ORIGINAL ARTICLE

Routine Functional Testing or Standard Care in High-Risk Patients after PCI

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ABSTRACT

BACKGROUND

There are limited data from randomized trials to guide a specific follow-up surveillance approach after myocardial revascularization. Whether a follow-up strategy that includes routine functional testing improves clinical outcomes among high-risk patients who have undergone percutaneous coronary intervention (PCI) is uncertain.

METHODS

We randomly assigned 1706 patients with high-risk anatomical or clinical characteristics who had undergone PCI to a follow-up strategy of routine functional testing (nuclear stress testing, exercise electrocardiography, or stress echocardiography) at 1 year after PCI or to standard care alone. The primary outcome was a composite of death from any cause, myocardial infarction, or hospitalization for unstable angina at 2 years. Key secondary outcomes included invasive coronary angiography and repeat revascularization.

RESULTS

The mean age of the patients was 64.7 years, 21.0% had left main disease, 43.5% had bifurcation disease, 69.8% had multivessel disease, 70.1% had diffuse long lesions, 38.7% had diabetes, and 96.4% had been treated with drug-eluting stents. At 2 years, a primary-outcome event had occurred in 46 of 849 patients (Kaplan–Meier estimate, 5.5%) in the functional-testing group and in 51 of 857 (Kaplan–Meier estimate, 6.0%) in the standard-care group (hazard ratio, 0.90; 95% confidence interval [CI], 0.61 to 1.35; P=0.62). There were no between-group differences with respect to the components of the primary outcome. At 2 years, 12.3% of the patients in the functional-testing group and 9.3% in the standard-care group had undergone invasive coronary angiography (difference, 2.99 percentage points; 95% CI, −0.01 to 5.99), and 8.1% and 5.8% of patients, respectively, had undergone repeat revascularization (difference, 2.23 percentage points; 95% CI, −0.22 to 4.68).

CONCLUSIONS

Among high-risk patients who had undergone PCI, a follow-up strategy of routine functional testing, as compared with standard care alone, did not improve clinical outcomes at 2 years. (Funded by the CardioVascular Research Foundation and Daewoong Pharmaceutical; POST-PCI ClinicalTrials.gov number, NCT03217877.)

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*A list of the investigators in the POST-PCI trial is provided in the Supplementary Appendix, available at NEJM.org.

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Patients who undergo myocardial revascularization for obstructive coronary artery disease should receive guideline-directed medical therapy and treatment according to other secondary prevention strategies after the revascularization procedure.[1-3] Although the clinical need for invasive coronary angiography and repeat revascularization after percutaneous coronary intervention (PCI) has declined markedly with use of drug-eluting stents and with improved medical care, patients — especially those with high-risk anatomical or clinical characteristics — still have recurrences of ischemia or ischemic cardiovascular events.

Despite the routine use of cardiac stress testing as an initial diagnostic tool for the detection of severe coronary disease,[4] previous studies have shown that functional testing is widely used in clinical practice after coronary revascularization[5-8]: more than half of all patients who had undergone PCI or coronary-artery bypass graft (CABG) surgery had functional testing within 2 years after revascularization. Current guidelines do not advocate the use of routine stress testing after coronary revascularization.[1,3,9] However, surveillance with the use of imaging-based stress testing may be considered in high-risk patients at 6 months after a revascularization procedure (class IIb recommendation), and routine imaging-based stress testing may be considered at 1 year after PCI and more than 5 years after CABG (class IIb recommendation).[1] There are limited data from randomized trials to support these recommendations.[10,11]

It remains undetermined whether routine stress testing in high-risk patients who have undergone PCI results in changes in subsequent management and preventive strategies (e.g., preemptive coronary revascularization or more aggressive medical therapies) leading to a reduction in ischemic cardiovascular events or death. Therefore, we designed the Pragmatic Trial Comparing Symptom-Oriented versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention (POST-PCI) to determine the effect on clinical outcomes of a follow-up strategy that includes routine functional testing in high-risk patients who had undergone PCI.[12]

Methods

Trial Design and Oversight

We conducted this multicenter, pragmatic, randomized superiority trial to compare an active follow-up strategy of routine functional testing with a standard-care strategy in high-risk patients who had undergone PCI and had complex anatomical or clinical characteristics. The trial design and methods have been published previously.[12] Details regarding the participating investigators and the organization of the trial are provided in Section A and Section B in the Supplementary Appendix (available with the full text of this article at NEJM.org). In brief, the POST-PCI trial was designed as a pragmatic comparative-effectiveness trial and was undertaken in real-world settings with usual care. To facilitate patient enrollment and data collection, the trial used the infrastructure of existing, nationwide observational PCI registries in South Korea.[13-15] The pragmatic features of the trial are described in Section C in the Supplementary Appendix.

This investigator-initiated trial was funded by the CardioVascular Research Foundation and Daewoong Pharmaceutical. The funders had no role in the design or conduct of the trial, the analysis of the data, or the preparation of the manuscript. An independent data and safety monitoring board approved the trial protocol and monitored patient safety. The protocol (available at NEJM.org) was approved by the institutional review board and ethics committee at each participating site. All the patients provided written informed consent. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first four authors and the last author had unrestricted access to the data, were involved in the analysis and interpretation of the data, wrote the first and subsequent drafts of the manuscript, and made the decision to submit the manuscript for publication.

Trial Population and Randomization

Patients older than 19 years of age who had undergone successful PCI with contemporary drug-eluting stents, bioresorbable scaffolds, or drug-coated balloons (only for in-stent restenosis) were eligible to participate. Eligible patients had to have at least one high-risk coronary-artery anatomical feature or clinical characteristic associated with an increased risk of ischemic or thrombotic events during follow-up.[12,16-18] Anatomical criteria for high risk included left main disease, bifurcation disease, an ostial lesion, a chronic total occlusion, multivessel coronary artery disease warranting stents for at least two vessels, a restenotic lesion, a long diffuse lesion (i.e., a lesion length

of >30 mm or a lesion warranting a stent length of >32 mm), and bypass graft disease. The clinical criteria for high-risk status were medically treated diabetes mellitus, chronic renal failure (serum creatinine level of ≥2.0 mg per deciliter [≥177 μmol per liter] or long-term hemodialysis), and enzyme-positive acute coronary syndrome. Details regarding inclusion and exclusion criteria are provided in Section D in the Supplementary Appendix.

After providing written informed consent, participants were randomly assigned, in a 1:1 ratio, to an active follow-up strategy of routine functional testing or to a conservative follow-up strategy of standard care alone, with stress testing performed when clinically indicated. Randomization was performed after the index PCI procedure and before discharge from the index hospitalization and was conducted with an interactive Web-based response system with the use of randomly permuted blocks of varying sizes, with stratification according to enrollment site and the presence or absence of diabetes.

TRIAL PROCEDURES AND FOLLOW-UP

In the functional-testing group, cardiac stress testing (exercise electrocardiography [ECG], nuclear stress testing, or stress echocardiography) was performed at 12 months (±2 months) after randomization. Given the high rate of false positive exercise ECG tests indicating ischemia, simple exercise ECG testing was discouraged; therefore, a combined noninvasive imaging approach was recommended.[12] The participating centers used standard equipment for functional testing in compliance with professional society guidelines. The results of all stress testing were interpreted in real time by qualified physicians at each participating site to ensure timely availability of results for patient treatment (Section E in the Supplementary Appendix). All clinical decisions regarding subsequent diagnostic or therapeutic procedures were at the discretion of the treating physician at each participating center; trial physicians and staff were not involved in decision making for subsequent management.

Patients underwent routine follow-up at 6, 12, 18, and 24 months after randomization. During follow-up, guideline-directed medical therapy and management of risk factors for intensive secondary prevention according to contemporary clinical guidelines were highly recommended. At each visit, all information regarding any clinical events and cardiovascular medications was systematically collected. Vital status was reconfirmed with the use of the national death registry of the Korean National Health Insurance Service database.[19]

OUTCOMES

The primary outcome was a composite of major cardiovascular events (death from any cause, myocardial infarction, or hospitalization for unstable angina) at 2 years after randomization. Secondary outcomes included the following: individual components of the primary composite outcome; a composite of death or myocardial infarction; hospitalization for any reason (for either cardiac causes or noncardiac causes); invasive coronary angiography; and repeat revascularization procedures (target-lesion or nontarget-lesion revascularization). All components of the primary and secondary outcomes were adjudicated by a clinical-events committee whose members were unaware of the trial-group assignments.

Standard definitions were used for the assessment of clinical outcomes.[20] Myocardial infarction was defined as spontaneous or procedural. Procedural infarction related to repeat revascularization procedures required an elevation in the cardiac troponin level (of >5 times after PCI or >10 times the 99th percentile of the upper reference limit after CABG) within 48 hours after the procedure among patients with normal baseline values or an increase in the cardiac troponin level of more than 20% if the baseline values were elevated. In addition, at least one of the following criteria was required: new pathologic Q waves or new left bundle-branch block; angiographically documented graft or native coronary artery occlusion, or new severe stenosis with thrombosis or diminished epicardial coronary blood flow; or evidence on imaging of new loss of viable myocardium or new regional wall-motion abnormality. Definitions of all trial outcomes are provided in Section F in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that enrollment of 1700 patients would provide the trial with 90% power to detect a 30% lower incidence of the primary outcome, with a hazard ratio of 0.68, at 2 years in the functional-testing group than in the standard-care group (assuming a 2-year incidence of 15% in the standard-care group) at a significance level of 0.05 on the basis of a two-sided log-rank test

of survival. The 2-year incidence of the primary outcome in the standard-care group was estimated on the basis of 2-year results from the RESOLUTE All Comers trial.[21] This final sample-size calculation assumed a 3% loss to follow-up and 4 years of total trial time, including the 2-year recruitment period. Additional details regarding the sample-size estimation are provided in Section G in the Supplementary Appendix.

Details regarding the statistical methods are provided in Section H in the Supplementary Appendix. Statistical comparisons of the two randomized groups were performed according to the intention-to-treat principle on the basis of time-to-first-event analyses. Cumulative-event probabilities were estimated with the use of the Kaplan–Meier method for outcomes. Hazard ratios and 95% confidence intervals were generated with the use of Cox proportional-hazards models. Although the proportional-hazards assumption was met for most of the primary and key secondary outcomes, this assumption was not met for the secondary outcomes of invasive coronary angiography and repeat revascularization ($P<0.001$ for time-by-treatment interaction). Therefore, prespecified landmark analyses were performed with the use of a 1-year cutoff, which corresponded to the planned period of routine functional testing — intervals during which proportional hazards were preserved. Absolute differences and 95% confidence intervals for the primary and secondary outcomes at 2 years were also calculated with the use of Kaplan–Meier estimates and Greenwood standard errors.[22] The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible and should not be used to infer definitive treatment effects. For prespecified subgroup analyses, the interaction term between randomized groups and key subgroups was evaluated for the primary outcome.

No interim analyses of the primary and secondary outcomes were performed; therefore, the alpha significance level in the final primary analysis was 0.05. All comparisons were performed with the use of two-sided significance tests. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 3.6 (R Foundation for Statistical Computing).

RESULTS

TRIAL POPULATION AND BASELINE CHARACTERISTICS

From November 15, 2017, through September 11, 2019, a total of 2153 patients were assessed for eligibility and 1706 underwent randomization at 11 sites in South Korea (Fig. 1). The baseline characteristics of the patients were well balanced between the two groups (Table 1, and Table S1 in the Supplementary Appendix). The mean (±SD) age was 64.7±10.3 years, and 79.5% of the patients were men. The percentages of patients with high-risk coronary-artery anatomical features and clinical characteristics that were criteria for trial inclusion were similar in the two groups; 21.0% of the patients had left main disease, 43.5% had bifurcation disease, 69.8% had multivessel disease, 70.1% had a diffuse long lesion, 38.7% had diabetes, and 19.4% had enzyme-positive acute coronary syndrome. Most patients (96.4%) were treated with drug-eluting stents; the mean number of stents per patient was 2.0, and the mean stent length was 57 mm. Fractional flow reserve was measured in 35.7% of the patients, and intravascular imaging was used in 74.4%.

FUNCTIONAL TESTING AND FOLLOW-UP

Among patients assigned to the functional-testing group, 92.5% of the patients who were eligible to undergo testing (those who did not die, withdraw, or have clinically driven angiography or revascularization and who were not lost to follow-up before 12 months) underwent functional testing at 12 months after randomization (Fig. 1). Reasons for not performing functional testing in the functional-testing group are provided in Table S2. In the standard-care group, 9.0% of the eligible patients underwent functional testing as clinically needed. Among 792 patients who underwent any stress testing, 415 (52.4%) had a single stress test, and 377 (47.6%) had multiple stress tests (Table S3). Details regarding medication use at baseline and during follow-up are provided in Table S4. Ascertainment of the primary and secondary outcomes at 2 years was completed in 97.9% of the patients, and data on vital status were obtained for all patients (Fig. 1).

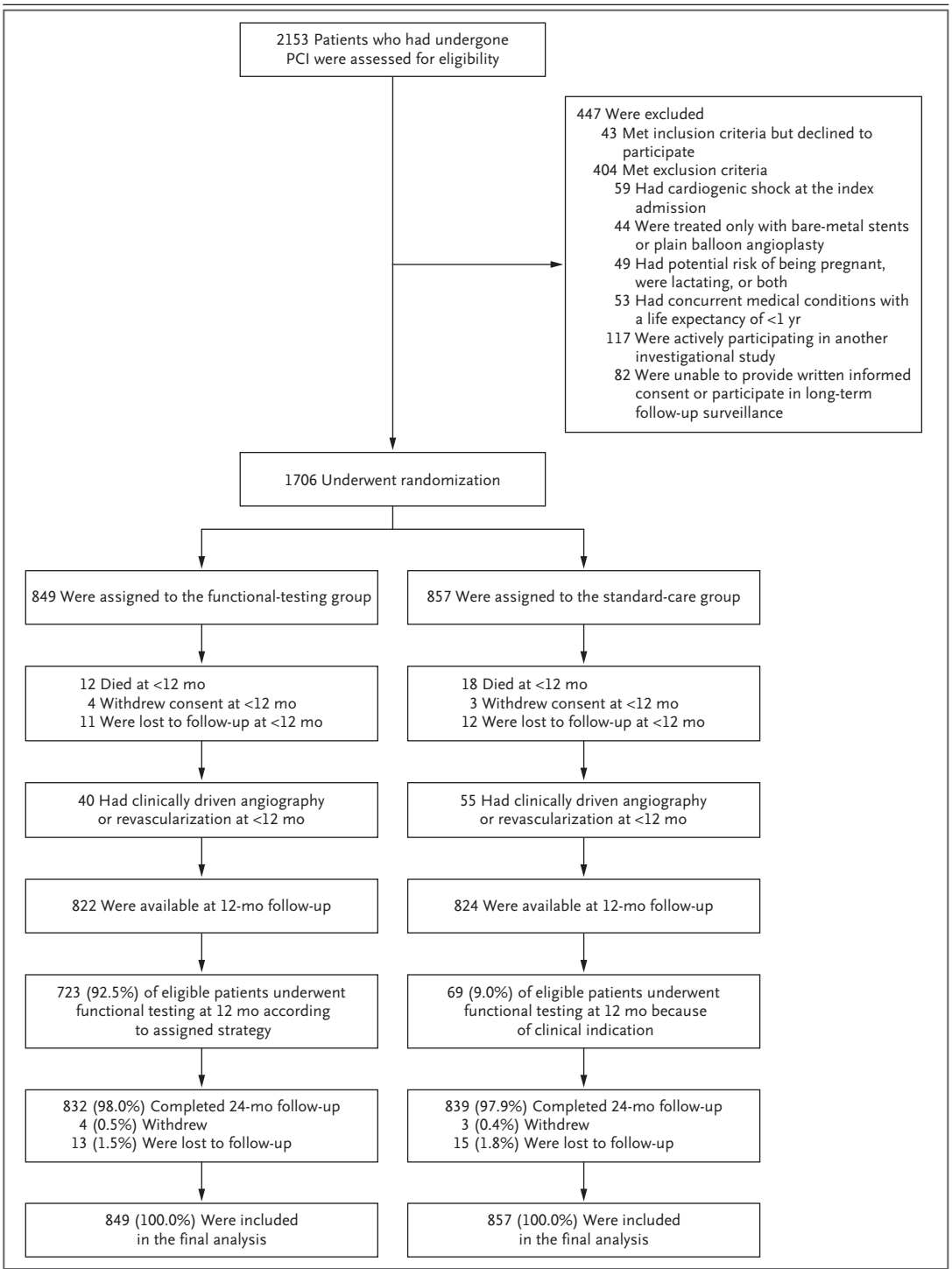

Figure 1. Enrollment, Randomization, and Follow-up.

Patients who were eligible to undergo functional testing were those who, at 12 months after randomization, had not died, had not withdrawn, were not lost to follow-up, and had not had clinically driven angiography or revascularization. Common reasons for not undergoing cardiac stress testing in the functional-testing group are provided in Table S2 in the Supplementary Appendix. The number of patients who underwent each type of stress test (nuclear stress imaging, exercise electrocardiography, or stress echocardiography) and the corresponding results are provided in Table S3. Patients may have had more than one reason for exclusion. Percentages may not total 100 because of rounding. PCI denotes percutaneous coronary intervention.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Functional Testing (N=849)	Standard Care (N=857)
Age — yr	64.6±10.3	64.8±10.3
Male sex — no. (%)	666 (78.4)	690 (80.5)
Body-mass index†	24.8±3.0	25.0±3.2
Criteria for high risk after PCI — no. (%)‡		
High-risk anatomical characteristics		
Left main disease	181 (21.3)	178 (20.8)
Bifurcation disease	373 (43.9)	369 (43.1)
Ostial lesion	128 (15.1)	127 (14.8)
Chronic total occlusion	152 (17.9)	190 (22.2)
Multivessel disease	589 (69.4)	602 (70.2)
≥2 vessels stented	376 (44.3)	389 (45.4)
Restenotic lesion	91 (10.7)	103 (12.0)
Diffuse long lesion§	585 (68.9)	611 (71.3)
Bypass graft disease	4 (0.5)	7 (0.8)
High-risk clinical characteristics		
Diabetes mellitus	321 (37.8)	339 (39.6)
Use of insulin	32 (3.8)	41 (4.8)
Chronic renal failure¶	42 (4.9)	45 (5.3)
Receipt of dialysis	23 (2.7)	26 (3.0)
Enzyme-positive acute coronary syndrome	161 (19.0)	170 (19.8)
Clinical indication for index PCI — no. (%)		
Stable angina or silent ischemia	598 (70.4)	582 (67.9)
Unstable angina	90 (10.6)	105 (12.3)
Non-STEMI	105 (12.4)	98 (11.4)
STEMI	56 (6.6)	72 (8.4)
Left ventricular ejection fraction — %‖	58.8±9.1	58.3±10.1
Procedural characteristics		
Total no. of diseased lesions per patient	2.2±1.2	2.3±1.1
Total no. of treated lesions per patient	1.4±0.7	1.5±0.7
Total no. of stents per patient	1.9±1.1	2.0±1.2
Total stent length per patient — mm	56.1±33.5	58.1±34.2
Use of drug-eluting stents — no. (%)	824 (97.1)	821 (95.8)
Use of bioabsorbable scaffold — no. (%)	6 (0.7)	10 (1.2)
Use of drug-coated balloon — no. (%)	46 (5.4)	59 (6.9)
Intravascular ultrasound guidance — no. (%)	622 (73.3)	647 (75.5)
Fractional flow reserve assessed — no. (%)	305 (35.9)	304 (35.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. PCI denotes percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 1 patient in the functional-testing group.
‡ Patients who were eligible for participation in the trial had to have at least one high-risk anatomical or clinical characteristic associated with an increased risk of ischemic or thrombotic events during follow-up.[12,16-18]
§ Diffuse long lesions were defined as lesions with a length of at least 30 mm or a stent length of at least 32 mm.
¶ Chronic renal failure was defined as a serum creatinine level of at least 2.0 mg per deciliter (177 μmol per liter) or long-term receipt of hemodialysis.
‖ Data were missing for 132 patients in the functional-testing group and 136 patients in the standard-care group.

PRIMARY AND SECONDARY OUTCOMES

At 2 years after randomization, 46 of 849 patients (Kaplan–Meier estimate, 5.5%) in the functional-testing group and 51 of 857 (Kaplan–Meier estimate, 6.0%) in the standard-care group had a primary-outcome event (hazard ratio, 0.90; 95% confidence interval [CI], 0.61 to 1.35; P=0.62) (Table 2 and Fig. 2A). There were no between-group differences in the incidences of the individual components of the primary composite outcome (Table 2 and Fig. 2B, 2C, and 2D) or the composite of death or myocardial infarction or rehospitalization (for any cardiac or noncardiac reason) at 2 years. At 2 years, invasive coronary angiography was performed in 12.3% of the patients in the functional-testing group and in 9.3% in the standard-care group (difference, 2.99 percentage points; 95% CI, −0.01 to 5.99); repeat revascularization was performed in 8.1% and 5.8%, respectively (difference, 2.23 percentage points; 95% CI, −0.22 to 4.68) (Table 2 and Fig. S1).

Results of functional testing reported by investigators at the individual trial sites and applied treatment strategies are summarized in Table S3. Positive stress tests were more common with nuclear imaging than with exercise ECG testing or stress echocardiography. Subsequent coronary angiography and repeat revascularization were more commonly performed in patients with positive results on nuclear stress imaging and exercise ECG testing than in those with discordant results between nuclear imaging and exercise ECG testing.

Table 2. Primary and Secondary Outcomes at 2 Years after Randomization.*

Outcome	Functional Testing (N=849)	Standard Care (N=857)	Difference in Event Rates (95% CI)	Hazard Ratio (95% CI)	P Value
	events (estimated percentage)		*percentage points*		
Primary composite outcome†	46 (5.5)	51 (6.0)	−0.53 (−2.76 to 1.70)	0.90 (0.61 to 1.35)	0.62
Death from any cause	23 (2.8)	28 (3.3)	−0.57 (−2.21 to 1.07)	0.82 (0.48 to 1.43)	
Myocardial infarction	4 (0.5)	10 (1.2)	−0.73 (−1.61 to 0.16)	0.40 (0.13 to 1.28)	
Hospitalization for unstable angina	19 (2.3)	14 (1.7)	0.63 (−0.72 to 1.98)	1.36 (0.68 to 2.72)	
Secondary outcomes					
Death or myocardial infarction	27 (3.2)	38 (4.5)	−1.28 (−3.12 to 0.56)	0.71 (0.43 to 1.17)	
Hospitalization					
Any reason	211 (25.5)	190 (22.8)	2.64 (−1.48 to 6.76)	1.12 (0.92 to 1.36)	
Cardiac reason	122 (14.8)	110 (13.3)	1.47 (−1.88 to 4.82)	1.10 (0.85 to 1.43)	
Noncardiac reason	89 (10.8)	80 (9.6)	1.16 (−1.75 to 4.07)	1.13 (0.83 to 1.52)	
Invasive coronary angiography	101 (12.3)	77 (9.3)	2.99 (−0.01 to 5.99)		
Showing restenosis or obstructive CAD	69 (68.3)	45 (58.4)			
Showing no restenosis or obstructive CAD	32 (31.7)	32 (41.6)			
Repeat revascularization	66 (8.1)	48 (5.8)	2.23 (−0.22 to 4.68)		
Target-lesion revascularization	34 (4.2)	26 (3.2)	1.00 (−0.81 to 2.81)		
Nontarget-lesion revascularization	32 (3.9)	22 (2.7)	1.24 (−0.48 to 2.96)		
PCI	64 (97.0)	45 (93.8)			
CABG	2 (3.0)	3 (6.3)			

* The number of events and estimated percentages were calculated with the use of a Kaplan–Meier survival analysis of data in the intention-to-treat population; therefore, the percentages may not reflect the ratio of the numerator and the denominator. Hazard ratios are for the routine functional-testing follow-up strategy as compared with the standard-care follow-up strategy. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. CABG denotes coronary-artery bypass grafting, and CAD coronary artery disease.

† The primary composite outcome was death from any cause, myocardial infarction, or hospitalization for unstable angina.

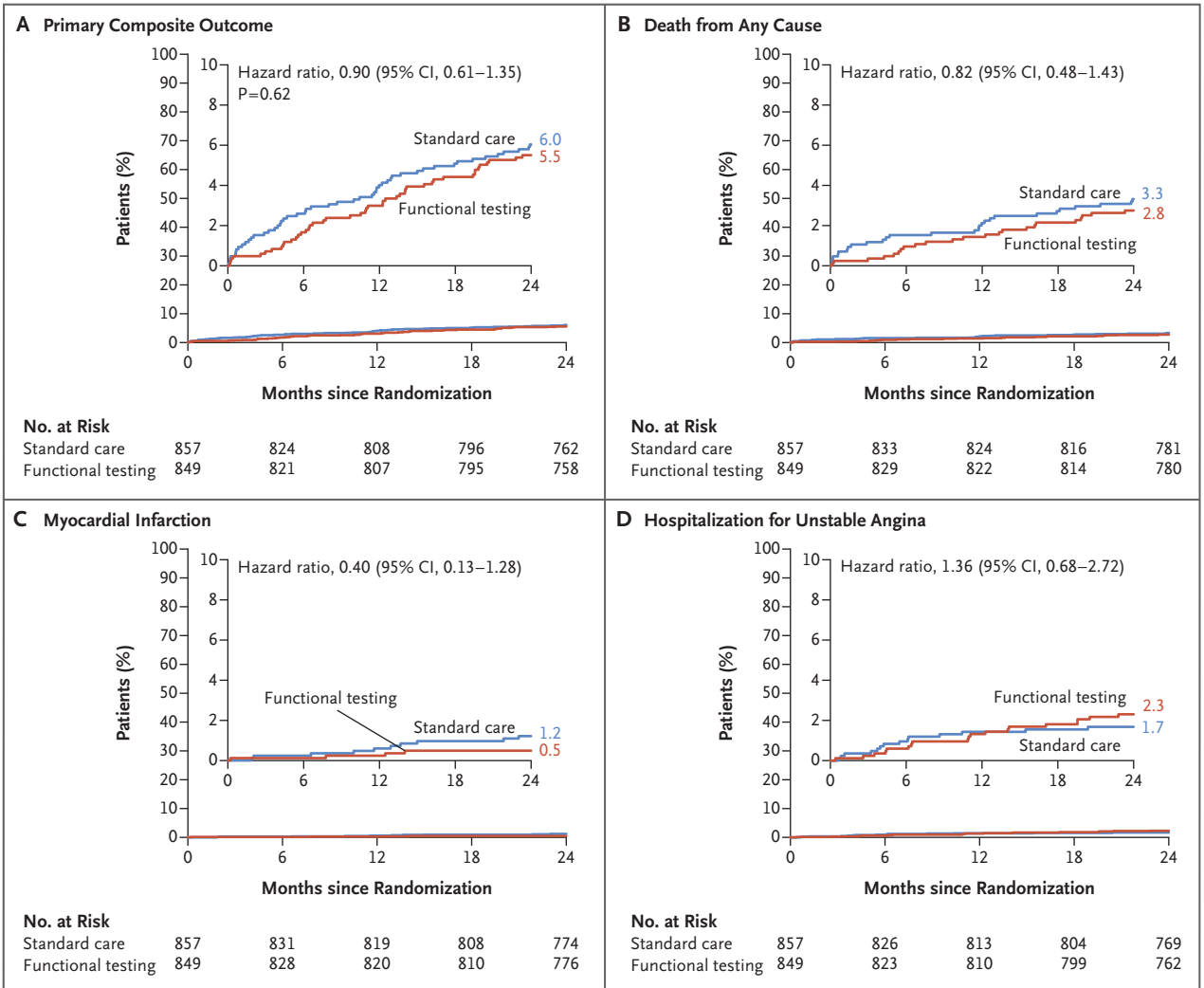

Figure 2. Time-to-Event Curves for the Primary Composite Outcome and the Components of the Primary Composite Outcome.

Shown is the cumulative incidence of the primary composite outcome of death from any cause, myocardial infarction, or hospitalization for unstable angina (Panel A), the cumulative incidence of death from any cause (Panel B), the cumulative incidence of myocardial infarction (Panel C), and the cumulative incidence of hospitalization for unstable angina (Panel D). The shown percentages are Kaplan–Meier estimates. The inset in each panel shows the same data on an enlarged y axis.

LANDMARK AND SUBGROUP ANALYSES

Landmark analyses at 1 year were performed for clinical outcomes (Table S5). The incidence of the primary outcome and its individual components within 1 year after randomization and between 1 year and 2 years were similar in the two groups (Fig. S2). There were no meaningful between-group differences in the incidence of key secondary outcomes within 1 year. However, after 1 year, 72 of 776 patients (9.3%) in the functional-testing group and 47 of 762 (6.2%) in the standard-care group were hospitalized for cardiac reasons; 64 of 785 patients (8.2%) and 25 of 772 (3.3%), respectively, had invasive coronary angiography; and 46 of 802 patients (5.8%) and 19 of 795 (2.4%), respectively, had repeat revascularization (Fig. S3). In the prespecified subgroup analyses, there was no evidence of a differential treatment effect on the primary outcome (Fig. S4). The results of post hoc analyses of each of the high-risk categories and the number of high-risk features are shown in Figure S5.

DISCUSSION

In this multicenter, pragmatic, randomized trial of routine functional testing as compared with standard care for guiding follow-up strategies in patients with high-risk anatomical or clinical characteristics who had undergone PCI, we found no significant between-group difference in the primary composite outcome of death, myocardial infarction, or hospitalization for unstable angina at 2 years. The routine stress-testing strategy appeared to be associated with more frequent invasive coronary angiography and repeat revascularization after 1 year, which did not result in a significant reduction in major cardiovascular events or mortality.

Previous observational studies have shown that elective stress testing after either PCI or CABG was common, but the diagnostic yield for subsequent coronary angiography and repeat revascularization was low.[5-8,23,24] Although abnormal findings on stress imaging were related to higher risks of death and major cardiac events,[25] the use of stress testing was not associated with a reduction in death or myocardial infarction, but it was associated with a higher incidence of repeat revascularization.[6,23] The Aggressive Diagnosis of Restenosis (ADORE) I and II trials assessed the effect of stress testing after PCI,[10,11] and the results showed that routine functional testing was associated with improved exercise endurance without significant differences in clinical outcomes. Unfortunately, these trials are not relevant to current practice because they were conducted when PCI was performed with bare-metal stents or with early-generation drug-eluting stents, and the trials were considerably underpowered (348 patients in the ADORE-I trial and 84 patients in the ADORE-II trial). In our large-scale, randomized trial involving high-risk patients who had undergone PCI, we found that routine functional testing, as compared with standard care, did not reduce the incidence of the primary or key secondary outcomes. In this clinical context, this trial can provide reliable evidence regarding the prognostic role of active surveillance with routine functional testing and offer definitive insights regarding the most appropriate follow-up strategy in high-risk patients who undergo PCI.

The key findings of the POST-PCI trial should be interpreted in the context of the results of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA).[26] The ISCHEMIA trial showed that an initial invasive strategy, as compared with an initial conservative strategy, did not reduce the risk of ischemic cardiovascular events or death among patients with stable coronary artery disease and moderate-to-severe ischemia on stress testing. Both the ISCHEMIA and POST-PCI trials show the benefits of a "less is more" concept (i.e., if more invasive strategies or testing are performed less frequently, it will result in better patient outcomes). Although the characteristics of the patients in both trials were quite different, a more invasive therapeutic approach (in the ISCHEMIA trial) as well as a more aggressive follow-up approach (in the POST-PCI trial) did not provide an additional treatment effect beyond a conservative strategy on the basis of guideline-directed medical therapy.

Although the sample size was determined on the basis of data from a previous pragmatic trial,[21] the observed number of primary-outcome events was lower than expected. This discrepancy might be explained in part by differences between clinical or lesion characteristics, interventional practice, or race or ethnic group. Also, it may be due to advances in PCI methods and improvements in cardiovascular care over the past decade, which include improved stent technology, more effective periprocedural and adjunctive pharmacologic treatment after stenting, and high levels of adherence to recommended medical therapy. These explanations are congruent with a recent trial that used contemporary PCI devices.[27] Strategy trials have also shown lower-than-expected event rates.[26,28] In addition, an increased use of intravascular imaging (in 74% of patients) and fractional flow reserve (in 36% of patients) during PCI might have reduced the incidence of major cardiovascular events.[29,30] Nevertheless, an extremely large study sample (>90,000 patients) would be required to detect a clinically relevant difference in the primary outcome (details are provided in Section I in the Supplementary Appendix).

Several limitations of the trial should be considered. First, it was not possible to mask the follow-up strategy from the patients and investigators, and the possibility of ascertainment bias cannot be excluded. Second, a 30% relative lower

risk of a primary-outcome event with active surveillance with stress testing than with standard care may be too ambitious with contemporary medical therapy. However, given that referent data were scant at the time the trial was designed, the relative effect size was determined on the basis of previous available trials with a similar concept or design.[28,31] Third, some nonadherence of stress testing in the functional-testing group was observed owing to several medical reasons; this could be interpreted in the context of the pragmatic trial design and enhances its generalizability to real-world settings. Fourth, routine stress testing included three different types of methods with diagnostic accuracy varying across the tests. Therefore, applying these different tests might result in inconsistent judgment of a patient's ischemic burden and affect clinical responses. Fifth, our trial did not address quality of life, cost-effectiveness, or radiation exposure, which could be crucial components of decision making and warrants further investigation. Finally, women were underrepresented in the trial, and the direct application of trial findings to "all-comer" populations of patients who have undergone PCI may be limited (Table S6).

In this trial involving high-risk patients who had undergone PCI, routine functional testing, as compared with standard care, did not result in a lower risk of ischemic cardiovascular events or death from any cause at 2 years.

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