Prognostic Impact of Subsequent Acute Coronary Syndrome and Unplanned Revascularization on Long-Term Mortality After an Index Percutaneous Coronary Intervention: A Report From a Japanese Multicenter Registry

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Background—Whereas composite end points are often used in clinical trials of percutaneous coronary interventions (PCI), the impact of individual components on subsequent survival is incompletely defined. We evaluated the association of subsequent acute coronary syndromes (ACS) and unplanned coronary revascularization post-PCI with long-term survival.

Methods and Results—From 2009 to 2011, the KiCS-PCI (Keio interhospital Cardiovascular Studies) consecutively enrolled patients undergoing PCI in 14 Japanese teaching hospitals. We identified patients who experienced ACS or unplanned coronary revascularization following their index PCI and compared subsequent survival during the 2-year follow-up period using propensity-matched cohorts of patients who did and did not experience these events. Cox proportional hazard models were used to assess 2-year all-cause mortality. Because unstable angina is less severe than acute myocardial infarction, we also generated a separate propensity-matched cohort for UA post-PCI. Among 3348 PCI patients (mean age, 67.5±10.7 years; 79.7% male), 214 (6.4%) experienced a subsequent ACS (168 events [78.5%] were unstable angina), and 198 (5.9%) underwent unplanned revascularization. In the propensity-matched cohorts, patients with a subsequent ACS admission had an increased risk of mortality as compared with those without (hazard ratio, 4.73; 95% confidence interval=1.35−16.6; *P*=0.015), whereas those with an unplanned revascularization did not have significantly higher risk (hazard ratio, 2.97; 95% confidence interval=0.57−14.3; *P*=0.19). Among unstable angina events, no association with mortality was observed (hazard ratio, 1.39; 95% confidence interval=0.48−4.00; *P*=0.54).

Conclusions—In the KiCS-PCI registry, the incidence of a subsequent ACS was associated with higher mortality, but this association was less apparent after unplanned coronary revascularization or unstable angina. The prognostic implications of different outcomes in a composite end point should be considered when interpreting the results of clinical trials in PCI. (***J Am Heart Assoc.*** 2017;6:e006529. DOI: 10.1161/JAHA.117.006529.)

Key Words: acute aortic syndrome • composite end point • percutaneous coronary intervention • revascularization

Composite end points have been widely used in contemporary clinical trials for acquiring sufficient statistical power to detect the difference in outcomes between groups.[1,2] In the field of ischemic heart disease, many trials examine the impact of therapy on combined clinical outcomes, including cardiovascular death, myocardial infarction (MI), stroke, unstable angina (UA) admissions, and revascularization procedures.[3–7] Although the clinical impact of the first 3 events are of uncontested importance, it remains unclear whether nonfatal events, such as UA and coronary revascularizations, are individually associated with subsequent survival and warrant inclusion as a component of major

Clinical Perspective

What Is New?

- This multicenter Japanese registry demonstrated that a subsequent acute coronary syndrome after the index percutaneous coronary intervention was associated with higher mortality.
- However, his association was less apparent after a subsequent unplanned coronary revascularization or an unstable angina event.

What Are the Clinical Implications?

- Whereas acute coronary syndrome readmissions seem to be an important component of clinical end points, the roles of unplanned revascularization or unstable angina alone as components of clinical trial end points need to be cautiously interpreted.
- Given the limited prognostic benefit from subsequent revascularization after the index percutaneous coronary intervention, the incremental value of performing routine angiographic assessment should be revisited.

adverse cardiovascular events (MACE). For example, in trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting for multivessel coronary artery disease, many demonstrate that the use of coronary artery bypass grafting, as compared with PCI, results in lower rates of MACE, mainly attributed to a higher rate of repeat revascularization with PCI. Given that these studies typically show no differences in hard end points (eg, mortality), but may be of insufficient duration for the full mortality benefit to be realized, more data on the long-term prognostic significance of different MACE components are needed.[5–7]

To better illuminate the prognostic importance of individual MACE components—including admissions for acute coronary syndromes (ACS) and unplanned coronary revascularizations —that often comprise composite end points in clinical trials of coronary artery disease, this study sought to evaluate the association of ACS admission and unplanned coronary revascularization with 2-year survival in 2 separate propensity-matched cohorts of patients who did and did not experience these clinical events from a contemporary large, regional Japanese PCI population.

Methods

Study Population

Data from the JCD-KiCS (Japan Cardiovascular Database Keio interhospital Cardiovascular Studies) were used to address our aims. JCD-KiCS is a prospective, multicenter registry designed to collect clinical variables and outcomes data on consecutive patients undergoing PCI for both acute and nonacute indications using dedicated clinical research coordinators at each site.[8–14] The clinical variables and in-hospital outcomes for the JCD-KiCS were aligned with the data elements of the National Cardiovascular Data Registry CathPCI Registry v4.1.[15,16] The participating hospitals in Kanto, Japan (Tokyo, Tochigi, Saitama, Chiba, and Kanagawa Prefecture) were mostly large tertiary care referral centers (more than 200 beds; N=12), but included a few mid-sized satellite hospitals (less than 200 beds; N=3). Trained data coordinators at participating hospitals consecutively recorded and registered hospital visits for PCI using an internet-based data collection infrastructure. This process was overseen by a senior study coordinator (Dr I.U.), and quality of the reporting was verified through on-site audits by the principal investigators (Drs S.K. and H.M.). This study was approved by each participating hospital's ethics review board, and written informed consent was obtained from each patient.

For the present report, JCD-KiCS data (4179 patients; January 1, 2009 to December 31, 2011) were analyzed. Staged PCI procedures were excluded from the present analysis (n=237 patients). Follow-up data were obtained from hospital charts or by contacting patients or referring physicians through mail or telephone. Relatively complete follow-up (84.9%) was obtained, with a total of 594 patients (15.1%) being excluded because of loss to follow-up (mean follow-up duration, 665 ± 147 days). In comparison with those completing at least 1-year follow-up (Table 1), those who were lost to follow-up had higher rates of past MI, PCI, or hemodialysis, but presented with less clinically significant manifestations. They often were more asymptomatic patients and less likely to present with an ACS. After these exclusions, 3348 patients were included in the study (Figure 1).

Definitions

The standard National Cardiovascular Data Registry CathPCI data definitions were used in JCS-KiCS.[17] The principal outcome measure for this analysis was all-cause death. ACS was defined as admission to a hospital for a primary diagnosis of UA or acute MI. Unplanned revascularization was defined as the first future revascularization after the index procedure. Staged PCI procedures were defined as PCI procedures that were performed during the same hospitalization of the index procedure or within 30 days after the index procedure in a setting other than ACS.

Statistical Analysis

All data are expressed as mean±SD for continuous variables and percentages for categorical variables. Differences in each

Table 1. Differences in Characteristics Between Patients With and Without at Least 1-Year Follow-up

Characteristic	Total N=3942	Missing Yes N=594	No N=3348	P Value
Demographics				
Male, n (%)	3159 (80.1)	489 (82.3)	2670 (79.7)	0.147
Age, y	67.5±10.9	67.5±11.7	67.5±10.7	0.977
BMI	24.2±3.6	23.9±3.8	24.3±3.6	0.034
Clinical factors (%)				
Smoking	1406 (35.7)	213 (35.9)	1193 (35.6)	0.043
Family history of CAD	569 (14.4)	75 (12.6)	494 (14.8)	0.037
Hypertension	2811 (71.3)	441 (74.2)	2370 (70.8)	0.086
Hypercholesterolemia	2532 (64.2)	375 (63.1)	2157 (64.4)	0.544
Diabetes mellitus	1624 (41.2)	267 (44.9)	1357 (40.5)	0.047
Renal dysfunction	702 (17.8)	141 (23.7)	561 (16.8)	<0.001
Past history of MI	826 (21.0)	195 (32.8)	631 (18.8)	<0.001
Past history of HF	307 (7.8)	59 (9.9)	248 (7.4)	0.098
Past PCI	1099 (27.9)	329 (55.4)	770 (23.0)	<0.001
Past CABG	216 (5.5)	31 (5.2)	185 (5.5)	0.762
Hemodialysis	164 (4.2)	46 (7.7)	118 (3.5)	<0.001
Cerebrovascular disease	337 (8.5)	53 (8.9)	284 (8.5)	0.724
Peripheral arterial disease	290 (7.4)	49 (8.2)	241 (7.2)	0.366
Chronic lung disease	119 (3.0)	24 (4.0)	95 (2.8)	0.264
Presentation (%)				
STEMI	1068 (27.1)	148 (24.9)	920 (27.5)	<0.001
UA/NSTEMI	1065 (27.0)	120 (20.2)	945 (28.2)	
Stable angina	1175 (29.8)	185 (31.1)	990 (29.6)	
Silent ischemia	584 (14.8)	128 (21.5)	456 (13.6)	
Other	47 (1.2)	11 (1.9)	36 (1.1)	
Angina (applied only to elective cases) (%)				
No symptoms	656 (37.3)	138 (44.1)	518 (35.8)	0.003
CCS class				
I	304 (7.7)	46 (14.7)	213 (14.7)	
II	596 (33.9)	96 (30.7)	500 (34.6)	
III	166 (9.4)	13 (4.2)	153 (10.6)	
IV	23 (1.3)	6 (1.9)	17 (1.2)	
Unknown	59 (3.4)	14 (4.5)	45 (3.1)	

All values are expressed as the mean±SD or as a number with the percentage of subjects in parentheses. BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS class, Canadian Cardiovascular Society angina class; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

variable between groups were evaluated using Student unpaired *t* test for continuous variables and chi-square or Fisher's exact tests for categorical variables.

First, we compared patients' characteristics by the presence or absence of subsequent ACS admission, and by the presence or absence of unplanned coronary revascularization. Then, we created 2 separate matched cohorts for each of the events (subsequent ACS admission or subsequent coronary revascularization) using the same methodology. In order to account for differences in characteristics between the 2 groups (patients
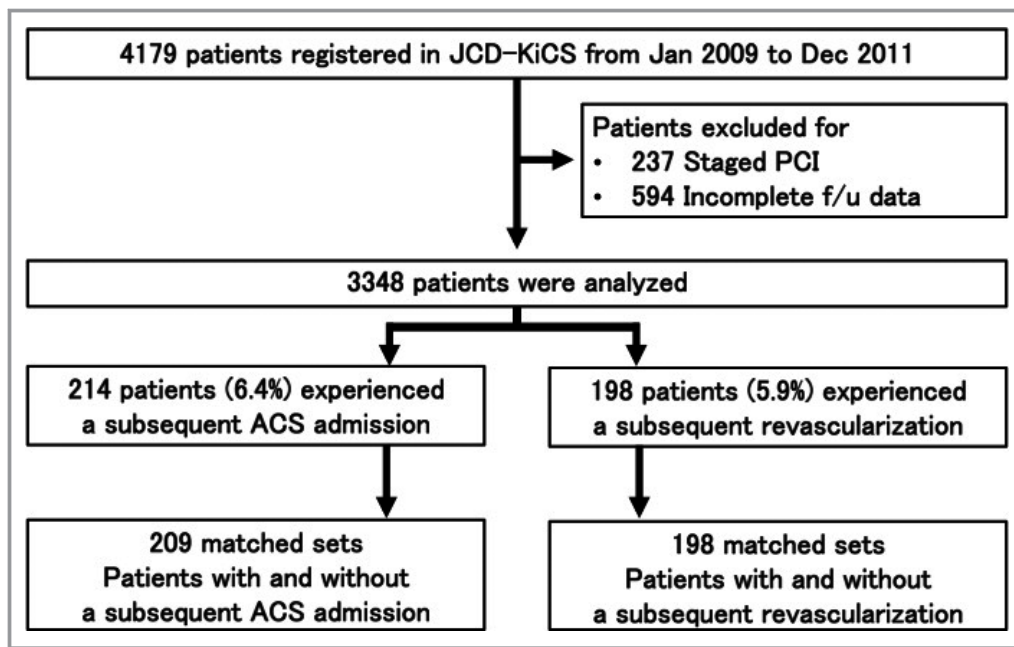
Figure 1. Flow chart of the study population. ACS indicates acute coronary syndrome; f/u, follow-up; PCI, percutaneous coronary intervention.

with ACS rehospitalization versus those without ACS rehospitalization, or patients with subsequent revascularization versus those without subsequent revascularization), we derived propensity scores to assess the probability of each event, by constructing nonparsimonious multivariable logistic regression models. In the propensity score model, the occurrence of each event was used as the dependent variable, and baseline characteristics were entered as covariates (age, sex, body mass index, previous history [diabetes mellitus, renal dysfunction, chronic obstructive pulmonary disease, MI, heart failure, peripheral artery disease, hypertension, hyperlipidemia, cerebrovascular disease, coronary artery disease, PCI, and coronary artery bypass grafting], presentation on admission [ST-elevation MI, shocked status, heart failure, and Canadian Cardiovascular Society >2], medication on admission [aspirin, clopidogrel, and beta-blocker], and laboratory data [postprocedural creatine kinase-MB]).

We then matched patients who had subsequent ACS admission or coronary revascularization to those without subsequent ACS admission or coronary revascularization using greedy matching on the logit of the propensity score (1:1). The caliper width was chosen as 0.2 times the pooled SD of the logit propensity scores for the groups. Balance between the groups was assessed by calculating the standardized differences, where <0.10 was considered to indicate good balance between the groups. Following the propensity matching, in order to assess the association of subsequent ACS admission or coronary revascularization on long-term mortality, in each matched data set, the starting

time was set to the time to the occurrence of each event for calculating the time to death or censoring. Finally, a Cox proportional hazards model for long-term mortality was stratified and weighted by matched sets with weighted K-M curves. Similar analysis was performed for coronary revascularization admissions. Finally, because UA is less severe than acute MI, we also generated a separate propensity-matched cohort for this post-PCI event.

Analyses of data were performed using SAS (version 9.1; SAS institute Inc, Cary, NC) and SPSS software (version 22; SPSS, Inc, Chicago, IL). All *P* values were 2-sided, and significance was defined as *P*<0.05 for all analyses.

Results

The cohort (Table 2) had a mean age of 67.5±10.7 years; 79.7% were male. When compared with patients without a future ACS event, those with a future ACS event were older and had a higher prevalence of renal dysfunction. Past histories of MI, heart failure, PCI, and coronary artery bypass grafting were also more frequently observed in patients with a subsequent ACS event than those without. Moreover, in patients with a future ACS event, coronary intervention had been more commonly performed for UA and non-ST-elevation MI. In contrast, baseline characteristics of patients with and without a future revascularization were not significantly different.

During the follow-up (mean follow-up duration, 665±147 days), a total of 214 ACS (6.4%) and 198 unplanned revascularization (5.9%) events occurred, and

Table 2. Baseline Characteristics in Study Cohort

Characteristic	Total N=3348	Future ACS Yes N=214	Future ACS No N=3134	P Value	Future Revascularization Yes N=198	Future Revascularization No N=3150	P Value
Demographics (%)							
Male	2670 (79.7)	169 (79.0)	2501 (79.8)	0.77	164 (82.8)	2506 (79.6)	0.266
Age, y	67.5±10.7	69.2±10.3	67.4±10.7	0.018	67.8±9.4	67.5±10.8	0.692
BMI	24.3±3.6	24.0±3.4	24.3±3.6	0.171	24.4±3.7	24.3±3.6	0.575
Clinical factors (%)							
Smoking	1193 (35.6)	78 (36.4)	1115 (35.6)	0.905	65 (32.8)	1128 (35.8)	0.651
Family history of CAD	494 (14.7)	36 (16.8)	458 (14.6)	0.651	29 (14.6)	465 (14.8)	0.312
Hypertension	2370 (70.8)	154 (72.0)	2216 (70.7)	0.898	134 (67.7)	2236 (71.0)	0.588
Hypercholesterolemia	2157 (64.4)	134 (62.6)	2023 (64.6)	0.818	146 (73.7)	2011 (63.8)	0.018
Diabetes mellitus	1357 (40.5)	90 (42.1)	1267 (40.4)	0.867	76 (38.4)	1281 (40.7)	0.79
Renal dysfunction	574/3094 (18.6)	55/194 (28.4)	519/2900 (17.9)	<0.001	30/189 (15.9)	544/2905 (18.7)	0.328
Past history of MI	631 (18.8)	57 (26.6)	574 (18.3)	0.003	33 (16.7)	598 (19.0)	0.419
Past history of HF	248 (7.4)	25 (11.7)	223 (7.1)	0.046	10 (5.1)	238 (7.6)	0.413
Past PCI	770 (23.0)	66 (30.8)	704 (22.5)	0.018	40 (20.2)	730 (23.2)	0.607
Past CABG	185 (5.5)	21 (9.8)	164 (5.2)	0.017	7 (3.5)	178 (5.7)	0.436
Hemodialysis	118 (3.5)	20 (9.3)	98 (3.1)	<0.001	2 (1.0)	116 (3.7)	0.048
Cerebrovascular disease	284 (8.5)	21 (9.8)	263 (8.4)	0.47	15 (7.6)	269 (8.5)	0.637
Peripheral arterial disease	241 (7.2)	16 (7.5)	225 (7.2)	0.871	9 (4.5)	232 (7.4)	0.136
Chronic lung disease	95 (2.8)	5 (2.3)	90 (2.9)	0.871	9 (4.5)	86 (2.7)	0.319
Presentation							
STEMI	921 (27.5)	54 (25.2)	867 (27.7)	<0.001	60 (30.3)	861 (27.3)	0.247
UA/NSTEMI	945 (28.2)	92 (43.0)	853 (27.2)		59 (29.8)	886 (28.1)	
Stable angina	990 (29.6)	50 (23.4)	940 (30.0)		48 (24.2)	942 (29.9)	
Silent ischemia	457 (13.6)	18 (8.4)	439 (14.0)		31 (15.7)	426 (13.5)	
Other	35 (1.0)	0 (0)	35 (1.1)		0 (0)	35 (1.1)	
Angina (applied to only elective cases) (%)							
No symptoms	519 (35.9)	18 (26.5)	501 (36.3)	0.167	31 (39.2)	488 (35.7)	0.091
CCS class							
I	213 (14.7)	11 (16.2)	202 (14.6)		8 (10.1)	205 (15.0)	
II	500 (34.6)	22 (32.4)	478 (34.7)		25 (31.6)	475 (34.7)	
III	153 (10.6)	13 (19.1)	140 (10.2)		15 (19.0)	138 (10.1)	
IV	17 (1.2)	2 (2.9)	15 (1.1)		0 (0)	17 (1.2)	
Unknown	45 (3.1)	2 (2.9)	43 (3.1)		0 (0)	45 (3.1)	

All values are expressed as the mean±SD or as a number with the percentage of subjects in parentheses. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS class, Canadian Cardiovascular Society angina class; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

all-cause mortality rate was 3.9% (N=131). Subsequent ACS events mostly consisted of UA (168 events; 78.5% of all ACS events). Propensity score matching was performed to adjust for differences in clinical variables, producing a total of 209 matched sets (patients with versus without subsequent ACS admission) and 196 matched sets (patients with versus without unplanned revascularization). The baseline demographic characteristics of the propensity-matched cohorts are presented in Tables 3 and 4. After greedy matching, baseline characteristics between matched sets were well balanced,

Table 3. Baseline Characteristics in Matched Cohort of a Subsequent ACS Readmission

Characteristic	Future ACS Admission		P Value
	Yes	No	
	N=209	N=209	
Demographics			
Male, n (%)	167 (79.9)	178 (85.2)	0.156
Age, y	68.9±10.3	68.6±9.8	0.784
BMI	24.0±3.4	24.0±3.4	0.933
Clinical factors (%)			
Smoking, n (%)	77 (36.8)	76 (36.4)	0.919
Family history of CAD	36 (17.3)	32 (15.2)	0.322
Hypertension, n (%)	150 (71.8)	151 (72.2)	0.913
Hypercholesterolemia, n (%)	133 (63.6)	153 (73.2)	0.035
Diabetes mellitus, n (%)	89 (42.6)	95 (45.5)	0.554
Renal dysfunction	23 (11.0)	25 (12.0)	0.759
Past history of MI	56 (26.8)	54 (25.8)	0.824
Past history of HF	24 (11.5)	18 (8.6)	0.329
Past PCI	65 (31.1)	82 (39.2)	0.082
Past CABG	21 (10.0)	12 (5.7)	0.103
Hemodialysis	20 (9.6)	22 (10.5)	0.745
Cerebrovascular disease	21 (10.0)	16 (7.7)	0.389
Peripheral arterial disease	16 (7.7)	21 (10.0)	0.389
Chronic lung disease	5 (2.4)	6 (2.9)	0.76
Presentation (%)			
STEMI	52 (25.0)	36 (17.1)	0.001
UA/NSTEMI	89 (42.8)	67 (31.9)	
Stable angina	49 (23.6)	69 (32.9)	
Asymptomatic myocardial ischemia	18 (8.7)	35 (16.7)	
Other	0 (0)	3 (1.4)	
Angina (applied to only elective cases) (%)			
No symptoms	43 (41.3)	18 (26.9)	0.208
CCS class			
I	11 (10.6)	11 (16.4)	
II	32 (30.8)	21 (31.3)	
III	16 (15.4)	13 (19.4)	
IV	0 (0)	2 (3.0)	
Unknown	2 (1.9)	2 (3.0)	

All values are expressed as the mean±SD or as a number with the percentage of subjects in parentheses. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS class, Canadian Cardiovascular Society angina class; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

and standardized differences were almost all below 0.1 (Figure 2).

Figure 3 shows Kaplan–Meier event-free survival curves for all-cause death (1) in patients with and without future ACS admission and (2) in patients with and without unplanned revascularization. Whereas patients with future ACS admission had a significantly lower survival rate during the follow-up period (P=0.007 by log-rank test), the mortality of patients with unplanned revascularization was not different from those without (P=0.173 by log-rank test). Cox regression analysis revealed the same trend that patients having a subsequent ACS admission were associated with worse survival (hazard ratio, 4.73; 95% confidence interval, 1.35–16.6; P=0.015), but patients having an unplanned revascularization were not (hazard ratio, 2.97; 95% confidence interval, 0.57–14.3; P=0.194).

To clarify the prognostic burden within each component of ACS, we evaluated the all-cause mortality in patients with versus without a future event stratified by UA and MI. Patients with a future MI were associated with an increased risk of all-cause mortality compared with those without (P=0.013 by log-rank test; Figure 4). In patients experiencing UA (161 matched sets), however, Kaplan–Meier event-free survival curve did not show the significant difference (Figure 5). Furthermore, in the adjusted analysis, no association with all-cause mortality was observed (hazard ratio, 1.39; 95% confidence interval, 0.48–4.00; P=0.54).

Discussion

In a contemporary PCI registry in Japan, the rates for ACS rehospitalization and unplanned revascularization during follow-up period were 6.4% and 5.9%, respectively, and the all-cause mortality rate was 3.9%. The incidence of a subsequent ACS, particularly MI, was associated with higher all-cause mortality, but this association was less clear after unplanned coronary revascularization or UA.

It is widely known that the experience of an ACS event could have an unfavorable impact on future prognosis.[18,19] In fact, a recent report from the GRACE (Global Registry of Acute Coronary Events) demonstrated that ≈5% of patients with ACS admission had died during the indexed hospitalization, and an additional 10% of patients experienced subsequent events, including death and MI within 6 months after discharge.[19] In accordance with this previous report, the overall ACS admission was associated with an increased risk of long-term mortality in our study. Recent guidelines, however, do not necessarily put much emphasis on discriminating between UA and MI events from a clinical perspective (especially in the event of a non-ST-elevation MI),[20] but the GRACE investigators also demonstrated minimal association between UA admission

Table 4. Baseline Characteristics in Matched Cohort of Unplanned Revascularization

| Characteristic | Future Revascularization Admission | | P Value |
	Yes N=196	No N=196	
Demographics			
Male, n (%)	162 (82.7)	166 (84.7)	0.585
Age, y	68.3±10.0	67.8±9.4	0.603
BMI	24.5±3.7	24.5±3.8	0.959
Clinical factors (%)			
Smoking, n (%)	64 (32.7)	60 (30.6)	0.664
Family history of CAD	28 (14.3)	32 (16.2)	0.726
Hypertension, n (%)	133 (67.9)	140 (71.4)	0.442
Hypercholesterolemia, n (%)	145 (74.0)	154 (78.6)	0.285
Diabetes mellitus, n (%)	75 (38.3)	82 (41.8)	0.453
Renal dysfunction	37 (18.9)	58 (29.6)	0.013
Past history of MI	33 (16.8)	37 (18.9)	0.598
Past history of HF	10 (5.1)	4 (2.0)	0.102
Past PCI	40 (20.4)	59 (30.1)	0.027
Past CABG	7 (3.6)	4 (2.0)	0.359
Hemodialysis	2 (1.0)	7 (3.6)	0.092
Cerebrovascular disease	15 (7.7)	13 (6.6)	0.695
Peripheral arterial disease	9 (4.6)	16 (8.2)	0.148
Chronic lung disease	8 (4.1)	10 (5.1)	0.629
Presentation (%)			
STEMI	58 (29.6)	32 (29.6)	0.007
UA/NSTEMI	59 (30.1)	58 (29.6)	
Stable angina	48 (24.5)	71 (36.2)	
Asymptomatic myocardial ischemia	31 (15.8)	33 (16.8)	
Other	0 (0)	2 (1.0)	
Angina (applied to only elective cases) (%)			
No symptoms	31 (39.2)	42 (40.4)	0.307
CCS class			
I	8 (10.1)	12 (11.5)	
II	25 (31.6)	38 (36.5)	
III	15 (19.0)	10 (9.6)	
IV	0 (0)	0 (0)	
Unknown	0 (0)	2 (1.9)	

All values are expressed as the mean±SD or as a number with the percentage of subjects in parentheses. BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS class, Canadian Cardiovascular Society angina class; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

and subsequent mortality as compared with an MI admission and long-term death.[19] Our findings are congruent with this observation. Although UA admissions accounted for the majority of subsequent ACS admissions following index PCI (78.5%), its adverse association with all-cause mortality was less clear in the propensity-matched analysis. Because of the limited sample size of patients with a future MI (N=46), a fully adjusted model could not be performed. However, the crude mortality rate was higher in patients with a future MI (10.9%) as compared with a subsequent UA episode (4.8%). In addition, unadjusted survival analysis also demonstrated a higher mortality in patients with a future MI than those without (*P*=0.013 by log-rank test; Figure 4). These findings indicate that MI, but not the UA component in ACS event, may largely explain the association between subsequent ACS with mortality. The specific prognostic importance of the different clinical presentations across the ACS spectrum requires further exploration.

It remains unclear whether a subsequent unplanned coronary revascularization is an appropriate component of MACE end points in the field of cardiovascular studies. For example, the FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2),[4] which evaluated the role of fractional flow reserve assessment in revascularization decisions for patients with stable angina, highlighted the need for answering this question. This trial was stopped prematurely by its safety and monitoring board, because of a significant difference in a composite outcome between patients with and without revascularization. This was mainly driven by the significantly different rates for the subsequent unplanned revascularization between groups, and critics expressed concerns that the trial design failed to ensure clarification of the effect of an fractional flow reserve–guided strategy on mortality. In our study, by creating the propensity-matched cohort to control the potential selection bias for an unplanned revascularization, we compared a subsequent mortality of patients with and without an unplanned revascularization, and the association of an unplanned revascularization and long-term mortality was not apparent. On the basis of our findings, critiques for the premature stop of the FAME 2 attributed to a significant difference in a composite outcome between groups would be considered reasonable.

Knowing the prognostic significance of an admission for coronary revascularization may be of particular importance in a Japanese context, given that follow-up anatomical assessment, including coronary artery angiography or coronary computed tomography angiography, is commonly performed ≈1 year after the index PCI.[21] This practice pattern could facilitate the detection of an asymptomatic lesion and the subsequent revascularization.[22–24] Past reports indicated that this practice is associated with an increased detection of
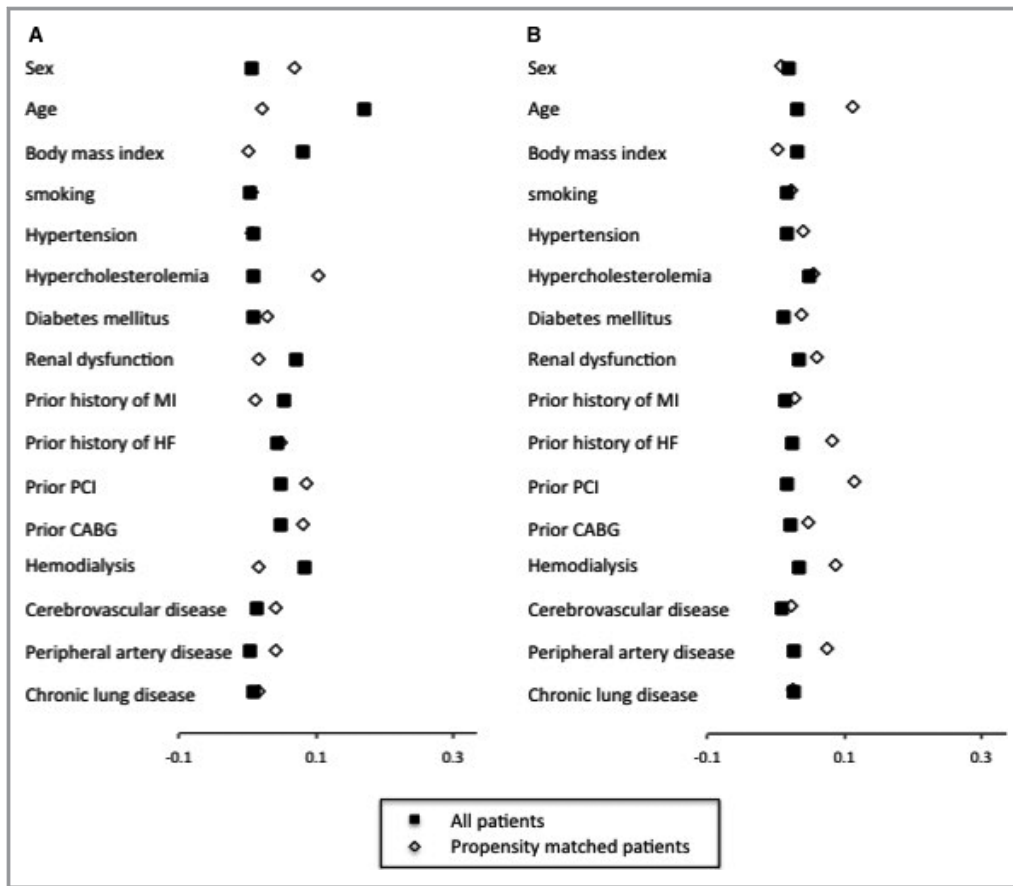
Figure 2. Standardized differences of baseline characteristics between pre- and postmatched cohorts. After greedy matching, baseline characteristics were well balanced, and standardized differences were almost all <0.1 in both (A) future ACS admission and (B) unplanned coronary revascularization matched cohorts. ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

restenosis and the implementation of revascularization.[22–24] In addition, a recent randomized, controlled trial demonstrated that routine follow-up angiography strategy after the initial PCI did not improve clinical outcomes, quantified as a composite of cardiovascular death, MI, and hospitalization for ACS and/or heart failure, compared with clinical follow-up alone.[25] However, few studies evaluated the prognostic impact of the subsequent revascularization after the initial PCI, and our study addresses this paucity of evidence. Therefore, the current findings in our study may open the further discussion about the added value of doing routine angiographic or coronary computed tomography angiography follow-up post-PCI, like the ones that are commonly performed within PCI treating facilities in Japan.

Limitations

Our findings should be interpreted in the context of several potential limitations. First, despite the fact that our registry covers more than 200 clinical variables and procedure-related factors in accordance with the National Cardiovascular Data Registry CathPCI registry in the United States, and propensity score matching was performed to control for many of these variables, the potential for unmeasured confounding remains. Second, in our registry, the follow-up survey focused only on clinically driven events: death; ACS; heart failure; ischemic and/or hemorrhagic stroke; and bleeding. Therefore, a subsequent revascularization was retrospectively reviewed, and some revascularization events may not have been captured, especially, for cases transferred to institutions outside of the JCD-KiCS network. Third, we were unable to obtain information on the 5% of patients that were lost to follow-up after 2 years in our data set, and our findings may not necessarily extend to those patients. Finally, because of the small sample size and limited statistical power, caution should be exercised when interpreting our results. Even though the effects of UA and unplanned revascularization on mortality were not statistically significant, the confidence intervals surrounding the hazard ratios were wide and further replication of our findings is needed.
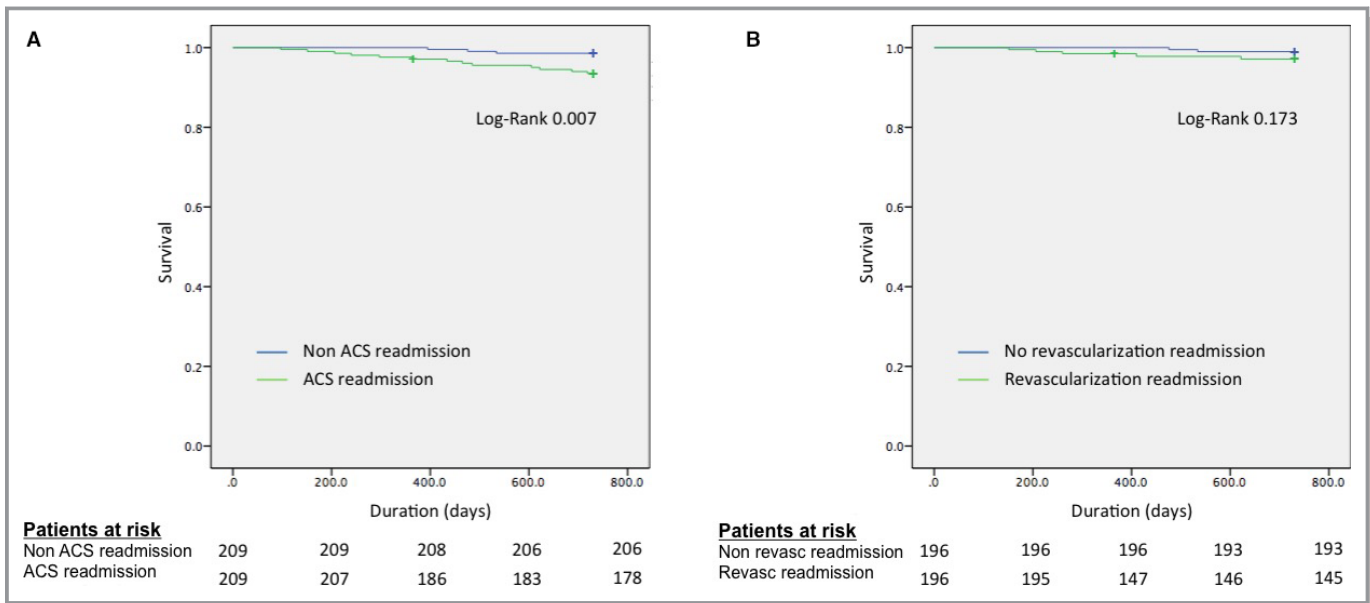
Figure 3. Kaplan–Meier survival curves for all-cause deaths (A) in patients with and without future ACS admission and (B) in patients with and without unplanned revascularization. ACS indicates acute coronary syndrome; Revasc, revascularization.

Future Directions

Our study identified several future directions with respect to research and clinical practice. From the research perspective, cardiovascular composite end points should potentially be reconsidered. Although ACS readmissions seem to be an important component of clinical end points, the roles of unplanned revascularization or UA alone as a component of trial end points warrants further study. From the clinical standpoint, given the lack of prognostic benefit

from the subsequent revascularization after the index PCI, thorough discussion about the added value of performing routine angiographic assessment after the index PCI is required.

Conclusions

In Japanese patients that underwent PCI, having a subsequent ACS, particularly an MI, was associated with worse prognosis,
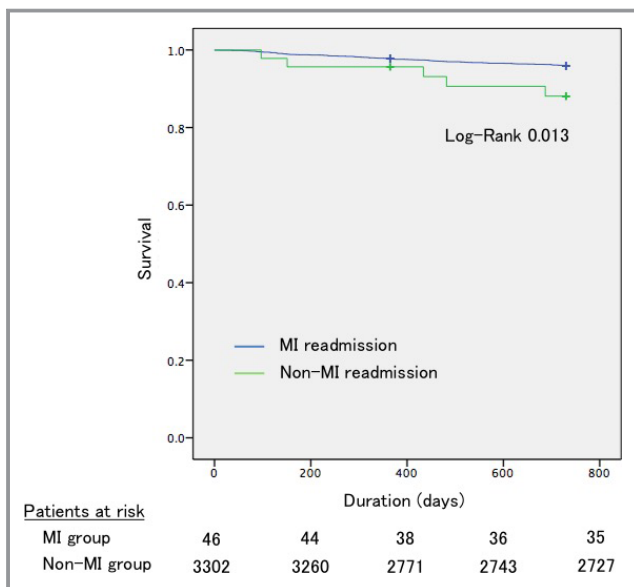
Figure 4. Kaplan–Meier survival curves for all-cause deaths in patients with a future MI readmission vs those without. MI indicates myocardial infarction.
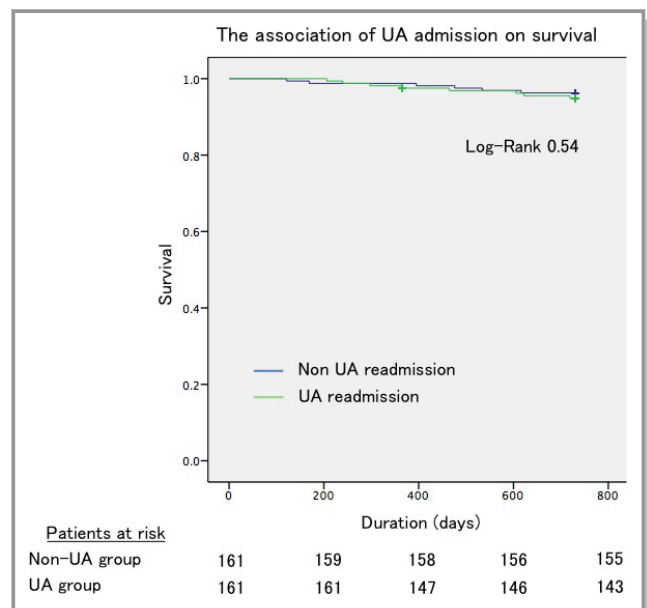
Figure 5. Kaplan–Meier survival curves for all-cause deaths in patients with and without future UA admission. UA indicates unstable angina.

but undergoing subsequent unplanned coronary revascularization or experiencing an episode of UA were not.

References

1. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA*. 2003;289:2554–2559.

2. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, Alonso-Coello P, Alonso J, Worster A, Upadhye S, Jaeschke R, Schunemann HJ, Permanyer-Miralda G, Pacheco-Huergo V, Domingo-Salvany A, Wu P, Mills EJ, Guyatt GH. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ*. 2007;334:786.

3. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.

4. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.

5. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA; Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117–1124.

6. Daemen J, Kuck KH, Macaya C, LeGrand V, Vrolix M, Carrie D, Sheiban I, Suttorp MJ, Vranckx P, Rademaker T, Goedhart D, Schuijer M, Wittebols K, Macours N, Stoll HP, Serruys PW; ARTS-II Investigators. Multivessel coronary revascularization in patients with and without diabetes mellitus: 3-year follow-up of the ARTS- II (Arterial Revascularization Therapies Study-Part II) trial. *J Am Coll Cardiol*. 2008;52:1957–1967.

7. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.

8. Inohara T, Kohsaka S, Miyata H, Ueda I, Ishikawa S, Ohki T, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness ratings of percutaneous coronary intervention in Japan and its association with the trend of noninvasive testing. *JACC Cardiovasc Interv*. 2014;7:1000–1009.

9. Inohara T, Kohsaka S, Miyata H, Ueda I, Noma S, Suzuki M, Negishi K, Endo A, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness of coronary interventions in Japan by the US and Japanese standards. *Am Heart J*. 2014;168:854–861.e11.

10. Inohara T, Kohsaka S, Abe T, Miyata H, Numasawa Y, Ueda I, Nishi Y, Naito K, Shibata M, Hayashida K, Maekawa Y, Kawamura A, Sato Y, Fukuda K. Development and validation of a pre-percutaneous coronary intervention risk model of contrast-induced acute kidney injury with an integer scoring system. *Am J Cardiol*. 2015;115:1636–1642.

11. Inohara T, Kohsaka S, Miyata H, Ueda I, Hayashida K, Maekawa Y, Kawamura A, Numasawa Y, Suzuki M, Noma S, Nishi Y, Fukuda K. Real-world use and appropriateness of coronary interventions for chronic total occlusion (from a Japanese Multicenter Registry). *Am J Cardiol*. 2015;116:858–864.

12. Inohara T, Miyata H, Ueda I, Maekawa Y, Fukuda K, Kohsaka S. Use of intra-aortic balliin pump in a Japanese multicenter percutaneous coronary intervention registry. *JAMA Intern Med*. 2015;175:1980–1982.

13. Kohsaka S, Miyata H, Ueda I, Masoudi FA, Peterson ED, Maekawa Y, Kawamura A, Fukuda K, Roe MT, Rumsfeld JS; JCD-KiCS and NCDR. An international comparison of patients undergoing percutaneous coronary intervention: a collaborative study of the National Cardiovascular Data Registry (NCDR) and Japan Cardiovascular Database-Keio interhospital Cardiovascular Studies (JCD-KiCS). *Am Heart J*. 2015;170:1077–1085.

14. Inohara T, Kohsaka S, Miyata H, Ueda I, Maekawa Y, Fukuda K, Cohen DJ, Kennedy KF, Rumsfeld JS, Spertus JA. Performance and validation of the U.S. NCDR acute kidney injury prediction model in Japan. *J Am Coll Cardiol*. 2016;67:1715–1722.

15. Brindis RG, Fitzgerald S, Anderson HV, Shaw RE, Weintraub WS, Williams JF. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. *J Am Coll Cardiol*. 2001;37:2240–2245.

16. Weintraub WS, McKay CR, Riner RN, Ellis SG, Frommer PL, Carmichael DB, Hammermeister KE, Effros MN, Bost JE, Bodycombe DP. The American College of Cardiology National Database: progress and challenges. American College of Cardiology database committee. *J Am Coll Cardiol*. 1997;29:459–465.

17. National Cardiovascular Data Registry (NCDR) CathPCI Registry. Available at: https://http://www.ncdr.com/webncdr/cathpci/. Accessed March 23, 2017.

18. Sabatine MS, Morrow DA, Giugliano RP, Murphy SA, Demopoulos LA, DiBattiste PM, Weintraub WS, McCabe CH, Antman EM, Cannon CP, Braunwald E. Implications of upstream glycoprotein IIb/IIIa inhibition and coronary artery stenting in the invasive management of unstable angina/non-ST-elevation myocardial infarction: a comparison of the thrombolysis in myocardial infarction (TIMI) IIIB trial and the treat angina with aggrastat and determine cost of therapy with invasive or conservative strategy (TACTICS)-TIMI 18 trial. *Circulation*. 2004;109:874–880.

19. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091.

20. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members, Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354–2394.

21. JCS Joint Working Group. Guidelines for noninvasive diagnosis of coronary artery lesions (JCS 2009). *Circ J*. 2009;73:1019–1089.

22. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, Cohen DJ, Kuntz RE. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol*. 2002;40:2082–2089.

23. ten Berg JM, Kelder JC, Suttorp MJ, Verheugt FW, Thijs Plokker HW. Influence of planned six-month follow-up angiography on late outcome after percutaneous coronary intervention: a randomized study. *J Am Coll Cardiol*. 2001;38:1061–1069.

24. Pinto DS, Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Mehran R, Na Y, Turco M, Caputo R, Popma JJ, Cutlip DE, Russell ME, Cohen DJ; TAXUS-IV Investigators. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: results from the TAXUS-IV trial. *J Am Coll Cardiol*. 2006;48:32–36.

25. Shiomi H, Morimoto T, Kitaguchi S, Nakagawa Y, Ishii K, Haruna Y, Takamisawa I, Motooka M, Nakao K, Matsuda S, Mimoto S, Aoyama Y, Takeda T, Murata K, Akao M, Inada T, Eizawa H, Hyakuna E, Awano K, Shirotani M, Furukawa Y, Kadota K, Miyauchi K, Tanaka M, Noguchi Y, Nakamura S, Yasuda S, Miyazaki S, Daida H, Kimura K, Ikari Y, Hirayama H, Sumiyoshi T, Kimura T; ReACT investigators. The ReACT trial: randomized evaluation of routine follow-up coronary angiography after percutaneous coronary intervention trial. *JACC Cardiovasc Interv*. 2017;10:109–117.