Doctor of Philosophy

급성 관상동맥 증후군으로 관상동맥 중재시술을 시행한 고 위험 환자에서 정기적인 심장 부하 검사의 효용성

Routine Surveillance Stress Testing in High-Risk Patient with Acute Coronary Syndrome After Percutaneous Coronary Intervention

The Graduate School

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Department of Medicine

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ABSTRACT

IMPORTANCE The appropriate follow-up surveillance strategy for patients with acute coronary syndromes (ACS) who underwent complex percutaneous coronary intervention (PCI) remains unknown.

OBJECTIVE To assess clinical outcomes according to follow-up strategy of routine stress-testing vs. standard-care alone in patients undergoing high-risk PCI with vs. without ACS.

DESIGN, SETTING, AND PARTICIPANTS The POST-PCI (Pragmatic Trial Comparing Symptom-Oriented versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention) study was a randomized trial that compared follow-up strategies of routine functional-testing or standard-care alone after high-risk PCI. Patients were categorized as presenting with or without ACS. Kaplan-Meier event rates through 2 years and Cox model hazard ratios were generated, and interactions were tested. Patients were enrolled in the trial from 2017 through 2019 and a total of 1706 underwent randomization at 11 sites in South Korea.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of death from any cause, myocardial infarction, or hospitalization for unstable angina at 2 years.

RESULTS Among 1706 patients (mean [±SD] age was 64.7 ± 10.3; 1356 [79.5%] male and 350 [20.5%] female) randomized to receive routine functional-testing (n = 849) or standard-care alone (n = 857), 526 (31%) had ACS. Patients with ACS had less frequent comorbidities and less complex anatomical or procedural characteristics than those without ACS. However, patients with ACS had a 55% greater risk of the primary composite outcome [hazard ratio (HR) 1.55; 95% confidence interval (CI) 1.03–2.33; P = 0.034] compared to those without ACS. The 2-year incidences of the primary composite outcome were similar between strategies of routine functional-testing or standard-care alone in patients with ACS (6.6% vs. 8.5%; HR 0.76; 95% CI 0.40–1.44; P = 0.39) and in patients without ACS (5.1% vs. 4.9%; HR 1.04; 95% CI 0.62–1.74; P = 0.88) (interaction term for ACS: P = 0.45). The incidences of invasive coronary

angiography and repeat revascularization 1 year after PCI occurred more frequently in the routine functional-testing group compared to the standard-care group, regardless of ACS status.

CONCLUSION AND RELEVANCE Despite being at higher risk for adverse clinical events, patients with ACS who had undergone high-risk PCI did not derive incremental benefit from routine surveillance stress-testing as compared with standard-care alone during follow-up.

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Introduction

Patients presenting with acute coronary syndrome (ACS) who are undergoing percutaneous coronary intervention (PCI) are amongst a very common and high-risk group of patients with atherosclerosis.[1] Although remarkable improvements have been made in ACS management with evolving PCI devices and antithrombotic therapies,[2] the residual ischemic risk and the recurrence of ischemic cardiovascular events in patients with ACS undergoing PCI remain major concern. Furthermore, the appropriate follow-up surveillance strategy for ACS patients who underwent PCI remains debated and theoretical arguments have been made to support an active surveillance follow-up strategy in patients with ACS who underwent PCI to reduce the risk of future ischemic events.[3] In real-world clinical practice, routine surveillance stress testing has been commonly implemented as part of post-PCI management,[3-5] but its prognostic value is still uncertain in high-risk patients presenting with ACS who had undergone PCI.

In the clinical context, given that patients with ACS have a higher incidence of recurrent cardiovascular events and mortality compared to patients with stable coronary artery disease (CAD),[6,7] it should be determined whether such high-risk ACS patients undergoing PCI could benefit from routine surveillance stress testing to reduce the risk of adverse cardiovascular events during follow-up. Therefore, using contemporary data from the POST-PCI (Pragmatic Trial Comparing Symptom-Oriented versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention) study, a randomized trial of follow-up strategy evaluation in high-risk patients who had undergone PCI,[8] we examined clinical outcomes according to randomized follow-up strategy of routine functional-testing versus standard-care alone in patients presenting with versus without ACS.

Methods

Study Design and Patients

The POST-PCI trial was a multicenter, pragmatic, randomized trial that compared an active follow-up strategy of routine functional-testing versus a standard-care alone strategy in high-risk patients with complex anatomical or clinical characteristics who underwent PCI.[8] This trial was conducted at 11 hospitals in South Korea from November 2017 to September 2019. Enrolled participants had at least one high-risk anatomical or clinical characteristic associated with an increased risk of ischemic or thrombotic events: (1) anatomical high-risk characteristics included multivessel CAD (requiring stenting of at least two vessels), left main disease, bifurcation disease, an ostial lesion, chronic total occlusion, a restenosis lesion, a long diffuse lesion, or bypass graft disease; and (2) clinical high-risk characteristics included medically treated diabetes mellitus, chronic renal failure, and enzyme-positive ACS. All patients underwent successful PCI with contemporary drug-eluting stents, bioresorbable scaffolds, or drug-coated balloons (only for in-stent restenosis). The trial was approved by the investigational review board or ethics committee at each participating center. All patients provided written informed consent before enrollment.

For this prespecified secondary analysis, patients were categorized according to whether or not they presented with ACS as the clinical indication for PCI. The ACS cohort had unstable angina or myocardial infarction (MI) with or without ST-segment elevation (STEMI or NSTEMI) and the non-ACS cohort had stable angina or silent ischemia.

Trial Procedures and Functional Testing

The trial procedures and randomized follow-up strategies have been previously described.[8] Patients in the routine functional-testing group were subjected to routine cardiac stress testing, comprising exercise electrocardiography (ECG), nuclear stress testing, or stress echocardiography, at 12 months after randomization. Due to the high likelihood of false-

positive exercise ECG tests indicating myocardial ischemia, simple exercise ECG testing only was discouraged; thus, a combined non-invasive imaging strategy was strongly recommended. In the standard-care group, stress testing was only performed when clinically indicated during follow-up.

In keeping with the pragmatic design of the POST-PCI trial, the test findings were based on real-time, site-based interpretation of all functional test results, thereby ensuring the timely availability of the results for patient management. All clinical decisions regarding further diagnostic or therapeutic procedures and subsequent treatment decision were made at the discretion of the treating physician at each participating center.

Clinical Outcomes and Follow-Up

The primary outcome was a composite of major cardiovascular events, consisting of death from any cause, MI, 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 non-target-lesion revascularization). Definitions of each clinical endpoint have been described previously,8 and all components of the primary and secondary clinical outcomes were independently adjudicated by a clinical events committee, the members of which were unaware of the treatment assignments.

Clinical follow-up was performed at 6, 12, 18, and 24 months as scheduled after randomization. During the follow-up period, it was strongly advised to follow contemporary clinical guidelines for guideline-directed medical therapy and the management of risk factors to achieve intensive secondary prevention. All information on clinical events and cardiovascular medicines was systematically obtained at each clinical visit. To ensure accuracy,

the vital status of the patients was verified by crosschecking with the national death registry of the Korean National Health Insurance Service database.

Statistical Analysis

For comparisons of patients with vs. without ACS, baseline characteristics were compared using the $\chi 2$ or Fisher exact test for categorial variables and the Kruskal–Wallis test for continuous variables. Time-to-event for clinical outcomes, including the primary composite outcome and secondary outcomes, was obtained by Kaplan–Meier estimates and were compared using the log-rank test.

A comparison between the groups randomized to different follow-up strategies (routine functional-testing versus standard-care alone) among patients with or without ACS was performed using a Cox proportional hazards model. Hazard ratios and 95% confidence intervals (CI) were calculated. The proportional hazards assumption was tested for each outcome using Schoenfeld residuals and visual inspection. Interactions between the randomized follow-up strategy and ACS status were also tested.

Although the proportional-hazards assumption was met for most of the primary and key secondary outcomes, it was not met for the secondary outcome of invasive coronary angiography and repeat revascularization ($P<0.05$ for the Schoenfeld residuals test). Therefore, prespecified landmark analyses were performed using a 1-year cutoff, which corresponded to the planned period of routine functional-testing, and during which proportional hazards were preserved.8 All tests were 2-sided, and $P<0.05$ was considered statistically significant for all endpoints with no adjustment for multiple testing; therefore, all findings of this study should be interpreted as exploratory given the potential for a type I error due to multiple comparisons. Analyses were performed by independent statisticians using commercially available software (SAS version 9.4 and Stata version 16.1).

Results

Study Population and Baseline Characteristics

Among 1706 patients randomized in the POST-PCI trial, 526 (30.8%) presented with ACS; among these, 331 (62.9%) presented with STEMI or NSTEMI and 195 (37.1%) presented with unstable angina. Among 526 ACS patients, 251 (47.7%) were randomized to the routine functional-testing strategy and 275 (52.5%) were randomized to the standard-care strategy. In 1180 non-ACS patients, 598 (50.6%) and 582 (49.3%) were randomized to the routine functional-testing and the standard-care strategy, respectively (**Figure 1**).

The baseline characteristics according to ACS status are shown in **Table 1**. As compared to those without ACS, patients with ACS were more likely to have current smoking and a lower left ventricular ejection fraction. However, non-ACS patients were more likely to have higher-risk profiles of clinical comorbidities, anatomical or procedural characteristics. The use of intravascular imaging-guided or physiology (i.e., fractional flow reserve)-guided PCI was more common in non-ACS patients than in ACS patients.

When subdivided by ACS presentation, the baseline characteristics of patients randomized to follow-up strategies with routine stress-testing versus standard-care alone were similar (**Supplemental Table 1**). Most of baseline characteristics were not significantly different according to the randomized follow-up strategy in each cohort of ACS and non-ACS.

Functional Testing and Follow-up

At 12 (± 2 months) following randomization, 203 (91.8%) of eligible patients (n = 243) with ACS in the routine functional-testing group (excluding those who died [n = 3], withdrew [n = 2], were lost to follow-up [n = 6], or underwent angiography or revascularization [n = 19] before 12 months) underwent functional testing, as did 24 (10.1%) of the eligible patients in the standard-care group, as clinically needed (excluding those who died [n = 9], withdrew [n = 0], were lost to follow-up [n = 3], or underwent angiography or revascularization [n = 25]

before 12 months) (**Figure 1**). Among patients without ACS, 92.7% of those in the functional-testing group and 8.5% of patients in the standard-care group underwent functional testing.

Since guideline-directed medical therapy was equally emphasized in both groups, the use of cardioactive medications was well-balanced between the functional-testing group and the standard-care group at baseline and during follow-up in each stratum of patients with and without ACS (**Supplemental Table 2**). Ascertainment of the primary and secondary outcomes at 2 years was completed in 97.9% of overall patients (97.8% of the ACS cohort and 97.9% of the non-ACS cohort) (**Figure 1**). Data on vital status were obtained for all patients.

Clinical Outcomes

ACS vs. not ACS

Clinical outcomes in patients with and without ACS are presented in **Table 2**. Despite being at lower risk for clinical risk factors or anatomical characteristics, the primary composite outcome of death from any cause, MI, or hospitalization for unstable angina at 2 years was significantly more frequent in patients with ACS than without ACS (7.6% and 5.0%; HR: 1.55; 95% CI: 1.03 to 2.33; P = 0.03) (**Figure 2**). The 2-year incidence of death or MI tended to be higher (5.0% vs. 3.4%; P = 0.09) and the rate of rehospitalization owing to cardiac causes was significantly higher (17.2% vs. 12.7%; P = 0.009) in ACS patients than in non-ACS patients (**Table 2**).

Routine Stress Testing vs. Standard-Care Alone

When outcomes were compared by randomized follow-up strategy, the rate of the primary composite outcome through 2 years was 6.6% in the functional-testing group as compared with 8.5% in the standard-care group (HR 0.76; 95% CI 0.40–1.44) among patients presenting with ACS, whereas the rates were 5.1% and 4.9% (HR 1.04; 95% CI 0.62–1.74) in patients without ACS (P-for-interaction = 0.45) (**Table 3 & Figure 3**). The pattern was similar for each

individual component of the primary outcome and other key secondary outcomes according to the presence or absence of ACS and the randomized follow-up strategy (**Table 3 & Figure 3**).

The rates of invasive coronary angiography and repeat revascularization tended to be higher in the functional-testing group compared to the standard-care group especially in non-ACS cohort (**Supplemental Figure 1**).

Landmark Analyses

To assess the time-dependent pattern of clinical outcomes, landmark analyses at 1 year were performed (**Supplemental Table 3**). Within the first year, there were no significant differences in the primary composite outcome, its individual components, or other secondary outcomes between the functional-testing and standard-care groups in patients with and without ACS (**Supplemental Figures 2, 3, 4, and 5**). By contrast, after 1 year, the rates of invasive coronary angiography and repeat revascularization were significantly higher in the functional-testing group than the standard-care group among non-ACS patients, but this trend was not remarkable among ACS patients (**Supplemental Figures 4 & 5**). In these landmark analyses, there were no significant interactions between ACS status and randomized follow-up strategy with respect to primary or secondary clinical outcomes (**Supplemental Table 3**).

Table 1. Baseline Characteristics of Patients with and without Acute Coronary Syndrome*

Characteristic	Overall (n = 1706)	ACS (n = 526)	No ACS (n = 1180)	P value
Demographics				
Age, years	64.7 ± 10.3	64.4 ± 11.5	64.8 ± 9.7	0.48
Male sex	1356 (79.4)	420 (79.8)	936 (79.3)	0.80
Body-mass index (kg/m^2)†	24.9 ± 3.1	24.7 ± 3.18	25.02 ±3.04	0.04
Cardiac risk factors and comorbidities				
Hypertension	1178 (69.0)	328 (62.3)	850 (72.0)	<0.001
Current smoker	462 (27.0)	184 (34.9)	278 (23.5)	<0.001
Dyslipidemia	1487 (87.1)	435 (82.6)	1052 (89.1)	<0.001
History of MI	113 (6.6)	38 (7.2)	75 (6.4)	0.51
Previous PCI	375 (21.9)	95 (18.0)	280 (23.7)	0.009
Previous CABG	42 (2.5)	6 (1.1)	36 (3.1)	0.019
History of stroke	109 (6.4)	33 (6.3)	76 (6.4)	0.90

History of heart failure	40 (2.3)	15 (2.9)	25 (2.1)	0.36
Peripheral artery disease	39 (2.3)	8 (1.5)	31 (2.6)	0.16
Chronic lung disease	46 (2.7)	13 (2.5)	33 (2.8)	0.70
Atrial fibrillation or atrial flutter	43 (2.5)	14 (2.7)	29 (2.5)	0.80
Left ventricular ejection fraction	58.5 ± 9.6	55.5 ± 10.8	60.0 ± 8.6	<0.001
Criteria for high risk after PCI‡				
High-risk anatomical characteristics				
Left main disease	359 (21.0)	89 (16.9)	270 (22.8)	0.005
Bifurcation disease	702 (41.1)	148 (28.1)	554 (46.9)	<0.001
Ostial lesion	255 (14.9)	49 (9.3)	206 (17.4)	<0.001
Chronic total occlusion	228 (13.3)	41 (7.8)	187 (15.8)	<0.001
Multivessel disease	765 (44.8)	203 (38.5)	562 (47.6)	<0.001
Restenotic lesion	147 (8.6)	37 (7.0)	110 (9.3)	0.12
Diffuse long lesion§	1002 (58.7)	234 (44.4)	768 (65.0)	<0.001
Bypass graft disease	4 (0.2)	1 (0.2)	3 (0.3)	>0.99

High-risk clinical characteristics				
Diabetes mellitus	660 (38.6)	195 (37.0)	465 (39.4)	0.36
Use of insulin	73 (4.3)	19 (3.6)	54 (4.6)	0.36
Chronic renal failure¶	87 (5.1)	28 (5.3)	59 (5.0)	0.78
Receipt of dialysis	49 (2.9)	13 (2.5)	36 (3.1)	0.51
Procedural characteristics				
Total no. of diseased lesions per patient	2.2 ± 1.2	2.0 ± 1.2	2.3 ± 1.1	<0.001
Total no. of treated lesions per patient	1.5 ± 0.7	1.5 ± 0.7	1.5 ± 0.7	0.97
Total no. of stents per patient	1.9 ± 1.2	1.8 ± 1.1	2.0 ± 1.2	<0.001
Total stent length per patient, mm	57.1 ± 33.8	49.6 ± 30.5	60.5 ± 34.7	<0.001
Use of drug-eluting stents	1645 (96.4)	511 (97.1)	1,134 (96.1)	0.28
Use of bioabsorbable scaffold	16 (0.9)	3 (0.6)	13 (1.1)	0.42
Use of drug-coated balloon	105 (6.2)	25 (4.8)	80 (6.8)	0.11
Intravascular ultrasound guidance	1269 (74.3)	353 (67.1)	916 (77.6)	<0.001
Fractional flow reserve assessed	609 (35.6)	86 (16.3)	523 (44.3)	<0.001

* Values are means ±SD or n (%) unless otherwise indicated. Percentages may not total 100 because of rounding.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡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.

§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.

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Clinical Outcomes at 2 Years According to the Presence or Absence of Acute Coronary Syndrome*

Outcome	ACS (n = 526)	No ACS (n = 1180)	HR (95% CI)	P value
Primary composite outcome†	39 (7.6)	58 (5.0)	1.55 (1.03–2.33)	0.03
Death from any cause	19 (3.7)	32 (2.8)	1.35 (0.77–2.39)	0.30
MI	7 (1.4)	7 (0.6)	2.28 (0.80–6.51)	0.12
Hospitalization for unstable angina	14 (2.8)	19 (1.7)	1.70 (0.85–3.38)	0.13
Secondary outcomes				
Death or MI	26 (5.0)	39 (3.4)	1.53 (0.93–2.51)	0.09
Hospitalization				
Any reasons	135 (26.6)	266 (15.3)	1.21 (0.98–1.48)	0.07
Cardiac reasons	87 (17.2)	145 (12.7)	1.42 (1.09–1.86)	0.009
Noncardiac reasons	48 (9.5)	121 (10.5)	0.91 (0.65–1.27)	0.56
Invasive coronary angiography	61 (11.6)	117 (9.9)	1.21 (0.89-1.65)	0.23
Showing restenosis or obstructive CAD	36 (6.8)	79 (6.7)	1.06(0.71-1.56)	0.78
Showing no restenosis or obstructive CAD	25 (4.8)	38 (3.2)	1.53(0.92-2.52)	0.10

Repeat revascularization	41 (8.1)	73 (6.4)	1.30 (0.88–1.90)	0.18
TLR	18 (3.6)	42 (3.7)	0.98 (0.56–1.69)	0.93
Non-TLR	23 (3.6)	31 (2.7)	1.71 (1.00–2.93)	0.052
PCI	39 (7.4)	70 (5.9)	1.28 (0.86-1.90)	0.21
CABG	2 (0.3)	3 (0.2)	1.53 (0.25-9.18)	0.64

*Results reported as no. or no. (%). The number of events and estimated percentages were calculated with the use of Kaplan–Meier estimates.

Hazard ratios are for patients with ACS as compared to those without ACS. 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.

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

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CABG, coronary artery bypass grafting; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target-lesion revascularization.

Table 3. Clinical Outcomes at 2 Years According to Presence or Absence of Acute Coronary Syndrome and Randomized Follow-Up Strategy.*

	ACS				Non-ACS				
Outcome	**Functional Testing (n = 251)**	**Standard Care (n = 275)**	**HR (95% CI)**	**P**	**Functional Testing (n = 598)**	**Standard Care (n = 582)**	**HR (95% CI)**	**P**	**P-for-interaction †**
Primary composite outcome‡	16 (6.6)	23 (8.5)	0.76 (0.40–1.44)	0.40	30 (5.1)	28 (4.9)	1.03 (0.62–1.73)	0.90	0.46
Death from any cause	8 (3.3)	11 (4.1)	0.80 (0.32–1.99)	0.64	15 (2.5)	17 (3.0)	0.85 (0.43–1.70)	0.64	0.92
MI	2 (0.8)	5 (1.9)	0.44 (0.08–2.26)	0.32	2 (0.3)	5 (0.9)	0.38 (0.07–1.98)	0.25	0.91
Hospitalization for unstable angina	6 (2.5)	8 (3.0)	0.82 (0.28–2.36)	0.71	13 (2.2)	6 (1.1)	2.09 (0.79–5.50)	0.13	0.20
Secondary outcomes									
Death or MI	10 (4.1)	16 (5.9)	0.68 (0.31–1.51)	0.35	17 (2.9)	22 (3.9)	0.74 (0.39–1.40)	0.36	0.88
Hospitalization									
Any reason	69 (28.6)	66 (24.8)	1.14 (0.81–1.59)	0.44	142 (24.2)	124 (21.9)	1.12 (0.88–1.42)	0.37	0.92
Cardiac reason	44 (18.3)	43 (16.2)	1.11 (0.74–1.70)	0.60	78 (13.3)	67 (12.0)	1.11 (0.80–1.54)	0.52	0.98
Noncardiac reason	25 (10.4)	23 (8.6)	1.19 (0.67–2.10)	0.53	64 (10.9)	57 (10.1)	1.09 (0.77–1.56)	0.61	0.80

Invasive coronary angiography	29 (11.6)	32 (11.6)	1.02 (0.62-1.69)	0.93	72 (12.0)	45 (7.7)	1.55 (1.06-2.25)	0.02	0.15
Showing restenosis or obstructive CAD	17 (6.8)	19 (6.9)	0.99 (0.52-1.90)	0.98	52 (8.7)	27 (4.6)	1.86 (1.17-2.97)	0.008	0.11
Showing no restenosis or obstructive CAD	12 (4.8)	13 (4.7)	1.04 (0.48- 2.28)	0.92	20 (3.3)	18 (3.1)	1.08 (0.57-2.04)	0.81	0.76
Repeat revascularization	22 (9.2)	19 (7.2)	1.27 (0.69-2.35)	0.43	44 (7.6)	29 (5.2)	1.46 (0.10-2.33)	0.11	0.73
TLR	11 (4.6)	7 (2.7)	1.73 (0.67-4.48)	0.25	23 (4.0)	19 (3.4)	1.16 (0.63-2.13)	0.63	0.48
Non-TLR	11 (4.6)	12 (4.5)	1.01 (0.44-0.28)	0.98	21 (3.6)	10 (1.8)	2.02 (0.95-4.29)	0.07	0.22
PCI	20 (7.9)	19 (6.9)	1.15 (0.62-2.17)	0.65	44 (7.6)	26 (4.4)	1.63 (1.00-2.64)	0.05	0.40
CABG	2 (0.7)	0 (0.0)	-	>0.99	0 (0.0)	3 (0.5)	-	>0.99	0.99

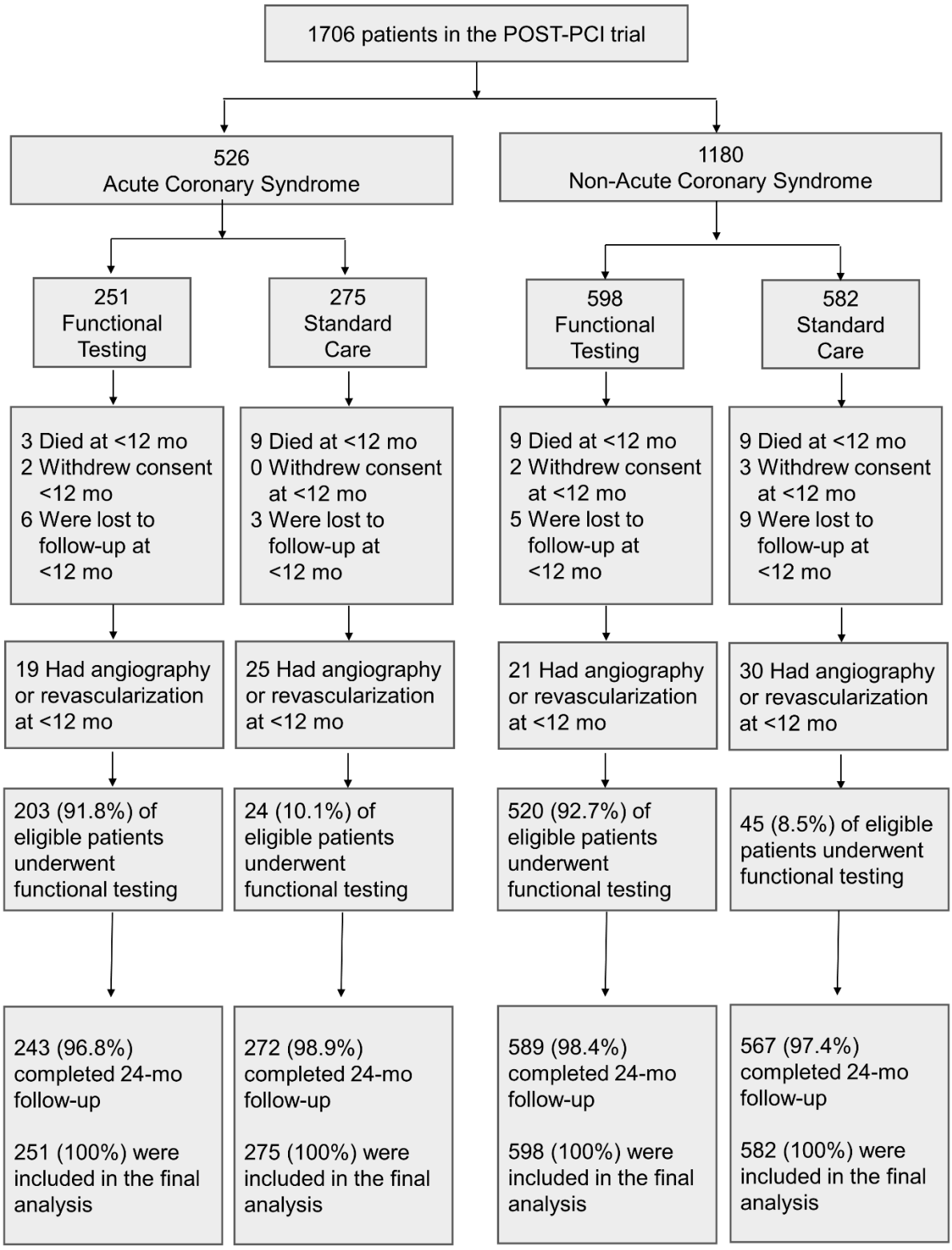
* The number of events and estimated percentages were calculated with the use of Kaplan–Meier survival estimates; therefore, the percentages may not reflect the ratio of the numerator and the denominator. Hazard ratios are for the routine functional-testing follow-up strategy as compared with the standard-care 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.

†P-value for interaction between the clinical status (SIHD vs. ACS) and the randomization group (functional testing vs. standard care).

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

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CABG, coronary artery bypass grafting; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

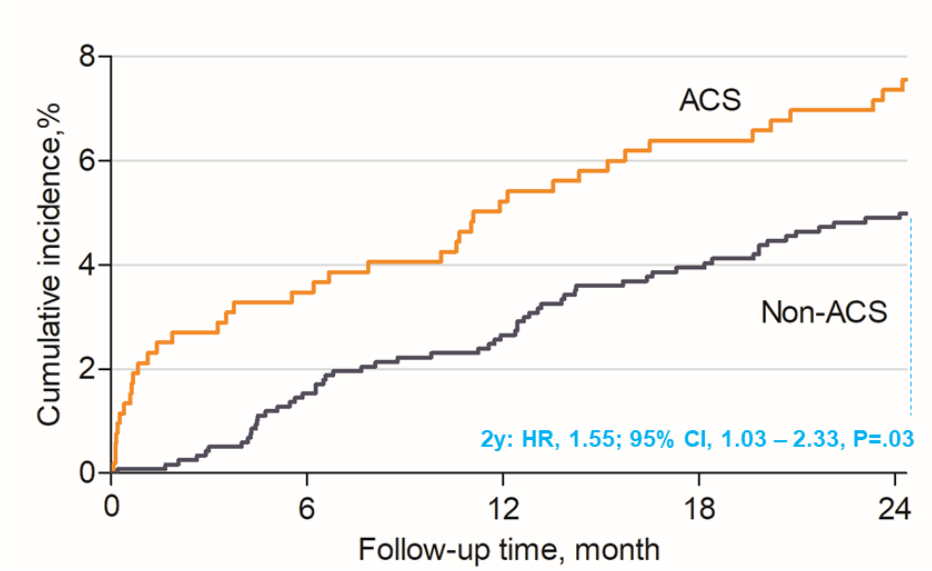
Figure 1. Study flow diagram.



Study flow diagram of patients stratified by the presence or absence of acute coronary syndrome. Patients who were eligible to undergo functional testing at 12 months after randomization included those who had not died, had not withdrawn, had not undergone clinically driven angiography or revascularization, and were not lost to follow-up. Percentages may not total 100 because of rounding.

PCI denotes percutaneous coronary intervention.

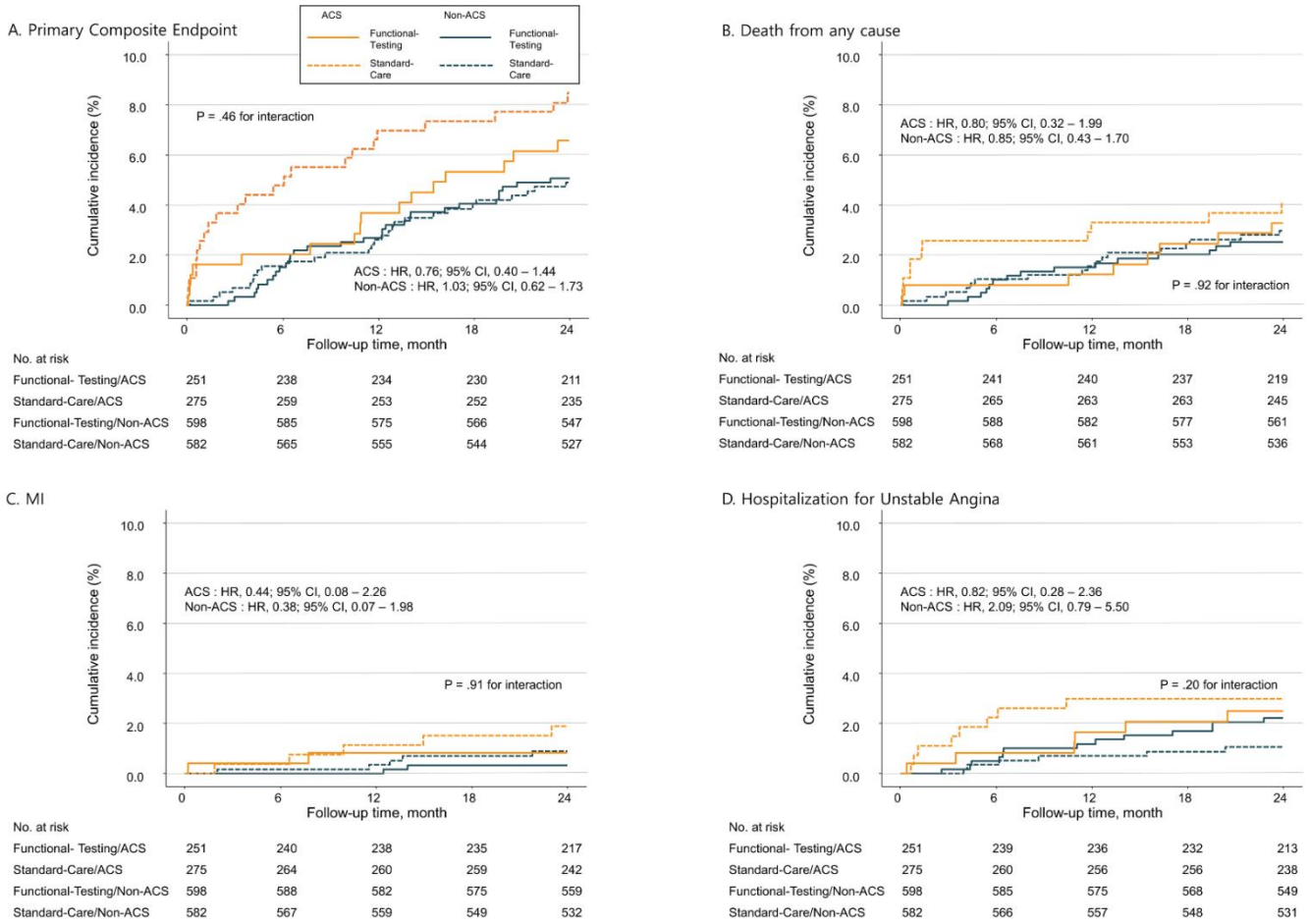
Figure 2. Time-to-Event Curves for the Primary Composite Outcome According to Presence or Absence of Acute Coronary Syndrome.



No. at risk					
ACS	526	498	489	483	446
Non-ACS	1180	1151	1131	1112	1074

Kaplan–Meier curves of the cumulative incidence of the primary composite outcome of death from any cause, myocardial infarction, or hospitalization for unstable angina in patients with and without acute coronary syndrome. The shown percentages are Kaplan–Meier estimates. The P values were determined by log-rank tests.

Figure 3. Time-to-event Curves for the Primary Composite Outcome and Its Component According to Acute Coronary Syndrome and Randomized Follow-Up Strategy



Kaplan–Meier curves of the cumulative incidence of the primary composite outcome of death from any cause, myocardial infarction, or hospitalization for unstable angina in patients with and without acute coronary syndrome (A). Kaplan–Meier curves of the cumulative incidence of death from any cause (B), and the cumulative incidence of myocardial infarction (C), and the cumulative incidence of hospitalization for unstable angina (D) in patients with and without acute coronary syndrome. The shown percentages are Kaplan–Meier estimates. The P values were determined by log-rank tests.

Discussion

In this prespecified analysis of the POST-PCI trial, we compared the outcomes according to different follow-up strategies with routine functional-testing or standard-care alone in patients with or without ACS. The major findings can be summarized as that: (1) patients presenting with ACS had fewer comorbidities and a lower risk of anatomical or procedural complexity compared to patients without ACS. However, ACS patients had higher rates of the primary composite outcome over the duration of follow-up; (2) the 2-year rates of the primary composite outcome were not significantly different between the routine functional-testing group and the standard-care group in patients with or without ACS; (3) invasive coronary angiography and repeat revascularization after 1 year occurred more frequently in the routine functional-testing group; however, this additional invasive management was not associated with a significant reduction of major cardiovascular events or mortality.

The findings of the present analysis address a clinically important gap in the evidence-base necessary to guide decisions about the follow-up strategy of patients with ACS who underwent PCI. Prior clinical studies evaluating patients with ACS undergoing PCI have been almost entirely conducted in observational or small clinical trials.[4,5,9-11] Moreover, no randomized trials to date have been powered to explore whether there is a relationship between the follow-up surveillance strategy and clinical outcomes specifically among patients with ACS and PCI. Therefore, the current study may provide the important insights on such unmet issue.

The patients with ACS enrolled in our trial were naturally different from those with stable coronary artery disease. Although patients with ACS have fewer comorbidities and less complex anatomical or procedural characteristics than those without ACS, ACS patients have a higher incidence of major cardiovascular events. These differences in clinical outcomes may be related to the myocardial injury occurring during ACS[12] as well as the difference in atherosclerotic burden of vulnerable plaque among patients presenting with versus without ACS.[13,14] A prior study also showed that patients with ACS had higher rates of long-term cardiovascular mortality or MI after coronary revascularization as compared to those without ACS.[15]

Cardiac stress testing has been widely implemented as an important part of the follow-up surveillance strategy after myocardial revascularization, including either PCI or CABG.[3-5] Nevertheless, it remains unclear whether this type of active surveillance strategy can improve clinical outcomes. It is well established that patients undergoing PCI have a substantial (~10%) risk of restenosis at the target-lesion.[16] Among patients with target-lesion failure after PCI, a majority require repeat revascularization and certain proportion of patients present with spontaneous MI.[16,17] Moreover, atherosclerotic plaque characteristics in ACS patients differ from those with stable CAD, particularly concerning non-culprit vulnerable plaques, which contribute to distinct clinical outcomes.[18,19] Given the heightened risk for recurrent events across the coronary tree after ACS, one might have anticipated a protective benefit of active follow-up surveillance with routine stress-testing in the ACS setting. However, this prespecified analysis from the POST-PCI provides important evidence for a class III recommendation for routine surveillance testing after PCI in ACS patients. Although the key findings of the POST-PCI were adopted in the new clinical guidelines for chronic coronary disease,[20] it should be further adopted in the future guidelines of ACS management.

It should be noted that the overall event rates in both the ACS and non-ACS groups in this trial were quite low and most likely reflect adherence to guideline recommendations. In addition, current guidelines recommend intravascular imaging (class IIa) for procedural guidance, particularly during high-risk PCI.[21,22] The use of intravascular imaging is associated with lower risks of major cardiovascular events;[23-25] thus, the much greater proportion of imaging-guided PCI in our study might be associated with favorable long-term outcomes. Furthermore, the impact of guideline-directed aggressive secondary preventive measures with modifications for risk factors and appropriate medical therapies (i.e., almost 99% of patients were taking statins during the follow-up period) might be substantial. These factors underscore the importance of proper procedural techniques and aggressive secondary prevention to improve outcomes after PCI, which mitigate the clinical impact of routine surveillance stress testing after PCI, among ACS and non-ACS patients.

Limitations. This study has several limitations. First, while patients with ACS were a pre-specified subgroup of interest for the original POST-PCI trial, there was no adjustment for multiple testing and thus these findings should be interpreted as hypothesis-generating. Second, this subgroup analysis might have an inherent limitation of statistical underpowering to detect clinically relevant events. Third, exact information on the status of complete revascularization for non-culprit lesions in ACS patients was lacking. This uncertainty could have influenced the clinical outcomes in patients with ACS. Third, this study was based on an Asian cohort and women were underrepresented in this study, which could potentially impact the generalizability of the study results. Lastly, the study's outcomes were measured based on a 2-year follow-up period, which might limit the assessment of long-term effects and potential changes in clinical outcomes beyond this timeframe.

Conclusion

In high-risk patients presenting with ACS who had undergone PCI, a follow-up strategy of routine surveillance functional-testing, compared with standard-care alone, did not reduce the risk of the primary composite outcome of death from any cause, MI, or hospitalization for unstable angina at 2 years. These findings were consistent regardless of ACS status. Although the present study had insufficient statistical power to allow for a firm conclusion, these findings may suggest that there is no incremental clinical benefit from routine surveillance functional-testing in ACS patients after PCI.

References

1. Steen DL, Khan I, Andrade K, Koumas A, Giugliano RP. Event Rates and Risk Factors for Recurrent Cardiovascular Events and Mortality in a Contemporary Post Acute Coronary Syndrome Population Representing 239 234 Patients During 2005 to 2018 in the United States. J Am Heart Assoc. 2022;11(9):e022198. doi:10.1161/JAHA.121.022198

2. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2023;44(38):3720-3826. doi:10.1093/eurheartj/ehad191

3. Bagai A, Madan M, Overgaard C, et al. Long-term Clinical Outcomes Following Cardiac Stress Testing After Percutaneous Coronary Intervention. Can J Cardiol. 2023;39(11):1513-1521. doi:10.1016/j.cjca.2023.06.422

4. Shah BR, McCoy LA, Federspiel JJ, et al. Use of stress testing and diagnostic catheterization after coronary stenting: association of site-level patterns with patient characteristics and outcomes in 247,052 Medicare beneficiaries. J Am Coll Cardiol. 2013;62(5):439-446. doi:10.1016/j.jacc.2013.02.093

5. Kini V, Parks M, Liu W, et al. Patient Symptoms and Stress Testing After Elective Percutaneous Coronary Intervention in the Veterans Affairs Health Care System. JAMA Netw Open. 2022;5(6):e2217704. doi:10.1001/jamanetworkopen.2022.17704

6. Alcock RF, Yong AS, Ng AC, et al. Acute coronary syndrome and stable coronary artery disease: are they so different? Long-term outcomes in a contemporary PCI cohort. Int J Cardiol. 2013;167(4):1343-1346. doi:10.1016/j.ijcard.2012.04.011

7. Park S, Ahn JM, Lee K, et al. Long-term (10-year) outcomes of stenting or bypass surgery for acute coronary syndromes and stable ischemic heart disease with unprotected left main coronary artery disease. Am Heart J. 2019;218:9-19. doi:10.1016/j.ahj.2019.08.014

8. Park DW, Kang DY, Ahn JM, et al. Routine Functional Testing or Standard Care in High-Risk Patients after PCI. N Engl J Med. 2022;387(10):905-915. doi:10.1056/NEJMoa2208335

9. 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(16):1328-1334. doi:10.1016/j.jacc.2010.03.093

10. Eisenberg MJ, Blankenship JC, Huynh T, et al. Evaluation of routine functional testing after percutaneous coronary intervention. Am J Cardiol. 2004;93(6):744-747. doi:10.1016/j.amjcard.2003.11.071

11. Eisenberg MJ, Wilson B, Lauzon C, et al. Routine functional testing after percutaneous coronary intervention: results of the aggressive diagnosis of restenosis in high-risk patients (ADORE II) trial. Acta Cardiol. 2007;62(2):143-150. doi:10.2143/AC.62.2.2020234

12. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013;368(21):2004-2013. doi:10.1056/NEJMra1216063

13. Mehta SR, Wood DA, Storey RF, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019;381(15):1411-1421. doi:10.1056/NEJMoa1907775

14. Gaba P, Gersh BJ, Muller J, Narula J, Stone GW. Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. Nat Rev Cardiol. 2023;20(3):181-196. doi:10.1038/s41569-022-00769-8

15. Gaba P, Christiansen EH, Nielsen PH, et al. Percutaneous Coronary Intervention vs Coronary Artery Bypass Graft Surgery for Left Main Disease in Patients With and Without Acute Coronary Syndromes: A Pooled Analysis of 4 Randomized Clinical Trials. JAMA Cardiol. 2023;8(7):631-639. doi:10.1001/jamacardio.2023.1177

16. Moussa ID, Mohananey D, Saucedo J, et al. Trends and Outcomes of Restenosis After Coronary Stent Implantation in the United States. J Am Coll Cardiol. 2020;76(13):1521-1531. doi:10.1016/j.jacc.2020.08.002

17. Kirov H, Caldonazo T, Rahouma M, et al. A systematic review and meta-analysis of percutaneous coronary intervention compared to coronary artery bypass grafting in non-ST-elevation acute coronary syndrome. Sci Rep. 2022;12(1):5138. doi:10.1038/s41598-022-09158-0

18. Xie Y, Mintz GS, Yang J, et al. Clinical outcome of nonculprit plaque ruptures in patients with acute coronary syndrome in the PROSPECT study. JACC Cardiovasc Imaging. 2014;7(4):397-405. doi:10.1016/j.jcmg.2013.10.010

19. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. JACC Cardiovasc Imaging. 2011;4(8):894-901. doi:10.1016/j.jcmg.2011.05.005

20. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023. doi:10.1161/CIR.0000000000001168

21. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165. doi:10.1093/eurheartj/ehy394

22. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(3):e18-e114. doi:10.1161/CIR.0000000000001038

23. Holm NR, Andreasen LN, Neghabat O, et al. OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions. N Engl J Med. 2023. doi:10.1056/NEJMoa2307770

24. Kang DY, Ahn JM, Yun SC, et al. Optical Coherence Tomography-Guided or Intravascular Ultrasound Guided Percutaneous Coronary Intervention: The OCTIVUS Randomized Clinical Trial. Circulation. 2023. doi:10.1161/circulationaha.123.066429

25. Kang DY, Ahn JM, Yun SC, et al. Guiding Intervention for Complex Coronary Lesions by Optical Coherence Tomography or Intravascular Ultrasound. J Am Coll Cardiol. 2023. doi:10.1016/j.jacc.2023.10.017

Supplemental material

Supplemental Table 1. Baseline Characteristics of Patients with or without Acute Coronary Syndrome According to Randomized Follow-Up Strategy.*

	ACS			No ACS		
Characteristic	**Functional Testing (n = 251)**	**Standard Care (n = 275)**	**P value**	**Functional Testing (n = 598)**	**Standard Care (n = 582)**	**P value**
Demographic						
Age, years	64.7 ± 11.4	64.1 ± 11.6	0.56	64.6 ± 9.8	65.1 ± 9.6	0.32
Male sex	194 (77.3)	226 (82.2)	0.19	472 (78.9)	464 (79.7)	0.79
Body-mass index†	24.4 ± 3.1	24.9 ± 3.2	0.09	25.0 ± 2.9	25.0 ± 3.2	0.74
Cardiac risk factors and comorbidities						
Hypertension	155 (61.8)	173 (62.9)	0.86	428 (71.6)	422 (72.5)	0.77
Current smoker	85 (33.9)	99 (36.0)	0.67	139 (23.2)	139 (23.9)	0.85
Dyslipidemia	202 (80.5)	233 (84.7)	0.24	532 (89.0)	520 (89.3)	0.91
History of MI	14 (5.6)	24 (8.7)	0.22	36 (6.0)	39 (6.7)	0.72
Previous PCI—no. (%)	40 (15.9)	55 (20.0)	0.27	147 (24.6)	133 (22.9)	0.53
Previous CABG—no. (%)	1 (0.4)	1 (1.8)	0.26	21 (3.5)	15 (2.6)	0.45
History of stroke	12 (4.8)	21 (7.6)	0.24	33 (5.5)	43 (7.4)	0.23
History of heart failure	3 (1.2)	12 (4.4)	0.06	10 (1.7)	15 (2.6)	0.38
Peripheral-artery disease—no. (%)	3 (1.2)	5 (1.8)	0.82	16 (2.7)	15 (2.6)	>0.99

Chronic lung disease	3 (1.2)	10 (3.6)	0.13	10 (1.7)	23 (4.0)	0.03
Atrial fibrillation or atrial flutter	5 (2.0)	9 (3.3)	0.52	15 (2.5)	14 (2.4)	>0.99
Left ventricular ejection fraction	55.3 ± 10.5	55.8 ± 11.1	0.61	60.4 ± 7.8	59.6 ± 9.4	0.16
Criteria for high risk after PCI‡						
High-risk anatomical characteristics						
Left main disease	40 (15.9)	49(17.8_	0.65	141 (23.6)	129 (22.2)	0.61
Bifurcation disease	68 (27.1)	80 (29.1)	0.68	284 (47.5)	270 (46.4)	0.75
Ostial lesion	20 (8.0)	29 (10.5)	0.39	108 (18.1)	98 (16.8)	0.63
Chronic total occlusion	10 (4.0)	31 (11.3)	0.003	91 (15.2)	96 (16.5)	0.60
Restenotic lesion	15 (6.0)	22 (8.0)	0.46	53 (8.9)	57 (9.8)	0.65
Diffuse long lesion§	106 (42.2)	128 (46.5)	0.37	385 (64.4)	383 (65.8)	0.65
Bypass graft disease	0 (0.0)	1 (0.4)	>0.99	2 (0.3)	1 (0.2)	>0.99
High-risk clinical characteristics						
Diabetes mellitus	97 (38.6)	98 (35.6)	0.53	224 (37.5)	241 (41.4)	0.18
Use of insulin	8 (3.2)	11 (4.0)	0.79	24 (4.0)	30 (5.2)	0.43
Chronic renal failure¶	12 (4.8)	16 (5.8)	0.74	30 (5.0)	29 (5.0)	>0.99
Receipt of dialysis	5 (2.0)	8 (2.9)	0.69	18 (3.0)	18 (3.1)	>0.99
Procedural characteristics						
Total no. of diseased lesions per patient	2.0 ± 1.1	2.1 ± 1.2	0.33	2.3 ± 1.2	2.3 ± 1.1	0.61
Total no. of treated lesions per patient	1.4 ± 0.7	1.5 ± 0.7	0.45	1.4 ± 0.7	1.5 ± 0.7	0.38
Total no. of stents per patient	1.7 ± 1.0	1.8 ± 1.1	0.54	2.0 ± 1.1	2.1 ± 1.2	0.30

Total stent length per patient, mm	48.5 ± 30.7	50.6 ± 30.2	0.42	59.3 ± 34.1	61.7 ± 35.4	0.26
Use of drug-eluting stents	242 (96.4)	269 (97.8)	0.48	582 (97.3)	552 (94.8)	0.04
Use of bioabsorbable scaffold	3 (1.2)	0 (0.0)	0.22	3 (0.5)	10 (1.7)	0.09
Use of drug-coated balloon	11 (4.4)	14 (5.1)	0.86	35 (5.9)	45 (7.7)	0.24
Intravascular ultrasound guidance	157 (62.5)	196 (71.3)	0.04	465 (77.8)	451 (77.5)	0.97
Fractional flow reserve assessed	37 (14.7)	49 (17.8)	0.40	268 (44.8)	255 (43.8)	0.77

* Values are means ± SD or n (%) unless otherwise indicated. Percentages may not total 100 because of rounding.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡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.

§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.

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Supplemental Table 2. Cardiac-Related Medications in Patients with or without Acute Coronary Syndrome According to Randomized Follow-Up Strategy.*

	ACS			Non-ACS		
Medications	**Functional Testing (n = 251)**	**Standard Care (n = 275)**	**P value**	**Functional Testing (n = 598)**	**Standard Care (n = 582)**	**P value**
At hospital discharge—no. (%)	n = 251	n = 275		n = 598	n = 582	
Aspirin	247 (98.4)	267 (97.1)	0.47	590 (98.7)	577 (99.1)	0.61
P2Y12 inhibitors	248 (98.8)	269 (97.8)	0.59	592 (99.0)	579 (99.5)	0.53
Oral anticoagulants†	6 (2.4)	10 (3.6)	0.56	22 (3.7)	12 (2.1)	0.14
Beta-blockers	177 (70.5)	203 (73.8)	0.46	405 (67.7)	371 (63.7)	0.17
ACE inhibitor or ARB	128 (51.0)	135 (49.1)	0.73	184 (30.8)	202 (34.7)	0.17
Calcium-channel blockers	108 (43.0)	98 (35.6)	0.10	431 (72.1)	448 (77.0)	0.06
Statins	244 (97.2)	267 (97.1)	>0.99	585 (97.8)	574 (98.6)	0.41
6 months after randomization—no. (%)	n = 242	n = 266		n = 592	n = 573	
Aspirin	221 (91.3)	239 (89.8)	0.68	505 (85.3)	481 (83.9)	0.57
P2Y12 inhibitors	227 (93.8)	252 (94.7)	0.79	563 (95.1)	538 (93.9)	0.44
Oral anticoagulants†	9 (3.7)	6 (2.3)	0.48	20 (3.4)	18 (3.1)	0.95
Beta-blockers	175 (72.3)	196 (73.7)	0.81	384 (64.9)	362 (63.2)	0.59
ACE inhibitor or ARB	112 (46.3)	133 (50.0)	0.45	186 (31.4)	199 (34.7)	0.26

Calcium-channel blockers	108 (44.6)	95 (35.7)	0.05	366 (61.8)	376 (65.6)	0.20
Statins	233 (96.3)	256 (96.2)	>0.99	574 (97.0)	560 (97.7)	0.53
12 months after randomization—no. (%)	n = 242	n = 264		n = 583	n = 565	
Aspirin	186 (76.9)	204 (77.3)	0.99	355 (60.9)	341 (60.4)	0.90
P2Y12 inhibitors	185 (76.4)	213 (80.7)	0.29	505 (86.6)	489 (86.5)	>0.99
Oral anticoagulants†	9 (3.7)	6 (2.3)	0.49	23 (3.9)	20 (3.5)	0.84
Beta-blockers	168 (69.4)	192 (72.7)	0.47	378 (64.8)	359 (63.5)	0.69
ACE inhibitor or ARB	108 (44.6)	134 (50.8)	0.20	192 (32.9)	203 (35.9)	0.31
Calcium-channel blockers	106 (43.8)	93 (35.2)	0.06	364 (62.4)	356 (63.0)	0.89
Statins	233 (96.3)	250 (94.7)	0.52	567 (97.3)	553 (97.9)	0.62
18 months after randomization—no. (%)	n = 238	n = 262		n = 575	n = 553	
Aspirin	155 (65.1)	183 (69.8)	0.30	326 (56.7)	281 (50.8)	0.06
P2Y12 inhibitors	157 (66.0)	186 (71.0)	0.27	453 (78.8)	449 (81.2)	0.35
Oral anticoagulants†	8 (3.4)	10 (3.8)	0.97	27 (4.7)	24 (4.3)	0.89
Beta-blockers	163 (68.5)	185 (70.6)	0.68	365 (63.5)	357 (64.6)	0.75
ACE inhibitor or ARB	105 (44.1)	129 (49.2)	0.29	205 (35.7)	204 (36.9)	0.71
Calcium-channel blockers	101 (42.4)	95 (36.3)	0.19	361 (62.8)	346 (62.6)	0.99
Statins	229 (96.2)	255 (97.3)	0.65	571 (99.3)	548 (99.1)	0.95
24 months after randomization—no. (%)	n = 238	n = 260		n = 574	n = 550	
Aspirin	151 (63.4)	176 (67.7)	0.37	319 (55.6)	276 (50.2)	0.08
P2Y12 inhibitors	155 (65.1)	185 (71.2)	0.18	453 (78.9)	449 (81.6)	0.28

Oral anticoagulants†	7 (2.9)	11 (4.2)	0.60	27 (4.7)	23 (4.2)	0.78
Beta-blockers	166 (69.7)	186 (71.5)	0.73	365 (63.6)	353 (64.2)	0.88
ACE inhibitor or ARB	108 (45.4)	129 (49.6)	0.39	201 (35.0)	203 (36.9)	0.55
Calcium-channel blockers	96 (40.3)	94 (36.2)	0.39	360 (62.7)	343 (62.4)	0.95
Statins	231 (97.1)	255 (98.1)	0.65	570 (99.3)	546 (99.3)	>0.99

*Percentages are from the intention-to-treat analysis. At each time point during follow-up, a window period (± 2 months) was allowed.

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

†Oral anticoagulants were vitamin K antagonists or non–vitamin K antagonist oral anticoagulants.

Supplemental Table 3. Landmark Analyses for Clinical Outcomes Occurring within the First 1 Year and Between 1 Year and 2 Years in Patients with or without Acute Coronary Syndrome According to Randomized Follow-Up Strategy.*

	ACS				Non-ACS				
	Functional Testing (n = 251)	Standard Care (n = 275)			Functional Testing (n = 598)	Standard Care (n = 582)			
Outcome	Events (estimated percentage)		HR (95% CI)	P	Events (estimated percentage)		HR (95% CI)	P	P-for-interaction†
From Randomization to 1 Year									
Primary composite endpoint‡	9 (3.7)	19 (6.9)	0.52 (0.23-1.14)	0.10	16 (2.7)	15 (2.6)	1.03 (0.51-2.08)	0.94	0.20
Death from any cause	3 (1.2)	9 (3.3)	0.36 (0.10-1.36)	0.13	9 (1.5)	9 (1.6)	0.97 (0.38-2.43)	0.94	0.24
Myocardial infarction	2 (0.8)	3 (1.1)	0.78 (0.13-4.95)	0.80	0 (0)	2 (0.4)	0.19 (0.01-6.03)	0.35	0.48
Hospitalization for unstable angina	4 (1.7)	8 (2.9)	0.55 (0.16-1.81)	0.32	7 (1.2)	4 (0.7)	1.69 (0.49-5.78)	0.40	0.20
Secondary endpoints									
Death or myocardial infarction	5 (2.0)	12 (4.4)	0.46 (0.16-1.30)	0.14	9 (1.5)	11 (1.9)	0.79 (0.33-1.90)	0.60	0.44
Hospitalization									
Any reason	41 (16.9)	48 (17.9)	0.93 (0.61-1.41)	0.72	66 (11.1)	68 (11.9)	0.94 (0.67-1.32)	0.71	0.96
Cardiac reason	24 (9.9)	29 (10.9)	0.90 (0.53-1.55)	0.71	27 (4.68)	34 (5.9)	0.76 (0.46-1.26)	0.29	0.65
Noncardiac reason	17 (7.0)	19 (7.1)	0.98 (0.51-1.88)	0.95	39 (6.6)	34 (5.9)	1.12 (0.71-1.77)	0.64	0.75
Invasive coronary angiography	16 (6.3)	24 (8.7)	0.83 (0.42-1.65)	0.60	21 (3.5)	28 (4.8)	0.86 (0.48-1.53)	0.61	0.82

Showing restenosis or obstructive CAD	9 (56.2)	13 (54.1)	0.92 (0.38-2.21)	0.85	13 (61.9)	19 (67.9)	0.97(0.47-1.99)	0.93	0.74
Showing no restenosis or obstructive CAD	7(43.7)	11(45.8)	0.72 (0.24-2.15)	0.56	8 (38.1)	9 (32.1)	0.69 (0.26-1.82)	0.45	0.95
Repeat revascularization	11 (4.6)	12 (4.5)	1.00 (0.44-2.27)	0.99	9 (1.5)	17 (2.9)	0.51 (0.23-1.14)	0.10	0.25
Target-lesion revascularization	5 (2.1)	5 (1.9)	1.09 (0.32-3.78)	0.88	6 (1.0)	9 (1.6)	0.64 (0.23-1.80)	0.40	0.52
Nontarget-lesion revascularization	6 (2.5)	7 (2.6)	0.94 (0.32-2.81)	0.91	3 (0.5)	8 (1.4)	0.36 (0.10-1.36)	0.13	0.27
PCI	11 (100.0)	12 (100.0)	1.01 (0.44-2.31)	0.99	9 (100.0)	15(88.2)	0.98 (0.42-2.28)	0.98	0.98
CABG	0 (0.0)	0 (0.0)	-	-	0 (0.0)	2 (11.8)	-	-	-
From 1 Year to 2 Years									
Primary composite endpoint‡	7 (3.0)	4 (1.6)	0.91 (0.56-6.52)	0.30	14 (2.4)	13 (2.4)	1.04 (0.49-2.20)	0.93	0.41
Death from any cause	5 (2.1)	2 (0.8)	2.76 (0.54-14.2)	0.22	6 (1.0)	8 (1.4)	0.72 (0.25-2.07)	0.54	0.18
Myocardial infarction	0 (0)	2 (0.8)	0.22 (0.01-6.86)	0.39	2 (0.3)	3 (0.5)	0.68 (0.11-4.29)	0.68	0.57
Hospitalization for unstable angina §	2 (0.8)	0 (0)	5.49(0.20-152.6)	0.32	6 (1.1)	2 (0.4)	2.51 (0.51-12.4)	0.26	0.68
Secondary endpoints									
Death or myocardial infarction	5 (2.1)	4 (1.6)	1.37 (0.37-5.11)	0.64	8 (1.4)	11 (2.0)	0.69 (0.28-1.73)	0.43	0.40
Hospitalization									
Any reason	28 (11.1)	18 (6.5)	1.71 (0.95-3.09)	0.07	76 (14.6)	56 (11.3)	1.34 (0.95-1.89)	0.10	0.48
Cardiac reason	20 (9.3)	14 (5.9)	1.56 (0.79-3.09)	0.20	51 (9.2)	33 (6.3)	1.48 (0.96-2.29)	0.08	0.89
Noncardiac reason	8 (3.6)	4 (1.6)	2.21 (0.67-7.36)	0.19	25 (4.6)	23 (4.4)	1.07 (0.61-1.88)	0.82	0.28
Invasive coronary angiography	13 (5.2)	8 (2.9)	1.76 (0.73-4.24)	0.21	51 (8.5)	17 (2.9)	2.92 (1.69-5.06)	<0.001	0.33
Showing restenosis or obstructive CAD	8 (61.5)	6 (75.0)	1.43 (0.49-4.14)	0.50	39 (76.4)	8 (47.0)	4.74 (2.21-10.1)	<0.001	0.53
Showing no restenosis or obstructive CAD	5 (38.5)	2 (25.0)	2.72 (0.07-1.90)	0.23	12 (23.5)	9 (52.9)	1.30 (0.55-3.09)	0.55	0.44

Repeat revascularization	11 (4.9)	7 (2.8)	1.74 (0.68-4.50)	0.25	35 (6.1)	12 (2.2)	2.82 (1.46-5.43)	0.002	0.41
Target-lesion revascularization	6 (2.6)	2 (0.8)	3.34 (0.68-16.5)	0.14	17 (2.9)	10 (1.8)	1.63 (0.75-3.57)	0.22	0.43
Nontarget-lesion revascularization	5 (2.0)	5 (2.0)	1.10 (0.32-3.79)	0.88	18 (3.1)	2 (0.4)	8.65 (2.01-37.3)	0.004	0.04
PCI	9 (81.8)	7 (100)	1.43 (0.53-3.83)	0.48	35 (100.0)	11 (91.6)	3.07 (1.56-6.05)	0.001	0.64
CABG	2 (18.2)	0 (0.0)	-	-	0 (0.0)	1 (8.4))	-	-	-

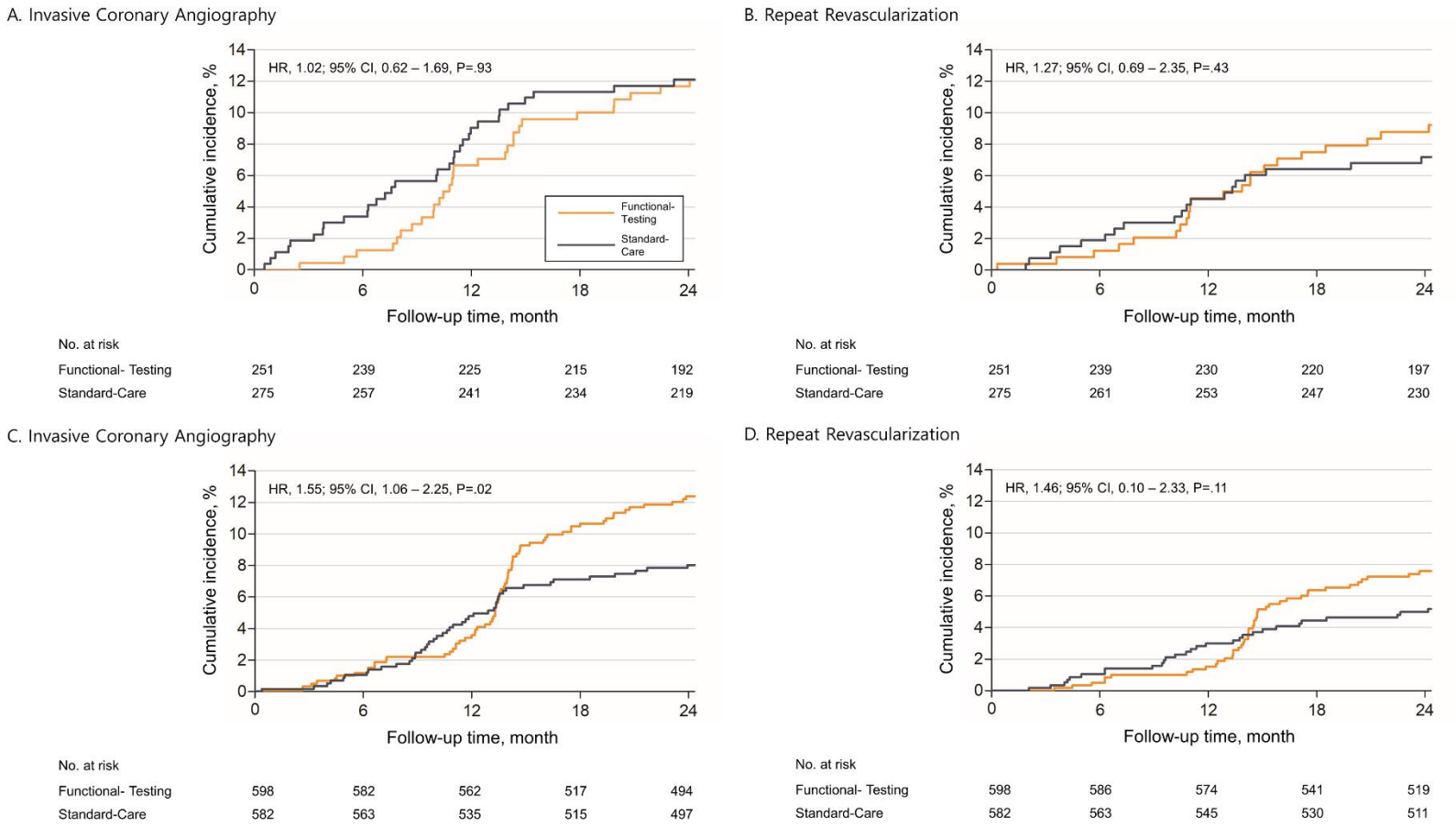
* Event rates (%) are shown as the incidences estimated with the use of a Kaplan–Meier survival analysis of data from the intention-to-treat population; therefore, the percentages may not reflect the ratio of the numerator and the denominator. Hazard ratios are for the routine functional-testing follow-up strategy as compared with the standard-care follow-up strategy. The 95% confidence intervals for secondary endpoints have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.

ACS, acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

†P-value for interaction between the diabetes status (diabetes vs. non-diabetes) and the randomization group (functional testing vs. standard care).

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

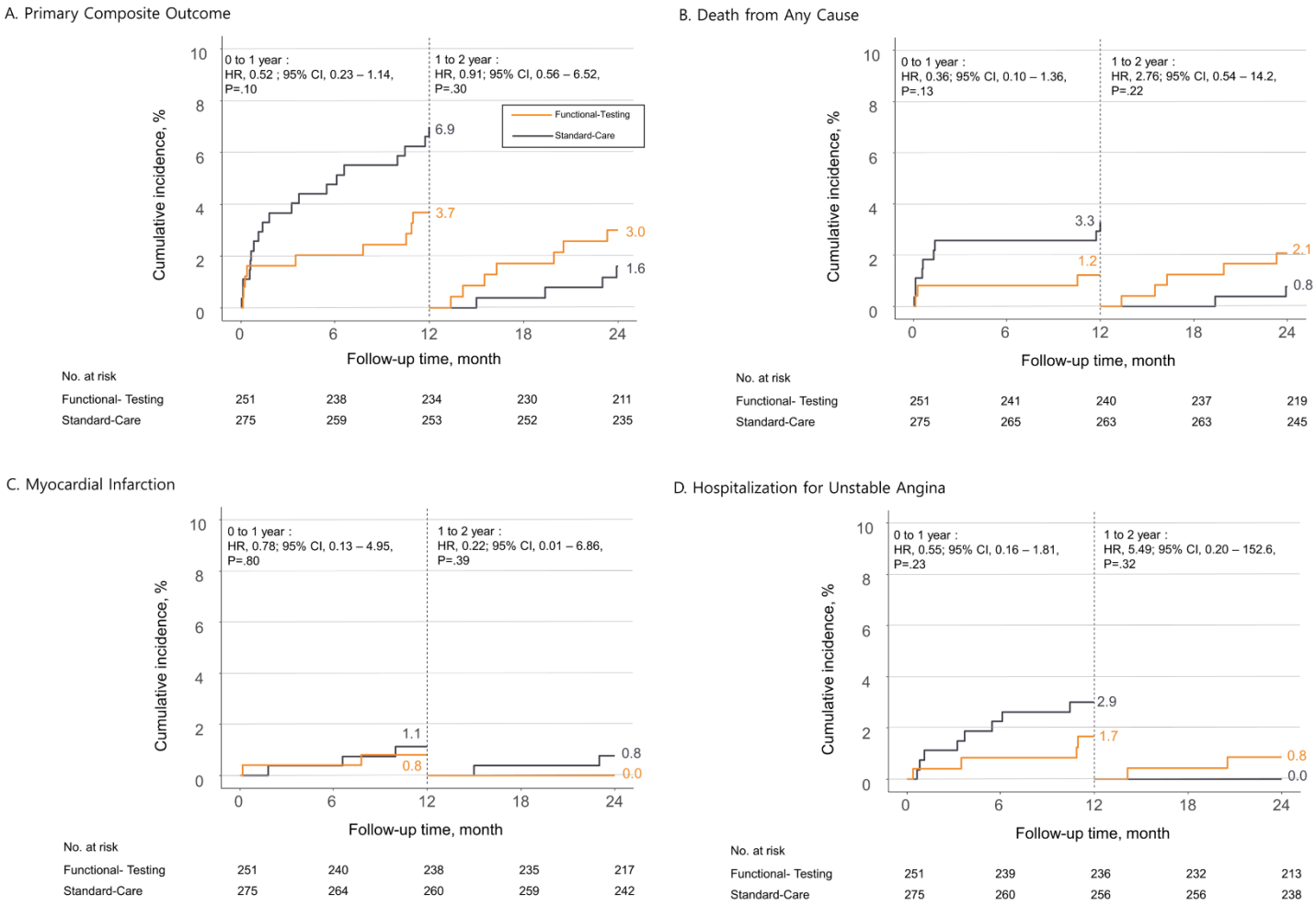
Supplemental Figure 1. Percentage of Patients Who Underwent Invasive Coronary Angiography and Coronary Revascularization During Follow-Up in Patients with or without Acute Coronary Syndrome



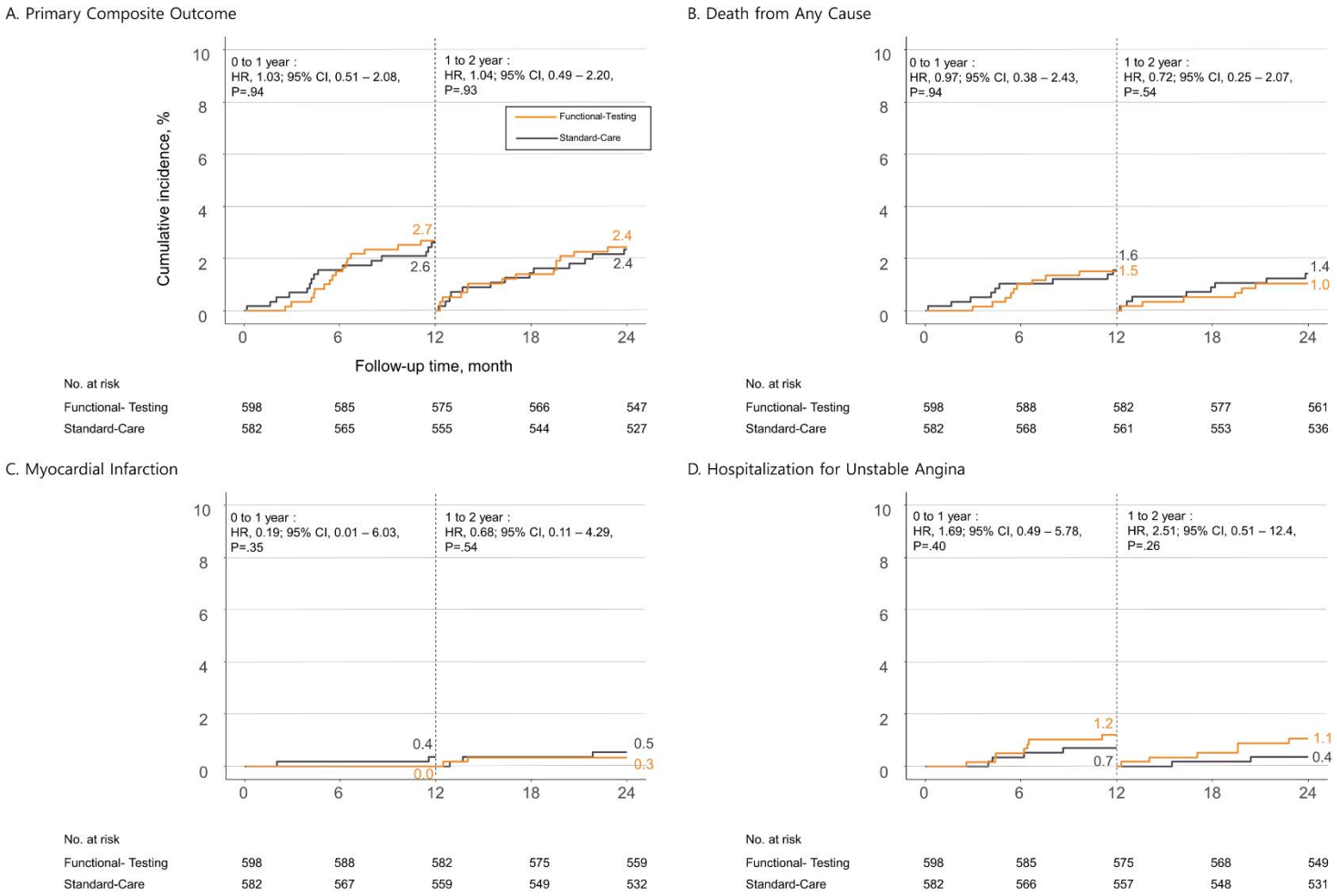
A. Invasive coronary angiography in ACS group; B. Repeat revascularization in ACS group;

C. Invasive coronary angiography in non-ACS group; D. Repeat revascularization in non-ACS group

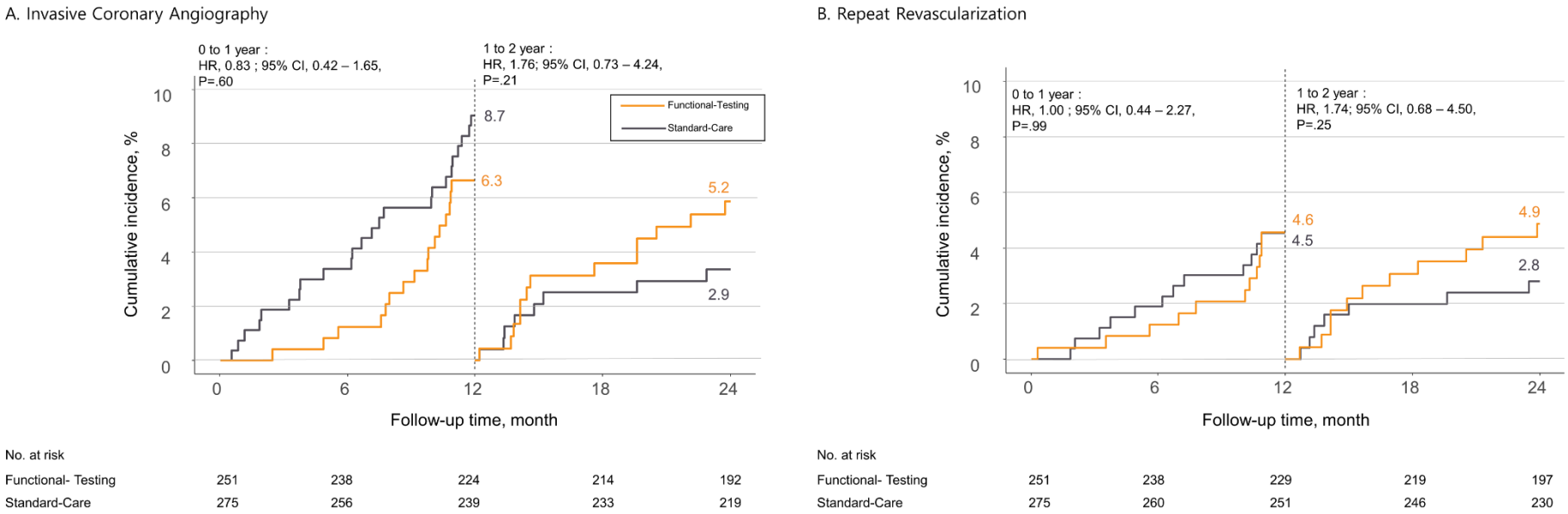
Supplemental Figure 2. Landmark Analysis for the Primary Composite Endpoint and Its Components in Patients with Acute Coronary Syndrome.



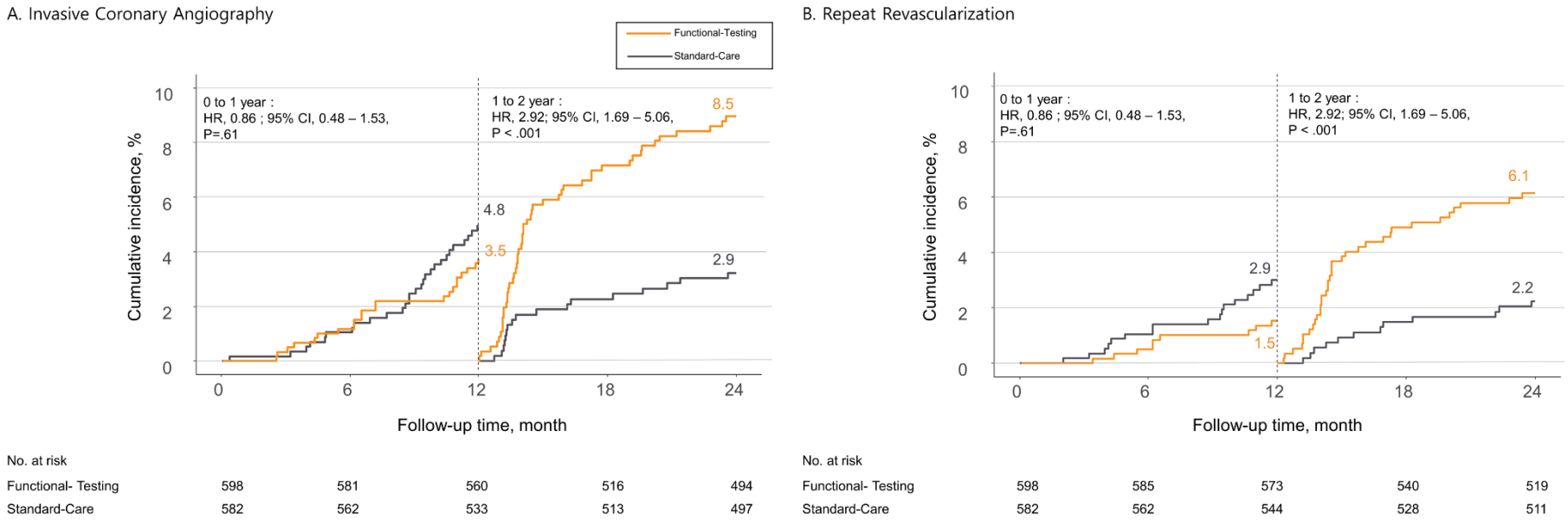
Supplemental Figure 3. Landmark Analysis for the Primary Composite Endpoint and Its Components in Patients without Acute Coronary Syndrome.



Supplemental Figure 4. Landmark Analysis for Invasive Coronary Angiography and Coronary Revascularization in Patients with Acute Coronary Syndrome.



Supplemental Figure 5. Landmark Analysis for Invasive Coronary Angiography and Coronary Revascularization in Patients without Acute Coronary Syndrome.



국문요약

연구 배경: 급성 관상동맥 증후군으로 경피적 관상동맥 중재술을 받은 환자에서 적절한 추적 관찰 전략은 아직 확립되지 않았다.

목적: 급성 관상동맥 증후군의 유무에 따라 관상동맥 중재술을 받은 환자들에서 정기적 심장부하 검사 와 일반 치료에 대해 임상 경과를 평가한다.

방법: POST-PCI (관상동맥 중재술을 시행한 고 위험 환자에서 정기적인 심장 부하 검사와 증상에 우선한 심장부하 검사의 비교) 연구에서 관상동맥 중재술을 시행한 환자에서 정기적인 심장 부하 검사와 일반 치료를 받은 환자를 비교하였다. 이 환자군들을 급성 관상동맥 증후군이 있었던 환자와 아닌 환자로 군을 나누고, 시술 2 년 이후에 모든 원인에 기인한 사망, 심근경색, 불안정 협심증으로 인한 재입원 등의 임상 경과를 일차 평가 지수로 놓고 평가하였다. 환자군들은 2017 년부터 2019 년까지 한국의 11 개의 기관에서 총 1706 명의 환자들이 등록되었다.

결과: 총 1706 명의 환자들을 분석하였고, 정기적인 심장 부하 검사를 받은 환자는 859 명, 일반 치료를 받은 환자군은 857 명 이었고 그 중 526 명 (31%) 가 급성 관상동맥 환자군에 해당하였다. 급성 관상동맥 증후군이었던 환자군은 아닌 환자군들에 비해 기저질환, 관상동맥의 해부학적 복잡성, 시술 복잡성들이 더 낮았다. 그러나 관상동맥 증후군 환자들이 일차 평가 지수는 관상동맥 증후군이 아닌 환자에 비해 55% 높을 위험성을 가지는 것을 확인하였다. 급성 관상동맥 증후군 환자에서 정기적인 심장 부하 검사와 일반 치료를 비교하였을 때 2 년 이후의 일차 평가 지수는 비슷하였고 (6.6% 대 8.7%) 급성 관상동맥 증후군이 아닌 환자에서도 비슷하였다. (5.1% 대 4.9%). 1 년 이후의 관상동맥 조영술 및

재관류 빈도는 급성 관상동맥의 유무와 관계없이 정기적인 심장 부하 검사를 시행한 군에서 더 높았다.

결론: 급성 관상동맥 증후군 환자들이 임상 경과가 더 안좋음에도 불구하고, 정기적인 심장 부하 검사는 일반 치료와 비교하였을 때 추가적인 이들을 보이지 않았다.