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**CLINICAL RESEARCH**
*Clinical trials*

# Routine stress testing in diabetic patients after percutaneous coronary intervention: the POST-PCI trial

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## Abstract

**Background and Aims** The optimal follow-up surveillance strategy for high-risk diabetic patients with had undergone percutaneous coronary intervention (PCI) remains unknown.

**Methods** 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 comparing a follow-up strategy of routine functional testing at 1 year vs. standard care alone after high-risk PCI. Randomization was stratified according to diabetes status. The primary outcome was a composite of death from any cause, myocardial infarction, or hospitalization for unstable angina at 2 years.

**Results** Among 1706 randomized patients, participants with diabetes ($n = 660$, 38.7%) had more frequent comorbidities and a higher prevalence of complex anatomical or procedural characteristics than those without diabetes ($n = 1046$, 61.3%). Patients with diabetes had a 52% greater risk of primary composite events [hazard ratio (HR) 1.52; 95% confidence interval (CI) 1.02–2.27; $P = .039$]. The 2-year incidences of the primary composite outcome were similar between strategies of routine functional testing or standard care alone in diabetic patients (7.1% vs. 7.5%; HR 0.94; 95% CI 0.53–1.66; $P = .82$) and non-diabetic patients (4.6% vs. 5.1%; HR 0.89; 95% CI 0.51–1.55; $P = .68$) (interaction term for diabetes: $P = .91$). The incidences of invasive coronary angiography and repeat revascularization after 1 year were higher in the routine functional-testing group than the standard-care group irrespective of diabetes status.

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

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## Structured Graphical Abstract

**Key Question**

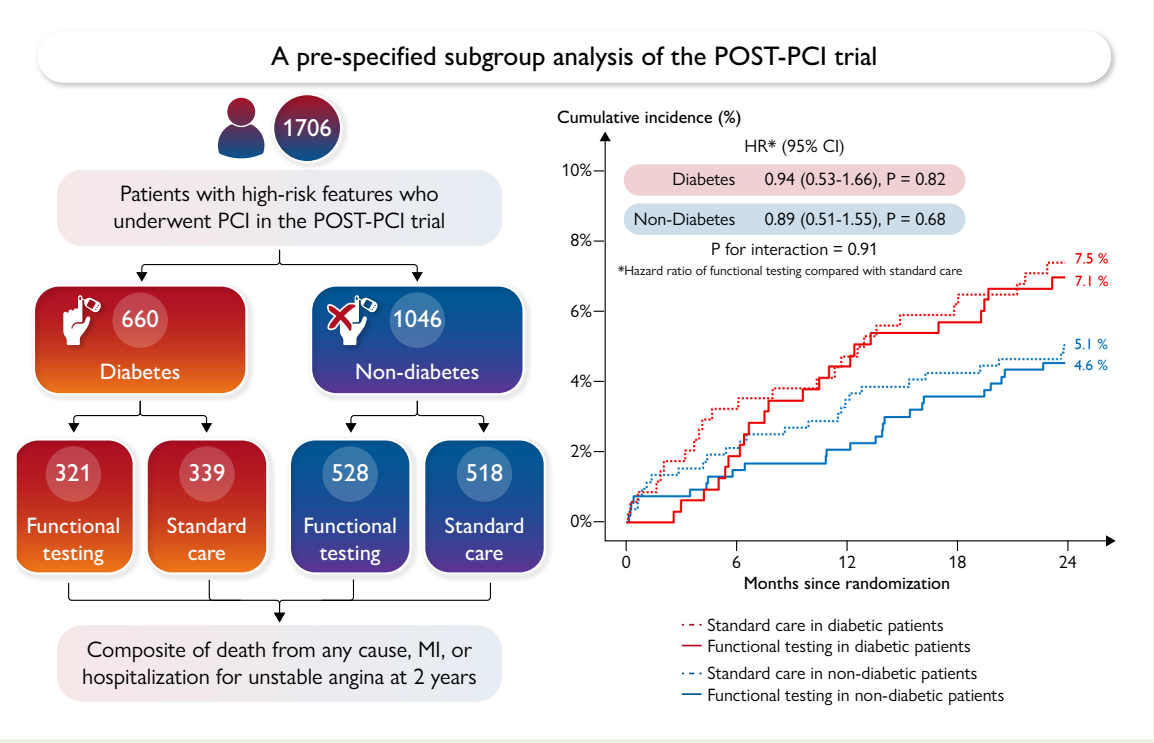
What is the optimal surveillance strategy for high-risk patients with diabetes after percutaneous coronary intervention (PCI)?

**Key Finding**

Diabetic patients had worse cardiovascular outcomes than non-diabetic patients after PCI. In both diabetic and non-diabetic patients, routine surveillance functional-testing at 1-year post-PCI, did not reduce major ischaemic cardiovascular events or mortality at 2 years as compared with standard care alone.

**Take Home Message**

In the absence of clinical signs or symptoms suggestive of stent failure or disease progression, routine surveillance stress testing after PCI should not be recommended among diabetic patients.




Study flow diagram of patients stratified by the presence of diabetes and Kaplan–Meier curves of the cumulative incidence of the primary composite outcome of death from any cause, myocardial infarction, or hospitalization for unstable angina according to diabetes status and randomization group. PCI, percutaneous coronary intervention; POST-PCI, Pragmatic Trial Comparing Symptom-Oriented versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.

**Keywords** Diabetes mellitus • Percutaneous coronary intervention • Functional stress test • Cardiovascular event

# Introduction

Diabetes is a common comorbidity among patients with chronic or acute coronary syndrome, and patients with diabetes have a more aggressive form of atherosclerosis and more extensive coronary artery disease (CAD).[1,2] In addition, diabetes is a major determinant of adverse clinical events after myocardial revascularization.[3,4] In daily clinical practice, patients with diabetes frequently undergo percutaneous coronary intervention (PCI), with these procedures often being more complex and anatomically challenging.[5] Because patients with diabetes are at higher risk of ischaemic cardiovascular events and mortality than those without diabetes, secondary prevention strategies after PCI, including guideline-directed medical therapy, comprehensive lifestyle changes, and attainment of multiple, specific risk factor goals, are strongly recommended.[6–8] Nevertheless, determining the optimal surveillance strategies after complex PCI in patients with diabetes has been difficult due to the lack of available clinical evidence. Although cardiac stress testing to determine the presence, location, and extent of ischaemia has been recommended in symptomatic patients who had prior coronary revascularization, a specific follow-up surveillance strategy remains uncertain in high-risk asymptomatic patients with diabetes who underwent PCI.[6,9,10]

Given that advanced CAD, complex procedures, and residual ischaemia are common in patients with diabetes who undergo PCI, it should be specifically determined whether diabetic patients who had undergone high-risk PCI could benefit from routine surveillance testing during follow-up, leading to a reduction of adverse cardiovascular events. To address this knowledge gap, we used 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 evaluation strategies in high-risk patients who had undergone PCI.[11,12] Acknowledging the importance of diabetes, randomization was stratified by the presence of this variable to ensure a balanced baseline in the diabetic and non-diabetic strata in POST-PCI. In the present study, differences in follow-up strategies, major cardiovascular outcomes, and mortality were compared in patients with and without diabetes. Most importantly, we assessed whether the risk of cardiovascular outcomes in patients with and without diabetes differed in patients who underwent routine functional testing and those who received standard care alone.

# Methods

## Study design and patient population

The trial design, methods, and primary results of the POST-PCI trial have been previously reported.[11,12] In brief, the POST-PCI trial was an investigator-initiated, multicentre, pragmatic randomized trial conducted at 11 hospitals in South Korea from November 2017 to September 2019. In POST-PCI, a total of 1706 patients with high-risk anatomical or clinical features who had undergone PCI were randomly assigned, in a 1:1 ratio, to undergo an active follow-up strategy of routine functional testing at 1 year after PCI ($n = 849$) or to undergo a conservative follow-up strategy of standard care ($n = 857$), with stress testing only performed when clinically indicated. The trial was approved by the investigational review board or ethics committee at each participating centre. All patients provided written informed consent before enrollment. The trial has been registered at www.clinicaltrials.gov as NCT03217877.

Enrolled patients had to have at least one high-risk anatomical or clinical characteristic associated with an increased risk of ischaemic or thrombotic events; (i) anatomical high-risk characteristics included left main disease, bifurcation disease, an ostial lesion, chronic total occlusion, multivessel CAD (requiring stenting of at least two vessels), a restenotic lesion, a long diffuse lesion, and bypass graft disease, and (ii) clinical high-risk characteristics included medically treated diabetes mellitus, chronic renal failure, and enzyme-positive acute coronary syndrome. All patients underwent successful PCI with contemporary drug-eluting stents, bioresorbable scaffolds, or drug-coated balloons (only for in-stent restenosis).

Randomization was stratified according to the presence of diabetes and participating site. In the POST-PCI trial, the presence of diabetes was based on patient- and site-identified medical history of diabetes or use of antihyperglycaemic medications (oral hypoglycaemic agents or insulin). Patients with diabetes at baseline were categorized according to the use or non-use of insulin.

## Trial procedures and follow-up

Detailed trial procedures and follow-up strategies have been described previously.[11,12] Patients randomized to undergo routine functional testing were subjected to cardiac stress testing, consisting of exercise electrocardiography (ECG), nuclear stress testing, or stress echocardiography, at 12 months after randomization. Simple exercise ECG testing as the sole diagnostic tool for assessing myocardial ischaemia was discouraged owing to the relatively high probability of false positive results that indicate ischaemia during exercise; subjects were therefore evaluated by combined non-invasive imaging.[12] 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 timely availability of results for patient management. All clinical decisions regarding further diagnostic or therapeutic procedures and subsequent management were made at the treating physician's discretion at each participating centre.

Patients underwent routine clinical follow-up at 6, 12, 18, and 24 months after randomization. Guideline-directed medical therapy and management of risk factors for intensive secondary prevention according to contemporary clinical guidelines were highly recommended during follow-up. Information on clinical symptoms such as angina class, any adverse clinical events, and cardiovascular medications were collected at each study visit. Vital status was reconfirmed by checking the national death registry of the Korean National Health Insurance Service database.[13]

## Study outcomes and definitions

The primary outcome of the POST-PCI trial was a composite of major cardiovascular events, consisting of death from any cause, myocardial infarction (MI), or hospitalization for unstable angina at 2 years after randomization. The secondary outcomes included the individual components of the primary composite outcome; a composite of death or MI; any hospitalization for cardiac or non-cardiac causes; invasive coronary angiography; and repeat revascularization procedures. All components of clinical outcomes were independently adjudicated by a clinical events committee, the members of which were unaware of the treatment assignments.[11]

Standard definitions were used for the assessment of clinical outcomes.[14] Myocardial infarction was defined as spontaneous or procedural. Procedural MI related to repeat revascularization procedures was defined as an elevation of cardiac troponin concentration > 5 times after PCI or >10 times the 99th percentile upper reference limit (URL) after coronary artery bypass grafting (CABG) within 48 h after the procedure in patients with normal baseline values or a >20% increase in cardiac troponin concentration in patients with elevated baseline values. 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 imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Hospitalization for unstable angina was defined as an event in which the final diagnosis was myocardial ischaemia and either of the following criteria was present: ischaemic discomfort or equivalent symptoms requiring hospitalization within 48 h of symptoms and lasting at least 10 min at rest, or ischaemic discomfort or equivalent symptoms occurring in an accelerated pattern within 48 h of hospitalization. In addition, at least one of the following criteria was required: dynamic ST-segment depression, ischaemia on stress testing, or significant epicardial coronary artery stenosis.[15] Angiographic restenosis was defined as a ≥50% stenosis of a stented target lesion, as determined by invasive coronary angiography. Obstructive CAD was defined as a new presence of ≥50% stenosis of any major epicardial vessel.[15] Repeat revascularization procedures may be either a PCI or a CABG, with target-lesion revascularization defined as repeat revascularization of the lesion treated during the index procedure.[11]

## Statistical analyses

Subgroup analysis according to diabetes status with formal interaction testing was pre-specified in the trial protocol. Baseline characteristics and procedural data were compared between groups using the Student's *t*-test for continuous variables and $\chi^2$ or Fisher's exact test for categorical variables. Outcomes of patients randomized to two groups were evaluated and stratified by the presence of diabetes according to the intention-to-treat principle based on time-to-first-event analyses. The cumulative incidences of primary and secondary outcomes in patients with and without diabetes, and by diabetes and follow-up strategy, were plotted by the Kaplan–Meier method and compared by log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional-hazards models. The proportional-hazards assumption regarding the treatment assignments was confirmed using Schoenfeld residuals tests.[16] Although the proportional-hazards assumption was met for most of the primary and key secondary outcomes, this assumption was not met for invasive coronary angiography and repeat revascularization ($P < .05$ by the Schoenfeld residuals test). Therefore, pre-specified landmarks were analysed at 1-year intervals, corresponding to the planned period of routine functional testing, during which proportional hazards were preserved.[11] The interaction terms for randomized groups and diabetic status for

primary and secondary outcomes were evaluated using formal interaction testing. In addition, as a sensitivity analysis, an Andersen–Gill intensity-model analysis using a robust variance estimate was performed to account for repeated clinical events among all components of the primary endpoint for the overall period.[17] All reported *P*-values were two-sided and were not adjusted for multiple testing. All statistical analyses were performed using SAS software (version 9.4) and R software (version 3.6.1).

# Results

## Study population and baseline characteristics

Of the 1706 patients enrolled in the POST-PCI trial, 660 (38.7%) had diabetes, in whom 73 (11.1%) were treated with insulin. Of the 660 patients with diabetes, 321 (48.6%) were randomized to the routine functional-testing group and 339 (51.4%) to the standard-care group. Of the 1046 patients without diabetes, 528 (50.5%) were randomized to the functional-testing group and 518 (49.5%) to the standard-care group (*Figure 1*).

The baseline characteristics of patients with and without diabetes are shown in *Table 1*. Compared with patients without diabetes, patients with diabetes were older; were more likely to be female; were more likely to have histories of hypertension, previous PCI, cerebrovascular disease, atrial fibrillation, multivessel CAD, and chronic renal failure; and had a higher number of diseased lesions. In contrast, patients with diabetes were less likely to have bifurcation and chronic total occlusion lesions, and were less likely to use bioabsorbable scaffolds. Because randomization of follow-up strategy was stratified according to the presence or absence of diabetes, most of the baseline characteristics, including

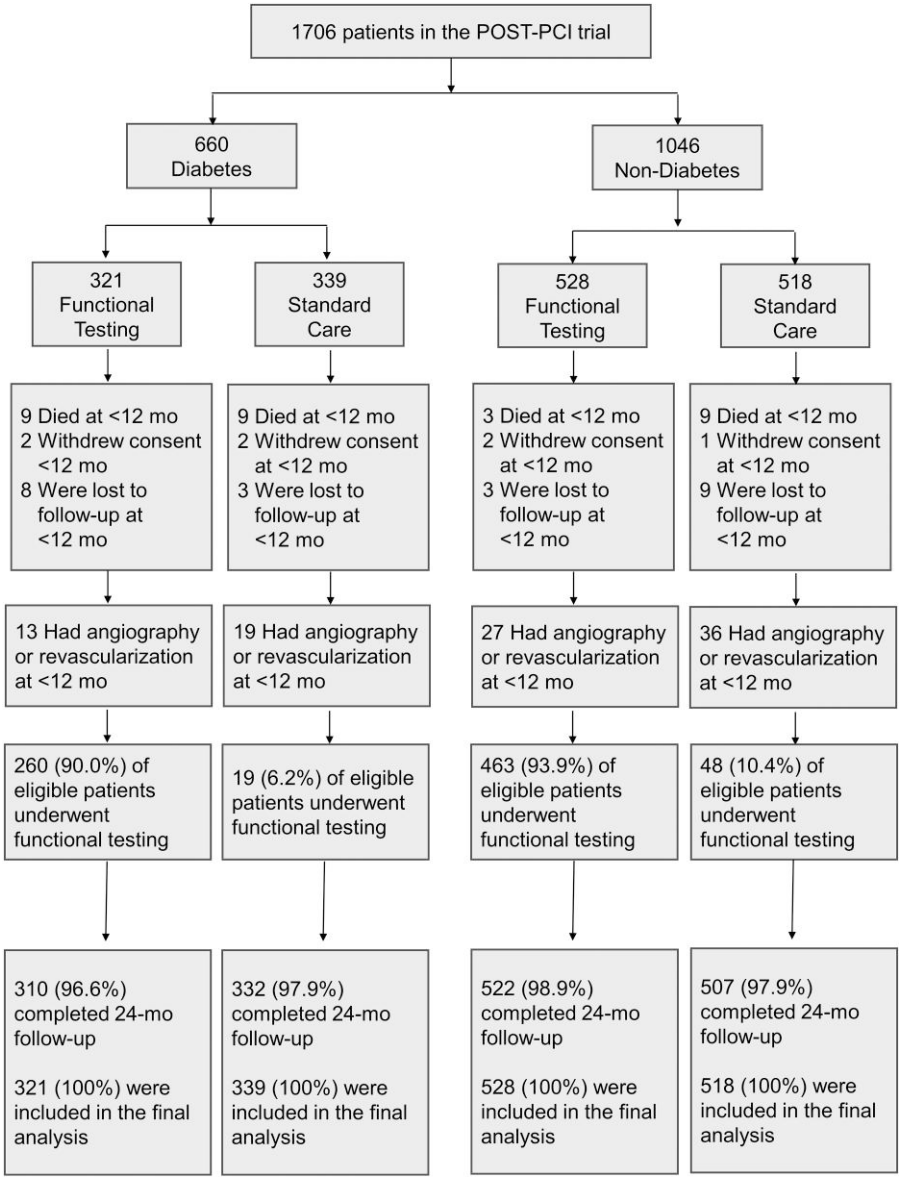



**Figure 1** Study flow diagram. Study flow diagram of patients stratified by the presence of diabetes. Patients who were eligible to undergo functional testing at 12 months after randomization included those who had not died, had not withdrawn, had not undergone clinically driven angiography or revascularization, and were not lost to follow-up. Percentages may not total 100 because of rounding. PCI, percutaneous coronary intervention

**Table 1 Baseline characteristics of patients with and without diabetes[a]**

| Characteristic | Overall (*n* = 1706) | Diabetes (*n* = 660) | Non-diabetes (*n* = 1046) | *P*-value |
|---|---|---|---|---|
| Randomized group | | | | .459 |
| Functional testing | 849 (49.77) | 321 (48.64) | 528 (50.48) | |
| Standard care | 857 (50.23) | 339 (51.36) | 518 (49.52) | |
| Age—yr, mean ± SD | 64.69 ± 10.28 | 66.43 ± 9.53 | 63.59 ± 10.59 | <.001 |
| Male sex—no. (%) | 1356 (79.48) | 505 (76.52) | 851 (81.36) | .016 |
| Body mass index—kg/m$^2$, mean ± SD | 24.91 ± 3.09 | 24.96 ± 3.18 | 24.88 ± 3.03 | .584 |
| Cardiac risk factors and comorbidities[b] | | | | |
| Hypertension—no. (%) | 1178 (69.05) | 513 (77.73) | 665 (63.58) | <.001 |
| Dyslipidaemia—no. (%) | 1487 (87.16) | 584 (88.48) | 903 (86.33) | .195 |
| Current smoker—no. (%) | 462 (27.08) | 174 (26.36) | 288 (27.53) | .596 |
| Family history of premature CAD—no. (%)[c] | 102 (5.98) | 36 (5.45) | 66 (6.31) | .468 |
| Previous myocardial infarction—no. (%) | 113 (6.62) | 43 (6.52) | 70 (6.69) | .886 |
| Previous PCI—no. (%) | 375 (21.98) | 172 (26.06) | 203 (19.41) | .001 |
| Previous CABG—no. (%) | 42 (2.46) | 19 (2.88) | 23 (2.2) | .377 |
| History of cerebrovascular disease—no. (%) | 109 (6.39) | 52 (7.88) | 57 (5.45) | .046 |
| History of peripheral-artery disease—no. (%) | 39 (2.29) | 20 (3.03) | 19 (1.82) | .102 |
| Atrial fibrillation or atrial flutter—no. (%) | 43 (2.52) | 24 (3.64) | 19 (1.82) | .020 |
| Criteria for high risk after PCI—no. (%) | | | | |
| High-risk anatomical characteristics | | | | |
| Left main disease | 359 (21.04) | 148 (22.42) | 211 (20.17) | .266 |
| Bifurcation disease | 742 (43.49) | 266 (40.3) | 476 (45.51) | .035 |
| Ostial lesion | 255 (14.95) | 99 (15) | 156 (14.91) | .961 |
| Chronic total occlusion | 342 (20.05) | 114 (17.27) | 228 (21.8) | .023 |
| Multivessel disease | 1191 (69.81) | 482 (73.03) | 709 (67.78) | .021 |
| ≥2 vessels stented | 765 (44.84) | 297 (45) | 468 (44.74) | .917 |
| Restenotic lesion | 194 (11.37) | 78 (11.82) | 116 (11.09) | .644 |
| Diffuse long lesion[d] | 1196 (70.11) | 448 (67.88) | 748 (71.51) | .111 |
| Bypass graft disease | 11 (0.64) | 5 (0.76) | 6 (0.57) | .759 |
| High-risk clinical characteristics—no. (%) | | | | |
| Diabetes on insulin | 73 (4.28) | 73 (11.06) | 0 (0) | |
| Chronic renal failure[e] | 87 (5.1) | 70 (10.61) | 17 (1.63) | <.001 |
| Receipt of dialysis | 49 (2.87) | 39 (5.91) | 10 (0.96) | <.001 |
| Enzyme-positive acute coronary syndrome | 331 (19.4) | 116 (17.58) | 215 (20.55) | .130 |
| Clinical indication for index PCI—no. (%) | | | | |
| Stable angina or silent ischaemia | 1180 (69.17) | 465 (70.45) | 715 (68.36) | .364 |
| Unstable angina | 195 (11.43) | 79 (11.97) | 116 (11.09) | |
| Non-STEMI | 203 (11.9) | 75 (11.36) | 128 (12.24) | |
| STEMI | 128 (7.5) | 41 (6.21) | 87 (8.32) | |

*Continued*

**Table 1** *Continued*

| Characteristic | Overall (*n* = 1706) | Diabetes (*n* = 660) | Non-diabetes (*n* = 1046) | *P*-value |
|---|---|---|---|---|
| Left ventricular ejection fraction—no. (%) | | | | |
| Procedural characteristics, mean ± SD | | | | |
| Total no. of diseased lesions per patient | 2.24 ± 1.16 | 2.35 ± 1.21 | 2.16 ± 1.12 | .002 |
| Total no. of treated lesions per patient | 1.45 ± 0.68 | 1.46 ± 0.67 | 1.45 ± 0.69 | .553 |
| Total no. of stents per patient | 1.95 ± 1.15 | 1.93 ± 1.11 | 1.97 ± 1.18 | .743 |
| Total stent length per patient—mm | 57.11 ± 33.84 | 55.94 ± 32.49 | 57.85 ± 34.66 | .364 |
| Use of drug-eluting stents—no. (%) | 1645 (96.42) | 640 (96.97) | 1005 (96.08) | .335 |
| Use of bioabsorbable scaffold—no. (%) | 16 (0.94) | 2 (0.3) | 14 (1.34) | .031 |
| Use of drug-coated balloon—no. (%) | 105 (6.15) | 42 (6.36) | 63 (6.02) | .776 |
| Intravascular ultrasound guidance—no. (%) | 1269 (74.38) | 490 (74.24) | 779 (74.47) | .915 |
| Fractional flow reserve assessed—no. (%) | 609 (35.7) | 236 (35.76) | 373 (35.66) | .967 |

CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST-segment elevation myocardial infarction.
[a]Mean ± SD. Percentages may not total 100 because of rounding.
[b]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 ischaemic or thrombotic events during follow-up.
[c]A family history of premature CAD was defined as diagnosis of the disease in a male first-degree relative before 55 years of age or in a female first-degree relative before 65 years of age.
[d]Diffuse long lesions were defined as lesions at least 30 mm long or with a stent length of at least 32 mm.
[e]Chronic renal failure was defined as a serum creatinine level of at least 2.0 mg per decilitre (177 μmol per litre) or long-term receipt of haemodialysis.

comorbidities, coronary anatomical characteristics, and procedural characteristics, were well balanced between the routine functional-testing group and the standard-care group in each stratum of patients with and without diabetes (see Supplementary data online, *Table S1*).

## Functional testing and follow-up

At 12 (±2) months following randomization, 260 (90%) of eligible patients (*n* = 289) with diabetes in the routine functional-testing group [excluding those who died (*n* = 9), withdrew (*n* = 2), were lost to follow-up (*n* = 8), or underwent angiography or revascularization (*n* = 13) before 12 months] underwent functional testing, as did 19 (6.2%) of the eligible patients in the standard-care group, as clinically needed [excluding those who died (*n* = 9), withdrew (*n* = 2), were lost to follow-up (*n* = 3), or underwent angiography or revascularization (*n* = 19) before 12 months] (*Figure 1*). Among patients without diabetes, 93.9% of those in the functional-testing group and 10.4% of patients in the standard-care group underwent functional testing. Medication use at discharge and during follow-up is presented in Supplementary data online, *Table S2*. The use of cardioactive medications were well balanced between the functional-testing and standard-care groups in each stratum of patients with and without diabetes.

## Primary and secondary outcomes by diabetes status

Primary and secondary outcomes in patients with and without diabetes are presented in *Table 2*. 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 diabetes than without diabetes (7.3% vs. 4.8%; HR 1.52; 95% CI 1.02–2.27; *P* = .039) (*Figure 2*). Evaluation of secondary outcomes showed that the rates of death from any cause, the composite of death or MI, and rehospitalization were significantly higher in patients with diabetes than without diabetes. The rates of invasive coronary angiography and repeat revascularization at 2 years, however, were similar between diabetic and non-diabetic patients.

Primary and secondary outcomes stratified by diabetic status and randomization group are summarized in *Table 3*. The incidences of primary composite outcome were similar between the routine functional-testing group and the standard-care group in patients with diabetes (7.1% vs. 7.5%; HR 0.94; 95% CI 0.53–1.66; *P* = .82) and those without diabetes (4.6% vs. 5.1%; HR 0.89; 95% CI 0.51–1.55; *P* = .68) (*Figure 3*). Thus, there was no significant interaction between diabetic status and randomized strategy (*P* for interaction = .91). The incidences of each individual component of the primary outcome, death, MI, or hospitalization for unstable angina were also similar between the functional-testing group and the standard-care group in both diabetic and non-diabetic patients (*Figure 4*).

In patients with diabetes, the rates of invasive coronary angiography (12.6% vs. 7.7%; difference 4.92%, 95% CI 0.19–9.64) and repeat revascularization (8.0% vs. 5.2%; difference 2.76%, 95% CI −1.14 to 6.66) were higher in the functional-testing group than in the standard-care group, respectively. In patients without diabetes, a higher trend of invasive coronary angiography (12.1% vs. 10.4%; difference 1.75%, 95% CI −2.13 to 5.63) and repeat revascularization (8.1% and 6.2%; difference 1.9%, 95% CI −1.26 to 5.06) in the functional-testing group than in the standard-care group was less prominent.

**Table 2 Primary and secondary outcomes at 2 years in patients with and without diabetes[a]**

| Outcome | Diabetes ($n = 660$) | Non-diabetes ($n = 1046$) | Hazard ratio (95% CI) | *P*-value |
|---|---|---|---|---|
| Primary composite outcome[b] | 47 (7.3) | 50 (4.8) | 1.52 (1.02–2.27) | .039 |
| Death from any cause | 28 (4.3) | 23 (2.2) | 1.97 (1.13–3.42) | .016 |
| Myocardial infarction | 8 (1.3) | 6 (0.6) | 2.17 (0.75–6.24) | .153 |
| Hospitalization for unstable angina | 11 (1.7) | 22 (2.2) | 0.81 (0.39–1.67) | .56 |
| Secondary outcomes | | | | |
| Death or myocardial infarction | 36 (5.6) | 29 (2.8) | 2.01 (1.23–3.28) | .005 |
| Hospitalization | | | | |
| Any reason | 187 (29.3) | 214 (20.9) | 1.49 (1.22–1.81) | <.001 |
| Cardiac reason | 87 (13.8) | 145 (14.2) | 0.97 (0.75–1.27) | .832 |
| Non-cardiac reason | 100 (10.0) | 69 (6.7) | 2.45 (1.80–3.32) | <.001 |
| Invasive coronary angiography | 63 (10.0) | 115 (11.3) | 0.89 (0.65–1.21) | .445 |
| Showing restenosis or obstructive CAD | 44 | 70 | | |
| Showing no restenosis or obstructive CAD | 19 | 45 | | |
| Repeat revascularization | 45 (6.5) | 73 (7.2) | 0.91 (0.62–1.34) | .631 |
| Target-lesion revascularization | 24 (3.8) | 36 (3.5) | 1.09 (0.65–1.82) | .753 |
| Non-target-lesion revascularization | 17 (2.7) | 37 (3.6) | 0.74 (0.42–1.32) | .311 |
| PCI | 39 | 70 | | |
| CABG | 2 | 3 | | |

Results reported as no. or no. (%).
CAD, coronary artery disease; CI, confidence interval; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.
[a]The number of events and estimated percentages were calculated by the Kaplan–Meier method, using data from the intention-to-treat population; therefore, the percentages may not reflect the ratio of the numerator and denominator. Hazard ratios are for patients with diabetes as compared with patients without diabetes. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons; therefore, inferences drawn from these intervals may not be reproducible.
[b]The primary composite outcome was death from any cause, myocardial infarction, or hospitalization for unstable angina.

## Landmark, sensitivity, and subgroup analyses

To assess time-dependent pattern of clinical outcomes, landmark analyses at 1 year were performed (see Supplementary data online, *Table S3*, Supplementary data online, *Figure S1*, and Supplementary data online, *Figure S2*). From randomization to 1 year and after 1 year, there were no significant differences in the primary composite outcome, its individual components, and other secondary outcomes between the functional-testing and standard-care groups in patients with and without diabetes. In 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 in both diabetic and non-diabetic patients. In these landmark analyses, there were no significant interactions between diabetes status and randomized group with respect to primary and secondary clinical outcomes.

The sensitivity analysis that was performed to account for multiple recurrent events (all components of the primary endpoint) suggested similar findings (see Supplementary data online, *Table S4*). Among patients with diabetes, there was no second recurrent event in the functional-testing group and there was one case of recurrent MI in the standard-care group without significant differences observed from the results not accounting for repeated clinical events. In patients without diabetes, there was one case of recurrent hospitalization for unstable angina in the functional-testing group and two cases of recurrent hospitalization for unstable angina in the standard-care group without significant differences observed from the results not accounting for repeated clinical events.

Subgroup analyses according to use of insulin in diabetic population were also conducted (see Supplementary data online, *Table S5*). The primary outcome rate was significantly higher in insulin-treated than in non-insulin-treated diabetic patients (see Supplementary data online, *Figure S3*). However, neither the primary outcome nor any of the key secondary outcomes differed significantly between the functional-testing group and the standard-care group in insulin- and non-insulin-treated diabetic patients. Analyses of the primary composite outcome in clinical and anatomical subgroups of patients with and without diabetes showed that there were no significant interactions between randomized strategy and each subgroup, except for complete revascularization (see Supplementary data online, *Figure S4* and Supplementary data online, *Figure S5*). In patients who

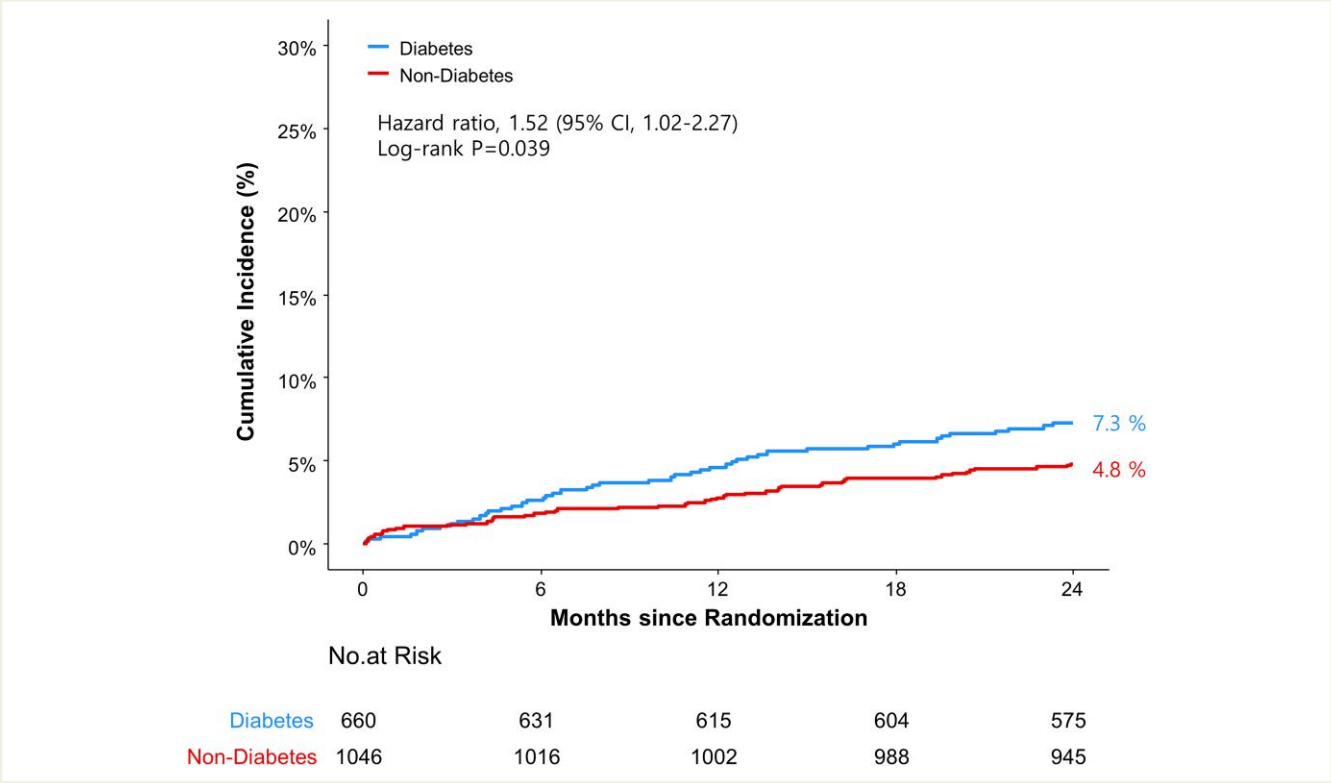



**Figure 2** Time-to-event curves for the primary composite outcome according to diabetes status. Kaplan–Meier curves of the cumulative incidence of the primary composite outcome of death from any cause, myocardial infarction, or hospitalization for unstable angina in patients with and without diabetes. The shown percentages are Kaplan–Meier estimates. The *P*-values determined by log-rank tests. CI, confidence interval

had compete revascularization, the routine functional testing, as compared with the standard care, was associated with a lower incidence of the primary composite outcome in both patients with and without diabetes.

# Discussion

In this pre-specified subgroup analysis of the POST-PCI trial, we assessed the role of routine surveillance stress testing on clinical outcomes in high-risk patients with diabetes who had undergone PCI. Three major findings were observed. First, patients with diabetes had higher clinical and anatomical risk profiles, and had an ~50% greater hazard of the primary composite outcome of death from any cause, MI, or hospitalization for unstable angina at 2 years compared to patients without diabetes. Second, the incidences of the primary outcome at 2 years were similar between the routine functional-testing group and the standard-care group in patients with diabetes and those without diabetes (*Structured Graphical Abstract*). Third, invasive angiography and repeat revascularization after 1 year occurred more frequently in the routine functional-testing group, irrespective of diabetes status; however, this additional invasive management was not associated with a significant reduction of major cardiovascular events or mortality.

Despite the lack of valid clinical evidence, surveillance with functional stress testing has been performed widely in patients who underwent coronary revascularization in daily clinical practice.[18–22] Previous studies have shown that presence of ischaemia on cardiac stress testing after coronary revascularization was associated with worse clinical outcomes.[9] However, the diagnostic yield of such cardiac stress testing leading to invasive coronary angiography or repeat revascularization was reported to be low.[19,21,22] Even if ischaemia was present on stress testing, the incidence of adverse cardiac events did not differ between patients who did and did not undergo repeat revascularization.[23] Unfortunately, most of these earlier reports were derived from retrospective observational studies, which were vulnerable to serious selection bias and unmeasured confounders. Therefore, these findings could not provide reliable evidence for routine surveillance testing after coronary revascularization; contemporary clinical practice guidelines provide a weak (class IIb) recommendation for surveillance stress testing after high-risk PCI.[6,8] In this clinical context, the POST-PCI trial provides compelling new evidence for a future class III recommendation for routine surveillance testing after high-risk PCI.[24]

Because diabetes is associated with more complex clinical and anatomical features, a poorer prognosis, and a higher rate of silent ischaemia, diabetic patients may require a more stringent, more active follow-up surveillance strategy after high-risk PCI with guideline-directed medical therapy to control risk factors.[25] To date, however, optimal surveillance strategies after coronary revascularization have not been determined for diabetic patients at higher risk of adverse cardiovascular events. The key results of the present study indicated that, compared with standard care alone, routine functional testing did not result in lower rates of ischaemic cardiovascular events or mortality in high-risk patients with diabetes who underwent complex PCI. Therefore, in the absence of other clinical signs or symptoms suggestive of stent failure, diabetic patients should not undergo routine surveillance stress testing after PCI. However, we

**Table 3** **Primary and secondary outcomes at 2 years according to diabetes status and randomization group[a]**

| Outcome | Diabetes | | | | Non-diabetes | | | | *P* for interaction[b] |
|---|---|---|---|---|---|---|---|---|---|
| | Functional testing (*n* = 321) | Standard care (*n* = 339) | Hazard ratio (95% CI) | *P*-value | Functional testing (*n* = 528) | Standard care (*n* = 518) | Hazard ratio (95% CI) | *P*-value | |
| Primary composite outcome[c] | 22 (7.1) | 25 (7.5) | 0.94 (0.53–1.66) | .818 | 24 (4.6) | 26 (5.1) | 0.89 (0.51–1.55) | .684 | .906 |
| Death from any cause | 14 (4.5) | 14 (4.2) | 1.07 (0.51–2.24) | .860 | 9 (1.7) | 14 (2.8) | 0.62 (0.27–1.43) | .264 | .340 |
| Myocardial infarction | 2 (0.7) | 6 (1.9) | 0.36 (0.07–1.76) | .210 | 2 (0.4) | 4 (0.8) | 0.48 (0.09–2.62) | .397 | .800 |
| Hospitalization for unstable angina | 6 (2.0) | 5 (1.5) | 1.28 (0.39–4.19) | .684 | 13 (2.5) | 9 (1.8) | 1.40 (0.60–3.27) | .442 | .907 |
| Secondary outcomes | | | | | | | | | |
| Death or myocardial infarction | 16 (5.1) | 20 (6.0) | 0.85 (0.44–1.64) | .633 | 11 (2.1) | 18 (3.5) | 0.59 (0.28–1.25) | .166 | .467 |
| Hospitalization | | | | | | | | | |
| Any reason | 101 (32.8) | 86 (26.1) | 1.30 (0.97–1.73) | .076 | 110 (21.1) | 104 (20.7) | 1.01 (0.77–1.32) | .939 | .213 |
| Cardiac reason | 46 (15.0) | 41 (12.6) | 1.19 (0.78–1.81) | .427 | 76 (14.6) | 69 (13.8) | 1.06 (0.76–1.46) | .743 | .67 |
| Non-cardiac reason | 55 (18.0) | 45 (13.7) | 1.35 (0.91–2.01) | .134 | 34 (6.5) | 35 (7.0) | 0.93 (0.58–1.50) | .775 | .238 |
| Invasive coronary angiography | 38 (12.6) | 25 (7.7) | | | 63 (12.1) | 52 (10.4) | | | |
| Showing restenosis or obstructive CAD | 28 (73.7) | 16 (64.0) | | | 41 (65.1) | 29 (55.8) | | | |
| Showing no restenosis or obstructive CAD | 10 (26.3) | 9 (36.0) | | | 22 (34.9) | 23 (44.2) | | | |
| Repeat revascularization | 24 (8.0) | 17 (5.2) | | | 42 (8.1) | 31 (6.2) | | | |
| Target-lesion revascularization | 13 (4.3) | 11 (3.4) | | | 21 (4.1) | 15 (3.0) | | | |
| Non-target-lesion revascularization | 11 (3.7) | 6 (1.8) | | | 21 (4.1) | 16 (3.2) | | | |
| PCI | 23 (95.8) | 16 (94.1) | | | 41 (97.6) | 29 (93.6) | | | |
| CABG | 1 (4.2) | 1 (5.9) | | | 1 (2.4) | 2 (6.4) | | | |

Results reported as no. (%).

CAD, coronary artery disease; CI, confidence interval; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

[a]The number of events and estimated percentages were calculated by the Kaplan–Meier method, using data from the intention-to-treat population; therefore, the percentages may not reflect the ratio of the numerator and denominator. Hazard ratios are for routine functional-testing compared with the standard-care group. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons; therefore, inferences drawn from these intervals may not be reproducible.

[b]*P* for interaction between diabetes status (diabetes vs. non-diabetes) and randomized group (functional testing vs. standard care).

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

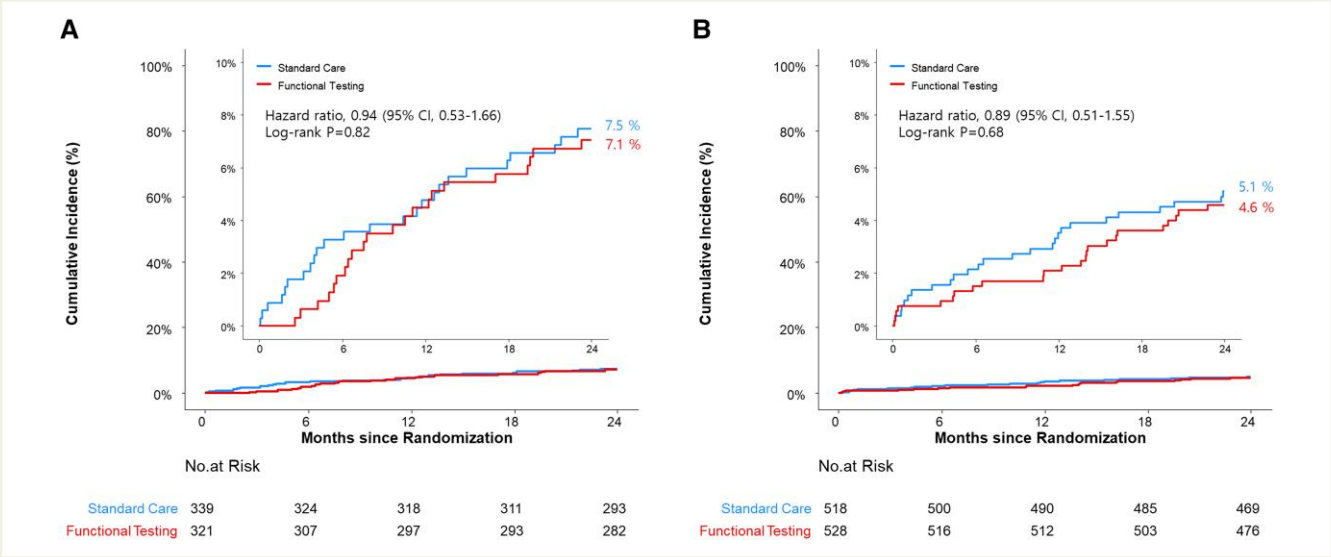



**Figure 3** Time-to-event curves for the primary composite outcome stratified by diabetes status and randomized follow-up strategy. Kaplan–Meier curves of the cumulative incidence of the primary composite outcome of death from any cause, myocardial infarction, or hospitalization for unstable angina in patients (*A*) with and (*B*) without diabetes. The shown percentages are Kaplan–Meier estimates. The *P*-values determined by log-rank tests. The inset in each panel shows the same data on an enlarged *y* axis. CI, confidence interval

acknowledge that the particulars of clinical practice in the institutions in this trial, as well as the pattern of follow-up strategy and the reimbursement policy for functional testing, may differ from those of other institutions and healthcare system, potentially limiting the reproducibility or generalizability of these results in other settings.

In a diabetic sub-study of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, patients with diabetes were at higher risk for death or MI than those without diabetes.[26] However, in the ISCHEMIA, diabetic patients also did not derive incremental benefit from routine invasive management compared with initial medical therapy alone. Therefore, the key findings of the present study could be interpreted in the context of such ISCHEMIA sub-study. Although major cardiovascular events, such as death or MI, occurred frequently in patients with diabetes, maintenance of guideline-directed medical therapy alone, with symptom-oriented surveillance strategy only, rather than routine functional testing during follow-up, could be a safe and effective strategy for managing high-risk patients with diabetes who undergo complex PCI.

In the present study, routine surveillance testing after PCI was associated with more invasive angiography and repeat revascularization after 1 year, but did not reduce major cardiovascular events even in diabetic patients. However, considering that differences in outcomes after PCI among patients with and without diabetes could have diverged over time,[26,27] the long-term effect of active surveillance with routine functional testing or other methods in high-risk patients with diabetes should be further evaluated through larger studies with longer-term follow-up. The appropriate-use-criteria guideline for the detection of stable ischaemic heart disease suggests that cardiac stress testing be rarely appropriate within 2 years after PCI and maybe appropriate after 2 years of PCI, which means that assessing development of adverse cardiovascular events would be reasonable after 2 years post-PCI.[10] Therefore, extended follow-up of the POST-PCI trial would be helpful to further evaluate the long-term impact of surveillance stress testing on clinical outcomes in high-risk patients with diabetes.

## Study limitations

This study has several limitations. First, as the POST-PCI trial suffered from the lower-than-expected primary-outcome events,[11] this prespecified subgroup analysis according to diabetic status may have inherent limitation of statistical underpower to detect clinically relevant events. Therefore, the findings of the present study should be interpreted as being hypothesis-generating, indicating unmet needs for additional clinical trials in patients with diabetes. Second, because detailed information on diabetes medications and data on glycaemic control during follow-up were not available, diabetes control status may have influenced clinical outcomes. However, the baseline characteristics and other cardiovascular medications use were well balanced among patients in the routine functional-testing or standard-care groups, regardless of diabetic status. Third, the number of patients with insulin-treated diabetes was too small to allow formal statistical analyses. Studies in larger groups of patients are warranted to assess the true effects of routine stress testing, especially in patients with insulin-treated diabetes. Fourth, in the present study, there was a lack of differentiation between type 1 and 2 diabetes; each type of diabetes has distinct pathophysiological mechanism and different prognostic impact on the prognosis of CAD.[28] However, considering that insulin-treated diabetes were only 11% of diabetic patients, the impact of diabetic type on observed outcomes might be limited. Lastly, because the present trial only evaluated the prognostic impact of routine stress testing at 1 year after PCI, whether annual cardiac stress testing might improve patients' outcomes could not be answered. Further trials evaluating the prognostic impact of the annual or specific time-interval cardiac stress testing on major cardiovascular events in high-risk PCI patients are warranted.

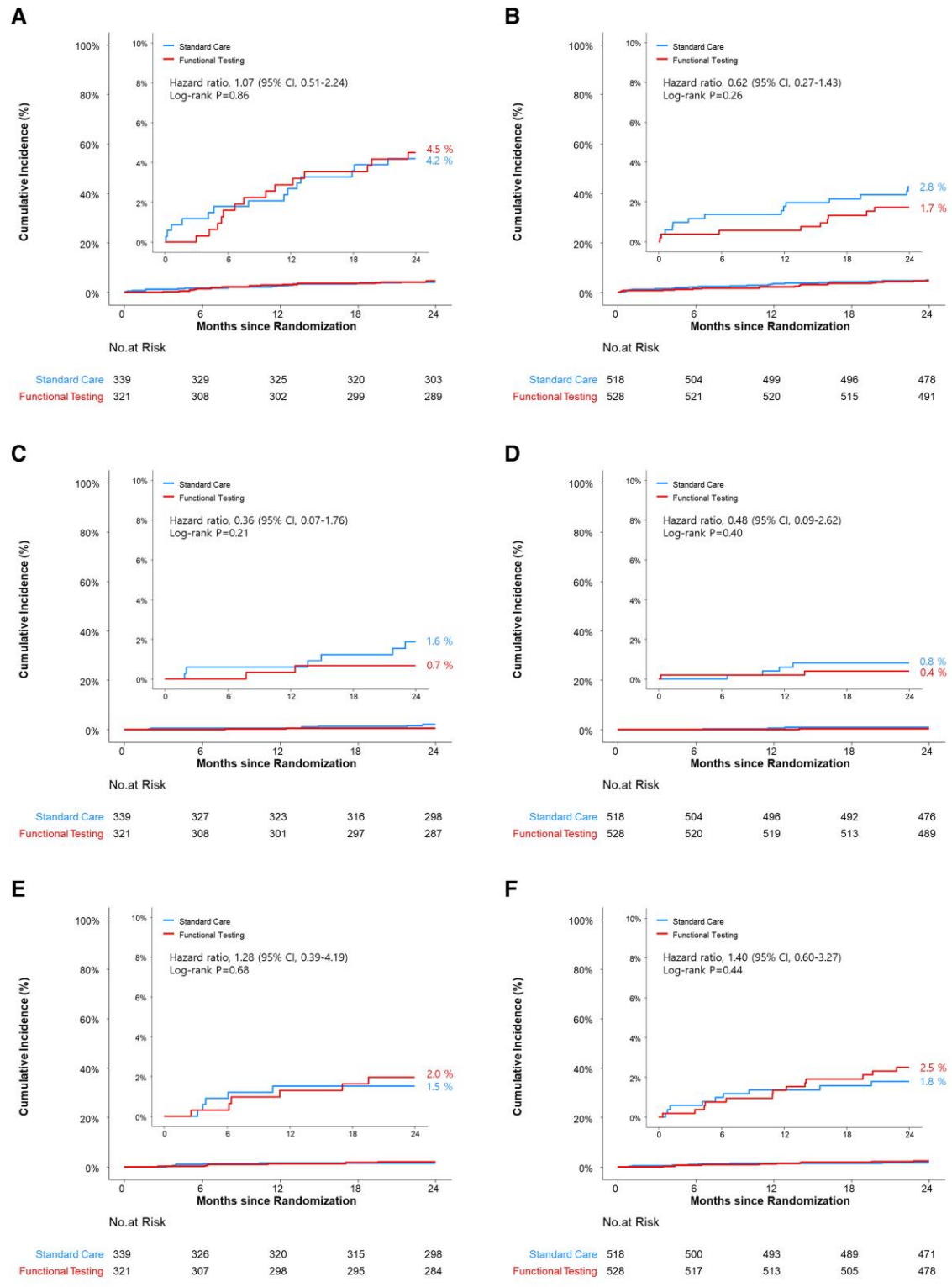



**Figure 4** Time-to-event curves for individual components of death, myocardial infarction, or hospitalization for unstable angina stratified by diabetes status and randomized follow-up strategy. Kaplan–Meier curves of the cumulative incidence of (*A*, *D*) death from any cause, (*B*, *E*) myocardial infarction, and (*C*, *F*) hospitalization for unstable angina in patients (*A*–*C*) with and (*D*–*F*) without diabetes. The shown percentages are Kaplan–Meier estimates. The *P*-values determined by log-rank tests. The inset in each panel shows the same data on an enlarged *y* axis. CI, confidence interval

# Conclusions

In this pre-specified analysis of the POST-PCI trial, patients with diabetes, especially those with insulin-treated diabetes, had worse cardiovascular outcomes than those without diabetes. However, routine surveillance stress testing, as compared with standard care alone, had no clinical benefits in reducing major ischaemic cardiovascular events or mortality at 2 years in high-risk patients with diabetes who underwent complex PCI. Therefore, in the absence of other clinical signs or symptoms suggestive of stent failure or CAD progression, routine surveillance stress testing after PCI should not be recommended among patients with diabetes who underwent PCI.

# Acknowledgements

We thank the staff members of the POST-PCI trial, the cardiologists, nurses, and technicians at the participating centres, and all research coordinators for their efforts in collecting clinical data and ensuring the accuracy and completeness of the data.

# Supplementary data

Supplementary data are available at *European Heart Journal* online.

# Declarations

## Disclosure of Interest

S.-J.P. reports research grants from Daewoong Pharm and CardioVascular Research Foundation related to this work; research grants or lecture fees from Daiichi-Sankyo, Abbott Vascular, Boston Scientific, Medtronic, or Edwards outside the submitted work. D.-W.P. reports research grants from Daewoong Pharm and CardioVascular Research Foundation related to this work; research grants or lecture fees from Daiichi-Sankyo, Abbott Vascular, Boston Scientific, Medtronic, or Edwards outside the submitted work. The other authors report no conflicts.

## Data Availability

The data regarding this article will be shared by the corresponding author upon reasonable request.

## Funding

Supported by grants from CardioVascular Research Foundation (Seoul, South Korea) and Daewoong Pharmaceutical (Seoul, South Korea).

## Ethical Approval

The trial was approved by the investigational review board or ethics committee at each participating centre. All patients provided written informed consent before enrollment.

## Pre-registered Clinical Trial Number

The pre-registered clinical trial number is < NCT03217877 >.

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