Randomized Evaluation of Routine Follow-up Coronary Angiography after Percutaneous Coronary Intervention Trial (ReACT)

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ABSTRACT

Background: Long-term clinical impact of routine follow-up coronary angiography (FUCAG) after percutaneous coronary intervention (PCI) in real world clinical practice has not been adequately evaluated yet.

Objectives: To evaluate long-term clinical impact of routine FUCAG after PCI in daily clinical practice in Japan.

Methods: In this prospective multicenter open-label randomized trial, patients who underwent successful PCI were randomly assigned to routine angiographic follow-up (AF) group, in which patients were to receive FUCAG at 8- to 12-month after PCI, or clinical follow-up alone (CF) group. Primary endpoint was defined as a composite of death, myocardial infarction, stroke, emergency hospitalization for acute coronary syndrome, or hospitalization for heart failure during minimum of 1.5 years follow-up.

Results: Between May 2010 and July 2014, a total of 700 patients were enrolled in the trial among 22 participating centers and were randomly assigned to AF group (N=349) or CF group (N=351). During median 4.6 (inter-quartile range: 3.1-5.2) years follow-up, the cumulative 5-year incidence of the primary endpoint was 22.4% in AF group and 24.7% in CF group (hazard ratio: 0.94, 95% confidence interval: 0.67-1.31, P=0.70). Any coronary revascularization within the first year was more frequently performed in AF group than in CF group (12.8% versus 3.8%,

log-rank P<0.001), although the difference between the 2 groups attenuated over time with similar cumulative 5-year incidence (19.6% versus 18.1%, log-rank P=0.92).

Conclusions: No clinical benefits were observed for routine FUCAG after PCI and early coronary revascularization rates were increased within routine FUCAG strategy in the current trial.

ClinicalTrials.gov number, NCT 01123291.

KEY WORDS: angiographic follow-up, percutaneous coronary intervention, stent, and prognosis.

CONDENSED ABSTRACT

Long-term clinical impact of routine follow-up coronary angiography (FUCAG) after percutaneous coronary intervention (PCI) in real world clinical practice has not been adequately evaluated yet. Between May 2010 and July 2014, a total of 700 patients were randomly assigned to angiographic follow-up (AF) group (N=349) or clinical follow-up alone (CF) group (N=351). During median 4.6 (inter-quartile range: 3.1-5.2) years follow-up, the cumulative 5-year incidence of a composite of death/myocardial infarction/stroke/acute coronary syndrome/heart failure was 22.4% in AF group and 24.7% in CF group (log-rank P=0.70). In conclusions, no clinical benefits were observed for routine FUCAG after PCI.

ABBREVIATIONS

ACS = acute coronary syndrome

AMI = acute myocardial infarction

BMS = bare-metal stents

CABG = coronary artery bypass grafting

DES = drug-eluting stents

FUCAG = follow-up coronary angiography

HF = heart failure

IQR = inter-quartile range

PCI = percutaneous coronary intervention

TLR = target-lesion revascularization

INTRODUCTION

In several previous studies, routine follow-up coronary angiography (FUCAG) after percutaneous coronary intervention (PCI) increased the rate of coronary revascularization, but did not improve clinical outcomes. (1-4) Based on these study results, the current clinical guidelines in the United States have already disregarded routine FUCAG even after PCI for left main coronary artery (LMCA) disease, while the current clinical guidelines in Europe regarded routine FUCAG after high-risk PCI as Class IIb. (5,6) However, previous studies in the drug-eluting stents (DES) era were conducted in the context of pivotal randomized trials of DES and there have been no randomized clinical trial evaluating long-term clinical impact of routine FUCAG after PCI in the real world clinical practice including high-risk patients for cardiovascular events risk such as complex coronary artery disease and acute myocardial infarction (AMI) presentation. (3,7,8) The current randomized clinical trial, therefore, was conducted to evaluate long-term clinical impact of routine FUCAG after PCI in real world clinical practice in Japan, where routine FUCAG after PCI is still commonly performed as the usual care. (4,9,10)

METHODS

Study Design and Patient Selection. Randomized evaluation of routine follow-up coronary Angiography after percutaneous Coronary intervention Trial (ReACT) is a prospective

multicenter open label randomized trial comparing the routine angiographic follow-up strategy with the clinical follow-up alone strategy in daily clinical practice in Japan. In this all-comer design trial, patients who underwent successful PCI without planned staged PCI were enrolled from 22 participating centers (List A in the Supplementary Appendix) without any exclusion criteria. The study protocol was approved by the institutional review board at each participating center. Written informed consent was obtained from all the study patients. The trial was registered with ClinicalTrials.gov number, NCT01123291.

Study Procedures. Patients were randomly allocated in a 1:1 ratio to routine angiographic follow-up (AF) group or clinical follow-up (CF) group. Randomization was performed before hospital discharge after the index PCI and stratified by centers and bare-metal stents (BMS) use. In AF group, patients were planned to receive routine FUCAG at 8- to 12-month after the index PCI, while in CF group, patients were planned to receive clinical follow-up only without routine FUCAG. During follow-up, any physiological stress tests such as treadmill exercise test or stress nuclear study were allowed to be performed, but coronary computed tomography angiography was not allowed in both groups. Clinically indicated coronary angiographic studies, such as those for acute coronary syndrome (ACS), for recurrence of angina, and/or for objective evidence of myocardial ischemia, were allowed based on the decision by the attending physicians.

Follow-up data were collected by the clinical research coordinators belonging to the

participating centers, or to the academic research organization (Research Institute for Production Development, Kyoto, Japan). Follow-up assessments were performed by means of hospital visit or telephone contact with the patient and/or the referring physician at 1-year and at final follow-up. Data collection for the final follow-up was started at February 1st, 2016, which was 1.5 years after the last patient enrollment.

Primary and Secondary Endpoints. The primary endpoint was defined as a composite of death, myocardial infarction (MI), stroke, emergency hospitalization for ACS, or hospitalization for heart failure (HF) during the minimum of 1.5 years clinical follow-up after the index PCI.

The secondary endpoints included all-cause death, MI, stroke, emergency hospitalization for ACS, hospitalization for HF, definite stent thrombosis, major bleeding, target-lesion revascularization (TLR), clinically-driven TLR, any coronary revascularization, and clinically-driven coronary revascularization.

MI and stent thrombosis were defined according to the Academic Research Consortium definitions. (11) Stroke during follow-up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 hours. ACS was diagnosed according to clinical symptoms, electrocardiographic changes compatible with acute myocardial ischemia, and elevation of cardiac biomarkers. AMI (ST-segment elevation AMI and non–ST-segment elevation AMI) and unstable angina (UA) were distinguished according to the presence or

absence of cardiac biomarker elevation. UA was adjudicated only in the presence of the angiographically evident culprit lesion. Hospitalization for HF was defined as hospitalization due to worsening heart failure requiring intravenous drug therapy. Major bleeding was defined as moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification. (12) TLR was defined as either PCI or coronary artery bypass grafting (CABG) due to restenosis or thrombosis of the target lesion that included the proximal and distal edge segments as well as the ostium of the side branches. Only those lesions treated at the time of the index PCI procedure were regarded as target lesions. Any coronary revascularization was defined as either PCI or CABG for any reasons. A coronary revascularization was considered clinically indicated if one of the following occurred: (1) a positive history of recurrent angina pectoris; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent); (3) abnormal results of any invasive functional diagnostic test (e.g. fractional flow reserve).

Adjudication of endpoint events by an independent clinical event committee (List. B in the Supplementary Appendix) was conducted in a blinded fashion regarding the assigned study groups. Clinical outcomes are analyzed according to the intention-to-treat principle.

Statistical Analyses. Categorical variables were expressed as number (%), and were compared with the chi-square test or Fisher's exact test. Continuous variables were expressed as mean

value ± SD or median with inter-quartile range (IQR). Continuous variables were compared using the Student's t-test or Wilcoxon rank sum test based on their distributions. The cumulative incidence of a clinical event was assessed by Kaplan-Meier method and compared by log-rank test. We developed the Cox proportional hazard model incorporating the random effect of center to take the differences in management between facilities into consideration. The effect of routine follow-up angiography for the primary endpoint was expressed by hazard ratio (HR) with its 95% confidence interval (CI). As a subgroup analysis, treatment effect of routine angiographic follow-up strategy relative to clinical follow-up strategy was evaluated in several clinically relevant subgroups including those patients with diabetes mellitus, restenotic lesion, LMCA disease, chronic total occlusion lesion, bifurcation lesion, multivessel disease, total stent length>= 40mm, and "post -hoc" high-risk group defined as having at least 1 high-risk features such as LMCA disease, bifurcation lesion, multivessel disease, and total stent length>= 40mm.

The trial was originally designed to enroll 3300 patients to ensure a power of 80% to detect a 15% relative reduction of the primary endpoint rate at 3 year in AF group as compared with that in CF group, in which the estimated primary endpoint event rate was 25% at 3 year based on the data from the j-Cypher registry.(13) The enrollment of study patients was started at May 2010. In June 2014, however, the protocol was amended to have a target enrollment of 700 patients with estimated median follow-up duration of 5 years, because of slow enrollment

resulting in longer follow-up interval. The sample size calculation were based on an estimated primary event rate of 47.7% in CF group, with a power of 80% to detect a relative reduction of 25% in AF group as compared with CF group for the primary endpoint, assuming 25% crossover and lost to follow-up. Interim analysis was not performed during the study period.

All statistical analyses were performed using JMP 8.0 (SAS Institute Inc, Cary, NC) and SAS 9.4 (SAS Institute, Inc, Cary, NC) software. All reported P values were two-sided and P values <0.05 were regarded as statistically significant.

RESULTS

Study Population. Between May 2010 and July 2014, a total of 700 patients were enrolled in the trial among 22 participating centers and were randomly assigned to AF group (N=349) or CF group (N=351) (Figure 1). The 2 study groups were balanced with regard to clinical, angiographic, and procedural characteristics (Table 1). The study population reflected the real-world clinical practice in Japan, including large proportions of patients with advanced age, diabetes mellitus, prior PCI, multivessel disease, and significant proportions of patients with AMI presentation, target of bifurcation lesion, and target of chronic total occlusion. Regarding the PCI procedure, DES was used in 85% of patients, in whom second-generation DES was used in 89% of patients (Table 1).

FUCAG during the first year including those due to clinical reasons were actually

performed in 298 patients (85.4%) in AF group, and in 42 patients (12.0%) in CF group. Median time to FUCAG in patients receiving FUCAG within 1-year after index PCI was 287 (IQR: 253-322) days in AF group (N=298/349), and 235 (IQR: 174-299) days in CF group (N=42/351). In the AF group, 21 patients (7%) underwent coronary angiography due to clinical reasons. In the CF group, the reasons for coronary angiography within the first year included 6 patients (14%) for ACS, 25 patients (60%) for recurrence of angina, 6 patients (14%) for other clinical reasons and 5 patients (12%) without any clinical reason (protocol violation) (Figure 1). Non-invasive physiological stress tests such as treadmill exercise test and stress nuclear study were more often performed in CF group than AF group within the first year after PCI (33.6% and 25.2%, P=0.01), and during the entire follow-up period (52.7% and 40.1%, P<0.001).

Clinical Outcomes. Median follow-up duration after the index PCI was 4.6 (IQR: 3.1-5.2) years in the entire study population (AF group: 4.5 [IQR: 3.1-5.2], and CF group: 4.6 [IQR: 3.1-5.2], P=0.87). Clinical follow-up rate was 98.6% at 1-year and 95.5% at 3-year (277 eligible patients) in AF group, and 99.4% at 1-year and 96.2% at 3-year (279 eligible patients) in CF group. The cumulative 5-year incidence of the primary endpoint was 22.4% in AF group and 24.7% in CF group (HR: 0.94, 95%CI: 0.67-1.31, P=0.70) (Table 2 and Figure 2).

The cumulative 5-year incidences of the individual components of the primary endpoint such as all-cause death, MI, stroke, emergency hospitalization for ACS, and hospitalization for

HF were also not significantly different between the AF and CF groups (Table 2). The cumulative 5-year incidence of major bleeding was also not different between the 2 groups (Table 2).

TLR within the first year after the index PCI was performed more frequently in AF group than in CF group (7.0% versus 1.7%, log-rank P<0.001) (Figure 3A and Supplementary Figure 1A). However, the cumulative 5-year incidence of TLR in AF group was not significantly different with that in CF group (10.4% versus 8.5%, log-rank P=0.12) (Table 2 and Figure 3A). Any coronary revascularization within the first year after the index PCI was also more frequently performed in AF group than in CF group (12.8% versus 3.8%, log-rank P<0.001) (Figure 3B). However, any coronary revascularization beyond the first year after the index PCI was more frequently performed in CF group than in AF group, and the difference in any coronary revascularization between the 2 groups attenuated over time with similar cumulative 5-year incidence (19.6% versus 18.1%, log-rank P=0.92) (Table 2, Figure 3B, and Supplementary Figure 1B).

Regarding the subgroup analyses, there was no significant interaction between the subgroup factors and the effect of AF relative to CF on the primary endpoint (Figure 4).

DISCUSSION

The main findings of the current trial were as follows; 1) Routine FUCAG after PCI did not

provide any clinical benefits as compared with clinical follow-up alone; 2) Increased 1-year rate of repeat coronary revascularization with routine angiographic follow-up attenuated with long-term follow-up.

Previous randomized trials in balloon angioplasty or BMS era and non-randomized studies in DES era consistently reported that routine FUCAG increased repeat coronary revascularization, but did not reduce major adverse cardiac events, although the rate of MI was slightly lower in angiographic follow-up than in clinical follow-up alone in the substudies of the Balloon Angioplasty and Anticoagulation Study (BAAS) and the TAXUS-IV trial. (1-3,7,8) However, the impact of routine FUCAG for high-risk patients in real world practice has not been fully evaluated, because all the previous studies included patients with relatively low-risk profile in terms of comorbidity and lesion complexity. Cassese S et al. reported that the presence of restenosis at FUCAG after PCI was predictive of 4-year mortality in their cohort of 10,004 patients with routine FUCAG.(14) However, as the authors correctly stated in their article, the understanding of a potential role for routine follow-up angiography was beyond the scope of their study. According to the findings of the current trial, which included high-risk patients in real clinical practice, routine FUCAG did not provide any clinical benefit including preventive effect of MI. Routine FUCAG after PCI is still commonly performed as the usual care in Japan without assured evidence of clinical benefit. (4,9,10) Considering the invasive nature of coronary

angiography and increased medical expenses, routine FUCAG after PCI would not be allowed as the usual clinical practice, unless patients have recurrent symptom or objective evidence of ischemia. On the other hands, there was no excess of adverse clinical events with routine angiographic follow-up strategy except for the increased rate of 1-year repeat coronary revascularization. Therefore, the scheduled angiographic follow-up would still be acceptable in the first-in-man coronary device trials, or as the mechanistic sub-study in the pivotal coronary device trials.

"Oculostenotic reflex" phenomenon, which means coronary revascularization for angiographic stenosis without objective evidence of ischemia, was reported as a negative aspect of routine FUCAG, which resulted in approximately 2-fold higher rate of repeat coronary revascularization as compared with clinical follow-up alone in several previous studies. (1-3) In the substudy of the SPRIT III trial evaluating newer generation DES, however, the cumulative incidence of repeat coronary revascularization was not significantly different between routine FUCAG and clinical follow-up alone in 3-year clinical follow-up (12.4% versus 11.3%, log-rank P=0.45). (8) Consistent with the results of the SPRIT III trial, long-term risks for TLR and any coronary revascularization were not significantly different between AF and CF groups in the current trial. Despite the 3-fold higher 1-year rate of TLR and any coronary revascularization in AF group, this large difference gradually attenuated with long-term follow-up in the current trial.

Annual 1.7% rate of late TLR beyond 1 year after PCI in CF group, which resulted in the attenuation of the difference in TLR between the 2 groups, was consistent with the annual 2.0-2.2% rate of late TLR beyond 1-year reported in first- and newer-generation DES studies. (15,16) On the other hands, the relatively lower 0.9% annual rate of late TLR in AF group might suggest that many of the lesions with late TLR in CF group actually had early restenosis within 1-year. Late TLR is one of the unsolved issues in contemporary PCI using DES. It would be a clinically relevant question whether the fully bioresorbable coronary scaffold could overcome the late adverse events related to the target-lesion after complete resorption of the scaffold. (17) The other possible reason for the attenuation of the between group difference in the coronary revascularization rate during long-term follow-up was higher rate of coronary revascularization for new lesions or progression of non-target lesions in CF group. The lesions treated at the time of FUCAG might anyway undergo clinically-driven revascularization with long-term follow-up, even if not detected by FUCAG within 1-year.

Limitations. The current trial has several limitations. First, the current trial was underpowered to detect modest differences in the primary endpoint due to the reduced final sample size and the actual event rate lower than anticipated, although the size of the present study was similar to the previous studies. Therefore, the current trial result might be “inconclusive” rather than “negative”, warranting future larger-scale studies. Furthermore, we were unable to address the

role of routine angiographic follow-up in the high-risk subgroups such as left main or multivessel coronary artery disease. Future dedicated studies are warranted to evaluate the role of routine angiographic follow-up in these high-risk subsets of patients. Second, slow patient enrollment might indicate patient's selection bias that would potentially influence the study results. Finally, because patient demographics, practice patterns including the indication of coronary revascularization, and clinical outcomes in Japan may be different from those outside Japan, generalizing the present study results to populations outside Japan should be done with caution.

CONCLUSIONS

No clinical benefits were observed for routine FUCAG after PCI and early revascularization rates were increased within this approach in the current trial. Thus, routine FUCAG cannot be recommended as a clinical strategy. However, the present study was underpowered to detect modest benefits (or harm) of routine FUCAG, and larger-scale trials (especially in high-risk patients) are warranted to definitively address this issue.

PERSPECTIVES

WHAT IS KNOWN?

Routine follow-up coronary angiography (FUCAG) after percutaneous coronary intervention (PCI) could not improve clinical outcomes but increased the rate of coronary revascularization due to “Oculostenotic reflex” in the previous studies. However, there have been no randomized clinical trial evaluating clinical impact of routine FUCAG after PCI in the real world clinical practice including high-risk patients for cardiovascular events risk.

WHAT IS NEW?

In this trial which included large proportion of high-risk patients for cardiovascular events risk in daily clinical practice in Japan, no clinical benefits were observed for routine FUCAG after PCI and early revascularization rates were increased within this approach.

WHAT IS NEXT?

Future larger-scale trials (especially in high-risk patients) are warranted to definitively address the role of routine FUCAG after PCI in high-risk subsets such as left main or multivessel coronary artery disease.

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FIGURE LEGEND

Figure 1. Study flow chart

AF indicates angiographic follow-up; CF, clinical follow-up; FUCAG, follow-up coronary angiography; and ACS, acute coronary syndrome.

Figure 2. Cumulative incidence of the primary endpoint

AF indicates angiographic follow-up; CF, clinical follow-up; ACS, acute coronary syndrome; and HF, heart failure.

Figure 3. Cumulative incidence of (A) target-lesion revascularization and (B) any coronary revascularization

AF indicates angiographic follow-up; and CF, clinical follow-up.

Figure 4. Subgroup analyses for the effect of AF relative to CF on the primary endpoint

The “post-hoc” high-risk subgroup was defined as having at least 1 high-risk feature such as LMCA disease, bifurcation lesion, multivessel disease, and total stent length>= 40mm.

AF indicates angiographic follow-up; CF, clinical follow-up; CTO=chronic total occlusion; LMCA=left main coronary artery.

Table 1 Baseline Clinical, Angiographic, and Procedural Characteristics, and Medications

	AF group (N=349)	**CF group (N=351)**
Clinical characteristics		
Age - years	68.9±10.0	68.2±9.1
Male sex	260 (75%)	291 (83%)
Body mass index	24.3±3.4	24.2±3.2
Hypertension	256 (73%)	279 (79%)
Diabetes mellitus	144 (41%)	169 (48%)
Dyslipidemia	268 (77%)	280 (80%)
eGFR - ml/min/1.73m^2	65.9±21.7	66.1±21.7
eGFR<30 ml/min/1.73m^2, not on hemodialysis	6 (1.8%)	5 (1.5%)
Hemodialysis	13 (3.7%)	12 (3.4%)
Current smoker	62 (18%)	65 (19%)
Prior myocardial infarction	60 (17%)	65 (19%)
Prior percutaneous coronary intervention	105 (30%)	121 (34%)
Prior coronary artery bypass grafting	9 (2.6%)	12 (3.4%)
Prior stroke	25 (7.2%)	36 (10%)
Past history of heart failure	18 (5.2%)	23 (6.6%)
Atrial fibrillation	19 (5.4%)	28 (8.0%)
Clinical characteristics		
Stable coronary artery disease	222 (64%)	222 (63%)
Unstable angina	56 (16%)	62 (18%)
Acute myocardial infarction	71 (20%)	67 (19%)
Peripheral artery disease	43 (12%)	41 (12%)
Malignancy	57 (16%)	38 (11%)
Angiographic and procedural characteristics		
Multivessel disease	145 (42%)	153 (44%)
Target-vessel location		
LMCA	15 (4.3%)	13 (3.7%)
LAD	194 (56%)	196 (56%)
LCX	98 (28%)	87 (25%)
RCA	123 (35%)	126 (36%)
Bypass graft	3 (0.9%)	3 (0.9%)
Target of STEMI culprit lesion	62 (18%)	51 (15%)

Target of bifurcation lesion	120 (34%)	107 (30%)
Target of chronic total occlusion	21 (6.0%)	15 (4.3%)
Target of restenosis lesion	25 (7.2%)	25 (7.1%)
Number of treated lesions per patient	1.29±0.57	1.28±0.55
Number of stents used (per patient)	1.54±0.94	1.46±0.81
Total stent length - mm (per patient)	32.9±23.9	31.5±20.8
Drug-eluting stents use	298 (85%)	299 (85%)
First-generation drug-eluting stents	33 (11%)	34 (11%)
Second-generation drug-eluting stents	265 (89%)	265 (89%)
Bare metal stents use	53 (15%)	52 (15%)
Medications		
Aspirin	348 (99.7%)	345 (98%)
Thienopyridine	345 (99%)	347 (99%)
Cilostazole	8 (2.3%)	12 (3.4%)
Statins	288 (83%)	290 (83%)
ACE-I/ARB	207 (59%)	213 (61%)
Beta blockers	124 (36%)	158 (45%)
Calcium channel blocker	133 (38%)	144 (41%)
Nitrates	76 (22%)	78 (22%)
Warfarin	19 (5.4%)	23 (6.6%)
Proton pump inhibitor	184 (53%)	167 (48%)
H2 blocker	46 (13%)	53 (15%)

Continuous variables are presented as mean ± standard deviation, and categorical variables as number (percentage).

eGFR indicates estimated glomerular filtration rates; LMCA, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; and H2 blocker, Histamine type-2 receptor blockers.

Table 2. Long-term (5-year) Clinical Outcomes

	AF group (N=349)	CF group (N=351)	HR (95% Cl)	P value
	Number of patients with at least 1 event (Cumulative 5-year incidence)	Number of patients with at least 1 event (Cumulative 5-year incidence)		
Primary Endpoint				
Death/MI/Stroke/ACS/HF	65 (22.4%)	70 (24.7%)	0.94 (0.67-1.31)	0.70
Secondary Endpoint				
All-cause death	30 (10.8%)	37 (12.5%)	0.81 (0.50-1.31)	0.39
MI	6 (2.7%)	9 (3.6%)	0.66 (0.24-1.86)	0.43
Stroke	11 (3.5%)	12 (4.2%)	0.92 (0.41-2.08)	0.84
Emergency hospitalization for ACS	24 (9.0%)	16 (6.3%)	1.50 (0.79-2.82)	0.21
Hospitalization for heart failure	14 (4.3%)	15 (6.0%)	0.91 (0.44-1.88)	0.79
Definite stent thrombosis	0 (0%)	2 (0.7%)	-	0.16
Major bleeding	9 (3.3%)	14 (5.3%)	0.63 (0.27-1.45)	0.28
Target lesion revascularization	34 (10.4%)	23 (8.5%)	1.51 (0.89-2.57)	0.12
Clinically-driven	19 (5.9%)	21 (7.9%)	0.89 (0.48-1.66)	0.72
Any coronary revascularization	63 (19.6%)	49 (18.1%)	1.36 (0.93-1.97)	0.11
Clinically-driven	47 (15.1%)	46 (16.8%)	1.02 (0.68-1.53)	0.94

Number of patients with at least 1 event was evaluated during the entire follow-up period, while the cumulative incidence was estimated at 5-year.

HR indicates hazard ratio; and CI, confidence interval; MI, myocardial infarction; ACS, acute coronary syndrome; and HF, heart failure.

Figure 1

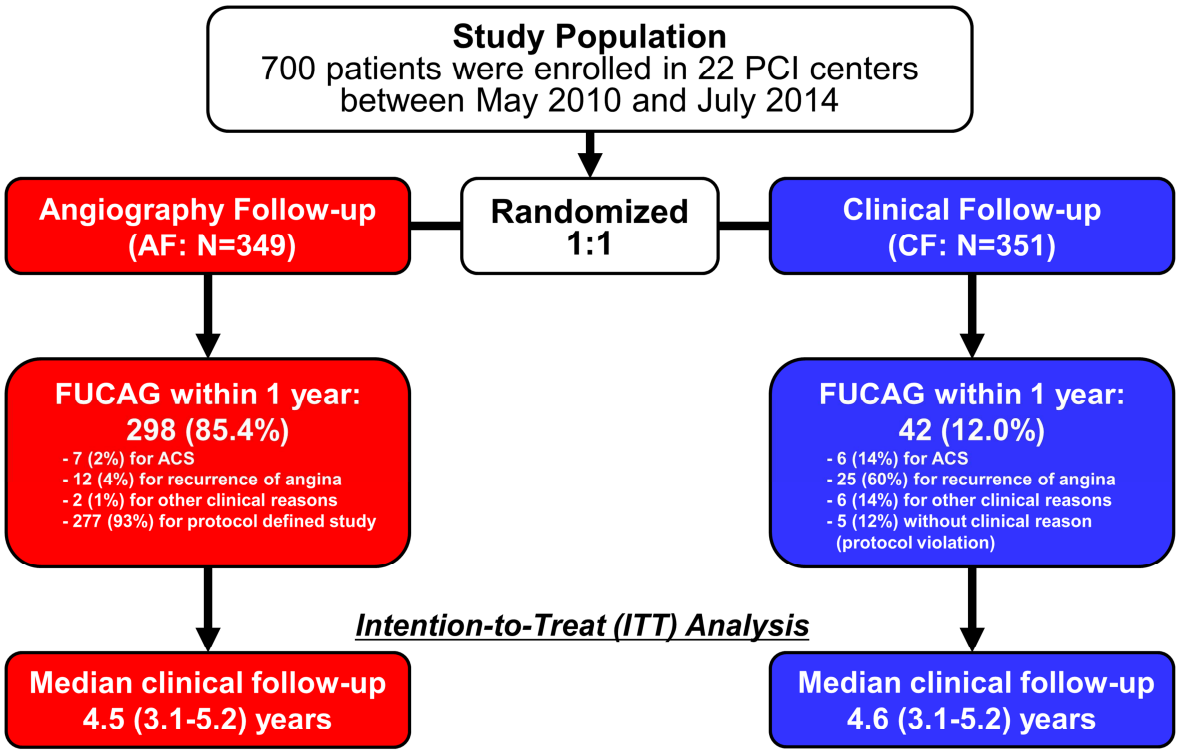
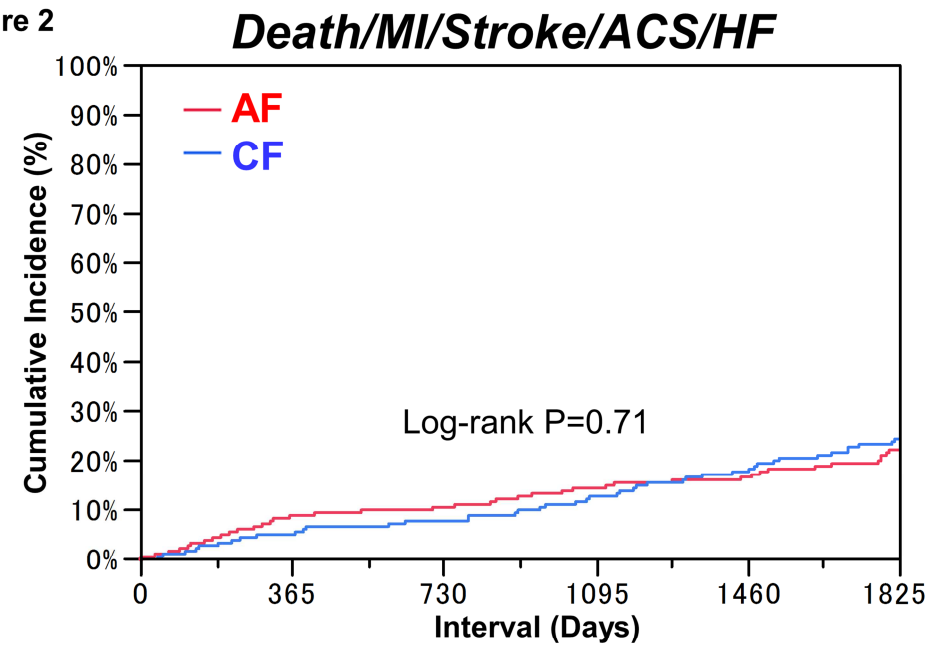
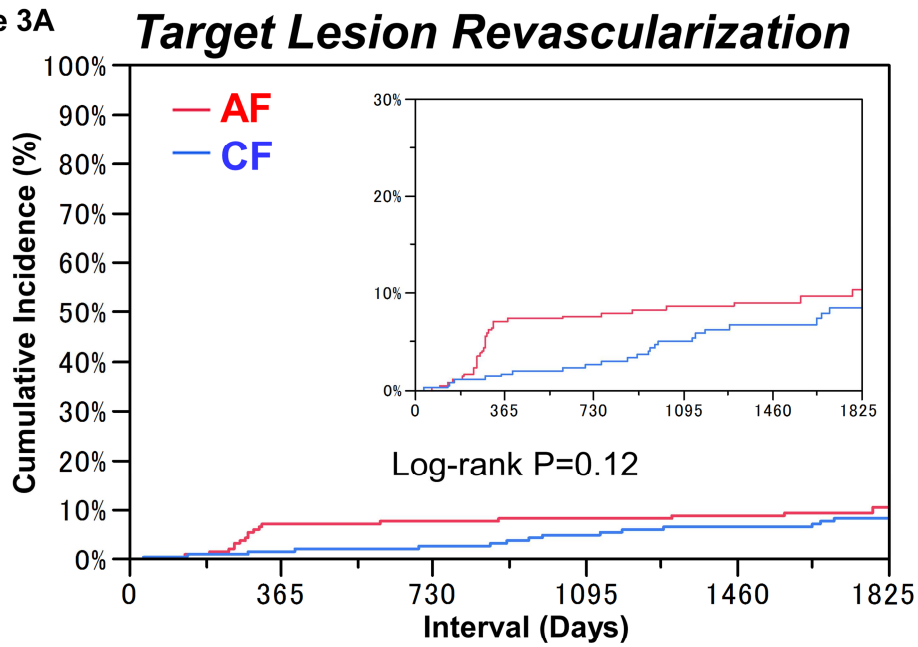


Figure 2



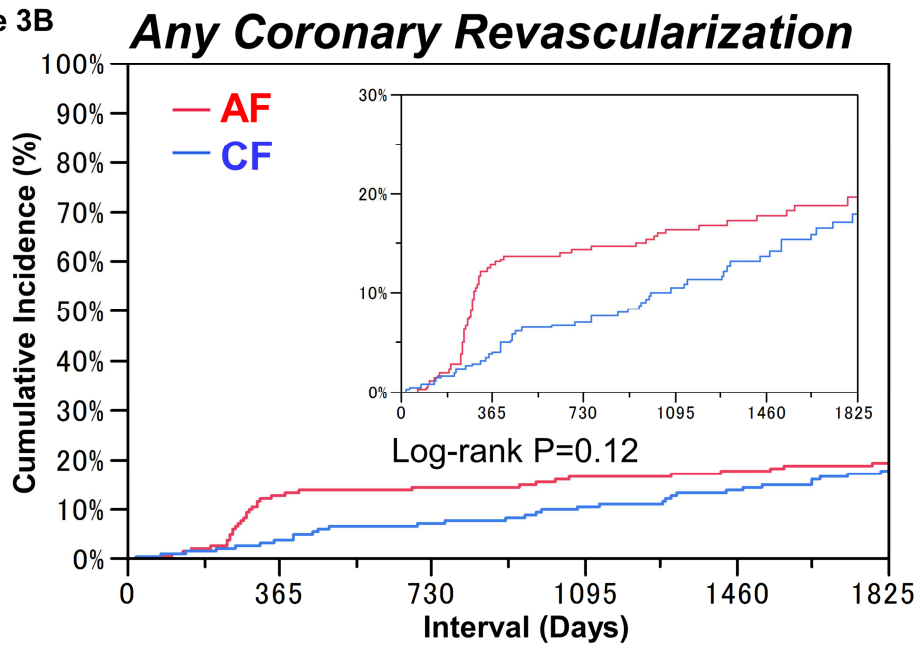
Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
AF group							
N of patients with at least 1 event		2	31	36	49	54	64
N of patients at risk	349	347	313	296	243	182	96
Cumulative incidence		0.6%	8.9%	10.4%	14.6%	16.6%	22.4%
CF group							
N of patients with at least 1 event		0	18	28	42	56	67
N of patients at risk	351	351	331	303	247	175	90
Cumulative incidence		0%	5.1%	8.0%	12.6%	18.4%	24.7%

Figure 3A



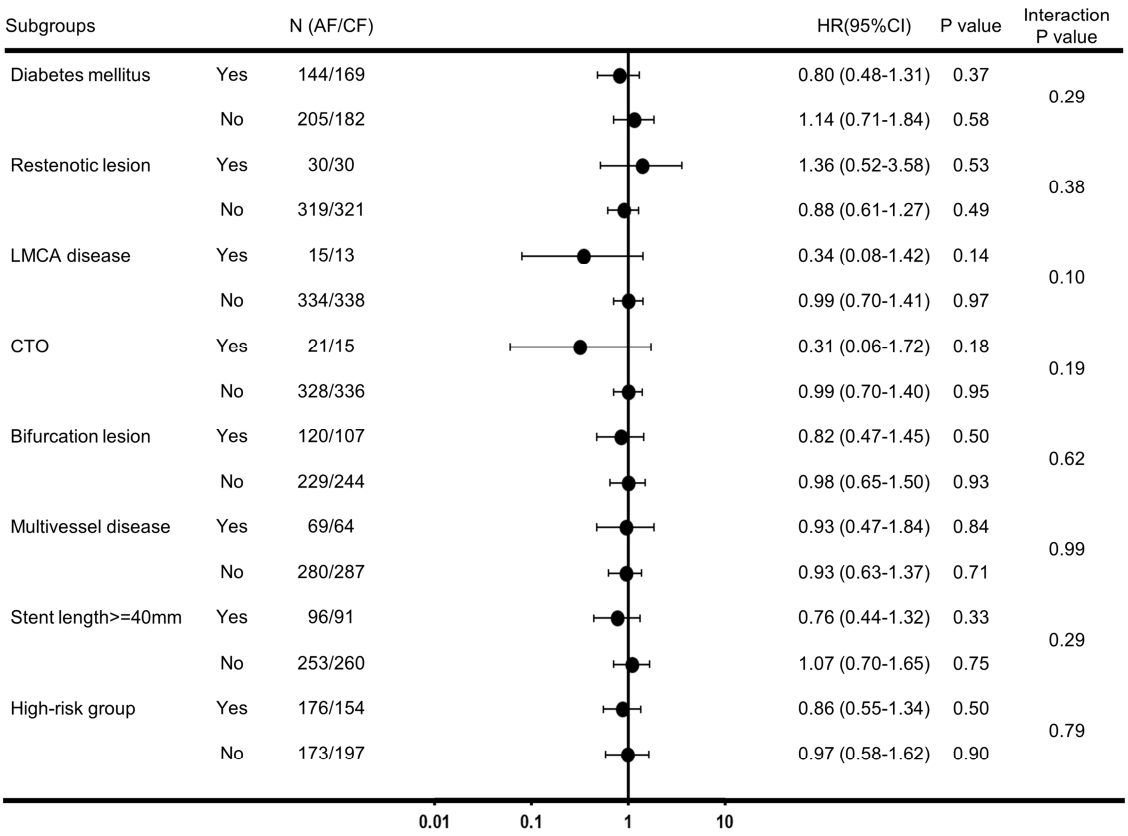
Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
AF group							
N of patients with at least 1 event		0	24	26	29	30	32
N of patients at risk	349	348	317	297	245	180	101
Cumulative incidence		0%	7.0%	7.6%	8.6%	9.0%	10.4%
CF group							
N of patients with at least 1 event		0	6	9	16	20	23
N of patients at risk	351	351	335	310	254	181	98
Cumulative incidence		0%	1.7%	2.6%	5.0%	6.7%	8.5%

Figure 3B



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
AF group							
N of patients with at least 1 event		0	44	49	55	58	61
N of patients at risk	349	348	297	275	221	164	93
Cumulative incidence		0%	12.8%	14.3%	16.4%	17.8%	19.6%
CF group							
N of patients with at least 1 event		1	13	24	34	41	48
N of patients at risk	351	350	328	295	239	165	89
Cumulative incidence		0.3%	3.8%	7.0%	10.5%	13.7%	18.1%

Figure 4



Supplementary Material

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Supplementary Appendix

List A. List of the participating centers and the investigators

Yokohama City University Medical Center: Kazuo Kimura, Kiyoshi Hibi

Kansai Denryoku Hospital: Katsuhisa Ishii, Kazuaki Kataoka

Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi

Kindai University Nara Hospital: Manabu Shirotani

Kindai University: Shunichi Miyazaki

Koto Memorial Hospital: Teruki Takeda

National Cerebral and Cardiovascular Center: Satoshi Yasuda, Kazuhiro Nakao

National Hospital Organization Kyoto Medical Center: Masaharu Akao, Mitsuru Ishii

Saiseikai Shimonoseki General Hospital: Eiji Momona

Sakakibara Heart Institute: Tetsuya Sumiyoshi, Itaru Takamisawa

Juntendo University Hospital: Hiroyuki Daida, Katsumi Miyauchi

New Tokyo Hospital: Satoru Mimoto, Sunao Nakamura

Kobe City Medical Center General Hospital: Yutaka Furukawa

Nishi-Kobe Medical Center: Shintaro Matsuda, Hiroshi Eizawa

Shizuoka City Shizuoka Hospital: Akinori Takizawa, Koichiro Murata

Osaka Red Cross Hospital: Masaru Tanaka, Tsukasa Inada

Tsukuba Medical Center Hospital: Yuichi Noguchi

Tenri Hospital: Yoshihisa Nakagawa, Makoto Motooka

Tokai University: Yuji Ikari

Kitaharima Medical Center: Kojiro Awano

Hirakata Kohsai Hospital: Yoshisumi Haruna, Shoji Kitaguchi

Nagoya Daini Red Cross Hospital: Haruo Hirayama, Mamoru Nanasato

List B. Study Organization.

Steering Committee:

Takeshi Kimura (Principal Investigator), Kazuo Kimura, Shunichi Miyazaki, Tetsuya Sumiyoshi, Hiroyuki Daida, Atsushi Nakamura, Yutaka Furukawa, Yuichi Noguchi, Yoshihisa Nakagawa, Yuji Ikari, Kojiro Awano, Shoji Kitaguchi, Haruo Hirayama Issei Komuro, and Haruo Kamiya.

Clinical Event Committee:

Kazushige Kadota and Hiroki Shiomi

Statistical Analysis:

Takeshi Morimoto

Data safety monitoring board:

Takaaki Isshiki, and Koichi Nakao

Coordinating Center: Research Institute for Production Development, Kyoto, Japan

Naoko Okamoto, Miya Hanazawa, Kumiko Kitagawa, Misato Yamauchi, Yumika Fujino, Saori Tezuka, Yuki Sato, Chikako Hibi, Hitomi Sasae, Emi Takinami, Yuriko Uchida, Yuko Yamamoto, Satoko Nishida, Asuka Takahashi, and Yui Kinoshita.

Supplementary Figure Legends

Supplementary Figure 1A: Cumulative incidences of target-lesion revascularization between 1 and 5 years by the 1-year landmark analysis.

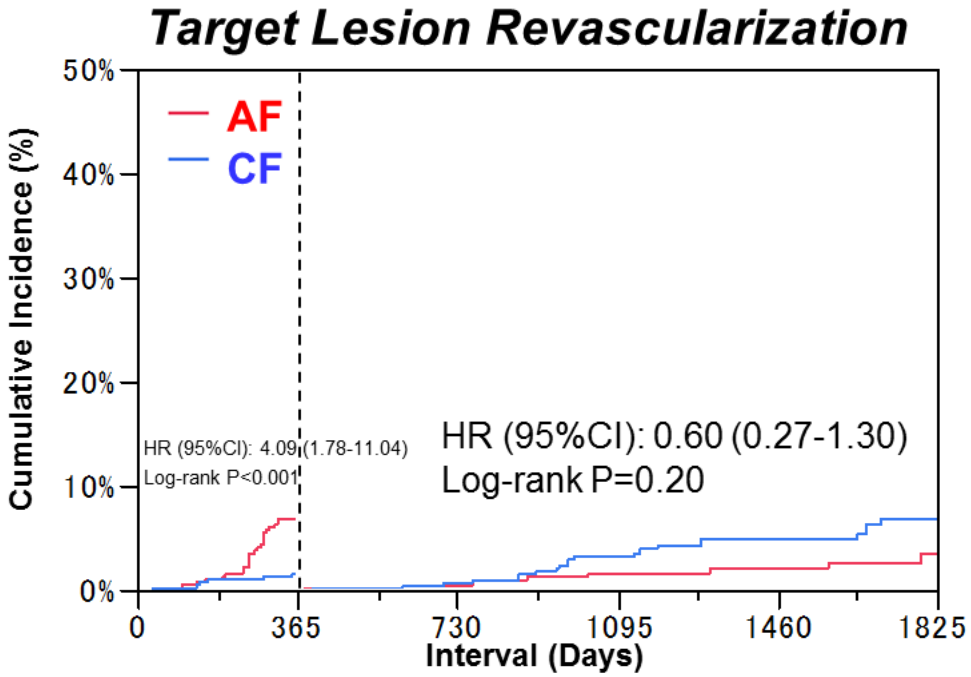
AF= angiographic follow-up, and CF=clinical follow-up

Supplementary Figure 1B: Cumulative incidences of any coronary revascularization between 1 and 5 years by the 1-year landmark analysis.

AF= angiographic follow-up, and CF=clinical follow-up

Supplementary Figures

Supplementary Figure 1A



Interval	0 day	30 days	1 year	2 years	3 years	4 years	5 years
AF group							
N of patients with at least 1 event		0	24	2	5	6	8
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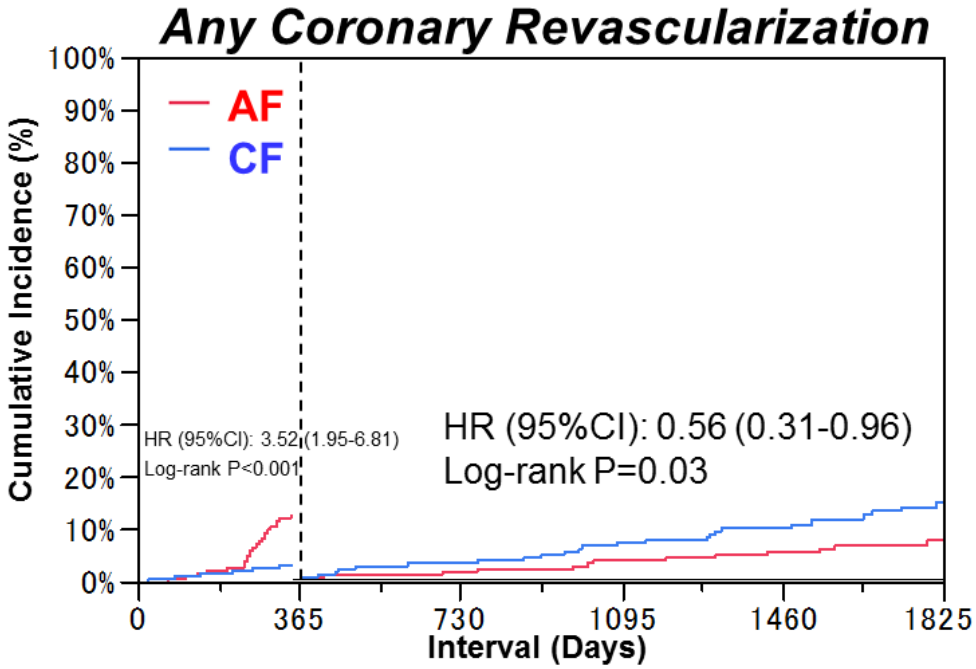
Cumulative incidence		0%	7.0%	0.6%	1.7%	2.2%	3.7%
CF group							
N of patients with at least 1 event		0	6	3	10	14	17
N of patients at risk	351	351	335	310	254	181	98
Cumulative incidence		0%	1.7%	0.9%	3.3%	5.0%	6.9%

Supplementary Figure 1B



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AF group							
N of patients with at least 1 event		0	44	5	11	14	17
N of patients at risk	349	348	297	275	221	164	93
Cumulative incidence		0%	12.8%	4.1%	5.7%	7.8%	11.0%
CF group							
N of patients with at least 1 event		1	13	11	21	28	35
N of patients at risk	351	350	328	295	239	165	89
Cumulative incidence		0.3%	3.8%	3.4%	7.0%	10.3%	14.9%