Stress Echocardiography

Stress Echo Results Predict Mortality: A Large-Scale Multicenter Prospective International Study

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OBJECTIVES   The purpose of this study was to assess the long-term value of pharmacologic stress echocardiography with either dipyridamole or dobutamine (DET) for prediction of cardiac death in patients with proven or suspected coronary artery disease (CAD).

BACKGROUND   Stress echocardiography is an established, cost-effective technique for the detection of CAD.

METHODS   From the Echo Persantine International Cooperative–Echo Dobutamine International Cooperative data bank, 7,333 patients (5,452 males; 59 ± 10 years) underwent pharmacologic stress echocardiography with either high-dose dipyridamole (0.84 mg/kg over 10 min) (n = 4,984) or high-dose dobutamine (up to 40 μg/kg/3 min) (n = 2,349) for diagnostic purposes. Patients were followed up for a mean of 2.6 years (range 1 to 206 months).

RESULTS   The DET was positive for myocardial ischemia in 2,854 (35%) patients and negative in 4,479 (61%) patients. During the follow-up there were 161 cardiac deaths (sudden death and fatal myocardial infarction) (2.1% of the total population). Kaplan-Meier survival estimates showed a significantly better outcome for those patients with a negative pharmacologic stress echocardiography test compared with those with a positive test (92 vs. 71.2%, p = 0.0000).

CONCLUSIONS   Pharmacologic stress echocardiography with either dipyridamole or dobutamine is effective in predicting cardiac death during a long-term follow-up. A negative stress echocardiography test result is related to a favorable outcome.   (J Am Coll Cardiol 2003;41:589–95) © 2003 by the American College of Cardiology Foundation

Pharmacologic stress echocardiography is an established, cost-effective technique for the detection of coronary artery disease (CAD) (1). According to the American College of Cardiology/American Heart Association guidelines, pharmacologic stress echocardiography with either dobutamine or dipyridamole (DET) is a class I indication (of documented effectiveness and usefulness) for the diagnosis of CAD and for the prognostic stratification of patients with known CAD (2,3). The widespread use in clinical practice has become possible only after evidence collected through large-scale, multicenter studies that demonstrated its feasibility, safety, and diagnostic and prognostic accuracy (4–8). All-cause and cardiac death are the most clinically meaningful prognostic end points (9–11). The purpose of this study was to assess the long-term value of DET for prediction of cardiac death in patients with known or suspected CAD in a large-scale, multicenter, observational, and prospective study design on the basis of evidence collected by 35 different echocardiographic laboratories.

PATIENTS AND METHODS

From the Echo Persantine International Cooperative–Echo Dobutamine International Cooperative and Institute of

Clinical Physiology data bank, between 1985 and 2000, 7,599 prospectively enrolled consecutive patients with known or suspected CAD performed a DET test and entered a follow-up program. A total of 266 patients (3%) were lost to follow-up; therefore, the final population consisted of 7,333 patients (5,452 males, mean age 59 ± 10 years). The most common indication for testing was risk evaluation after infarction (29%); 2,737 (37%) had a test performed for the evaluation of chest pain. Known CAD was present in 2,696 (37%) patients, reflecting previous myocardial infarction in 29% and revascularization in 6%. Risk factors were highly prevalent, with 30% of the patients having hypertension and 40% hypercholesterolemia. The pretest likelihood of CAD was estimated from age, gender, and symptoms (12); patients with known CAD were assigned a value of 100%. The estimated likelihood of CAD was less than 50% in 849 patients (11.5.%), 50% to 80% in 2,556 patients (34.8%), and greater than 80% in 3,928 patients (53.6%). According to individuals needs and physician's choices, 5,542 patients were evaluated after antianginal drugs had been discontinued, and 1,791 patients were evaluated during antianginal treatment (nitrates and/or calcium antagonists and/or beta-blockers).

Stress protocols. Two-dimensional echocardiography and 12-lead electrocardiographic (ECG) monitoring were performed in combination with either high-dose dipyridamole (up to 0.84 mg over 10 min) or high-dose dobutamine (up to 40 g/kg body weight per min with coadministration of

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Abbreviations and Acronyms

CAD	=	coronary artery disease
CI	=	confidence interval
DET	=	pharmacologic stress echocardiography with either dobutamine or dipyridamole
ECG	=	electrocardiograph/electrocardiographic
RR	=	relative risk
WMSI	=	wall motion score index

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atropine up to 1 mg), according to well-established protocols (3). During the procedure, blood pressure and the ECG were recorded each minute. Low-dose positivity was considered to have occurred during the dose of 0.56 mg/kg in 4 min of dipyridamole or during the following 4 min or at the dose ≤20 μg/kg/min of dobutamine. Quality control of stress echo performance and reading in enrolled centers was previously described in depth (5). Briefly, the reader from each recruiting center met the predefined criteria for stress echo reading. At that point, the center could start recruiting patients and reading of stress echo from the recruiting center was directly entered in the data bank.

Follow-up data. By inclusion criteria, follow-up data were obtained in all patients. 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 (SPSS Inc., Chicago, Illinois), and p values <0.05 were considered to be statistically significant. Receiver-operating characteristics

Table 1. Rest and Stress Findings in the Study Population

No. of patients	7,333
Age (yrs)	59 ± 11
Gender (male:female)	5,452:1,881
Hypertension	2,101 (29%)
Diabetes	1,024 (14%)
Hypercholesterolemia	2,904 (40%)
History of angina	2,737 (37%)
Left bundle-branch block	239 (3.3%)
Previous myocardial infarction	2,153 (29%)
Previous coronary revascularization	453 (6.1%)
Dobutamine stress echo	2,349 (32%)
Dipyridamole stress echo	4,984 (68%)
Positive DET	2,854 (39%)
Wall motion score index at rest	1.3 ± 0.4
Wall motion score index at peak stress	1.4 ± 0.4
ECG changes during DET	2,631 (36%)
Chest pain during DET	1,807 (25%)
Test performed on antianginal therapy	1,791 (24.4%)
Coronary angiography	4,037
Normal coronary artery disease	546
1-vessel disease	1,459
2- and 3-vessel disease	2,032

DET = dipyridamole or dobutamine stress echocardiography; ECG = electrocardiographic.

analysis was used to determine the optimal cutoff value for prediction of cardiac death with respect to the variation of wall motion score index (WMSI) and the number of ischemic segments during the test. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity.

RESULTS

The main clinical and echocardiographic data are reported in Table 1.

Follow-up data. Patients were followed for a mean of 2.6 ± 3 years. The total mortality was 336 individuals (4.5%), among whom death was attributed to cardiac causes in 161 (2.1%). Myocardial revascularization was performed in 2,077 patients who were censored from follow-up at this time.

Cardiac and total mortality. Considering cardiac mortality, there were 80 events in patients with a positive test versus 81 events in patients with a negative test (2.8% vs.

Table 2. Univariate Predictors of Total and Cardiac Mortality

	Cardiac Mortality		Total Mortality	
	RR (95% CI)	**p Value**	**RR (95% CI)**	**p Value**
Age	1.05 (1.03–1.06)	0.0000	1.06 (1.05–1.07)	0.0000
Male gender	1.7 (1.21–2.6)	0.0032	1.4 (1.13–1.8)	0.0030
Hypertension			1.2 (1.0–1.5)	0.0495
Previous non–Q-wave MI	1.8 (1.14–2.8)	0.0107	1.6 (1.18–2.2)	0.0030
LBBB	2.3 (1.3–4.2)	0.0039	1.68 (1.04–2.7)	0.0321
Previous Q-wave MI	2.5 (1.8–3.4)	0.0000	1.6 (1.32–2.09)	0.0000
Test positivity	2.2 (1.6–3.1)	0.0000	2.09 (1.68–2.5)	0.0000
Rest WMSI	5.8 (4.2–8.1)	0.0000	3.8 (3.01–4.9)	0.0000
Peak WMSI	6.0 (4.4–8.1)	0.0000	4.02 (3.2–5.0)	0.0000

CI = confidence interval; LBBB = left bundle-branch block; MI = myocardial infarction; RR = relative risk; WMSI = wall motion score index.
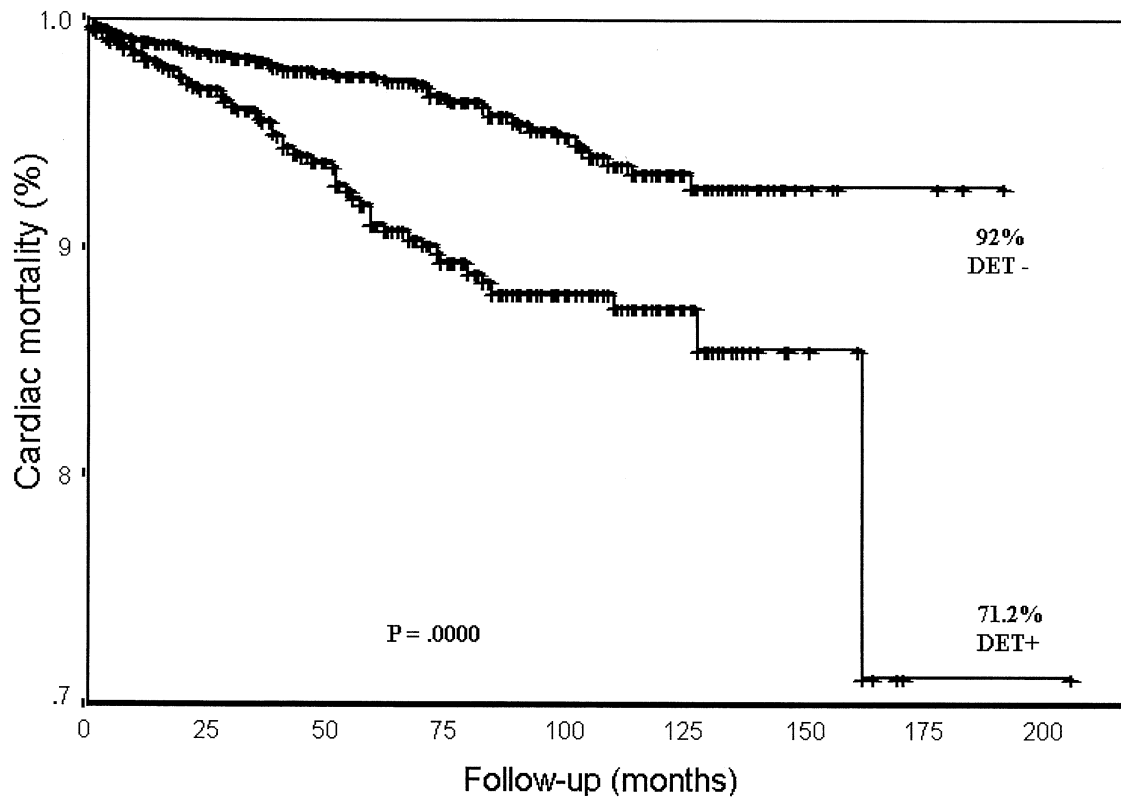
Figure 1. Kaplan-Meier survival curves (considering cardiac death as an end point) in patients with presence (DET +) and absence (DET −) of myocardial ischemia at pharmacologic stress echocardiography. Survival is worse in patients with inducible ischemia.
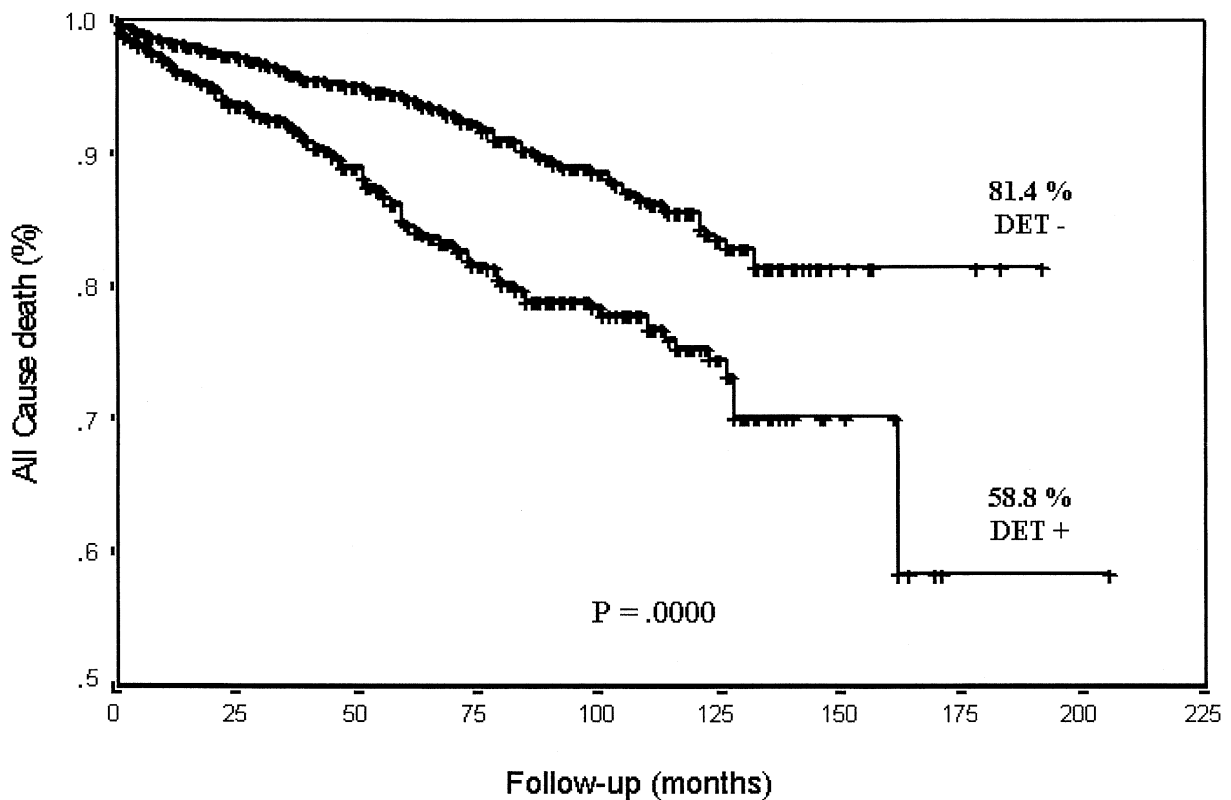

Figure 2. Kaplan-Meier survival curves (considering total mortality as an end point) in patients with presence (DET +) and absence (DET −) of myocardial ischemia pharmacologic stress echocardiography. Survival is worse in patients with inducible ischemia.
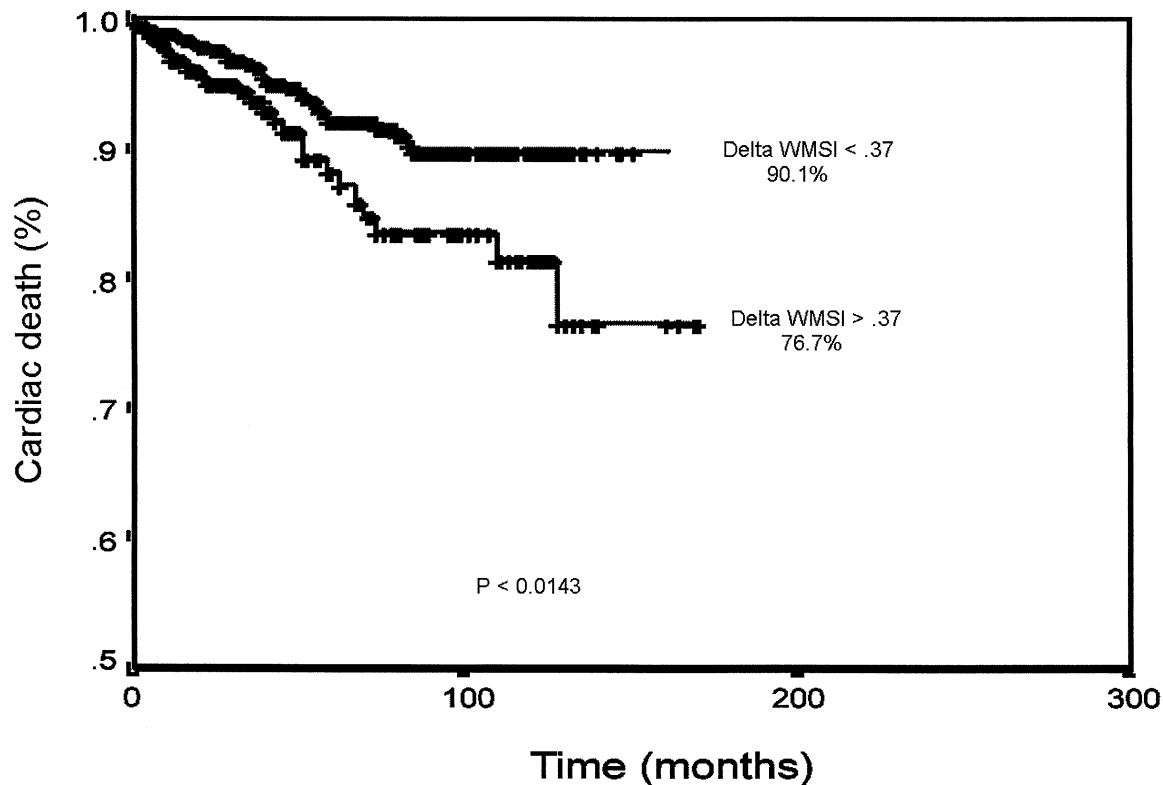
Figure 3. Kaplan-Meier survival curves (considering death as an end point) in patients with a positive pharmacologic stress echo test separated on the basis of the extent of the inducible ischemia identified by the delta wall motion score index (WMSI) set at 0.37. The survival is worse for larger variations of WMSI; Delta WMSI >0.37 versus Delta WMSI <0.37.

1.81%, $p = 0.0046$). Univariate predictors of cardiac death and total mortality are reported in Table 2. Using Cox's proportional hazards model, age (relative risk [RR] 1.05, 95% confidence interval [CI] 1.03 to 1.06), previous Q-wave myocardial infarction (RR 1.44, 95% CI 1.02 to 2.03), previous non–Q-wave myocardial infarction (RR 1.81, 95% CI 1.02 to 2.03), and peak WMSI (RR 5.1, 95% CI 3.6 to 7.03) were independent predictors of cardiac death. Kaplan-Meier survival estimates for cardiac mortality and total mortality are reported in Figures 1 and 2. Delta WMSI is highly predictive of cardiac death in patients with a positive stress test (Fig. 3). In Figure 4, the cumulative survival rates in patients with stress test positivity stratified according to pharmacologic dose infused is reported ($p <$ 0.0000 between high-dose and low-dose positivity). When clinically, realistic sequential models for the prediction of cardiac mortality were used, stress echocardiography showed incremental value versus clinical evaluation and resting left ventricular function identified by the rest WMSI (Fig. 5). The same was found for total mortality (Fig. 6).

Stress echo results and coronary angiography. The prognostic value of pharmacologic stress echocardiography relative to coronary angiography was addressed in a subgroup of 4,037 patients who also underwent coronary angiography within a year of the pharmacologic stress echocardiography without an intervening procedure. Of these individuals, 546

had no significant CAD, 1,459 had single-vessel disease, and 2,032 had multivessel coronary disease. With an interactive procedure, we analyzed the predictivity of the model for cardiac death considering the variables in clinical order: clinical variable first, stress echocardiographic parameters, and coronary angiography. Coronary angiography parameters did not add significant predictive power to the model compared with stress echocardiographic variables (Fig. 7).

DISCUSSION

In patients with known or suspected CAD, DET is an independent predictor of cardiac death, incremental to other parameters. The addition of coronary angiographic data added little prognostic power to the results of stress echocardiography.

Comparison with previous studies. Previous studies have demonstrated that the extent of inducible ischemia evidenced at stress echocardiography is related to outcome (5–8,10,11,13–22). The major merit of the present study is the sample size, consisting of 7,333 patients, large enough to provide prognostic information only analyzing hard end points such as total and cardiac mortality, with no need to include surrogate or composite end points in order to increase the power of prognostication.
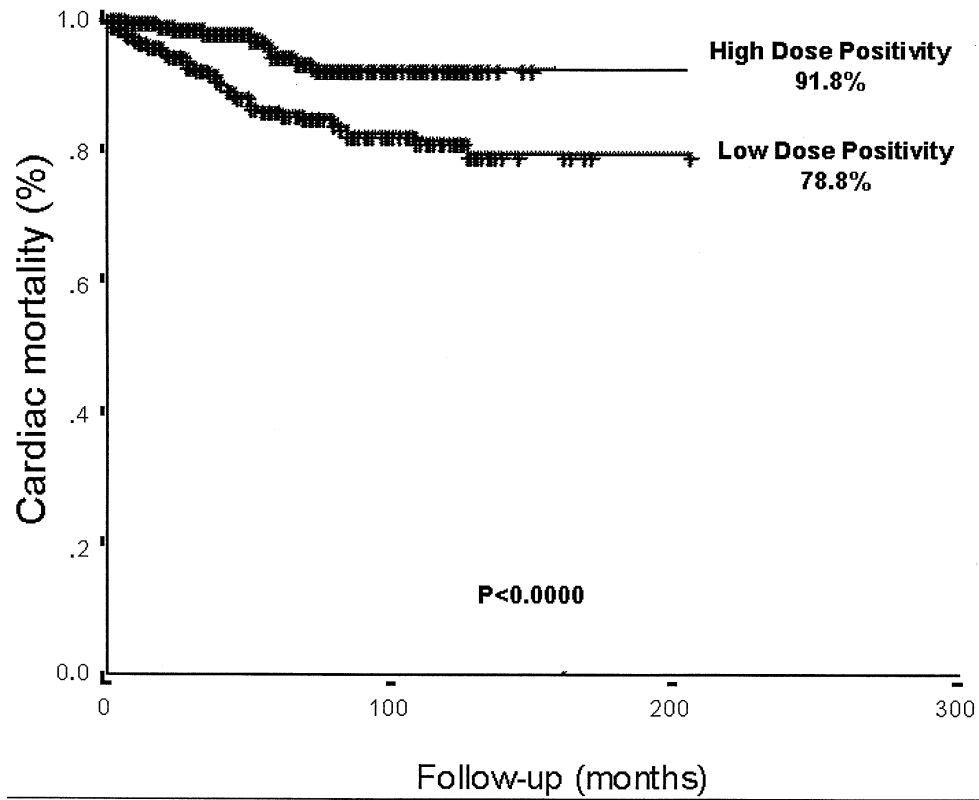
Figure 4. Kaplan-Meier survival curves (considering cardiac death) in patients stratified according to DET test results in relation to the pharmacologic dose achieved. Low-dose positivity was considered to have occurred during the dose of 0.56 mg/kg in 4 min of dipyridamole or during the following 4 min or at the dose ≤20 μg/kg/min of dobutamine (high-dose positivity vs. low-dose positivity, p = 0.0000).

Limitations of the study. The results of the test, available to the referring physicians, might have influenced the clinical management of the patients, especially regarding coronary revascularization, but this might have only lowered the prognostic power of the test, as patients were censored at the time of the procedure.
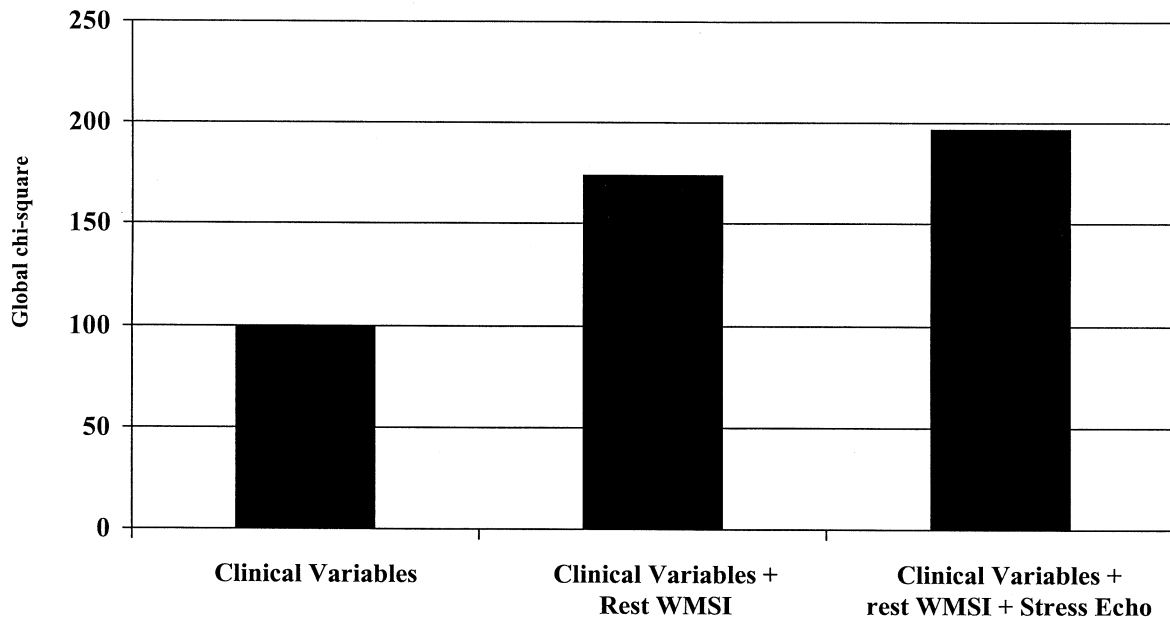

Figure 5. Bar graph showing global chi-square value of significant predictor modeling of cardiac mortality according to an interactive procedure. In the model, stress echocardiographic parameters still added significant information to clinical variables and rest echocardiographic parameters. WMSI = wall motion score index.

Figure 6. Bar graph showing global chi-square value of significant predictor modeling of total mortality according to an interactive procedure. In the model, stress echocardiographic parameters still added significant information to clinical variables and rest echocardiographic parameters. WMSI = wall motion score index.
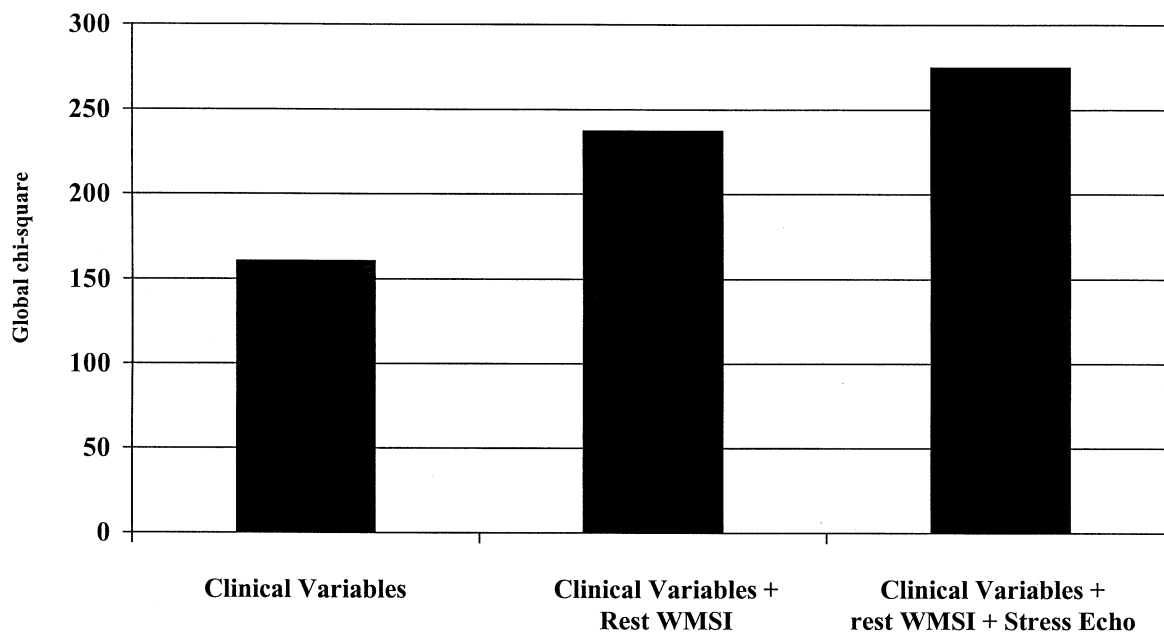
Clinical implications. Patients with a negative stress echo are at very low risk for death (<1%/year). It is very difficult to demonstrate that even the most aggressive treatments might lower this rate of death. These patients can be treated medically without referral to coronary angiography (21), because the practice of performing anatomy-driven coronary revascularization in the absence of inducible ischemia is a frequent but nonrecommended therapeutic option (23). In patients with positive stress echo, coronary angiography is warranted and ischemia-driven revascularization can have maximal beneficial prognostic effects (21,24). The more severe the inducible ischemia (i.e., the higher the rest stress variation in WMSI or the lower the dose achieved), the more urgent is the indication for ischemia-driven revascularization.
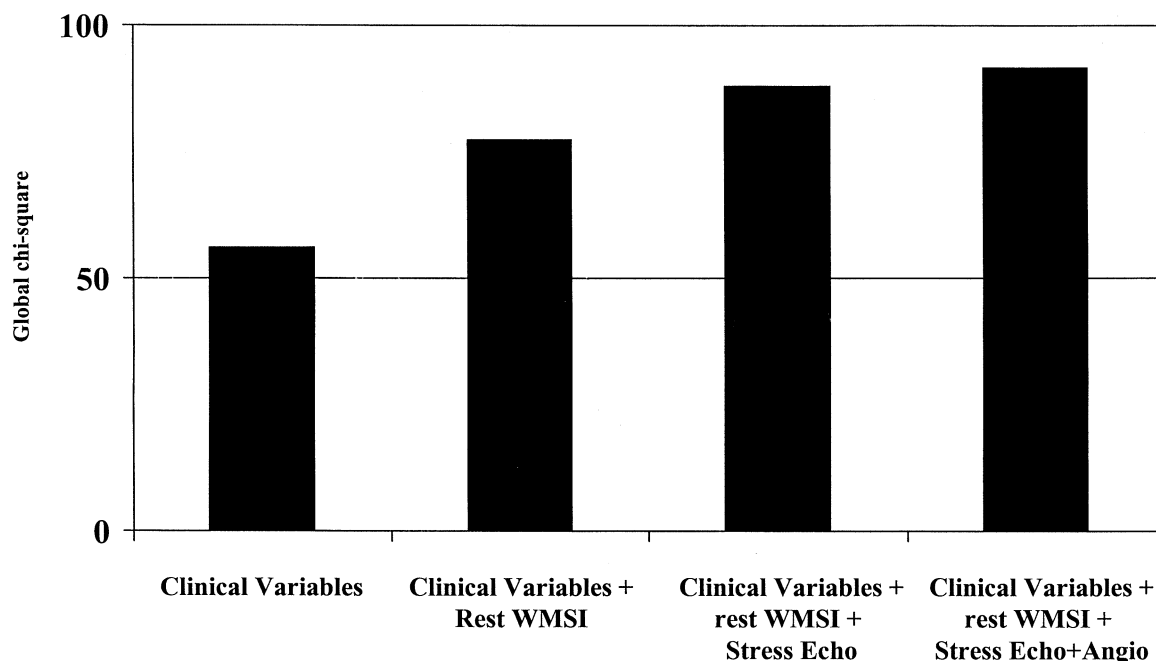

Figure 7. Bar graph showing incremental value of pharmacologic stress echocardiography results to clinical characteristics and coronary angiography for prediction of cardiac outcome in 4,037 patients who underwent pharmacologic stress echocardiography and coronary angiography. WMSI = wall motion score index.

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