Differential Effect of Previous Antiplatelet Use on Stroke Severity According to Stroke Mechanism

Wook-Joo Kim; Youngchai Ko; Mi Hwa Yang; Sun-Hye Im; Jung Hyun Park; JiSung Lee; Juneyoung Lee; Moon-Ku Han; Hee-Joon Bae

Background and Purpose—The effect of previous antiplatelet use on stroke severity is controversial. We assume that this controversy is attributable to its difference according to the stroke mechanism.

Methods—Using a prospective stroke registry, patients who were hospitalized because of ischemic stroke and had relevant lesions on MRI were selected. Patients who were using anticoagulants or whose stroke subtype was categorized as stroke of other determined etiology or undetermined etiology were excluded. Baseline stroke severity was measured using the National Institutes of Health Stroke Scale scores at presentation and was compared between no previous antiplatelet users and previous antiplatelet users with stratification by stroke subtypes.

Results—Among the 1622 patients, a total of 490 (30.2%) patients reported use of an antiplatelet within 1 week of stroke onset. The baseline National Institutes of Health Stroke Scale score showed no difference between the nonantiplatelet and antiplatelet groups by crude comparison. However, the interaction between previous antiplatelet use and stroke subtype was significant \((P=0.023)\) in a multivariable analysis; when the study subjects were stratified by stroke subtype, the difference in baseline National Institutes of Health Stroke Scale between the nonantiplatelet and platelet groups was significant in the large artery atherothrombosis group but not in those with cardioembolism and small-vessel occlusion before and after adjustments.

Conclusions—Our study suggests that the reduction of initial stroke severity in the previous antiplatelet users may differ by stroke mechanism. (Stroke. 2010;41:1200-1204.)

Key Words: antiplatelet drugs ■ cerebral infarction ■ stroke classification

The number of people using antiplatelet drugs is increasing. A population-based incidence study in Oxfordshire, United Kingdom, reported that the proportion of patients using antiplatelet drugs increased 10-fold from 1981 to 2004.\(^1\) According to the data from the Behavioral Risk Factor Surveillance System,\(^2\) a random-digit-dial telephone survey of the noninstitutionalized U.S. population, daily or every-other-day aspirin use was increasing up to 36.2% in 2003.

Aspirin and other antiplatelet drugs have well-established effects in preventing the incidence of ischemic stroke. Two large, randomized, clinical trials have shown that early use of aspirin after stroke onset significantly reduced mortality and improved outcome.\(^3,4\) However, with respect to reducing stroke severity, the efficacy of previous use is controversial. Some reports have suggested that previous antiplatelet users have less severe stroke than do nonusers,\(^5-11\) whereas others have shown no effect.\(^12-16\) These apparent variations may have been attributed to small sample size,\(^12,16\) different baseline characteristics (residual confounding),\(^14\) and difficulties in adequate outcome measurements.\(^15\)

Our hypothesis is that these variations might be caused by not considering the difference in stroke mechanism. Platelets play a critical role in initiating thrombosis and constitute up to 50% of thrombus volume, and an antiplatelet drug can reduce stroke severity by limiting the size and extent of thromboses and subsequent emboli.\(^17\) Its effect may benefit further by improving cerebral microcirculation in the ischemic penumbra through inhibiting platelet-derived vasoconstriction products such as thromboxane A\(_2\).\(^18-20\) Anti-inflammatory and neuroprotective effects can be included as other mechanisms.\(^21-23\) The contribution of these effects to reduction of stroke severity may differ by stroke mechanism. Difference in recurrence rate with antiplatelet use between cardioembolic and noncardioembolic stroke can be regarded as supporting evidence of this assumption.\(^24,25\)

The purpose of this study was to investigate whether the effect of previous antiplatelet use on stroke severity may be different among 3 major subtypes of ischemic stroke, ie, large-artery atherothrombosis (LAA), small-vessel occlusion (SVO), and cardioembolic stroke (CE), as defined according
Subjects and Methods

Based on the prospective Korean stroke registry,22 a consecutive series of ischemic stroke patients hospitalized in Seoul National University Bundang Hospital, between January 2004 and August 2008, were identified. We selected patients who were hospitalized within 7 days of symptom onset and had relevant ischemic lesions on diffusion-weighted MRI. Patients were excluded from the study if they were using oral anticoagulants at stroke onset or if their stroke subtypes were classified as attributable to stroke of other determined etiology or undetermined etiology according to TOAST criteria.26

Included patients were classified into LAA, SVO, or CE groups based on the TOAST classification.26 We modified the criteria of lesion size for SVO as <20 mm because the size of ischemic lesion is generally larger on diffusion-weighted MRI than on CT or conventional MRI at its acute stage.28 To determine the stroke subtype in each subject, the following tests were performed: MRI (98.7%), MRA (97.2%), electrocardiography (100%), transcranial Doppler (77.9%), 24-hour cardiac Holter monitoring (32.5%), transthoracic echocardiography (87.9%), transesophageal echocardiography (19.0%), and conventional angiography (21.9%). Stroke subtypes were primarily determined by physicians in charge during hospitalization and reviewed by stroke neurologists (W.J.K., Y.K., and J.H.P.) after discharge. Discrepancies were solved during weekly registry meeting by consensus. To ensure the consistency of classification and the appropriateness in applying the criteria, each subject’s stroke subtype was rechecked by one investigator (S.H.I.).

Baseline stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) by treating neurologists when patients were presented, and was then rechecked by one experienced stroke nurse (M.H.Y.) immediately after admission.29 Clinical and laboratory information, including use of antiplatelet drugs before hospitalization, age, gender, history of transient ischemic attack or stroke, hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, systolic and diastolic blood pressure at admission, blood glucose at presentation, previous use of lipid-lowering drug, pre-stroke modified Rankin scales,30 and time interval from stroke onset to presentation, were gathered and prospectively entered into the stroke registry database. Previous use of antiplatelet drugs was defined as self-reporting of using aspirin, clopidogrel, ticlopidine, triflusal, aspirin plus dipyridamole, or cilostazol within 7 days from stroke onset. With respect to previous use of antiplatelet drugs, medical records of all the subjects were reviewed again by one investigator (S.H.I.). “Smoker” was defined as current smoker or those who quit within the previous 5 years. The study was approved by the local institutional review board.

Statistical Analyses

Continuous variables are expressed as the mean±standard deviation (SD) or the median (interquartile range), whereas categorical variables are presented by using their absolute values and percentages. Study subjects were categorized into previous antiplatelet users (PA group) and nonusers (non-PA group), and their baseline NIHSS scores were compared using Mann-Whitney U test. Clinical and demographic characteristics were also compared using the Pearson χ² test, Mann-Whitney U test, and Student t test, if appropriate. Study subjects were stratified into 3 subtypes of ischemic stroke and a comparison of baseline NIHSS between the non-PA and PA groups was repeated in each stratum using Mann-Whitney U test.

Analysis of covariance was used for the multivariable analyses with logarithmic transformation of baselines NIHSS score because of its right-skewed distribution. In addition to TOAST classification, variables showing P<0.1 in bivariate analyses with previous antiplatelet use and with baseline NIHSS were included in the multivariable model. To justify the subgroup analysis according to stroke subtype, we introduced an interaction term (previous antiplatelet use×TOAST classification) into the multivariable model. After confirming a significant interaction between TOAST classification and the previous antiplatelet use, the multivariable analysis was repeated in each stratum of the three subtypes. P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS 15.0 for Windows (SPSS).

Results

During the study period, a consecutive series of 2106 patients who had relevant ischemic lesions on diffusion-weighted MRI were hospitalized to our institution because of acute ischemic stroke. Among these, 50 patients were excluded because of use of anticoagulants at stroke onset, and 434 patients were excluded because of stroke mechanism (Figure). The final study subjects were 1622. Four-hundred ninety patients (30.2%) had used antiplatelet drugs at least once within 7 days preceding stroke onset (PA group), whereas 1132 patients had not used any antiplatelet drugs (non-PA group). In the PA group, aspirin was the most frequently used drug (N=430; 87.8%), followed by clopidogrel (N=131; 26.7%). Types of antiplatelet drugs are presented in Table 1.
Comparisons of demographic and clinical characteristics between the non-PA and PA groups are presented in Table 2. There was no significant difference in gender, previous use of statin, thrombolysis, or interval from stroke onset to presentation. Age and blood glucose at presentation were higher in the PA group, whereas systolic and diastolic blood pressures were higher in the non-PA group. History of stroke or transient ischemic attack, hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation were more common in the PA group. Prestroke modified Rankin scale score and TOAST classification were also different.

Crude comparison of the baseline NIHSS between the non-PA and PA groups did not show any significant difference (P=0.726 by Mann-Whitney U test; Table 3). The median was 4 (interquartile range, 2–7) in the non-PA group and 4 (interquartile range, 2–8) in the PA group. However, stratification by stroke mechanism revealed somewhat different results. In SVO and CE, the difference in baseline NIHSS between the non-PA and PA groups was not significant (P=0.432 and 0.294, respectively; Table 3) independent of age, history, diastolic blood pressure, hyperlipidemia, and prestroke modified Rankin scale score.

In a multivariable analysis, we first examined the interaction between previous antiplatelet use and TOAST classification, which was statistically significant (P=0.023; Tables 3 and 4). When the study subjects were stratified by stroke subtype, the analysis of covariance showed that the difference in baseline NIHSS between the non-PA and PA groups was significant in LAA (P<0.001) but not in SVO and CE (P=0.432 and 0.294, respectively; Table 3) independent of age, history, diastolic blood pressure, hyperlipidemia, and prestroke modified Rankin scale score.

**Discussion**

To the best of our knowledge, this is the first study to prove the differential effect of previous use of antiplatelet drugs on baseline stroke severity by stroke mechanism.

In patients with atrial fibrillation, the most common cause of cardioembolic stroke, antiplatelets were more effective for preventing noncardioembolic stroke than were cardioembolic stroke, and anticoagulants were more effective for preventing cardioembolic stroke than noncardioembolic stroke.

**Table 1. Type of Antiplatelet Drugs Used in the Study Population**

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>310</td>
<td>63.3</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>33</td>
<td>6.7</td>
</tr>
<tr>
<td>Triflusal</td>
<td>15</td>
<td>3.1</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Aspirin + clopidogrel</td>
<td>98</td>
<td>20.0</td>
</tr>
<tr>
<td>Aspirin + cilostazol</td>
<td>11</td>
<td>2.2</td>
</tr>
<tr>
<td>Aspirin + triflusal</td>
<td>7</td>
<td>1.4</td>
</tr>
<tr>
<td>Aspirin + ticlopidine</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Aspirin + dipyridamole</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>490</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2. Demographic and Clinical Characteristics of Non-PA and PA Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-PA Group</th>
<th>PA Group</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66.36±12.76</td>
<td>69.52±10.15</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Male</td>
<td>670 (59.2%)</td>
<td>276 (56.3%)</td>
<td>0.283</td>
</tr>
<tr>
<td>History of TIA</td>
<td>57 (5.0%)</td>
<td>41 (8.4%)</td>
<td>0.010</td>
</tr>
<tr>
<td>History of stroke</td>
<td>138 (12.2%)</td>
<td>184 (37.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>643 (56.8%)</td>
<td>365 (74.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>286 (25.3%)</td>
<td>192 (39.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>172 (15.2%)</td>
<td>97 (19.8%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Smoking</td>
<td>367 (32.4%)</td>
<td>114 (23.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>126 (11.1%)</td>
<td>88 (18.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>161.99±28.15</td>
<td>158.35±27.28</td>
<td>0.016†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>87.36±16.68</td>
<td>84.08±15.18</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Blood glucose at presentation, mg/dL</td>
<td>146.54±65.75</td>
<td>155.06±66.75</td>
<td>0.017†</td>
</tr>
<tr>
<td>Prestroke modified Rankin scale score</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous statin use</td>
<td>79 (7.0%)</td>
<td>27 (5.5%)</td>
<td>0.272</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>112 (9.9%)</td>
<td>50 (10.2%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Interval from onset to presentation, hr</td>
<td>12.5 (3.7–43.5)</td>
<td>12.5 (3.7–43.4)</td>
<td>0.502‡</td>
</tr>
<tr>
<td>TOAST classification</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD or median (interquartile range), whereas categorical variables are presented as number of subjects (percentage).

*P calculated by Pearson χ² test unless indicated.
†P is calculated by Student t test.
‡P calculated by Mann-Whitney U test.

common in LAA compared to other subtypes and were significantly reduced by antiplatelet medication. Large infarcts were found less frequently in patients who used aspirin previous to stroke, especially when their stroke was caused by LAA, although it was not proven explicitly through showing the association between the previous use of aspirin and the baseline stroke severity after adjusting potential confounders. All the studies mentioned correspond well with our conclusion of the differential effect of previous antiplatelet use by stroke mechanism. Recently, the Registry of Canadian Stroke Network investigators reported that preadmission antiplatelet treatment reduced stroke severity at presentation in patients with atrial fibrillation. The disagreement be-
an outcome variable. Of course, they have been used for looking into the effect of previous antiplatelet use on stroke severity can be attributed to neglect of stroke subtype.

The matter of stroke subtypes was not properly handled in previous studies on the effect of previous antiplatelet use on stroke severity. Most studies did not investigate stroke subtypes; furthermore, a few studies that did look at subtypes did not adjust or stratify stroke subtypes. To the best of our knowledge, no study has considered an interaction between previous antiplatelet use and TOAST classification.

Some studies adopted mortality or functional disability as an outcome variable. Of course, they have been used frequently as outcome variables in various stroke research. However, so many factors, including interventions, complications, and even stroke recurrence, can happen after stroke onset and the appropriateness of mortality or functional disability as an outcome variable is dubious in terms of looking into the effect of previous antiplatelet use on stroke severity.

Therefore, with these observations and our study results, it is cautiously suggested that most of the controversy surrounding previous studies about the effect of previous antiplatelet use on stroke severity can be attributed to neglect of stroke subtypes and inappropriate choice of outcome variables. In fact, Sanossian et al also succeeded in showing a positive correlation between previous antiplatelet use and baseline stroke severity by adopting baseline NIHSS as an outcome variable and adjusting stroke subtypes.

Our study has limitations. First, this is a single hospital-based, retrospective, observational study. It should be pointed out that unmeasured differences may exist between the non-PA and the PA groups and may distort the study results. A larger-scale, multicenter, or community-based prospective study with more extensive gathering of potential confounders, including socioeconomic status and health-related behaviors, is warranted.

Second, a randomized, controlled trial is the best method for proving evidence about an effect of antiplatelet drugs according to stroke mechanism. However, such a method seems to be unethical because antiplatelet is already known to be effective for stroke. Third, this study had an eligible time window of 7 days from stroke onset. Severity of stroke changes with time. A 7-day window may be too long of a period to capture baseline stroke severity in each individual. However, the time interval from stroke onset to presentation was not different between the non-PA and PA groups. Moreover, repeating the analysis with patients who arrived within 24 hours of stroke onset did not change the results. Fourth, we relied on self-reports or guardian reports for obtaining the history of antiplatelet use previous to stroke. Fifth, we admit that there was a possibility of “misclassification bias” related to TOAST. Last, the size of population was different among stroke subtypes. This difference might contribute to the differential effect of previous antiplatelet use.

In the forthcoming era of a stroke epidemic, our study has implications. First, this study demonstrates that the effect of...
previous antiplatelet use on stroke severity differs according to stroke mechanism. This means that future studies about the effect of antiplatelet agents on stroke should consider stroke mechanism in their design. Second, previous use of antiplatelet drugs, mainly aspirin, lessens the severity of stroke, at least in LAA. Considering the current underutilization of aspirin, our results would provide an important public message about the necessity of promoting the use of antiplatelet drugs for primary and secondary prevention of stroke.

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Disclosures
None.

References
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