Ischemic and Bleeding Risk After Percutaneous Coronary Intervention in Patients With Prior Ischemic and Hemorrhagic Stroke

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ORIGINAL RESEARCH

Ischemic and Bleeding Risk After Percutaneous Coronary Intervention in Patients With Prior Ischemic and Hemorrhagic Stroke

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***Background*—**Prior stroke is regarded as risk factor for bleeding after percutaneous coronary intervention (PCI). However, there is a paucity of data on detailed bleeding risk of patients with prior hemorrhagic and ischemic strokes after PCI.

***Methods and Results*—**In a pooled cohort of 19 475 patients from 3 Japanese PCI studies, we assessed the influence of prior hemorrhagic (n=285) or ischemic stroke (n=1773) relative to no-prior stroke (n=17 417) on ischemic and bleeding outcomes after PCI. Cumulative 3-year incidences of the co-primary bleeding end points of intracranial hemorrhage, non-intracranial global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) moderate/severe bleeding, and the primary ischemic end point of ischemic stroke/myocardial infarction were higher in the prior hemorrhagic and ischemic stroke groups than in the no-prior stroke group (6.8%, 2.5%, and 1.3%, $P<0.0001$, 8.8%, 8.0%, and 6.0%, $P=0.001$, and 12.7%, 13.4%, and 7.5%, $P<0.0001$). After adjusting confounders, the excess risks of both prior hemorrhagic and ischemic strokes relative to no-prior stroke remained significant for intracranial hemorrhage (hazard ratio (HR) 4.44, 95% CI 2.64–7.01, $P<0.0001$, and HR 1.52, 95% CI 1.06–2.12, $P=0.02$), but not for non-intracranial bleeding (HR 1.18, 95% CI 0.76–1.73, $P=0.44$, and HR 0.94, 95% CI 0.78–1.13, $P=0.53$). The excess risks of both prior hemorrhagic and ischemic strokes relative to no-prior stroke remained significant for ischemic events mainly driven by the higher risk for ischemic stroke (HR 1.46, 95% CI 1.02–2.01, $P=0.04$, and HR 1.49, 95% CI 1.29–1.72, $P<0.0001$).

***Conclusions*—**Patients with prior hemorrhagic or ischemic stroke as compared with those with no-prior stroke had higher risk for intracranial hemorrhage and ischemic events, but not for non-intracranial bleeding after PCI. **(*J Am Heart Assoc*. 2019;8: e013356. DOI: 10.1161/JAHA.119.013356.)**

Key Words: coronary artery disease • percutaneous coronary intervention • stroke

Patients with prior stroke constitute 8% to 12% of the population undergoing percutaneous coronary intervention (PCI).[1,2] Patients with prior stroke are generally regarded as having high bleeding risk, in whom consideration might be needed to shorted the duration of a dual antiplatelet therapy (DAPT) after PCI. In patients with acute (<12–24 hours) ischemic stroke or transient ischemic attack (TIA), 3 previous studies, CHANCE (the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events), SOCRATES (the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes), and POINT (the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)

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Accompanying Appendix S1, Tables S1 through S3, Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013356

*A complete list of the CREDO-Kyoto PCI/CABG registry cohort-2, RESET and NEXT trial investigators can be found in the Supplemental Material.

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Clinical Perspective

What Is New?

- There is a paucity of data evaluating the bleeding risk of patients with prior hemorrhagic and ischemic stroke separately.

What Are the Clinical Implications?

- Our study findings suggest that prior hemorrhagic or ischemic stroke are associated with higher risk for intracranial hemorrhage and ischemic events, but not for non-intracranial bleeding after percutaneous coronary intervention.

suggested that short-term (≈90 days) DAPT or ticagrelor monotherapy as compared with aspirin monotherapy significantly reduced ischemic stroke without increase in hemorrhagic stroke.[3–5] However, in patients with recent (≈90–180 days) ischemic stroke or TIA, 3 other previous studies, MATCH (the Management of Atherothrombosis with Clopidogrel in High-Risk Patients), PRoFESS (the Prevention Regimen for Effectively Avoiding Second Strokes), and SPS3 (the Secondary Prevention of Small Subcortical Strokes) demonstrated that long-term (1.5–3 years) DAPT as compared with clopidogrel or aspirin monotherapy increased major bleeding and intracranial hemorrhage (ICH) without reduction in ischemic stroke.[6–8] Therefore, in the 2018 American Stroke Association/American Heart Association guidelines, DAPT initiated within 24 hours is recommended for early secondary prevention during the initial 90 days, but is not recommended for routine long-term secondary prevention after a minor stroke or TIA.[9] DAPT is also not recommended for routine long-term secondary prevention after major stroke.[10]

Trials of potent DAPT after acute coronary syndrome have excluded patients with prior hemorrhagic stroke, but not prior ischemic stroke/TIA. The risk for ICH was higher in patients with prior stroke than those without when treated with more potent P2Y12 inhibitors such as prasugrel, ticagrelor, or vorapaxar, while it was discordant when treated with clopidogrel.[11–13] The current PCI guidelines do not provide recommendations on DAPT duration specific for patients with prior ischemic stroke.[14,15] Furthermore, there is a paucity of data about DAPT in patients with prior hemorrhagic stroke. Therefore, we sought to evaluate the impact of prior stroke, stratified by hemorrhagic or ischemic subtypes, on ischemic and bleeding events after PCI in a large Japanese database.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Study Population

We performed a patient-level pooled analysis of the 3 PCI studies conducted after the introduction of a drug-eluting stent in Japan including CREDO-Kyoto (The Coronary Revascularization Demonstrating Outcome study in Kyoto) PCI/coronary artery bypass grafting registry cohort-2, RESET (the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial), and NEXT (NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial) (Figure 1).[16–18] The CREDO-Kyoto PCI/coronary artery bypass grafting (CABG) registry cohort-2 is an investigator-initiated multicenter registry enrolling consecutive patients who underwent first coronary revascularization procedures among 26 centers in Japan between January 2005 and December 2007.[16] RESET and NEXT are prospective, multicenter, randomized trials in Japan comparing everolimus-eluting stent with sirolimus-eluting stent and comparing biolimus-eluting stent with everolimus-eluting stent, respectively.[17,18] The relevant review boards in all the participating centers for each study approved each research protocol for the 3 studies. Because of retrospective enrollment, written informed consents from the patients were waived in the CREDO-Kyoto PCI/CABG registry cohort-2; however, we excluded those patients who refused participation in the study when contacted for follow-up. Written informed consents were obtained from all the study patients in the RESET and NEXT trials. Patients with recent strokes and/or ICH were not excluded from the CREDO-Kyoto registry cohort-2, RESET, and NEXT.

Among the total 19 489 PCI patients in these 3 studies, the current study population consisted of 19 475 patients after excluding 14 patients in whom the type of stroke was unknown (Figure 1). Among them, 2058 patients had prior stroke (10.6%) including 285 patients with prior hemorrhagic stroke (hemorrhagic stroke group: 1.5%), and 1773 patients with prior ischemic stroke (ischemic stroke group: 9.1%), whereas 17 417 patients (89.4%) had no prior stroke (no-prior stroke group). Cerebral hemorrhage subsequent to ischemic stroke was not regarded as hemorrhagic stroke, but was regarded as ischemic stroke. Patients who had histories of both hemorrhagic and ischemic stroke were allocated to the hemorrhagic stroke group. Among 285 patients with prior hemorrhagic stroke, 61 patients (21%) also had prior ischemic stroke. Prior TIA was not regarded as prior stroke.

Procedural anticoagulation was achieved with unfractionated heparin based on the local site protocols. The recommended antiplatelet regimen included aspirin (≥81 mg/day) indefinitely and thienopyridines (75 mg of clopidogrel or 200 mg of ticlopidine daily) for ≥3 months across 3 studies regardless of the stent types. The actual DAPT duration was left to the discretion of each attending physician. The status

of antiplatelet therapy was evaluated throughout the follow-up period by the same methodology across all the studies. Discontinuation of DAPT was defined as the persistent discontinuation of either aspirin or thienopyridine for 2 months or longer.[19]

Definitions

Definitions of the baseline characteristics were consistent across the 3 studies. The primary ischemic end point was defined as a composite of ischemic stroke or myocardial infarction (MI), while the co-primary bleeding end points were ICH and non-intracranial major bleeding defined as the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) moderate/severe bleeding.[20] Stroke during follow-up was defined as that requiring hospitalization with symptoms lasting >24 hours. Cerebral hemorrhage subsequent to ischemic stroke was not regarded as hemorrhagic stroke, but regarded as ischemic stroke, while it was included in the bleeding event. Traumatic brain bleeding was not regarded as hemorrhagic stroke, but included in intracranial bleeding. MI was adjudicated by the definition of ARTS (Arterial Revascularization Therapies Study) in CREDO Kyoto PCI/CABG registry cohort-2, and by the definition of Academic Research Consortium consensus criteria in the RESET and NEXT.[21,22] However, both the ARTS and the Academic Research Consortium definitions adopted the same criteria for spontaneous MI (biomarker elevation above upper limit of normal). The definitions for the outcomes other than MI were identical across the 3 studies. Stent thrombosis was defined according to the definition of the Academic Research Consortium.[22] Target-lesion revascularization was defined as either PCI or CABG attributable 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. All clinical events were adjudicated by the independent clinical event committees in each study.

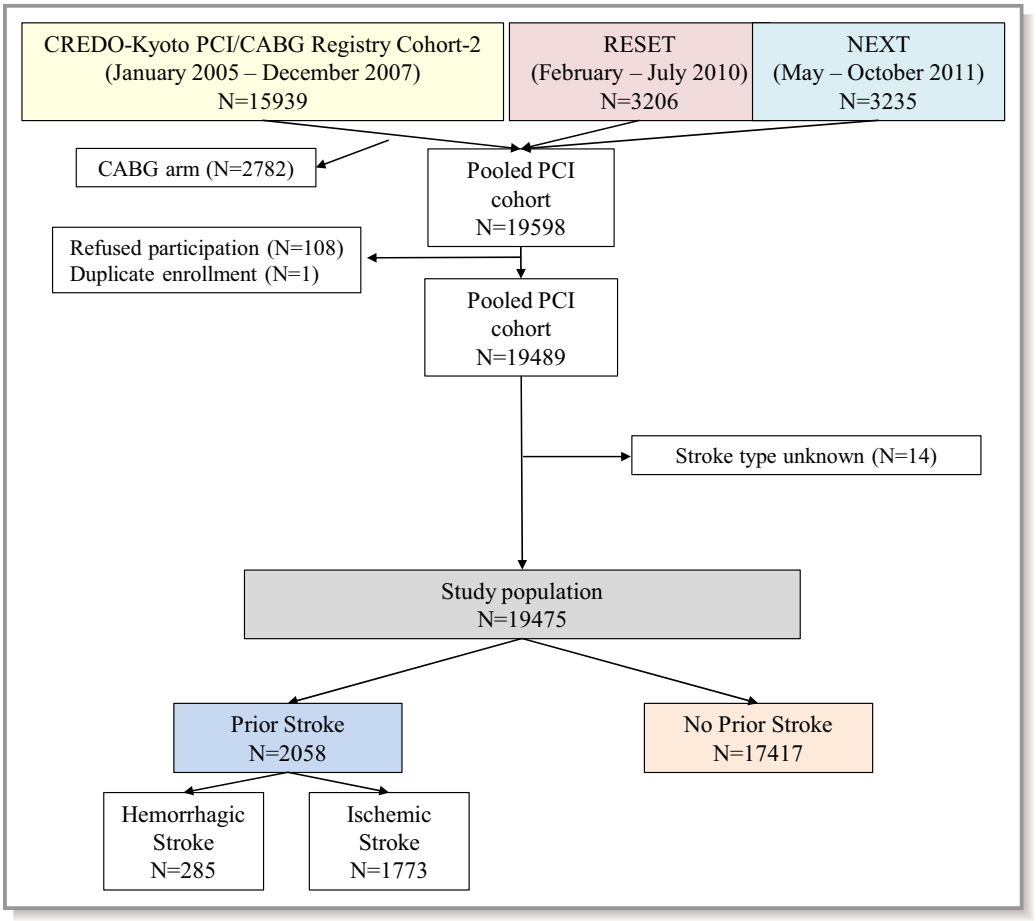


Figure 1. Study patient flow. CABG indicates coronary artery bypass grafting; CREDO-Kyoto, the Coronary Revascularization Demonstrating Outcome study in Kyoto; NEXT, NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent TrialPCI, percutaneous coronary intervention; RESET, the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial.

Data Collection and Follow-Up

In all 3 studies, demographic, angiographic, and procedural data were collected from hospital charts or databases in each participating center according to the pre-specified definitions by the site investigators or by the experienced clinical research coordinators in the study management center (Research Institute for Production Development, Kyoto, Japan). Follow-up data were obtained from hospital charts or by contacting patients or referring physicians with questions on vital status, subsequent hospitalization, and status of antiplatelet therapy. The follow-up duration was 5 years in the CREDO-Kyoto PCI/CABG registry cohort-2, and 3 years in the RESET and NEXT. In the present analysis, follow-up was truncated at 3 years to standardize the follow-up duration.

Statistical Analysis

Categorical variables were presented as number and percentage and were compared with the Chi-square test. Continuous variables were expressed as mean value±SD, and were compared with analysis of variance or Kruskal–Wallis based on the distributions. Cumulative incidence was estimated by the Kaplan–Meier method and differences were assessed with the log-rank test.

We used Cox proportional hazard models to estimate the risk of the prior hemorrhagic and ischemic stroke groups, respectively, relative to no-prior stroke group for clinical end points adjusting the clinically relevant factors for the patient characteristics and medications. We chose 17 clinically relevant factors for both bleeding and ischemic events shown in Table 1 as the risk adjusting variables in consistent with our previous studies.[23] The continuous variables were dichotomized by clinically meaningful reference values. Prior hemorrhagic and ischemic stroke and the 17 risk-adjusting variables were simultaneously included in the Cox proportional hazard model for the adjusted analyses. In the Cox proportional hazard model, we developed dummy code variables for prior hemorrhagic stroke and prior ischemic stroke with no-prior stroke as the reference. We also developed dummy codes for the RESET and the NEXT trials with the CREDO-Kyoto Registry cohort-2 as the reference to adjust for the differences in studies. The effects of the prior hemorrhagic and ischemic stroke groups as compared with no-prior stroke reference group were expressed as hazard ratio (HR) and their 95% CI. We constructed the same Cox proportional hazard model to estimate the HRs for prior hemorrhagic stroke and prior ischemic stroke compared with no-prior stroke in the subgroup of acute myocardial infarction. We calculated the type 3 *P* values for interaction between prior stroke status and subgroup factor. Statistical analyses were conducted by a physician (Natsuaki M) and a statistician (Morimoto T) with the use of JMP 10.0 software. All the statistical analyses were 2-tailed. $P<0.05$ were considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics were much different in several aspects across the 3 groups (Table 1). Patients in the hemorrhagic and ischemic stroke groups were significantly older than those in the no-prior stroke group. Body mass index in the hemorrhagic stroke group was significantly lower than that in the no-prior stroke group. Patients in the hemorrhagic stroke group more often had hypertension, multivessel disease, chronic kidney disease, atrial fibrillation, and anemia than patients in the no-prior stroke group. Patients in the ischemic stroke group more often had hypertension, diabetes mellitus, heart failure, multivessel disease, peripheral vascular disease, chronic kidney disease, atrial fibrillation, and anemia than patients in the no-prior stroke group. Patients in both the hemorrhagic and ischemic stroke groups less often had current smoking than patients in the no-prior stroke group (Table 1). On the procedural characteristics, total stent length was significantly longer in the hemorrhagic and ischemic stroke groups than those in the no-prior stroke group. For the baseline medications, DAPT was implemented in the vast majority of patients in the 3 groups. Patients in the hemorrhagic and ischemic stroke groups less often received statins, while they more often received inhibitors of the renin-aldosterone system and calcium channel blockers. Patients in the ischemic stroke group more often received warfarin than patients in the no-prior stroke group (Table 1).

Clinical Outcomes Through 3 Years

During 3-year follow-up, cumulative incidence of persistent discontinuation of DAPT was significantly lower in the ischemic stroke group than the other 2 groups, while it was not different between the hemorrhagic stroke group and the no-prior stroke group. Substantial proportion of patients in the hemorrhagic stroke group had received prolonged DAPT (58.8% at 1 year and 43.6% at 3 years) (Figure 2).

Cumulative incidence of ICH was much higher in the hemorrhagic stroke group than in the other 2 groups (6.8%, 2.5%, and 1.3%, $P<0.0001$) (Table 2 and Figure 3). Cumulative incidences of non-intracranial bleeding, gastrointestinal bleeding, and any GUSTO moderate/severe bleeding were also higher in the hemorrhagic and ischemic stroke groups than patients in the no-prior stroke group (8.8%, 8.0%, and 6.0%, $P=0.001$, and 3.7%, 3.0%, and 2.2%, $P=0.04$, and 15.1%,

Table 1. Baseline Characteristics and Medications

	Hemorrhagic Stroke (n=285)	Ischemic Stroke (n=1773)	No Prior Stroke (n=17 417)	*P* Value	SMD
Clinical characteristics					
Age, y	71.0±9.2	72.3±9.0	68.1±10.8	<0.0001	0.39
Age ≥75 y*	109 (38%)	771 (43%)	5231 (30%)	<0.0001	0.29
Men*	212 (74%)	1332 (75%)	12 781 (73%)	0.27	0.04
BMI	23.2±3.3	23.5±3.5	23.9±3.5	<0.0001	0.2
BMI <25.0*	205/275 (75%)	1151/1685 (68%)	11 088/16 989 (65%)	0.0002	0.2
Acute myocardial infarction*	77 (27%)	394 (22%)	4590 (26%)	0.0006	0.09
Hypertension*	261 (92%)	1545 (87%)	14 082 (81%)	<0.0001	0.29
Diabetes mellitus*	117 (41%)	853 (48%)	6847 (39%)	<0.0001	0.18
On insulin therapy	25 (8.8%)	208 (12%)	1435 (8.2%)	<0.0001	0.12
Current smoking*	65 (23%)	322 (18%)	5012 (29%)	<0.0001	0.24
Heart failure*	57 (20%)	450 (25%)	2903 (17%)	<0.0001	0.23
Multivessel disease	165 (58%)	1773 (61%)	9037 (51%)	<0.0001	0.18
Mitral regurgitation grade 3/4	9 (3.2%)	79 (4.5%)	538 (3.1%)	0.01	0.08
LVEF, %	57.8±13.3 (237)	57.5±13.3 (1447)	59.1±12.7 (14 635)	<0.0001	0.13
Prior myocardial infarction*	53 (19%)	322 (18%)	2870 (16%)	0.14	0.06
Peripheral vascular disease*	26 (9.1%)	259 (15%)	1092 (6.3%)	<0.0001	0.32
Moderate CKD*	107 (38%)	718 (41%)	5214 (30%)	<0.0001	0.23
Severe CKD*	33 (12%)	232 (13%)	1241 (7.1%)	<0.0001	0.22
eGFR <30 mL/min per 1.73 m^2, not on dialysis	16 (5.6%)	122 (6.9%)	544 (3.1%)	<0.0001	0.2
Dialysis	17 (6.0%)	110 (6.2%)	697 (4.0%)	<0.0001	0.11
Atrial fibrillation*	36 (13%)	253 (14%)	1267 (7.3%)	<0.0001	0.26
Anemia (hemoglobin <11 g/dL)*	47 (16%)	334 (19%)	1929 (11%)	<0.0001	0.24
Platelet <100×10^9/L*	7 (2.5%)	31 (1.8%)	255 (1.5%)	0.31	0.08
COPD	9 (3.2%)	74 (4.2%)	535 (3.1%)	0.054	0.06
Liver cirrhosis*	6 (2.1%)	41 (2.3%)	335 (1.9%)	0.54	0.03
Malignancy*	24 (8.4%)	183 (10%)	1429 (8.2%)	0.01	0.08
Procedural characteristics					
Number of target lesions	1 (1–2)	1 (1–2)	1 (1–2)	0.003	0.07
	1.42±0.71	1.43±0.71	1.38±0.69		
Target of proximal LAD	159 (56%)	907 (51%)	9363 (54%)	0.08	0.09
Target of unprotected LMCA	9 (3.2%)	77 (4.3%)	559 (3.2%)	0.051	0.07
Target of CTO	32 (11%)	198 (11%)	1767 (10%)	0.35	0.04
Target of bifurcation	77 (27%)	499 (28%)	5125 (29%)	0.37	0.05
Side-branch stenting	8 (2.8%)	66 (3.7%)	627 (3.6%)	0.73	0.05
Total number of stents	1 (1–2)	2 (1–2)	1 (1–2)	<0.0001	0.12
	1.85±1.22 (275)	1.87±1.21 (1688)	1.74±1.11 (16 614)		
Total stent length, mm	28 (18–50)	30 (18–51)	28 (18–46)	<0.0001	0.12
	39.2±29.0 (275)	40.1±29.3 (1687)	36.7±26.4 (16 603)		
Minimum stent size, mm	3.0 (2.5–3.0)	2.75 (2.5–3.0)	3.0 (2.5–3.0)	<0.0001	0.16
	2.88±0.42 (275)	2.85±0.41 (1687)	2.92±0.43 (16 602)		

Continued

Table 1. Continued

	Hemorrhagic Stroke (n=285)	Ischemic Stroke (n=1773)	No Prior Stroke (n=17 417)	*P* Value	SMD
Baseline medication					
Medication at hospital discharge					
Antiplatelet therapy					
Thienopyridine	279 (97.9%)	1730 (97.6%)	17 052 (97.9%)	0.67	0.02
Ticlopidine	200 (70%)	1120 (63%)	10 979 (63%)	0.04	0.15
Clopidogrel	79 (28%)	606 (34%)	6011 (35%)	0.051	0.15
Aspirin	281 (98.6%)	1737 (98.0%)	17 241 (99.0%)	0.002	0.1
Cilostazole	49 (17%)	273 (15%)	2579 (15%)	0.45	0.07
Other medications					
Statins	133 (47%)	943 (53%)	10 539 (61%)	<0.0001	0.28
Beta-blockers	101 (35%)	555 (31%)	5723 (33%)	0.26	0.09
ACE-I/ARB	194 (68%)	1094 (62%)	10 268 (59%)	0.0007	0.19
Nitrates	92 (32%)	595 (34%)	5659 (32%)	0.66	0.03
Calcium channel blockers	145 (51%)	857 (48%)	7105 (41%)	<0.0001	0.2
Warfarin	23 (8.1%)	227 (13%)	1324 (7.6%)	<0.0001	0.19

Values are expressed as mean±SD, median (interquartile range), or number (%). ACE-I indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; LMCA, left main coronary artery; SMD, standardized mean differences.
*Potential independent variables selected in multivariable analysis.

10.3%, and 7.1%, $P<0.0001$) (Table 2 and Figure 3). Cumulative incidence of the primary ischemic end point of ischemic stroke/MI was significantly higher in the hemorrhagic and ischemic stroke groups than in the no-prior stroke group (12.7%, 13.4%, and 7.5%, $P<0.0001$) (Table 2 and Figure 4A). Cumulative incidence of ischemic stroke was much higher in the hemorrhagic and ischemic stroke groups than in the no-prior stroke group, while there was no significant difference in the cumulative incidence of MI across the 3 groups (7.1%, 7.7%, and 2.6%, $P<0.0001$, and 6.5%, 6.3%, and 5.2%, $P=0.09$) (Table 2 and Figure 4B, 4C). Cumulative incidence of all-cause death was also higher in the hemorrhagic and ischemic stroke groups than in the no-prior stroke group (14.7%, 17.1%, and 9.0%, $P<0.0001$) (Table 2).

After adjusting the confounders, the excess risk of the hemorrhagic and ischemic stroke groups relative to the no-prior stroke group remained significant for ICH, but not for non-intracranial bleeding. Patients in the hemorrhagic stroke group, but not those in the ischemic stroke group, had higher risk for any GUSTO moderate/severe bleeding than patients in the no-prior stroke group. Patients in the hemorrhagic and ischemic stroke groups had significantly higher adjusted risk for ischemic stroke/MI than patients in the no-prior stroke group, which was mainly driven by the higher risk for ischemic stroke. Patients in the ischemic stroke group, but not those in the hemorrhagic stroke group, had higher mortality risk than patients in the no-prior stroke group (Figure 5).

Clinical Outcomes Through 3 Years in Patients With or Without Acute Myocardial Infarction

Cumulative incidence of intracranial bleeding was significantly higher in the hemorrhagic and ischemic stroke groups than in the no-prior stroke group in those with and without acute myocardial infarction (3.1%, 2.8%, and 1.1%, $P=0.01$ and 8.0%, 2.4%, and 1.3%, $P<0.0001$). Cumulative incidence of ischemic stroke/MI was also significantly higher in the hemorrhagic and ischemic stroke groups than in the no-prior stroke group in those with and without acute myocardial infarction (13.0%, 15.3%, and 7.3%, $P<0.0001$ and 12.7%, 12.9%, and 7.6%, $P<0.0001$). There was no significant interaction between clinical presentation and prior stroke (Table S1).

Clinical Outcomes Through 3 Years in Patients With or Without Atrial Fibrillation in the Prior Ischemic Stroke Group

In the prior ischemic stroke group, cumulative incidence of GUSTO moderate/severe bleeding and ischemic stroke/MI

was significantly higher in patients with atrial fibrillation than in those without (14.7% versus 9.6%, *P*=0.02, and 18.9% versus 12.5%, *P*=0.01). Cumulative incidence of ischemic stroke was markedly higher in patients with atrial fibrillation than in those without (14.1% versus 6.7%, *P*<0.0001) (Table S2).

Clinical Outcomes in Patients With or Without DAPT Between 4 Months and 3 Years By the Landmark Analysis at 4 Months

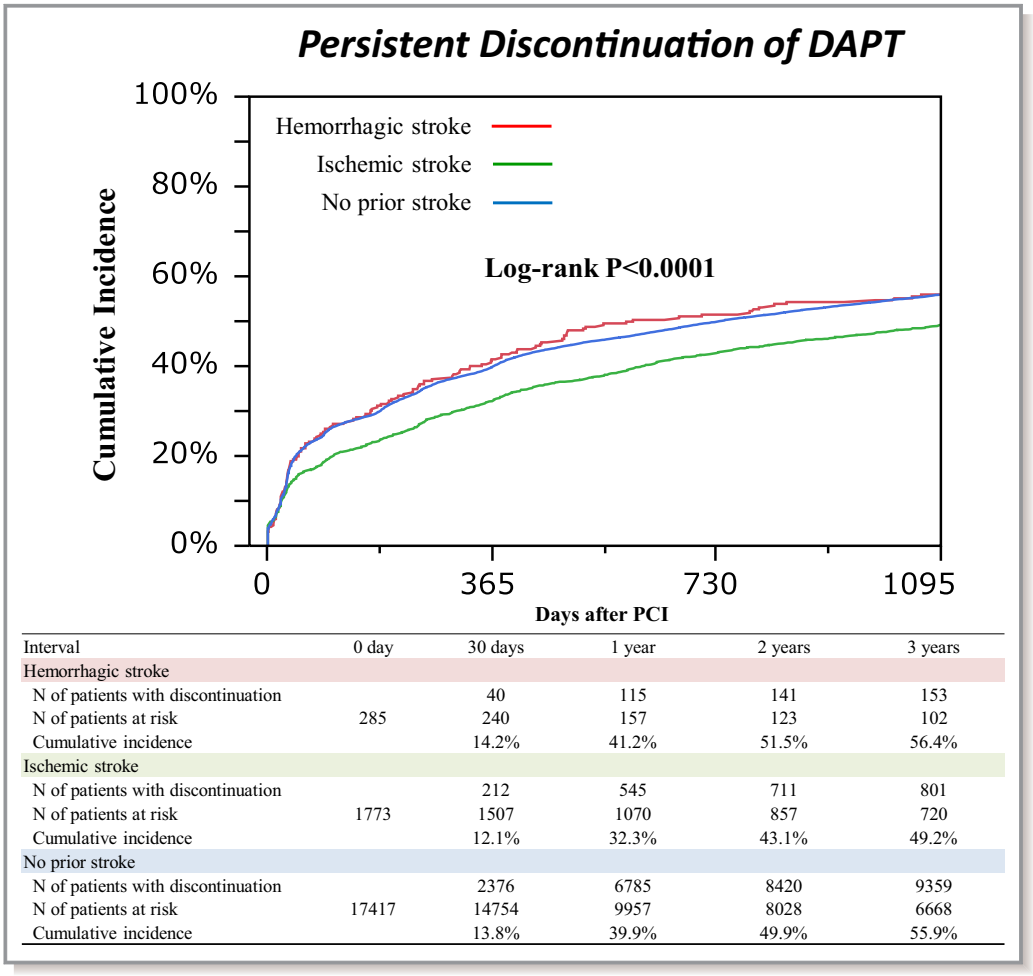
Cumulative incidences of non-intracranial bleeding and ischemic stroke/MI between 4 months and 3 years tended to be higher in the prior hemorrhagic and ischemic stroke groups than in the no-prior stroke group in patients with and without DAPT at 4 months (Table S3). However, cumulative incidence of ICH in the prior hemorrhagic stroke group was higher than in the no-prior stroke group in patients on-DAPT at 4 months, but not in patients off-DAPT at 4 months.

Antiplatelet Therapy at the Onset of ICH and Ischemic Stroke

More than 70% of patients had DAPT at the time of ICH throughout the follow-up period (0–30 days: 87.5%, 31–180 days: 76.7%, 181–365 days: 71.9%, 366–1095 days: 71.5%). On the other hand, patients with DAPT at the onset of ischemic stroke decreased with longer-term follow-up (0–30 days: 87.6%, 31–180 days: 66.3%, 181–365 days: 65.6%, 366–1095 days: 55.9%) (Figure S1).

Discussion

The main findings of this study were as follows: (1) Patients with prior hemorrhagic or ischemic stroke had higher adjusted risk for ICH, but not for non-intracranial bleeding; (2) Patients in the hemorrhagic stroke group, but not those in the ischemic stroke group, had higher risk for any GUSTO moderate/severe bleeding than patients in the no-prior stroke group; (3) Patients with prior hemorrhagic or ischemic stroke had significantly



Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with discontinuation		40	115	141	153
N of patients at risk	285	240	157	123	102
Cumulative incidence		14.2%	41.2%	51.5%	56.4%
Ischemic stroke					
N of patients with discontinuation		212	545	711	801
N of patients at risk	1773	1507	1070	857	720
Cumulative incidence		12.1%	32.3%	43.1%	49.2%
No prior stroke					
N of patients with discontinuation		2376	6785	8420	9359
N of patients at risk	17417	14754	9957	8028	6668
Cumulative incidence		13.8%	39.9%	49.9%	55.9%

Figure 2. Cumulative incidence of persistent discontinuation of dual antiplatelet therapy. DAPT indicates dual antiplatelet therapy; PCI, percutaneous coronary intervention.

Table 2. Clinical Outcomes Through 3 Years

	Hemorrhagic Stroke	Ischemic Stroke	No Prior Stroke	
	No. of Patients With Events (Cumulative 3-year Incidence)	No. of Patients With Events (Cumulative 3-year Incidence)	No. of Patients with Events (Cumulative 3-year Incidence)	
	(n=285)	(n=1773)	(n=17 417)	*P* Value
GUSTO moderate/severe bleeding	41 (15.1%)	172 (10.3%)	1195 (7.1%)	<0.0001
GUSTO severe bleeding	22 (8.3%)	81 (4.9%)	526 (3.2%)	<0.0001
Hemorrhagic stroke	11 (4.2%)	28 (1.7%)	148 (0.9%)	<0.0001
Intracranial bleeding	18 (6.8%)	40 (2.5%)	209 (1.3%)	<0.0001
Non-intracranial bleeding	24 (8.8%)	133 (8.0%)	1004 (6.0%)	0.001
Gastrointestinal bleeding	10 (3.7%)	49 (3.0%)	368 (2.2%)	0.04
MI/Ischemic stroke	35 (12.7%)	221 (13.4%)	1270 (7.5%)	<0.0001
MI	18 (6.5%)	107 (6.3%)	877 (5.2%)	0.09
Ischemic stroke	19 (7.1%)	123 (7.7%)	425 (2.6%)	<0.0001
Stroke	30 (11.3%)	147 (9.1%)	570 (3.5%)	<0.0001
Death	41 (14.7%)	298 (17.1%)	1552 (9.0%)	<0.0001
Cardiac death	13 (4.8%)	160 (9.3%)	778 (4.6%)	<0.0001
Non-cardiac death	28 (10.5%)	138 (8.5%)	774 (4.7%)	<0.0001
Death/MI/stroke	75 (26.7%)	475 (27.1%)	2631 (15.3%)	<0.0001
Definite/Probable ST	4 (1.6%)	17 (1.0%)	216 (1.3%)	0.63
TLR	44 (16.1%)	229 (14.1%)	2657 (15.9%)	0.11
Any coronary revascularization	72 (26.5%)	423 (26.2%)	4650 (28.0%)	0.15

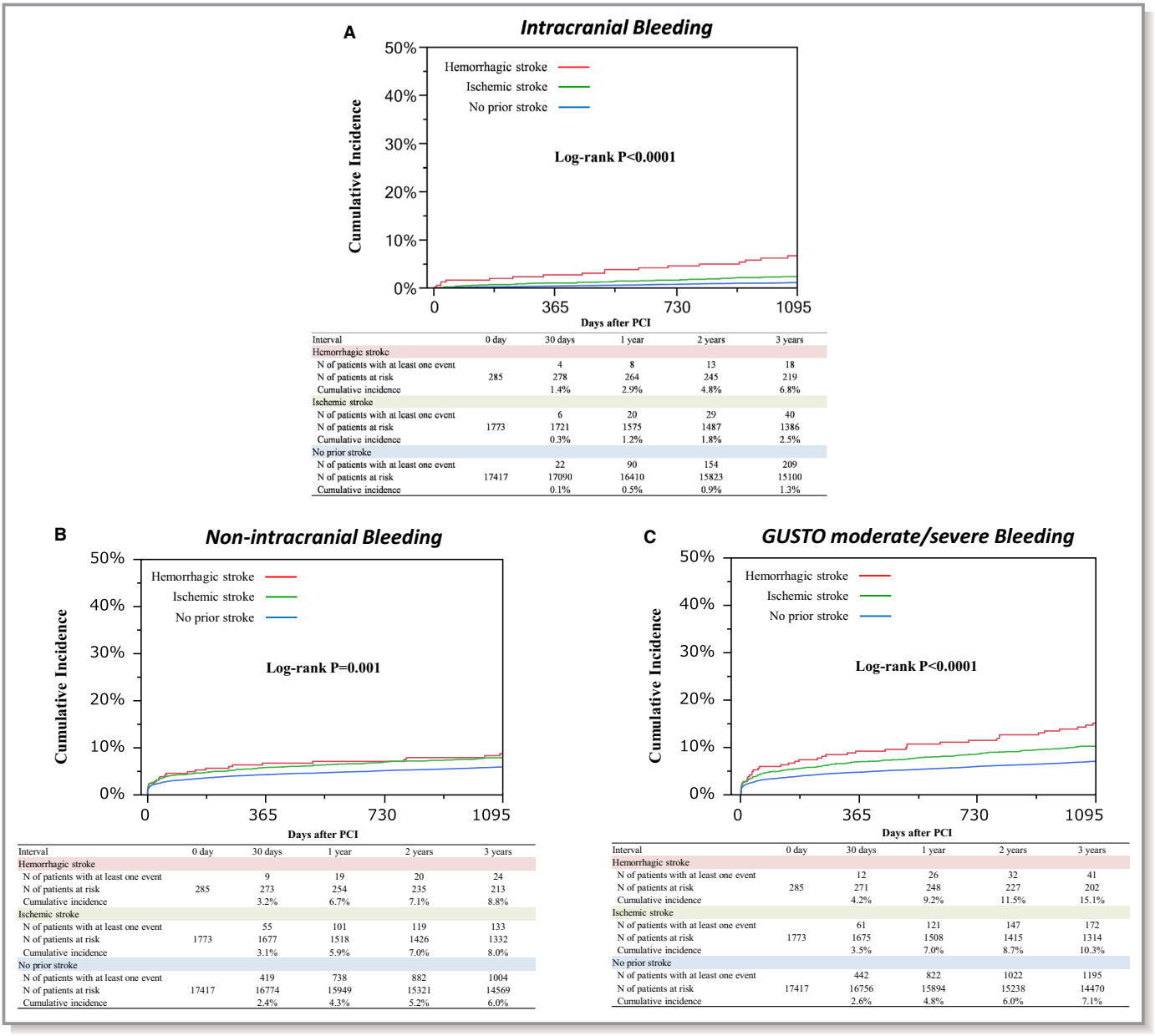
GUSTO bleeding criteria: Severe=intracerebral hemorrhage or resulting in substantial hemodynamic compromise requiring treatment. Moderate=requiring blood transfusion but not resulting in hemodynamic compromise. GUSTO indicates global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; MI, myocardial infarction; ST, stent thrombosis; TLR, target-lesion revascularization.

higher ischemic risk (ischemic stroke/MI), which was mainly driven by the higher risk for ischemic stroke.

The impact of prior stroke on bleeding after PCI might be different according to the type of bleeding. In predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT [the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy]) the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy study including 8 trials enrolled between 2007 and 2014, patients with prior stroke had similar risk of thrombolysis in myocardial infarction major/minor bleeding as compared with those without (HR 1.16, 95% CI 0.54–2.48, *P*=0.70).[24] In the PARIS (patterns of non-adherence to anti-platelet regimens in stented patients) registry, rates of BARC (the Bleeding Academic Research Consortium) 3 or 5 bleeding in patients with and without previous stroke were also similar (4.1% versus 3.5%, respectively, *P*=0.66).[25] Indeed, prior stroke is not included as a risk factors for major bleeding in several bleeding risk scores.[23–25] On the other hand, patients with previous stroke had higher risk for hemorrhagic stroke after PCI in the British Cardiovascular Intervention Society database (HR 4.07, 95% CI 1.13–14.62, *P*=0.03).[26] Therefore, prior stroke might be associated with higher risk for ICH after PCI. However, impact of prior hemorrhagic and ischemic stroke on bleeding was not evaluated separately in these studies.

In the PLATO (Platelet Inhibition and Patient Outcomes) trial excluding those with previous bleeding events, the risk for major bleeding was not significantly different between patients with or without prior ischemic stroke (adjusted HR 1.18, 95% CI 0.98–1.43, *P*=0.09), although this trial might not have enough power for the risk evaluation of major bleeding. On the other hand, patients with prior ischemic stroke had significantly higher rate of ICH than those without (0.8% versus 0.2%, *P*=0.0005).[12] In line with the results of the PLATO trial, patients with prior ischemic stroke in the present study were not associated with higher risk for GUSTO moderate/severe bleeding, while they had significantly higher risk for ICH and hemorrhagic stroke. Therefore, prior ischemic stroke could be the risk for ICH after PCI, but not for non-intracranial bleeding.

The data in patients with prior hemorrhagic stroke are scarce because most previous studies did not differentiate between ischemic and hemorrhagic stroke.[23–25] Furthermore, patients with prior hemorrhagic stroke had been excluded from the randomized trials considering the risk for the



Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with at least one event		4	8	13	18
N of patients at risk	285	278	264	245	219
Cumulative incidence		1.4%	2.9%	4.8%	6.8%
Ischemic stroke					
N of patients with at least one event		6	20	29	40
N of patients at risk	1773	1721	1575	1487	1386
Cumulative incidence		0.3%	1.2%	1.8%	2.5%
No prior stroke					
N of patients with at least one event		22	90	154	209
N of patients at risk	17417	17090	16410	15823	15100
Cumulative incidence		0.1%	0.5%	0.9%	1.3%

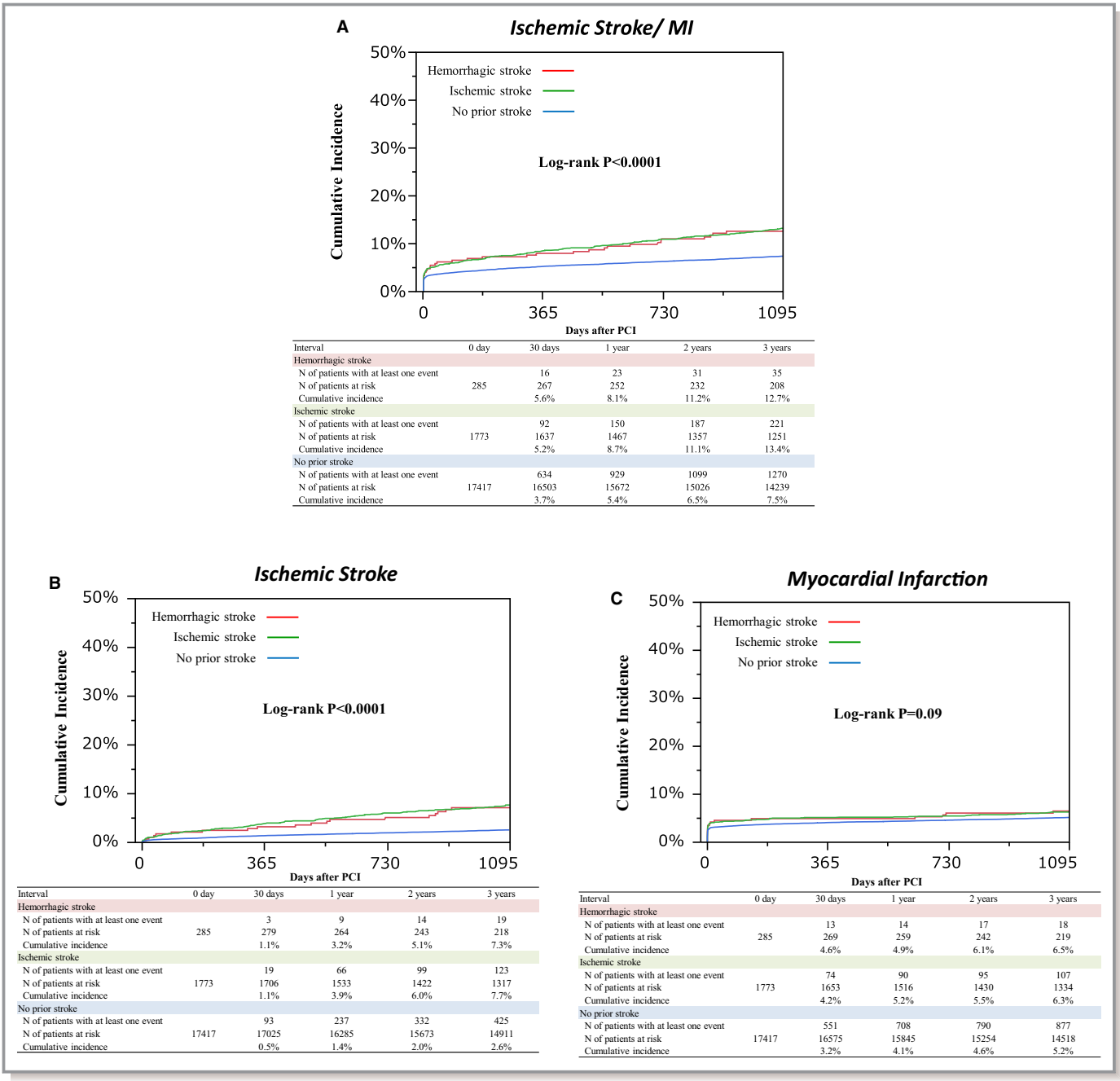
Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with at least one event		9	19	20	24
N of patients at risk	285	273	254	235	213
Cumulative incidence		3.2%	6.7%	7.1%	8.8%
Ischemic stroke					
N of patients with at least one event		55	101	119	133
N of patients at risk	1773	1677	1518	1426	1332
Cumulative incidence		3.1%	5.9%	7.0%	8.0%
No prior stroke					
N of patients with at least one event		419	738	882	1004
N of patients at risk	17417	16774	15949	15321	14569
Cumulative incidence		2.4%	4.3%	5.2%	6.0%

Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with at least one event		12	26	32	41
N of patients at risk	285	271	248	227	202
Cumulative incidence		4.2%	9.2%	11.5%	15.1%
Ischemic stroke					
N of patients with at least one event		61	121	147	172
N of patients at risk	1773	1675	1508	1415	1314
Cumulative incidence		3.5%	7.0%	8.7%	10.3%
No prior stroke					
N of patients with at least one event		442	822	1022	1195
N of patients at risk	17417	16756	15894	15238	14470
Cumulative incidence		2.6%	4.8%	6.0%	7.1%

Figure 3. Cumulative incidence of bleeding events through 3 years. **A**, Kaplan–Meier curves for intracranial bleeding through 3 years. **B**, Kaplan–Meier curves for non-intracranial bleeding through 3 years. **C**, Kaplan–Meier curves for GUSTO moderate/severe bleeding through 3 years. GUSTO indicates global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; MI, myocardial infarction; PCI, percutaneous coronary intervention.

recurrence of bleeding events.[27,28] In the present study, patients with prior hemorrhagic stroke were associated with markedly higher risk for ICH than those with no prior stroke. Therefore, DAPT duration after PCI should be as short as possible in patients with prior hemorrhagic stroke. However, DAPT duration after PCI was similar in patients with prior hemorrhagic stroke and in patients with no-prior stroke, highlighting the need for a practice change. Furthermore, given their markedly higher ICH risk, the threshold for PCI should be higher in patients with prior hemorrhagic stroke, in whom optimal medical treatment alone or CABG might be more preferable to PCI requiring DAPT.

In the PARIS registry, rate of coronary thrombotic events in patients with previous stroke was significantly higher than in those without (7.0% and 3.3%, P=0.01).[25] In PLATO, patients with prior stroke had significantly higher rates of MI and stroke than those without (11.5% versus 6.0%, P<0.0001, and 3.4% versus 1.2%, P<0.0001, respectively).[12] In line with these previous reports, patients with either prior hemorrhagic and ischemic stroke were associated with higher ischemic risk



Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with at least one event		16	23	31	35
N of patients at risk	285	267	252	232	208
Cumulative incidence		5.6%	8.1%	11.2%	12.7%
Ischemic stroke					
N of patients with at least one event		92	150	187	221
N of patients at risk	1773	1637	1467	1357	1251
Cumulative incidence		5.2%	8.7%	11.1%	13.4%
No prior stroke					
N of patients with at least one event		634	929	1099	1270
N of patients at risk	17417	16503	15672	15026	14239
Cumulative incidence		3.7%	5.4%	6.5%	7.5%

Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with at least one event		3	9	14	19
N of patients at risk	285	279	264	243	218
Cumulative incidence		1.1%	3.2%	5.1%	7.3%
Ischemic stroke					
N of patients with at least one event		19	66	99	123
N of patients at risk	1773	1706	1533	1422	1317
Cumulative incidence		1.1%	3.9%	6.0%	7.7%
No prior stroke					
N of patients with at least one event		93	237	332	425
N of patients at risk	17417	17025	16285	15673	14911
Cumulative incidence		0.5%	1.4%	2.0%	2.6%

Interval	0 day	30 days	1 year	2 years	3 years
Hemorrhagic stroke					
N of patients with at least one event		13	14	17	18
N of patients at risk	285	269	259	242	219
Cumulative incidence		4.6%	4.9%	6.1%	6.5%
Ischemic stroke					
N of patients with at least one event		74	90	95	107
N of patients at risk	1773	1653	1516	1430	1334
Cumulative incidence		4.2%	5.2%	5.5%	6.3%
No prior stroke					
N of patients with at least one event		551	708	790	877
N of patients at risk	17417	16575	15845	15254	14518
Cumulative incidence		3.2%	4.1%	4.6%	5.2%

Figure 4. Cumulative incidence of ischemic events through 3 years. **A**, Kaplan–Meier curves for the primary ischemic end point through 3 years. **B**, Kaplan–Meier curves for ischemic stroke through 3 years. **C**, Kaplan–Meier curves for myocardial infarction through 3 years. Primary ischemic end point was defined as a composite of ischemic stroke or MI. MI indicates myocardial infarction; PCI, percutaneous coronary intervention.

(ischemic stroke/MI) in the present study. However, the higher ischemic risk in patients with prior hemorrhagic and ischemic stroke was mainly driven by the higher risk for stroke, while their risk for MI was not different from that in patients with no prior stroke. The risk for stroke and MI might be different according to the types of ischemic stroke such as embolic versus athero-thrombotic stroke. Indeed, the risk for recurrent ischemic stroke was markedly higher in patients with atrial fibrillation than in those without. Considering their higher ICH risk, prolonged DAPT would better be avoided in patients with prior ischemic stroke despite their high ischemic risk, and defining optimal antithrombotic regimen is challenging in patients with prior stroke, representing an unmet clinical need.

Study Limitation

Some limitations to our study should be considered. First, this study is the pooled analysis of the retrospective registry and

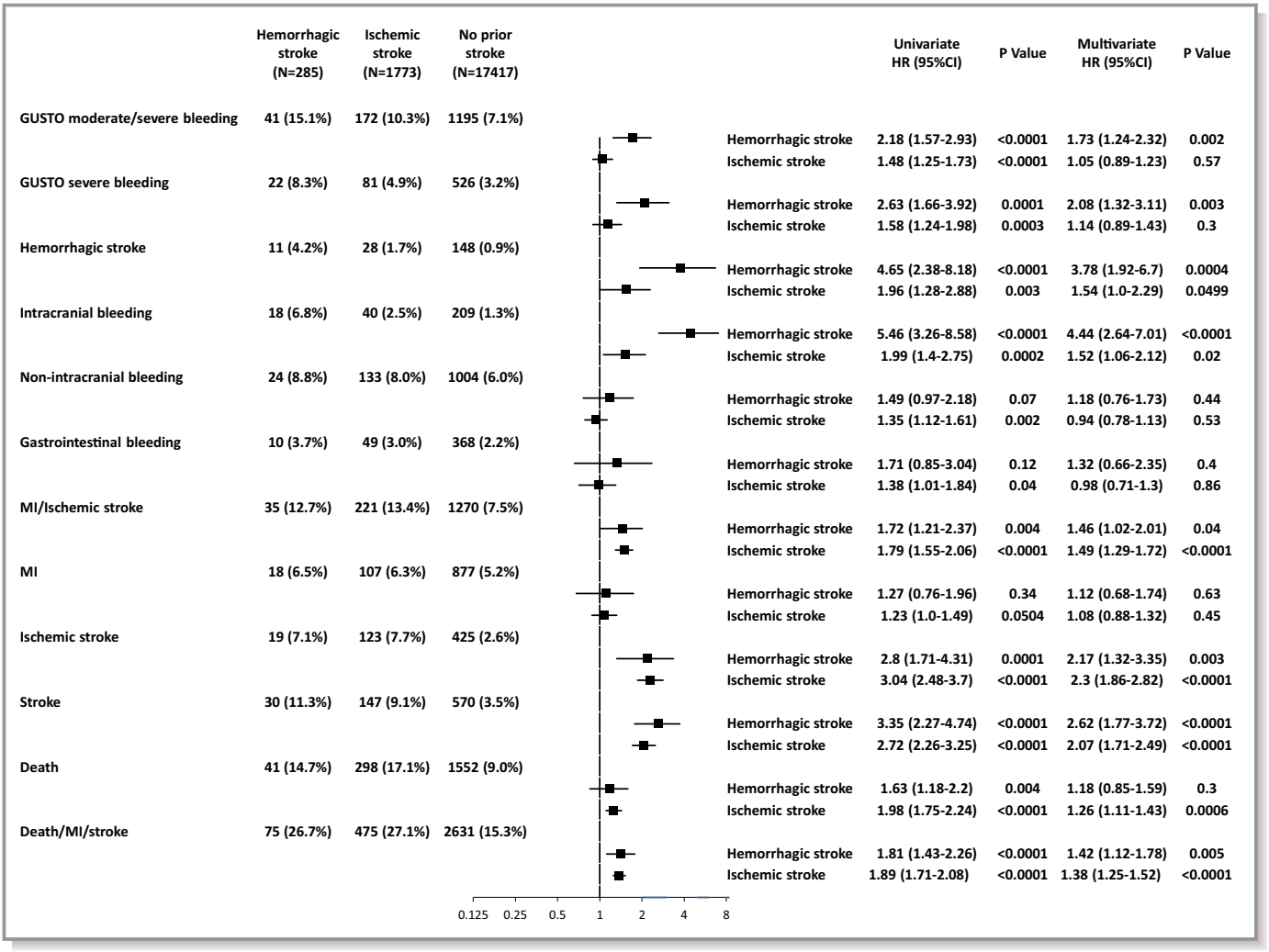


Figure 5. Forrest plot for the adjusted hazard ratios of prior hemorrhagic and ischemic stroke relative to no prior stroke for the clinical events. GUSTO indicates global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; HR, hazard ratio; MI, myocardial infarction.

randomized controlled trials. Despite the adjustment for the study, we could not exclude the possibility for the presence of unmeasured confounding related to the pooling of patients from different types of studies. Second, this analysis includes only Japanese patients and race is well known to be associated with a different ischemic-to-bleeding tradeoff. Therefore, we should be cautious to extrapolate the current study results outside of Japan. Third, substantial proportion of patients received ticlopidine as a P2Y12 receptor blocker, which is no longer used in the current clinical practice. Prasugrel or ticagrelor were not available in the enrollment period between 2005 and 2011 in Japan. Considering these differences in antiplatelet therapy, it remains unclear how the findings from this analysis can be translated into current clinical practice. Fourth, patients were enrolled between 2005 and 2011 in this pooled cohort. Many of the patients were treated with protocols that are no longer recommended, so the applicability of the findings to patients in current practice might be somewhat questionable. Fifth, the timing of the onset of prior stroke was unknown in this study. Therefore, we could not evaluate the relationship between the timing of stroke and clinical outcomes after PCI, although the risk for ICH or ischemic events might be different according to the time interval between prior stroke and PCI. Sixth, the details of the types of stroke and stroke severity were unknown in this study. Finally, we did not perform head-computed tomography or magnetic resonance imaging systematically to evaluate the previous history of stroke. Therefore, there is a possibility for underreporting of the previous history of stroke.

Conclusions

Patients with prior hemorrhagic or ischemic stroke as compared with those with no prior stroke had higher risk for ICH and ischemic events (ischemic stroke/MI), but not for non-intracranial bleeding after PCI.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Appendix

List of the participating centers and the investigators

List A. CREDO-Kyoto registry cohort-2

Kyoto University Hospital: Takeshi Kimura

Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka

Tenri Hospital: Yoshihisa Nakagawa

Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi

Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi

Maizuru Kyosai Hospital: Ryozo Tatami

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Shizuoka City Shizuoka Hospital: Akinori Takizawa

Hamamatsu Rosai Hospital: Masaaki Takahashi

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura

Shimabara Hospital: Mamoru Takahashi

Kagoshima University Medica and Dental Hospital: Chuwa Tei, Shuichi Hamasaki

Shizuoka General Hospital: Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi

Kurashiki Central Hospital: Kazuaki Mitsudo, Kazushige Kadota

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi

Kumamoto University Hospital: Hisao Ogawa, Seigo Sugiyama

Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki

Juntendo University Shizuoka Hospital: Satoru Suwa

List B. RESET Trial

Caress Sappro Tokeidai Memorial Hospital: Kazushi Urasawa, Ryoji Koshida

Teine Keijinkai Hospital: Mitsugu Hirokami

Cardio-vascular Center Hokkaido Ohno Hospital: Takehiro Yamashita, Masato Nagashima

Caress Sappro Hokko Memorial Hospital: Yoichi Nozaki

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Table S1. Clinical Outcomes Through 3 Years in Patients With or Without AMI.

		Hemorrhagic stroke	Ischemic stroke	No prior stroke	Log-rank P		Univariate HR (95%CI)	P Value	Multivariate HR (95%CI)	P Value	Interaction P
GUSTO moderate/severe bleeding	AMI	8/77 (11.0%)	51/394 (14.3%)	431/4590 (9.8%)	0.02						
						Hemorrhagic stroke	1.12 (0.51-2.1)	0.76	0.93 (0.42-1.76)	0.85	
						Ischemic stroke	1.5 (1.11-1.98)	0.009	0.96 (0.71-1.29)	0.81	
	Non-AMI	33/208 (16.4%)	121/1379 (9.2%)	764/12827 (6.1%)	<0.0001						0.06
						Hemorrhagic stroke	2.79 (1.93-3.89)	<0.0001	2.2 (1.52-3.07)	<0.0001	
						Ischemic stroke	1.52 (1.25-1.84)	<0.0001	1.09 (0.89-1.32)	0.39	
Intracranial bleeding	AMI	2/77 (3.1%)	9/394 (2.8%)	47/4590 (1.1%)	0.01						
						Hemorrhagic stroke	2.66 (0.43-8.59)	0.24	2.31 (0.37-7.61)	0.31	
						Ischemic stroke	2.55 (1.17-4.95)	0.02	2.07 (0.92-4.15)	0.08	
	Non-AMI	16/208 (8.0%)	31/1379 (2.4%)	162/12827 (1.3%)	<0.0001						0.48
						Hemorrhagic stroke	6.28 (3.61-10.16)	<0.0001	4.9 (2.8-7.99)	<0.0001	
						Ischemic stroke	1.85 (1.23-2.67)	0.004	1.42 (0.94-2.08)	0.1	
Non-intracranial bleeding	AMI	6/77 (7.9%)	42/394 (11.6%)	386/4590 (8.7%)	0.15						
						Hemorrhagic stroke	0.93 (0.37-1.9)	0.86	0.79 (0.31-1.62)	0.56	
						Ischemic stroke	1.37 (0.98-1.86)	0.06	0.86 (0.61-1.18)	0.36	
	Non-AMI	18/208 (8.9%)	91/1379 (6.9%)	618/12827 (5.0%)	0.0005						0.33
						Hemorrhagic stroke	1.83 (1.11-2.84)	0.02	1.44 (0.87-2.23)	0.15	
						Ischemic stroke	1.41 (1.12-1.75)	0.003	0.99 (0.79-1.24)	0.96	
MI/Ischemic stroke	AMI	9/77 (13.0%)	50/394 (15.3%)	311/4590 (7.3%)	<0.0001						
						Hemorrhagic stroke	1.79 (0.85-3.26)	0.12	1.58 (0.75-2.9)	0.21	
						Ischemic stroke	2.12 (1.55-2.82)	<0.0001	1.59 (1.15-2.14)	0.006	
	Non-AMI	26/208 (12.7%)	171/1379 (12.9%)	959/12827 (7.6%)	<0.0001						0.76
						Hemorrhagic stroke	1.7 (1.12-2.46)	0.01	1.42 (0.94-2.05)	0.1	
						Ischemic stroke	1.71 (1.45-2.01)	<0.0001	1.45 (1.23-1.71)	<0.0001	
MI	AMI	2/77 (3.2%)	19/394 (5.9%)	174/4590 (4.1%)	0.33						
						Hemorrhagic stroke	0.69 (0.11-2.16)	0.58	0.66 (0.11-2.07)	0.16	
						Ischemic stroke	1.39 (0.84-2.18)	0.19	1.16 (0.69-1.85)	0.55	
	Non-AMI	16/208 (7.8%)	88/1379 (6.5%)	703/12827 (5.6%)	0.14						0.64
						Hemorrhagic stroke	1.42 (0.83-2.25)	0.19	1.24 (0.72-1.97)	0.41	
						Ischemic stroke	1.18 (0.94-1.47)	0.15	1.05 (0.84-1.31)	0.65	
Ischemic stroke	AMI	8/77 (11.7%)	33/394 (10.3%)	141/4590 (3.3%)	<0.0001						
						Hemorrhagic stroke	3.59 (1.61-6.84)	0.003	2.92 (1.31-5.63)	0.01	
						Ischemic stroke	3.11 (2.1-4.48)	<0.0001	2.07 (1.37-3.04)	0.0007	
	Non-AMI	11/208 (5.5%)	90/1379 (7.0%)	284/12827 (2.3%)	<0.0001						0.54
						Hemorrhagic stroke	2.41 (1.24-4.18)	0.01	1.82 (0.93-3.17)	0.08	
						Ischemic stroke	3/1 (2.44-3.92)	<0.0001	2.36 (1.84-2.99)	<0.0001	

AMI=acute myocardial infarction, GUSTO=Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries, MI=myocardial infarction.

Table S2. Clinical Outcomes Through 3 Years in Patients With or Without Atrial Fibrillation in the Prior Ischemic Stroke Group.

	AF N of patients with events (Cumulative 3-year Incidence)	No-AF N of patients with events (Cumulative 3-year Incidence)	P value
	(N=253)	(N=1520)	
GUSTO moderate/ severe bleeding	34 (14.7%)	138 (9.6%)	0.02
Hemorrhagic stroke	6 (2.8%)	22 (1.6%)	0.21
Intracranial bleeding	10 (4.6%)	30 (2.2%)	0.03
MI/Ischemic stroke	42 (18.9%)	179 (12.5%)	0.01
MI	14 (6.3%)	93 (6.3%)	0.79
Ischemic stroke	31 (14.1%)	92 (6.7%)	<0.0001
Stroke	37 (16.8%)	110 (7.9%)	<0.0001

AF=atrial fibrillation, GUSTO=Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries, MI=myocardial infarction.

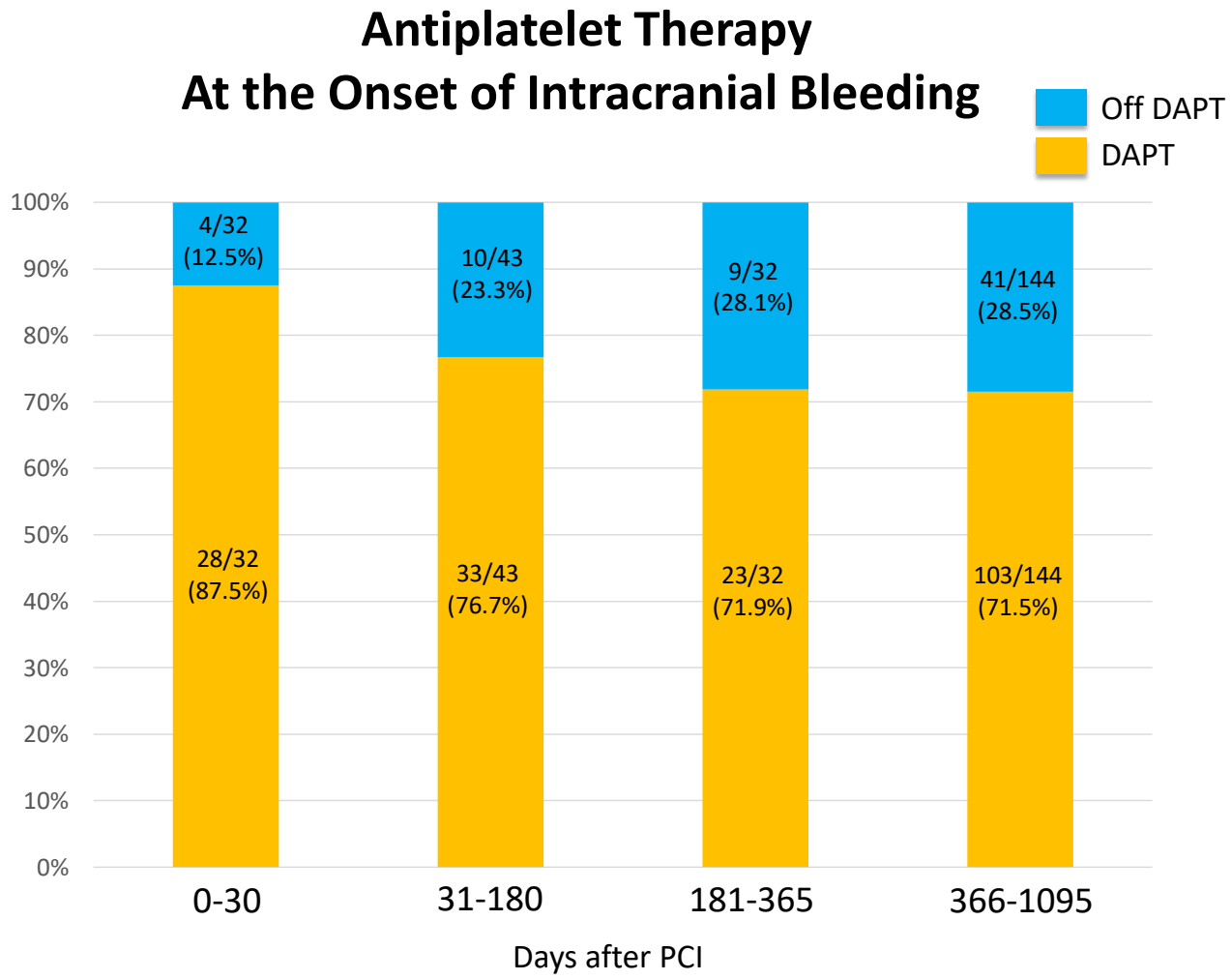
Table S3. Clinical Outcomes Between 4-month and 3-year in Patients With or Without DAPT by the Landmark analysis at 4-month.

	Hemorrhagic stroke N of patients with events	Ischemic stroke N of patients with events	No prior stroke N of patients with events	P value
On-DAPT at 4-month				
Intracranial bleeding	13/197 (7.0%)	20/1310 (1.6%)	119/12277 (1.0%)	<0.0001
Non-intracranial bleeding	8/192 (4.2%)	48/1282 (4.0%)	323/12125 (2.8%)	0.03
Ischemic stroke/MI	12/188 (6.7%)	90/1239 (7.7%)	361/11808 (3.2%)	<0.0001
Off-DAPT at 4-month				
Intracranial bleeding	0/72 (0%)	8/323 (2.8%)	32/4416 (0.8%)	0.001
Non-intracranial bleeding	3/70 (4.9%)	9/302 (3.2%)	113/4201 (2.8%)	0.63
Ischemic stroke/MI	3/69 (5.0%)	17/302 (6.0%)	156/4260 (3.9%)	0.14

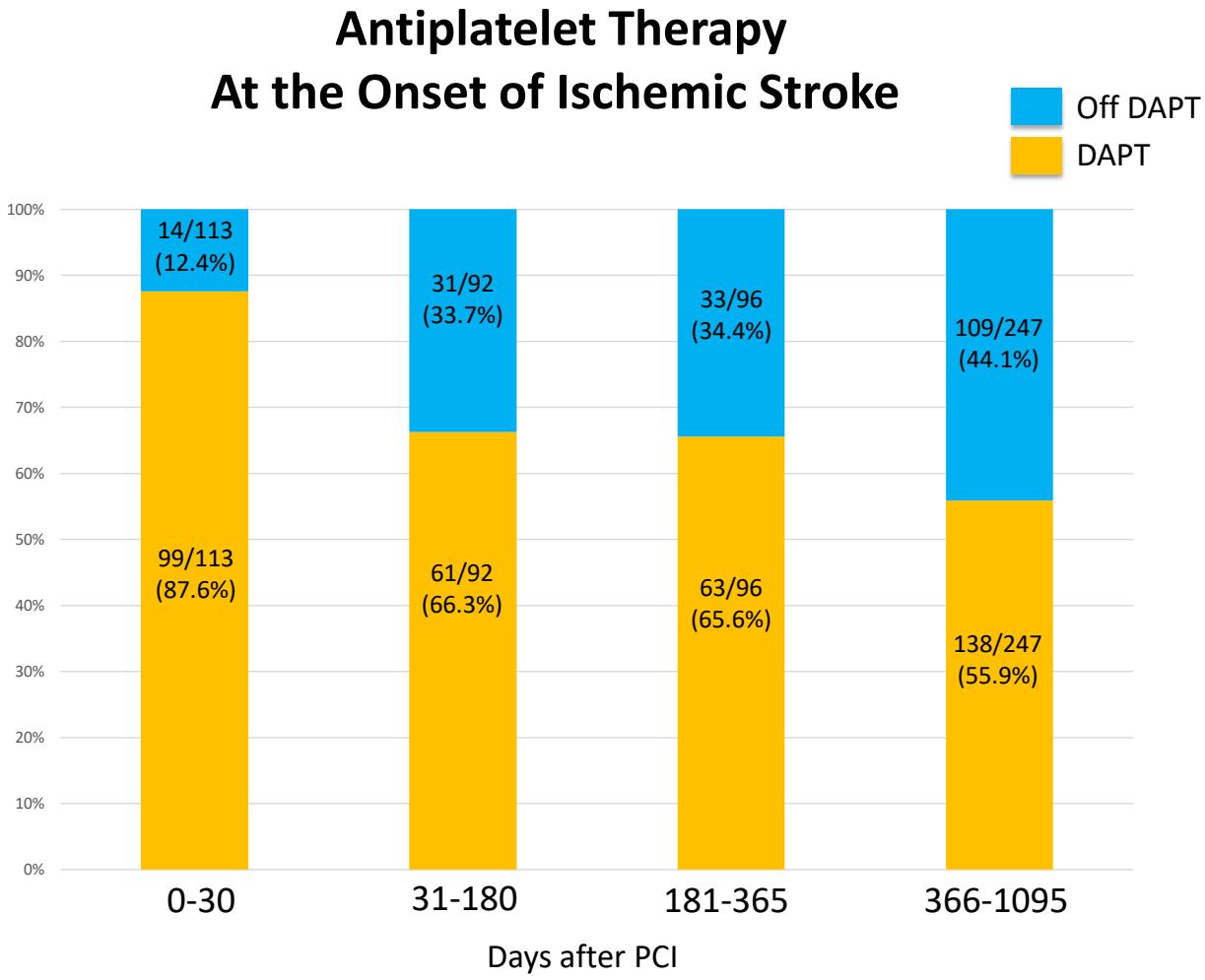
DAPT=dual antiplatelet therapy, GUSTO=Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries, MI=myocardial infarction.

Figure S1. (A)Antiplatelet therapy at the onset of intracranial bleeding. (B) Antiplatelet therapy at the onset of ischemic stroke.

(A)



(B)



DAPT=dual-antiplatelet therapy, and PCI=percutaneous coronary intervention.