LESS IS MORE

Exercise Testing in Asymptomatic Patients After Revascularization

Are Outcomes Altered?

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Background: Although exercise echocardiography (ExE) of asymptomatic patients early (<2 years after percutaneous coronary intervention [PCI] or <5 years after coronary bypass graft surgery [CABG]) after revascularization is considered inappropriate, the appropriateness of later testing is indeterminate. Treatment responses to positive test results in either setting have uncertain outcome implications. We sought to identify whether predictors of increased risk by ExE could lead to interventions that change outcome in asymptomatic patients with previous coronary revascularization.

Methods: Exercise echocardiography was performed in 2105 asymptomatic patients (mean [SD] age, 64 [10] years; 310 [15%] were women; 845 [40%] had a history of myocardial infarction; 1143 [54%] had undergone PCI and 962 [46%] had undergone CABG 4.1 [4.7] years prior to the ExE). Ischemia was identified as a new or worsening wall motion abnormality. Patients were followed for a mean (SD) period of 5.7 (3.0) years for cardiac mortality. The association of ischemia during ExE with survival was assessed using Cox proportional hazard models, and an interaction with revascularization was sought.

Results: Of 262 patients with ischemia (13%), only 88 (34%) underwent subsequent revascularization. Mortality (97 patients [4.6%]) was associated with ischemia (hazard ratio, 2.10; 95% CI, 1.05-4.19; $P = .04$) in groups tested both early ($P = .03$) and late (≥2 years after PCI or ≥ 5 years after CABG) ($P = .001$). However, the main predictors of outcome were clinical and stress testing findings rather than echocardiographic features. Subgroup analysis showed that asymptomatic patients without diabetes mellitus, with normal ejection fraction (≥50%), and normal exercise capacity (>6 METs [metabolic equivalent for task]) were unlikely to have a positive test result or events. Even high-risk patients did not seem to benefit from repeated revascularization.

Conclusions: Asymptomatic patients who undergo ExE after coronary revascularization may be identified as being at high risk but do not seem to have more favorable outcomes with repeated revascularization. From a health economic standpoint, appropriateness of such testing must be carefully reviewed.

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RECURRENT ISCHEMIA AND cardiac events are common after coronary revascularization procedures—both percutaneous coronary intervention (PCI) and coronary bypass graft surgery (CABG).[1,2] This reflects the progression of coronary artery disease as well as progressive failure of treatment, including in-stent restenosis and graft atherosclerosis. In symptomatic patients after revascularization, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend evaluation with stress imaging tests,[3] including exercise stress echocardiography (ExE). The evaluation of asymptomatic patients is more controversial. The presence of ischemia on a stress echocardiogram is predictive of adverse outcome in post-PCI and post-CABG patients.[4-6] However, there is no evidence that repeated revascularization (RVS) based on positive testing changes the course of the disease or patient outcomes.

See Invited Commentary and Editor's Note at end of article

The inappropriate use of noninvasive testing is not only costly but also could lead to unnecessary downstream testing and interventions such as coronary angiography and revascularization. While stress echocardiography in postrevascularization patients with ischemic symptoms is appropriate,[7] appropriateness in asymp-

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tomatic patients depends on the timing relative to intervention. Testing is considered inappropriate early after PCI (<2 years) and CABG (<5 years),[7] but the justification for these cutoffs is ill defined. We sought to study the effectiveness of testing asymptomatic patients early and late postrevascularization by examining the frequency of a positive response, the association of test results with subsequent revascularization and mortality, and the presence of any interaction of revascularization with these event rates.

METHODS

STUDY DESIGN

This was an observational retrospective cohort study using prospectively obtained data in consecutive asymptomatic patients with a history of PCI or CABG who were referred for ExE at the Cleveland Clinic, Cleveland, Ohio, from January 2000 through November 2010. Our institution has no formal protocol regarding the assessment of patients who have had CABG or PCI and are symptom free; referral for ExE is solely at the discretion of individual physician treating the patient, usually on the basis of concerns regarding risk factor status or incomplete revascularization.

CLINICAL INFORMATION

Before each ExE, a structured interview and medical chart review were done to gather data on demographics (age, sex), previous cardiac revascularization procedure (type, date), symptoms (chest pain, dyspnea), medications (aspirin, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], statins, β-blockers), coronary risk factors (hypertension, diabetes mellitus, obesity [body mass index, calculated as weight in kilograms divided by height in meters squared, >30], smoking), previous cardiovascular events (myocardial infarction [MI], stroke), and several cardiac and noncardiac diagnoses (atrial fibrillation [AF], congestive heart failure [CHF], and chronic obstructive pulmonary disease [COPD]). This clinical information was entered prospectively into the stress-testing database. The symptom status of patients was assessed by 2 independent reviewers who were blinded to each other's assessments and who were both unaware of the hypothesis of this study: 1 reviewer was from the registry group while the other was the exercise physiologist supervising the study. Only patients who were considered to be symptom free by both reviewers were included. Based on Appropriate Use Criteria,[7] "early" testing was defined by investigation as testing less than 2 years after PCI or less than 5 years after CABG.

Information regarding revascularization was obtained by matching to the Cardiovascular Information Registry, a comprehensive database describing clinical and surgical characteristics of revascularized patients,[8] which includes prospective follow-up for death, recurrent symptoms, and RVS. The databases and linkage were approved by the institutional review board.

EXERCISE TESTING

Patients were prepared for exercise echocardiography in the traditional way,[9] including abstaining from β blockade for 24 hours before the test. Maximal treadmill protocols, selected according to the patient age and functional status, were performed, and standard test end points were used.[10] Ischemic symptoms, changes in ST segment, exercise capacity, and hemodynamic response to exercise were recorded for each patient. Exercise time, maximum ST-segment deviation, and the presence of exercise angina were used to calculate the Duke Treadmill score.[11] In addition, we combined clinical (age, sex, angina, diabetes mellitus, smoking, hypertension) and stress data (exercise capacity, ST depression, angina, heart-rate recovery, ectopy during recovery) to derive a 5-year mortality risk index[12] as previously described.

ECHOCARDIOGRAPHY

Baseline and stress images (performed immediately after cessation of exercise) were acquired from standard echocardiographic windows, including apical, parasternal, and subcostal.[13] Studies were interpreted by experienced physicians, aware of the test indication but not of other clinical details of the patient. Standard left ventricular (LV) segmentation was used for LV regional wall motion analysis.[14] Normal resting function with no worsening after exercise identified a normal test. Scar was characterized by akinesis or dyskinesis at rest. Ischemia was defined by new or worsening wall motion abnormalities. To express the extent of ischemia, myocardial segments were combined into vascular territories. Study results were considered abnormal if more than 1 segment showed evidence of ischemia or MI, and a normal study was defined by a normal response in all segments.

END POINTS

The primary end points were RVS and cardiac as well as all-cause mortality during a mean (SD) follow-up period of 5.7 (3.0) years. Repeated revascularization was attributed to the ExE result if it was performed within 6 months. End points were identified from the electronic medical record, state death records, and a national social security death index. End points were verified by reviewers who were not aware of stress testing or echocardiography results.

STATISTICAL ANALYSIS

Differences in mortality between patients with and without ischemia during exercise echocardiography were evaluated by log-rank χ^2 tests and compared using Kaplan-Meier survival curves. Adjusted estimates and tests were obtained using Cox proportional hazard models with adjustment for age, sex, type of prior revascularization (PCI vs CABG), ejection fraction, exercise capacity, smoking status, diabetes mellitus, hypertension, cardiovascular medications (aspirin, β-blockers, ACE inhibitors, ARBs, and statins), and cardiac history of AF, CHF, and MI. Log-likelihood ratio tests were used to evaluate any interaction terms. A series of subgroup analyses were performed in asymptomatic patients with low ejection fraction (EF <50%), diabetes mellitus, and low exercise capacity (<6 METs [metabolic equivalent for task]). Nested Cox regression models were used to assess the contribution of clinical factors, stress testing findings, and echocardiographic features in the prediction of mortality.

RESULTS

PATIENT CHARACTERISTICS

We identified 2105 patients with previous revascularization—1143 with prior PCI (54%) and 962 with prior CABG (46%)—who were asymptomatic at time of referral for the first follow-up ExE from January 2000

Table 1. Baseline Characteristics of 2105 Asymptomatic Patients With Prior Revascularization at Time of First Follow-up ExE

Characteristic	Patients, No. (%) Total (N = 2105)	Prior CABG (n = 962)	Prior PCI (n = 1143)
Age, mean (SD), y	64 (10)	66 (9)	62 (10)
Female	310 (15)	111 (12)	197 (17)
Early testing[a]	1236 (59)	527 (55)	709 (62)
Medical history			
Atrial fibrillation	99 (5)	55 (6)	44 (4)
CHF	110 (5)	69 (7)	41 (4)
MI	845 (40)	306 (32)	537 (47)
Other conditions/risk factors			
COPD	56 (3)	32 (3)	24 (2)
Stroke	120 (6)	70 (7)	50 (4)
Obesity	299 (14)	148 (15)	174 (15)
Current smoker	160 (8)	58 (6)	102 (9)
Hypertension	1573 (75)	715 (74)	857 (75)
Diabetes mellitus	419 (20)	203 (21)	215 (19)
Use of cardiac medications			
Aspirin	1767 (84)	779 (81)	986 (86)
ACE inhibitors	1022 (49)	429 (45)	593 (52)
β-Blockers	1473 (70)	628 (65)	843 (74)
ARB	213 (10)	96 (10)	116 (10)
Statins	1796 (85)	799 (83)	995 (87)
Duke treadmill score			
Abnormal, <5	467 (22)	217 (22)	250 (22)
ST-segment uninterpretable	239 (11)	142 (15)	96 (8)
Normal, ≥5	1399 (66)	603 (63)	797 (70)
ExE test result			
Ischemia	262 (13)	125 (13)	137 (12)
Nondiagnostic or scar only	685 (32)	349 (36)	336 (29)
Normal	1158 (55)	488 (51)	670 (59)
Maximum METs, mean (SD)	8.7 (2.4)	8.4 (2.3)	8.9 (2.4)
Ejection fraction, mean (SD)	53 (8)	52 (9)	53 (8)
5-y Survival index, mean (SD)	0.93 (0.08)	0.92 (0.09)	0.95 (0.07)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ExE, exercise echocardiography; MET, metabolic equivalent for task; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Early testing: less than 2 years after PCI and less than 5 years after CABG.

through November 2010. Their baseline clinical characteristics are summarized in **Table 1**. Of note, 40% had a history of MI, and the revascularization procedure had been performed at a mean (SD) of 4.1 (4.7) years prior to the exercise echocardiogram. Late testing (>2 years post-PCI and >5 years post-CABG) was performed in 434 PCI patients (38%) and 435 CABG patients (45%). The stress results overall suggested low risk—the mean exercise capacity was 8.7 (2.4) METs and the mean resting ejection fraction was 53% (8%). Ischemia was noted in 262 patients (13%), but only 1158 (55%) were completely normal.

REPEATED TESTING

Ischemia was detected at the index test in 262 patients, of whom 88 (34%) underwent RVS. Among those with a nonischemic index test, 908 patients (49%) had a second or subsequent test (**Figure 1**). Of these patients, the rate of initial or subsequent revascularization ranged from about 33% of those with a positive test result to 17% of symptomatic patients without ischemia and 12% to 14% of asymptomatic patients without ischemia.

REPEATED REVASCULARIZATION

In total, RVS was performed in 354 patients (17%) after a mean (SD) interval of 3.7 (3.2) years from the index ExE—mostly as PCI (12%), although 4% had CABG and 1% had both PCI and CABG (**Table 2**). The relationship between ischemia on the initial ExE and RVS is summarized as follows: 262 patients (13%) had ischemia, and of those, 174 (66%) did not undergo RVS. A total of 1845 patients (87%) did not have ischemia, and of these, 1579 (86%) did not undergo RVS. Among those who underwent RVS, 266 (75%) did not have ischemia on the initial exercise echocardiogram. However, RVS was associated with the detection of ischemia on subsequent testing (63 patients [24%]) performed for the development of spontaneous symptoms. Patients who developed symptoms were about twice as likely undergo RVS. By comparison, of the 1579 who did not undergo RVS, 197 (12%) became symptomatic at follow-up. The decision to proceed with RVS was based more on the clinical status of the patient than on the sole result of the test. **Table 3**, showing patients who had ischemia at any test, compares clinical characteristics in those who did and did not

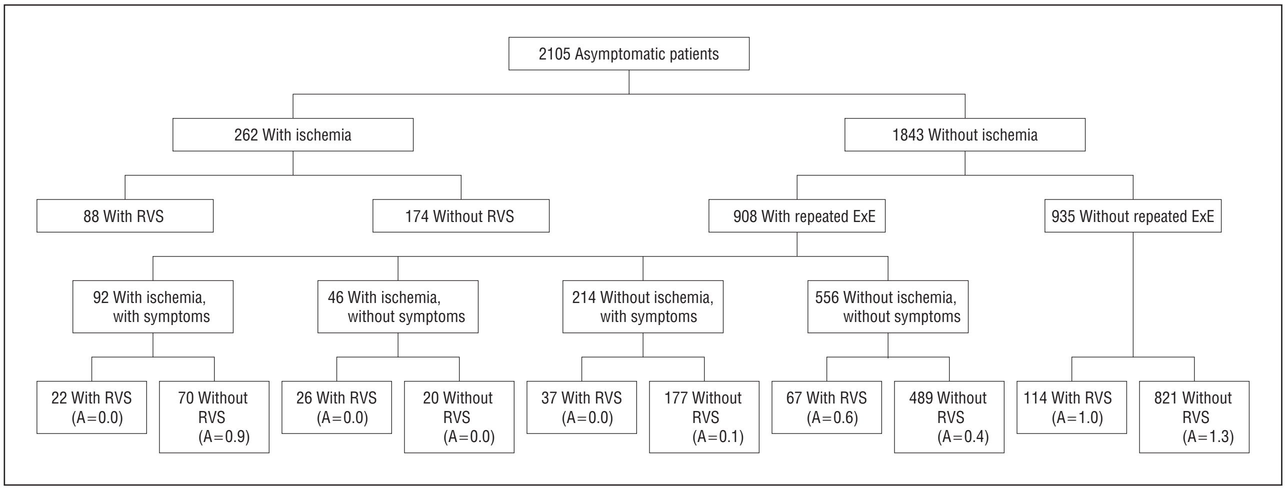

Figure 1. Index exercise echocardiogram and outcomes. A indicates annualized mortality rate in percentages; ExE, exercise echocardiography; and RVS, repeated revascularization.

Table 2. Characteristics of Index Revascularization and Subsequent Revascularizations

	Patients, No. (%)		
Characteristic	Total (N=2105)	CABG (n=962)	PCI (n=1143)
Time from index revascularization to first ExE, mean (SD), y	4.0 (4.7)	6.0 (5.6)	2.4 (2.7)
Ever symptomatic at a subsequent ExE	285 (14)	120 (12)	165 (14)
Time to development of symptoms, mean (SD), y	2.9 (2.0)	3.0 (2.0)	2.8 (2.1)
Revascularizations after initial ExE			
No revascularizations	1751 (83)	830 (86)	921 (81)
PCI	260 (12)	89 (9)	171 (15)
CABG	77 (4)	38 (4)	39 (3)
PCI + CABG	17 (1)	5 (1)	12 (1)
Time to repeated revascularization after the initial ExE, mean (SD), y	3.7 (3.2)	4.8 (3.3)	3.2 (3.0)

Abbreviations: CABG, coronary artery bypass graft; ExE, exercise echocardiography; PCI, percutaneous coronary intervention.

Table 3. Characteristics of Patients With Ischemia at Any ExE Postrevascularization (First or Subsequent Follow-ups) and Referral for Repeated Revascularization (RVS)

	Patients, %		
Characteristic	Repeated RVS	No Repeated RVS	*P* Value
Symptomatic at time of ExE	17.0	11.9	.008
Age > 65 y	50.7	56.1	.34
Male	87.5	81.8	.12
DM	22.1	25.0	.63
HTN	70.6	75.8	.26
Smoking	9.6	7.2	.41
Low EF <50%	33.1	31.4	.74
Abnormal Ex capacity <6 METs	11.9	8.9	.59
Marked ischemia on the ExE	25.8	22.0	.42

Abbreviations: DM, diabetes mellitus; EF, ejection fraction; Ex, exercise; ExE, exercise echocardiography; HTN, hypertension; MET, metabolic equivalent for task.

undergo RVS. Symptom status was the only variable significantly associated with the decision to proceed with RVS among patients with ischemia (*P* = .008).

MORTALITY DURING FOLLOW-UP

Ninety-seven deaths (4.6%) occurred over a mean (SD) period of 5.7 (3.0) years of follow-up, an annualized mortality rate of 0.8%. Patients with ischemia on any postrevascularization ExE had a higher mortality compared with those without ischemia (8.0% vs 4.1%; *P* = .03). **Figure 2** summarizes the difference in cardiac and all-cause mortality between patients with and without ischemia. Most deaths (76 patients [78%]) occurred in patients without ischemia, among whom the annualized mortality rate was 0.7% with RVS and 0.8% in patients without RVS (*P* = .15). There were 21 deaths in patients with ischemia, among whom the annualized mortality rates were 1.4% with RVS and 2.1% in patients without RVS (*P* = .38). By comparison, there were 20 deaths in the scar group (annualized mortality rate, 1.0%) and 32 deaths in the nondiagnostic group (annualized mortality rate, 1.4%).

The independent associations of clinical, stress testing, and echocardiographic characteristics with mortality are summarized in **Table 4**. Ischemia on exercise echocardiography was strongly associated with death (hazard ratio [HR], 2.10; 95% CI, 1.05-4.19; *P* = .04). Prior CABG, an abnormal ExE result even without ischemia (ie, scar or nondiagnostic), an EF of less than 50%, an exercise capacity of less than 6 METs, and diabetes mellitus were also associated with death. However, to be useful clinically, ExE needs to be not only of independent value but also incremental value. In nested models (**Table 5**), clinical and stress testing findings, but not echocardiographic features, were associated with both all-cause and cardiac mortality. Accordingly, we applied the predictive index based on clinical and exercise but no echo-

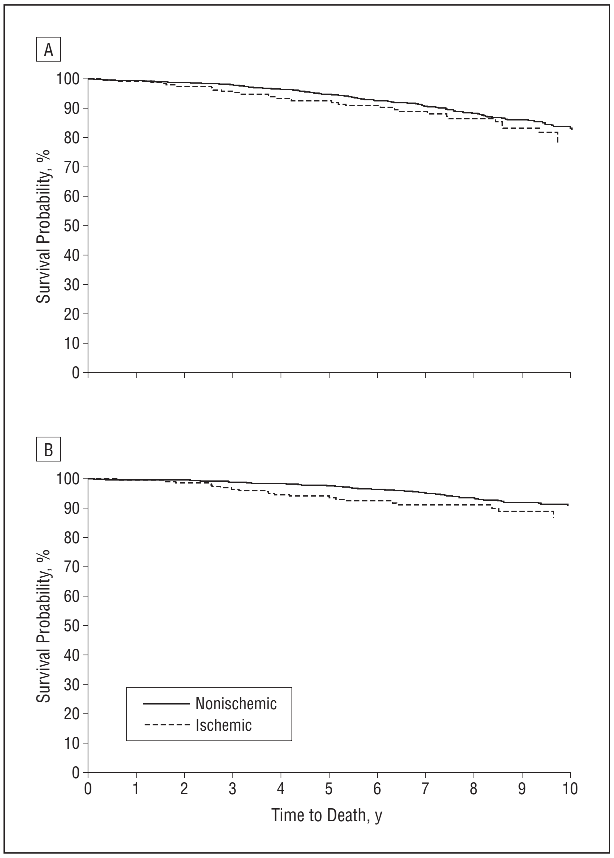

Figure 2. Survival by ischemia status at first postrevascularization stress echo among 2105 asymptomatic patients. A, All-cause death; B, cardiac-related death.

cardiographic variables. When comparing patients with a predicted probability of 5-year survival below the median (ie, >4.0% risk of mortality over 5 years) to patients with higher predicted survival, the first group had a higher incidence of ischemia (15.7% vs 9.3%; $P < .001$) and a higher mortality rate (13.3% vs 3.9%; $P < .001$).

PROGNOSTIC IMPACT OF RVS

In the overall population, RVS was not significantly associated with survival ($P = .67$); **Figure 3** compares the adjusted survival of patients according to the presence of ischemia and subsequent revascularization. This lack of association persisted even after considering interaction with an abnormal ExE ($P = .70$ for interaction with ischemia; $P = .41$ for interaction with other abnormal findings, ie, scar or nondiagnostic). Subanalysis based on the magnitude of ischemia comparing patients with mild ischemia with those with moderate or marked ischemia showed that there was no difference regarding benefit from revascularization. Using stratification by groups defined by a single cardiac risk factor, including EF of less than 50%, exercise capacity of less than 6 METs, incomplete revascularization, prior CHF or MI, or presence of diabetes mellitus or hypertension, we were unable to isolate subgroups of asymptomatic patients who might benefit from testing and revascularization. Because the study was underpowered to detect differential risks among small subgroups, we also examined a composite measure of cardiac risk. Patients at low risk (age <65 years, no diabetes mellitus, nonsmoker) accounted for 775 patients (37%), and 91% had no ischemia (in contrast with 85% among the 1330 [63%] high-risk patients; $P < .001$). Although the RVS rate was similar (15% vs 18%; $P = .14$), the mortality of the low-risk group was less (4.3% vs 11.2%; $P < .001$). **Table 6** presents an alternative stratification based on the 5-year mortality index.

Table 4. Multivariate Cox Regression Model Predicting Risk of Cardiac Death With Interactions Between ExE Test Result and Subsequent Revascularization

Characteristic	HR (95% CI)	*P* Value
Age	1.00 (0.98-1.03)	.87
Female	0.67 (0.35-1.28)	.22
Prior CABG	2.39 (1.42-3.99)	<.001
Revascularization	1.57 (0.21-11.9)	.66
Cardiac history		
MI	0.63 (0.39-1.02)	.06
Atrial fibrillation	0.80 (0.19-3.39)	.76
CHF	1.71 (0.93-3.14)	.08
Risk factors		
Diabetes mellitus	1.66 (1.05-2.61)	.03
Current smoker	1.07 (0.48-2.42)	.87
Hypertension	1.50 (0.86-2.63)	.16
Obesity	1.17 (0.66-2.07)	.60
Stroke	1.15 (0.56-2.36)	.71
COPD	1.25 (0.50-3.09)	.63
Drug use		
Aspirin	0.79 (0.49-1.29)	.36
ACE inhibitors	1.25 (0.77-2.01)	.37
β-Blockers	0.70 (0.45-1.11)	.13
ARB	1.38 (0.71-2.70)	.35
Statins	0.92 (0.56-1.52)	.75
EF	0.97 (0.95-0.99)	.02
Early vs late ExE	0.89 (0.56-1.40)	.61
ExE ischemia	2.10 (1.05-4.19)	.04
Other, scar, nondiagnostic	1.95 (1.07-3.54)	.03
Exercise capacity, maximum METs	0.82 (0.73-0.93)	.003
Interactions		
Ischemia × revascularization	0.63 (0.06-6.88)	.71
Other finding × revascularization	0.31 (0.02-5.33)	.42

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ExE, exercise echocardiography; HR, hazard ratio; MET, metabolic equivalent for task; MI, myocardial infarction.

OUTCOMES ACCORDING TO TIMING OF THE ExE

The appropriateness criteria distinguish between testing early and late postrevascularization. Early testing was performed in 709 PCI patients (62%), and 527 CABG patients (55%). RVS was less associated with early than late ischemia (28% vs 38%; $P < .001$). Ischemia on ExE was a predictor of mortality in patients tested early ($P = .03$) and late after revascularization ($P = .001$). However, RVS did not significantly improve survival in patients tested either early or late. The timing of the ExE (early vs late) did not predict mortality in multivariate Cox regression (HR, 0.89; 95% CI, 0.56-1.40; $P = .61$) (Table 4).

Table 5. Contribution of Clinical, Stress Testing, and Exercise Echocardiography (ExE) Results in Prediction of Mortality From Nested Cox Regression Models

Type of Mortality	Model[a]	−2 Log Likelihood	Likelihood Ratio χ^2	*df*	*P* Value
All-cause mortality					
Null model	0	2407.7			
Clinical variables	1	2299.0	109.0	17	<.001
Stress testing measures	2	2260.0	39.0	5	<.001
ExE test results	3	2259.2	0.8	4	.94
Cardiac-related mortality					
Null model	0	1265.6			
Clinical variables	1	1187.9	77.7	17	<.001
Stress testing measures	2	1147.7	40.2	5	<.001
ExE test results	3	1145.9	1.8	4	.78

[a] Model 1: Clinical variables: age, sex, diabetes mellitus, hypertension, coronary artery bypass graft vs percutaneous coronary intervention, use of cardioprotective agents (aspirin, angiotensin-converting enzyme inhibitors, β blockers, angiotensin II receptor blockers, statins), cardiac event history (history of atrial fibrillation, congestive heart failure, myocardial infarction), current smoker, obesity, history of stroke, and chronic obstructive pulmonary disease. Model 2: Cardiac-risk index, ejection fraction, exercise capacity (maximum metabolic equivalent for task), and Duke treadmill results. Model 3: Level of ischemia, level of scar, nondiagnostic reading, and Wall Motion Stress Index at stress.

COMMENT

There are 5 major findings from this study of asymptomatic postrevascularization patients. First, only 262 (13%) had evidence of ischemia. Second, abnormal test results were associated with increased risks for subsequent overall and cardiac death in both early- and late-tested groups. Third, the main predictor of outcome was exercise capacity, suggesting that risk evaluation could be obtained from a standard exercise test rather than exercise echocardiography. Fourth, ischemic results were often not acted on; among patients with evidence of ischemia, 66% did not undergo RVS, and of those who underwent RVS, 75% did not have ischemia on their ExE. The decision to proceed with RVS was based more on the change in the clinical status of the patient with development of ischemic symptoms than on the sole result of the test. Finally, RVS was not associated with more favorable outcomes.

RATIONALE FOR SCREENING IN REVASCULARIZED PATIENTS

Coronary revascularization is highly effective for symptom control, and changes the outcome of selected patient groups with extensive coronary disease.[15] Unfortunately, no revascularization procedures are curative, and recurrent coronary problems are common, owing to stent restenosis, graft closure or new native coronary lesions.[1,2] Screening tests are often considered in the hope of identifying and resolving these problems electively and reducing the likelihood of acute presentations.

Based on previous prognostic studies, the appropriate use criteria[7] identify ExE as being of indeterminate value late after PCI (≥2 years) and CABG (≥5 years), and inappropriate before this time frame. These judgments were made on the basis of expert opinion and, in relation to prognostic value, do not seem to be supported by our data. Previous studies have shown that stress echocardiography is an accurate diagnostic tool for identifying significant coronary stenoses after either PCI[16,17] or CABG.[18,19] Studies of moderate size have shown stress echocardiography to have prognostic value in asymptomatic patients postrevascularization.[4-6] Other functional tests (eg, exercise nuclear perfusion imaging)[20,21] have identified the detection of ischemia after 5 years as being associated with adverse outcome. In contrast with stress echocardiography, the nuclear appropriateness criteria conclude that stress testing is appropriate in asymptomatic patients 5 or more years after CABG, and indeterminate at less than 5 years after CABG.[22] However, the appropriate use criteria indicate that the value of risk assessment with single-photon emission computed tomography in asymptomatic post-PCI patients is uncertain, with no evidence of survival benefit.[22,23] Moreover, the exercise testing and nuclear guidelines are discordant about the value of testing in selected asymptomatic, high-risk patients.[24,25]

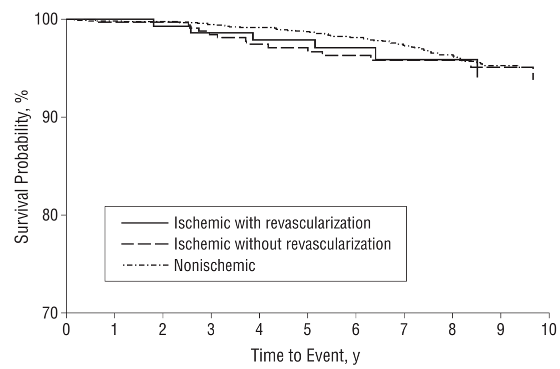

Figure 3. Adjusted survival based on multivariate Cox regression models at mean of covariates, according to the presence of ischemia and subsequent revascularization.

APPROPRIATENESS OF TESTING

Unfortunately, it has not been well established as to whether the information provided by testing asymptomatic patients alters treatment, and, if so, whether such treatment changes alter outcomes. This is a critical issue because the detection of clinically silent coronary disease progression may expose the patient to the risks and expense of further revascularization without a survival benefit. There are also

Table 6. Test Results, Mortality, and Revascularization by Risk Status[a]

Characteristic	Lower Risk of Death (n = 1052)	Higher Risk of Death (n = 1053)	*P* Value
5-y Mortality index			
Ischemia	98 (9.3)	164 (15.7)	<.001
Total mortality	42 (3.9)	140 (13.3)	<.001
Revascularization	160 (15.2)	194 (18.4)	.048
Clinical characteristics	(n = 775)	(n = 1330)	
Ischemia	69 (8.9)	193 (14.5)	<.001
Total mortality	33 (4.3)	149 (11.2)	<.001
Revascularization	118 (15.2)	236 (17.7)	.14

[a] Two risk scores are applied: 5-year mortality index (a composite score derived from clinical and stress testing results) and composite of clinical characteristics (low risk: age <65 years, without diabetes mellitus, and nonsmoking status).

barriers to RVS, including comorbidities, lack of suitable target vessels, potential revascularization of nonischemic territory based on suitability of anatomy rather than physiology, and difficulties in balancing the risk of another procedure with the risk of adverse outcome from ischemia. Probably as a consequence, ischemic results were often not acted on. In addition, it seems that RVS did not provide prognostic benefit even among the asymptomatic patients at highest risk.

The results of our study also somewhat contradict the current guidelines about the selection of standard exercise electrocardiography (ECG) and stress imaging tests after revascularization. The ACC/AHA stress testing guidelines state that among patients who can attain an adequate level of exercise, symptom-limited treadmill or bicycle exercise is the preferred form of stress because it provides the most information concerning patient symptoms, exercise capacity, cardiovascular function, and the hemodynamic response during usual forms of activity.[24] However, for *diagnostic* purposes in the postrevascularization population, stress imaging tests are proposed in preference to the standard exercise ECG, because a number of ECG changes are nonspecific in this group.[26] Our results suggest that from a prognostic standpoint, a combination of clinical and exercise data is effective in identifying patients at the highest risk, even though they are unlikely to benefit from RVS. To our knowledge, no previous study of exercise echocardiography in asymptomatic patients postrevascularization addressed the incremental value of imaging to clinical and stress testing findings—all previous studies included either mixed stress modalities (exercise and pharmacologic) and/or had a combination of asymptomatic and symptomatic patients. In the nuclear literature, a single-exercise, thallium-perfusion testing study[20] had a comparable population in asymptomatic patients after CABG. In that work, Lauer et al[20] found that impaired exercise capacity was more predictive of death (adjusted relative risk [RR], 4.16, 95% CI, 2.38-7.29) and major events (adjusted RR, 3.61; 95% CI, 2.22-5.87) than thallium-perfusion defects (adjusted RR, 2.78; 95% CI, 1.44-5.39 for death and adjusted RR, 2.63; 95% CI, 1.49-4.66 for major events) in asymptomatic patients after CABG.

STUDY LIMITATIONS

This is an observational study, which shows associations but cannot ascribe causality. However, while it is conceivable that some patients may have a more favorable outcome with RVS, this seems unlikely on the basis that risk stratification failed to identify asymptomatic patients who will benefit from RVS. Likewise, although these patients were treated as a specialized referral center, the levels of risk and risk factors seen in this study are compatible with the usual postrevascularization patient. Finally, all of our patients were tested with exercise echocardiography, raising the question whether the results of this study are generalizable to all forms of stress testing.

In conclusion, the results of this study suggest that asymptomatic patients who undergo treadmill ExE after coronary revascularization may be identified as being at high risk but do not seem to have more favorable outcomes with RVS. Given the very large population of post-PCI and post-CABG patients, careful consideration is warranted before the screening of asymptomatic patients is considered appropriate at any stage after revascularization.

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REFERENCES

1. Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet*. 1995;346(8984):1184-1189.
2. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335(4):217-225.
3. Fraker TD Jr, Fihn SD, Gibbons RJ, et al; 2002 Chronic Stable Angina Writing Committee; American College of Cardiology; American Heart Association. 2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the management of Patients With Chronic Stable Angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol*. 2007;50(23):2264-2274.
4. Cortigiani L, Bigi R, Sicari R, Landi P, Bovenzi F, Picano E. Stress echocardiography for the risk stratification of patients following coronary bypass surgery. *Int J Cardiol*. 2010;143(3):337-342.
5. Cortigiani L, Sicari R, Bigi R, et al. Usefulness of stress echocardiography for risk stratification of patients after percutaneous coronary intervention. *Am J Cardiol*. 2008;102(9):1170-1174.
6. Arruda AM, McCully RB, Oh JK, Mahoney DW, Seward JB, Pellikka PA. Prognostic value of exercise echocardiography in patients after coronary artery bypass surgery. *Am J Cardiol*. 2001;87(9):1069-1073.

7. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP, Weiner RB. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart failure Society of America, Heart Rhythm Society, Society of Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society of Cardiovascular Magnetic Resonance [published online November 19, 2010]. *J AM Coll Cardiol*. doi:10.1016/j.jacc.2010.11.002.
8. Cosgrove DM, Loop FD, Lytle BW, et al. Determinants of 10-year survival after primary myocardial revascularization. *Ann Surg*. 1985;202(4):480-490.
9. Froelicher VF, Marcondes GD. Methodology. In: Froelicher VF, Myers J, eds. *Manual of Exercise Testing*. 3rd ed. St Louis, MO: Mosby; 2007:17-50.
10. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104(14):1694-1740.
11. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106(6):793-800.
12. Lauer MS, Pothier CE, Magid DJ, Smith SS, Kattan MW. An externally validated model for predicting long-term survival after exercise treadmill testing in patients with suspected coronary artery disease and a normal electrocardiogram. *Ann Intern Med*. 2007;147(12):821-828.
13. Ryan T, Feigenbaum H. Exercise echocardiography. *Am J Cardiol*. 1992;69(20):82H-89H.
14. Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for Chamber Quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440-1463.
15. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47(1):e1-e121.
16. Dori G, Denekamp Y, Fishman S, Bitterman H. Exercise stress testing, myocardial perfusion imaging and stress echocardiography for detecting restenosis after successful percutaneous transluminal coronary angioplasty: a review of performance. *J Intern Med*. 2003;253(3):253-262.
17. Crouse LJ, Vacek JL, Beauchamp GD, Kramer PH. Use of exercise echocardiography to evaluate patients after coronary angioplasty. *Am J Cardiol*. 1996;78(10):1163-1166.
18. Chin AS, Goldman LE, Eisenberg MJ. Functional testing after coronary artery bypass graft surgery: a meta-analysis. *Can J Cardiol*. 2003;19(7):802-808.
19. Kafka H, Leach AJ, Fitzgibbon GM. Exercise echocardiography after coronary artery bypass surgery: correlation with coronary angiography. *J Am Coll Cardiol*. 1995;25(5):1019-1023.
20. Lauer MS, Lytle B, Pashkow F, Snader CE, Marwick TH. Prediction of death and myocardial infarction by screening with exercise-thallium testing after coronary-artery-bypass grafting. *Lancet*. 1998;351(9103):615-622.
21. Palmas W, Bingham S, Diamond GA, et al. Incremental prognostic value of exercise thallium-201 myocardial single-photon emission computed tomography late after coronary artery bypass surgery. *J Am Coll Cardiol*. 1995;25(2):403-409.
22. Brindis RG, Douglas PS, Hendel RC, et al; American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group; American Society of Nuclear Cardiology; American Heart Association. ACCF/ASNC Appropriateness Criteria for Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by the American Heart Association. *J Am Coll Cardiol*. 2005;46(8):1587-1605.
23. Zellweger MJ, Weinbacher M, Zutter AW, et al. Long-term outcome of patients with silent versus symptomatic ischemia six months after percutaneous coronary intervention and stenting. *J Am Coll Cardiol*. 2003;42(1):33-40.
24. Gibbons RJ, Balady GJ, Bricker JT, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 Guideline Update for Exercise Testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*. 2002;106(14):1883-1892.
25. Klocke FJ, Baird MG, Lorell BH, et al; American College of Cardiology; American Heart Association; American Society for Nuclear Cardiology. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol*. 2003;42(7):1318-1333.
26. Krone RJ, Hardison RM, Chaitman BR, et al. Risk stratification after successful coronary revascularization: the lack of a role for routine exercise testing. *J Am Coll Cardiol*. 2001;38(1):136-142.

INVITED COMMENTARY

Routine Periodic Stress Testing in Asymptomatic Patients Following Coronary Revascularization

Is It Worth the Effort?

The confluence of increasing budgetary restrictions and the proliferation of medical imaging make the appropriateness of routine periodic stress testing in asymptomatic patients following coronary revascularization a hotly debated topic.[1,2] Routine periodic stress testing is still used by many physicians. Putative reasons include surveillance for restenosis after percutaneous coronary intervention (PCI), identification of graft patency after coronary artery bypass graft (CABG) surgery, and determination of completeness of revascularization. However, the usefulness of routine periodic stress testing in asymptomatic patients following coronary revascularization remains unknown.

Stress testing can be performed with exercise alone or in combination with echocardiographic or nuclear imaging. Many studies have demonstrated the prognostic ability of these tests, with ischemia demonstrated on routine testing indicating worse prognosis.[3] The addition of ventricular imaging to exercise testing alone increases sensitivity, specificity, and prognostic ability. Unfortunately, there are little data to support the idea that revascularizing asymptomatic patients on the basis of these studies actually improves prognosis.

Guidelines and appropriateness statements abound that touch on the issue of routine periodic stress testing after coronary revascularization. We have statements about PCI, CABG, stress testing, echocardiography, and nuclear