angiography. Total and cardiac mortality were identified over nine years of follow-up (mean 3.8 ± 1.9). Cox models were used to analyze the effect of ischemia and other variables, independent of other determinants of mortality.

**RESULTS** The dobutamine echocardiogram was abnormal in 1,575 patients (50%). Death occurred in 716 patients (23%), 259 of whom (8%) were thought to have died from cardiac causes. Patients with normal DbE had a total mortality of 8% per year and a cardiac mortality of 1% per year over the first four years of follow-up. Ischemia and the extent of abnormal wall motion were independent predictors of cardiac death, together with age and heart failure. In sequential Cox models, the predictive power of clinical data alone (model chi-square 115) was strengthened by adding the resting left ventricular function (model chi-square 138) and the results of DbE (model chi-square 181). In the subgroup undergoing coronary angiography, the power of the model was increased to a minor degree by the addition of coronary anatomy data.

**CONCLUSIONS** Dobutamine echocardiography is an independent predictor of death, incremental to other data. While a normal dobutamine echocardiogram predicts low risk of cardiac death (on the order of 1% per year), this risk increases with the extent of abnormal wall motion at rest and stress. (J Am Coll Cardiol 2001;37:754–60) © 2001 by the American College of Cardiology

Dobutamine echocardiography (DbE) is an accurate alternative to exercise testing for the diagnosis of coronary artery disease (CAD) in patients who are unable to exercise (1,2), and it is also a valuable tool for the assessment of viable myocardium (3,4). There are substantial data supporting the use of this technique for prediction of short-term (i.e., perioperative) risk (5,6). However, most studies of the prognostic implications of DbE in patients with stable coronary disease have investigated the ability of the test to predict composite end points over short-to-intermediate-term follow-up (7).

In order to justify the cost of testing, it is important to show that investigations alter outcome. The ability to predict low risk would justify a conservative approach to management in patients with a negative test. Conversely, the demonstration that DbE adds information incremental to clinical and resting data for the prediction of mortality might have important implications for the selection of different therapies. This could be especially important in situations where anatomic data regarding coronary disease extent are also available, in which case the results may justify medical over interventional therapy. Given the relatively low cardiac mortality of patients with stable chronic coronary disease, such a study would require a large number of patients followed over a significant duration. We, therefore, established a multicenter study to address whether DbE could independently identify the risk of cardiac and total mortality and to examine the implications of a negative test over prolonged follow-up. As increasing attention is being paid to the appropriate indications for stress imaging, we sought also to evaluate how to integrate the results with the assessment of clinical risk and the findings of coronary angiography.

## METHODS

**Study design.** Between 1988 to 1994, 3,156 consecutive patients (1,801 men and 1,355 women, age 63 ± 12 years) with known or suspected coronary disease underwent DbE at the Cleveland Clinic Foundation or Indiana University. Clinical characteristics and indications for testing were recorded prospectively. Follow-up of all patients was approved by the Ethics Committee of the Cleveland Clinic Foundation and was completed at the end of 1998.

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**Abbreviations and Acronyms**

CAD = coronary artery disease
DbE = dobutamine echocardiography
LV = left ventricular
SPECT = single photon emission computed tomography

**Clinical evaluation.** The most common indication for testing was risk evaluation following infarction (23%) and before noncardiac surgery (37%); 544 patients (17%) had the test performed for the evaluation of chest pain. Known CAD was present in 941 patients (30%), reflecting prior myocardial infarction in 23% and revascularization in 6%. Typical angina was present in 708 patients (23%); atypical pain was present in 2,091 (66%), and the remaining 357 patients (11%) had no or noncardiac pain. The pretest probability of CAD in those without known disease, determined on the basis of age, gender and symptom status (8) was 55 ± 24%. The risk of mortality at one year was 3.1 ± 2.5%, based on a simple score obtained from the Duke database involving the variables of age, chest pain, cardiac history, risk factors and comorbidity (9). Risk factors were highly prevalent with 58% of the patients having diabetes and 42% having hypertension. An abnormal electrocardiogram was present in 71% of patients, most commonly due to prior myocardial infarction.

Most patients (71%) were receiving medical therapy for ischemic heart disease at the time of recruitment; 18% were taking beta-adrenoceptor antagonists; 36% of patients received calcium antagonists, and 19% of patients received angiotensin-converting enzyme inhibitors. The combination of digoxin and diuretic therapy was used to define heart failure requiring therapy.

**DbE.** A resting echocardiogram was performed in parasternal and apical views and digitized on-line into a quad-screen display. With the patient under continuous clinical, electrocardiographic and echocardiographic monitoring, dobutamine was infused using a standard incremental dosing protocol from 5 to 40 μg/kg/min (1). The test was terminated after completion of the final stage or earlier if necessitated, by severe ischemia (severe angina, >2 mm ST depression, extensive wall motion abnormalities), hypertension (systolic blood pressure >220 mm Hg), hypotension (decrement of systolic blood pressure >20 mm Hg), arrhythmias or side-effects intolerable to the patient. Over most of the period of the original stress study (1988 to 1994), the administration of atropine had not yet become standard practice (10). Therefore, a small proportion of patients who failed to attain 85% of age-predicted maximal heart rate at peak dose was administered atropine (1 mg intravenous).

The study sought to address the prognostic value of the test in routine practice, so the results of each study were interpreted at the time of the original examination by echocardiographers trained in stress echocardiography. Resting left ventricular (LV) function was evaluated on the basis of the extent of resting wall motion abnormalities as normal, mild, moderately or severely impaired. Infarction was recognized on the basis of akinesis or dyskinesis at rest. Stress echocardiography was interpreted by comparison of rest and stress images in a digitized quad-screen display. Review of videotaped images was obtained, if desired, by the interpreting physician, but the policy at each center was to interpret the study independent of clinical, stress or angiographic data. Segments with normal resting function without any deterioration induced by dobutamine stress were characterized as normal. Segments with a resting wall motion abnormality that demonstrated augmentation of function were considered viable, but this was not recognized as a discrete response at the time of some of the initial interpretations (1988 to 1994). Ischemia was identified in the presence of a new or worsening wall motion abnormality. The extent of ischemia was classified as indicative of no, one, two or three vessel CAD by combining the myocardial segments into vascular territories. For this purpose, the apex, anteroseptal, septal and anterior walls were attributed to the left anterior descending, the lateral to the left circumflex and the inferior and basal septal to the right coronary. Because of the variable balance between the circumflex and right coronary, the posterior wall was attributed to whichever was abnormal, based on involvement of other segments, unless it was involved in isolation, in which case it was ascribed to the circumflex vessel. A negative study was characterized by a normal response in all segments, and a study was designated as abnormal if one or more segments showed evidence of infarction or ischemia. The results of the dobutamine echocardiograms were made available to the physicians responsible for the patient.

**Follow-up.** Cardiac and total mortality were the primary end points; hospital and physician records and death certificates were used to ascertain the cause of death, which was attributed to a cardiac etiology if a cardiac illness provoked the final presentation or if death was sudden and unexpected. For the analysis of cardiac mortality, patients dying from other causes were censored from follow-up at the time of death. Coronary bypass surgery or coronary angioplasty was not identified as a cardiac event, and patients were censored at the time of these procedures.

**Statistical analysis.** The statistical analyses included descriptive statistics (frequency and percentage of categorical variables and mean and standard deviation of continuous variables), Kaplan-Meier survival curves and Cox proportional hazards models. Differences between survival curves were compared with the log-rank test. All analyses were performed using SPSS statistical software (SPPS Inc., Chicago, Illinois), and p values $<0.05$ were considered to be statistically significant. In the situation of making multiple comparisons, significant p values were defined by the Bonferroni method.

## RESULTS

**Dobutamine response.** The end points of dobutamine stress were comparable with those in the literature; 84% of patients completed the protocol; the dose was limited by side-effects in 9%, and 7% had the test stopped prematurely due to ischemia. The patients attained 83 ± 12% of age-predicted maximal heart rate, and the peak rate-pressure product was 19 ± 5 × $10^3$ beats × mm Hg.

Echocardiographic images were interpreted in all patients who completed the test. Half of the patients had a normal study. Of the remainder, 609 (19%) had a resting wall motion abnormality alone; 517 (16%) showed ischemia, 166 (5%) viability, and 283 (9%) had a mixture of abnormalities.

**Events during follow-up.** Patients were followed for up to nine years (mean 3.8 ± 1.9 years), and follow-up data were successfully obtained in 3,115 patients (99%). The total mortality was 716 (23%), among whom death was attributed to cardiac causes in 259 patients (8%). Myocardial revascularization was performed in 332 patients who were censored from follow-up at this time.

**Association with total and cardiac mortality.** The total and cardiac survivals of patients with normal, ischemic and scar findings at DbE are summarized in Figure 1. The findings of DbE provide risk-stratification for total and cardiac mortality. Moreover, the total extent of dysfunction at peak stress is predictive of outcome (Fig. 2).

The risk of cardiac or any mortality conferred by DbE findings relative to other variables is summarized in Table 1. These multivariate models were derived from significant univariate correlates of death, including clinical variables (age, gender, diabetes, pretest probability of CAD, previous myocardial infarction and revascularization, clinical risk), medical treatment (digoxin, diuretics and angiotensin-converting enzyme inhibitors), resting echocardiography and stress variables (maximum heart-rate, peak systolic blood pressure, rate-pressure product and ischemia). Resting LV dysfunction and inducible ischemia were independent predictors of death.

Sequential models for the prediction of mortality were devised to assess the incremental contribution of stress echocardiography to clinical evaluation and resting assessment of LV function (Fig. 3). For cardiac death, age, gender and heart failure therapy entered the clinical model (chi-square 132, $p < 0.00001$). The addition of resting LV function increased the power of the model (chi-square 143, $p < 0.00001$). The addition of stress testing data (extent of ischemia and rate-pressure product) further increased the power of the model (chi-square 157, $p < 0.00001$). The same factors entered the clinical model for total mortality (chi-square 200, $p < 0.00001$); the addition of resting LV function again increased the power of the model (chi-square 271, $p < 0.00001$), which was increased further by stress data (chi-square 292, $p < 0.00001$).

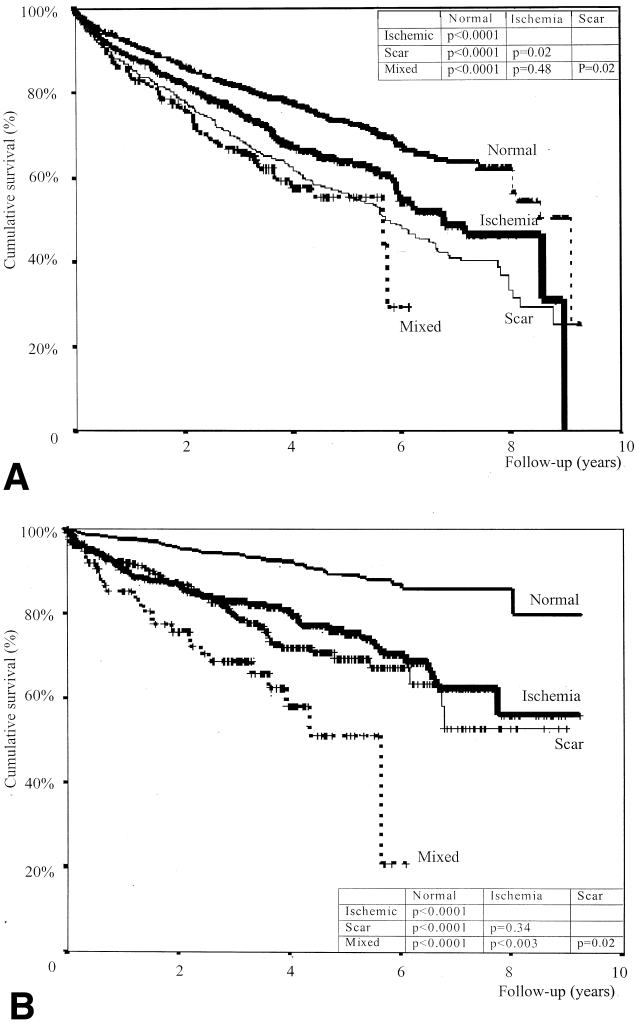


**Figure 1.** Kaplan-Meyer survival curves for the prediction of total **(A)** and cardiac **(B)** mortality based on results of dobutamine echocardiography. The outcome of patients with a normal scan was significantly different from those with scar, ischemia or a mixed pattern.

**Outcome of patients with a negative dobutamine echocardiogram.** The outcome of the 1,581 patients with a negative dobutamine echocardiogram is illustrated in Figure 1. A normal study is associated with a cardiac mortality of approximately 1% per year over the first four years of follow-up, and this event rate accelerates slightly thereafter. The difference between the average total mortality of 8% per year and the cardiac mortality of 1% per year reflects the high prevalence of comorbidity in these patients undergoing DbE.

Table 2 summarizes the features of 60 patients with a normal study who died of cardiac causes during follow-up. These patients were older and more likely to be receiving therapy for heart failure than patients with a normal test but having no events. In patients with heart failure but a negative dobutamine echocardiogram, age <65 years was not associated with an increment of risk, but patients 65 to 75 years of age had a yearly cardiac mortality of 4%, increasing to 6% yearly in patients >75 years old. Patients with events were also more likely to have attained a lower

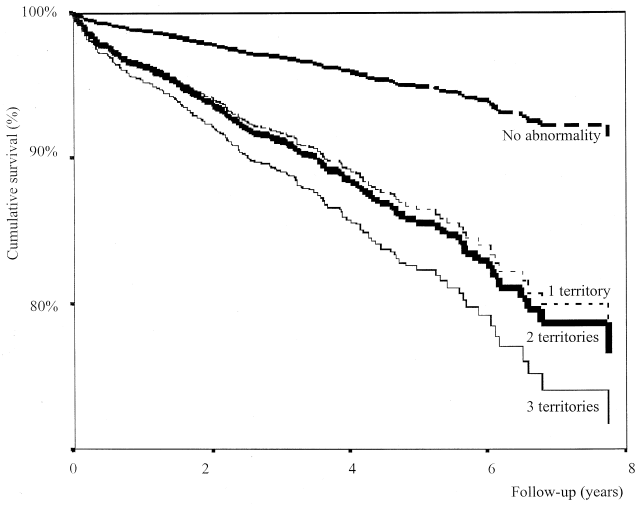


**Figure 2.** Survival curves derived from the Cox model showing the relation of extent of abnormal function at peak stress to outcome. The outcome of patients with a normal scan was significantly different from those with functional abnormalities of increasing severity ($p < 0.0001$).

workload (rate-pressure product) although patients receiving beta-adrenergic blocking agents and calcium antagonist therapy were comparable to those without events.

**Integration with clinical data.** Stress imaging tests have become widely used, and the appropriateness of this testing may be questioned. By correlating the initial clinical evaluation with subsequent outcomes independent of other predictors in the Cox model, we sought to identify a low-risk group that might not need prognostic testing. Neither pretest probability of coronary disease nor clinical risk index was an independent determinant of outcome (Table 1). Neither were the indications for testing the source of significant variation in outcome. The group tested for the assessment of viable myocardium had the most adverse outcome (reflecting the presence of LV dysfunction), and those undergoing diagnostic evaluation for chest pain fared the best (reflecting a proportion of patients without coronary disease). No group could be identified in this data set as being at low risk on clinical grounds, reflecting appropriate selection for testing.

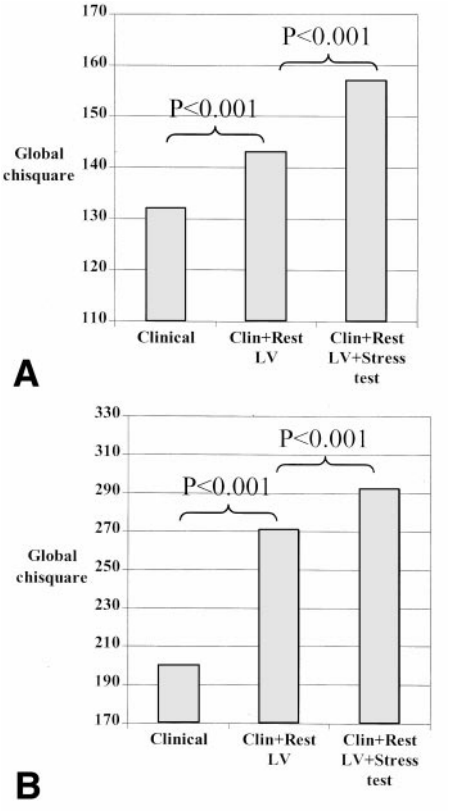


**Figure 3.** Incremental value (expressed on y axis as model chi-square) of dobutamine stress echocardiography results to clinical characteristics and resting LV function for prediction of cardiac outcome. See text for components of models. LV = left ventricular.

**Integration with coronary angiography.** The prognostic value of DbE relative to coronary angiography was addressed in a subgroup of 1,073 patients who also underwent coronary angiography within a year of the dobutamine echocardiogram without an intervening procedure. Of these individuals, 327 (31%) had no significant coronary disease; 218 (20%) had single-vessel disease, and 528 (49%) had multivessel coronary disease. Sequential Cox regression models were developed in this subgroup to reflect the sequence of obtaining data in clinical practice. A model using clinical variables only (age, heart failure and hyper-

**Table 1.** Independent Predictors of Total Cardiac Mortality Based on Clinical Variables and Results of Dobutamine Echocardiography

| | Total Mortality | | Cardiac Mortality | |
|---|---|---|---|---|
| | RR (95% CI) | p Value | RR (95% CI) | p Value |
| Age (yrs) | 1.02 (1.01–1.03) | < 0.0001 | 1.03 (1.02–1.04) | < 0.0001 |
| Male gender | 1.28 (1.11–1.48) | 0.001 | 1.49 (1.11–1.98) | 0.007 |
| Digoxin | 1.44 (1.20–1.72) | 0.0001 | 2.02 (1.46–2.80) | 0.0001 |
| Diuretic | 1.35 (1.17–1.56) | 0.0001 | 1.47 (1.09–1.98) | 0.012 |
| ACE inhibitors | | | 1.70 (1.24–2.34) | 0.0009 |
| LV dysfunction (EF < 50%) | 1.28 (1.19–1.37) | 0.0001 | 2.60 (1.90–3.40) | < 0.0001 |
| Resting heart rate | 1.01 (1.00–1.02) | < 0.0001 | | |
| Peak rate-pressure product < 15,000 | 1.30 (1.50–1.13) | 0.0001 | | |
| Ischemia by echocardiography | 1.39 (1.20–1.62) | 0.0001 | 1.83 (1.36–2.47) | 0.0001 |

ACE = angiotensin-converting enzyme; CI = confidence interval; EF = ejection fraction; LV = left ventricular; RR = relative risk.

**Table 2.** Predictors of Cardiac Death in Patients With Negative Dobutamine Echocardiograms

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | RR (95% CI) | p Value | RR (95% CI) | p Value |
| Clinical | | | | |
| Age (yrs) | 1.05 (1.03–1.07) | < 0.0001 | 1.05 (1.03–1.07) | < 0.0001 |
| Male gender | 1.42 (0.87–2.29) | 0.16 | | |
| Pretest probability of CAD | 1.01 (1.00–1.02) | 0.02 | | |
| Angina | 5.50 (0.70–41.5) | 0.14 | | |
| Previous coronary bypass | 1.09 (0.40–3.01) | 0.86 | | |
| Previous myocardial infarction | 1.19 (0.54–2.60) | 0.66 | | |
| Diabetes | 1.46 (0.76–2.80) | 0.25 | | |
| Hypertension | 5.0 (1.5–16.0) | 0.009 | | |
| One-year clinical risk | 1.02 (1.01–1.03) | 0.0003 | | |
| Stress testing | | | | |
| Resting heart rate | 1.01 (0.99–1.03) | 0.009 | | |
| Resting systolic blood pressure | 1.01 (1.00–1.02) | 0.05 | | |
| Maximum heart rate | 0.99 (0.98–1.00) | 0.08 | | |
| % age-predicted max heart rate | 1.01 (0.99–1.04) | 0.25 | | |
| Peak systolic blood pressure | 0.99 (0.98–1.00) | 0.005 | | |
| Peak rate-pressure product < 15,000 | 2.21 (1.35–3.63) | 0.002 | 2.09 (1.27–3.45) | 0.004 |
| Therapy | | | | |
| Beta-adrenoceptor antagonists | 0.65 (0.31–1.36) | 0.25 | | |
| Calcium antagonists | 1.36 (0.84–2.22) | 0.21 | | |
| Long-acting nitrates | 3.06 (0.96–9.77) | 0.059 | | |
| Digoxin | 2.47 (1.34–4.53) | 0.004 | 1.93 (1.04–3.60) | 0.04 |
| Diuretic | 1.50 (0.91–2.47) | 0.111 | | |
| ACE inhibitors | 2.0 (1.17–3.39) | 0.011 | 2.05 (1.19–3.51) | 0.01 |

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CI = confidence interval; RR = relative risk.

tension) gave an overall chi-square of 43.2. Addition of stress echocardiography (total extent score) increased this to 57.4, while adding angiography (number of involved vessels) increased the chi-square further to 61.7 (Fig. 4).

## DISCUSSION

This follow-up study of DbE addresses the ability of this test to predict cardiac and total mortality. A negative dobutamine echocardiogram accurately identifies low-risk patients with a cardiac mortality of about 1% per year over the first few years of follow-up, with a subsequent increase reflecting the progression of coronary disease. This test is an independent predictor of the risk of death, incremental to clinical and resting echocardiographic data, and the degree of risk parallels the increasing extent of abnormal function. Indeed, the addition of angiographic data added little prognostic power to the results of clinical evaluation and stress echocardiography.

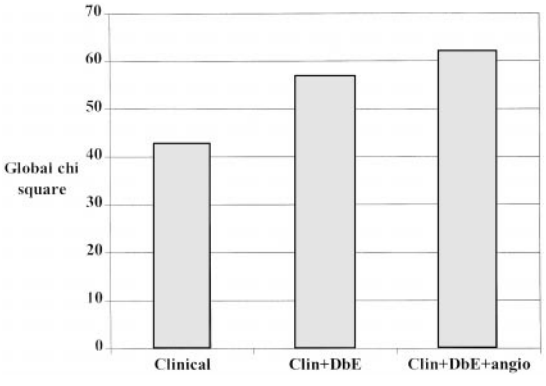


**Figure 4.** Incremental value (expressed on y axis as model chi-square) of dobutamine stress echocardiography results to clinical characteristics and coronary angiography for prediction of cardiac outcome. Multivariate analysis of independent predictors of outcome in 1,073 patients who underwent dobutamine echocardiography and coronary angiography. DbE = dobutamine echocardiography.

**Identification of low-risk patients.** The ability to detect patients at low risk for cardiac events has been shown in large trials using single photon emission computed tomography (SPECT) imaging. Stress echocardiography is a relatively younger technique, and the value of the test for risk evaluation has been questioned (11). A number of studies involving smaller numbers of patients and shorter follow-up have now been published for dobutamine stress echocardiography (12–22). The comparison of these studies has been clouded by the use of different end points in various studies, but in those that have examined cardiac death or hard events, the yearly event rate with a negative exercise or DbE has been on the order of 1% per year. These findings are confirmed by our study, which also shows that, in terms of total mortality, the group studied by DbE is at high-risk for death, probably because of a high prevalence of comorbidity. Our findings also show that the low-risk "warranty" of a negative test is conferred for up to four years. Later in follow-up, the cardiac events in individuals with a negative test probably reflect the presence of progressive coronary disease.

No test can be expected to be completely effective in predicting freedom from subsequent events. In our experience, the predictors of events in individuals with a negative

test include increasing age and heart failure. In previous work examining composite end points, "false negative" exercise echocardiograms were also predicted by low-workload, anginal symptoms despite the absence of identifiable wall motion abnormalities and left ventricular hypertrophy (23).

**Stratification of risk in patients with positive tests.** Even in the era before current therapy, patients with stable chronic coronary disease were reported to have a relatively low cardiac mortality of 4% per year (24). Our findings indicate that the presence and extent of abnormalities at stress echocardiography is incremental to clinical variables in the prediction of cardiac events.

Clinical factors have been shown to quite effectively identify risk in patients with stable CAD (25), and the use of clinical scores to identify patients at the extremes of risk on clinical grounds may help to avoid inappropriate investigations. However, the impact of clinical risk status has been better evaluated in the nuclear literature than with echocardiography (26–28). Our findings are that, although clinical risk is a predictor of outcome, it is not possible to identify a low-risk group other than those at low probability for CAD on diagnostic grounds.

The extent and severity of perfusion defects have been shown to correlate very well with the outcomes of patients studied using SPECT, among which the strongest predictor is the extent of malperfused tissue (29), reflecting both the extent and severity of rest- and stress-perfusion defects. The results of this study indicate that an analogous measure of the number of ischemic and infarcted vascular territories is predictive of outcome using DbE. The ability to identify a spectrum of risk may facilitate the selection of medical and interventional treatments; indeed, arguments have been made against the use of interventions in individuals with small fixed or reversible SPECT defects.

**Prognostic implications relative to angiographic data.** The prognostic implications of DbE relative to coronary angiography were studied in a subgroup of 1,073 patients who underwent coronary angiography. The benign prognostic implications of a negative DbE may alleviate clinicians' concern regarding "false negative" stress echocardiograms and reduce the rate of angiography in patients with ongoing symptoms but negative stress tests. The addition of the angiographic data to the clinical and stress data increased the ability to predict cardiac outcomes. This analysis could have been influenced by the process of censoring patients who underwent revascularization, because this particular group would have undergone angiography. On the other hand, these individuals may have their natural history altered by intervention, which would reduce the event rate and, therefore, the predictive power of each diagnostic technique.

**Interpretation of stress echocardiography.** The interpretation of regional wall motion is currently based on the qualitative interpretation of regional wall motion abnormalities, and this subjective approach, together with the use of multiple observers, was used to mimic the behavior of the test in daily practice. Data on interobserver variability were not gathered for this study; previous work has suggested that observers at each center share an interpretation style (30). The sites selected for this study have a concordant reading style, reflecting previous training and teaching collaboration so that interinstitution discordance (31) was not considered to be an important factor. Finally, as in other multicenter stress-imaging studies (26,32), we sought to simplify assessment of disease extent into involvement of coronary vascular territories rather than selecting a more complicated score in order to enhance the wide applicability of the results.

**Cardiac and total mortality.** Although recent work from the nuclear imaging literature has focused on the prediction of cardiac death (27,28), this approach is subject to problems of ascertainment between cardiac and noncardiac mortality. The accuracy of this approach has been recently criticized (33), and, although the overall 2% cardiac mortality in this study is within the expected range for chronic stable CAD, the overall 6% total mortality may be due to misrepresentation of some deaths as noncardiac as well as the high prevalence of comorbidity. Because of the advantages and disadvantages of each approach, we have expressed both total and cardiac mortality. The retention of cardiac death as a focus of the paper facilitates comparison with the older literature and addresses the likelihood of many noncardiac deaths among older patients with multiple comorbidities.

**Study limitations.** An inherent limitation of follow-up studies is that they reflect the performance of a technique as it was applied years before the completion of the study. This methodologic drift is apparent in this study, which involved administration of currently standard doses of dobutamine, but largely without the addition of atropine. Use of atropine might have led to the identification of additional patients with coronary disease, with reduction in the number of patients having events after a negative scan. A related problem might be termed diagnostic drift—by intention, the data gathered in this study were the original test interpretations to reflect the behavior of the test in clinical practice. However, this precluded the recognition of myocardial viability in many patients, which was not widely recognized during DbE until later in the study period. Finally, the test results may have influenced the clinical management of patients, especially decisions to perform revascularization. The revascularization of patients with positive test results likely reduced the prognostic power of ischemia, as patients were censored at the time of this procedure.

**Conclusions.** Dobutamine echocardiography provides prognostic information regarding total and cardiac mortality, independent and incremental to standard predictors of outcome. Assessment of the extent of ischemia and clinical variables may be used to make outcome-based decisions regarding patient management.

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