Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 63, No. 13, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.11.052

Yield of Downstream Tests After Exercise Treadmill Testing

A Prospective Cohort Study

Mitalee P. Christman,* Marcio Sommer Bittencourt, MD, MPH,† Edward Hulten, MD, MPH,† Ekta Saksena, BA,‡ Jon Hainer, BSc,† Hicham Skali, MD,† Raymond Y. Kwong, MD,§ Daniel E. Forman, MD,§ Sharmila Dorbala, MD,† Patrick T. O'Gara, MD,§ Marcelo F. Di Carli, MD,† Ron Blankstein, MD†

Boston, Massachusetts

Objectives The purpose of this study was to estimate the frequency and results of downstream testing after exercise treadmill tests (ETTs).

Background The utility of additional diagnostic testing after ETT is not well characterized.

Methods We followed consecutive individuals without known coronary artery disease referred for clinical ETT at a large medical center. We measured the frequency and results of downstream imaging tests and invasive angiography within 6 months of ETT and the combined endpoint of survival free from cardiovascular death, myocardial infarction, and coronary revascularization.

Results Among 3,656 consecutive subjects who were followed for a mean of 2.5 ± 1.1 years, 332 (9.0%) underwent noninvasive imaging and 84 (2.3%) were referred directly to invasive angiography after ETT. The combined endpoint occurred in 76 (2.2%) patients. The annual incidence of the combined endpoint after negative, inconclusive, and positive ETT was 0.2%, 1.3%, and 12.4%, respectively ($p < 0.001$). Rapid recovery of electrocardiography (ECG) changes during ETT was associated with negative downstream test results and excellent prognosis, whereas typical angina despite negative ECG was associated with positive downstream tests and adverse prognosis ($p < 0.001$). Younger age, female sex, higher metabolic equivalents of task achieved, and rapid recovery of ECG changes were predictors of negative downstream tests.

Conclusions Among patients referred for additional testing after ETT, the lowest yield was observed among individuals with rapid recovery of ECG changes or negative ETT, whereas the highest yield was observed among those with typical angina despite negative ECG or a positive ETT. These findings may be used to identify patients who are most and least likely to benefit from additional testing. (J Am Coll Cardiol 2014;63:1264–74) © 2014 by the American College of Cardiology Foundation

Coronary artery disease (CAD) remains the leading cause of death in men and women. Although advances in cardiovascular imaging have greatly improved our ability to diagnose and treat CAD, the rising costs of noninvasive testing have generated concern regarding its potential overuse (1).

The current American Heart Association and American College of Cardiology guidelines recommend exercise treadmill tests (ETTs) in the initial evaluation for ischemic heart disease in patients who are able to exercise and have a normal electrocardiogram (ECG) at baseline (2,3). In addition to testing for ischemic ECG changes, this test provides other data that have important prognostic implications, such as functional capacity, arrhythmias, and exercise-induced symptoms (4).

See page 1275

Thus, a common and economically-appealing strategy is to perform ETT as an initial test and then, among patients with positive or inconclusive results, to selectively use noninvasive imaging or invasive angiography to guide further care (5). Although recent studies assessed patterns of downstream

From the *Harvard Medical School, Boston, Massachusetts; †Department of Medicine (Cardiovascular Division) and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ‡Boston University, Boston, Massachusetts; and the §Department of Medicine (Cardiovascular Division), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. This study was supported in part by the National Heart, Lung, and Blood Institute of the National Institutes of Health, under award No. K23HL092299. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 4, 2013; revised manuscript received October 30, 2013, accepted November 12, 2013.

testing after percutaneous coronary intervention (PCI) (6,7) and use of invasive angiography after stress testing (8), to our knowledge, no data exist on the incidence and results of downstream noninvasive testing after ETT in patients without known CAD.

Therefore, the aim of our study was to identify the frequency and results of downstream testing after ETT and to identify predictors of patients who are most and least likely to benefit from additional testing.

Methods

Population. The study population consisted of all consecutive patients who underwent clinically-indicated ETT at Brigham and Women's Hospital between January 1, 2009, and December 31, 2010. We excluded patients with known CAD; prior coronary artery bypass grafting, PCI, or myocardial infarction (MI); and nonclinical indications for testing such as participation in a research protocol or post–heart transplant evaluation. The Partners Institutional Review Board approved this study.

Clinical information. Demographics, clinical history, medications, and indications for testing were collected prospectively through the use of a standardized patient interview. The electronic medical record, which includes all physicians' notes, was used to identify the presence or absence of the following risk factors: hypertension, diabetes, hyperlipidemia, and family history of CAD. We estimated pre-test probability of CAD by use of the Morise score (9).

Exercise treadmill testing. ETTs were performed with the use of a symptom-limiting Bruce protocol according to established guidelines (2) as part of routine clinical care. The target heart rate was determined as 85% of the maximum predicted heart rate (MPHR) (MPHR = 220 − age). All ST-segment measurements were performed 80 ms after the J point. The Duke Treadmill Score (DTS) was calculated for each patient who completed the Bruce protocol as: exercise time (min) − (5 × maximal ST-segment depression [mm]) − (4 × angina index [0, no angina; 1, angina; 2, angina as reason for stopping test]) (10).

We categorized each test result as positive, negative, or inconclusive through the use of conventional criteria (2). Positive tests were defined as upsloping ST-segment depressions ≥1.5 mm or downsloping or horizontal depressions ≥1.0 mm in at least 2 leads. Inconclusive tests were defined to include any result that may be interpreted as indeterminate and comprised the following categories: 1) negative ECG with reduced sensitivity as the result of submaximal exercise (<85% MPHR and rate-pressure product <25,000); 2) positive ECG with reduced specificity as the result of baseline ECG abnormalities; 3) positive ECG with reduced specificity as the result of rapid recovery of ECG changes, defined as changes that resolve within 60 s; 4) typical angina; 5) inappropriate dyspnea despite negative ECG findings, and 6) clinically significant rhythm disturbances (any sustained arrhythmia or >3 beats of ventricular tachycardia). Typical angina was defined as exertional chest discomfort that was substernal and was relieved with rest or nitroglycerin.

Downstream testing. For each patient, we identified the use of all noninvasive imaging and invasive angiography tests performed within 6 months after ETT through review of the electronic medical record. The decision to undergo further testing was at the discretion of the referring physician. We chose the 6-month cutoff to capture any downstream testing that was probably triggered by the ETT results.

Noninvasive imaging. We included all possible subsequent noninvasive imaging tests available at our institution: nuclear stress tests, stress echocardiograms, coronary computed tomography angiography (CCTA), and stress magnetic resonance imaging (MRI). All tests were performed and reported according to institutional protocols.

We categorized all nuclear stress tests (positron emission tomography and single-photon emission computed tomography [SPECT]) results as follows: negative (summed stress score ≤2); inconclusive (equivocal scan results or negative perfusion imaging with submaximal heart rate response [<85% of MPHR]); and positive for "abnormal" or "probably abnormal" results (11).

We categorized CCTA results as negative for reports of no plaque or stenosis ≤50% and positive for stenosis >70% (or >50% in the left main coronary). We defined as inconclusive for the evaluation of ischemia any studies that were uninterpretable or had moderate (51% to 70%) stenosis, given that such lesions may not be associated with ischemia and have uncertain hemodynamic significance (12).

We categorized cardiac MRI results as negative if no ischemia was detected, inconclusive if image quality precluded interpretation, and positive if ischemia was identified.

We categorized results of echocardiograms as positive, negative, or inconclusive on the basis of the presence or absence of stress-induced wall motion abnormalities. Tests were defined as inconclusive when reduced image quality limited the evaluation or if patients failed to achieve 85% of the MPHR.

Invasive coronary angiography. We defined obstructive CAD as a stenosis ≥50% in the left main coronary artery or ≥70% in any other coronary vessel (13).

Patient follow-up for nonfatal MI and revascularization. We reviewed all patient charts to identify incident nonfatal MI and coronary revascularization, which comprised all PCI and coronary artery bypass grafting procedures. MI was defined by means of universal criteria (14).

Abbreviations and Acronyms

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

DTS = Duke Treadmill Score

ECG = electrocardiogram

ETT = exercise treadmill test

METs = metabolic equivalents of task

MI = myocardial infarction

MPHR = maximum predicted heart rate

MRI = magnetic resonance imaging

PCI = percutaneous coronary intervention

SPECT = single-photon emission computed tomography

Patient follow-up for mortality and cause of death. We determined patients' vital status through the use of the Social Security Death Index and the cause of death through the use of chart review, autopsy findings, and hospice notes where available. If the chart lacked information to determine the cause of death, we used death certificates obtained from the Massachusetts Registry of Vital Records and Statistics. Two cardiologists blinded to ETT results adjudicated the cause of death for each patient. Deaths were considered to be of cardiovascular origin if the primary cause was acute MI, atherosclerotic coronary vascular disease, congestive heart failure, valvular heart disease, arrhythmic heart disease, stroke, or sudden and unknown (15). Major adverse cardiovascular events were the combined endpoint of cardiovascular death, nonfatal MI, and coronary revascularization.

Statistical analysis. Continuous variables are expressed as mean ± SD or median and interquartile range, as appropriate. Categorical variables are presented as frequencies. Differences between groups were tested with the use of chi-square or Fisher exact tests for discrete variables and 1-way analysis of variance for continuous variables.

We constructed Kaplan-Meier curves to illustrate survival free from cardiovascular events and tested for differences between subgroups with the use of the log-rank test. We built multivariable Cox proportional hazards models adjusted for age and sex. The assumption of non–proportional hazards was tested with the use of Schoenfeld residuals and resulted in nonsignificant findings in all analyses. We performed a sensitivity analysis that excluded all patients without complete follow-up for all cardiovascular events.

To identify individuals in whom further testing may not be necessary, we built multivariable logistic regression models identifying predictors of negative downstream testing and event-free survival. Our model was based on the assumption that changes in patient treatment occur on the basis of the identification of disease; therefore, patients with negative test results who had event-free survival did not benefit from testing. Our models used all of the clinical knowledge that physicians might have at hand when deciding whether or not to perform additional testing. Candidate predictor variables were selected among relevant clinical variables because such an approach with the use of external clinical judgment has been shown to be superior to a p value–driven method (16). Model variables included age, sex, risk factors, symptoms, metabolic equivalents of task (METs) achieved, and ETT results. The first model included age, sex, risk factors, and presenting symptoms. The second model added the ETT

Table 1 Baseline Characteristics Stratified by ETT Results

	All (n = 3,656)	Negative ETT (n = 2,478)	Inconclusive ETT (n = 1,043)	Positive ETT (n = 135)	p Value
Male	1,681 (46.0)	1,141 (46.0)	471 (45.2)	69 (51.1)	0.423
Age, yrs	53 ± 13	52 ± 13	57 ± 12	61 ± 11	<0.001
Hypertension	1,681 (46.0)	1,015 (41.0)	588 (56.4)	78 (57.8)	<0.001
Diabetes	470 (12.9)	287 (11.6)	162 (15.5)	21 (15.6)	0.004
Hyperlipidemia	1,537 (42.0)	975 (39.3)	494 (47.4)	68 (50.4)	<0.001
Current smoker	468 (12.8)	267 (10.8)	181 (17.4)	20 (14.8)	<0.001
Family history of CAD	1,633 (44.7)	1,096 (44.2)	470 (45.1)	67 (49.6)	0.449
BMI, kg/m^2	28 ± 6	28 ± 6	29 ± 7	28 ± 6	<0.001
Morise score	10.4 ± 4.5	9.8 ± 4.5	11.6 ± 4.3	12.6 ± 4.2	0.059
Morise pre-test probability of CAD	35%	32%	40%	46%	<0.001
Asymptomatic*	214 (5.9)	143 (6.0)	66 (6.0)	5 (4.0)	0.202
Nonanginal chest pain	1,676 (45.8)	1,207 (48.7)	418 (40.1)	51 (37.8)	<0.001
Atypical chest pain	297 (8.1)	200 (8.1)	80 (8.0)	17 (13.0)	<0.001
Typical chest pain	241 (6.6)	113 (5.0)	111 (11.0)	17 (13.0)	<0.001
Dyspnea only	345 (9.4)	206 (8.3)	126 (12.0)	13 (10.0)	<0.001
Arrhythmia or palpitations only	440 (12.0)	315 (12.7)	116 (11.1)	9 (7.0)	<0.001
Other or unknown symptoms	443 (12.1)	294 (11.9)	126 (12.0)	23 (17.0)	<0.001
Lipid-lowering therapy	1,045 (28.6)	627 (25.3)	366 (35.1)	52 (39.0)	<0.001
Aspirin	1,103 (30.2)	669 (27.0)	376 (36.0)	58 (43.0)	<0.001
Beta-blocker	746 (20.4)	300 (12.1)	405 (38.8)	41 (30.0)	<0.001
METs	11 ± 4	12 ± 4	9 ± 3	10 ± 3	<0.001
Duke Treadmill Score	9 ± 5	10 ± 4	6 ± 6	−0.33 ± 5	<0.001
No symptoms during test	2,420 (66.2)	1,831 (73.9)	524 (50.2)	65 (48.0)	<0.001
Typical angina during test	147 (4.0)	0	113 (11.0)	34 (25.0)	<0.001
Atypical angina during test	185 (5.0)	119 (5.0)	62 (6.0)	4 (3.0)	0.182
Dyspnea during test	459 (12.6)	193 (8.0)	238 (22.8)	28 (21.0)	<0.001
Other symptoms during test	445 (12.2)	335 (13.5)	106 (10.0)	4 (3.0)	<0.001

Values are n (%) or mean ± SD. *Asymptomatic individuals also included examinations performed for pre-operative evaluation, pre-transplant evaluation, and exercise prescription.

BMI = body mass index; CAD = coronary artery disease; ETT = exercise treadmill test; METs = metabolic equivalents of task.

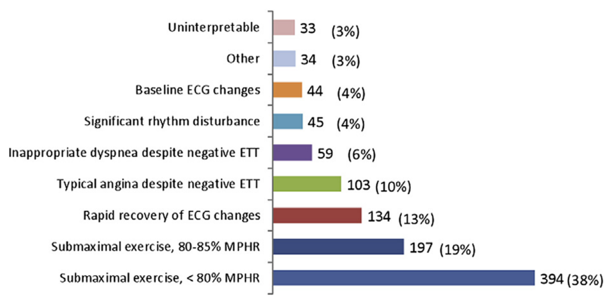

Figure 1 **Exercise Treadmill Test Results**

Frequency of inconclusive exercise treadmill test (ETT) results (N = 1,043).

results to the first model. All tests were 2-sided, and a value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed with the use of Stata version 12.0 (Statacorp, College Station, Texas).

Results

Study population. Among 4,262 consecutive patients referred for ETT, we excluded 509 patients with prior diagnoses of CAD, 9 patients age <18 years, and 88 patients with indications other than CAD evaluation. The final study population included 3,656 patients, and 3,270 (90%) of these patients had complete follow-up for all clinical events.

Compared with those with complete follow-up, patients with incomplete follow-up achieved higher METs, had a higher DTS, and were less likely to have typical angina symptoms ($p < 0.001$ for all comparisons). Patients with incomplete follow-up for downstream clinical events (who still had complete information on downstream testing) also had a lower rate of downstream testing (6.5% vs. 11.9%, $p = 0.001$). Additionally, 100% follow-up for all-cause mortality was available. When evaluating for differences between those with complete versus incomplete follow-up for cardiovascular outcomes, we found a similar annual incidence of all-cause mortality (0.53% vs. 0.49%; $p = 0.95$).

A sensitivity analysis excluding all patients with incomplete follow-up had similar results (Online Appendix 1A).

Baseline characteristics. The baseline characteristics of the patient population (age 54 ± 13 years; 46.0% men) stratified by ETT examination results are presented in Table 1. As expected, patients with positive and inconclusive ETT results were older and had a higher frequency of risk factors.

The ETTs were negative for ischemia in 2,478 (67.7%), inconclusive in 1,043 (28.5%), and positive for ischemia in 135 (3.7%) patients. The most common types of inconclusive results were submaximal exercise (56.7%), followed by rapid recovery of ECG changes (12.9%) and typical angina despite no ECG changes (9.9%) (Fig. 1). Among 318 patients with ST-segment depressions, 314 (98.7%) had horizontal or downsloping ST-segment depressions ≥1.0 mm, whereas 4 (1.3%) had upsloping ST-segment

Table 2 **Yield of Downstream Testing After ETT**

	All (n = 416 [11.4])	Negative ETT (n = 63 [3])	Inconclusive ETT (n = 260 [24.9])	Positive ETT (n = 94 [70])
Nuclear MPI	270 (64.9%)	40 (63%)	184 (71%)	47 (50%)
Normal	233 (86%)	37 (93%)	159 (86%)	37 (79%)
Inconclusive	11 (4%)	1 (3%)	9 (5%)	1 (2%)
Abnormal	26 (10%)	1 (3%)	16 (9%)	9 (19%)
Stress echocardiogram	39 (9%)	10 (16%)	25 (10%)	4 (4%)
Normal	32 (82%)	10 (100%)	18 (72%)	4 (100%)
Inconclusive*	6 (15%)	0	6 (24%)	0
Abnormal	1 (3%)	0	1 (4%)	0
Coronary CTA	17 (4%)	3 (5%)	12 (5%)	2 (2%)
No plaque or stenosis <50%	13 (76%)	2 (67%)	11 (92%)	0
Inconclusive				
Uninterpretable	1 (6%)	0	0	1 (50%)
Stenosis 50% to70%	1 (6%)	0	0	1 (50%)
Stenosis >70%	2 (12%)	1 (33%)	1 (8%)	0
Stress MRI (all negative)	6 (1%)	1 (2%)	5 (2%)	0
Invasive angiography	84 (20%)	9 (14%)	34 (13%)	41 (44%)
No obstructive CAD, no revascularization	43 (51%)	7 (78%)	19 (56%)	17 (41%)
Obstructive CAD, no revascularization	4 (5%)	0	3 (9%)	1 (2%)
PCI	24 (29%)	1 (11%)	12 (35%)	11 (28%)
CABG	13 (15%)	1 (11%)	0	12 (29%)

Values are n (%). *All inconclusive stress echocardiogram results were due to submaximal exercise.
CABG = coronary artery bypass grafting; CTA = computed tomography angiography; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

JACC Vol. 63, No. 13, 2014
April 8, 2014:1264–74

depressions ≥1.5 mm. For patients with rapid recovery of ECG changes, the median time to resolution of ST-segment changes was 32 s (interquartile range: 27 to 60 s).

Downstream testing. Further testing was undertaken in 416 (11.4%) subjects within 6 months of ETT: 332 (9.1%) underwent noninvasive imaging and 84 (2.3%) were referred directly to invasive angiography.

When evaluating the rate of all downstream testing by ETT results, 63 (3%) individuals with negative ETT results, 260 (24.9%) individuals with inconclusive ETT results, and 94 (70%) individuals with positive ETT results underwent further testing. Notably, the 260 patients with inconclusive ETT accounted for the highest proportion (62.4%) of downstream tests. Within this group, 81 (60%) of 134 patients with rapid recovery of ECG changes underwent downstream testing compared with 41 (40%) of 103 patients with typical angina despite negative ECG results.

Among patients referred for subsequent imaging, 270 (81.3%) underwent nuclear stress tests, 39 (12%) underwent stress echocardiograms, 17 (5%) underwent CCTA, and 6 (2%) underwent cardiac MRI. Because only 12 patients (0.3%) received more than 1 noninvasive imaging test within 6 months of ETT 6 nuclear stress tests followed by CCTA, 1 nuclear stress tests followed by MRI, 5 nuclear stress tests followed by stress echocardiology), only the first test after ETT was included in the present analysis. Overall, exercise stress testing was performed in 233 of 315 (73.9%) imaging stress tests. However, among those who did not achieve adequate heart rate response on the initial ETT, the majority (46 of 59, 78%) underwent pharmacological stress testing with SPECT or stress echocardiography. Among the 12 patients who were referred for exercise testing with SPECT after a submaximal ETT, 8 (67%) received regadenoson at peak stress to induce maximal hyperemia and improve the diagnostic accuracy of the examination (17).

The results of all downstream tests are summarized in Table 2. Among the 26 patients with positive nuclear tests, 1 patient had a fixed defect, whereas all others had ischemia.

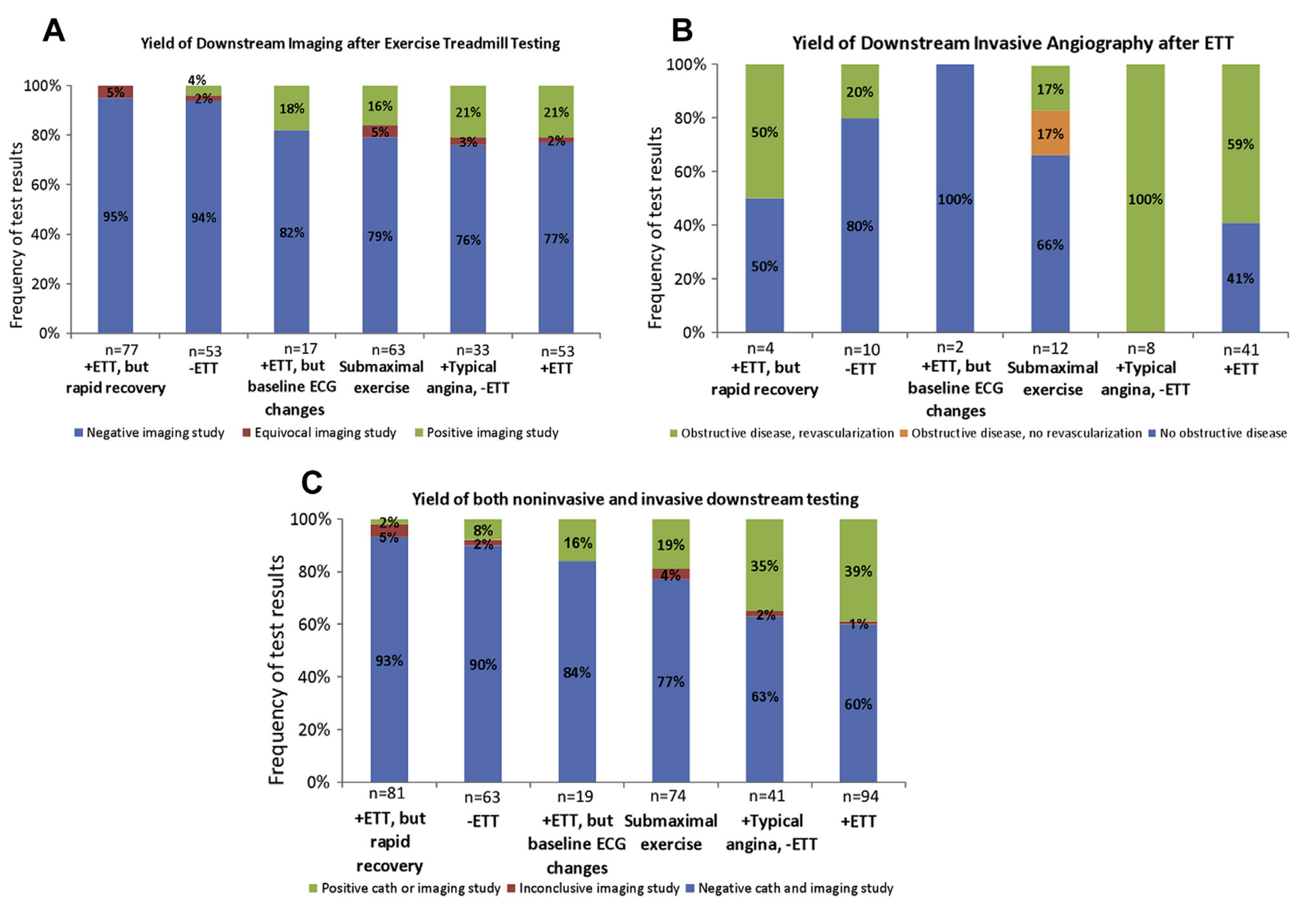

Figure 2 **Results of Downstream Testing**

Results of noninvasive imaging **(A)**, invasive angiography **(B)**, and all imaging **(C)** obtained within 6 months after ETT stratified by test results. The rate of positive results (yield) ranges from 0% to 21%, being lowest after rapid recovery of ECG changes and highest after typical angina despite negative ECG results or a positive ETT result. **(C)** Results from **A** and **B** are combined. Obstructive disease denotes stenosis ≥50% in the left main coronary or ≥70% in all other coronary vessels. Positive angiography results denote either obstructive disease or coronary revascularization within 6 months after the most recent test. Negative angiography denotes absence of obstructive disease. Abbreviations as in Figure 1.

Among the different indications, the yield of downstream noninvasive imaging tests varied from 0% to 21% (Fig. 2A). The lowest yield was observed among tests that demonstrated rapid recovery of ECG changes: none of the 77 imaging tests were positive. Notably, this was similar to the yield observed after negative ETT (2 of 53, 4%). On the other hand, the highest yield (21%) was observed among tests that demonstrated typical angina despite no ECG changes: 7 of 33 were positive. This was similar to the positive imaging rate after positive ETT (11 of 53, 21%). Similar results were obtained when the analysis of yield of downstream testing was restricted to patients undergoing nuclear stress testing (Online Appendix 1B).

Among patients with typical angina but no ECG changes who were referred directly to invasive angiography after ETT, all 8 (100%) underwent coronary revascularization. Among those referred with rapid recovery of ECG changes, 2 of 4 (50%) patients underwent coronary revascularization (Fig. 2B).

A yield similar to that of noninvasive imaging was observed when the results of both noninvasive and invasive imaging were combined (Fig. 2C). The rates of positive downstream testing after negative, inconclusive, and positive ETT were 8%, 14%, and 39%, respectively. Whereas the overall number of patients with high-risk DTS ($\leq$−11) was low, when we examined the yield of downstream testing in those with a low-risk ($\geq$5) versus intermediate-risk DTS (between −10 and 4), there was no significant difference ($p = 0.268$). In a comparison of patients with positive versus negative downstream tests, a higher proportion of patients with positive downstream tests were male, older, and had a lower DTS and typical angina during ETT (Online Appendix 1C).

Among patients with typical angina and no ECG changes, those with positive downstream tests were more likely to be male (79% vs. 37%; $p = 0.012$) and older (62 years vs. 53 years; $p = 0.049$) than those with negative or equivocal downstream tests; however, METs achieved and DTS were not significantly different between these groups. Among the 7 patients who had positive imaging tests after ETTs with typical angina but no ST depressions, 1 had severe stenosis (>70%) on CCTA. Among the 6 patients who had positive nuclear imaging, 3 patients had mild ischemia (summed difference score <4), 1 patient had moderate ischemia (summed difference score 4 to 7), and 2 patients had severe ischemia (summed difference scores $\geq$8). One patient who had severe ischemia also had transient ischemic dilation of the left ventricle as well as a decrease in ejection fraction from rest to stress on positron emission tomography imaging. Among patients with negative downstream testing in this group ($n = 25$), there were no high-risk features such as transient ischemic dilation of the left ventricle or a decrease in ejection fraction from rest to peak stress.

Figure 3 depicts the yield of invasive angiography after imaging tests that followed ETT. Subsequent revascularization was performed in 10 of 17 (59%) of patients with positive imaging and 2 of 8 (25%) patients with negative imaging.

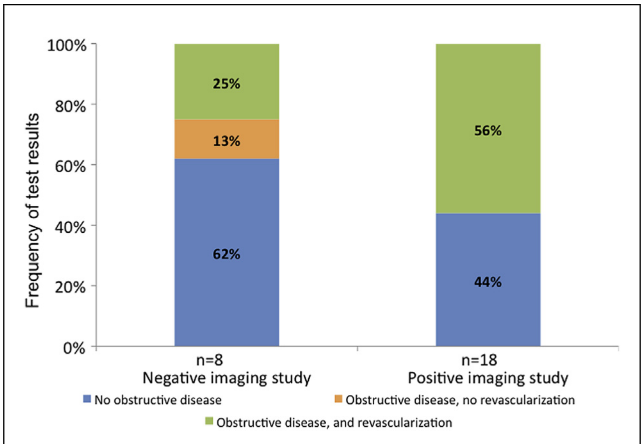

Figure 3 **Results of Invasive Angiography in Patients Who Underwent Imaging After Exercise Treadmill Testing**

All invasive angiography studies that occurred within 6 months after imaging are shown. The yield of invasive angiography was higher after positive imaging (56%) than after negative imaging (25%). Obstructive disease denotes stenosis $\geq$50% in the left main coronary or $\geq$70% in all other coronary vessels.

Outcomes. During the 8,282 person-years of follow-up (median 2.7 years; interquartile range: 2.1 to 3.3 years), 47 (1.3%) patients died: 9 (0.25%) as the result of cardiovascular causes, 11 (0.3%) patients had MI, and 69 (2%) patients required coronary revascularization. Overall, 76 (2.2%) patients had the combined endpoint of major adverse cardiovascular events. The annual incidence of the combined endpoint after negative, inconclusive, and positive ETT was 0.2%, 1.3%, and 12.4%, respectively ($p < 0.001$). Among patients with rapid recovery of ECG changes, the annual incidence was 0.7%, whereas among those with typical angina but negative ECG the incidence was 7.4%.

Figure 4 shows unadjusted Kaplan-Meier cumulative event curves for nonfatal MI or cardiovascular death (Fig. 4A) and nonfatal MI, revascularization, or cardiovascular death (Figs. 4B and 4C) according to ETT results. Patients with inconclusive ETTs had a lower rate of survival free from cardiovascular death or MI than those with a negative ETT ($p < 0.001$) (Fig. 4A). When specifically examining patients with inconclusive ETTs, rapid recovery of ECG changes was associated with favorable prognosis, whereas typical angina despite negative ECG findings was associated with adverse prognosis (Fig. 4C). When further stratifying the most common inconclusive groups by functional capacity, a higher exercise capacity was associated with a better prognosis only for the group with submaximal exercise ($p = 0.013$) (Fig. 5).

Individuals less likely to benefit from additional testing. Table 3 shows the results of multivariable models predicting negative downstream tests and no downstream events after

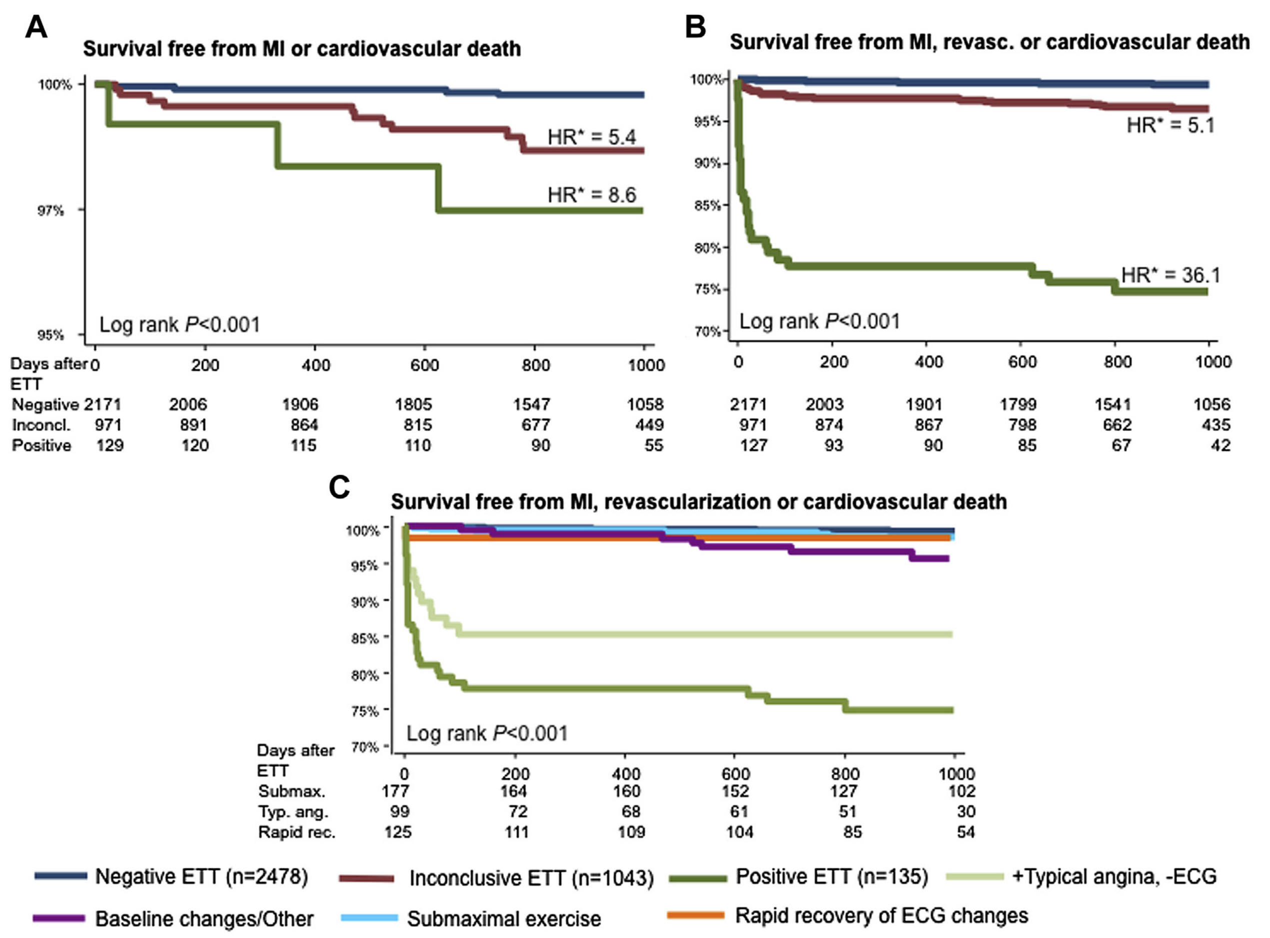

Figure 4 **Kaplan-Meier Curves Examining Outcomes According to Exercise Treadmill Testing Results**

(A) Survival free from myocardial infarction (MI) or cardiovascular death (CVD). Rates of MI or CVD were higher among patients with inconclusive exercise treadmill test (ETT) (hazard ratio [HR]: 5.4; $p = 0.004$) and positive ETT (HR: 8.6; $p = 0.006$) than among those with negative ETT results. **(B and C)** Survival free from the combined endpoint of MI, CVD, or coronary revascularization. Rates of the combined endpoint were higher among patients with inconclusive ETT results (HR: 5.1; $p < 0.001$) and positive ETT results (HR: 36.1; $p < 0.001$). Patients with typical angina despite negative ECG had a higher incidence of the combined endpoint than other types of inconclusive ETT. *HRs were derived from Cox proportional hazards models adjusted for age and sex.

ETT. Younger age ($p < 0.001$), female sex ($p < 0.001$), higher METs ($p = 0.037$), and rapid recovery of ECG changes ($p = 0.013$) were independent predictors of negative downstream tests and event-free survival.

Discussion

In the present study, we examined patterns of downstream testing and outcomes in a cohort of 3,656 patients without prior CAD referred for ETT. Although we found an overall low rate of referral for downstream testing (11%)—consistent with the high prevalence of negative ETT results—there was a substantially higher rate of referral for additional testing among patients with positive (70%) or inconclusive (25%) test results. Moreover, we found that 28% of the patients in our study had inconclusive ETT results; despite a favorable prognosis, this group accounted for 63% of all the downstream tests. In our analysis of inconclusive results, we identified that patients who had rapid recovery of ECG changes had an excellent prognosis and a low yield of additional testing, whereas patients who had typical angina despite negative ECG results had a worse prognosis and higher yield of downstream testing.

An important finding of our study is that patients with typical angina but negative ETT represent a relatively higher-risk cohort in which the yield of additional testing is relatively higher and comparable to the yield after positive ETT. These results are particularly important in light of a recent study by Cheng et al. (18), which suggested that the prevalence of obstructive CAD by CCTA is vastly overestimated in patients with typical angina. However, the study by Cheng et al. (18) used patient-reported symptoms, whereas, in our study, physicians and exercise physiologists identified symptoms at the time of testing. Our results

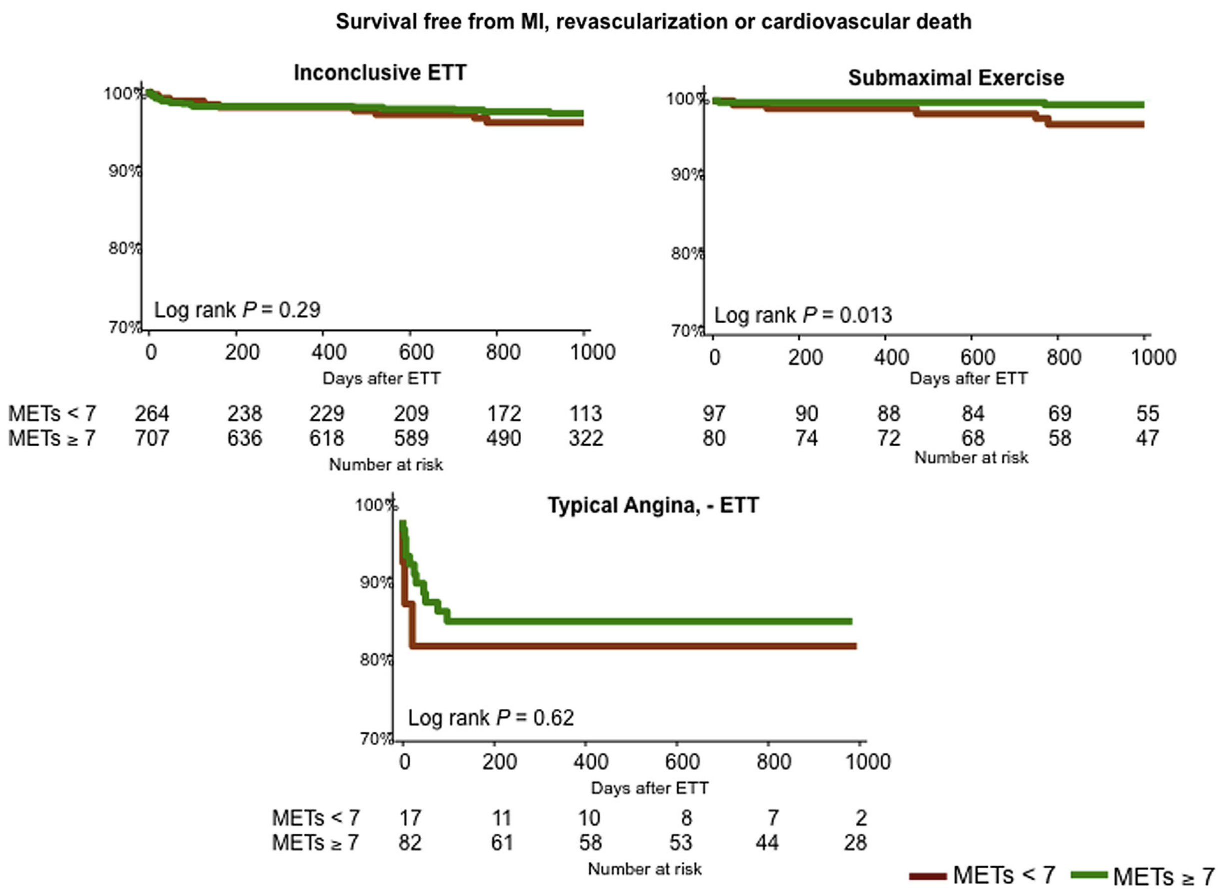

Figure 5 **Kaplan-Meier Curves**

Kaplan-Meier curves describe survival free from the combined endpoint of MI, revascularization, or CVD for inconclusive ETTs stratified by functional capacity as measured by metabolic equivalents of task (METs) achieved during ETT (4). Whereas there are no differences in event-free survival by functional capacity in the inconclusive ETT and typical angina groups, among patients with submaximal exercise, patients who achieved ≥7 METs had a lower event rate ($p = 0.013$, log-rank test). Abbreviations as in Figure 4.

suggest that patients who have development of typical angina during ETT, even in the presence of a good exercise capacity, warrant further evaluation. Bairey et al. (19) showed that among 190 patients with typical angina but negative ETT, an abnormal thallium myocardial perfusion study was found in 24% (similar to our findings) and that such testing provided significant prognostic value.

Another noteworthy finding from our study is that patients with rapid recovery of ECG changes had a low yield on subsequent imaging and few adverse outcomes. Although it is recognized that ST-segment depressions that resolve rapidly have a lower specificity for detecting obstructive CAD (20), to our knowledge, no prior studies have investigated the yield of imaging and prognosis of such patients. In our study, 81 (60%) of the 134 patients who had positive ECG changes with rapid recovery underwent downstream testing. Among the 77 patients referred for noninvasive imaging, there were no positive results and no subsequent deaths or MIs. Two of 4 patients, who, per treating physician discretion, were referred directly to coronary angiography underwent coronary revascularization procedures. One of these patients achieved 10.1 METs and had typical angina with 2.0-mm horizontal ST-segment depressions in leads V_3 to V_6 that resolved within 1 min into recovery, whereas the second patient achieved 7.8 METs and had dyspnea on exertion with 1.0-mm horizontal ST-segment depressions in leads V_5 to V_6, which resolved 30 s into recovery.

Given the concerns regarding overuse of imaging tests, a key objective of our study was to identify individuals who can safely avoid further testing after ETT. As is consistent with established risk factors for obstructive CAD, a younger age, female sex, and higher exercise capacity during ETT were all independently associated with negative downstream testing and event-free survival. In addition, rapid recovery of ECG changes was independently associated with negative downstream testing and event-free survival.

Patel et al. (21) have demonstrated a low yield of identification of obstructive CAD in noninvasive testing compared with invasive angiography; however, their study

Table 3 Predictors of Negative Downstream Tests and No Events

	Univariate Predictors	p Value	Multivariable Model 1	p Value	Multivariable Model 2	p Value
Likelihood ratio chi-square	—		61.49	<0.001	80.67	0.002*
ROC	—		0.7149	—	0.7451	0.018*
AIC	—		560.26	—	551.07	—
Age (per 10 yrs)	0.67 (0.56–0.78)	<0.001	0.65 (0.54–0.78)	<0.001	0.72 (0.60–0.88)	0.001
Female	2.69 (1.81–4.01)	<0.001	2.89 (1.89–4.44)	<0.001	3.17 (2.00–5.01)	<0.001
≤1 risk factor†	1.00	Reference	1.00	Reference	1.00	Reference
≥2 risk factors†	0.66 (0.42–1.01)	0.0564	0.59 (0.37–0.95)	0.030	0.65 (0.40–1.06)	0.087
Presenting symptoms						
None	1.00	Reference	1.00	Reference	1.00	Reference
Non anginal chest pain	1.16 (0.74–1.81)	0.527	0.83 (0.51–1.35)	0.442	0.89 (0.54–1.48)	0.656
Atypical angina	0.65 (0.33–1.28)	0.216	0.52 (0.25–1.07)	0.079	0.62 (0.29–1.31)	0.209
Typical angina	0.53 (0.29–0.94)	0.029	0.40 (0.21–0.76)	0.005	0.50 (0.25–1.01)	0.052
ETT results						
METs achieved (per MET)	1.08 (1.03–1.15)	0.005	—	—	1.09 (1.01–1.17)	0.037
Negative ETT	1.00	Reference	—	—	1.00	Reference
Typical angina, negative ECG	0.73 (0.35–1.52)	0.401	—	—	0.95 (0.40–2.26)	0.911
Rapid recovery of ECG changes	3.64 (1.62–8.19)	0.002	—	—	2.67 (1.15–6.22)	0.013
Inconclusive for other reasons	1.06 (0.62–1.81)	0.832	—	—	1.32 (0.71–2.45)	0.380
Positive ETT	0.59 (0.33–1.06)	0.076	—	—	0.64 (0.34–1.21)	0.173

Values are fit statistic or odds ratio (95% confidence interval). *Comparing models 1 and 2. †Risk factors included hypertension, diabetes, dyslipidemia, current smoking, and family history of premature coronary artery disease.

AIC = Akaike Information Criterion; ROC = receiver-operating characteristic curve; other abbreviations as in Table 1.

included several types of tests (including rest-only echocardiogram and ECG). In our study, among patients referred for invasive angiography after a positive imaging study, the yield was 59% (Fig. 3), higher than the 41% observed by Patel et al. (21). However, it should be recognized that discordant findings are not unexpected when tests that evaluate ischemia are compared with an anatomical reference standard (12).

Our findings are similar to those of Mudrick et al. (8), who followed 80,676 patients who underwent stress testing (54% nuclear; 25% ETT; 21% stress echocardiography): within 60 days after testing, the incidence of invasive angiography among ETT patients was 6.9%, whereas the incidence of coronary revascularization was 2.3%. Interestingly, these rates were higher than those observed in our study. This could be explained by increased use of noninvasive imaging in our population, although Mudrick et al. (8), who used an administrative database, did not report data on the use of noninvasive testing.

Consistent with prior studies (8), the rates of positive ETT results and adverse events observed in our study were low, in keeping with the fact that patients referred for ETT alone are generally at lower risk that those who are referred for noninvasive imaging. Furthermore, we excluded patients with CAD. These results highlight the challenges of the use of diagnostic testing to mitigate the risk of events in an already low-risk population. For instance, approximately 40% of patients with a positive ETT result had a positive downstream test, reflecting the low specificity of ECG changes for predicting abnormal imaging or angiography. Nevertheless, despite the overall low event rate of our cohort, we were able to identify subgroups of patients (e.g., typical angina) in which additional testing provided clinically important data as well as subgroups (e.g., rapid recovery of ECG changes) in which excessive testing was performed despite an event rate that was lower than that observed among individuals who had negative ETT testing.

When selecting an imaging test after equivocal ETT results, the reason for the inconclusive ETT results should be considered. For instance, among patients who are unable to achieve their target heart rate with exercise, future testing should use pharmacological stress testing with either vasodilators or dobutamine (22). In our study, some patients were referred for exercise SPECT despite a suboptimal heart rate response on ETT and were administered regadenoson at peak exercise to induce maximal hyperemic response and thus improve the diagnostic accuracy while reducing the likelihood of inconclusive results (18).

Study limitations. Given the observational single-center design of our study, our results may be less applicable to other institutions. For instance, centers probably vary by how they interpret and report ETT findings as well as which testing options are available or used when further testing is obtained. However, our primary aim was to identify the frequency of downstream testing after ETT and to identify predictors of patients who are most and least likely to benefit from additional testing. Although the pattern of downstream use of imaging modalities differs across centers, we would not expect our findings to change even if different modalities of downstream testing were obtained. Nevertheless, our center is well-suited for this study, given that: 1) ETT is commonly used as the first test to evaluate patients with no CAD; and 2) we have an integrated multi modality noninvasive lab oratory with a detailed database that includes all patient characteristics as well as all noninvasive and invasive testing performed. Although we assumed that any testing within 6 months of the ETT examination was attributable to the test results, it is possible that some downstream testing occurred because of changes in clinical status.

Certain assumptions are implied by our analysis. We defined a "benefit" (e.g., yield) of a downstream test as a positive result because we assumed that positive test results are more likely to affect patient treatment. However, our definition of yield might discount the value of reassurance provided by negative test results. Moreover, because not all patients in our cohort underwent secondary testing, referral bias may influence the frequency of positive downstream test results across some of the subgroups of patients referred for invasive angiography or noninvasive testing. However, our aim was to observe the yield in actual clinical practice because such results may be more applicable to patients in whom physicians are contemplating performing additional testing.

We defined inconclusive ETT results broadly to compare different subgroups. As a result, the rate of inconclusive studies may be higher than would be expected if a more conservative definition were used. However, our rate of inconclusive studies (28%) was similar to that reported by others (3,23). Moreover, our findings regarding the yield and prognosis associated with various ETT findings would not be expected to change even if some of the inconclusive subgroups listed in Figure 1 were reclassified as positive or negative. Nevertheless, several of the subgroups of patients with inconclusive ETT results were small, thus limiting our power to detect differences in outcomes. Finally, our findings at this time represent only medium-term follow-up, and it is possible that longer-term follow-up would identify more events.

Conclusions

To our knowledge, this is the first study to assess downstream noninvasive testing after ETT among patients without CAD. In recognition of the increased concerns regarding overuse of cardiovascular imaging, it is essential to develop effective patient-centered algorithms to identify the best initial testing option for a given patient. Given the overall good prognosis as well as low need for downstream testing, our results suggest that ETT represents a reasonable initial testing option for many patients without prior CAD who are able to exercise and have a normal baseline ECG. Furthermore, we identify that in the absence of any high-risk features, patients with rapid recovery of ECG changes do not benefit from additional diagnostic testing. On the other hand, we found that patients with typical angina have an absolutely low but relatively higher yield of downstream testing, which suggests that some of these patients might warrant further evaluation and/or treatment. Our findings could be used to reduce the number of inconclusive results and downstream testing by more definitely reclassifying ETT results as positive or negative. In establishing the optimal threshold for any diagnostic test, there is a trade-off between sensitivity and specificity. Our findings imply that the potential gain in sensitivity is extremely small and is probably unjustified for patients with rapid recovery of ECG changes.

Acknowledgments
The authors are grateful for the outstanding dedication of the exercise physiologists and imaging technologists at Brigham and Women's Hospital.

Reprint requests and correspondence: Dr. Ron Blankstein, Cardiovascular Division and Department of Radiology, Brigham and Women's Hospital, 75 Francis Street, Room Shapiro 5096, Boston, Massachusetts 02115. E-mail: rblankstein@partners.org.

REFERENCES

1. Iglehart JK. The new era of medical imaging–progress and pitfalls. N Engl J Med 2006;354:2822–8.
2. Gibbons RJ, Balady GJ, Bricker JT, et al. 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). J Am Coll Cardiol 2002;40:1531–40.
3. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation 2010;122:1756–76.
4. Bourque JM, Holland BH, Watson DD, Beller GA. Achieving an exercise workload of > or = 10 metabolic equivalents predicts a very low risk of inducible ischemia: does myocardial perfusion imaging have a role? J Am Coll Cardiol 2009;54:538–45.
5. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 2009;53:2201–29.
6. Mudrick DW, Shah BR, McCoy LA, et al. Patterns of stress testing and diagnostic catheterization after coronary stenting in 250 350 Medicare beneficiaries. Circulation Cardiovasc Imaging 2013;6:11–9.
7. Shah BR, Cowper PA, O'Brien SM, et al. Patterns of cardiac stress testing after revascularization in community practice. J Am Coll Cardiol 2010;56:1328–34.
8. Mudrick DW, Cowper PA, Shah BR, et al. Downstream procedures and outcomes after stress testing for chest pain without known coronary artery disease in the United States. Am Heart J 2012;163:454–61.
9. Morise A, Evans M, Jalisi F, et al. A pretest prognostic score to assess patients undergoing exercise or pharmacological stress testing. Heart 2007;93:200–4.
10. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. Circulation 1998;98:1622–30.
11. Abidov A, Hachamovitch R, Hayes SW, et al. Are shades of gray prognostically useful in reporting myocardial perfusion single-photon emission computed tomography? Circulation Cardiovasc Imaging 2009;2:290–8.

12. Blankstein R, Di Carli MF. Integration of coronary anatomy and myocardial perfusion imaging. Nature Rev Cardiol 2010;7:226–36.
13. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;58:e44–122.
14. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.
15. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
16. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–37.
17. Partington SL, Lanka V, Hainer J, et al. Safety and feasibility of regadenoson use for suboptimal heart rate response during symptom-limited standard Bruce exercise stress test. J Nucl Cardiol 2012;19:970–8.
18. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation 2011;124:2423–32.
19. Bairey CN, Rozanski A, Maddahi J, et al. Exercise TL-201 scintigraphy and prognosis in typical angina-pectoris and negative exercise electrocardiographY. Am J Cardiol 1989;64:282–7.
20. Sakuragi S, Takaki H, Taguchi A, et al. Diagnostic value of the recovery time-course of ST slope on exercise ECG in discriminating false-from true-positive ST-segment depressions. Circ J 2004;68:915–22.
21. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.
22. Blankstein R, Devore AD. Selecting a noninvasive imaging study after an inconclusive exercise test. Circulation 2010;122:1514–8.
23. Diercks DB, Gibler WB, Liu T, et al. Identification of patients at risk by graded exercise testing in an emergency department chest pain center. Am J Cardiol 2000;86:289–92.

Key Words: downstream testing ▪ exercise testing ▪ imaging.

APPENDIX

For supplemental figures and a table, please see the online version of this article.