Effect of preceding antiplatelet agents on ischemic stroke severity in patients with a history of stroke

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Abstract

Background: Antiplatelet agents are effective in secondary prevention of ischemic stroke and can reduce the severity of first-ever ischemic stroke. However, it remains controversial whether prophylactic administration of antiplatelet agents can reduce the severity of recurrent ischemic stroke. This study aimed to determine the effect of preceding antiplatelet treatment on ischemic stroke severity in patients with a prior history of stroke.

Methods: From the prospective hospital registry of 1338 consecutive patients with ischemic stroke within 7 days of symptom onset, we identified patients with a prior history of stroke who were admitted due to cerebral thrombosis, which included large-artery atherosclerosis, small vessel occlusion, and branch atheromatous disease. Patients were categorized into 2 groups according to preceding medication: antiplatelet (AP) group and none (N) group. Those with preceding anticoagulant agents or unknown prior medication were excluded. Stroke severity (National Institutes of Health Stroke Scale: NIHSS) on admission was compared between the 2 groups.

Results: A total of 88 patients were analyzed. Out of these, 66 were identified in the AP group (median age 78, male 71%), and 22 in the N group (median age 71, male 73%). The median NIHSS on admission was lower in the AP group than in the N group (3 vs 5, $p=0.043$). In multivariate analysis, preceding antiplatelet treatment was independently associated with mild stroke ($\text{NIHSS} \leq 4$) on admission (odds ratio 5.77, 95% confidence interval 1.73-21.6, $p=0.004$).

Conclusion: Preceding antiplatelet treatment in patients with a prior history of stroke may reduce the severity of subsequent cerebral thrombosis.

Background

Antiplatelet agents have well-established effectiveness in the secondary prevention of ischemic stroke, and there is evidence that prior antiplatelet use is associated with a reduction of stroke severity in patients with first-ever ischemic stroke [1–3]. It has been controversial, however, as to whether preceding treatment with antiplatelet agents reduces the severity of recurrent ischemic stroke [4–6].

We aimed to assess the association between preadmission treatment with antiplatelet agents and stroke severity on admission in patients with ischemic stroke and a prior history of stroke.

Methods

This study was a retrospective analysis based on data from a hospital-based stroke registry, in which consecutive patients with ischemic stroke who were admitted to our hospital within 7 days of symptom onset were prospectively enrolled since April 2014.

Demographics, including information of prior medications, previous medical history, vascular risk factors, laboratory data, physiological and radiological findings, stroke severity and subtypes, as well as age and sex, were collected for each patient. Regarding physiological and radiological findings, all patients underwent brain computed tomography (CT) and/or magnetic resonance imaging (MRI), duplex sonography of the carotid and vertebral arteries, electrocardiogram, and transthoracic echocardiogram. If necessary, transesophageal echocardiogram was added to screen for right-to-left shunt or aortic arch lesions. Stroke severity was evaluated according to the National Institutes of Health Stroke Scale (NIHSS) on admission and during hospitalization, and dichotomized into mild (NIHSS ≤ 4) and moderate to severe (NIHSS ≥ 5). Stroke subtypes, except for branch atheromatous disease (BAD), were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [7]. Clinical diagnosis of BAD was made based on acute MRI, as we reported previously [8]. Briefly, BAD of the lenticulostriate arteries was defined as infarcts more than 10 mm in diameter on axial slice and visible for 3 or more axial slices at a slice thickness of 7 mm, and that of the anterior pontine arteries was defined as unilateral infarcts extending to the basal surface of the pons, without a potential cardiac source of embolism or $>50\%$ stenosis of extracranial or intracranial large arteries.

Aortogenic cerebral infarction is included among the other determined etiology. Written informed consent was obtained from each patient or their next to kin for participation in this registry.

From this registry, we identified consecutive patients with a prior history of ischemic or hemorrhagic stroke and who were admitted due to cerebral thrombosis, which included large-artery atherosclerosis (LAA), small-vessel occlusion (SVO), and BAD. Patients using anticoagulant agents (warfarin, dabigatran, apixaban, edoxaban, rivaroxaban, or heparin) at the stroke onset, regardless of antiplatelet agents were excluded from analysis.

For the purpose of the study, prior medications at the stroke onset were categorized into 2 groups: none as the reference, N and antiplatelet agent(s) (aspirin, ticlopidine, clopidogrel, prasugrel, cilostazol, or a combination of these), AP. Patients who were stopped antithrombotic agents due to major surgery or bleeding complications or withdrew these agents by themselves for 1 week or longer prior to the stroke symptoms were included in the N group.

This study was approved by the institutional review board. The approval number was Sp 2020-05.

Statistical analysis:

Demographics, vascular risk factors, stroke severity were compared among the groups using Wilcoxon rank-sum test or chi-squared test. Univariate and multivariate logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence interval (CI) for mild stroke (NIHSS ≤ 4). The variables in the multivariate models were included age, male, premorbid modified Rankin Scale (mRS) ≤ 2 , atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, smoking, antiplatelet agent(s).

Two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed with the JMP software package (version 12.1.0; SAS Institute, Cary, NC).

Results

Among 1338 patients with ischemic stroke within 7 days of symptom onset who were enrolled in the hospital-based stroke registry between April 2014 and March 2018, 252 (18.8%) had a prior history of stroke. Of these, 103 patients were admitted due to cerebral thrombosis (LAA in 50, SVO in 35, and BAD in 18 patients). We excluded one patient with LAA who had no information about prior medication, and 14 patients who had taken anticoagulant agents. Finally, we analyzed 88 patients (Median age, 76 [48-96] years; number of males, 63[72%]) in this study.

Of these, 66 were treated with antiplatelet agents (AP group: median age, 78 [48-92] years; male, 47 [71%]), and the remaining 22 had no antiplatelet agent (N group: median age, 71 [59-96] years; male, 16 [73%]) on admission. In the AP group, antiplatelet regimens were aspirin in 18, clopidogrel in 18, ticlopidine in 2, cilostazol in 13, and a combination of them in 15.

The clinical characteristics are shown in Table 1. There were no significant differences among the demographics between the groups, except for dyslipidemia. Regarding stroke severity on admission, patients in the AP group had lower NIHSS scores (median 3, interquartile range 2-5) than those in the N group (5, 2-7) ($P=0.043$). Patients with mild stroke ($\text{NIHSS} \leq 4$) were more frequently observed in the AP group (48 patients, 72%) than in the N group (10, 45%) ($P=0.036$) (Table 2).

Table 1
Baseline characteristics

	N	AP	p
	(n=22)	(n=66)	
Median age, year	71 (59-96)	78 (48-92)	0.094*
Male	16 (73%)	47 (71%)	0.891†
Atrial fibrillation	2 (9%)	2 (3%)	0.237†
Hypertension	20 (91%)	63 (95%)	0.425†
Diabetes mellitus	7 (32%)	21 (32%)	1.000†
Dyslipidemia	8 (36%)	45 (68%)	0.008†
Current or past smoker	12 (55%)	33 (50%)	0.712†
Pre-mRS ≤ 2	18 (82%)	52 (79%)	0.760†
LAA	13 (59%)	31 (47%)	0.325†
SVO	6 (27%)	24 (36%)	0.436†
BAD	3 (14%)	11 (17%)	0.737†
Data are expressed as the median (range), or number (%) of patients.			
mRS: modified Rankin Scale, LAA: large-artery atherosclerosis, SVO: small-vessel occlusion, BAD: branch atheromatous disease			
*Wilcoxon rank-sum test, †chi-squared test			

Table 2
Stroke severity and outcome

	N	AP	p
	(n=22)	(n=66)	
NIHSS on admission	5 (2-7)	3 (2-5)	0.043*
NIHSS ≤ 4 on admission	10 (45%)	48 (72%)	0.019†
Data are expressed as the median (IQR), or number (%) of patients.			
NIHSS: National Institutes of Health Stroke Scale			
*Wilcoxon rank-sum test, †chi-squared test			

In multivariate logistic regression analysis, premorbid independent (mRS ≤ 2) and preceding antiplatelet treatment were independently associated with mild stroke (NIHSS ≤ 4). (OR 4.90, 95%CI 1.50-17.4,

p=0.008; OR 5.77, 95%CI 1.73-21.6, p=0.004; respectively) (Table 3).

Table 3
Logistic regression analysis for mild stroke (NIHSS≤4)

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p	OR (95%CI)	p
Age	1.02 (0.97-1.08)	0.281	1.02 (0.97-1.09)	0.432
Male	2.31 (0.88-6.07)	0.087	1.88 (0.54-6.77)	0.322
Pre-mRS ≤2	4.22 (1.45-13.0)	0.008	4.90 (1.50-17.4)	0.008
Atrial fibrillation	0.50 (0.06-4.34)	0.503	0.84 (0.08-9.31)	0.880
Hypertension	1.31 (0.17-8.34)	0.777	1.79 (0.16-17.0)	0.619
Diabetes mellitus	0.90 (0.35-2.36)	0.827	0.82 (0.28-2.47)	0.725
Dyslipidemia	0.82 (0.32-2.02)	0.668	0.42 (0.12-1.25)	0.120
Smoking	1.61 (0.66-3.97)	0.292	1.18 (0.36-3.82)	0.780
Antiplatelet agent(s)	3.20 (1.19-8.88)	0.022	5.77 (1.73-21.6)	0.004
CI: confidence interval, OR: odds ratio, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale				

Discussion

We found that prior treatment with antiplatelet agents was associated with a reduction of stroke severity in patients with cerebral thrombosis who had a prior history of stroke. Antiplatelet agents may limit the size and extent of thromboses, even if patients with stroke experience subsequent thrombotic infarction [9].

Antiplatelet agents are considered to reduce stroke severity as well as the risk of ischemic stroke [1–6, 9, 11–14], like anticoagulant agents [10]. Several studies, however, have reported negative results [15–23]. The largest report was from the International Stroke Trial, in which previous aspirin use was associated with rather greater stroke severity, although this association was not significant after adjustment for confounding factors [17]. In those negative reports, there were imbalances of demographic data between antiplatelet users and non-users [15, 17, 18, 23]. In comparison with non-users, antiplatelet users tend to be older, and to have more vascular risk factors, including atrial fibrillation and comorbidities [1–3, 12, 15, 17, 18, 23].

According to previous report, patients treated with antiplatelet agents were approximately 2-3 times more likely to have a previous stroke than those without [4, 9, 12, 15, 18, 23]. It has been shown that among antiplatelet users, 41.4% had a previous stroke or TIA, compared with 11.3% in the non-users [23].

Prior stroke may considerably affect the premorbid disability and severity at the second stroke onset. To avoid this bias, some studies have only included first-ever stroke, but the results have been controversial [1–3, 19, 22]. On the other hand, there have been few investigations in patients with a history of stroke. In terms of secondary stroke prevention, two old studies showed a protective effect of antiplatelet agents on the severity of subsequent stroke in patients with a history of TIA [5, 6]. In another study, pretreatment with antiplatelet agents reduce stroke severity in those with no history of stroke or TIA, but not in those with a prior history of stroke or TIA [4]. In those studies, however, analysis of patients with a prior history of only stroke was not provided.

There has also been an imbalance in stroke subtypes between those with and without antiplatelet treatment. In previous reports, cardioembolism, which is the most severe subtype of ischemic stroke, was significantly more frequent in stroke patients with prior antiplatelet treatment than in those without [1–4, 12, 15, 18]. It has been well established that anticoagulant agents are superior to antiplatelet agents in the prevention of cardioembolism, while antiplatelet agents are recommended for non-cardioembolic stroke such as LAA, SVO, and BAD. Because platelets are the main culprit in arterial thrombus formation, antiplatelet treatment is expected to limit thrombus size due to suppression of increased platelet activation [14]. Some researchers have reported that the effect of antiplatelet agents on stroke severity was most remarkable in patients with LAA [1, 12] and in patients without potential cardiac sources of embolism, such as atrial fibrillation and prosthetic heart valve [11].

To overcome an imbalance of clinical background between those with and without antiplatelet treatment, some researchers have used multivariate analysis [2, 13, 23], particularly in using propensity score matching [3, 12]. Again, there has been no previous study that targeted patients with a prior history of stroke, i.e., secondary stroke prevention. So, we focused on secondary stroke prevention by including only patients with a history of stroke and excluding patients with cardioembolism or prior use of anticoagulant agents. Narrowing the inclusion to patients with a history of stroke and cerebral thrombosis may eliminate any significant imbalance, except dyslipidemia, between those with and without prior antiplatelet use, and it may enhance the effect of prior use of antiplatelet agents at the time of a second stroke.

There are several limitations to this study. First, this study was a single center cohort with a small number of patients, and was a retrospective observational study. The results should be confirmed by a large, multi-center, prospective study. Second, a previous stroke may include hemorrhagic stroke. Only a prospective study could evaluate bleeding risk. Third, the duration from symptom onset to admission was long, because some types of stroke could be getting worse for hours or days from onset, even in patients treated with antiplatelet agents. Fourth, there was no data regarding drug resistance, which might occur in some patients with a recurrent cerebral thrombosis. Aspirin and clopidogrel resistance should be considered in future studies. Despite these limitations, the results of this study are clinically important in the current stroke practice.

Conclusions

Recurrent ischemic stroke, especially cerebral thrombosis in patients with prior antithrombotic agents is a less severe neurological symptom than in those without.

Abbreviations

NIHSS

National Institutes of Health Stroke Scale

BAD

branch atheromatous disease

TOAST

Trial of Org 10172 in Acute Stroke Treatment

LAA

large-artery atherosclerosis

SVO

small vessel occlusion

N

no antiplatelet agent

AP

antiplatelet agent(s)

OR

odds ratio

TIA

transient ischemic attack

Declarations

Ethics approval: The use of human subjects for this study has been approved by our institutional review board (Sp2020-05).

Consent to participate: Written informed patients' consent was not required in this study.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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drafting the manuscript for intellectual content. All authors read and approved the final manuscript.

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References

1. Lin J, Han Z, Yi X, Luo H, Zhou Q, Zhou J. Prestroke Aspirin Use is Associated with Clinical Outcomes in Ischemic Stroke Patients with Atherothrombosis, Small Artery Disease, and Cardioembolic Stroke. *J Atheroscler Thromb*. 2019 Jun;26(6):528–37. <https://doi.org/10.5551/jat.46136>.
2. Bembenek JP, Niewada M, Karlinski M, Czlonkowska A. Effect of prestroke antiplatelets use on first-ever ischaemic stroke severity and early outcome. *Int J Clin Pract*. 2016 Jun;70(6):477–81. <https://doi.org/10.1111/ijcp.12804>.
3. Jung JM, Choi J, Eun MY, Seo WK, Cho KH, Yu S, et al. Prestroke antiplatelet agents in first-ever ischemic stroke: clinical effects. *Neurology*. 2015 Mar;84(11):1080–9. <https://doi.org/10.1212/WNL.0000000000001361>.
4. Sanossian N, Saver JL, Rajajee V, Selco SL, Kim D, Razinia T, et al. Premorbid antiplatelet use and ischemic stroke outcomes. *Neurology*. 2006 Feb;66(3):319–23. <https://doi.org/10.1212/01.wnl.0000195889.05792.f1>.
5. Carolei A, Prencipe M, Fiorelli M, Fieschi C. Severity of stroke and aspirin. *Neurology*. 1986 Jul;36(7):1010–1. <https://doi.org/10.1212/wnl.36.7.1010-b>.
6. Grotta JC, Lemak NA, Gary H, Fields WS, Vital D. Does platelet antiaggregant therapy lessen the severity of stroke? *Neurology*. 1985 May;35(5):632–636. <https://doi.org/10.1212/wnl.35.5.632>.
7. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993 Jan;24(1):35–41. <https://doi.org/10.1161/01.str.24.1.35>.
8. Yamamoto Y, Ohara T, Hamanaka M, Hosomi A, Tamura A, Akiguchi I. Characteristics of intracranial branch atheromatous disease and its association with progressive motor deficits. *J Neurol Sci*. 2011 May;304(1-2):78–82. <https://doi.org/10.1016/j.jns.2011.02.006>.
9. Wilterdink JL, Bendixen B, Adams HP Jr, Woolson RF, Clarke WR, Hansen MD. Effect of prior aspirin use on stroke severity in the trial of Org 10172 in acute stroke treatment (TOAST). *Stroke*. 2001 Dec;32(12):2836–40. <https://doi.org/10.1161/hs1201.099384>.
10. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, et al. Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation. *JAMA*. 2017 Mar;317(10):1057–67. <https://doi.org/10.1001/jama.2017.1371>.
11. Tziomalos K, Giampatzis V, Bouziana SD, Spanou M, Kostaki S, Papadopoulou M, et al. Treatment with Clopidogrel Prior to Acute Non-Cardioembolic Ischemic Stroke Attenuates Stroke Severity. *Cerebrovasc Dis*. 2016;41(5-6):226–32. <https://doi.org/10.1159/000443745>.

12. Park JM, Kang K, Cho YJ, Hong KS, Lee KB, Park TH, et al. Comparative Effectiveness of Prestroke Aspirin on Stroke Severity and Outcome. *Ann Neurol*. 2016 Apr;79(4):560–568.
<https://doi.org/10.1002/ana.24602>.
13. Dowlatshahi D, Hakim A, Fang J, Sharma M. Investigators of the Registry of the Canadian Stroke, Network. Pre admission antithrombotics are associated with improved outcomes following ischaemic stroke: a cohort from the Registry of the Canadian Stroke Network. *Int J Stroke*. 2009 Oct;4(5):328–34. <https://doi.org/10.1111/j.1747-4949.2009.00331.x>.
14. Joseph R, Han E, Tsering C, Grunfeld S, Welch KM. Platelet activity and stroke severity. *J Neurol Sci*. 1992 Mar;108(1):1–6. [https://doi.org/10.1016/0022-510x\(92\)90180-s](https://doi.org/10.1016/0022-510x(92)90180-s).
15. Agayeva N, Topcuoglu MA, Arsava EM. The Interplay between Stroke Severity, Antiplatelet Use, and Aspirin Resistance in Ischemic Stroke. *J Stroke Cerebrovasc Dis*. 2016 Feb;25(2):397–403.
<https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.10.011>.
16. Sacco S, Toni D, Bignamini AA, Zaninelli A, Gensini GF, Carolei A, et al. Effect of prior medical treatments on ischemic stroke severity and outcome. *Funct Neurol*. 2011 Jul-Sep;26(3):133–9.
17. Kumar S, Savitz S, Schlaug G, Caplan L, Selim M. Antiplatelets, ACE inhibitors, and statins combination reduces stroke severity and tissue at risk. *Neurology*. 2006 Apr;66(8):1153–8.
<https://doi.org/10.1212/01.wnl.0000208406.45440.84>.
18. Ricci S, Lewis S, Sandercock P, Group ISTC. Previous use of aspirin and baseline stroke severity: an analysis of 17,850 patients in the International Stroke Trial. *Stroke*. 2006 Jul;37(7):1737–40.
<https://doi.org/10.1161/01.STR.0000226740.29910.91>.
19. Greisenegger S, Tentschert S, Weber M, Ferrari J, Lang W, Lalouschek W. Prior therapy with antiplatelet agents is not associated with outcome in patients with acute ischemic stroke/TIA. *J Neurol*. 2006 May;253(5):648–52. <https://doi.org/10.1007/s00415-006-0088-0>.
20. Libman R, Sharfstein S, Barr W. Stroke outcome in patients already taking aspirin. *J Stroke Cerebrovasc Dis*. 1999 Nov-Dec;8(6):423–5. [https://doi.org/10.1016/s1052-3057\(99\)80050-0](https://doi.org/10.1016/s1052-3057(99)80050-0).
21. Sivenius J, Cunha L, Diener HC, Forbes C, Laaks M, Lowenthal A, et al. Antiplatelet treatment does not reduce the severity of subsequent stroke. European Stroke Prevention Study 2 Working Group. *Neurology*. 1999 Sep;53(4):825–9. <https://doi.org/10.1212/wnl.53.4.825>.
22. De Keyser J, Herroelen L, De Klippel N. Early outcome in acute ischemic stroke is not influenced by the prophylactic use of low-dose aspirin. *J Neurol Sci*. 1997;145(1):93–6.
[https://doi.org/10.1016/s0022-510x\(96\)00250-x](https://doi.org/10.1016/s0022-510x(96)00250-x).
23. Karepov V, Bornstein NM, Hass Y, Korczyn AD. Does daily aspirin diminish severity of first-ever stroke? *Arch Neurol*. 1997 Nov;54(11):1369–71.
<https://doi.org/10.1001/archneur.1997.00550230042014>.