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Use of Exercise Echocardiography for Prognostic Evaluation of Patients With Known or Suspected Coronary Artery Disease

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Objectives. **This study prospectively compared the incremental prognostic benefit of exercise echocardiography with that of exercise testing in a large cohort.**

Background. **Exercise echocardiography is widely accepted as a diagnostic tool, but the prognostic information provided by this test, incremental to clinical and stress testing evaluation, is ill-defined.**

Methods. **Clinical, exercise and echocardiographic variables were studied in a consecutive group of 500 patients undergoing exercise echocardiography. After exclusion of patients who underwent revascularization within 3 months of the stress test (n = 16, 3%) and those lost to follow-up (n = 21, 4%), the remaining 463 patients (mean [±SD] age 57 ± 12 years, 302 men) were followed-up for 44 ± 11 months. Outcome was related to the exercise and echocardiographic findings, and the incremental prognostic benefit of exercise echocardiography was compared with that of standard exercise testing.**

Results. **Cardiac events occurred in 81 patients (17%), including 33 (7%) with spontaneous events (cardiac death, myocardial infarction and unstable angina) and 48 with late revascularizations due to progressive symptoms. In a multivariate Cox proportional hazards model, the likelihood of *any cardiac event* was increased in the presence of ischemia (relative risk [RR] 5.06, 95% confidence interval [CI] 3.09 to 8.29, p < 0.001) and lessened by more maximal stress, measured as percent age-predicted maximal heart rate (RR per 5% increment 0.84, 95% CI 0.77 to 0.92, p < 0.001). *Spontaneous events* were more strongly predicted by ischemia (RR 8.20, 95% CI 3.41 to 19.71, p < 0.001) and percent age-predicted maximal heart rate (RR per 5% increment 0.78, 95% CI 0.67 to 0.91, p < 0.001). An interactive logistic regression model showed that the addition of echocardiographic to exercise and clinical data offered incremental predictive value.**

Conclusions. **The presence of ischemia on the exercise echocardiogram can predict whether patients will experience an event. This relation is independent of, and incremental to, clinical and exercise data.**

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Exercise echocardiography is an accepted test for the detection of coronary artery disease (1–4). It is most commonly used in situations where the exercise electrocardiogram (ECG) is unreliable (5–7) or when treatment decisions may be dependent on demonstrating the site or extent of ischemia. From a prognostic standpoint, however, clinical evaluation and the results of exercise testing are known to be predictive of subsequent coronary events (8,9). In the current medical economic environment, there is a need to demonstrate that exercise echocardiography adds data predictive of patient outcome, and that this is incremental rather than duplicative of prognostic information available from conventional sources.

In patients who are unable to exercise, pharmacologic stress echocardiography is used for the diagnosis of coronary artery disease. The presence of ischemia during this test has been shown to be associated with an adverse outcome in patients with stable chronic coronary artery disease (10–13), in those who have had a myocardial infarction (14) and in those having cardiac risk evaluated before vascular surgery (15,16). However, patients who are unable to exercise may have a particularly high event rate, which may not be representative of patients submitted to exercise testing. Moreover, exercise stress testing itself offers useful prognostic information (8,9), and whether this attenuates the incremental prognostic utility of the echocardiographic component has not been defined.

This study sought to define the prognostic implications of exercise echocardiography in a large and consecutive group of patients undergoing the test and followed up for cardiac events over 5 years. These findings were interpreted in the context of prognostic information available from clinical and exercise data to define the incremental value of exercise echocardiography.

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Methods

Patient selection. We prospectively studied 500 consecutive patients (mean [±SD] age 57 ± 12 years, 302 men) who underwent their initial exercise echocardiogram between October 1989 and October 1991. Patients were then followed up

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Abbreviations and Acronyms

CI	=	confidence interval
ECG	=	electrocardiogram
METs	=	metabolic equivalents
RR	=	relative risk

for 5 years after the initial presentation. The investigations were performed in accordance with the usual ethical guidelines of the Cleveland Clinic Foundation.

The original test was performed for follow-up of known stable chronic coronary artery disease in 266 patients (53%) and for the diagnosis of suspected coronary artery disease in 234 patients. Antianginal therapy was highly prevalent—153 patients were taking calcium antagonists, 71 were on beta-adrenoceptor blockers and 73 were taking nitrates. If patients underwent multiple examinations, only the results of the first examination were analyzed.

Exercise testing. Patients were questioned regarding their presenting symptoms, cardiac history and medical therapy on presentation to the exercise testing laboratory, and these data were gathered prospectively. After a rest 12-lead ECG was performed, an exercise protocol (usually Bruce, modified Bruce or Naughton) was selected in accordance with the cardiovascular and general physical capacity of each subject. Standard end points of exercise testing (17) were used: severe symptoms (most commonly fatigue, severe angina, severe dyspnea), severe ischemia (>0.3-mV ST segment depression), increasing complex ectopy or ventricular tachycardia, exaggerated blood pressure response (>250 mm Hg systolic, >130 mm Hg diastolic) or evidence of cardiac decompensation (pallor, dizziness, >20-mm Hg drop with increasing stress). The hemodynamic response to stress (peak heart rate, percent age-predicted maximal heart rate, peak systolic blood pressure, peak rate–pressure product) were noted. Exercise capacity was estimated from published tables for each stress protocol (18). Previous studies have shown an increment of risk when exercise capacity is <5 to 7 metabolic equivalents (METs) (8,19). In this study, exercise capacity was analyzed in patients who exercised for <6 and ≥6 METs, in addition to analysis as a continuous variable.

The ECG was interpreted by independent observers at rest and after stress. Results were classified as *positive* (horizontal or downsloping ST segment depression >0.1 mV at an interval of 0.08 s after the J point in any lead), *nondiagnostic* due to an abnormal baseline ST segment (left ventricular hypertrophy, left bundle branch block, and digitalis effect) or *negative*.

Exercise echocardiography. Rest two-dimensional echocardiography was performed in the left lateral decubitus position using standard ultrasound imaging equipment. Images were obtained in parasternal long- and short-axis and apical four- and two-chamber views before and immediately after (usually <1 min) treadmill exercise. In addition to being recorded on 0.5-in. (1.27-cm) VHS videotape, these data were digitized on-line (PreVue or ImageVue, Nova Microsonics), with the resulting files stored on floppy and optical discs.

Both digital and videotaped data were interpreted in consecutive patients, irrespective of image quality, at the time of the examination. This interpretation was based on the consensus of at least two observers who had no knowledge of the clinical, exercise electrocardiographic and coronary arteriographic data and who used a standard 16-segment model of the left ventricle to identify ischemia and infarction. Ischemia was identified by the development of a new or worsening wall motion abnormality, whereas rest akinesia or dyskinesia (irrespective of exercise response) was defined as infarction. Patients were subclassified into four groups based on these segmental data: normal, ischemia alone, infarction alone and ischemia with infarction.

Follow-up. Follow-up was performed by clinic review or telephone contact at a mean of 44 ± 11 months after exercise echocardiography. A record was kept of the occurrence and timing of cardiac and noncardiac death, myocardial infarction, unstable angina or late revascularization. The cause of death was obtained from hospital or physician records; deaths were ascribed to ischemic heart disease if a cardiac illness provoked the final presentation. Myocardial infarction was identified by the physicians caring for the patient on the basis of history, enzymes and ECG changes. Unstable angina was defined by angina at rest or progressive angina requiring hospital admission. Late revascularization was defined by the performance of coronary angioplasty or coronary artery bypass graft surgery >3 months after the original stress test, reflecting new or progressive symptoms. Analyses were performed for the prediction of all events (cardiac death, myocardial infarction, unstable angina and late revascularization) and spontaneous events (events excluding revascularization).

Statistical analysis. The statistical analyses included descriptive statistics (mean ± SD of continuous variables and frequency and percentage of categoric variables), Kaplan-Meier analysis and Cox proportional hazards models. Two sets of Kaplan-Meier tests were performed, comparing the type of exercise echocardiographic response and the relation between exercise echocardiography and exercise electrocardiography. Differences between survival curves were compared using the log-rank test. The Cox proportional hazards model was run using univariate and stepwise multivariate approaches. Data were also analyzed using an interactive model, as discussed subsequently. In all analyses, $p < 0.05$ was considered to be statistically significant, except in the analysis of incremental benefit, as described subsequently.

The incremental benefit of exercise echocardiography was studied using Cox proportional hazards regression to model event-free survival as a function of three successive sets of predictors—clinical data, exercise testing and exercise echocardiography. Variables were added in stepwise fashion and retained if they had significance at $p \leq 0.10$. First, we included clinical variables measured on entry into the study, including age, gender, body surface area and previous myocardial infarction. The second step included the significant clinical data,

Table 1. Clinical Features of Patients Undergoing Follow-Up Examination or Primary Revascularization Versus Patients Lost to Follow-Up

	Follow-Up [n = 463 (93%)]	Primary Revasc [n = 16 (3%)]	Lost to Follow-Up [n = 21 (4%)]
Age (yr)	57 ± 13	55 ± 13	57 ± 11
Male gender	302 (65%)	14 (88%)	18 (86%)
BSA (m^2)	2.12 ± 3.54	1.98 ± 0.24	2.0 ± 0.3
Prior MI	83 (18%)	9 (56%)	10 (48%)
Ex capacity (METs)	7.9 ± 3.0	6.9 ± 3.8	6.4 ± 3.7
Peak HR (beats/min)	148 ± 24	143 ± 27	137 ± 34
% age-predicted HR	91 ± 12	86 ± 11	84 ± 16
Peak SBP (mm Hg)	177 ± 29	161 ± 33	174 ± 41
Peak RPP (mm Hg × beats/min)	$26 \pm 6 \times 10^3$	$22.8 \pm 6.9 \times 10^3$	$23.3 \pm 7.7 \times 10^3$
No isch or MI	293 (63%)	2 (12%)	5 (24%)
Isch alone	70 (15%)	6 (38%)	6 (28%)
MI alone	36 (8%)	3 (19%)	8 (38%)
Isch + MI	64 (14%)	5 (31%)	2 (10%)

Data presented are mean value ± SD or number (%) of patients. BSA = body surface area; HR = heart rate; isch = ischemia; METs = metabolic equivalents; MI = myocardial infarction; RPP = rate–pressure product; SBP = systolic blood pressure.

together with exercise data (METs, ST segment depression, peak heart rate, blood pressure and rate–pressure product). Finally, we added the echocardiographic findings (ischemia or infarction) to the significant clinical and stress data. At each step, the likelihood ratio chi-square was obtained, and these values were compared to measure the predictive value between the steps.

Results

Stress testing. Exercise ECGs were identified as positive (>0.1-mV ST segment depression) in 160 (32%) of the 500 patients; nondiagnostic responses were recorded in 54 patients (11%). The peak heart rate was 147 ± 25 beats/min (90 ± 12% of age-predicted maximum), and 128 patients (26%) exercised submaximally (<85% of age-predicted maximal heart rate). The peak systolic blood pressure was 176 ± 30 mm Hg, giving a peak rate–pressure product of $26.0 \pm 6.5 \times 10^3$ beats/min × mm Hg. The mean estimated work capacity of the group was 7.9 ± 3.0 METs.

Exercise echocardiography was abnormal in 200 (40%) of the 500 patients; 153 (31%) had ischemia either alone or in the presence of infarction. These findings were then compared with the results of follow-up for total cardiac events (death, infarction, unstable angina and late revascularization).

Cardiac events. Of the original 500 patients, 21 (4.2%) were lost to follow-up. Of the remaining 479 patients, 16 (3.2%) underwent coronary angioplasty or bypass surgery within 3 months of the stress test. Although the majority of these patients had a positive stress echocardiogram, it was anticipated that the decision to proceed with revascularization was biased by the results of the stress test. Hence, these decisions were not identified as cardiac events, and these individuals were excluded from further analysis. None of these patients had subsequent spontaneous cardiac events. The characteristics of the three groups—those who underwent follow-up, had primary revascularization and were lost to follow-up—are listed in Table 1. Those undergoing primary revascularization had an expectedly high prevalence of ischemia, which involved the territories of multiple vessels in 9 (64%) of 14 patients.

The clinical, exercise and echocardiographic descriptors of the remaining 463 patients are listed in Table 1. Eighty-one (17%) of these 463 patients had some cardiac event during the follow-up period. Fifteen patients (3%) presented with unstable angina, four (1%) had a nonfatal myocardial infarction and 18 (4%) died of cardiac causes. Late revascularization (>3 months after the index stress test), usually provoked by recurrent ischemic symptoms, accounted for 48 (10%) of these events. Patients who had late revascularization did not differ much from the remaining patients with events with respect to age (61 ± 10 years), heart rate response (88 ± 12% age-predicted maximal heart rate), peak work load (8.0 ± 2.1 METs) or prevalence of abnormal echocardiograms (69%).

Relation of stress responses to total events. *Prediction of cardiac events.* A univariate Cox model was used to identify clinical, exercise and echocardiographic variables in the 81 patients with any cardiac event. Of the clinical variables, age (relative risk [RR] 1.02, p = 0.05), male gender (RR 2.07, p = 0.008), diabetes (RR 2.10, p = 0.001) and previous myocardial infarction (RR 2.3, p = 0.0004) were associated with subsequent cardiac events, but the presence of chest pain was not (RR 1.0, p = 1.00). Of the exercise and echocardiographic variables, exercise capacity in METs (RR 0.94, p = 0.10), percent predicted maximal heart rate (RR 0.97, p = 0.0001), peak rate–pressure product (RR 0.96, p = 0.01) and exercise ST segment depression (RR 1.45, p = 0.01) were associated with an adverse outcome. The strongest univariate predictors

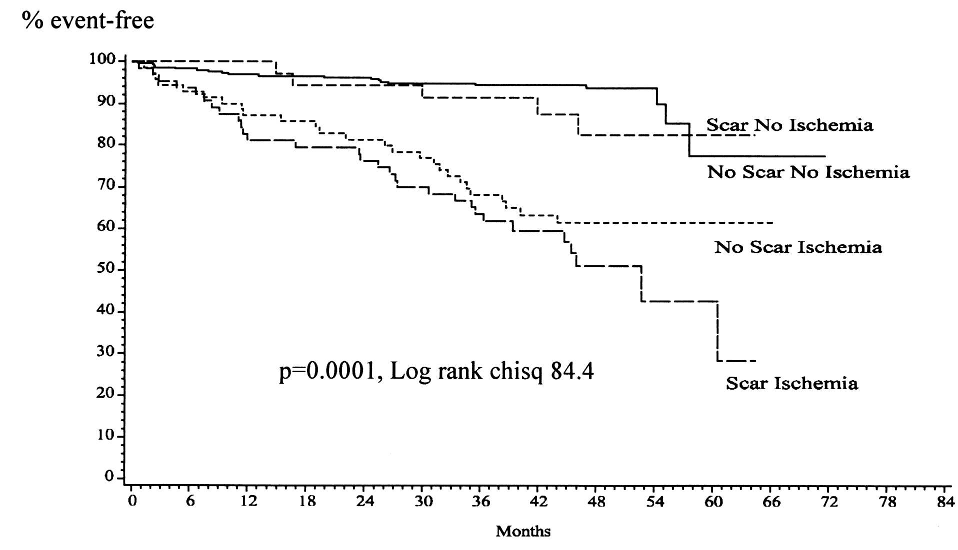


Figure 1. Event-free survival classified according to the exercise echocardiographic result. chisq = chi-square.

were echocardiographic evidence of ischemia (RR 6.47, p = 0.0001) or scar (RR 3.05, p = 0.0001). Of 170 patients with echocardiographic abnormalities for whom follow-up data were available, 28 (41%) of 69 with abnormalities in multiple vascular territories had an event compared with 33 (33%) of 101 patients with abnormalities in a single territory (p = 0.30).

In the stepwise multivariate model (Table 2), the presence of ischemia on the echocardiogram was the strongest predictor of events, and the only other independent predictor of outcome was percent age-predicted maximal heart rate achieved. Previous myocardial infarction, exercise capacity (in METs), peak heart rate and rate–pressure product, stress-induced ST segment depression and echocardiographic evidence of myocardial infarction were not sufficiently predictive to be included in the model.

The relative contributions of ischemia and infarction identified at exercise echocardiography are illustrated in Figure 1. In patients with a normal exercise echocardiogram, events were uncommon (<5%) for 2 years after the test, but increased to 10% after an interval of 4.5 years, suggesting the progression of subclinical lesions in this time frame. The survival of patients with rest wall motion abnormalities was proportionate to the level of rest left ventricular dysfunction. In those patients without events, 0.5 ± 1.3 segments were abnormal at rest compared with 1.5 ± 2.4 segments in patients with events in the absence of ischemia (p < 0.001). However, the presence of ischemia, alone or in combination with infarction, was significantly associated with cardiac events (chi-square 84.4, p = 0.0001).

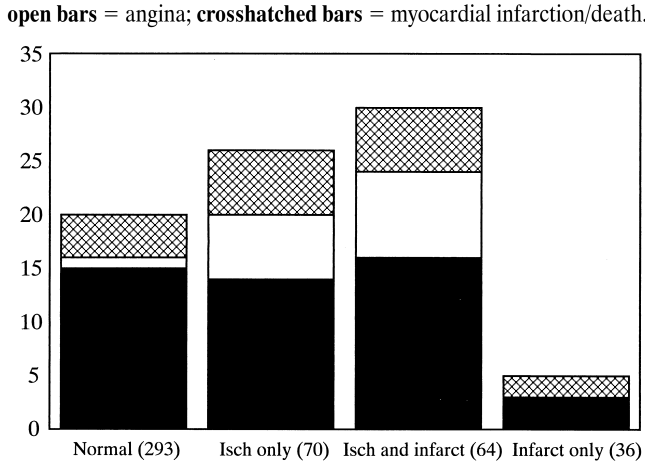
Figure 2 demonstrates the nature of the cardiac events in each of these groups. Although 20 (7%) of 293 patients with negative exercise echocardiograms had cardiac events, 15 (75%) of these were due to late revascularization, compared with 30 (54%) of 56 patients with ischemia (p = 0.09). Five of the 20 events that followed a negative exercise echocardiogram occurred in patients who had exercised submaximally. However, patients with false negative echocardiograms could not otherwise be discriminated from the remainder of the patients with events, having a similar age (58 ± 11 years), exercise capacity (8.3 ± 2.6 METs) and ECG response (37% with ischemic changes). Of these 20 patients, three were treated with beta-blockers and nine with calcium antagonists.

Table 2. Association of Clinical, Stress Testing and Echocardiographic Features With Total Cardiac Events by Multivariate Proportional Hazards Survival Analysis

	Multivariate Proportional Hazards Analysis		
Variable	Chi-Square	RR (95% CI)	p Value
Age (yr)	0.38	1.01 (0.99–1.03)	0.33
Male gender	3.16	1.69 (0.92–2.94)	0.09
% max HR	14.7	0.97 (0.95–0.98)	0.0002
ExE (any isch)	38.3	4.80 (2.92–7.89)	0.0001

CI = confidence interval; ExE = exercise echocardiogram; RR = relative risk; other abbreviations as in Table 1.

Figure 2. Nature of cardiac events in patients with exercise echocardiograms showing normal responses, ischemia (Isch) alone, infarction alone or infarction and ischemia. **Solid bars** = late revascularization; **open bars** = angina; **crosshatched bars** = myocardial infarction/death.



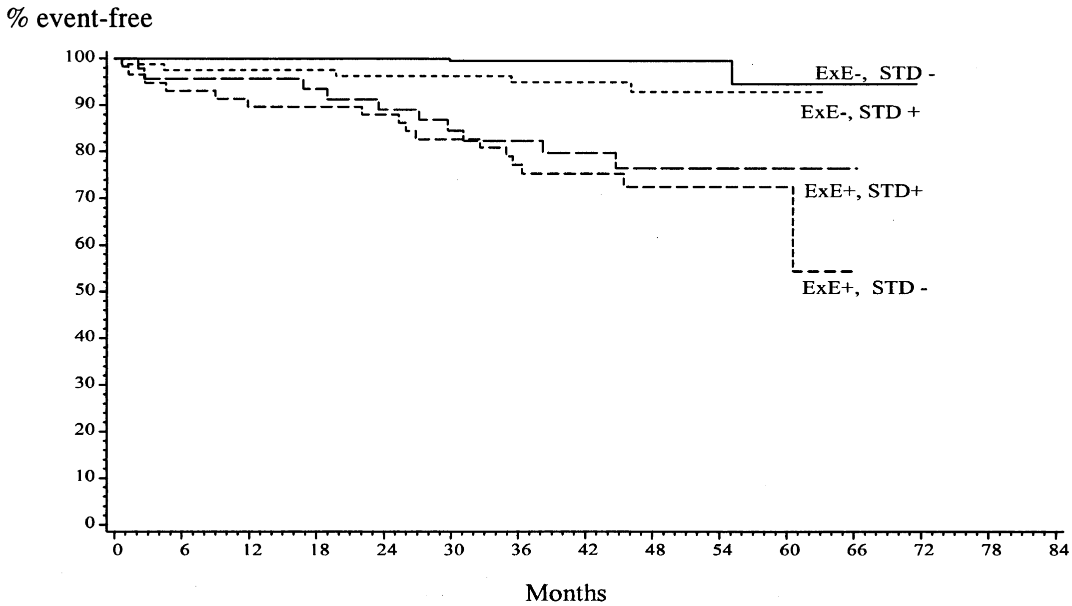


Figure 3. Event-free survival (for all cardiac events) classified according to the presence of echocardiographic evidence of ischemia and ST segment depression. Patients with ischemia on both the exercise echocardiogram (ExE+) and exercise ECG (STD+) had an event rate similar to those with ischemia on the exercise echocardiogram without ST segment changes (p = 0.5), but a significantly higher event rate than those without ischemia at echocardiography (ExE−), with (p = 0.009) or without (p < 0.001) ischemia on the exercise ECG. The event rate of patients with ischemia on the exercise echocardiogram without ST segment changes was greater than that in patients without ischemia, with (p = 0.001) or without (p < 0.001) ischemia on the ECG. In patients without echocardiographic ischemia, those with ST segment changes had a worse prognosis than those without ST segment changes (p = 0.003).

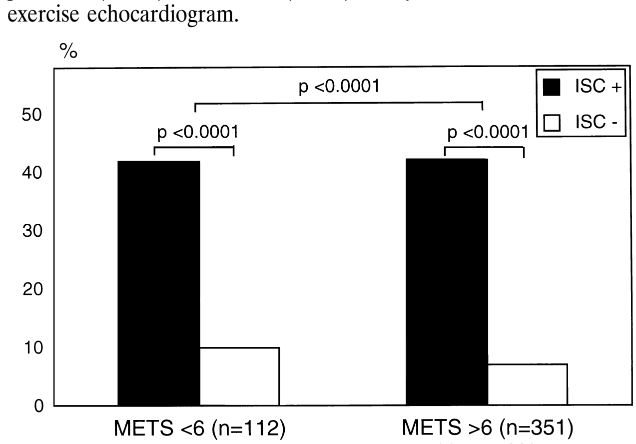
Relation of echocardiographic and stress testing data. The presence of exercise-induced ST segment depression was associated with an adverse outcome on univariate analysis. However, on multivariate analysis, this was outweighed by the association of echocardiographic ischemia with subsequent events. The relative prognostic influence of stress-induced ST segment changes and stress-induced wall motion abnormalities is illustrated in Figure 3. The event rate in the presence and absence of echocardiographic ischemia was slightly greater in the presence of ST segment depression, but the major correlate of subsequent events was the presence of echocardiographic ischemia.

Exercise capacity has been correlated with cardiac events in previous follow-up studies of patients undergoing stress testing. One hundred twelve patients had an exercise capacity <6 METs, 25 of whom had cardiac events (22%). Fifty-six events occurred in 351 patients attaining work loads ≥6 METs (16%, p = 0.03). However, comparison of ischemia with exercise capacity showed events to occur more frequently in patients with ischemia than in patients without ischemia, whether METs were <6 (42% vs. 10%, p < 0.0001) or ≥6 (42% vs. 7%, p < 0.0001), as illustrated in Figure 4.

In this study, the best index of cardiac work load was percent attained of age-predicted maximal heart rate, which emerged as an independent predictor of outcome on multivariate analysis. Cardiac events occurred in 35 (31%) of 112 patients with follow-up who failed to attain 85% of age-predicted maximal heart rate, compared with 56 (16%) of 351 who exercised maximally (p < 0.01).

Incremental benefit of echocardiographic over clinical and stress data. Calculation of the incremental benefit of performing exercise echocardiography for prediction of all events was obtained by sequential application of Cox models, as described previously. The first analysis (clinical variables) showed previous myocardial infarction (RR 2.0, 95% confidence interval [CI] 1.23 to 3.26) to be the principal clinical predictor of outcome; the clinical model had a chi-square statistic of 19.2 (p = 0.0007). The second analysis, which combined this clinical

Figure 4. Cumulative event rates in patients with low (<6 METs) and adequate (≥6 METs) exercise capacity, classified according to the presence (ISC+) or absence (ISC−) of myocardial ischemia on the exercise echocardiogram.



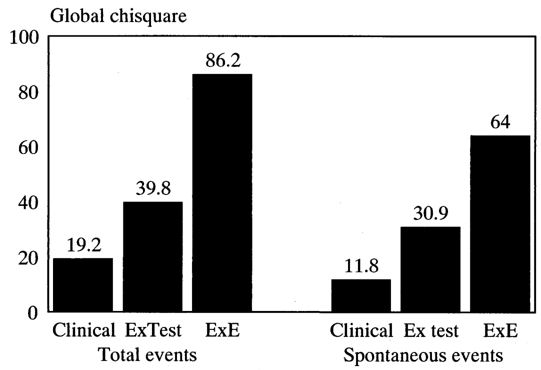


Figure 5. Comparison of the global chi-square analysis of strategies involving clinical, exercise (Ex) testing and exercise echocardiographic (ExE) approaches for the prediction of total and spontaneous cardiac events.

predictor with exercise-induced ST segment depression and percent age-predicted maximal heart rate achieved, showed the heart rate response (RR 0.97, 95% CI 0.95 to 0.98) and ST segment depression (RR 1.56, 95% CI 1.15 to 2.12). The clinical and exercise model had a chi-square statistic of 39.8 ($p = 0.0001$). Finally, combination of these significant correlates with echocardiographic findings showed ischemia (RR 5.04, 95% CI 3.09 to 8.23) to exert a significant independent influence on prognosis, after these other factors had been taken into account. The chi-square statistic of the final model was 86.2 ($p < 0.0001$), and the significant increment of prediction of cardiac events with each stepwise model is illustrated in Figure 5.

Relation of stress responses to spontaneous events. Thirty-three patients had spontaneous cardiac events. In this group, age (RR 1.01, $p = 0.35$) and male gender (RR 1.3, $p = 0.43$) were less predictive of events than when revascularization was considered as an event, probably reflecting a greater prevalence of revascularization in men and the elderly. Of the clinical variables, previous myocardial infarction (RR 3.45, $p = 0.0005$), but neither chest pain nor diabetes, was associated with spontaneous events. Exercise capacity (measured as estimated METs) showed a stronger univariate correlation with spontaneous events (RR 0.85, $p = 0.015$) than with total events, but the relative risks associated with other clinical and hemodynamic indices were comparable. Echocardiographic evidence of infarction (RR 4.04, $p = 0.0001$) and evidence of ischemia by electrocardiography (RR 1.75, $p = 0.01$) and echocardiography (RR 12.1, $p = 0.0001$) were the strongest univariate correlates of spontaneous events. In the multivariate model, the presence of ischemia during exercise echocardiography was the strongest independent predictor of spontaneous events (Table 3) and showed even greater correlation than it did with total events (RR 10.3, $p = 0.0001$).

The interactive model was repeated for the analysis of spontaneous events. Again, previous myocardial infarction was found to be the principal clinical predictor of outcome (clinical model chi-square statistic 9.38, $p = 0.05$), and heart rate response and ST segment depression were the best stress-based predictors (clinical and stress test chi-square statistic 30.7, $p = 0.0006$). A combination of these variables with echocardiographic findings also showed ischemia to exert a significant independent influence on prognosis (chi-square statistic 58.7, $p < 0.0001$). These chi-square differences are illustrated in Figure 5.

Table 3. Association of Clinical, Stress Testing and Echocardiographic Features With Spontaneous Cardiac Events by Multivariate Proportional Hazards Survival Analysis

	Multivariate Proportional Hazards Analysis		
Variable	Chi-Square	RR (95% CI)	p Value
Age (yr)	0.04	1.0 (0.96–1.03)	0.85
Male gender	0.12	0.86 (0.38–1.96)	0.73
Prior MI	3.61	2.10 (0.98–4.50)	0.06
Ex ST seg depression	3.32	1.62 (0.96–2.73)	0.07
Peak RPP	10.6	0.95 (0.92–0.98)	0.001
ExE (any ischemia)	22.1	8.2 (4.41–19.7)	0.0001

seg = segment; other abbreviations as in Tables 1 and 2.

Discussion

The results of this study indicate that the finding of ischemia on the exercise echocardiogram is highly predictive of total and spontaneous coronary events. Moreover, the relative risk associated with this finding exceeds that associated with clinically significant increments of exercise capacity and heart rate. The independent prognostic effect of ischemia, shown with the conventional stepwise approach, was also apparent when the data were analyzed using an interactive model, which permitted analysis of data in a sequence mimicking that of the clinical encounter with the patient. Interestingly, the incremental benefit of exercise echocardiography (measured as global chi-square) was similar to that reported using similar analyses with myocardial perfusion imaging (20,21).

Prognostic value of exercise stress testing. Although chest pain and ST segment depression are the standard diagnostic indices of a positive exercise test, these variables in isolation are not powerful predictors of prognosis (8,9). Neither of these variables has a high specificity for ischemia, and although patients with severe ST segment depression at low work loads are prone to subsequent events, many patients with ST segment depression have a benign outcome. In this study, >30% of patients demonstrated ST segment depression, but the predictive power of this variable was outweighed by the finding of ischemia at exercise echocardiography (Fig. 3), analogous to the greater diagnostic accuracy of stress imaging approaches over the exercise ECG results alone (1).

A reduction in exercise capacity has been shown to be related to the subsequent occurrence of cardiac events (8,9), presumably because this reflects both left ventricular dysfunction and ischemia. This variable was important prognostically in this study, although less so than the presence of ischemia (Fig. 4). Nonetheless, although the addition of exercise echocardiography provided incremental information regarding prognosis, clinical and exercise testing data (shown in the second of the sequential models) were strongly predictive of outcome, with a global chi-square of 39.8. Indeed, whether the increment of prognostic data supplied by exercise echocardiography justifies the additional cost needs to be defined.

Use of stress echocardiography for prediction of outcome. Clinical evaluation and noninvasive testing (9,10,22,23) offer extensive prognostic data in patients with known or suspected coronary artery disease, to the extent that these "functional" data exceed the prognostic value of coronary angiography (24). However, the relative significance of the results of various tests is less important than the knowledge of how much they add to the available information about each patient. The use of exercise testing and myocardial perfusion imaging as clinical tools has therefore been potentiated by the knowledge that these data, used individually or sequentially, are of value in the assessment of risk and therefore in planning treatment.

Although stress echocardiography has become established as a diagnostic tool for coronary artery disease, the *prognostic* significance of the findings of stress echocardiography is less well established. In particular, studies demonstrating the efficacy of stress echocardiography for diagnostic purposes (1–4) have necessarily involved groups of patients who have had angiography, and these patients clearly constitute a higher risk group than the majority of patients who are studied using noninvasive techniques. There is therefore a need to ascertain that ischemia is not missed in patients who do not have angiography.

Ismail et al. (25) recently confirmed the benign prognosis conferred by a negative exercise echocardiogram, as initially reported by Sawada et al. (26). In the latter series, failure to predict events by stress echocardiography was associated with the inability to attain an adequate heart rate response. The importance of adequate stress for the results of exercise echocardiography to be reliable is supported by our experience, and these findings are concordant with studies that have demonstrated that the sensitivity of stress echocardiography was compromised in the setting of a submaximal heart rate response (4). Such findings should be identified as being nondiagnostic.

The predictive implications of a positive exercise echocardiogram were initially explored by Krivokapich et al. (27). Over a 1-year follow-up period, the event rate in this study was 14%—the majority of these events being angioplasty (7%) or bypass surgery (6%)—and a discrimination was not made between early and late interventions. As in our study, the finding of a positive stress echocardiogram was a strong independent predictor of outcome, although the odds ratio (OR) of 3.1 (95% CI 1.5 to 6.5) was less than that associated with poor exercise capacity, defined by performing <6 min of a Bruce protocol (OR 5.9, 95% CI 2.8 to 12.4). The relatively high event rate at early follow-up in this study probably reflected the inclusion of primary revascularization. Most importantly, the incremental value of ischemia in the light of clinical and exercise data was not defined.

Small studies, involving less than 50 patients, have been reported regarding the efficacy of exercise echocardiography for risk stratification after myocardial infarction (28–30). However, the number of events in these studies was small, and comparison with exercise data was limited. Moreover, evaluation of patients with postinfarction differs from that of ambulatory patients with suspected or known stable chronic coronary artery disease.

In patients who are unable to exercise, pharmacologic stress echocardiography has been shown to be an accurate test for the identification of coronary artery disease, and ischemia at either dipyridamole or dobutamine stress echocardiography has been associated with a RR of 2.7 to 4.1 (10,11,13,31). However, the incremental benefit of the stress test in relation to clinical data was not defined. Moreover, in patients who are able to exercise, an exercise stress test is desirable, as the stress may be correlated to the patient's symptoms, useful ST segment data may be obtained and exercise data are prognostically important.

Study limitations. The results of this study pertain to medically treated patients, because individuals undergoing revascularization within 3 months of the stress were excluded from the analysis. In these excluded patients, the performance of revascularization was predicated on the results of the stress echocardiogram, and inclusion of these patients would have artificially increased the prognostic power of both exercise testing and exercise echocardiography. However, exclusion of these patients, who would have likely had some form of event if they had not been revascularized, reduced the total event rate in this study, and probably explains the relatively benign outcome of patients with a relatively high prevalence of known coronary artery disease. Similarly, analysis of spontaneous events, with exclusion of all patients undergoing revascularization, reduces the total event rate for the group, although ischemia remains predictive of outcome in this analysis.

This study comprised a consecutive series of patients undergoing exercise echocardiography. Because the decision to perform angiography is usually based on these functional data, angiographic data were incomplete in this study group. Because of concerns regarding selection bias and incomplete data, angiographic fundings were not included in the analysis. Analysis of the incremental prognostic role of exercise echocardiography in patients with known coronary anatomy will need to be identified in another patient group.

Clinical implications. The results of this study indicate that a negative stress echocardiogram is associated with a very low serious event rate over an average follow-up of nearly 4 years. If the test is positive for ischemia, the risk of a significant cardiac event is substantial and is hardly influenced by other exercise testing variables. Although, traditionally, major events have taken precedence in these studies, in the current medical economic environment, avoidance of acute hospital admissions in patients with unstable angina may represent an important cost-effective measure. Further investigation of patients with a positive stress echocardiogram appears prudent on the basis of these results.

In addition to pointing out the prognostic significance of exercise echocardiography in patients who are undergoing this test, the results of the study pose some suggestions with respect to the selection of this test in individuals who are able to undergo exercise testing. In this group of relatively high risk individuals, many of whom had known coronary artery disease, the exercise ECG is suboptimal for locating the site and extent of ischemia. The results of this study further justify the use of echocardiography in this group for risk stratification.

From a prognostic standpoint, this study demonstrates that stress echocardiography offers incremental benefit to clinical and exercise data and should be considered in lieu of the standard stress test. Additional studies are needed to identify the circumstances under which the greater cost of stress echocardiography is justified for this purpose.

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