Periprocedural Stroke After Coronary Revascularization (from the CREDO-Kyoto PCI/CABG Registry Cohort-3)

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There is a scarcity of data on incidence, risk factors, especially clinical severity, and long-term prognostic impact of periprocedural stroke after coronary revascularization in contemporary real-world practice. Among 14,867 consecutive patients undergoing first coronary revascularization between January 2011 and December 2013 (percutaneous coronary intervention [PCI]: N = 13258, and coronary artery bypass grafting [CABG]: N = 1609) in the Coronary Revascularization Demonstrating Outcome Study in Kyoto PCI/CABG registry Cohort-3, we evaluated the details on periprocedural stroke. Periprocedural stroke was defined as stroke within 30 days after the index procedure. Incidence of periprocedural stroke was 0.96% after PCI and 2.13% after CABG (log-rank p <0.001). Proportions of major stroke defined by modified Rankin Scale ≥2 at hospital discharge were 68% after PCI, and 77% after CABG. Independent risk factors of periprocedural stroke were acute coronary syndrome (ACS), carotid artery disease, advanced age, heart failure, and end-stage renal disease after PCI, whereas they were ACS, carotid artery disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, and frailty after CABG. There was excess long-term mortality risk of patients with periprocedural stroke relative to those without after both PCI and CABG (hazard ratio 1.71 [1.25 to 2.33], and hazard ratio 4.55 [2.79 to 7.43]). In conclusion, incidence of periprocedural stroke was not negligible not only after CABG, but also after PCI in contemporary real-world practice. Majority of patients with periprocedural stroke had at least mild disability at hospital discharge. ACS and carotid artery disease were independent strong risk factors of periprocedural stroke after both PCI and CABG. Periprocedural stroke was associated with significant long-term mortality risk after both PCI and CABG. **(Am J Cardiol 2021;142:35−43)**

Periprocedural stroke after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is one of the most serious complications, leading to impaired quality of life that is a crucially important issue for the patients and their family members.[1−9] Previous studies in 1990s have reported that incidence of periprocedural stroke after CABG was about 1.6%.[6−7] In the report from the Society of Thoracic Surgeons database, it was 1.6% in 2000, and decreased to 1.2% in 2009, at least partly due to the evolution of preventive strategy for stroke.[8] On the

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

See page 42 for disclosure information.

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other hand, incidence of periprocedural stroke after PCI differs from study to study (0.1% to 0.6%),[1–5,9] and some studies have reported that it has been slightly increasing possibly due to the increase in elderly patients with co-morbidities from 2000s to 2010s,[3,5] although it is still regarded as a rare complication after PCI. However, there is a scarcity of data on the incidence, risk factors, and prognostic impact of periprocedural stroke in contemporary real-world practice of rapidly aging societies. In addition, to the best of our knowledge, there was no previous study evaluating the clinical severity of periprocedural stroke. Therefore, we sought to investigate those details on periprocedural stroke during or after PCI or CABG using 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 noncoronary surgery among 22 Japanese centers between January 2011 and December 2013 (Supplemental Appendix). The design and patient enrollment of the CREDO-Kyoto PCI/CABG registry Cohort-3 were described in the Supplemental Appendix. Among 14,927 patients enrolled in the registry, the current study population consisted of 13,258 patients who underwent first PCI and 1,609 patients who underwent first CABG, excluding 60 patients who refused study participation. The study population was divided into 2 groups with and without periprocedural stroke within 30 days after the index coronary revascularization (Supplemental Figure 1).

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.

Periprocedural stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours or until death within 30 days after the index coronary revascularization, in accordance with the definition provided by the Neurologic Academic Research Consortium (Neuro ARC).[10] Ischemic stroke with hemorrhagic conversion was classified as ischemic stroke. We assessed clinical severity of periprocedural stroke by using modified Rankin Scale at hospital discharge.[11] Major stroke was defined as stroke with modified Rankin Scale ≥2. Those died during the hospitalization was classified as modified Rankin Scale of 6. The clinical event committee adjudicated modified Rankin Scale referring to the original source documents (Supplemental Appendix).

Clinical, angiographic, and procedural data were collected from hospital charts or hospital databases according to the prespecified definitions by the experienced clinical research coordinators belonging to an independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix). Follow-up data of stroke and death 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 we obtained follow-up data beyond July 1, 2017. The clinical event committee adjudicated the all events (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 compared with the Student's *t* test or Wilcoxon rank sum test based on their distributions. Cumulative 30-day incidence of stroke was estimated by the Kaplan-Meier method, and the differences between PCI and CABG were assessed with the log-rank test. We estimated the cumulative 30-day incidence of stroke stratified by the subgroups based on the acute coronary syndrome (ACS) presentation at the index coronary revascularization, and the tertiles of age (<66 years of age, 66 to 75 years of age, and ≥ 76 years of age) (Table 1). We chose these 2 particular subgroups, because these are clinically important factors when considering the indication for coronary revascularization, selection of coronary revascularization modalities, and the risk of periprocedural stroke (Table 1). Multivariable logistic regression analysis was performed to explore the variables in the baseline clinical characteristics that were independently associated with the occurrence of periprocedural stroke. We selected the candidate variables by their univariate associations with the periprocedural stroke. The association with the occurrence of periprocedural stroke was expressed as odds ratios (ORs) and their 95% confidence intervals (CIs). To investigate the effect of the procedural variables such as access site and thrombus aspiration (PCI stratum), and off pump surgery (CABG stratum), we added these procedural variables into the main models as an exploratory analysis. To evaluate the influence of periprocedural stroke on the mortality endpoints, we performed 30-day landmark analysis. Within 30 days, we used the chi-square test in comparing the event rates between the 2 groups with and without periprocedural stroke. The effects of periprocedural stroke relative to no periprocedural stroke for the endpoints were expressed as hazard ratios (HRs) and their 95% CIs. The HRs were estimated by the Cox proportional hazard models adjusting for the 29 clinically relevant factors listed in Table 2 and Supplemental Table 2. Continuous variables were dichotomized by clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with our previous reports.[12–13] All 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

Complete 30-day clinical follow-up information were obtained in 99.4% of patients in the PCI stratum, and 96.8% of patients in the CABG stratum. In the current study population, the incidence of periprocedural stroke was

Table 1
Incidence of periprocedural stroke

	N of patients with event/N of patients at risk (Cumulative 30-day incidence)		Log-rank p
	PCI	CABG	
All stroke			
Entire population	125/13258 (0.96%)	34/1609 (2.13%)	<0.001
Clinical subgroup			
ACS	90/5521 (1.68%)	11/232 (4.82%)	<0.001
Non-ACS	35/7737 (0.45%)	23/1377 (1.68%)	<0.001
Age subgroup (years)			
<66	34/4580 (0.75%)	3/497 (0.60%)	0.73
66-75	35/4435 (0.80%)	15/668 (2.25%)	<0.001
>=76	56/4243 (1.35%)	16/444 (3.64%)	<0.001
Ischemic stroke			
Entire population	110/13258 (0.84%)	32/1609 (2.00%)	<0.001
Clinical subgroup			
ACS	78/5521 (1.45%)	11/232 (4.82%)	<0.001
Non-ACS	32/7737 (0.41%)	21/1377 (1.53%)	<0.001
Age subgroup (years)			
<66	29/4580 (0.64%)	3/497 (0.60%)	0.93
66-75	30/4435 (0.66%)	15/668 (2.25%)	<0.001
>=76	51/4243 (1.23%)	14/444 (3.18%)	0.001
Hemorrhagic stroke			
Entire population	16/13258 (0.12%)	2/1609 (0.13%)	0.97
Clinical subgroup			
ACS	12/5521 (0.22%)	0/232 (0%)	0.48
Non-ACS	4/7737 (0.05%)	2/1377 (0.15%)	0.21
Age subgroup (years)			
<66	5/4580 (0.11%)	0/497 (0%)	0.46
66-75	5/4435 (0.11%)	0/668 (0%)	0.39
>=76	6/4243 (0.15%)	2/444 (0.46%)	0.14

Cumulative 30-day incidence was estimated by the Kaplan-Meier method, and the differences between PCI and CABG were assessed with the log-rank test. One patient in the PCI stratum (non-ACS, and >=76 years of age) had both ischemic and hemorrhagic periprocedural stroke.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

significantly higher in the CABG stratum than in the PCI stratum (2.13% vs 0.96%, log-rank p <0.001) (Table 1 and Figure 1). The vast majority of periprocedural stroke was ischemic stroke in both PCI and CABG strata (Table 1). The incidence of periprocedural stroke was higher in patients with ACS and advanced age than those without in both PCI and CABG strata (Table 1).

Among 131 (82%) of patients with periprocedural stroke in whom modified Rankin Scale at hospital discharge were available, the proportion of major stroke defined by modified Rankin Scale ≥2 with at least mild disability was 68% in the PCI stratum, and 77% in the CABG stratum (Table 3). The severity of periprocedural stroke was numerically greater in the CABG stratum than in the PCI stratum, although the proportion of patients with modified Rankin Scale 5 or 6 was similar in both PCI and CABG strata. Among 15 patients with modified Rankin Scale 6, periprocedural stroke itself was not regarded as the direct cause of death in all but 1 patient (Table 3). The timing of periprocedural stroke onset was within 24 hours in 28% in the PCI stratum and in 35% in the CABG stratum, beyond 24 hours and within 7 days in 30% in both PCI and CABG strata, and beyond 7 days in 42% in the PCI stratum and in 35% in the CABG stratum (Supplemental Figure 2). The detailed types of periprocedural stroke were shown in the Supplemental Table 1.

Patients with periprocedural stroke were older and more often had ACS presentation, cardiogenic shock, previous stroke, untreated carotid artery disease, and severe frailty than those without in both PCI and CABG strata. The prevalence of carotid artery disease after stenting or endarterectomy was low and not significantly different between the 2 groups in both strata. In the PCI stratum, patients with periprocedural stroke more often had heart failure and end-stage renal disease than those without, whereas in the CABG stratum, patients with periprocedural stroke more often had atrial fibrillation, chronic obstructive pulmonary disease, and malignancy than those without (Table 2). Regarding angiographic and procedural characteristics, patients with periprocedural stroke more often had 3-vessel disease than those without in the PCI stratum, whereas patients with periprocedural stroke more often had left main coronary artery disease than those without in the CABG stratum. In the PCI stratum, femoral access and thrombus aspiration were more often used in patients with periprocedural stroke than in those without. In the CABG stratum, off pump surgery was less often performed in patients with periprocedural stroke than in those without (Table 2). Baseline medications were shown in the Supplemental Table 2.

In the PCI stratum, independent risk factors of periprocedural stroke were age ≥75 years, ACS, heart failure, carotid

Table 2
Baseline characteristics

	PCI stratum (N = 13258)			CABG stratum (N = 1609)		
	Periprocedural stroke			Periprocedural stroke		
Variable	Yes (N = 125)	No (N = 13133)	p value	Yes (N = 34)	No (N = 1575)	p value
Age (years)	72.0±12.9	69.4±11.2	0.03	73.7±7.6	69.3±9.7	0.008
>=75*	63 (50.4%)	4618 (35.2%)	<0.001	17 (50.0%)	511 (32.4%)	0.03
Men*	85 (68.0%)	9587 (73.0%)	0.21	28 (82.4%)	1233 (78.3%)	0.57
Body mass index (kg/m^2)	23.4±3.5	23.8±3.6	0.19	23.4±4.3	23.7±3.5	0.61
<25.0 kg/m^2*	87 (69.6%)	8814 (67.1%)	0.56	25 (73.5%)	1071 (68.0%)	0.49
Acute coronary syndrome*	90 (72.0%)	5431 (41.4%)	<0.001	11 (32.4%)	221 (14.0%)	0.003
Acute myocardial infarction	89 (71.2%)	5227 (39.8%)	<0.001	10 (29.4%)	184 (11.7%)	0.002
STEMI	76 (60.8%)	4005 (30.5%)	<0.001	4 (11.8%)	89 (5.7%)	0.13
NSTEMI	13 (10.4%)	1222 (9.3%)	0.68	6 (17.7%)	95 (6.0%)	0.006
Cardiogenic shock	26 (20.8%)	750 (5.7%)	<0.001	2 (5.9%)	22 (1.4%)	0.03
Cardiopulmonary arrest	9 (7.2%)	206 (1.6%)	<0.001	0 (0%)	3 (0.2%)	0.8
Unstable angina pectoris	1 (0.8%)	204 (1.6%)	0.5	1 (2.9%)	37 (2.3%)	0.82
Hypertension*	107 (85.6%)	10793 (82.2%)	0.32	28 (82.4%)	1316 (83.6%)	0.85
Diabetes mellitus*	50 (40.0%)	4989 (38.0%)	0.64	22 (64.7%)	800 (50.8%)	0.11
on insulin therapy	14 (11.2%)	1077 (8.2%)	0.22	6 (17.6%)	289 (18.3%)	0.92
Current smoker*	26 (20.8%)	3646 (27.8%)	0.08	5 (14.7%)	276 (17.5%)	0.67
Heart failure*,†	63 (50.4%)	3054 (23.3%)	<0.001	10 (29.4%)	438 (27.8%)	0.84
Current heart failure at index hospitalization	59 (47.2%)	2736 (20.8%)	<0.001	8 (23.5%)	248 (15.8%)	0.22
Prior hospitalization for heart failure	7 (5.6%)	568 (4.3%)	0.49	4 (11.8%)	254 (16.1%)	0.49
Prior myocardial infarction*	10 (8.0%)	1450 (11.0%)	0.28	6 (17.6%)	342 (21.7%)	0.57
Prior stroke (symptomatic)*	27 (21.6%)	1672 (12.7%)	0.003	12 (35.3%)	269 (17.1%)	0.006
Prior ischemic stroke	25 (20.0%)	1441 (11.0%)	0.001	10 (29.4%)	246 (15.6%)	0.03
Prior hemorrhagic stroke	3 (2.4%)	301 (2.3%)	0.94	2 (5.9%)	41 (2.6%)	0.24
Peripheral vascular disease*	10 (8.0%)	1203 (9.2%)	0.65	4 (11.8%)	193 (12.3%)	0.93
Carotid artery disease‡	13 (10.4%)	463 (3.5%)	<0.001	9 (26.5%)	218 (13.8%)	0.04
Untreated	11 (8.8%)	355 (2.7%)	<0.001	8 (23.5%)	187 (11.9%)	0.04
After stenting or endarterectomy	2 (1.6%)	108 (0.8%)	0.34	1 (2.9%)	31 (2.0%)	0.69
eGFR <30 mL/min/1.73m^2 or hemodialysis	24 (19.2%)	1173 (8.9%)	<0.001	4 (11.8%)	225 (14.3%)	0.68
eGFR <30 mL/min/1.73m^2, without hemodialysis*	16 (12.8%)	570 (4.3%)	<0.001	2 (5.9%)	99 (6.3%)	0.92
Hemodialysis*	8 (6.4%)	603 (4.6%)	0.34	2 (5.9%)	126 (8.0%)	0.65
Atrial fibrillation*	10 (8.0%)	1276 (9.7%)	0.52	7 (20.6%)	119 (7.6%)	0.005
Anemia (Hemoglobin <11.0 g/dL)*	22 (17.6%)	1610 (12.3%)	0.07	5 (14.7%)	292 (18.5%)	0.57
Thrombocytopenia (Platelet <100 × 10^9/L)*	5 (4.0%)	257 (2.0%)	0.1	3 (8.8%)	47 (3.0%)	0.052
Chronic obstructive pulmonary disease*	6 (4.8%)	513 (3.9%)	0.61	6 (17.6%)	83 (5.3%)	0.002
Liver cirrhosis*	3 (2.4%)	332 (2.5%)	0.93	0 (0%)	47 (3.0%)	0.31
Malignancy	19 (15.2%)	1658 (12.6%)	0.39	8 (23.5%)	181 (11.5%)	0.03
Active malignancy*	4 (3.2%)	266 (2.0%)	0.35	1 (2.9%)	34 (2.2%)	0.76
Severe frailty§	14 (11.2%)	536 (4.1%)	<0.001	3 (8.8%)	28 (1.8%)	0.003
Procedural characteristics						
Number of coronary arteries narrowings			0.02			0.02
1	46 (36.8%)	5611 (42.7%)		0 (0%)	19 (1.2%)	
2	32 (25.6%)	4119 (31.4%)		2 (5.9%)	154 (9.8%)	
3	36 (28.8%)	2747 (20.9%)		11 (32.4%)	834 (53.0%)	
LMCA	11 (8.8%)	656 (5.0%)		21 (61.8%)	568 (36.1%)	
3-vessel or LMCA*	47 (37.6%)	3403 (25.9%)	0.003	32 (94.1%)	1402 (89.0%)	0.34
Number of target lesions or anastomoses	1.4±0.7	1.5±0.8	0.65	3.1±0.9	3.2±0.9	0.35
Target of proximal LAD*	62 (49.6%)	7937 (60.4%)	0.01	30 (88.2%)	1375 (87.3%)	0.87
Target of chronic total occlusion*	10 (8.0%)	1321 (10.1%)	0.45	7 (20.6%)	619 (39.3%)	0.03
Emergency procedure	93 (74.4%)	5310 (40.4%)	<0.001	12 (35.3%)	191 (12.1%)	<0.001
Staged PCI	17 (13.6%)	2633 (20.1%)	0.07	-	-	-
Access site			0.03			-
Radial	33 (26.4%)	4940 (37.7%)		-	-	
Femoral	80 (64.0%)	6907 (52.7%)		-	-	
Brachial	12 (9.6%)	1271 (9.7%)		-	-	

(*continued*)

Table 2 (***Continued***)

	PCI stratum (N = 13258)			**CABG stratum (N = 1609)**		
	Periprocedural stroke			Periprocedural stroke		
Variable	Yes (N = 125)	No (N = 13133)	p value	Yes (N = 34)	No (N = 1575)	p value
Thrombus aspiration	14 (11.3%)	857 (6.5%)	0.03	-	-	-
Internal thoracic artery graft use	-	-	-	31 (91.2%)	1515 (96.2%)	0.14
Bilateral internal thoracic arteries graft use	-	-	-	10 (29.4%)	428 (27.2%)	0.77
Saphenous vein graft use	-	-	-	32 (94.2%)	1358 (86.2%)	0.18
Off pump surgery	-	-	-	13 (38.2%)	914 (58.0%)	0.02

Continuous variables were expressed as mean ± standard deviation, or median (interquartile range). Categorical variables were expressed as number (percentage). Values were missing for access site in 15 patients, and for thrombus aspiration in 10 patients.

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

† Heart failure included previous hospitalization for heart failure and/or current heart failure.

‡ Carotid artery disease was regarded as present when these diagnoses were recorded in the hospital charts.

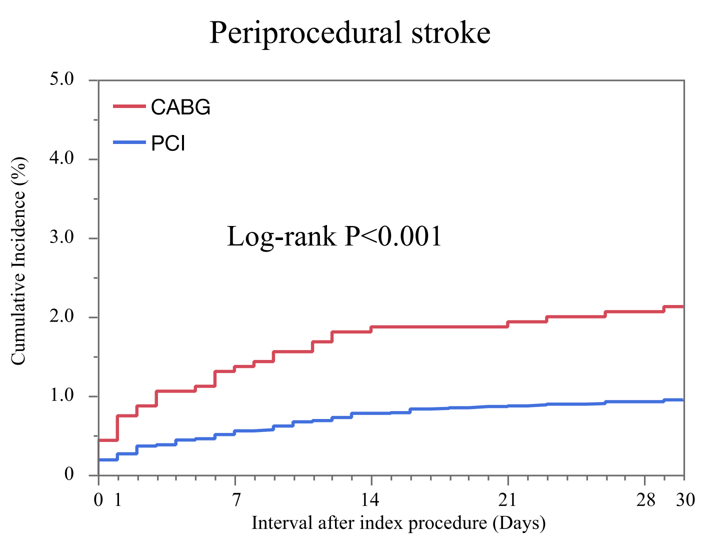
§ Severe frailty was regarded as present when the inability to perform usual activities of daily living was documented in the hospital charts.

eGFR = estimated glomerular filtration rate; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; NSTEMI = Non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction. Other abbreviations are as in Table 1

artery disease, and end-stage renal disease, whereas in the CABG stratum, they were ACS, carotid artery disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, and severe frailty (Table 4). In the exploratory analyses including procedural characteristics, access site and thrombus aspiration did not emerge as the independent risk factor of periprocedural stroke in the PCI stratum, whereas off pump surgery emerged as the independent protective factor of periprocedural stroke in the CABG stratum (Supplemental Table 3).

Median follow-up duration was 5.7 (interquartile range: 4.4 to 6.7) years, and complete 1-, 3-, and 5-year clinical follow-up information were obtained in 97.5%, 94.7%, and 82.9% of patients, respectively, in the PCI stratum, whereas median follow-up duration was 5.7 (interquartile range: 4.3 to 6.5) years, and complete 1-, 3-, and 5-year clinical follow-up information were obtained in 92.2%, 89.7%, and 80.6% of patients, respectively, in the CABG stratum.

Within 30 days after the index procedure, the incidence of all-cause death was significantly higher in patients with



Interval	0 day	1 day	7 days	14 days	30 days
CABG					
N of patients with at least 1event		12	22	30	34
N of patients at risk	1609	1602	1580	1563	1510
Cumulative incidence		0.75%	1.37%	1.87%	2.13%
PCI					
N of patients with at least 1event		35	73	102	125
N of patients at risk	13258	13185	12986	12879	12753
Cumulative incidence		0.26%	0.55%	0.78%	0.96%

Figure 1. Incidence of periprocedural stroke: PCI versus CABG (Also Central Illustration)
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Table 3
Severity of periprocedural stroke assessed by modified Rankin Scale

	N of patients with event (Proportion among patients with periprocedural stroke)	
	PCI	CABG
Periprocedural stroke	101	30
Modified Rankin Scale		
Minor	32 (31.7%)	7 (23.3%)
0	15 (14.9%)	2 (6.7%)
1	17 (16.8%)	5 (16.7%)
Major	69 (68.3%)	23 (76.7%)
2	16 (15.8%)	5 (16.7%)
3	8 (7.9%)	3 (10.0%)
4	15 (14.9%)	6 (20.0%)
5	19 (18.8%)	5 (16.7%)
6	11 (10.9%)	4 (13.3%)
Cause of death		
Stroke (Hemorrhagic)	0	1
Myocardial infarction	8	3
Sudden cardiac death	1	0
Cardiac procedure related	1	0
Infection or sepsis	1	0

Among patients with periprocedural stroke (PCI: N = 125, and CABG: N = 34), modified Rankin Scale at hospital discharge was available in 101 (80%) patients in the PCI stratum, and 30 patients (88%) in the CABG stratum. Definitions of the modified Rankin Scale were as follows; Grade 0: No symptoms at all, Grade 1: No significant disability despite symptoms (able to carry out all usual duties and activities), Grade 2: Slight disability (unable to carry out all previous activities but able to look after own affairs without assistance), Grade 3: Moderate disability (requiring some help, but able to walk without assistance), Grade 4: Moderately severe disability (unable to walk without assistance, and unable to attend to own bodily needs without assistance, Grade 5: Severe disability (bedridden, inconsistent, and requiring constant nursing care and attention), and Grade 6: Dead at hospital discharge regardless of the direct causes of death [13]. Major stroke was defined as stroke with modified Rankin Scale >=2.

Abbreviations are as in Table 1.

periprocedural stroke than in those without in the PCI stratum, whereas it was not significantly different between the 2 groups in the CABG stratum (Supplemental Table 4). In all patients with periprocedural stroke who died within 30 days, death was not directly related to the stroke event (Supplemental Table 5).

Table 4
Independent risk factors of periprocedural stroke

Variables	Odds ratio [95% CI]	p value
PCI stratum		
Age >=75 years	1.48 [1.02-2.15]	0.04
Acute coronary syndrome	3.68 [2.47-5.49]	<0.001
Heart failure	2.60 [1.80-3.76]	<0.001
Prior stroke (symptomatic)	1.37 [0.86-2.18]	0.19
Carotid artery disease	3.13 [1.68-5.83]	<0.001
eGFR <30 ml/min/1.73m^2 or hemodialysis	1.83 [1.14-2.94]	0.01
Severe frailty	1.52 [0.83-2.78]	0.17
CABG stratum		
Age >=75 years	1.40 [0.68-2.87]	0.37
Acute coronary syndrome	3.76 [1.68-8.39]	0.001
Prior stroke (symptomatic)	2.10 [0.98-4.49]	0.06
Carotid artery disease	2.76 [1.18-6.48]	0.02
Atrial fibrillation	2.59 [1.06-6.35]	0.04
Chronic obstructive pulmonary disease	3.29 [1.24-8.72]	0.02
Malignancy	2.50 [1.05-5.93]	0.04
Severe frailty	4.88 [1.23-19.31]	0.02

Odds ratios with 95% CIs of the variables for periprocedural stroke were estimated by the multivariable logistic regression models.

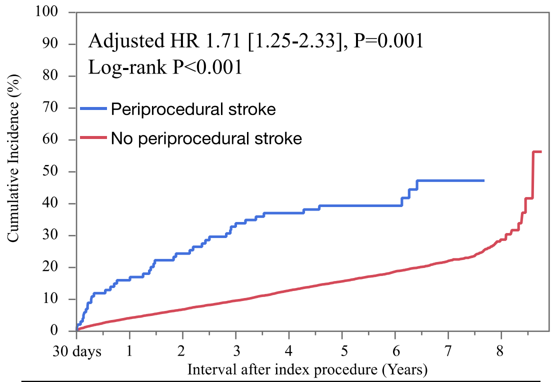
CI = confidence interval; Other abbreviations are as in Table 1-2.

Beyond 30 days, the cumulative 5-year incidence of all-cause death was significantly higher in patients with periprocedural stroke than in those without in both PCI and CABG strata (39.2% vs 15.2%, log-rank p <0.001, and 51.1% vs 14.9%, log-rank p <0.001, respectively) (Figure 2). Even after adjusting confounders, the risk of patients with periprocedural stroke relative to those without remained significant for all-cause death in both PCI and CABG strata (HR, 1.71; 95% CI, 1.25 to 2.33; p = 0.001, and HR, 4.55; 95% CI, 2.79 to 7.43; p <0.001, respectively) (Supplemental Table 6). For cardiovascular death, the adjusted risk of patients with periprocedural stroke relative to those without remained significant in both PCI and CABG strata, whereas for noncardiovascular death, it was no longer significant in both PCI and CABG strata (Supplemental Table 6).

Discussion

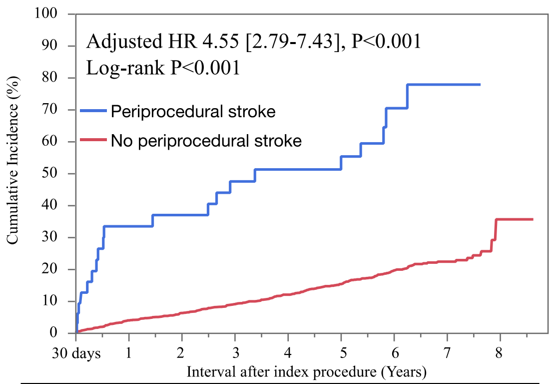
The main findings of this study reflecting real-world clinical practice in Japan were as follows; (1) The incidence of periprocedural stroke was 1.0% after PCI and 2.1% after CABG, and was higher in patients with ACS, and advanced age; (2) Among patients with periprocedural stroke, the proportion of patients with at least mild disability was 68% in the PCI stratum, and 77% in the CABG stratum at hospital discharge; (3) The independent risk factors of periprocedural stroke were ACS, carotid artery disease, advanced age, heart failure, and end-stage renal disease in the PCI stratum, whereas they were ACS, carotid artery disease

(A) All-cause death (PCI stratum)



Interval	30 days	1 year	3 years	5 years
Periprocedural stroke				
N of patients with event		16	31	38
N of patients at risk	107	84	66	50
Cumulative incidence		15.8%	31.6%	39.2%
No periprocedural stroke				
N of patients with event		460	1136	1842
N of patients at risk	12747	12050	11011	8743
Cumulative incidence		3.6%	9.1%	15.2%

(B) All-cause death (CABG stratum)



Interval	30 days	1 year	3 years	5 years
Periprocedural stroke				
N of patients with event		10	13	15
N of patients at risk	34	20	17	12
Cumulative incidence		33.3%	43.9%	51.1%
No periprocedural stroke				
N of patients with event		52	126	209
N of patients at risk	1506	1390	1276	1047
Cumulative incidence		3.6%	8.8%	14.9%

Figure 2. Kaplan-Meier curves for all-cause death beyond 30 days: Periprocedural stroke group versus no-periprocedural stroke group
(A) PCI stratum, and (B) CABG stratum
Abbreviations are as in Figure 1.

atrial fibrillation, chronic obstructive pulmonary disease, malignancy, and severe frailty in the CABG stratum; (4) Patients with periprocedural stroke had higher long-term mortality risk than those without in both PCI and CABG strata, and excess long-term mortality risk was numerically higher in patients undergoing CABG than in patients undergoing PCI.

The incidence of periprocedural stroke after PCI and CABG was apparently higher in this study than in the previous studies.[1−9] One of the reasons for the higher incidence of periprocedural stroke in this study might be related to the differences in baseline characteristics. The patients in the present study were older by 5 years, and more often had previous stroke and heart failure than those in the previous studies. Furthermore, in most of the previous observational studies reporting the incidence of periprocedural stroke, only in-hospital stroke was regarded as periprocedural stroke. Some stroke might occur after index hospital discharge, because of the staged procedure, new onset atrial fibrillation after procedure, and other reasons.[14] In fact, periprocedural stroke is defined as stroke that occurred within 30 days after procedure in Neuro ARC statement,[10] and more than one-third of periprocedural stroke occurred beyond 7 days from index coronary revascularization in this study. Therefore, the periprocedural stroke after PCI or CABG might not be a rare complication, especially in patients with ACS or advanced age. Furthermore, to the best of our knowledge, no previous studies have reported the clinical severity of periprocedural stroke after PCI or CABG. In the present study, the majority of patients with periprocedural stroke had stroke with neurological sequelae, and 30% of patients with periprocedural stroke had stroke associated with severe disability at hospital discharge. These results of this study should be provided for patients in the appropriate shared making decision process when we consider invasive coronary revascularization on top of optimal medical therapy in patients with coronary artery disease.

The independent risk factors of periprocedural stroke in this study were almost consistent with previous studies.[1−5] In both PCI and CABG strata, ACS was the most potent risk factor of periprocedural stroke in this study. It would be important to note that the prevalence of cardiogenic shock among patients with acute myocardial infarction was much higher in patients with periprocedural stroke than in those without. Hemodynamic compromise might be mechanistically linked to the occurrence of periprocedural stroke.[2,5] In patients undergoing PCI, use of intra-aortic balloon pumping and thrombus aspiration has been reported as risk factors of periprocedural stroke,[1, 3−4,15] and these procedures, which are more often performed in patients with ACS, might be associated with higher risk of periprocedural stroke in ACS, although thrombus aspiration was not an independent risk factor in this study. Heart failure was also the potent risk factor of periprocedural stroke. It would also be important to note that the prevalence of current heat failure at index hospitalization, but not previous hospitalization for heart failure, was much higher in patients with periprocedural stroke than in those without, suggesting again the importance of hemodynamic conditions at the time of coronary revascularization on the occurrence of periprocedural stroke. Effective approach to reduce periprocedural stroke is controversial.[16−18] Shoji S et al showed that radial approach was associated with a reduced risk of periprocedural stroke compared with femoral approach.[17] On the other hand, Jurga J et al suggested that radial approach generated more particulate cerebral microemboli than the femoral approach.[18] In this study, radial approach was not independent risk factor, consistent with a meta-analysis.[16] In patients undergoing CABG, the preventive strategy for stroke has evolved in recent years, including off pump surgery, carotid artery disease screening, no-touch technique on the ascending aorta, and epiaortic ultrasonographic scanning.[8,19−22] The benefit of off pump surgery was also observed in this study. It has been reported that use of bilateral internal thoracic arteries was associated with lower incidence of periprocedural stroke because of avoidance for proximal anastomoses,[7] although the prevalence of bilateral internal thoracic arteries graft use was not significantly different between the 2 groups with and without periprocedural stroke in this study. Carotid artery disease, particularly when untreated, was a strong independent risk factor of periprocedural stroke not only in the CABG stratum, but also in the PCI stratum in this study. These results might suggest the importance of screening for carotid artery disease and prophylactic carotid revascularization in patients undergoing PCI or CABG, although the benefit of prophylactic carotid revascularization to reduce periprocedural stroke is controversial.[22−24] It might be warranted for us to discuss the preventing strategy for periprocedural stroke in a multidisciplinary team including a neurologist when we plan not only CABG, but also PCI.

There were several important limitations in this study. First, complete 30-day clinical follow-up was lower in the CABG stratum than in the PCI stratum, suggesting that the incidence of periprocedural stroke might be underestimated in CABG patients. Second, we could not include variables related to hemodynamic compromise in the multivariable logistic regression models exploring the risk factor of periprocedural stroke, because those variables were collected only in patients with acute myocardial infarction. Moreover, the number of patients with periprocedural stroke was small especially in the CABG stratum, and the multivariable logistic regression model in the CABG stratum might be overfitting. Third, we did not have any information on the medical therapies performed during hospital admission including antithrombotic drugs in periprocedural period. Moreover, we did not have those information such as use of intra-aortic balloon pumping, details on carotid artery disease, severity of ascending aortic atherosclerosis, use of epiaortic ultrasonographic scanning, the duration of on-pump or cross clump, and presence of proximal anastomoses that are related to the occurrence of periprocedural stroke. Fourth, there were no data about the influence of periprocedural stroke on long-term disability, cognitive function, and quality of life. Finally, it is unknown whether the higher long-term mortality risk of patients with periprocedural stroke was related to the stroke event per se. We could not deny the presence of unknown confounders, because patients with periprocedural stroke were sicker and had more serious initial presentation such as ACS than those without periprocedural stroke. Finally, there could be a difference in the risk of stroke between Japanese and US/European patients, because it has been reported that Japanese patients have higher hemorrhagic stroke risk compared with US/European patients.[25]

Disclosures

Dr. Morimoto reports honoraria from Bayer and Kowa, and expert witness from Boston Scientific and Sanofi. Dr. Shiomi reports honoraria from Abbott Vascular, and Boston Scientific. 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.

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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.2020.11.031.

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