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ORIGINAL ARTICLE

Follow-up tests and outcomes for patients undergoing percutaneous coronary intervention: analysis of a Japanese administrative database

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Abstract

Follow-up tests after percutaneous coronary intervention (PCI) are considered inappropriate for asymptomatic patients. Despite this perception, many cardiologists conduct follow-up tests as routine practice. The objective of this study was to investigate the survival benefits of follow-up testing after PCI in a real-world setting in Japan. A nationwide Japanese administrative database was used to identify unselected patients who underwent PCI with stent implantation between January 2010 and December 2013. We used time-dependent Cox proportional hazards models to evaluate the association between follow-up testing and outcomes. The primary outcome was the composite of all-cause death and acute myocardial infarction (AMI). Among a total of 21,409 patients, 15,095 (70.5%) completed follow-up testing, of whom 9814 (45.0%) underwent coronary angiography. During a median of 2.7 years of observation, the primary outcome occurred less frequently for patients who underwent follow-up testing (1.21 vs. 4.51% per year; adjusted hazard ratio, 0.59; 95% CI 0.52–0.67; $p < 0.001$). Individual rates of all-cause death and AMI were also lower for the patients who underwent follow-up testing. Follow-up testing was associated with a lower risk of all-cause death and/or AMI. However, because of the unexpectedly large effect and many limitations of the administrative data, our findings should be further investigated to assess the net benefit of follow-up tests. In addition, we do not intend to encourage routine follow-up tests for patients without clear clinical indications. Follow-up tests should be conducted in accordance with clinical indications.

Keywords Coronary artery disease · Stress test · Coronary angiography · Percutaneous coronary intervention

Introduction

Although the use of drug-eluting stents (DES) has remarkably reduced restenosis rates compared with bare metal stents, restenosis and the need for repeat revascularization remain major problems after percutaneous coronary intervention (PCI) [1]. An analysis of a nationwide large database in the United States (US) showed that 60% of patients underwent some type of follow-up testing after PCI, and noninvasive stress tests were used for 80% of patients [2].

Previous studies repeatedly showed that follow-up testing increased the number of repeat revascularization procedures without any concomitant decrease in mortality or acute myocardial infarction (AMI) rates. Semi-automatic stenting of perceived occlusions by interventional cardiologists, known as "oculostenotic reintervention," and follow-up testing, especially coronary angiography (CAG), for asymptomatic patients have been considered triggers for reintervention [3–5]. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines and ACCF appropriate use criteria were developed to limit the inappropriate use of cardiac procedures. According to the ACCF/AHA 2013 multimodality appropriate use criteria for detection and risk assessment of stable ischemic heart disease, follow-up testing within 2 years after PCI was rated as rarely appropriate unless the patient had new or worsening symptoms [6, 7].

Recommendations noted in these guidelines and appropriate use criteria were based on previous studies and expert opinions. However, most studies were underpowered to

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evaluate survival benefits because sample sizes were small and high-risk patients were excluded from some studies [8, 9]. In addition, recent studies showed that angiographic restenosis on CAG or ischemic findings on stress myoperfusion scintigraphy or stress echocardiography were associated with a high rate of all-cause death [10, 11]. Therefore, the appropriateness of follow-up testing after PCI may require reevaluation using a larger-scale study involving higher risk patients. We aimed to examine the survival benefits of follow-up testing using a nationwide Japanese administrative database.

Materials and methods

Study design and data source

This retrospective cohort study was performed using a hospital-based database provided by Medical Data Vision Co. Ltd. (Tokyo, Japan). The database includes administrative claims data and discharge abstracts stored in electronic information systems and has been used for epidemiological research [12, 13]. It contains data for 16 million patients from 275 acute care hospitals with diagnosis procedure combination reimbursement and represents approximately 12% of acute care hospitals in Japan. It also includes the following data: anonymized patient identifiers; admission and discharge date; type of admission (emergency or staged); the outcome at discharge (inclusive of in-hospital death); primary diagnosis at the time of index PCI; comorbidities at admission and complications after admission according to the *International Classification of Diseases, 10th Revision* (ICD-10) codes; drugs, devices, diagnostic tests, and therapeutic procedures according to Japanese procedural codes or claims codes; and number of hospital beds classified into three categories (less than 200, 200 to 499, and more than or equal to 500).

Patient inclusion and exclusion criteria

Using Japanese procedural codes (K546.x–550.x), we searched for patients aged 18 years or older who underwent PCI between January 1, 2010, and December 31, 2013. The first PCI procedure for each patient was considered the index PCI.

Exclusion criteria were as follows: hospitalization for more than 90 days; missing or duplicated values for admission date, discharge date, body mass index, smoking status, activities of daily living (ADL), or in-hospital outcomes; did not undergo stent implantation; or underwent stenting with both bare metal stents and DES. We also excluded patients who died or were readmitted for AMI or whose follow-up period after the index PCI was 90 days or fewer. In addition, patients who underwent stress echocardiography, stress MRI, or positron emission tomography were also excluded because these studies were rarely performed for this cohort (Fig. 1).

Exposure and outcome variables

Stress electrocardiography (ECG), myocardial perfusion scintigraphy (MPS), coronary computed tomography (CT) angiography, and CAG were defined according to the procedure codes as follow-up tests. Patients were classified into two groups (test group and nontest group). The test group included patients who underwent at least one follow-up test during the interval from 90 days after the index PCI to the end of follow-up, whereas the nontest group included patients who did not undergo follow-up tests within that period. Patients were classified according to the first follow-up test before any AMI admission or death. If a patient underwent a first follow-up test during or after admission for AMI, the patient was classified as belonging to the nontest group. We excluded diagnostic tests within 90 days after the index PCI because diagnostic tests during this period might have been performed for the purposes of cardiac rehabilitation, to determine the need for additional procedures, to assess functional capacity, or due to residual cardiac symptoms after PCI [14]. We did not exclude patients who underwent coronary revascularization procedures within 90 days from the index PCI because these could be regarded as staged procedures for multivessel disease.

The primary outcome was a composite of all-cause death and AMI. Secondary outcomes included all-cause death, AMI, and coronary revascularization including PCI and coronary artery bypass grafting surgery. Coronary revascularization procedures within 90 days of the index PCI were not regarded as outcomes because revascularization during this period preceded the start of follow-up testing in normal clinical practice.

Baseline variables

The following baseline variables were identified: patient characteristics, including age and sex; primary diagnosis at the time of index PCI; comorbidities; ADL at discharge; hospital characteristics, including type of hospital (teaching or nonteaching) and the number of beds; prescribed drugs; and procedural characteristics, such as stent type and number of stents. Comorbidities were defined in relation to the Charlson Comorbidity Index, which was validated in another Japanese administrative database [15, 16]. Patients were classified as having a lower ability to perform ADL if the Barthel index at discharge was less than 100 [17].

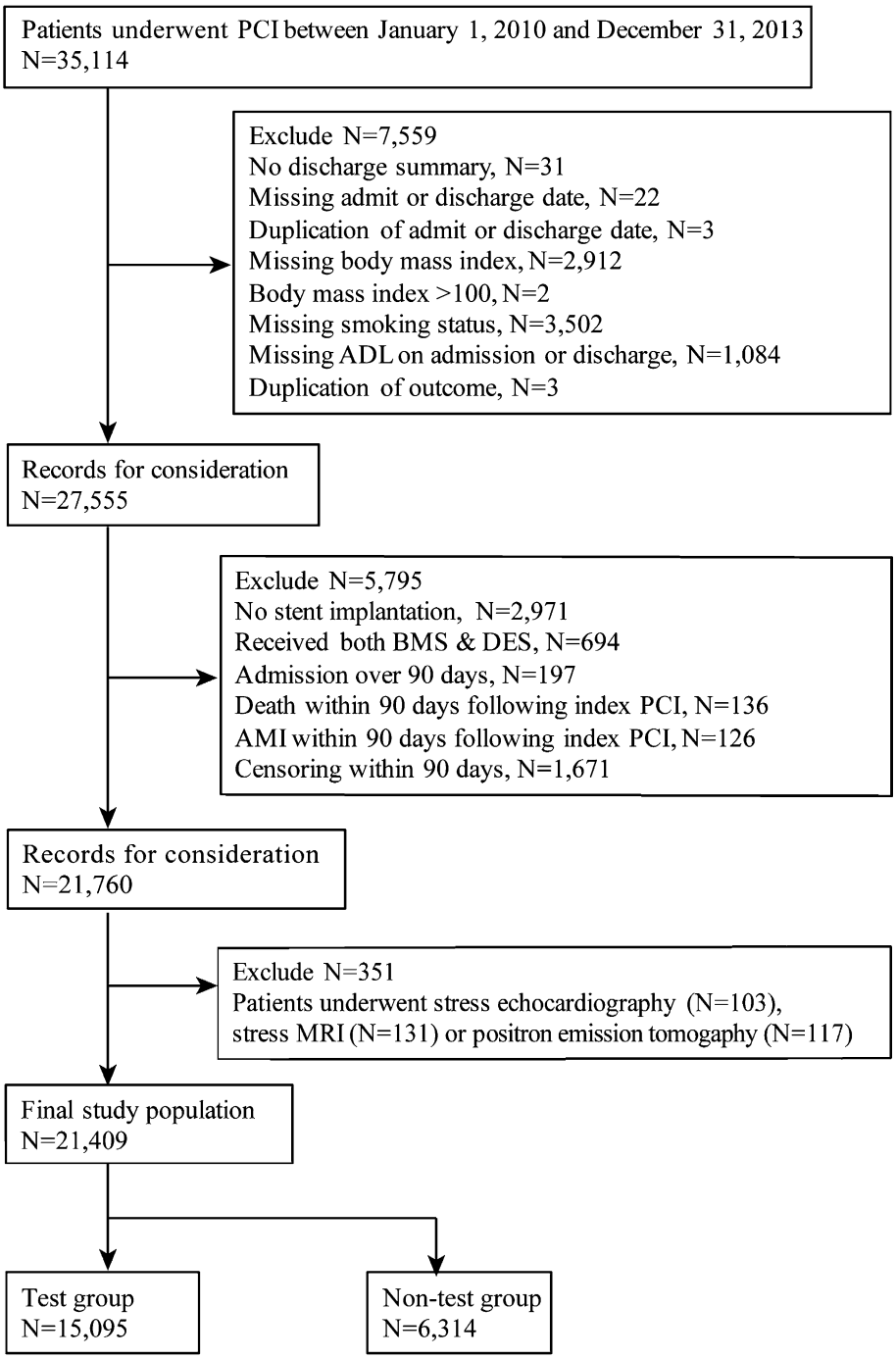

Fig. 1 Study flowchart. Flow diagram showing the process used to define the study population. *PCI* percutaneous coronary intervention, *BMI* body mass index, *BMS* bare metal stent, *DES* drug-eluting stent, *AMI* acute myocardial infarction

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were presented as median and interquartile range (IQR). The follow-up period was calculated as the period from 90 days after the index PCI to the date of each outcome or the end of follow-up, whichever came first. The Student two-sample *t* test, Fisher's exact test, and Mann–Whitney–Wilcoxon rank-sum test were used to compare the differences between groups for continuous, categorical, and ordinal variables, respectively. The incidence rates of a clinical event were assessed by the Kaplan–Meier method and compared using the log-rank test. We constructed multivariate Cox proportional hazards models with a time-dependent covariate to adjust the imbalance between groups and to evaluate the impact of follow-up testing relative to nontesting on the primary and secondary outcomes. Differences in unadjusted and adjusted analysis were expressed as hazard ratios (HR) with 95% confidence intervals (CI). This model included

31 variables: age, sex, body mass index, smoking history, primary diagnosis at the time of index PCI (acute coronary syndrome or acute myocardial infarction); comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, diabetes mellitus with chronic complications, diabetes mellitus without chronic complications, renal disease, malignancy, and metastatic solid tumor, low ADL ability at discharge); type of hospital, and number of beds; drugs (aspirin, P2Y12 receptor inhibitors, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, oral anticoagulants, and proton pump inhibitors); and procedural characteristics (number of stents, DES, intravascular ultrasound, rotational atherectomy, and intra-aortic balloon pumping). The time-dependent covariate was based on the first follow-up test to account for differences in the timing of testing and outcomes. Patients who underwent follow-up testing could not have exhibited any outcome during the period from 90 days after the index PCI until the first follow-up test. Because of this, the effects of exposure (i.e., follow-up test) may have been overestimated; this phenomenon is referred to as "immortal time bias," and a time-dependent model minimizes this bias [18].

We performed subgroup analyses to evaluate the efficacy of the follow-up test in relation to the primary outcome in several clinically relevant subgroups classified by patient characteristics such as age, sex, procedural characteristics, or hospital characteristics. In this analysis, we used the period between exposure and the end of follow-up as survival time.

We conducted four sensitivity analyses to evaluate the extent of various biases in the present study. First, to evaluate a potential bias caused by missing data, we conducted a multiple imputation analysis to replace the missing baseline variables [19, 20]. Second, because the 90-day blanking period from the index PCI could be arbitrary, we used a different cutoff period for study inclusion, exposure, and outcomes (90 days for the primary analysis and 30 days without the blanking period for the sensitivity analysis). Third, we performed a 1:1 propensity score (PS)-matching analysis to confirm the results of the primary analysis. The PS for each patient was the conditional probability of undergoing follow-up testing and it was estimated using a logistic regression model including all variables listed here. Using a nearest-neighbor algorithm without replacement, each patient who underwent follow-up testing was matched with a patient who did not undergo follow-up test, thus restricting the PS matches within 0.2 of the standard deviation of the log PS. Finally, we performed an analysis without patients who experienced the primary outcome or were censored within 365 days from index date to see how much immortal time bias amplified our estimates.

We considered two-sided $p < 0.05$ as statistically significant. All analyses were conducted using JMP 12.2.0 and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

We identified 35,114 patients who underwent PCI between January 1, 2010, and December 31, 2013; of these, 13,705 patients met the exclusion criteria. Therefore, the final study population included 21,409 patients (Fig. 1). The median follow-up period was 2.7 years [interquartile range (IQR) 1.8–3.8]. Among these patients, 15,095 (70.5%) underwent follow-up testing as follows: as their first test, 1180 (5.5%) underwent stress ECG; 2274 (10.6%) underwent MPS; 1827 (8.5%) underwent coronary CT angiography; and 9814 (45.8%) underwent CAG. Among 8973 of the 9814 (91.4%) follow-up CAG examinations that we could link with discharge summary and diagnostic codes, 8581 (95.6%) were conducted for those with nonacute admissions. The median period from 90 days after the index PCI to the follow-up test was 155 days (IQR 101–225); 14,692 (97.3%) patients underwent follow-up testing within 2 years. The median intervals from 90 days after the index PCI to each test were as follows: 107 days (IQR 42–200) for stress ECG; 158 days (IQR 99–241) for MPS; 175 days (IQR 107–279) for coronary CT angiography; and 155 days (IQR 106–214) for CAG.

Patient and hospital characteristics according to follow-up testing status

The follow-up period was shorter for the nontest group. Patients in the nontest group were older (with a greater proportion aged 65 years or older), including more women and more with a lower body mass index. They were less likely to have a history of smoking, including more with acute coronary syndrome as a primary diagnosis; comorbidities including peripheral vascular disease; cerebrovascular disease; chronic pulmonary disease; diabetes mellitus with and without chronic complications; renal disease; malignancy; and metastatic solid tumors, and included more who were considered to have a lower ability to perform ADL. They underwent more intravascular ultrasound, rotational atherectomy, and intra-aortic balloon pumping procedures. They received a larger number of stents, more oral anticoagulants, fewer statins, and they were more likely to be admitted to a larger and/or teaching hospital (Table 1).

Clinical outcomes

The incidence rates of primary composite outcomes of all-cause death and AMI were 1.21% per year for the test group

Table 1 Baseline clinical, procedural, and hospital characteristics and medications

	Overall ($N=21,409$)	Nontest group ($N=6314$)	Test group ($N=15,095$)	p value
Clinical characteristics				
Follow-up period (year)	2.6 (1.6–3.6)	2.4 (1.2–3.4)	2.7 (1.8–3.7)	<0.001
Age (years)	70 (63–77)	73 (65–80)	69 (62–76)	<0.001
<50	1089 (5.1)	261 (4.1)	828 (5.5)	
50–64	5445 (25.4)	1313 (20.8)	4132 (27.4)	
65–74	7442 (35)	1931 (31)	5511 (37)	
75+	7433 (34.7)	2809 (44.5)	4624 (30.6)	
Male	16,025 (74.9)	4577 (72.5)	11,448 (75.8)	<0.001
Body mass index, kg/m^2	24 (22–26)	23 (21–26)	24 (22–26)	<0.001
Smoking history	10,667 (49.8)	2962 (46.9)	7705 (51.0)	<0.001
Congestive heart failure	4922 (23.0)	1530 (24.2)	3392 (22.5)	0.11
Peripheral vascular disease	1766 (8.3)	582 (9.2)	1184 (7.8)	0.004
Cerebrovascular disease	1518 (7.1)	512 (8.1)	1006 (6.7)	0.02
Chronic pulmonary disease	673 (3.1)	238 (3.8)	435 (2.9)	0.001
Liver disease	343 (1.6)	97 (1.5)	246 (1.6)	0.25
DM without chronic complications	5372 (25.1)	1653 (26.2)	3719 (24.6)	0.007
DM with chronic complications	1471 (6.9)	549 (8.7)	922 (6.1)	<0.001
Renal disease	1417 (6.6)	569 (9.0)	848 (5.6)	<0.001
Malignancy	557 (2.6)	203 (3.2)	354 (2.4)	0.001
Metastatic solid tumor	25 (0.1)	14 (0.2)	11 (0.1)	0.01
Acute coronary syndrome	10,821 (50.5)	3285 (52.0)	7536 (49.9)	0.005
Acute myocardial infarction	5886 (27.5)	1727 (27.4)	4159 (27.6)	0.78
Low ADL ability at discharge	2560 (12.0)	1258 (19.9)	1302 (8.6)	<0.001
Procedural characteristics				
Number of stents used				<0.001
1	15,662 (73.2)	4442 (70.4)	11,220 (74.3)	
2	4242 (19.8)	1346 (21.3)	2896 (19.2)	
>3	1505 (7.0)	526 (8.3)	979 (6.5)	
DES used (%)	16,236 (75.8)	4824 (76.4)	11,412 (75.6)	0.21
IVUS used (%)	17,681 (82.6)	5079 (80.4)	12,602 (83.5)	<0.001
Rotational atherectomy used (%)	496 (2.3)	181 (2.9)	315 (2.1)	0.001
IABP used (%)	890 (4.2)	295 (4.7)	595 (3.9)	0.02
Hospital characteristics				
Number of beds				<0.001
≤199	1538 (7.2)	269 (4.3)	1269 (8.4)	
200–499	13,832 (64.6)	4588 (72.7)	9244 (61.2)	
500≤	6039 (28.2)	1457 (23.1)	4582 (30.4)	
Teaching hospital (%)	16,313 (76.2)	5048 (80.0)	11,265 (74.6)	<0.001
Medications				
Aspirin	17,086 (79.8)	5031 (79.7)	12,055 (79.9)	0.77
$P2Y_{12}$ receptor inhibitors	18,685 (87.3)	5486 (86.9)	13,199 (87.4)	0.27
Statins	12,726 (59.4)	3419 (54.2)	9307 (61.7)	<0.001
ACE inhibitors/ARBs	9772 (45.6)	2883 (45.7)	6889 (45.6)	0.98
Beta blockers	8200 (38.3)	2400 (38.0)	5800 (38.4)	0.58
Oral anticoagulants	1921 (9.0)	660 (10.5)	1261 (8.4)	<0.001
Proton pump inhibitors	12,539 (58.6)	3674 (58.2)	8865 (58.7)	0.47

Values are median (interquartile range) or N (%)

The body mass index was calculated as the weight in kilograms divided by the square of the height in meters

DM diabetes mellitus, *ADL* activities of daily living, *DES* drug-eluting stent, *IVUS* intravascular ultrasound, *IABP* intra-aortic balloon pumping, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blockers

and 4.51% per year for the non-test group. An unadjusted HR of 0.26 (95% CI 0.23–0.29; $p < 0.001$) and adjusted HR of 0.59 (95% CI 0.52–0.67; $p < 0.001$) were significantly lower for the test group than for the nontest group (Fig. 2 and Table 2). The individual rates of all-cause death and AMI, which were the components of the primary outcome, were also lower for the test group. In contrast, the rate of coronary revascularization was higher for the test group (Table 2).

The subgroup analysis showed that the lower rate of the primary outcome was consistent across all subgroups and

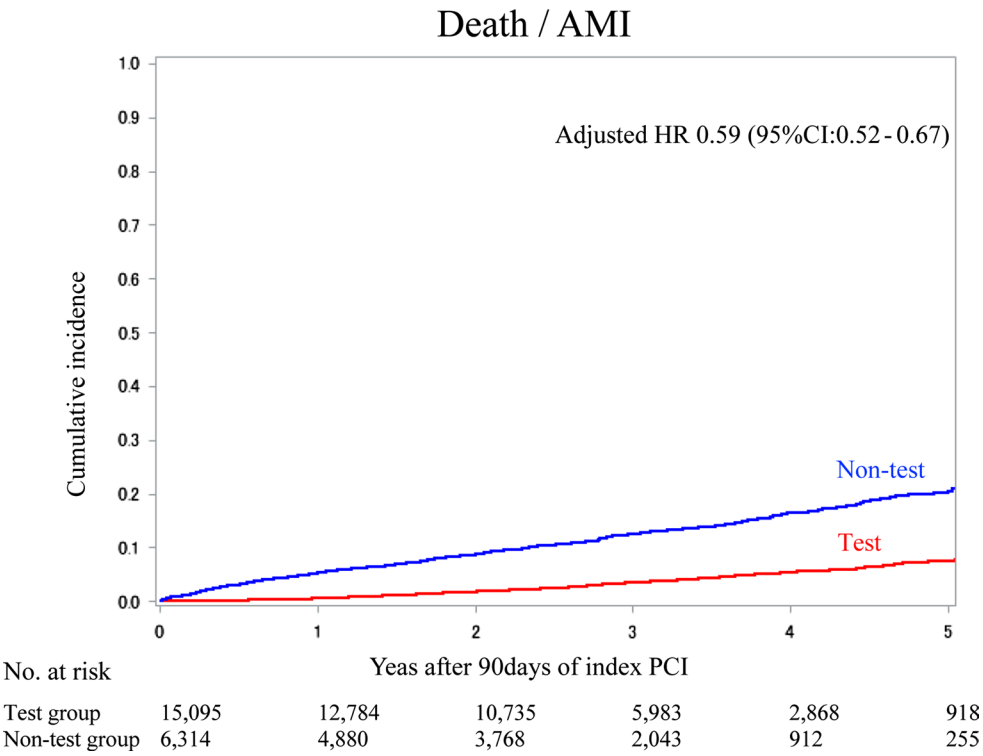

Fig. 2 Kaplan–Meier survival curves for the primary outcome. *PCI* percutaneous coronary intervention, *AMI* acute myocardial infarction, *HR* hazard ratio, *CI* confidence interval

Table 2 Primary and secondary outcomes

	Nontest group ($N = 6314$)		Test group ($N = 15{,}095$)		HR (95% CI)		Adjusted *p* value
	No. of events	% Per year	No. of events	% Per year	Unadjusted	Adjusted[a]	
Primary outcome[b]							
Death/AMI	679	4.51	497	1.21	0.26 (0.23–0.29)	0.59 (0.52–0.67)	<0.0001
Secondary outcomes[c]							
All-cause death	596	3.96	479	1.17	0.29 (0.26–0.33)	0.64 (0.56–0.73)	<0.0001
AMI	99	0.67	19	0.05	0.08 (0.05–0.12)	0.20 (0.11–0.34)	<0.0001
Coronary revascularization	2555	27.17	2932	8.34	0.34 (0.33–0.36)	1.8 (1.7–1.9)	<0.0001

Coronary revascularization includes percutaneous coronary intervention and coronary artery bypass graft surgery

HR < 1 favors follow-up testing

HR hazard ratio, *CI* confidence interval, *AMI* acute myocardial infarction

[a]Adjusted for age, sex, body mass index, smoking history, primary diagnosis of the percutaneous coronary intervention index (acute coronary syndrome, acute myocardial infarction), comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, liver disease, diabetes with or without chronic complications, renal disease, malignancy, metastatic solid tumor), low ability to perform activities of daily living at discharge, device (drug-eluting stent, intra-aortic balloon pump, intravascular ultrasound, rotational atherectomy) used, no. of stents used (1, 2, ≥ 3), medications (aspirin, P2Y12 receptor inhibitor, statins, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta blocker, oral anticoagulant, proton pump inhibitor, no. of hospital beds (< 200, 200–499, ≥ 500), teaching hospital, and follow-up test. The follow-up test was treated as a time-dependent variable

[b]If a patient experienced more than one event of the primary outcome, then only the first event was considered

[c]More than one type of event (initial and subsequent event) was allowed per patient

that there were significant interactions between follow-up testing and age, sex, or the primary diagnosis at the time of the index PCI (Fig. 3).

Among four different types of sensitivity analyses, the lower rates of the primary outcome after each analysis were consistent with the results of the primary analysis (Table 3).

Discussion

Among more than 20,000 patients undergoing PCI in Japan, follow-up tests were performed for 70%, with CAG being the most common. In comparison with the nontest group, the follow-up tests were associated with a higher rate of repeat coronary revascularization; however, they were also associated with a lower risk of death and/or AMI within a median of 2.7 years after the index PCI.

The utility of follow-up tests following PCI, particularly CAG, has been questioned in guidelines issued in the US and Europe [7, 21]. In the US, the proportion of follow-up tests was approximately 60% among patients post-PCI, but CAG accounted for only one-sixth of all types of follow-up tests [2]. In the present study, however, we found that 70% of patients underwent follow-up tests and that CAG was performed for two-thirds of these patients. This difference can be explained by the different recommendations for post-PCI follow-up tests among countries. In contrast to the guidelines in the US and Europe, the Japanese guidelines include a clear recommendation for routine follow-up CAG, regardless of symptoms and the results of the noninvasive tests, without supporting evidence [22]. The high rate of follow-up CAG in this study could have resulted from compliance with this recommendation.

Our results showed that the follow-up tests were associated with a significantly higher rate of coronary revascularization but a lower risk of death and/or AMI. The lower mortality and morbidity rates of the present study were inconsistent with the current perspective. Many studies

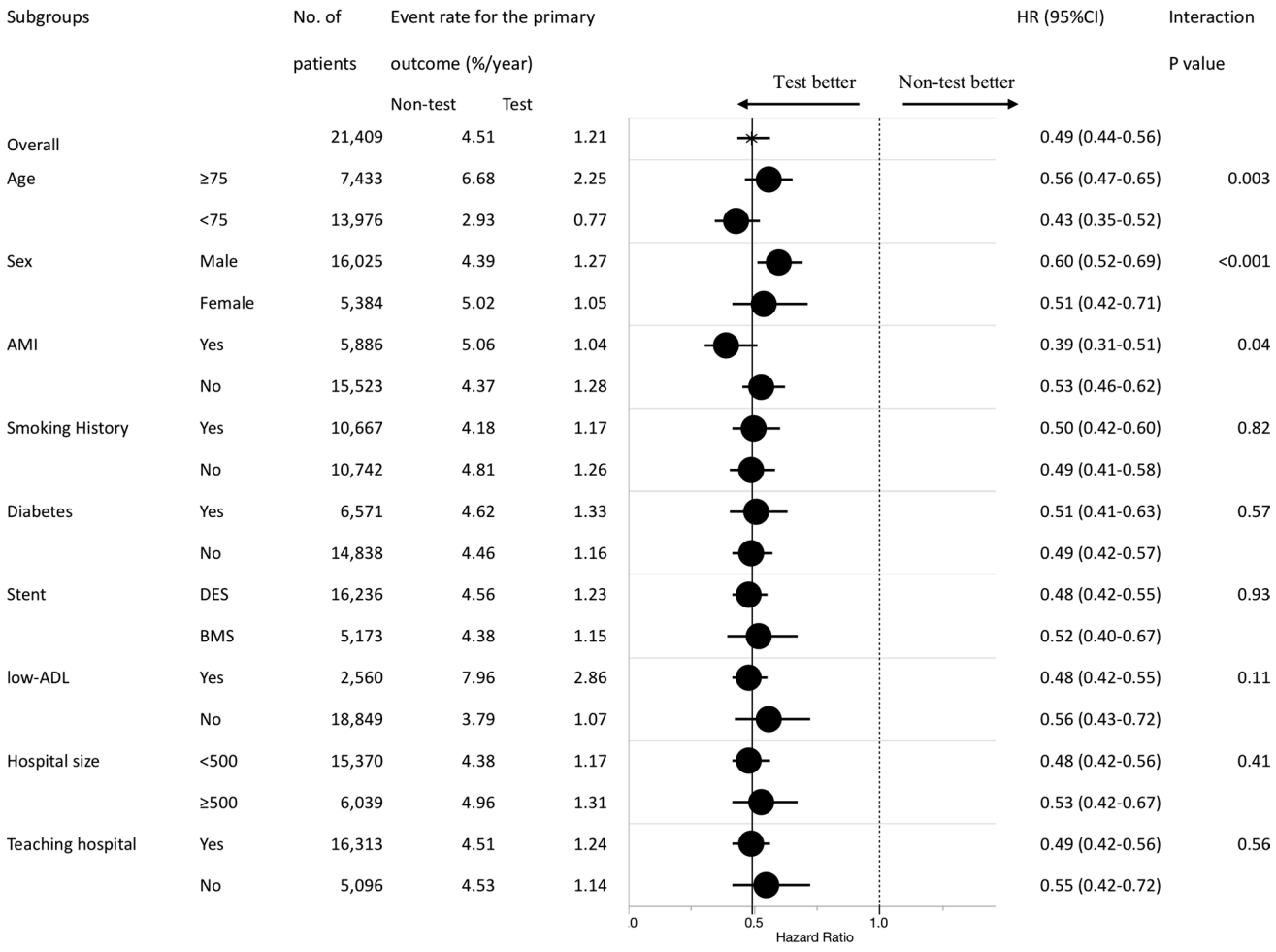

Fig. 3 Subgroup analysis. Subgroup analysis of the effects of follow-up testing compared with no testing on the primary endpoint for the specified subgroups. *ADL* activities of daily living, *AMI* acute myocardial infarction, *HR* hazard ratio, *CI* confidence interval

Table 3 Sensitivity analyses of the primary outcome: composite of all-cause death and AMI

	N (Test/Nontest)	Nontest group % per year	Test group % per year	Adjusted HR (95% CI)[a]	*p* value
Without blanking period[b,c]	23,485 (14,311/9174)	8.50	1.39	0.61 (0.54–0.69)	< 0.001
With 30-day blanking period[b,c]	22,027 (14,705/7322)	4.47	1.20	0.61 (0.54–0.70)	< 0.001
Multiple imputations[b,c]	26,271 (18,466/7805)	4.71	1.25	0.60 (0.54–0.68)	< 0.001
Landmark analysis starting at 365 days after the index PCI[b,d]	17,726 (11,632/6094)	3.43	1.56	0.61 (0.53–0.70)	< 0.001
Propensity score-matching[c,e]	12,552 (6276/6276)	4.55	1.61	0.52 (0.45–0.60)	< 0.001
Original analysis (reference)[b,c]	21,409 (15,095/6314)	4.51	1.21	0.59 (0.52–0.67)	< 0.001

All analyses were conducted for the primary outcome (composite of all-cause death and acute myocardial infarction)

HR hazard ratio, *CI* confidence interval, *AMI* acute myocardial infarction, *PCI* percutaneous coronary intervention

Abbreviations as in Table 1

[a]HR < 1 favors follow-up testing

[b]Adjusted for patient factors (e.g., demographic data, comorbidities, procedures, devices, or medication) and hospital factors (e.g., bed numbers); see Table 2 for details

[c]Follow-up test was treated as a time-dependent variable

[d]Only patients alive at the landmark time of 365 days from the index PCI were included in the analysis, with survival probability estimates since this landmark day

[e]Propensity score was estimated using a logistic regression model including all variables listed here. Each patient who underwent follow-up testing was matched with a patient who did not undergo follow-up testing

consistently showed that the follow-up testing increased repeat revascularization but did not decrease cardiac events [3–5, 23]. Our findings may be explained by early detection of silent ischemia, the large sample size, and inclusion of patients at higher risk.

Some previous studies have shown that ischemic findings and angiographic restenosis were associated with a greater number of cardiovascular events. A systematic review of 29 studies showed that abnormal findings on stress myoperfusion scintigraphy or stress echocardiography were associated with higher rates of all-cause death [10]. Similarly, angiographic restenosis, which was associated with lower 4-year mortality rates, was detected in approximately one of every four patients who underwent routine follow-up CAG between 6 and 8 months after PCI; however, half of the patients were asymptomatic [11]. It is plausible that early detection of silent ischemia or restenosis could reduce cardiovascular mortality and morbidity by allowing for subsequent interventions such as lifestyle modifications and optimal medical therapy; however, recent randomized control trials and systematic reviews did not show additional benefits of PCI over optimal medical therapy [24, 25].

The present study included 21,409 patients. This large sample size enabled detection of the survival benefits of follow-up tests. A recent randomized control trial that included 700 patients showed a 6% risk reduction for patients who underwent routine follow-up CAG, but the result was not statistically significant [23]. An analysis of a study involving 250,000 patients also showed that noninvasive stress testing was associated with a 19% lower risk of death or AMI, and this result was statistically significant [2]. Similarly, a recent systematic review including 4584 patients showed that the follow-up CAG was associated with a lower rate of AMI; however, it was not associated with all-cause mortality rates [26].

Patients in the present study were approximately 10 years older than the populations involved in the subanalyses of the randomized controlled studies and more patients underwent the index PCI for acute coronary syndrome [3–5]. We assumed that the large sample size and the inclusion of patients at higher risk increased the statistical power of the present study.

We acknowledge that our study might have overestimated the effect of follow-up testing because of confounding and unmeasured confounding. The rate of the primary outcome for the non-test group was 4.5% per year, which was more than 2–3% higher per year that noted in previous studies; however, rates were similar or lower for the test group compared to previous studies [3–5, 22]. We assumed that the higher event rate for the non-test group might have been attributed to two causes. First, in the present study, the non-test group included more patients with severe cases than the test group. Patients in the non-test group were older, received a larger number of stents, received more oral anticoagulants, received less statins, had more comorbidities, and had a lower ability to perform ADL. A larger number of stents seemed to be related to a larger proportion of follow-up tests. The phenomenon that patients at lower risk are more likely to undergo invasive diagnostic testing or therapy than patients at higher risk is known as the risk-treatment

paradox [27]. Second, patients who experienced outcomes before follow-up testing were classified as belong to the non-test group, thus increasing the event rate. Third, patients who underwent follow-up testing should be more adherent to treatment than patients who did not. Previous studies showed that worse patient adherence to treatment was an independent risk factor for mortality even though a placebo was used [28]. Although we tried to adjust for imbalances using a time-dependent Cox proportional hazards model, bias and residual confounding might have distorted our results.

Subgroup analysis showed that the follow-up testing had significant effects across all subgroups. In addition, we found significant interactions between follow-up tests and age, sex, and primary diagnosis at the time of the index PCI. Follow-up tests were more closely associated with lower risk in limited subgroups, such as younger patients, female patients, or patients with AMI. Because of the lack of detailed clinical data, we were unable to evaluate the effect of follow-up tests on other relevant subgroups, such as patients with left main coronary artery stenosis or low left ventricular ejection fraction. However, a recent observational study of patients with left main coronary artery stenosis also showed that the follow-up CAG was associated with a significantly lower rate of death [29]. Further studies may be warranted to identify a subset of patients who may benefit most from follow-up testing.

Study limitations

The present study had several important limitations related to the observational design and the use of administrative data. First, we were unable to investigate a possible causative effect because the results of the present study had inherent flaws related to confounding by indication and nonrandom allocation to treatment. Second, we could not distinguish follow-up tests conducted due to cardiac symptoms from routine follow-up tests for asymptomatic patients because cardiac symptoms were not included when the patient underwent noninvasive follow-up tests in an outpatient setting. Therefore, the positive results of the present study might reflect the effects of follow-up testing for symptomatic patients. Prospective data collection is necessary to clarify whether follow-up testing is appropriate for asymptomatic patients after PCI. Third, because of the nature of the administrative data, our study included detailed claims data regarding procedures, medications, and devices. Conversely, this study did not include sufficient clinical data, such as those related to vital signs, laboratory test results, cardiac functions, and the extent of coronary artery disease. As a result, the adjustment of the results may have been insufficient. Fourth, baseline characteristics and outcomes could have been underreported because our database did not include the procedures, admissions, and outcomes that occurred at other institutions. For example, the proportions of aspirin and P2Y12 receptor inhibitor prescriptions for patients without AMI were lower in the present study than in previous studies [30]. The most likely reason is that these patients were prescribed these medications at other institutions. Fifth, we might have underestimated the rates of death and AMI because any linkage between MDV and other databases, including the National Death Registry, was not possible. For example, we could not detect the outcomes that patients experienced at other institutions. However, we expected that the specificity of death should be high in the present study because a validation study using another Japanese administrative database showed very high specificity (99.9%) and positive predictive value (94.8%) and relatively low sensitivity (28–91%) for death [31]. Administrative databases in Japan tend to miss myocardial infarction, with a sensitivity of 52% and specificity of nearly 100% [16]. In fact, the rates of AMI and the proportion of comorbidities were lower than those of previous studies and other comorbidities had a similar trend. Conversely, a secondary outcome AMI may be overestimated because it included both type 1 and type 2 MI, and ICD-10 codes, which were used to define the AMI, did not distinguish such categories. Sixth, in the present study, more patients underwent PCI without an acute indication and underwent CAG or coronary CT angiography as the first follow-up test compared with patients in the US [32]. Therefore, this difference in practice patterns may limit the generalizability of our results. Seventh, our results should not be extrapolated to patients who underwent implantation of a bioresorbable vascular scaffold or balloon angioplasty. Eighth, we did not evaluate the difference between CAG and other noninvasive tests. Therefore, we could not evaluate which test was preferable. Finally, because the follow-up period was relatively short, we could not evaluate the efficacy of the follow-up test regarding the late catch-up phenomenon.

Conclusions

This observational study using a nationwide Japanese administrative database revealed the following findings. Follow-up testing after PCI is commonly performed in Japan and CAG is the most frequent follow-up test. Furthermore, follow-up testing is associated with a significantly lower risk of the primary composite outcome of death and AMI and of both components of the primary outcome. However, our findings regarding the protective effects of follow-up tests may be optimistic because the results were attributed to the follow-up tests themselves and to many apparent and unknown confounding factors; therefore, further studies, such as an RCT with a sufficiently large sample size, may be required. In addition, we do not intend to encourage follow-up tests for

patients without a clear indication. Follow-up tests should be conducted only in accordance with clinical indications.

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Compliance with ethical standards

Conflicts of interest Dr. Kawakami received honoraria from Astellas, Eisai, Abbie, Takeda Pharmaceutical Company Limited, Novartis KK, Santen, Bayer Yakuhin, Sanofi K.K., Kyowa Hakko Kirin, and Otsuka Pharmaceutical and consult fees from Olympus and Kaken Pharmaceutical. There are no patents, products in development, or marketed products to declare that are relevant to those companies. Other authors: None declared.

Research involving human participants and/or animals The present study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (R0705).

Informed consent Because all data were anonymized, the requirement for informed consent was waived.

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