Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graftinge Among Patients with Unprotected Left Main Coronary Artery Disease in the New-Generation Drug-Eluting Stents Era (From the CREDO-Kyoto PCI/CABG Registry Cohort-3)

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Long-term safety of percutaneous coronary intervention (PCI) as compared with coronary artery bypass grafting (CABG) is still controversial in patients with unprotected left main coronary artery disease (ULMCAD), and there is a scarcity of real-world data on the comparative long-term clinical outcomes between PCI and CABG for ULMCAD in new-generation drug-eluting stents era. The CREDO-Kyoto PCI/CABG registry Cohort-3 enrolled 14927 consecutive patients undergoing first coronary revascularization with PCI or isolated CABG between January 2011 and December 2013, and we identified 855 patients with ULMCAD (PCI: N = 383 [45%], and CABG: N = 472 [55%]). The primary outcome measure was all-cause death. Median follow-up duration was 5.5 (interquartile range: 3.9 to 6.6) years. The cumulative 5-year incidence of all-cause death was not significantly different between the PCI and CABG groups (21.9% vs 17.6%, Log-rank p = 0.13). After adjusting confounders, the excess risk of PCI relative to CABG remained insignificant for all-cause death (HR, 1.00; 95% CI, 0.68 to 1.47; p = 0.99). There were significant excess risks of PCI relative to CABG for myocardial infarction and any coronary revascularization (HR, 2.07; 95% CI, 1.30 to 3.37; p = 0.002, and HR, 2.96; 95% CI, 1.96 to 4.46;

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Disclosures: Dr. Shiomi reports honoraria from Abbott Vascular, and Boston Scientific. Dr. Morimoto reports honoraria from Bayer and Kowa, and expert witness from Boston Scientific and Sanofi. Dr. Ehara reports honoraria from Abbott Vascular, Bayer, Boston Scientific, Medtronic, and Terumo. Dr. Furukawa reports honoraria from Bayer, Kowa, and Sanofi. Dr. Nakagawa reports research grant from Abbott Vascular and Boston Scientific, and honoraria from Abbott Vascular, Bayer, and Boston Scientific. Dr. Kimura reports honoraria from Abbott Vascular, Astellas, AstraZeneca, Bayer, Boston Scientific, Kowa, and Sanofi. The remaining authors have nothing to disclose.

Funding: This work was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan).

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https://doi.org/10.1016/j.amjcard.2020.12.078

p < 0.001), whereas there was no significant excess risk of PCI relative to CABG for stroke (HR, 0.85; 95% CI, 0.50 to 1.41; p = 0.52). In conclusion, there was no excess long-term mortality risk of PCI relative to CABG, while the excess risks of PCI relative to CABG were significant for myocardial infarction and any coronary revascularization in the present study population reflecting real-world clinical practice in Japan. **(Am J Cardiol 2021;145:47−57)**

Percutaneous coronary intervention (PCI) has widely spread in daily clinical practice as an alternative therapy to coronary artery bypass grafting (CABG) in patients with unprotected left main coronary artery disease (ULMCAD).[1,2] Based on the favorable results in several randomized clinical trials, PCI is recommended in patients with ULMCAD as a class I for those with low SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, or as a class IIa for those with intermediate SYNTAX score in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guideline, and as a class IIa for those with low SYNTAX score or non-bifurcation ULMCAD in the American College of Cardiology/American Heart Association guideline.[3−8] However, long-term safety of PCI in patients with ULMCAD is still controversial. The EACTS has withdrawn the support for the European Society of Cardiology/EACTS guideline recommendations regarding revascularization for ULMCAD due to concerns of higher long-term risks for all-cause death and myocardial infarction in the PCI arm reported in the 5-year follow-up of the EXCEL (Evaluation of Xience versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.[5] In addition, previous randomized clinical trials have excluded high-risk patients such as those with heart failure, and severe chronic kidney disease, and some observational studies have suggested that PCI compared with CABG was associated with higher mortality risk in such high-risk patients.[9−12] At present, there is still a scarcity of real-world data on the comparative long-term clinical outcomes between PCI and CABG for ULMCAD in contemporary new-generation drug-eluting stents (DES) era. We, therefore, reported the long-term clinical outcomes of PCI compared with CABG in patients with ULMCAD in the new-generation DES era from a large observational database of patients undergoing first coronary revascularization in Japan.

Methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry Cohort-3 is a physician-initiated, noncompany-sponsored, multicenter registry enrolling consecutive patients who underwent first coronary revascularization with PCI or isolated CABG without combined non-coronary surgery among 22 Japanese centers between January 2011 and December 2013 (Supplemental Appendix). The relevant ethics committees in all the participating centers approved the study protocol. Because of the retrospective enrollment, written informed consents from the patients were waived; however, we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

A total of 14,927 patients who had undergone first coronary revascularization with PCI or isolated CABG (PCI: N = 13307, and CABG: N = 1620) were enrolled in the CREDO-Kyoto PCI/CABG registry Cohort-3 (Supplemental Figure 1). In consistent with the report from the CREDO-Kyoto PCI/CABG registry Cohort-2, we further excluded those patients who refused study participation (N = 60), acute myocardial infarction (N = 5510), and without ULMCAD (N = 8502), and identified 855 patients with ULMCAD for the comparison of long-term clinical outcomes between PCI and CABG (Figure 1).[13]

The primary outcome measure of this study was all-cause death. The secondary outcome measures included cardiovascular death, cardiac death, sudden cardiac death, noncardiovascular death, noncardiac death, myocardial infarction, definite stent thrombosis or symptomatic graft occlusion, stroke, hospitalization for heart failure, major bleeding, target-vessel revascularization (TVR), LMCA-related revascularization, any coronary revascularization, and a composite of all-cause death, myocardial infarction, or stroke. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Cardiovascular death included cardiac death, and other vascular death related to stroke, renal disease, and vascular disease. Death of unknown cause and any death during the index hospitalization for coronary revascularization were regarded as cardiac death. Sudden cardiac death was defined as unexplained death in previously stable patients. Definitions of other outcome measures are described in Supplemental Appendix.

Clinical, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by the experienced clinical research coordinators from an independent clinical research organization (Research Institute for Production Development, Kyoto, Japan; Supplemental Appendix). Follow-up data were collected from the hospital charts and/or obtained by contacting with patients, their relatives or referring physicians between January 2018 and December 2019. Follow-up was regarded as completed, if follow-up data beyond July 1, 2017 were obtained. The clinical event committee adjudicated those events such as death, myocardial infarction, definite stent thrombosis or symptomatic graft occlusion, stroke, and major bleeding (Supplemental Appendix). Coronary anatomic complexity was evaluated according to the SYNTAX score, which was evaluated by the experienced cardiologists (Supplemental Appendix).

Categorical variables were presented as number and percentage, and compared with the chi-square test. Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Continuous variables were

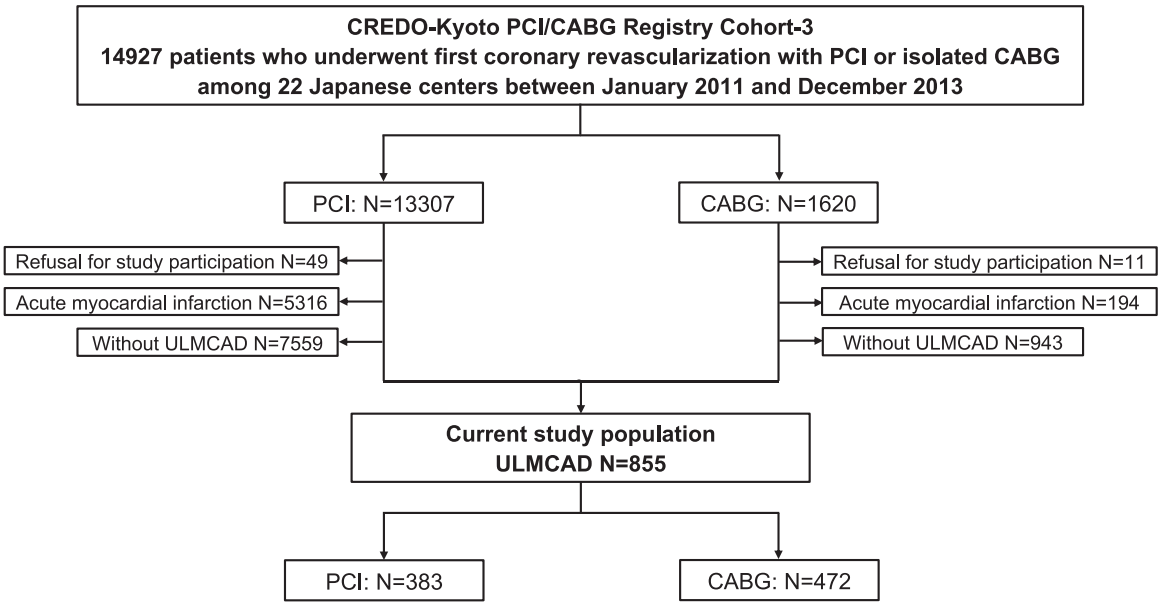


Figure 1. Study flow chart. CABG, coronary artery bypass grafting; CREDO-Kyoto PCI/CABG Registry Cohort-3, Coronary Revascularization Demonstrating Outcome study in Kyoto PCI/CABG Registry Cohort-3; PCI, percutaneous coronary intervention; ULMCAD, unprotected left main coronary artery disease.

compared with the Student's t test or Wilcoxon rank sum test based on their distributions. Cumulative incidence of the outcome measures was estimated by the Kaplan-Meier method, and the differences were assessed with the log-rank test. We also performed 30-day landmark analysis to estimate the cumulative incidence of myocardial infarction, stroke, and major bleeding. The effects of PCI relative to CABG for the outcome measures were expressed as hazard ratios (HRs) and their 95% confidence intervals (CIs). The HRs were estimated by the Cox proportional hazard models adjusting for the 27 clinically relevant factors listed in Table 1. Continuous variables were dichotomized by clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with our previous reports.[13] To avoid overfitting, we constructed the parsimonious models with 8 risk-adjusting variables including advanced age (≥75 years), men, diabetes, heart failure, prior myocardial infarction, prior stroke, end-stage renal disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 or hemodialysis), and severe frailty for the outcome measures with <100 patients with event. We did not perform a multivariable analysis for the outcome measures with <30 patients with event. Because the issues of selection bias are inherent limitations of observational studies, propensity score matching analyses were conducted as sensitivity analyses (Supplemental Appendix). In the subgroup analyses, all-cause death and cardiovascular death were compared between PCI and CABG in the subgroups stratified by age, sex, diabetes, heart failure, end-stage renal disease, extent of coronary artery disease, the SYNTAX score, and LMCA true bifurcation or trifurcation lesion. In the subgroup analyses, the multivariable analyses were performed only for all-cause death with the parsimonious model described previously. Statistical analyses were performed with JMP 14.0 software (SAS Institute, Inc., Cary, North California). All statistical analyses were 2 tailed, and p values of <0.05 were considered statistically significant.

Results

Among the 855 current study patients, 383 patients (45%) underwent PCI, while 472 patients (55%) underwent CABG (Figure 1). Patients in the PCI group were significantly older and more often had severe frailty and peripheral vascular disease than those in the CABG group, whereas patients in the CABG group had higher prevalence of chronic obstructive pulmonary disease than those in the PCI group (Table 1). Regarding angiographic and procedural characteristics, patients with isolated LMCA or LMCA+1-vessel disease (VD) were almost exclusively treated by PCI (95.2%), patients with LMCA+2-VD were treated equally with PCI (50.0%) or CABG (50.0%), and patients with LMCA+3-VD were dominantly treated by CABG (71.4%). The CABG group compared with the PCI group had greater number of target lesions or anastomoses, and higher coronary anatomic complexity as indicated by the greater number of chronic total occlusion target and higher SYNTAX score (Table 1). Among 685 patients (80.1%) in whom LMCA lesion morphology was evaluated, the prevalence of bifurcation or trifurcation lesion, true bifurcation or trifurcation lesion, and heavily calcified lesion were significantly higher in the CABG group than in the PCI group, while the prevalence of aorto-ostial lesion was significantly higher in the PCI group than in the CABG group (Supplemental Table 1). In terms of baseline medications, thienopyridines were used in 104 patients (22.0%) in the CABG group during the index hospitalization, but discontinued before the index procedure in 53 patients (11.2%; Table 1). Newly diagnosed atrial fibrillation after the index procedure was observed in 102 (21.6%) of

Table 1
Baseline characteristics and management during the index hospitalization

Variable	PCI (N = 383)	CABG (N = 472)	p value
Age (years)	72.3±9.7	70.2±9.1	0.002
Age ≥75 years*	168 (43.9%)	160 (33.9%)	0.003
Men*	288 (75.2%)	376 (79.7%)	0.12
Body mass index (kg/m^2)	23.5±3.52	23.5±3.41	0.94
Body mass index <25.0 kg/m^2*	274 (71.5%)	331 (70.1%)	0.82
Unstable angina pectoris	10 (2.6%)	21 (4.5%)	0.15
Hypertension*	316 (82.5%)	384 (81.4%)	0.66
Diabetes mellitus*	163 (42.6%)	230 (48.7%)	0.07
on insulin therapy	51 (13.3%)	80 (16.9%)	0.14
Current smoking*	68 (17.8%)	66 (14.0%)	0.13
Heart failure*	101 (26.4%)	113 (23.9%)	0.41
LVEF	59.4±14.1	61.6±13.0	0.02
LVEF ≤40%	44 (13.8%)	42 (9.4%)	0.054
Mitral regurgitation grade ≥3/4	25 (7.8%)	31 (6.9%)	0.65
Prior myocardial infarction*	76 (19.8%)	88 (18.6%)	0.66
Prior stroke (symptomatic)*	66 (17.2%)	82 (17.4%)	0.96
Peripheral vascular disease*	68 (17.8%)	44 (9.3%)	<0.001
eGFR <30 mL/min/1.73 m^2 or hemodialysis	43 (11.2%)	52 (11.0%)	0.92
eGFR <30 mL/min/1.73 m^2, without hemodialysis*	20 (5.2%)	18 (3.8%)	0.32
Hemodialysis*	23 (6.0%)	34 (7.2%)	0.48
Atrial fibrillation*	39 (10.2%)	35 (7.4%)	0.15
Anemia (Hemoglobin <11.0 g/dL)*	70 (18.3%)	73 (15.5%)	0.27
Thrombocytopenia (Platelet <100 × 10^9/L)*	9 (2.4%)	13 (2.8%)	0.71
Chronic obstructive pulmonary disease*	11 (2.9%)	31 (6.6%)	0.01
Liver cirrhosis*	8 (2.1%)	12 (2.5%)	0.66
Malignancy	55 (14.4%)	60 (12.7%)	0.48
Active malignancy*	13 (3.4%)	8 (1.7%)	0.11
Severe frailty*	20 (5.2%)	8 (1.7%)	0.004
Number of target lesions or anastomoses	2.1±1.2	3.1±0.9	<0.001
Target of LMCA	350 (91.4%)	472 (100%)	<0.001
Target of proximal LAD*	205 (53.5%)	360 (76.3%)	<0.001
Target of chronic total occlusion*	52 (13.6%)	114 (24.2%)	<0.001
Emergency procedure	36 (9.4%)	41 (8.7%)	0.72
Extent of coronary artery disease			<0.001
Isolated LMCA	25 (6.5%)	0 (0%)	
LMCA + 1-vessel disease	95 (24.8%)	6 (1.3%)	
LMCA + 2-vessel disease	127 (33.2%)	127 (26.9%)	
LMCA + 3-vessel disease	136 (35.5%)	339 (71.8%)	
SYNTAX score	27.5 (22-36)	31 (23-38)	0.002
Low <23	113 (29.8%)	85 (22.0%)	0.01
Intermediate 23-32	136 (35.9%)	131 (33.9%)	
High ≥33	130 (34.3%)	170 (44.0%)	
Total number of stents	2 (1-4)	-	-
Total stent length (mm)	52 (27-91)	-	-
Stent use	379 (99.0%)	-	-
DES use	358 (93.5%)	-	-
New-generation DES use	356 (93.0%)	-	-
Everolimus-eluting stent (XIENCE) use	186 (48.6%)	-	-
Everolimus-eluting stent (PROMUS) use	66 (17.2%)	-	-
Biolimus-eluting stent (NOBORI) use	180 (47.0%)	-	-
Zotarolimus-eluting stent (RESOLUTE) use	23 (6.0%)	-	-
Zotarolimus-eluting stent (ENDEAVOR) use	10 (2.6%)	-	-
IVUS or OCT use	354 (92.4%)	-	-
IVUS use	353 (92.2%)	-	-
OCT use	6 (1.6%)	-	-
Staged PCI	91 (23.8%)	-	-
2-stent technique for LMCA bifurcation lesion	53 (15.1%)	-	-
Internal thoracic artery graft use	-	460 (97.5%)	-
Off pump surgery	-	275 (58.3%)	-
Baseline medications			

(*continued*)

Table 1 (***Continued***)

Variable	PCI (N = 383)	CABG (N = 472)	p value
Antiplatelet therapy			
Thienopyridine	382 (99.7%)	104 (22.0%)	<0.001
Ticlopidine	14 (3.7%)	14 (3.0%)	
Clopidogrel	368 (96.1%)	90 (19.1%)	
Aspirin	379 (99.0%)	466 (98.7%)	0.76
Cilostazol	21 (5.5%)	16 (3.4%)	0.13
Other medications			
Statins*	287 (74.9%)	284 (60.2%)	<0.001
High-intensity statins	8 (2.1%)	6 (1.3%)	0.35
Beta-blockers*	119 (31.1%)	229 (48.5%)	<0.001
ACE-I/ARB*	220 (57.4%)	133 (28.2%)	<0.001
Nitrates	86 (22.5%)	66 (14.0%)	0.001
Calcium channel blockers*	178 (46.5%)	175 (37.1%)	0.006
Nicorandil	81 (21.1%)	157 (33.3%)	<0.001
Oral anticoagulants*	32 (8.4%)	231 (48.9%)	<0.001
Warfarin	30 (7.8%)	227 (48.1%)	<0.001
DOAC	2 (0.5%)	4 (0.9%)	0.57
Proton pump inhibitors or histamine type-2 receptor blockers*	289 (75.5%)	455 (96.4%)	<0.001
Proton pump inhibitors	236 (61.6%)	419 (88.8%)	<0.001
Histamine type-2 receptor blockers	57 (14.9%)	41 (8.7%)	0.005

Continuous variables were expressed as mean ± standard deviation, or median (interquartile range). Categorical variables were expressed as number (percentage). Values were missing for LVEF in 8 patients, for mitral regurgitation in 84 patients, and for SYNTAX score in 90 patients.

* Risk adjusting variables selected for the Cox proportional hazard models.

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; DES, drug-eluting stent; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SYNTAX, SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

patients in the CABG group, which was one of the reasons for the higher prescription rate of oral anticoagulants in the CABG group than in the PCI group.

Median follow-up duration was 5.5 (interquartile range: 3.9 to 6.6) years, and complete 1-, 3-, and 5-year clinical follow-up information were obtained in 93.3%, 91.2%, and 79.9% of patients, respectively. Complete 1-, 3-, and 5-year follow-up rates were lower in the CABG group than in the PCI group (89.8% vs 97.7%, 88.1% vs 95.0%, and 78.0% vs 82.3%, respectively).

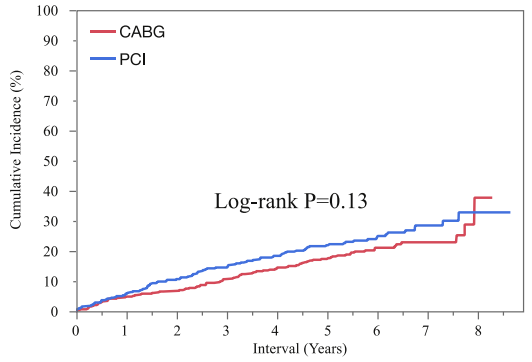
The cumulative 5-year incidence of all-cause death was not significantly different between the PCI and CABG groups (21.9% vs 17.6%, log-rank p = 0.13; Figure 2). After adjusting confounders, the excess risk of PCI relative to CABG was not significant for all-cause death (HR, 1.00; 95% CI, 0.68 to 1.47; p = 0.99; Table 2). The cumulative 5-year incidence of cardiovascular death was also not significantly different between the 2 groups (8.1% vs 7.2%, log-rank p = 0.62; Figure 2). After adjusting confounders, the risk of PCI relative to CABG remained insignificant for cardiovascular death (HR, 1.04; 95% CI, 0.64 to 1.68; p = 0.87; Table 2). The cumulative 5-year incidence of noncardiovascular death was numerically higher in the PCI group than in the CABG group (15.0% vs 11.2%, log-rank p = 0.12; Figure 2). After adjusting confounders, the excess risk of PCI relative to CABG remained insignificant for noncardiovascular death (HR, 1.33; 95% CI, 0.81 to 2.18; p = 0.26; Table 2). Detailed causes of death are shown in Supplemental Table 2.

The cumulative 5-year incidences of and the adjusted risks for myocardial infarction, TVR, and any coronary revascularization were significantly higher in the PCI group than in the CABG group, while those for LMCA-related revascularization were not significantly different between the 2 groups (Figure 3 and Table 2). There was no definite stent thrombosis in the PCI group, and symptomatic graft occlusion occurred only in 2 patients in the CABG group (Table 2). The cumulative 5-year incidence of and the adjusted risk for major bleeding were significantly lower in the PCI group than in the CABG group (Table 2). The cumulative 1-, 3-, and 5-year incidence of persistent discontinuation of DAPT in the PCI group was 21.1%, 44.5%, and 60.9% of the patients, respectively (Supplemental Figure 2). The results of the 30-day landmark analyses are shown in Supplemental Tables 3 to 5. The cumulative 30-day incidences of stroke and major bleeding were significantly lower in the PCI group than in the CABG group (Supplemental Tables 4 and 5).

After propensity score matching in the sensitivity analyses, baseline characteristics of the PCI and CABG groups were much more comparable than those in the entire population (Supplemental Table 6). The results in the propensity score matching analyses were fully consistent with the results in the main analyses (Supplemental Table 7).

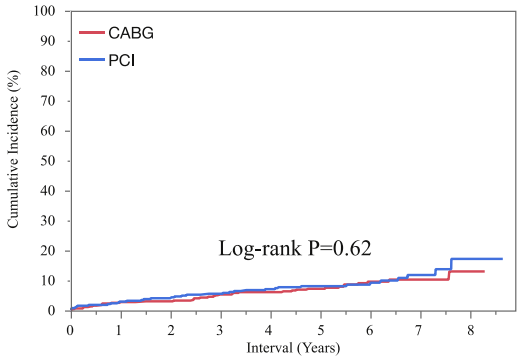
In the subgroup analyses, there were no significant interactions between the subgroup factors and the effects of PCI relative to CABG for all-cause death and cardiovascular death, except for the subgroup of patients with heart failure (Table 3 and Supplemental Table 8). The cumulative 5-year

(A) All-cause death



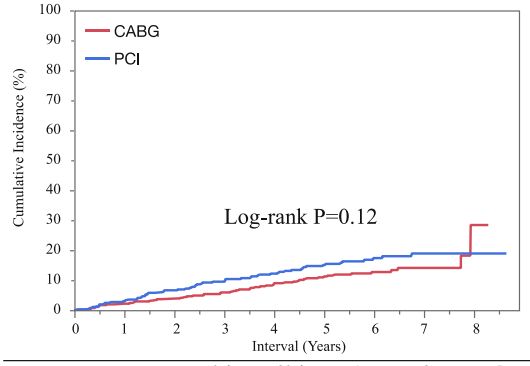
Interval	0 day	30 days	1 year	3 years	5 years
CABG group					
N of patients with event		3	21	46	73
N of patients at risk	472	450	404	371	296
Cumulative incidence		0.7%	4.9%	10.9%	17.6%
PCI group					
N of patients with event		4	22	54	80
N of patients at risk	383	377	353	310	235
Cumulative incidence		1.1%	5.8%	14.5%	21.9%

(B) Cardiovascular death



Interval	0 day	0 30 days	1 year	3 years	5 years
CABG group					
N of patients with event		3	12	22	29
N of patients at risk	472	450	404	371	295
Cumulative incidence		0.7%	2.8%	5.3%	7.2%
PCI group					
N of patients with event		3	11	20	28
N of patients at risk	383	376	352	310	235
Cumulative incidence		0.8%	2.9%	5.6%	8.1%

(C) Non-cardiovascular death



Interval	0 day	30 days	1 year	3 years	5 years
CABG group					
N of patients with event		0	9	24	44
N of patients at risk	472	450	403	370	296
Cumulative incidence		0.0%	2.1%	5.9%	11.2%
PCI group					
N of patients with event		1	11	34	52
N of patients at risk	383	377	353	310	235
Cumulative incidence		0.3%	3.0%	9.5%	15.0%

Figure 2. Kaplan-Meier event curves for all-cause death, cardiovascular death, and noncardiovascular death. (A) all-cause death, (B) cardiovascular death, and (C) noncardiovascular death. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

incidence of and the adjusted risk for all-cause death were significantly higher in the PCI group than in the CABG group in patients with heart failure, while those were not significantly different between 2 groups in patients without heart failure (Table 3).

Discussion

The main findings of this study comparing PCI with CABG in patients with ULMCAD in the new-generation DES era were as follows; (1) In the present study population reflecting real-world clinical practice in Japan between 2011 and 2013, 45% of patients with ULMCAD underwent PCI as the first coronary revascularization, and selection of coronary revascularization modalities appeared to be mainly based on the extent of coronary artery disease with isolated LMCA or LMCA+1-VD almost exclusively treated by PCI, and with LMCA+3-VD dominantly treated by CABG; (2) There was no excess long-term mortality risk of PCI relative to CABG; (3) The excess risks of PCI relative to CABG were significant for myocardial infarction and any coronary revascularization.

The current clinical guidelines recommend PCI in selected patients with ULMCAD.[7,8] However, the finding of higher 5-year mortality in the PCI group than in the CABG group in the EXCEL trial has raised uncertainty regarding the safety of PCI as compared with CABG in patients with ULMCAD.[5] Nevertheless, the authors of the EXCEL trial (PCI: N = 948, and CABG: N = 957) have argued that all-cause death was one of the underpowered secondary endpoints in this trial, and the difference in mortality between the 2 groups was mainly driven by

Table 2
Clinical outcomes

Endpoints	PCI (N = 383) N of patients with event (Cumulative 5-year incidence)	CABG (N = 472) N of patients with event (Cumulative 5-year incidence)	Crude HR [95% CI]	p value	Adjusted HR [95% CI]	p value
All-cause death	94 (21.9%)	89 (17.6%)	1.25 [0.94-1.67]	0.13	1.00 [0.68-1.47]	0.99
Cardiovascular death	35 (8.1%)	37 (7.2%)	1.12 [0.71-1.79]	0.62	1.04 [0.64-1.68]*	0.87
Cardiac death	32 (7.3%)	25 (4.8%)	1.52 [0.90-2.59]	0.11	1.42 [0.82-2.47]*	0.21
Sudden cardiac death	6 (1.1%)	6 (1.1%)	1.21 [0.38-3.86]	0.75	NA	NA
Noncardiovascular death	59 (15.0%)	52 (11.2%)	1.34 [0.92-1.95]	0.12	1.33 [0.81-2.18]	0.26
Noncardiac death	62 (15.8%)	64 (13.5%)	1.15 [0.81-1.63]	0.44	1.08 [0.68-1.70]	0.75
Myocardial infarction						
ARC definition	46 (11.6%)	28 (6.1%)	2.03 [1.28-3.28]	0.003	2.07 [1.30-3.37]*	0.002
ARTS definition	27 (6.8%)	8 (1.9%)	4.14 [1.97-9.76]	<0.001	4.40 [1.99-9.73]*	<0.001
Definite stent thrombosis or symptomatic graft occlusion	0 (0%)	2 (0.5%)	NA	NA	NA	NA
Stroke	27 (7.3%)	36 (7.7%)	0.89 [0.54-1.47]	0.66	0.85 [0.50-1.41]*	0.52
Ischemic stroke	20 (5.8%)	27 (5.9%)	0.89 [0.49-1.58]	0.69	0.91 [0.49-1.66]*	0.76
Hemorrhagic stroke	10 (2.5%)	9 (1.9%)	1.30 [0.52-3.27]	0.57	NA	NA
Major stroke	25 (6.6%)	29 (6.2%)	1.03 [0.60-1.77]	0.9	1.01 [0.58-1.75]*	0.98
Hospitalization for heart failure	44 (12.0%)	35 (7.4%)	1.53 [0.98-2.40]	0.06	1.57 [0.99-2.48]*	0.053
Major bleeding						
BARC type 3, 4, or 5	81 (22.7%)	164 (34.9%)	0.54 [0.41-0.70]	<0.001	0.46 [0.33-0.65]	<0.001
BARC type 5	2 (0.6%)	9 (2.0%)	0.26 [0.04-1.01]	0.051	NA	NA
GUSTO moderate or severe	74 (20.7%)	285 (60.4%)	0.26 [0.20-0.34]	<0.001	0.25 [0.19-0.35]	<0.001
GUSTO severe	36 (9.7%)	49 (10.7%)	0.87 [0.56-1.34]	0.53	0.76 [0.48-1.17]*	0.21
Target-vessel revascularization	92 (25.5%)	42 (9.8%)	2.79 [1.95-4.06]	<0.001	2.71 [1.72-4.28]	<0.001
Ischemia-driven target-vessel revascularization	47 (13.0%)	23 (5.5%)	2.51 [1.54-4.21]	<0.001	2.62 [1.60-4.41]*	<0.001
LMCA-related revascularization	29 (7.7%)	23 (5.4%)	1.49 [0.87-2.61]	0.15	1.51 [0.87-2.65]*	0.15
Ischemia-driven LMCA-related revascularization	16 (4.1%)	12 (2.9%)	1.59 [0.75-3.43]	0.22	NA	NA
Any coronary revascularization	119 (33.3%)	49 (11.5%)	3.21 [2.32-4.52]	<0.001	2.96 [1.96-4.46]	<0.001
Ischemia-driven any coronary revascularization	57 (16.0%)	27 (6.5%)	2.62 [1.68-4.21]	<0.001	2.81 [1.79-4.54]*	<0.001
A composite of death, myocardial infarction, or stroke	144 (34.4%)	125 (26.1%)	1.42 [1.12-1.81]	0.004	1.26 [0.92-1.72]	0.16

Number of patients with event was counted until the end of follow-up. Cumulative 5-year incidence was estimated by the Kaplan-Meier method. HRs with 95% CIs of the PCI group relative to the CABG group for the outcome measures were estimated throughout the entire follow-up period by the Cox proportional hazard models.

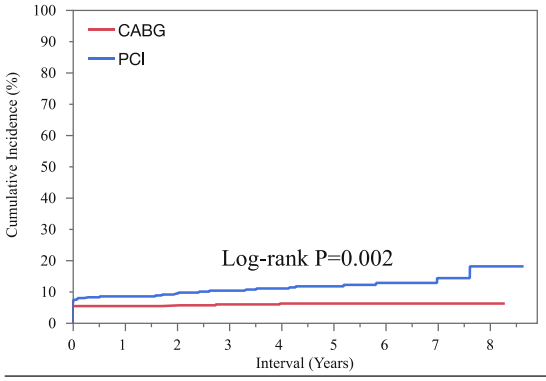
* For the outcome measures of number of patients with event less than 100, we selected parsimonious models with 8 risk-adjusting variables (age≥75, men, diabetes mellitus, heart failure, prior myocardial infarction, prior stroke, eGFR <30 mL/min/1.73 m^2 or hemodialysis, and severe frailty). For the outcome measures of number of patients with event less than 30, we did not perform a multivariable analysis.

ARC, Academic Research Consortium; ARTS, Arterial Revascularization Therapies Study; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CI, confidence interval; eGFR, estimated glomerular filtration rate; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, hazard ratio; LMCA, left main coronary artery; NA, not assessed; PCI, percutaneous coronary intervention.

noncardiovascular deaths. The excess mortality risk with PCI in the EXCEL trial was discordant with the 10-year results of the ULMCAD cohort in the SYNTAX trial (PCI: N = 357, and CABG: N = 348), the 10-year results of the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial (PCI: N = 300, and CABG: N = 300), and the updated 5-year results of the NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trial (PCI: N = 592, and CABG: N = 592).[3,4,6,14] In the present study comparing PCI with CABG in patients with ULMCAD in the new-generation DES era, there was no excess long-term mortality risk of PCI relative to CABG.

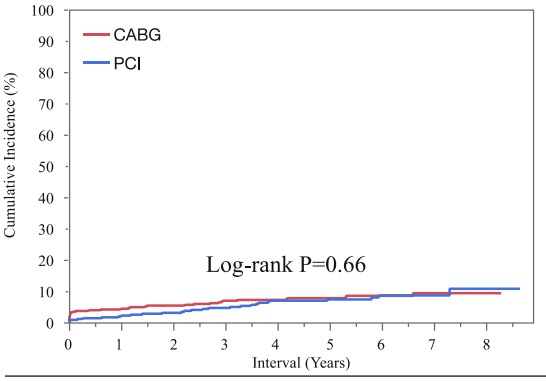
The present study demonstrated that patients with isolated LMCA or LMCA+1-VD were almost exclusively treated by PCI, patients with LMCA+2-VD were treated equally with PCI or CABG, and patients with LMCA+3-VD were dominantly treated by CABG in the current analysis, which was in line with other observational studies and guidelines recommendations.[1,2,7,8] CABG might have been largely performed in selected patients with low risk for surgery, and it might be inappropriate to compare these 2 substantially different subsets of patients with ULMCAD. Nevertheless, it would be important to note that there was no excess long-term mortality risk of PCI relative to CABG in the real-world clinical practice, suggesting that the physician's judgment on the choice of coronary revascularization strategies might not have been reckless in the current study population. It is still unclear whether PCI could be safely performed in patients with ULMCAD and concomitant extensive coronary artery disease. Intuitively, CABG rather than PCI would be more suitable in patients with ULMCAD and concomitant extensive diffuse coronary artery disease. However, utility of the SYNTAX score for selection of revascularization modalities was not clearly demonstrated in the EXCEL and NOBLE trials.[5,6] In the present study, there was also no significant interaction

(A) MI



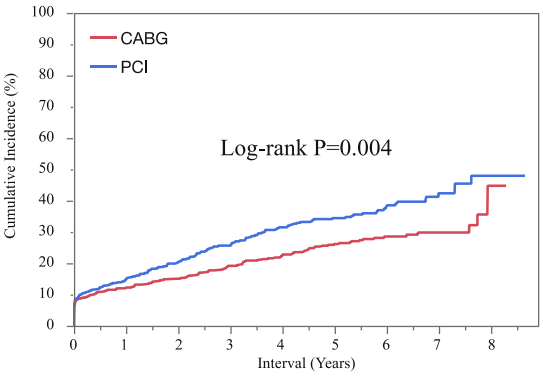
Interval	0 day	30 days	1 year	3 years	5 years
CABG group					
N of patients with at least 1 event		25	25	27	28
N of patients at risk	472	427	383	350	277
Cumulative incidence		5.3%	5.3%	5.8%	6.1%
PCI group					
N of patients with at least 1 event		29	32	38	42
N of patients at risk	383	348	323	278	208
Cumulative incidence		7.6%	8.4%	10.2%	11.6%

(B) Stroke



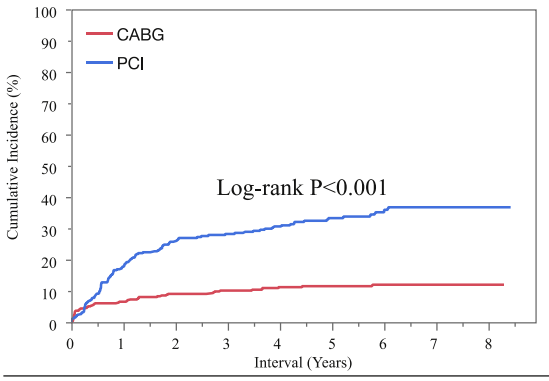
Interval	0 day	30 days	1 year	3 years	5 years
CABG group					
N of patients with at least 1 event		16	20	30	33
N of patients at risk	472	434	392	357	282
Cumulative incidence		3.4%	4.4%	6.9%	7.7%
PCI group					
N of patients with at least 1 event		3	8	16	24
N of patients at risk	383	373	345	299	223
Cumulative incidence		0.8%	2.2%	4.6%	7.3%

(C) A composite of death, MI, or stroke



Interval	0 day	30 days	1 year	3 years	5 years
CABG group					
N of patients with at least 1 event		41	56	85	113
N of patients at risk	472	413	373	338	266
Cumulative incidence		8.7%	12.2%	19.2%	26.1%
PCI group					
N of patients with at least 1 event		35	57	96	127
N of patients at risk	383	346	318	269	198
Cumulative incidence		9.2%	15.0%	25.6%	34.4%

(D) Any coronary revascularization



Interval	0 day	30 days	1 year	3 years	5 years
CABG group					
N of patients with at least 1 event		17	29	43	48
N of patients at risk	472	433	379	336	267
Cumulative incidence		3.7%	6.5%	10.1%	11.5%
PCI group					
N of patients with at least 1 event		6	65	100	114
N of patients at risk	383	371	290	222	151
Cumulative incidence		1.6%	17.8%	28.2%	33.3%

Figure 3. Kaplan-Meier event curves for other outcome measures. (A) MI, (B) stroke, (C) a composite of death, MI, or stroke, and (D) any coronary revascularization. MI was adjudicated according to the Academic Research Consortium (ARC) definition. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

between the SYNTAX score and the mortality risk of PCI relative to CABG. Further investigation would be warranted to identify better criteria regarding anatomic complexity that could appropriately stratify the mortality risk of PCI relative to CABG in patients with ULMCAD.

The lower risks of CABG relative to PCI for myocardial infarction and repeat revascularization were clearly demonstrated in the current study, which was in line with previous studies.[5,6] However, the excess risks of PCI relative to CABG for myocardial infarction and repeat revascularization were not translated into excess mortality risk. Furthermore, we should also recognize that previous studies have clearly demonstrated that CABG as compared with PCI was associated with markedly higher rates of major periprocedural adverse events such as stroke, major bleeding requiring transfusion, major arrhythmia, infection, renal failure, etc.[15,16] Indeed, in the present study, the incidences of stroke and major bleeding within 30 days were much higher in the CABG group than in the PCI group. The more invasive nature and higher risk for periprocedural adverse events of CABG are not subtle issues, but are crucially important for patients, particularly for elderly patients. Therefore, we should make appropriate shared decision making with patients, providing unbiased information on the risk-benefit balance between PCI and CABG. Based on the present study results, patients might be informed that

Table 3
Subgroup analyses for the primary outcome measure (all-cause death)

Subgroups	PCI (N = 383) N of patients with event/N of patients at risk (Cumulative 5-year incidence)	CABG (N = 472) N of patients with event/N of patients at risk (Cumulative 5-year incidence)	Crude HR [95% CI]	p value	Adjusted HR [95% CI]	p value	p value for interaction
Age							
≥75 years	58/168 (33.2%)	51/160 (30.9%)	1.03 [0.70-1.50]	0.89	1.17 [0.78-1.75]	0.46	0.79
<75 years	36/215 (13.4%)	38/312 (10.9%)	1.31 [0.83-2.07]	0.25	1.19 [0.75-1.89]	0.46	
Sex							
Men	76/288 (23.1%)	72/376 (18.3%)	1.35 [0.98-1.87]	0.07	1.32 [0.94-1.84]	0.11	0.19
Women	18/95 (18.4%)	17/96 (15.1%)	0.97 [0.50-1.89]	0.92	0.76 [0.36-1.60]	0.48	
Diabetes mellitus							
Yes	46/163 (25.7%)	53/230 (21.7%)	1.17 [0.79-1.74]	0.43	1.19 [0.79-1.78]	0.4	0.91
No	48/220 (19.1%)	36/242 (13.9%)	1.42 [0.92-2.20]	0.11	1.15 [0.73-1.81]	0.55	
Heart failure							
Yes	47/101 (43.6%)	27/113 (22.6%)	2.30 [1.44-3.75]	<0.001	2.40 [1.45-4.04]	0.001	0.001
No	47/282 (14.4%)	62/359 (16.1%)	0.87 [0.59-1.27]	0.48	0.81 [0.55-1.19]	0.28	
eGFR <30 mL/min/1.73 m^2 or hemodialysis							
Yes	19/43 (43.6%)	24/52 (61.2%)	0.77 [0.41-1.40]	0.39	0.76 [0.40-1.44]	0.4	0.29
No	75/340 (19.4%)	65/420 (13.3%)	1.39 [0.999-1.94]	0.051	1.27 [0.90-1.80]	0.17	
Extent of coronary artery disease							
Isolated LMCA/LMCA+1-VD/LMCA+2-VD	59/247 (21.8%)	24/133 (18.8%)	1.28 [0.80-2.09]	0.31	0.88 [0.54-1.46]	0.6	0.87
LMCA+3-VD	35/136 (22.2%)	65/339 (17.2%)	1.30 [0.85-1.94]	0.22	1.32 [0.85-2.01]	0.21	
SYNTAX score							
Low <23	26/113 (21.4%)	11/85 (15.5%)	1.67 [0.85-3.53]	0.14	1.45 [0.70-3.18]	0.33	0.74
Intermediate 23-32	30/136 (23.3%)	24/131 (18.0%)	1.19 [0.70-2.05]	0.52	0.91 [0.50-1.65]	0.75	
High ≥33	36/130 (20.9%)	33/170 (16.8%)	1.36 [0.85-2.19]	0.2	1.51 [0.92-2.48]	0.1	
LMCA true bifurcation or trifurcation lesion*							
Yes	33/121 (23.4%)	37/214 (14.9%)	1.48 [0.92-2.37]	0.1	1.54 [0.94-2.51]	0.08	0.77
No	49/204 (21.6%)	24/146 (18.7%)	1.48 [0.92-2.44]	0.11	1.31 [0.79-2.21]	0.29	

Number of patients with event was counted until the end of follow-up. Cumulative 5-year incidence was estimated by the Kaplan-Meier method. The primary outcome measure in the present study was all-cause death. HRs with 95% CIs of the PCI group relative to the CABG group for the primary outcome measure were estimated throughout the entire follow-up period by the Cox proportional hazard models.

* LMCA true bifurcation or trifurcation lesion indicated bifurcation lesion with Medina classification (1,1,1), (1,0,1), or (0,1,1) or trifurcation lesion with 3 or 4 diseased segments among the proximal main branch, distal main branch, and side branches. We used the parsimonious models with 8 risk-adjusting variables (age≥75, men, diabetes mellitus, heart failure, prior myocardial infarction, prior stroke, eGFR <30 mL/min/1.73 m^2 or hemodialysis, and severe frailty) due to the small numbers of patients with event. Values were missing for SYNTAX score in 90 patients, and for LMCA true bifurcation or trifurcation lesion in 170 patients.

CABG, coronary artery bypass grafting; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; SYNTAX, SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; VD, vessel disease.

more invasive CABG compared with less invasive PCI is associated with higher risk for periprocedural adverse events, better protection for myocardial infarction and repeat revascularization, but similar long-term mortality, although the recommendations should be tailored for individual patients.

There were several important limitations in this study. First and most importantly, the observational study design precluded any definitive conclusions regarding the superiority of either PCI or CABG due to selection bias and residual confounders. In an attempt to overcome the issues related to selection bias, we evaluated severe frailty. However, we could not deny ascertainment bias for severe frailty, because the prevalence of severe frailty in the present study was apparently lower than those reported in previous studies.[17] Furthermore, due to the retrospective study design, we could not assess other important factors such as moderate frailty and cognitive impairment, which might have great influence on the choice between PCI and CABG, as well as on clinical outcomes. Second, the number of enrolled patients was relatively small. However, we had enough number of patients with all-cause death to make extensive multivariable adjustment, although the results of some secondary outcome measures and the subgroup analyses were inconclusive due to lack of adequate power. Third, complete follow-up rate was lower in the CABG group than in the PCI group, which was also seen in the EXCEL trial.[5] The incidences of adverse event might have been underestimated in the CABG group. Fourth, the prevalence of intracoronary imaging device use in the present study was much higher than those in the previous studies,[1,3,5,6] but it was unknown whether we achieved appropriate stent expansion,

which was reported to be associated with better clinical outcomes.[18] Finally, the use patterns of important procedural techniques and medications in the present study might be different from those in the contemporary clinical practice. Duration of DAPT after PCI was relatively long in the current study, although recent studies have suggested clinical benefit with very short DAPT after PCI.[19,20] Indeed, the rate of major bleeding beyond 30 days in the present study was substantially higher in the PCI group than in the CABG group. In addition, the prescription rate of statin increased from our previous report in the first-generation DES era,[13] but was not enough high. Especially, the prescription rate of high-intensity statin therapy was extremely low, although the efficacy of high-intensity statin therapy was established in preventing cardiovascular events in patients with coronary artery disease.[21] Furthermore, prescription rate of oral anticoagulants was especially high in the CABG group. Postoperative atrial fibrillation might be one of the reasons. Besides, there might be oral anticoagulants use for prevention of graft occlusion, although it is not recommended to use oral anticoagulants to improve graft patency in patients without an indication for anticoagulants.[22]

Author contribution

Ko Yamamoto: Methodology, Formal analysis, Investigation, Data curation, Writing - Original Draft. Hiroki Shiomi: Methodology, Investigation, Data curation, Writing-Review and Editing, Supervision, Project administration. Takeshi Morimoto: Methodology, Formal analysis, Writing-Review and Editing, Supervision. Kazushige Kadota: Investigation, Resources. Tomohisa Tada: Investigation, Resources. Yasuaki Takeji: Investigation, Data curation. Yukiko Matsumura-Nakano: Investigation, Data curation. Yusuke Yoshikawa: Investigation, Data curation. Kazuaki Imada: Investigation, Data curation. Takenori Domei: Investigation, Resources. Kazuhisa Kaneda: Investigation, Resources. Ryoji Taniguchi: Investigation, Resources. Natsuhiko Ehara: Investigation, Resources. Ryuzo Nawada: Investigation, Resources. Masahiro Natsuaki: Writing - Review and Editing. Kyohei Yamaji: Investigation, Resources, Writing - Review and Editing. Mamoru Toyofuku: Investigation, Resources. Naoki Kanemitsu: Investigation, Resources. Eiji Shinoda: Investigation, Resources. Satoru Suwa: Investigation, Resources. Atsushi Iwakura: Investigation, Resources. Toshihiro Tamura: Investigation, Resources. Yoshiharu Soga: Investigation, Resources. Tsukasa Inada: Investigation, Resources. Mitsuo Matsuda: Investigation, Resources. Tadaaki Koyama: Investigation, Resources. Takeshi Aoyama: Investigation, Resources. Yukihito Sato: Investigation, Resources. Yutaka Furukawa: Investigation, Resources. Kenji Ando: Investigation, Resources. Fumio Yamazaki: Investigation, Resources. Tatsuhiko Komiya: Investigation, Resources. Kenji Minatoya: Investigation, Resources. Yoshihisa Nakagawa: Investigation, Resources. Takeshi Kimura: Conceptualization, Methodology, Writing - Review and Editing, Supervision, Project administration, Funding acquisition.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We appreciate the support and collaboration of the co-investigators participating in the CREDO-Kyoto PCI/CABG Registry Cohort-3. We are indebted to the clinical research coordinators for data collection.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.078.

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