Prestroke antiplatelet agents in first-ever ischemic stroke

Clinical effects

Jin-Man Jung, MD, PhD
Jungsoon Choi, PhD
Mi-Yeon Eun, MD
Woo-Keun Seo, MD, PhD
Kyung-Hee Cho, MD, PhD
Sungwook Yu, MD, PhD
Kyungmi Oh, MD, PhD
Soonwoong Hong, MD
Kwang-Yeol Park, MD, PhD

Correspondence to Dr. Jung: sodium75@medimail.co.kr

ABSTRACT

Objective: To investigate whether prestroke antiplatelet agent (PA) use was associated with initial stroke severity.

Methods: This was a retrospective, case-control study based on data from a prospectively collected hospital-based stroke registry (Korea University Stroke Registry). A total of 3,025 patients who were admitted with a diagnosis of first-ever ischemic stroke within 5 days of symptom onset were included. Stroke severity was measured with the NIH Stroke Scale (NIHSS). NIHSS score ≤4 at admission was categorized as mild stroke. Patients from the PA group were matched with those from the non-PA group using estimated propensity scores at a 1:1 ratio. Stepwise multivariable logistic regression analyses were performed on patients in the matched datasets with initial mild stroke.

Results: Patients' mean age was 66.3 ± 13.0 years, and 1,850 were men (61.5%). A total of 748 patients had been taking antiplatelet agents prior to stroke onset; 644 patients (86.1%) were taking a single antiplatelet agent. Among these agents, aspirin (83.7%) was the most common. A total of 102 patients (13.6%) were taking 2 antiplatelet agents. Multivariable analysis after propensity score matching demonstrated that PA use was associated with initial mild stroke (odds ratio 1.344; 95% confidence interval 1.014–1.782).

Conclusions: PA use was associated with decreased first-ever stroke severity, suggesting that it has a beneficial effect.

Classification of evidence: This study provides Class II evidence that prestroke use of antiplatelet agents reduces stroke severity in patients with first-ever acute ischemic stroke. *Neurology®* 2015;84:1080–1089

GLOSSARY

ASD = absolute standardized differences; **KUSR** = Korea University Stroke Registry; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PA** = prestroke antiplatelet agents; **SVO** = small vessel occlusion; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Numerous studies have investigated the effect of prestroke aspirin treatment on clinical outcome. Prestroke antiplatelet agents (PA) have been assumed to decrease platelet aggregation, thrombus propagation, and thrombus formation,[1] leading to lower thrombus burden. In addition, studies in animal models have demonstrated that aspirin has neuroprotective effects.[2] These findings suggest that prestroke aspirin treatment improves initial stroke severity.[3,4] However, findings from other studies have been contradictory.[5,6] These discrepant clinical findings might be caused by small sample sizes, especially in groups already taking aspirin[7]; uneven baseline characteristics; different outcome assessment methods (neurologic scales)[3,6]; diverse outcome measure timing; inconsistent confounding factors in statistical analyses; and stroke heterogeneity due to several mechanisms, including atherothrombotic, cardioembolic, and lacunar infarctions.[8] Moreover, many studies have focused exclusively on aspirin pretreatment and

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From the Department of Neurology (J.-M.J.), Korea University Ansan Hospital, Korea University College of Medicine, Ansan; the Department of Mathematics (J.C.), School of Natural Sciences, Hanyang University, Seoul; the Department of Neurology (M.-Y.E.), KEPCO Medical Center, Seoul; the Department of Neurology (W.-K.S., K.O.), Korea University Kuro Hospital, Korea University College of Medicine, Seoul; the Department of Neurology (K.-H.C., S.Y., S.H.), Korea University Anam Hospital, Korea University College of Medicine, Seoul; and the Department of Neurology, Chung-Ang University Hospital (K.-Y.P.), Chung-Ang University College of Medicine, Seoul, Korea.

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not on other antiplatelet agents that are superior or similar to aspirin in terms of stroke risk reduction.[9] Additionally, one study investigated only patients with first-ever stroke,[7] while others studied those with recurrent and first-ever stroke. As expected, patients with PA use had more vascular risk factors and comorbidities, such as coronary and peripheral artery disease.[10] These confounding factors can affect outcomes and prognoses in observational studies, suggesting that PA and non-PA groups are not comparable. Therefore, it is necessary to balance the baseline characteristics of these 2 groups when investigating the effects of PA. One method to overcome this problem is to use propensity score analyses to balance characteristic differences between treated and untreated patients.

In this study, we used propensity score matching to investigate whether PA use had an additional effect on initial stroke severity in patients with first-ever stroke.

METHODS Our primary research question was whether PA use predicted initial severity in first-ever stroke with a retrospective, hospital-based, case-cohort study (class II evidence).

Data collection and patient selection. We screened patients who were admitted to 3 university hospitals (Anam, Guro, and Ansan) from October 2007 to September 2012 due to ischemic stroke and enrolled them in a prospectively collected hospital-based stroke registry (Korea University Stroke Registry [KUSR]). Patients admitted to Ansan Hospital were enrolled commencing October 2009. These university hospitals are all arms of the Korea University Medical Center and share the Web-based KUSR electronic documentation format, but are located in separate urban areas. Clinical, laboratory, and radiologic information, as well as Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification according to stroke mechanism, were collected for each patient.

Patients who were admitted within 5 days of symptom onset with a diagnosis of exclusively first-ever symptomatic ischemic stroke were included. We excluded patients who presented with recurrent stroke because residual neurologic impairments from the previous stroke could affect baseline stroke severity and those who were taking oral anticoagulants prior to hospitalization according to the aim of this study focusing on the effect of antiplatelet agents prior to stroke.

Standard protocol approvals, registrations, and patient consents. The study design and protocol received Institutional Review Board approval. Written informed consent was not required due to the retrospective design of the study.

Clinical profiles and risk factors. Data were collected on patient demographics and vascular risk factors, which were determined according to previously reported definitions.[11] Previous TIA was diagnosed by positive history. Coronary artery disease was diagnosed in cases with a history of acute myocardial infarction, stable or unstable angina, or coronary revascularization procedures. Congestive heart failure or valvular heart disease was diagnosed by positive history. Peripheral artery disease was diagnosed by ultrasonography documentation, an ankle brachial index $\leq$0.9, or a history of previous limb revascularization procedures. Atrial fibrillation was diagnosed by electrocardiographic evidence of arrhythmia.[10]

Assessment of prior medications. Prior medications were determined by interviews with patients, their family or primary physician, or preadmission prescriptions. Previous use of antiplatelet agents, antihypertensive drugs, antidiabetic agents, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), and nonsteroidal anti-inflammatory drugs was inspected. Additionally, pharmacists in each hospital identified them through drug information available in print and South Korean Internet sites with complete drug information registration resources. Patients were classified as users or nonusers for each medication type. In addition, patients or their families were questioned regarding drug compliance. Patients who had not been taking antiplatelet agents 7 days before admission were classified into the non-PA group.

Clinical, radiologic, and laboratory evaluations. Routine evaluations, including neurologic, cardiac, and laboratory examinations, were conducted for each patient. Stroke severity on admission was assessed by the NIH Stroke Scale (NIHSS). Cardiac evaluations included electrocardiography, transthoracic echocardiography, Holter monitoring, and, if needed, transesophageal echocardiography. Initial diffusion-weighted imaging was performed as soon as possible upon admission. A few days later, follow-up brain imaging and contrast magnetic resonance angiography were conducted. Brain CT was conducted in cases with contraindications for MRI. Laboratory examinations included complete blood cell counts, blood chemistries, urinalyses, coagulation tests, and fibrinogen analyses on admission. Lipid profiles, including total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, were assessed after at least 8 hours of fasting.

Stroke subtypes. The following stroke subtypes were recognized: large-artery atherosclerosis, cardioembolism, small vessel occlusion (SVO), other, or undetermined according to TOAST criteria.[12] In addition, SVO lesion size was modified from $<$15 mm to $\leq$20 mm because the former size criterion is not suitable for demonstrating acute cytotoxic or vasogenic edema due to infarction in imaging studies.[13]

Registration of patients into KUSR was performed independently in each hospital arm. After patients were discharged, stroke subtype classification was preliminarily determined by physicians and then reviewed at the regular monthly meeting of stroke neurologists of each arm (Anam: S.Y., K.-H.C.; Guro: W.-K.S., K.O., M.-Y.E.; Ansan: W.-K.S., J.-M.J.). Discrepancies were resolved by consensus.

Outcomes. We assessed initial stroke severity at the time of admission. Stroke severity was measured with the NIHSS by well-trained physicians or stroke neurologists. Stroke severity was divided into mild stroke vs moderate/severe stroke. Mild stroke was defined as a NIHSS score $\leq$4.[14]

Statistical analyses. ***Imputation of missing data.*** A complete set of baseline data was essential for the development of the propensity model since patients with any missing data should be excluded from matching process. We replaced missing values with the mean for that variable.

Propensity (matched) model. Propensity score was estimated by multiple logistic regression of PA treatment vs PA nontreatment (propensity model). After patient matching by estimated propensity scores via a conditional logistic regression method, multiple logistic regression analysis was performed. Using the logit estimated from the log odds of the propensity score of each patient, we matched a randomly selected PA patient with a non-PA patient who had the nearest estimated logit value by one-to-one matching, rather than replacement.[15] An estimated logit width within 0.1 SDs was used to match selected PA and non-PA patients. For each covariate of the propensity model, absolute standardized differences (ASD) before and after matching were calculated (figure 1). ASD <10% implied good balance between the 2 groups.

Comparison of baseline characteristics. Pearson χ^2 tests were used to compare categorical variables between the 2 groups for 3 datasets (1 unmatched and 2 propensity-matched). For continuous variables, Student *t* tests or Mann-Whitney *U* tests were used depending upon variable normality.

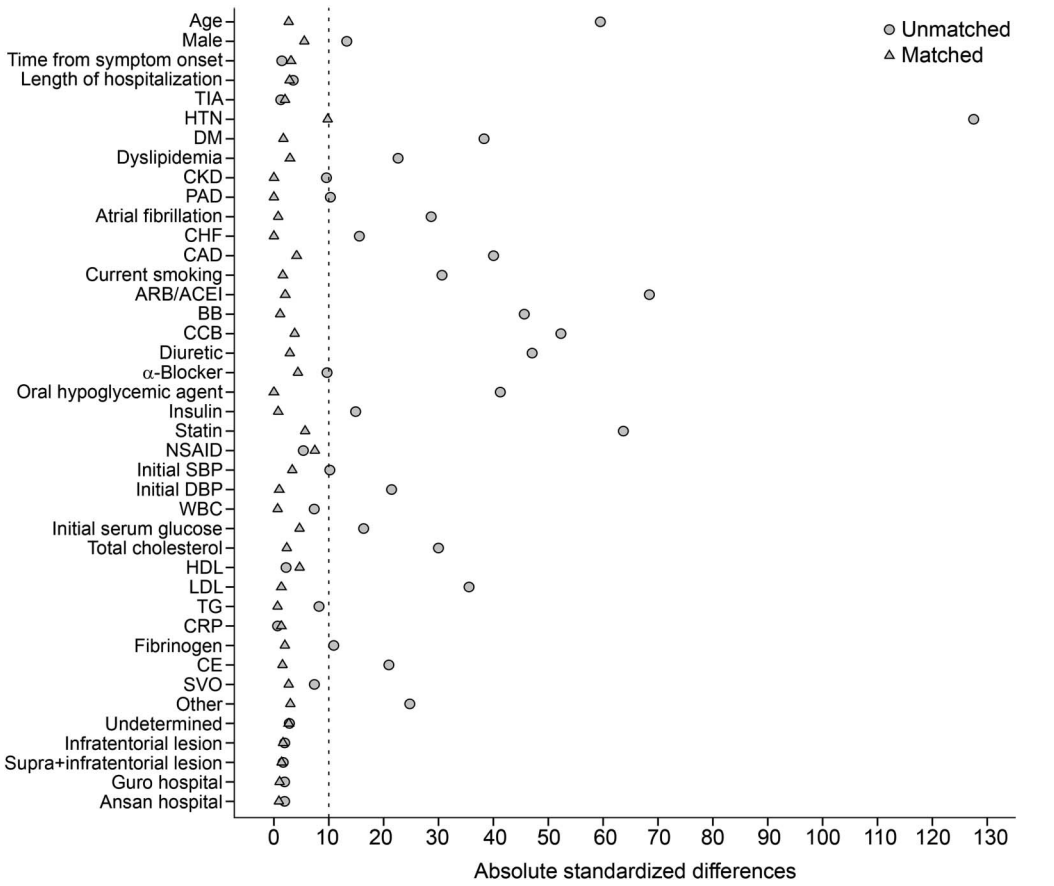
Multivariable analysis. All covariates included in the propensity score matching for outcomes were considered in univariable analyses. Variables ($p < 0.1$) were subjected to multivariable analysis for outcome. Stepwise multiple logistic regression analysis was used with the backward elimination technique to adjust for potential confounders. Hosmer-Lemeshow goodness of fit was used to assess the appropriateness of modeling. In addition, interactions between PA use and other variables included in the model were evaluated.

Sensitivity analysis. We further performed multivariable multinomial regression analysis to explore the association between stroke severity categories as the dependent variable with other variables, especially prestroke antiplatelet usage. Stroke severity was as follows: mild (NIHSS 0-4) vs moderate (5-15) vs moderate to severe (16-20) vs severe (≥21).[16]

SPSS 12.0 for Windows (IBM Corporation, Armonk, NY) was used for 2-group comparisons and multivariable analyses of outcome. Propensity score matching was performed with *R* (http://www.r-project.org/). SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used to perform multivariable multinomial regression and interaction analyses. *p* Values less than 0.05 were considered statistically significant.

RESULTS A total of 4,876 patients were registered in the KUSR during the study period, of which 3,025

Figure 1 **Absolute standardized difference in pre and post propensity score matching with regard to initial stroke severity**

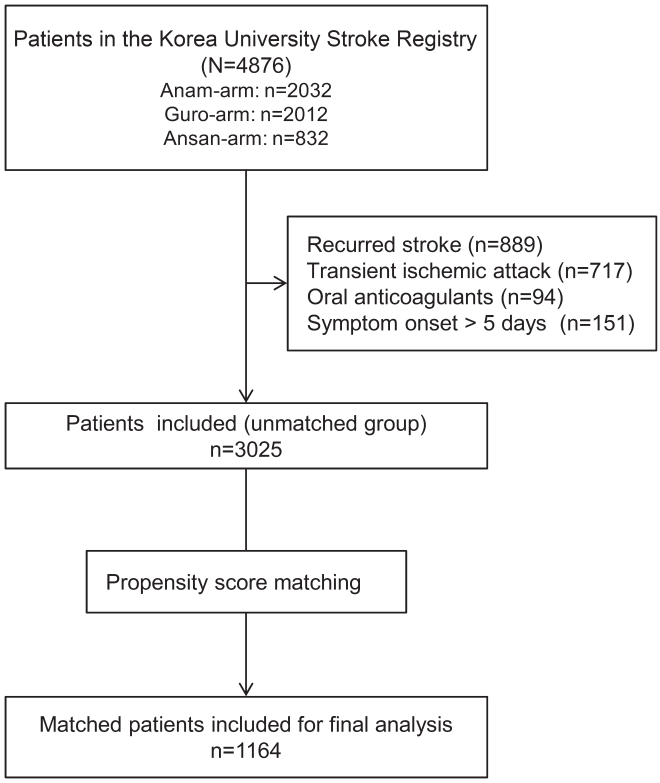


Large-artery atherosclerosis, supratentorial lesion, and Anam Hospital were excluded as a reference of variables such as stroke subtype, lesion location, and admission hospital, respectively. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-blocker; CAD = coronary artery disease; CCB = calcium channel blocker; CE = cardioembolism; CHF = congestive heart failure; CKD = chronic kidney disease; CRP = C-reactive protein; DBP = diastolic blood pressure; DM = diabetes mellitus; HDL = high-density lipoprotein; HTN = hypertension; LDL = low-density lipoprotein; NSAID = nonsteroidal anti-inflammatory drug; PAD = peripheral artery disease; SBP = systolic blood pressure; SVO = small vessel occlusion; TG = triglycerides; WBC = white blood cell.

were included in the study (figure 2). Mean patient age was 66.3 ± 13.0 years, and 1,850 were men (61.5%). A total of 748 patients took antiplatelet agents prior to stroke onset; 644 (86.1%) were taking one antiplatelet agent (aspirin [83.7%], clopidogrel [10.2%], cilostazol [3.6%], or triflusal [2.5%]). A total of 102 patients (13.6%) were taking 2 antiplatelet agents (aspirin + clopidogrel [83.3%], aspirin + cilostazol [12.7%], aspirin + triflusal [2.0%]). Two patients took 3 antiplatelet agents (aspirin + clopidogrel + cilostazol or aspirin + triflusal + clopidogrel). In 39 patients for whom MRI was contraindicated because of MRI-incompatible devices (n = 37), including intracranial coils and prosthetic heart valves, or claustrophobia (n = 2), initial and follow-up brain CTs were performed.

Propensity score matching and baseline characteristic comparisons. Missing values were present in total cholesterol level (n = 3), high-density lipoprotein (n = 5), low-density lipoprotein (n = 5), triglycerides (n = 5), C-reactive protein (n = 11), and fibrinogen (n = 49). All these were substituted with the mean for the corresponding variable. Several variables were selected as propensity score matching covariates for initial stroke severity. Baseline characteristic comparisons between the PA and non-PA groups in unmatched and matched datasets are presented in table 1. All variables in table 1 were included as propensity score matching covariates. PA patients were significantly older, had more vascular risk factors, had more diverse previous medications, had more comorbidities, and had lower lipid levels than non-PA patients. These differences, however, were not significant after propensity matching compared to the unmatched dataset. The ASD of the variables after propensity score matching did not exceed the threshold of 10%, suggesting that the samples were well matched (figure 1).

Figure 2 Flow chart of patients



Multivariable analysis of initial stroke severity. Multivariable analysis after propensity score matching revealed that initial mild stroke was associated with age, time from onset to visit, TIA, atrial fibrillation, PA use, systolic blood pressure, fibrinogen, TOAST classification, and lesion location (table 2). PA use was not associated with initial mild stroke in the unmatched dataset, but it was an independent factor associated with initial mild stroke after propensity score matching. When an interaction term (PA use × TOAST classification) was added to the multiple logistic regression model, there was no interaction effect between these. Thus, the TOAST classification independently predicted initial mild stroke; specifically, SVO was more strongly associated with mild stroke than any other subtype. Patients taking antiplatelet agents who had large artery atherosclerosis or cardioembolism had an increased odds ratio (OR) of mild stroke than those without, as shown in figure e-1 on the *Neurology*® Web site at Neurology.org. Otherwise, patients with SVO had a nonsignificant tendency for mild stroke in cases of no antiplatelet agent use prior to stroke. There was no interaction between PA use and other variables.

In sensitivity analysis, patients who took antiplatelet agents prior to stroke had a significantly lower risk of moderate to severe stroke over mild stroke compared to those who did not (OR 0.509; 95% confidence interval 0.287–0.903) (table e-1). A nonsignificant decrease in the risk of experiencing moderate or severe stroke compared to mild stroke was observed for patients who took antiplatelet agents prior to stroke compared to those who did not.

DISCUSSION This is the first study to investigate the beneficial effect of PA on clinical outcomes based on propensity score–matched analysis. In our large cohort of patients from a multicenter stroke registry, PA use had a positive effect on initial stroke severity in first-ever stroke.

The main finding of our study was that the odds of a stroke being initially mild was significantly higher (by 34.4%) in patients who used PA than those who did not prior to the stroke after adjustment for possible confounding factors. However, this association was not found in unmatched multivariable analysis. Only

Table 1 Comparison of baseline characteristics with regard to initial stroke severity

	Unmatched			Propensity score matched		
	Non-PA (n = 2,277)	PA (n = 748)	*p*	Non-PA (n = 582)	PA (n = 582)	*p*
Age, y	64.9 ± 13.5	70.8 ± 10.1	<0.001	69.9 ± 11.3	70.2 ± 10.2	0.665
Male	62.8	56.1	0.001	58.6	55.81	0.343
Time from onset to visit, h	12.5 (3.4, 34.8)	12.4 (3.1, 30.0)	0.542	12.7 (3.6, 30.9)	12.5 (3, 31.7)	0.884
Length of hospitalization, d	7 (6, 7)	7 (6, 7)	0.101	7 (6, 7)	7 (6, 7)	0.826
Systolic BP, mm Hg	150 (130, 170)	141.5 (130, 161)	0.036	145 (130, 160)	141.5 (130, 161)	0.640
Diastolic BP, mm Hg	90 (80, 100)	83 (80, 90)	<0.001	86 (80, 94)	88 (80, 93)	0.916
Hypertension	58.8	92.5	<0.001	93.1	90.5	0.108
Diabetes mellitus	26.9	46	<0.001	41.1	41.9	0.819
Dyslipidemia	56.4	67.6	<0.001	59.8	61.2	0.631
Atrial fibrillation	13.8	26.5	<0.001	24.1	23.7	0.891
TIA	7.2	7.1	0.914	6.0	6.5	0.717
Coronary artery disease	5.4	22.1	<0.001	12.7	14.4	0.392
Congestive heart failure	2.6	7.0	<0.001	5.7	5.7	1.000
Chronic kidney disease	1.7	3.5	0.004	2.7	2.7	1.000
Peripheral artery disease	0.4	1.7	<0.001	0.9	0.9	1.000
Current smoker	36.7	23.5	<0.001	24.6	25.3	0.786
Prior medication						
ARB/ACEI	18	52.1	<0.001	44.5	45.5	0.724
β-Blocker	8.4	29.2	<0.001	23.5	24.1	0.836
Calcium channel blocker	22.9	49.1	<0.001	49.1	47.3	0.519
Diuretic	11.7	34.0	<0.001	29	30.4	0.608
α-Blocker	1.0	2.5	0.004	1.4	2.1	0.367
Oral hypoglycemic agent	15.1	35.3	<0.001	31.6	31.6	1.000
Insulin	1.9	5.2	<0.001	4.0	4.1	0.882
Statin	6.3	37.3	<0.001	22.0	24.7	0.268
NSAID	1.8	2.7	0.119	4.0	2.7	0.254
Admission hospital			0.696			0.954
Anam	36.7	38.4		37.8	38.7	
Guro	45.4	44.4		45	44.5	
Ansan	17.9	17.2		17.2	16.8	
TOAST classification			<0.001			0.959
Large-artery atherosclerosis	38.7	28.3		30.1	29.6	
Cardioembolism	17	26.3		22.9	23.5	
Small vessel occlusion	24.1	27.3		27.3	28.5	
Other	4.1	1.2		1.7	1.4	
Undetermined	16.1	16.8		18.0	17.0	
Lesion location			0.834			0.923
Supratentorial	71	71.4		72.0	71.0	
Infratentorial	21.7	21.9		22.0	22.7	
Supratentorial and infratentorial	7.3	6.7		6.0	6.4	
Initial glucose, mg/dL	123 (105, 152)	128.5 (108, 172)	<0.001	129 (109, 165)	128 (108, 168.3)	0.942
Leukocytes, $\times 10^3/\mu L$	7.79 (6.24, 9.7)	7.5 (6.2, 9.3)	0.016	7.7 (6.2, 9.5)	7.5 (6.1, 9.3)	0.243
Total cholesterol, mg/dL	179 (155, 206)	165 (141, 191)	<0.001	170 (148, 199)	171 (146, 196)	0.508
Triglycerides, mg/dL	111 (79, 159)	107 (77, 153)	0.064	109 (78.8, 157)	109 (78, 156)	0.619

Continued

Table 1 Continued

	Unmatched			Propensity score matched		
	Non-PA (n = 2,277)	PA (n = 748)	p	Non-PA (n = 582)	PA (n = 582)	p
High-density lipoprotein, mg/dL	43 (36, 51)	43 (35, 51)	0.702	42 (35, 50)	43 (35, 51)	0.270
Low-density lipoprotein, mg/dL	107 (86, 129)	95 (74, 118)	<0.001	98 (79, 119.3)	98 (79, 121)	0.941
C-reactive protein, mg/dL	1.22 (0.42, 4.14)	1.26 (0.45, 4.75)	0.282	1.4 (0.47, 5.63)	1.25 (0.47, 4.61)	0.451
Fibrinogen, mg/dL	320 (269, 390)	331 (276, 416.1)	0.002	336 (282, 401)	332.5 (275, 409.3)	0.574

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; NSAID = nonsteroidal anti-inflammatory drug; PA = prestroke antiplatelet agents; TOAST = Trial of Org 10172 in Acute Stroke Treatment.
Results are expressed as column %, mean ± SD, or median (interquartile range) as appropriate.

after balancing the baseline differences between the PA and non-PA groups was PA an independent predictor of mild stroke. In sensitivity analysis using multinomial logistic regression to complement the weaknesses of analyzing dichotomous outcomes and arbitrarily determining the cutoff point for mild stroke, the relationship between PA and stroke severity was sustained. These findings are consistent with several studies that have shown that PA use is an important determinant of baseline lower stroke severity as measured by the NIHSS[3,17] and the Canadian Neurological Scale.[4] It has been plausibly proposed that PA use results in a decreased burden of thrombosis (e.g., thromboembolus size/extent) or perilesional edema. This corresponds well with a study that reported that PA use is associated with lower infarct volume in diffusion-weighted MRI.[18] Additionally, experimental studies have shown that antiplatelet agents have multifunctional actions including neuroprotective effects, vascular effects, and anti-inflammatory effects.[2]

In our study, TOAST classification was an independent factor associated with initial mild stroke, and this association was stronger for SVO than large artery atherosclerosis. Therefore, SVO itself could be a default etiology of mild stroke, because a positive association between stroke severity scale and lesion volume was reported[19] and SVO was shown to be related to lower severity of stroke in previous studies.[20,21] However, we were not able to investigate whether prestroke antiplatelet usage can determine stroke subtype because we balanced TOAST classification after propensity score matching. This issue deserves further exploration.

TIA history has been shown to be associated with lower stroke severity.[22] Experimental models have suggested that short ischemic preconditioning enables the brain to endure subsequent longer ischemic events.[23] Thus, prior brain ischemia, which is clinically similar to TIA, could have neuroprotective effects. Our study results support this hypothesis. However, it is possible that TIA as a predictor for mild stroke may be due to the confounding healthy patient effect. It is unclear if TIA has neuroprotective effects based on the results of human observational studies.[24,25]

Several experimental[26] and observational[27] studies suggested that statin pretreatment had neuroprotective effects, which could lower stroke severity. Other studies have shown no difference in initial severity as rated by NIHSS[28] and Canadian Neurological Scale[29] scores after prestroke statin use. In our study, statin use was not associated with initial severity in unmatched or matched analyses. A recent population-based study of first-ever stroke demonstrated that prestroke statin therapy did not affect initial stroke severity.[30] Thus, the effect of statins on initial severity is controversial in contrast to the effects of statins on functional outcome and survival based on meta-analysis.[31] Conflicting results[32,33] have also been reported for specific antihypertensive medications, such as angiotensin converting enzyme inhibitors/angiotensin receptor blockers; in our study, these medications did not have an effect on initial stroke severity.

This study had several limitations, and cautious interpretation of our results is therefore warranted. First, it was a retrospective and hospital-based study. Although baseline characteristics were balanced through propensity score matching, our results are unlikely to be free from all potential sources of bias and confounding factors inherent in a retrospective observational study. For example, there was a recall bias in history taking of TIA, because TIA was based wholly on patient recall. Second, propensity score matching resulted in a substantial decrease in sample size; therefore results were skewed by the abstracted results from matched patients. Third, although aspirin was the most common agent, we did not examine if other antiplatelet agents[4] or combinations of 2 antiplatelet agents had different effects. In a Canadian stroke registry, both aspirin and clopidogrel prior to stroke were associated with less severe stroke.[4] However, the effects of cilostazol or triflusal were not determined. Furthermore, dual antiplatelet drug use was not found to have an advantage over single antiplatelet drug use with respect to clinical outcomes in a

Table 2 Univariable and multivariable analyses of predictors of initial mild stroke

	Unmatched				Propensity score matched			
	Univariable analysis		Multivariable analysis[a]		Univariable analysis		Multivariable analysis[b]	
Variables	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0.972 (0.966-0.978)	<0.001	0.984 (0.977-0.991)	<0.001	0.947 (0.935-0.960)	<0.001	0.962 (0.948-0.977)	<0.001
Male	1.389 (1.192-1.618)	<0.001	1.276 (1.052-1.548)	0.013	1.747 (1.369-2.229)	<0.001	1.307 (0.972-1.758)	0.077
Time from onset to visit	1.016 (1.013-1.019)	<0.001	1.015 (1.011-1.018)	<0.001	1.022 (1.016-1.027)	<0.001	1.017 (1.011-1.023)	<0.001
TIA	2.175 (1.548-3.055)	<0.001	2.306 (1.601-3.322)	<0.001	3.561 (1.807-7.019)	0.004	3.596 (1.734-7.459)	0.001
Dyslipidemia	1.199 (1.030-1.396)	0.019			1.088 (0.851-1.392)	0.501		
Current smoker	1.209 (1.030-1.420)	0.021	0.735 (0.596-0.906)	0.004	1.771 (1.315-2.384)	<0.001		
Atrial fibrillation	0.276 (0.226-0.336)	<0.001	0.540 (0.398-0.732)	<0.001	0.253 (0.119-0.335)	<0.001	0.578 (0.360-0.928)	0.023
Congestive heart failure	0.350 (0.238-0.516)	<0.001			0.394 (0.238-0.650)	<0.001		
Coronary artery disease	0.670 (0.523-0.857)	0.001			0.705 (0.501-0.993)	0.046		
Chronic kidney disease	0.898 (0.540-1.495)	0.68			0.883 (0.427-1.825)	0.737		
Admission hospital		0.793				0.155		
Anam	Reference				Reference			
Guro	0.989 (0.837-1.168)	0.894			0.923 (0.706-1.208)	0.561		
Ansan	0.93 (0.750-1.153)	0.509			0.713 (0.504-1.008)	0.055		
Prestroke antiplatelet	1.023 (0.859-1.217)	0.801			1.256 (0.986-1.599)	0.065	1.344 (1.014-1.782)	**0.04**
β-Blocker	0.656 (0.531-0.811)	<0.001			0.616 (0.467-0.812)	0.001		
Diuretic	0.777 (0.640-0.943)	0.011			0.753 (0.580-0.976)	0.032		
Statin	0.911 (0.735-1.129)	0.395			0.947 (0.713-1.258)	0.706		
SBP	0.999 (0.996-1.002)	0.527			0.994 (0.989-0.999)	0.01	0.99 (0.985-0.995)	<0.001
DBP	0.998 (0.993-1.004)	0.547			0.992 (0.983-1.000)	0.064		
Initial glucose	1.000 (0.999-1.001)	0.839			1.001 (0.999-1.003)	0.182		
Leukocytes	0.932 (0.910-0.956)	<0.001	0.967 (0.942-0.992)	0.01	0.936 (0.899-0.975)	0.002		
Total cholesterol	1.002 (1.001-1.004)	0.008			1.000 (0.997-1.003)	0.903		
Low-density lipoprotein	1.002 (0.999-1.004)	0.155			0.999 (0.995-1.003)	0.604		
Triglycerides	1.005 (1.004-1.006)	<0.001	1.003 (1.001-1.004)	<0.001	1.004 (1.003-1.006)	<0.001		
C-reactive protein	0.986 (0.983-0.990)	<0.001	0.996 (0.992-0.999)	0.017	0.990 (0.986-0.995)	<0.001		
Fibrinogen	0.997 (0.996-0.998)	<0.001	0.998 (0.997-0.999)	<0.001	0.997 (0.995-0.998)	<0.001	0.997 (0.996-0.999)	0.004
TOAST		<0.001		<0.001		<0.001		<0.001
Large-artery atherosclerosis	Reference		Reference		Reference		Reference	

Continued

Table 2 Continued

	Unmatched				Propensity score matched			
	Univariable analysis		Multivariable analysis[a]		Univariable analysis		Multivariable analysis[b]	
Variables	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Cardioembolism	0.515 (0.42–0.632)	<0.001	1.174 (0.861–1.601)	0.311	0.441 (0.319–0.611)	<0.001	0.946 (0.562–1.594)	0.835
Small vessel occlusion	4.507 (3.496–5.811)	<0.001	4.134 (3.171–5.389)	<0.001	4.634 (3.077–6.98)	<0.001	4.43 (2.868–6.843)	<0.001
Other	0.932 (0.618–1.406)	0.739	0.933 (0.587–1.484)	0.770	0.722 (0.278–1.875)	0.503	0.835 (0.267–2.613)	0.757
Undetermined	0.923 (0.743–1.147)	0.470	1.364 (1.065–1.746)	0.014	0.895 (0.627–1.277)	0.540	1.397 (0.918–2.127)	0.118
Lesion location		<0.001		<0.001		<0.001		<0.001
Supratentorial	Reference		Reference		Reference		Reference	
Infratentorial	3.565 (2.823–4.503)	<0.001	3.128 (2.436–4.016)	<0.001	3.395 (2.373–4.858)	<0.001	2.432 (1.632–3.622)	<0.001
Supratentorial + infratentorial	0.600 (0.450–0.801)	0.001	0.900 (0.652–1.243)	0.523	0.773 (0.476–1.254)	0.297	1.060 (0.608–1.847)	0.838

Abbreviations: CI = confidence interval; DBP = diastolic blood pressure; OR = odds ratio; SBP = systolic blood pressure; TOAST = Trial of Org 10172 in Acute Stroke Treatment.
Variables ($p < 0.1$) in the univariable analyses were included.
[a] Overall prediction of the model: 73.4%; Hosmer-Lemeshow goodness of fit test: $p = 0.144$.
[b] Overall prediction of the model: 75.3%; Hosmer-Lemeshow goodness of fit test: $p = 0.235$.

previous population-based study.[34] There is no evidence that combining aspirin with other antiplatelet drugs improves stroke clinical outcomes compared to aspirin alone.[35] Finally, we did not experimentally evaluate antiplatelet response (i.e., determine aspirin or clopidogrel resistance as a laboratory phenomenon through ex vivo tests). Impaired responsiveness to aspirin or clopidogrel has been reported, especially in ischemic stroke patients.[35,36] In cases of platelet responsiveness to aspirin, the degree of responsiveness can affect clinical outcome, stroke severity, and ischemic lesion volume.[37,38] However, the biggest problem is a lack of a standardized and global platelet function measure due to considerable differences between platelet function test results and the limitations of testing.[39]

A substantial number of patients with PA use experienced a first ischemic stroke. PA was associated with initial lower stroke severity, suggesting that use of antiplatelet agents prior to ischemic stroke can still have a beneficial effect, even if the antiplatelet agents fail to prevent stroke.

AUTHOR CONTRIBUTIONS

J.-M. Jung designed the study, collected the data, performed statistical analyses, and wrote the manuscript. K.-Y. Park contributed to the manuscript as co-first author. J. Choi recommended the study design and performed statistical analyses. M.-Y. Eun, W.-K. Seo, K.-H. Cho, S. Yu, K. Oh, and S. Hong collected and qualified the data. W.-K. Seo supervised the project and critically revised the manuscript.

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Comment: The benefits of antiplatelets on stroke—More arguments to keep patients adherent

The role of antiplatelet agents in stroke prevention is well documented, especially for secondary prevention, but many patients with no previous stroke but with other risk factors (high cardiovascular risk, women with diabetes mellitus, chronic kidney disease, peripheral artery disease, or asymptomatic carotid stenosis) can also benefit. The findings of Jung et al.[1] are therefore clinically relevant and can be used to reassure patients that even if antiplatelet agents fail to prevent stroke, they can mitigate its severity. Although it is an observational study, a randomized trial to test the effect of antiplatelet agents on ischemic stroke severity might not be ethically acceptable.

To date, only the effect of statin pretreatment on ischemic stroke severity has been tested with propensity scoring. Thus this study contributes substantially by helping to clarify previously inconsistent findings on the possible benefit of prior antiplatelet use on stroke-associated neurologic deficit. It addressees the discrepancies and heterogeneity seen in prior studies using propensity matching in a large patient sample. Propensity scoring is a recognized technique to produce semirandomized settings for treatment comparison, although it is not ideal and cannot eliminate completely between-group imbalances, especially for unknown treatment predictors. Nevertheless, the preventive benefit of antiplatelet agents, like antithrombotics in patients with atrial fibrillation, seems to apply to the severity of ischemic stroke. Considering different pharmacokinetics and mechanisms of action, it would be of interest to estimate the effects of different antiplatelet agents on stroke severity—is it class effect?

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Maciej Niewada, MD

From the Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland.
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