Low-Dose Prasugrel vs Clopidogrel-Based Tailored Premedication for Endovascular Treatment of Cerebral Aneurysms

Won-Sang Cho, MD, PhD[‡*]
Joongyub Lee, MD, PhD[§*]
Eun Jin Ha, MD[‡]
Kyung Hyun Kim, MD[‡]
Jeongjun Lee, MD[¶]
Young Dae Cho, MD[¶]
Jeong Eun Kim, MD, PhD[‡]
Moon Hee Han, MD, PhD[¶]
Hyun-Seung Kang, MD, PhD[‡]

[‡]Department of Neurosurgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; [§]Department of Prevention and Management, Inha University Hospital, School of Medicine, Inha University, Incheon, Korea; [¶]Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

*These authors contributed equally to this work.

Correspondence:
Hyun-Seung Kang, MD, PhD,
Department of Neurosurgery,
Seoul National University Hospital,
Seoul National University College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul 03080, Korea.
E-mail: hsk4428@yahoo.com

Received, January 9, 2018.
Accepted, June 25, 2018.

BACKGROUND: Antiplatelet premedication is widely accepted for interventional treatment of cerebral aneurysms to prevent thromboembolism. However, antiplatelet resistance sometimes limits the effectiveness of premedication.

OBJECTIVE: To compare 2 groups administered low-dose prasugrel (PSG group) or clopidogrel-based tailored antiplatelet (CPG group) in terms of platelet function and procedure-related complications.

METHODS: A total of 411 patients with 505 unruptured aneurysms who underwent endovascular treatment within the past 17 mo were retrospectively enrolled in this study. The PSG (225 patients with 277 aneurysms) and CPG groups (186 patients with 228 aneurysms) were administered the respective medication prior to endovascular treatment. We measure the response to the antiplatelet medication with a laboratory test. Episodes of periprocedural bleeding and thromboembolism were compared between the 2 groups.

RESULTS: There were significant differences between the 2 groups in terms of the mean $P2Y_{12}$ reaction unit values (125.7 in the PSG group vs 251.0 in the CPG group; $P < .001$) and percentage inhibition (57.8% vs 18.7%, respectively; $P < .001$). Drug resistance was 29.6% per patient in the CPG group and 2.7% per patient in the PSG group. The PSG group reported 1 thromboembolism and bleeding each; meanwhile, the CPG group reported 7 thromboembolism and 3 bleeding. Compared to clopidogrel administration, prasugrel administration significantly decreased the risk of thromboembolism (weighted hazard ratio, 0.17; 95% confidence interval, 0.03-0.99). However, the risk of bleeding was not significant.

CONCLUSION: Prasugrel was found to be more effective in reducing periprocedural thromboembolism compared to clopidogrel.

KEY WORDS Cerebral aneurysms, Endovascular treatment, Prasugrel, Clopidogrel, Thromboembolism

Neurosurgery 0:1–8, 2018 DOI:10.1093/neuros/nyy341 www.neurosurgery-online.com

Thromboembolism and cerebral ischemia are among the major complications in coil embolization of unruptured cerebral aneurysms.[1] Many clinicians have used antiplatelet medication to prevent periprocedural thromboembolism,[2,3] and some authors have tried to establish a tailored protocol based on individual reactivity to the clopidogrel.[4-6] Clopidogrel resistance is known to occur in up to 44% of the population. The rate is variable and depends on the loading dose, duration of medication, genetic predisposition, comorbidities, concomitant drug administration, age, race, etc.[7] Because patients who are resistant to clopidogrel have a higher risk of thromboembolism,[4,8,9] either additional administration of clopidogrel or different types of antiplatelet agents are used in such cases. Now we have a new generation of $P2Y_{12}$ receptor antagonists that have less variability in their responsiveness, rapid onset of action, and increased potency, thereby exhibiting superior clinical outcomes in the field of cardiovascular diseases.[10-12] However, the use of this latest generation of $P2Y_{12}$ receptor antagonists is still limited in the field of cerebrovascular diseases

ABBREVIATIONS: CI, confidence interval; **HR,** hazard ratio; **IPW,** inverse probability weight; **PRU,** P2Y12 reaction unit; **PSs,** propensity scores

Supplemental digital content is available for this article at www.neurosurgery-online.com.

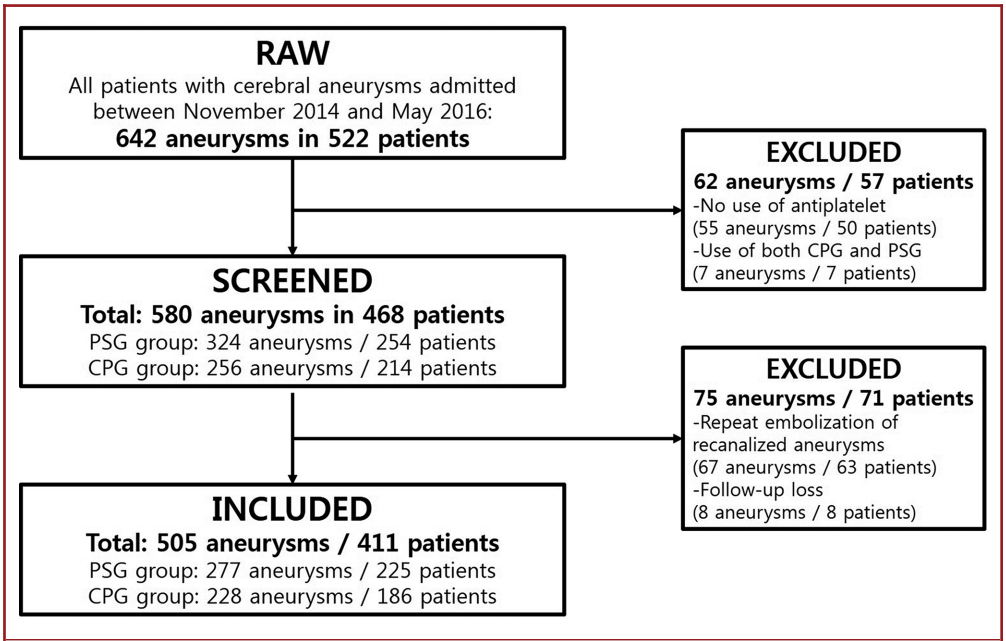

FIGURE . *Study flow chart. PSG indicates low-dose prasugrel; CPG, clopidogrel-based tailored antiplatelet.*

because of the high risk of bleeding events and lack of clinical data.[11,13-15] The authors of this study have previously reported lower resistance and more powerful inhibition with the reduced dose prasugrel regimen in patients undergoing interventional treatment of cerebral aneurysms.[11] Here, we aimed to determine the clinical efficacy and safety of low-dose prasugrel medication.

METHODS

Patient Selection

Under the approval of the institutional review board, 522 consecutive patients with 642 aneurysms who underwent endovascular treatment for intracranial aneurysms between November 2014 and May 2016 were considered for this study; a total of 411 patients with 505 aneurysms were enrolled (Figure 1). Informed consent was waived by the review board. The exclusion criteria were as follows: age less than 18 yr; presence of infectious, traumatic, or ruptured aneurysms; repeat embolization; previous use of an antiplatelet regimen or no antiplatelet agent use; and a follow-up shorter than 90 d after treatment. The selected patients were divided into 2 groups: the PSG group with low-dose prasugrel and the CPG group with clopidogrel-based tailored premedication. The types of antiplatelet medication were determined by the preference of the referring physicians. The PSG group included 225 patients with 277 aneurysms, and the CPG group comprised 186 patients with 228 aneurysms. The patients selected in this study include a portion of the previously published report: among 411 patients with 505 aneurysms in this study, 171 patients with 199 aneurysms are overlapped with the patient population in the previous report.[11] We expanded the patient population to elucidate the clinical implication of more powerful inhibition of platelet activity by low-dose prasugrel over clopidogrel.

Periprocedural Antiplatelet Medication

Loading doses of antiplatelet medication were given the day before the procedure. In the PSG group, the loading and maintenance doses were 20 mg and 5 mg, respectively.[11] In the CPG group, the loading and maintenance doses were 300 mg and 75 mg, respectively.[5] We administered an additional antiplatelet agent in patients showing a high $P2Y_{12}$ reaction unit (PRU) value. If a stent-assisted procedure was anticipated, we gave an additional aspirin to the patient, and cilostazol (200 mg per day) in patients of PRU value high than 285.[4]

After the procedures, antiplatelet medication was maintained or not depending on the accompanying atherosclerotic diseases, stent placement, or protruding coil loops.[5] Patients in the CPG group undergoing stent implantation were recommended dual or triple (for poor responders to CPG) antiplatelet agents for at least 3 mo; patients received 5 mg of PSG for 3 mo in the PSG group; afterward, a lifelong aspirin regimen was recommended.

Measurement of Platelet Activity

The VerifyNow assay (Accumetrics, San Diego, California) was used to measure platelet reactivity. Six hours after loading with antiplatelet agents, whole blood was obtained. Reduced effectiveness of $P2Y_{12}$ receptor antagonist therapy is represented by high PRU value.[11]

Procedural and Procedure-Related Complications

Endovascular coil embolization was performed using a standardized protocol.[17] Systemic heparinization was conducted upon initiation of the procedure. A bolus of 3000 IU heparin was given after the femoral sheath insertion. Additional 1000 IU of heparin was infused hourly under the monitoring of the activated clotting time. A variety of devices including coils, balloons, and stents were used at the discretion of the operators.

The radiological results of the endovascular treatment were categorized as complete occlusion, residual neck, and residual aneurysm

following the Raymond classification.[16] The coil packing density was calculated as the ratio of the volume of the deployed coils to the volume of the aneurysm.[17]

Procedure-related thromboembolism was defined as procedural thrombus formation and/or distal embolism, or clinically recognized transient or fixed ischemic deficits (including transient ischemic attack) within 90 d of the treatment.[11] Other etiologies were ruled out with evaluations by stroke neurologists. Procedure-related bleeding was defined as clinically recognized hemorrhagic events occurring within 90 d of the procedure. These events included intraprocedural aneurysm leakage, delayed aneurysm rupture, and intracerebral hemorrhage while the patient was administered clopidogrel or prasugrel.

Statistical Analyses

Categorical variables were presented as the values and percentage, and continuous variables were summarized as the means and standard deviations. We found 10 variables with missing values within the analyzed dataset: 1 case (0.2%) in hypertension, 1 (0.2%) in diabetes mellitus, 13 (2.6%) in low-density lipoprotein cholesterol, 10 (2.0%) in high-density lipoprotein cholesterol, 10 (2.0%) in triglyceride, 7 (1.4%) in the maximal diameter of the aneurysm, 2 (0.4%) in the neck of the aneurysm, 2 (0.4%) in the dome of the aneurysm, 2 (0.4%) in the volume of the aneurysm, and 8 (1.6%) in the packing density. To address missing data without reducing variability, we adopted the multiple imputation method, which consisted of constructing 5 datasets using the Markov Chain Monte Carlo method, analyzing each dataset to derive parameter estimates, and combining the 5 parameter estimates for inference. Following the multiple imputations, propensity scores (PSs) for the choice of clopidogrel were calculated from a logistic regression model that included baseline characteristics as independent variables for each dataset from the multiple imputations; these characteristics were used to calculate the inverse probability weight (IPW) of treatment for the CPG (1/PS) and PSG (1/(1 – PS)) groups. The IPW method made pseudo-populations without accounting for baseline characteristics to estimate the unbiased treatment effect. Standardized differences for each imputed dataset were presented before and after the IPW for the comparison of the baseline characteristics.

We expected that measurements from aneurysms within the same subject would be correlated because they shared the common subject-specific characteristics including demographic factors and genetic factors. For the survival analysis to compare the procedure-related bleeding and thromboembolism considering the clustering of data within each patient, we used the frailty model for each dataset after balancing the baseline characteristics using IPW. To explain the underlying biological mechanism for the difference of the clinical outcomes, we compared values from the platelet function test using generalized estimating equations to take the intrasubject correlation into consideration.

All statistical tests were 2-sided and $P < .05$ was considered significant. SAS® 9.4 (SAS Institute Inc, Cary, North Carolina) was used for the statistical analysis. Angiographic and clinical data were reviewed by noninterventionist authors, and the collected data were analyzed by a statistician.

RESULTS

The mean age was 58.2 ± 10.5 yr in the PSG group and 58.8 ± 10.1 yr in the CPG group, and females comprised 70.2% of the PSG group and 66.7% of the CPG group. Standardized differences between the 2 groups were greater than 0.2 in the following variables: total cholesterol, hematocrit, and platelet count (Table 1). The mean volume of the aneurysms was 86.2 ± 407.4 mm^3 for the PSG group and 92.7 ± 306.8 mm^3 for the CPG group. The internal carotid artery was the most frequent location of the aneurysms, and more than 97% of the aneurysms presented a saccular shape. Stent-assisted treatment was performed in approximately 20% of the patients in both groups. No characteristics of the aneurysms and treatment techniques showed significant differences; standardized differences were more than 0.1 in the aneurysmal location and immediate treatment results (Table 2).

The IPW after the multiple imputation for missing data showed that the pseudo-populations had good balance for all the variables between the 2 groups with an absolute value of the standardized difference less than 0.1. We found that all 5 baseline tables generated from the multiple imputation methods achieved good balances between the PSG and CPG groups measured by standardized differences throughout the baseline characteristics (**Table**, **Supplemental Digital Content**).

In the VerifyNow $P2Y_{12}$ assay, the PSG group showed a higher percentage inhibition and lower PRU values than the CPG group (each $P < .001$; Table 3). When we set the PRU of 285 as the cut-off value to define the resistance to $P2Y_{12}$ receptor blockade,[4] 54 patients with 65 aneurysms in the CPG group showed resistance (29.6% per patient and 28.5% per aneurysm), while 6 patients with 7 aneurysms in the PSG group exhibited resistance to low-dose prasugrel loading (2.7% per patient and 2.5% per aneurysm).

We observed 1 thromboembolism and bleeding each in the PSG group over a total of 24 930 periprocedural aneurysm days, while 7 thromboembolism and 3 bleedings occurred in the CPG group over a total of 20 520 aneurysm days. The cumulative incidence of events per 1000 aneurysm-years was 14.6 for thromboembolism and bleeding each in the PSG group and 124.5 for thromboembolism and 53.4 for bleeding in the CPG group. Use of prasugrel decreased the risk of thromboembolism by 88% in the crude hazard ratio (HR) with a 95% confidence interval (CI) of 0.01-0.96. However, the risk of bleeding was not significantly different ($P = .26$). When adjusted for baseline characteristics, the risk of thromboembolism remained significant (weighted HR, 0.17; 95% CI, 0.03-0.99; Table 4). A detailed description of the thromboembolism and bleeding cases is presented in Table 5.

DISCUSSION

We compared 2 antiplatelet medications—low-dose prasugrel and standard-dose clopidogrel—in the endovascular intervention of cerebral aneurysms in terms of platelet function test and procedure-related complications such as thromboembolism and bleeding using specific statistical methods in order to revise biases. Compared to the CPG group, the PSG group achieved significantly more powerful inhibition of adenosine

TABLE 1. Baseline Characteristics of the Patients.

Characteristics	Data with missing values		
	PSG (n = 277)	CPG (n = 228)	Standardized difference
Sociodemographics			
Age, yr, mean ± SD	58.2 ± 10.5	58.8 ± 10.1	0.0549
Female, n (%)	158 (70.2)	124 (66.7)	−0.1179
Body weight, kg, mean ± SD	62.1 ± 10.3	62.8 ± 9.7	0.0484
Height, cm, mean ± SD	159.5 ± 8.7	159 ± 8.1	−0.0174
Body mass index, mean ± SD	24.4 ± 3.5	24.8 ± 3.1	0.0618
Cigarette smoking, n (%)	71 (25.6)	56 (24.6)	−0.0247
Alcohol drinking, n (%)	67 (29.8)	46 (24.7)	−0.1554
Comorbidity, n (%)			
Hypertension	94 (41.8)	87 (47)	0.0929
Diabetes mellitus	19 (8.4)	22 (11.9)	0.1073
Coronary heart disease	7 (3.1)	7 (3.8)	0.0574
Cerebrovascular disease	12 (5.3)	19 (10.2)	0.1010
Laboratory tests, mean ± SD			
LDL cholesterol, mg/dL	108 ± 30.0	102.8 ± 32.5	−0.2004
HDL cholesterol, mg/dL	55.6 ± 16.5	53.6 ± 15.1	−0.1934
Total cholesterol, mg/dL	184.6 ± 34.5	176.4 ± 37.9	−0.2782
Triglyceride, mg/dL	115.6 ± 72.4	109.5 ± 47.7	−0.0839
White blood cell count, $\times 10^3/\mu L$	6.0 ± 1.5	6.1 ± 1.8	−0.0089
Hematocrit, %	38.7 ± 4.2	39.6 ± 4.2	0.2608
Platelet count, $\times 10^3/\mu L$	225.4 ± 55.5	237.4 ± 55.5	0.1839
Activated partial thromboplastin time, s	31.7 ± 4.0	32.0 ± 3.4	0.1078
Prothrombin time, INR	1.0 ± 0.1	1.0 ± 0.1	0.0270

PSG, low-dose prasugrel group; CPG, clopidogrel-based tailored antiplatelet group; SD, standard deviation;, LDL, low-density lipoprotein; HDL, high-density lipoprotein; INR, international normalized ratio

diphosphate receptor-mediated platelet aggregation and exhibited much lower drug resistance. Notably, periprocedural thromboembolism complications occurred less frequently in the PSG group, and the bleeding rate was similar between the 2 groups. Next-generation $P2Y_{12}$ receptor antagonists such as prasugrel are well known to reduce thromboembolism but are accompanied with higher bleeding risks when used for cardiovascular intervention.[11,13-15] In this study, we demonstrated the efficacy and safety of low-dose prasugrel in cerebrovascular intervention using laboratory and clinical perspectives.

Clopidogrel has been generally used to reduce periprocedural thromboembolism during cerebrovascular intervention, even in standard intervention without stent assistance.[3-6,8] However, the variable responsiveness of individuals to clopidogrel compromises its efficacy, and additional doses of clopidogrel or other kinds of antiplatelet agents are needed for poor responders.[4,6,7] Higher PRU values are well known to be associated with increase in the periprocedural thromboembolic complications.[4-6,8] Supplementing regimens with additional doses or other kinds of drugs can be complex and demand additional costs. The additive effect of other kinds of antiplatelet agents is sometimes unpredictable in laboratory tests. Prasugrel, one of the latest generation of $P2Y_{12}$ receptor antagonists, has been widely used for coronary heart disease since the late 2000s based on its results of consistent responsiveness, potent and rapid action, and lower risks of adverse events.[18] However, clinical data of prasugrel in the field of cerebrovascular diseases are still limited.[11,13-15] In a previous study,[11] the use of prasugrel with a 20-mg loading dose and 5-mg maintenance doses showed more potent and consistent inhibition of platelet activity than clopidogrel administration. The differences in the laboratory and clinical results between prasugrel and clopidogrel seem to originate from their metabolism. Clopidogrel is absorbed in the intestine and metabolized in the liver from a prodrug form; approximately 85% of clopidogrel is hydrolyzed to inactive carboxylic acid derivatives by carboxylesterase 1, and only 15% is transformed to active metabolites via two sequential oxidative steps by cytochrome P450 enzymes.[19,20] Furthermore, a genetic polymorphism of CYP2C19, one of the hepatic cytochrome P450 enzymes, is known to be closely related to resistance to clopidogrel and the occurrence of adverse cardiovascular events.[21,22] In contrast, prasugrel is not influenced by the inactivating pathway of carboxylesterase 1 and the genetic polymorphism of cytochrome P450, and most of the drug is rapidly transformed into active metabolites via one step.[23]

Despite the consistently higher efficacy of prasugrel, its higher risk of hemorrhagic complications has been indicated as a weak

TABLE 2. Baseline Characteristics of the Aneurysms and Treatment.

Characteristics	PSG (n = 277)	CPG (n = 228)	Standardized difference
Aneurysm volume, mm^3, mean ± SD	86.2 ± 407.4	92.7 ± 306.8	0.0194
Location, n (%)			−0.1880
Anterior circulation	230 (83.0)	172 (75.4)	
Internal carotid artery	111 (40.1)	78 (34.2)	
Anterior cerebral artery	67 (24.2)	49 (21.5)	
Middle cerebral artery	52 (18.8)	45 (19.7)	
Posterior circulation	47 (17.0)	56 (24.6)	
Shape, n (%)			−0.0066
Saccular	270 (97.5)	222 (97.4)	
Others	7 (2.5)	6 (2.6)	
Fusiform	0 (0.0)	3 (1.3)	
Dissecting	5 (1.8)	3 (1.3)	
Thrombosed	2 (0.7)	0 (0.0)	
Treatment technique, n (%)			0.0717
Single microcatheter	87 (31.4)	65 (28.5)	
Double microcatheters	83 (30.0)	72 (31.6)	
Balloon	38 (13.7)	25 (11.0)	
Balloon + double microcatheters	0 (0.0)	2 (0.9)	
Stent	56 (20.2)	48 (21.1)	
Stent + balloon	4 (1.4)	4 (1.8)	
Stent + double microcatheters	7 (2.5)	10 (4.4)	
Flow diverter	2 (0.7)	2 (0.9)	
Treatment results, n (%)			0.12736
Complete occlusion	212 (76.5)	118 (78.0)	
Residual neck	58 (21.0)	40 (17.6)	
Residual sac	7 (2.5)	10 (4.4)	
Packing density, %, mean ± SD	34.6 ± 8.0	34.1 ± 7.6	−0.06372

PSG, low-dose prasugrel group; CPG, clopidogrel-based tailored antiplatelet group; SD, standard deviation

TABLE 3. Comparison of Platelet Function Test Results With VerifyNow $P2Y_{12}$ Assay

	PSG (n = 277)	CPG (n = 228)	*P*-value[a]
Base, mean (range)	299.3 (217.0-381.6)	305.3 (213.6-397.0)	.20
PRU, mean (range)	125.7 (116.5-134.9)	251.0 (243.0-259.0)	< .001
Percentage inhibition, %, mean (range)	57.8 (54.8-60.8)	18.7 (16.5-20.8)	< .001

PSG, low-dose prasugrel group; CPG, clopidogrel-based tailored antiplatelet group; PRU, $P2Y_{12}$ reaction unit
[a]Calculated using generalized estimating equation.

TABLE 4. Comparison of Procedure-Related Complications.

Complications	PSG (n = 277)	Cumulative incidence[a]	CPG (n = 228)	Cumulative incidence[a]	Crude HR (95% CI)	*P*-value	Weighted HR (95% CI)[b]	*P*-value
Follow-up duration	24 930 d		20 520 d					
Pooled HR for bleeding	1	14.6	3	53.4	0.27 (0.03-2.64)	.26	0.33 (0.04-2.66)	.30
Pooled HR for thromboembolism	1	14.6	7	124.5	0.12 (0.01-0.96)	.04	0.17 (0.03-0.99)	.05

PSG, low-dose prasugrel group; CPG, clopidogrel-based tailored antiplatelet group; HR, hazard ratio; CI, confidence interval
[a]Events/1000 aneurysm-year.
[b]The estimates were combined from an HR estimates of 5 frailty models, adjustment was performed using inverse probability weighting methods.

TABLE 5. Complicated Cases.

	Thromboembolic events							
	PSG	CPG						
Case no.	1	1	2	3	4	5	6	7
Age, yr/sex	50/F	51/F	41/F	65/M	59/F	66/M	60/F	70/F
Aneurysm location/volume, mm^3	ACoA/35	PCoA/9	ICA/104	MCA/38	MCA/54	MCA/7	MCA/28	PCA/384
PRU/percentage inhibition	185/48%	288/11%	331/5%	254/10%	214/24%	191/23%	317/0%	259/0%
Treatment techniques	DM	SA	SA	SA	DM	DM	SA	SA
Events	Delayed transiently symptomatic embolism at ACA in 12 d	Transiently symptomatic embolism at MCA	Transiently symptomatic embolism at retinal artery	Delayed transiently symptom atic embolism at MCA in 12 d	Asymptom atic proce-dural throm-bosis at MCA	Asymptom atic procedural thrombosis at MCA	Transiently symptomatic procedural thrombosis at MCA	Asymptom atic procedural in-stent thrombosis
mRS[a]	0 → 0	0 → 0	0 → 0	0 → 0	0 → 0	0 → 0	0 → 0	0 → 0
	Bleeding Events							
	PSG	CPG						
Case no.	1	1	2	3				
Age, yr/sex	49/F	66/F	50/F	55/F				
Aneurysm location/volume, mm^3	ACoA/13	ACoA/91	ICA/2611	Bilateral ICAs/86, 270				
PRU/percentage inhibition	295/15%	283/25%	140/39%	281/11%				
Treatment techniques	DM	SA	Flow diverter	SA				
Events	Aneurysmal leakage	Aneurysmal leakage	Delayed aneurysm rupture in 3 wk	Delayed temporal lobe hemorrhage in 6 d				
mRS[a]	0 → 0	1 → 1	1 → 6	0 → 0				

PSG, low-dose prasugrel group; CPG, clopidogrel-based tailored antiplatelet group; ACoA, anterior communicating artery; PCoA, posterior communicating artery; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PRU, $P2Y_{12}$ reaction unit; SA, stent-assisted technique; DM, double microcatheter technique; mRS, modified Rankin score

[a]mRS scores just before treatment and 90 d after treatment.

point.[12,13,18] Periprocedural hemorrhagic complications such as intracerebral hemorrhage might cause detrimental neurological sequelae. We speculate that the recommended loading and maintenance dosages may be set slightly higher than necessary. As the drug dose increases, its complication rate and its efficacy are known to increase proportionally.[24,25] Previous reports showing a higher hemorrhagic risk of prasugrel used a protocol of 60 mg as a loading dose and 10 mg as the maintenance dose.[12,13,18] Recent randomized controlled studies showed that a lower loading dose of prasugrel (30 mg) achieved higher inhibition of platelet activity than an elevated loading dose of clopidogrel of 600 mg.[25-27] In a study comparing the inhibitory capacity among various doses of prasugrel (10/2.5 mg, 15/3.75 mg, and 20/5 mg of loading/maintenance doses, respectively) and clopidogrel (300/75 mg), administration of 15/3.75 mg or higher doses of prasugrel showed more rapid and potent effects than clopidogrel.[25] In our previous and present studies, low-dose prasugrel with 20/5 mg achieved more powerful inhibition of platelet activity and a lower rate of resistance than 300/75 mg of clopidogrel.[11] Moreover, this study demonstrated the accompanying clinical benefit of prasugrel over clopidogrel in lowering thromboembolism with similar bleeding risks. There are black box warnings on the bleeding risk of prasugrel, which states that significant and sometimes fatal bleeding may occur and it is contraindicated in patients with active bleeding or history of stroke and transient ischemic attack.[28] This may potentially limit the use of prasugrel for the United States-based practitioners. We believe that the warning need to be kept in mind, and our results demonstrate that low-dose prasugrel regimen as monotherapy can be safely applied in patients undergoing endovascular treatment for unruptured aneurysms without further risk of bleeding.

Limitations

There are some limitations to this study. This is a retrospective study in nature, although specific statistical methods were applied in its interpretation. The platelet activity was measured only

once after the antiplatelet agents were loaded. The inhibitory status of platelet aggregation was not monitored during the maintenance period in patients who underwent stent-assisted coil embolization. There are some reports showing that the prasugrel can be more potent in the Asian population than in the Western population.[29,30] Therefore, our results with low-dose prasugrel can be applied to clinical practice with a back-up based on laboratory tests for platelet activity. Further studies are needed to reinforce the efficacy and safety of the new generation of $P2Y_{12}$ receptor antagonists among different ethnic populations with regard to efficacy, appropriate dosage, and short-term and long-term clinical outcomes. Prasugrel is often not covered by insurance, which may lead to noncompliance. We anticipate that the new generation of $P2Y_{12}$ receptor antagonist will be reimbursed soon.

CONCLUSION

Low-dose prasugrel medication showed effective inhibition of platelet activity and a reduction in thromboembolism without escalating bleeding compared to clopidogrel premedication in patients undergoing endovascular treatment for intracranial aneurysms. The latest generation of $P2Y_{12}$ receptor antagonists is expected to play an important role in cerebrovascular intervention.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Derdeyn CP, Cross DT, 3rd, Moran CJ, et al. Postprocedure ischemic events after treatment of intracranial aneurysms with Guglielmi detachable coils. *J Neurosurg*. 2002;96(5):837-843.
2. Ries T, Buhk JH, Kucinski T, et al. Intravenous administration of acetylsalicylic acid during endovascular treatment of cerebral aneurysms reduces the rate of thromboembolic events. *Stroke*. 2006;37(7):1816-1821.
3. Yamada NK, Cross DT, 3rd, Pilgram TK, Moran CJ, Derdeyn CP, Dacey RG, Jr. Effect of antiplatelet therapy on thromboembolic complications of elective coil embolization of cerebral aneurysms. *Am J Neuroradiol*. 2007;28(9):1778-1782.
4. Kang HS, Kwon BJ, Kim JE, Han MH. Preinterventional clopidogrel response variability for coil embolization of intracranial aneurysms: clinical implications. *AJNR Am J Neuroradiol*. 2010;31(7):1206-1210.
5. Kang HS, Han MH, Kwon BJ, et al. Is clopidogrel premedication useful to reduce thromboembolic events during coil embolization for unruptured intracranial aneurysms? *Neurosurgery*. 2010;67(5):1371-1376.
6. Hwang G, Huh W, Lee JS, et al. Standard vs Modified antiplatelet preparation for preventing thromboembolic events in patients with high on-treatment platelet reactivity undergoing coil embolization for an unruptured intracranial aneurysm. *JAMA Neurol*. 2015;72(7):764-772.
7. Gurbel PA, Tantry US. Clopidogrel resistance? *Thromb Res*. 2007;120(3):311-321.
8. Kim MS, Jo KI, Yeon JY, et al. Association between postprocedural infarction and antiplatelet drug resistance after coiling for unruptured intracranial aneurysms. *AJNR Am J Neuroradiol*. 2016;37(6):1099-1105.
9. Asai T, Miyachi S, Izumi T, et al. Relationship between low response to clopidogrel and periprocedural ischemic events with coil embolization for intracranial aneurysms. *J NeuroIntervent Surg*. 2016;8(7):752-755.
10. Gan XD, Wei BZ, Fang D, et al. Efficacy and safety analysis of new P2Y12 inhibitors versus clopidogrel in patients with percutaneous coronary intervention: a meta-analysis. *Curr Med Res Opin*. 2015;31(12):2313-2323.
11. Ha EJ, Cho WS, Kim JE, et al. Prophylactic antiplatelet medication in endovascular treatment of intracranial aneurysms: low-dose prasugrel versus clopidogrel. *AJNR Am J Neuroradiol*. 2016;37(11):2060-2065.
12. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
13. Akbari SH, Reynolds MR, Kadkhodayan Y, Cross DT, 3rd, Moran CJ. Hemorrhagic complications after prasugrel (Effient) therapy for vascular neurointerventional procedures. *J NeuroIntervent Surg*. 2013;5(4):337-343.
14. Sedat J, Chau Y, Gaudart J, Sachet M, Beuil S, Lonjon M. Prasugrel versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. *Interv Neuroradiol*. 2017;23(1):52-59.
15. Stetler WR, Chaudhary N, Thompson BG, Gemmete JJ, Maher CO, Pandey AS. Prasugrel is effective and safe for neurointerventional procedures. *J NeuroIntervent Surg*. 2013;5(4):332-336.
16. Raymond J, Guilbert F, Weill A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke*. 2003;34(6):1398-1403.
17. Kang HS, Han MH, Kwon BJ, et al. Short-term outcome of intracranial aneurysms treated with polyglycolic acid/lactide copolymer-coated coils compared to historical controls treated with bare platinum coils: a single-center experience. *Am J Neuroradiol*. 2005;26(8):1921-1928.
18. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet North Am Ed*. 2008;371(9621):1353-1363.
19. Lins R, Broekhuysen J, Necciari J, Deroubaix X. Pharmacokinetic profile of 14C-labeled clopidogrel. *Semin Thromb Hemost*. 1999;25(suppl 2):29-33.
20. Caplain H, Donat F, Gaud C, Necciari J. Pharmacokinetics of clopidogrel. *Semin Thromb Hemost*. 1999;25(suppl 2):25-28.
21. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost*. 2007;5(12):2429-2436.
22. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360(4):354-362.
23. Jakubowski JA, Winters KJ, Naganuma H, Wallentin L. Prasugrel: a novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. *Cardiovasc Drug Rev*. 2007;25(4):357-374.
24. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—summary article: A report of the American college of cardiology/American heart association task force on practice guidelines(ACC/AHA/SCAI writing committee to update the 2001 guidelines for percutaneous coronary intervention). *Cathet Cardiovasc Intervent*. 2006;67(1):87-112.
25. Yokoi H, Kimura T, Isshiki T, Ogawa H, Ikeda Y. Pharmacodynamic assessment of a novel P2Y12 receptor antagonist in Japanese patients with coronary artery disease undergoing elective percutaneous coronary intervention. *Thromb Res*. 2012;129(5):623-628.
26. Kim MH, Zhang HZ, Jung DK. Pharmacodynamic comparisons for single loading doses of prasugrel (30mg) and clopidogrel (600mg) in healthy Korean volunteers. *Circ J*. 2013;77(5):1253-1259.
27. Lee DH, Kim MH, Guo LZ, Park MK, Yi SJ. Lower loading dose of prasugrel compared with conventional loading doses of clopidogrel and prasugrel in korean patients undergoing elective coronary angiography: a randomized controlled study evaluating pharmacodynamic efficacy. *Korean Circ J*. 2014;44(6):386-393.
28. Food and Drug Administration. Full Prescribing Information for Effient. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s002lbl.pdf. Accessed April 17, 2018.
29. Small DS, Payne CD, Kothare P, et al. Pharmacodynamics and pharmacokinetics of single doses of prasugrel 30 mg and clopidogrel 300 mg in healthy Chinese and white volunteers: an open-label trial. *Clin Ther*. 2010;32(2):365-379.
30. Small DS, Kothare P, Yuen E, et al. The pharmacokinetics and pharmacodynamics of prasugrel in healthy Chinese, Japanese, and Korean subjects compared with healthy Caucasian subjects. *Eur J Clin Pharmacol*. 2010;66(2):127-135.

Supplemental digital content *is available for this article at www.neurosurgery-online.com.*

Supplemental Digital Content. Table. Standardized differences between the CPG group and the PSG group before and after the inverse probability weighting (IPW) for baseline characteristics following the multiple imputation for missing data.

COMMENT

The authors compared the safety of 2 antiplatelet regimens (low-dose prasugrel vs clopidogrel) in patients undergoing endovascular treatment of unruptured intracranial aneurysms. Prasugrel is not a typical antiplatelet agent used for endovascular procedures. The study indicated that prasugrel may be superior to clopidogrel for the prevention of thromboembolic complications, yet shares a similar low bleeding risk. Thromboembolic and safety complications are (fortunately) rare, however it means that a large number of patients is needed to detect and confirm clinically-significant differences among currently available antiplatelet agents. A number of retrospective studies, including the current manuscript, suggest that alternative antiplatelet agents may be superior to clopidogrel in terms of safety and efficacy. As is often the case, the data obtained from retrospective studies needs to be interpreted with caution, because important nuances such as differences in timing and administration of a loading dose can be missed.

Maxim Mokin
Elad Levy
Buffalo, New York