Prediction of Mortality by Exercise Echocardiography

A Strategy for Combination With the Duke Treadmill Score

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***Background*—**In studies generally involving short follow-up, exercise echocardiography has been shown to predict composite end points. We sought to study the prediction of mortality with this test and to devise a strategy for combination with standard exercise testing.

***Methods and Results*—**Clinical, exercise testing, and echocardiographic data were collected in 5375 patients (aged 54±14 years, 3880 men) undergoing exercise echocardiography. The Duke treadmill score was derived from the results of treadmill exercise testing. Resting left ventricular (LV) function and the presence and severity of ischemia were interpreted by expert observers. Follow-up at 10.6 years (mean 5.5±1.9 years) was complete in 5211 patients (97%). The Duke score classified 59% of patients as low risk, 39% as intermediate risk, and 2% as high risk. Resting LV dysfunction was present in 1445 patients (27%), and the exercise echocardiogram was abnormal in 2525 patients (47%). Death occurred in 649 patients (12%). Over the first 6 years of follow-up, those with normal exercise echocardiograms had a mortality of 1% per year. Ischemia was an independent predictor of mortality. In sequential Cox models, the predictive power of clinical data was strengthened by adding the Duke score, resting LV function, and the results of exercise echocardiography. Exercise echocardiography was able to substratify patients with intermediate-risk Duke scores into groups with a yearly mortality of 2% to 7%.

***Conclusions*—**A normal exercise echocardiogram confers a low risk of death, and positive results are an independent predictor of death; ischemia is incremental to other data. This test may be particularly useful in patients with intermediate-risk Duke treadmill scores. **(*Circulation*. 2001;103:2566-2571.)**

Key Words: exercise ■ echocardiography ■ coronary disease ■ mortality ■ prognosis

Exercise echocardiography is a routine test in patients with known or suspected coronary artery disease who have repolarization abnormalities that make the exercise ECG uninterpretable.[1] Current exercise testing guidelines state that a standard exercise ECG should be the first investigation in patients with a diagnostic ECG who are able to exercise maximally.[2] However, the accuracy of exercise echocardiography exceeds that of the exercise ECG, even when the ECG is interpretable.[3] These guidelines would be supported if the relative prognostic implications of exercise echocardiography and exercise ECG were similar.

Although extensive outcome literature surrounds the use of pharmacological stress echocardiography,[4–6] the outcome data available for exercise echocardiography are quite limited.[7–12] Previous studies have suggested that the predictive value of a negative test is very high, although the predictive value of a positive test ranges from 17% to 35%. Echocardiographic identification of ischemia is an independent predictor of subsequent events, with these data being incremental to the prognostic information supplied by exercise testing.[9] However, these previous studies are of relatively small size, generally have focused on composite end points, and have compared the results of exercise echocardiography with isolated exercise test characteristics. The latter approach does not account for the utility of standard exercise ECG testing as an excellent tool for allocation of risk when evidence of ischemia and exercise capacity are combined.[13] Several schemes of combining these variables have been reported, but to date, none of these quantitative approaches has been compared with exercise echocardiography.

Thus, the purpose of the present study was to examine the ability of exercise echocardiography to predict mortality in patients with chronic stable coronary artery disease. We sought to define the predictive value of a negative test over prolonged follow-up and to explore the prognostic implications of a positive exercise echocardiogram, particularly in comparison with the Duke treadmill score.[14]

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Methods

Study Design

Exercise echocardiography was performed between 1988 and 1994 in 5375 consecutive patients with known or suspected coronary disease: 2416 at Asheville Cardiology Associates and 2959 at the Cleveland Clinic Foundation. Of the latter, 851 patients were involved in 2 previous studies that used separate end points.[9,10] The clinical, exercise, and echocardiographic data of these patients were prospectively entered into separate databases, and follow-up was obtained from 1998 to 1999, after which the data were merged. Consent was obtained before testing, and the study was approved by the Institutional Review Board.

Clinical Evaluation

These patients were aged 54±14 years and included 3880 men (73%). The most frequent risk factor was hypertension (36%), followed by smoking (12%) and diabetes (11%). The most common indications for testing were diagnostic testing (2356 patients [44%]) and prognostic assessment (47%). Typical or atypical chest pain was present in 3765 (70%) of the patients. Coronary artery disease was known in 20% of the patients, 7% of whom had experienced previous myocardial infarction and 11% of whom had undergone previous bypass surgery. The pretest probability of coronary artery disease was calculated on the basis of age, sex, and symptom status[15] in those without known disease. A high probability (>85%) of coronary artery disease was present in 34% of the patients; 32% were at intermediate probability, and 34% were at low probability (<15%). The likelihood of coronary artery disease in the overall group was 31±25%. At the time of the study, 20% of patients were treated with β-adrenoceptor antagonists; 15%, with calcium antagonists; 17%, with ACE inhibitors; 16%, with digitalis; and 5%, with diuretics.

Exercise Testing

Patients were prepared for exercise testing in the usual fashion.[16] All exercise testing involved maximal treadmill protocols selected in accordance with the age and functional status of the patient; most common were the Bruce (67%) and modified Bruce (22%) protocols. Patients underwent continuous clinical and ECG monitoring throughout the exercise test. Standard end points were used, and the test was stopped for fatigue, severe ischemia (severe angina, >2 mm ST depression), hypertension (systolic blood pressure >220 mm Hg), hypotension (decrement of systolic blood pressure >20 mm Hg), or arrhythmias.

Angina, ST-segment changes, hemodynamic response to exercise, and exercise capacity were archived for each patient. The Duke treadmill score[14] was calculated from the exercise capacity, the maximum ST-segment deviation, and the presence of limiting or nonlimiting angina.

Echocardiography

A standard resting echocardiogram was captured digitally into a quad-screen display. Because we sought to address the prognostic value of the test in routine practice, this analysis used the original interpretations of the studies by echocardiographers trained in exercise echocardiography (3 in Asheville and 10 in Cleveland). Studies were interpreted independently of clinical, exercise, or angiographic data, and results were made available to the physicians responsible for the patients.

Resting LV function was evaluated as normal, mild, moderate, or severely reduced on the basis of qualitative assessment of the extent of abnormal wall motion. Exercise echocardiography was interpreted by comparison of rest and exercise images with use of the quad-screen digital display, with review of videotape if desired. A normal response was characterized by normal resting function, with no deterioration induced by exercise. Infarction was defined by akinesis or dyskinesis at rest. Ischemia was identified by new or worsening wall motion abnormalities. Myocardial segments were combined into vascular territories for the purpose of expressing the extent of ischemia as 1-, 2-, or 3-vessel coronary artery disease. The apex, anteroseptal, septal, and anterior walls were attributed to the left anterior descending coronary artery; the lateral wall, to the left circumflex artery; and the inferior and basal septal walls, to the right coronary artery. The posterior wall was attributed to the circumflex or right coronary artery if either was abnormal; in patients with isolated posterior wall abnormalities, these were ascribed to the left circumflex artery. Studies were designated as abnormal if >1 segment showed evidence of infarction or ischemia, and a normal study was characterized by a normal response in all segments. Because previous studies in the nuclear literature[17] showed that the total extent of malperfused myocardium at peak stress is predictive of outcome, we produced an analogous "summed stress score" by counting the number of territories showing either rest or stress-induced changes.

Follow-Up

Follow-up data were gathered after 5.5±1.9 years (range 0.7 to 10.6 years) by clinic review or telephone contact with the patient or patient's physician in 5211 patients (97%). The primary end point was total mortality. Patients were censored at the time of coronary bypass surgery or coronary angioplasty, which were not identified as events.

Statistical Analysis

Descriptive statistics are expressed as mean±SD of continuous variables and frequency and percentage of categorical variables. Differences between Kaplan-Meier survival curves were compared with the log-rank test. Cox proportional hazards models were developed to investigate the effects of ischemia on outcome, independent of clinical, exercise, and resting echocardiographic variables in patients with complete clinical data and to investigate the interaction of exercise score, resting LV function, and ischemia in all patients. All analyses were performed with the use of SPSS statistical software (SPPS Inc), and a value of $P<0.05$ was considered to be statistically significant. In the situation of making multiple comparisons, significant probability values were defined by the Bonferroni method.

Results

Exercise Response

A maximal exercise test was attempted by all patients; the average workload was 7.7±2.8 metabolic equivalents. A submaximal heart rate (<85% predicted for age) was achieved by 376 patients; the peak heart rate was 88±18% of that predicted. Angina was induced in 9% patients, and significant ST-segment changes were recorded in 1439 patients (27%). The Duke treadmill score identified 39% of the patients as being at intermediate risk (score 4 to −10), 2% as being at high risk (score −10 or less), and 59% as being at low risk (score ≥5).

Echocardiography

Echocardiographic images were interpreted in all patients. Rest and stress images were considered normal in 2829 patients (53%). Normal resting function was reported in 4352 patients (83%); in the remainder of the patients, the severity of LV dysfunction was classified as mild (ejection fraction 40% to 50%) in 11%, moderate (ejection fraction 30% to 39%) in 4%, and severe (ejection fraction <30%) in 2%. Exercise-induced wall motion abnormalities were reported in 1080 patients (20%), 472 of whom also showed resting wall motion abnormalities.

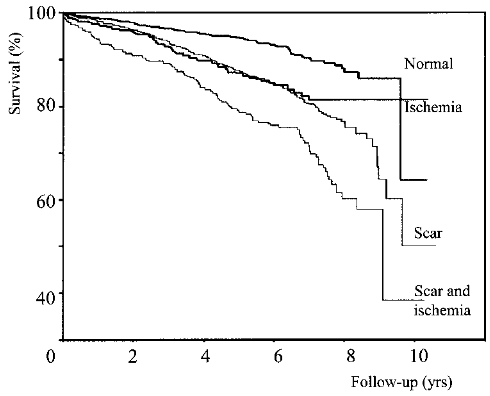

Figure 1. Survival of patients with normal results, ischemia, scar, and combined scar and ischemia.

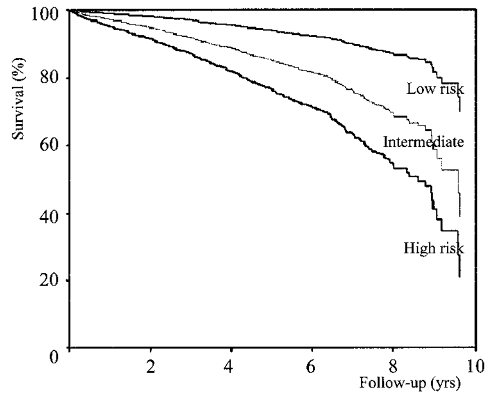

Figure 2. Outcome of patients in low-, intermediate-, and high-risk Duke score categories.

Mortality During Follow-Up

Over a follow-up to 10 years (mean follow-up 5.5±1.9 years), 649 patients died (11%). Patients undergoing myocardial revascularization (n=606, 11%) were censored from follow-up at the time of this procedure.

Implications of Normal Exercise Echocardiogram

The average yearly mortality associated with a normal study was 1% per year for the first 6 years, with a small increase of events after 6 years (Figure 1). In a multivariate model, predictors of events in patients with a normal study included age, smoking, submaximal exercise, an intermediate- or high-risk Duke score, and digoxin therapy; β-blocker therapy was protective against events (Table 1).

Prediction of Death

A low-risk Duke treadmill score was associated with a 94% five-year survival, compared with 85% and 76% survival with intermediate- and high-risk scores (Figure 2). Ischemia, scar, and especially both ischemia and scar are also associated with death during follow-up (Figure 1). In a model predicting death with the use of clinical, exercise, and echocardiographic variables, ischemia at exercise echocardiography was found to be an independent predictor of mortality (Table 2). This model was developed at one center and applied at the second site; Figure 3 illustrates similar outcomes in the 2 populations divided into quintiles of risk.

Because not all patients presenting with known or suspected coronary disease would have all investigations performed in standard practice, we attempted to mimic this by a sequence of models, initially evaluating clinical variables, then exercise testing, and resting and exercise echocardiography (Table 3). Each step in the investigation produced a significant increment in the ability to predict death.

The risk associated with an abnormal test varied from 2% to 4% per year. Part of the incremental risk of a combination of both scar and ischemia is that these patients have more extensive disease; the impact of increasing disease extent is illustrated in Figure 4. Another means of identifying a greater spectrum of risk is to combine these variables. In a multivariate model comprising exercise testing results, resting LV function, and summed stress score, a high-risk Duke score (relative risk [RR] 3.8, 95% CI 2.4 to 6.2; $P<0.0001$) or intermediate-risk Duke score (RR 2.4, 95% CI 2.0 to 2.8; $P<0.0001$), resting LV dysfunction (RR 2.1, 95% CI 1.8 to

TABLE 1. Independent Predictors of Death in Patients With Negative Exercise Echocardiogram

	RR (95% CI)	*P*
Age		
>80 y	6.43 (3.03–13.59)	<0.0001
70–80 y	4.99 (3.00–8.27)	<0.0001
60–70 y	2.70 (1.64–4.45)	0.0001
Smoking	1.84 (1.29–2.61)	0.0007
Peak heart rate <85% predicted	1.58 (1.13–2.20)	0.0072
β-Blocker therapy	0.56 (0.34–0.91)	0.0191
Duke score		
High risk	4.09 (1.62–10.33)	0.0029
Intermediate risk	1.82 (1.31–2.54)	0.0004

TABLE 2. Independent Predictors of Death

	RR (95% CI)	*P*
Smoking	1.56 (1.17–2.09)	0.003
Diabetes mellitus	1.89 (1.35–2.64)	0.0002
Age		
>80 y	8.25 (4.08–16.68)	<0.0001
70–80 y	4.44 (2.63–7.49)	<0.0001
60–70 y	2.99 (1.81–4.94)	<0.0001
Digoxin therapy	1.88 (1.36–2.59)	0.0001
Duke score		
Intermediate	1.96 (1.42–2.70)	<0.0001
High	2.21 (1.06–4.57)	0.03
Heart rate <85% predicted	1.44 (1.07–1.95)	0.02
Extent of WMA		
2 territory	1.88 (1.18–3.02)	0.009
3 territory	4.44 (2.28–8.66)	<0.0001

Values were obtained by analysis of outcome in all patients. WMA indicates wall motion abnormality.

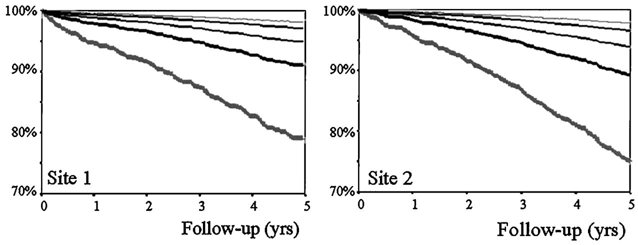

Figure 3. Outcome of patients at 2 sites, divided into quintiles of risk by using same model.

2.5; $P<0.0001$), and multiple territory wall motion abnormalities (RR 1.9, 95% CI 1.5 to 2.4; $P<0.0001$) predicted death at 5 years. These factors may be combined to predict risk associated with low-, intermediate-, and high-risk Duke scores (Table 4). In the 2% of patients at high risk, the yearly mortality (nearly 10% per year) justifies further evaluation and possibly intervention without recourse to imaging. Conversely, in the 59% of the patients at low risk, although the extent of abnormality at exercise echocardiography is able to differentiate levels of risk, the numbers of patients with extensive abnormalities are small, and the efficacy of more than resting imaging could be questioned. Therefore, the greatest benefit of exercise echocardiography is in the evaluation of the 39% of patients at intermediate risk by the Duke score, in whom subcategories of risk ranging from 2% to 7% can be identified. Thus, the use of exercise echocardiography may be used to focus further assessment on a small number of these patients.

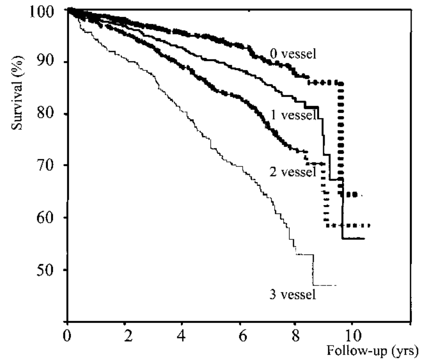

Figure 4. Mortality of patients according to total extent of wall motion abnormalities (summed stress score) at peak stress.

Discussion

Exercise echocardiography is a powerful tool for the prediction of death in patients with chronic stable coronary disease. The Duke treadmill score is predictive of outcome, and the greatest benefit of exercise echocardiography relates to those individuals having an intermediate-risk Duke score.

TABLE 3. Multivariate Predictors of Mortality in Patients Undergoing Exercise Echocardiography in Sequential Models Involving Clinical Variables, Clinical and Exercise Variables, Clinical, Exercise, and Resting Echo Variables, and Clinical, Exercise, and Stress-Echo Variables

	Clinical Model		Clinical With Exercise Model		Clinical, Exercise, and LV Function Model		Clinical, Exercise, LV Function, and Ischemia Model	
Parameter	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Decade								
>80 y	13.2 (6.6–26.1)	<0.0001	6.2 (3.0–12.7)	<0.0001	6.4 (3.1–13.0)	<0.0001	6.3 (3.1–12.8)	<0.0001
70–79 y	6.2 (3.7–10.4)	<0.0001	4.2 (2.5–7.0)	<0.0001	4.0 (2.4–6.7)	<0.0001	3.8 (2.3–6.5)	<0.0001
60–69 y	3.6 (2.2–6.0)	<0.0001	2.9 (1.8–4.8)	<0.0001	2.8 (1.7–4.6)	0.0001	2.8 (1.7–4.6)	0.0001
Diabetes	2.1 (1.5–2.9)	<0.0001	2.3 (1.7–3.2)	<0.0001	2.1 (1.5–2.9)	<0.0001	2.0 (1.4–2.8)	0.0001
Smoking	1.5 (1.1–2.0)	0.006	1.6 (1.2–2.1)	<0.0001	1.5 (1.1–2.0)	0.005	1.5 (1.1–2.0)	0.009
ACE inhibition	1.4 (1.0–2.0)	0.04	…	…	…	…	…	…
Digoxin	1.9 (1.4–2.7)	0.0001	1.7 (1.3–2.4)	0.0009	1.7 (1.2–2.4)	0.001	1.7 (1.3–2.4)	0.0008
β-Blockers	0.4 (0.3–0.7)	0.0005	0.4 (0.2–0.6)	<0.0001	0.4 (0.2–0.6)	<0.0001	0.3 (0.2–0.6)	<0.0001
RPP/1000	…	…	0.94 (0.92–0.96)	0.004	0.94 (0.92–0.97)	<0.0001	0.94 (0.93–0.97)	<0.0001
Duke category								
Intermediate	…	…	2.0 (1.4–2.7)	<0.0001	1.9 (1.4–2.7)	<0.0001	1.9 (1.3–2.6)	0.0002
High risk	…	…	2.9 (1.4–5.9)	0.004	2.8 (1.4–5.8)	0.005	2.5 (1.2–5.1)	0.01
LV dysfunction								
Mild	…	…	…	…	1.6 (1.1–2.2)	0.01	1.5 (0.2–2.1)	0.04
Moderate	…	…	…	…	1.6 (0.8–3.4)	0.19	1.5 (0.7–3.2)	0.24
Severe	…	…	…	…	5.3 (1.9–14.8)	0.001	5.7 (2.0–15.9)	0.0009
Ischemia	…	…	…	…	…	…	1.5 (1.0–2.1)	0.03
Global χ^2	284	…	314	…	368	…	374	…

RPP indicates rate-pressure product.

TABLE 4. Prediction of 5-y Mortality Based on Exercise Testing Results and Resting and Stress Echocardiography

	Duke Risk Category (Low)			Duke Risk Category (Intermediate)			Duke Risk Category (High)		
	Normal Rest	SSS in Patients With Abnormal Resting Function: SV	SSS in Patients With Abnormal Resting Function: MV	Normal Rest	SSS in Patients With Abnormal Resting Function: SV	SSS in Patients With Abnormal Resting Function: MV	Normal Rest	SSS in Patients With Abnormal Resting Function: SV	SSS in Patients With Abnormal Resting Function: MV
Relative risk	1	2.1	4.1	2.4	5.2	9.8	3.8	8.1	15.7
Predicted mortality, %/y	0.7	1.5	2.9	1.7	3.6	6.7	2.7	5.7	11
Patients, n	2029	990	44	1257	664	102	71	20	10
Observed mortality, %/y	0.7	1.8	3	2.4	3.7	7	4.6	5	12

SSS indicates summed stress score (total extent of abnormal segments after exercise). SV, single-vessel territory; and MV, multivessel territory. A total of 5187 patients are listed; the remaining 24 were excluded because of incomplete results regarding their extent scores.

Assessment of Risk in Patients With Stable Chronic Coronary Disease

The risk of mortality in stable coronary artery disease is low.[18] Nonetheless, the few patients with advanced or extensive disease are at high risk of an event, which may be reduced by coronary revascularization.[13] However, although the evidence base favoring intervention is based on the anatomic extent of coronary disease, most patients undergo assessment with functional testing.

In patients who are unable to exercise, the expense of pharmacological stress imaging techniques is unavoidable, and a large evidence base has accumulated with respect to their value in prognostic assessment.[4–6] In contrast, the additional cost has been more difficult to rationalize in patients who are able to exercise, because this test is an excellent tool for assessing risk in patients with coronary artery disease. In the Coronary Artery Surgery Study (CASS) registry, the presence of a positive test at low workload conferred a 5-fold increment of risk compared with a negative test at high workload.[19] Similarly, the Duke database has been used to derive a treadmill score that confers a 5-fold increment of risk in high-risk compared with low-risk patients. Although intervention is appropriate for high-risk patients (5-year survival of 65%) and medical treatment is best for low-risk patients (5-year survival of 97%), the appropriate response to intermediate-risk patients is less clear, and angiographic assessment is often performed to identify extensive coronary artery disease.

A number of studies have shown the prognostic application of nuclear cardiology techniques[17,20,21] to demonstrate low levels of risk (<1% per year) in the setting of a normal test. Scintigraphic studies have shown imaging data to be of independent and incremental prognostic value to standard investigations, and selective application of this modality in combination with standard risk variables[22] may reduce expenditure on subsequent invasive investigations, while at the same time having no adverse impact on outcome.[23]

Previous studies with exercise echocardiography have indicated that the imaging component of this test adds incremental and independent information to the results of standard exercise testing.[7–12] A normal exercise echocardiogram is associated with a risk of <1% per year over the first 6 years of follow-up, with a subsequent small increase that most likely reflects progressive coronary artery disease. Although the comparison with nuclear imaging results is difficult because of differences in the selection of patients, 2 studies that compared the techniques in the same patients have shown the prognostic implications to be similar. However, the event rate in patients with a positive study ranges from 18% to 35%, and many previous studies were limited by insufficient sample size, mandating the use of composite end points. No previous study has had sufficient mortality or follow-up to substratify positive test results. The results of the present study suggest that although exercise echocardiography offers incremental prognostic information in the group as a whole, this is of limited value in nearly 50% of the patients who are at high or low risk on the basis of the Duke score. In the remaining individuals at intermediate levels of risk, the results of exercise echocardiography are able to further stratify risk and may therefore reduce the cost of subsequent investigations.

Limitations of the Study

Earlier studies of stress echocardiography have had the advantage of assessing the performance of the test before it became used as a clinical tool. The results in the present study reflect the progressive acceptance of the test as a clinical tool. Consequently, patients with positive tests tend to proceed to angiography and thence to revascularization (and removal from our analysis). Failure to censor patients at the time of revascularization would have the effect of improving the outcome of patients with positive test results.

As currently performed, exercise echocardiography is interpreted subjectively. Although we sought to replicate "real life" by studying the performance of the test in a referral center and a large independent laboratory, the tests were interpreted by experts who have a similar approach to test interpretation, reflecting previous collaborative teaching and training activities. Nonetheless, an important limitation in the assessment of disease extent has been in the accordance of wall motion scoring between observers, and for this reason, disease extent was characterized on the number of coronary vascular territories involved. Indeed, the same approach has been used in multicenter nuclear cardiology studies.[24] It is hoped that the development of a quantitative echocardiographic approach may facilitate a subtler means of assessing disease extent in the future.

Clinical Application

The findings of the present study apply to patients with known or suspected coronary artery disease who are able to exercise maximally and whose symptom status does not mandate revascularization. The first step is to exclude individuals at low risk on clinical grounds. The application of the treadmill score is then able to identify almost 50% of the patients who are either at low risk (in which case, further intervention would not be necessary in most cases on prognostic grounds) or at high risk (in which case, further stratification would in most instances be deemed inappropriate). The remaining patients, who account for approximately half of the total, merit further evaluation by exercise echocardiography, which is able to substratify patients. This investigative approach may potentially reduce the performance of coronary angiography while at the same time identifying patients at risk of subsequent cardiac events.

Acknowledgments

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