The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2019; 26: 528-537. http://doi.org/10.5551/jat.46136

Prestroke Aspirin Use is Associated with Clinical Outcomes in Ischemic Stroke Patients with Atherothrombosis, Small Artery Disease, and Cardioembolic Stroke

Jing Lin[1], Zhao Han[2], Xingyang Yi[3], Hua Luo[4], Qiang Zhou[1] and Ju Zhou[3]

Zhao Han and Xingyang Yi contributed equally to this work.

[1]Department of Neurology, Third Affiliated Hospital of Wenzhou Medical University, Zhejiang, China
[2]Department of Neurology, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Zhejiang, China
[3]Department of Neurology, People's Hospital of Deyang City, Sichuan, China
[4]Department of Neurology, the Affiliated Hospital of Southwest Medical University, Sichuan, China

Aim: To evaluate the effect of prestroke aspirin (PA) use on initial stroke severity, early neurologic deterioration (END), stroke recurrence, hemorrhagic transformation (HT), and functional outcome in patients with ischemic stroke (IS).

Methods: This was a prospective, observational, multicenter cohort study. The acute IS patients with atherothrombosis (AT), small artery disease (SAD), or cardioembolic (CE) stroke within 24 hours of symptom onset were identified. National Institutes of Health Stroke Scale (NIHSS) scores on admission, clinical outcomes (END, recurrent ischemic stroke [RIS], myocardial infarction [MI], death, and hemorrhagic episodes), and functional outcome (modified Rankin Scale [mRS] scores) at three months after admission were compared between PA users and nonusers.

Results: Among the 1,862 patients, 401 (21.5%) reported PA use. The PA users had a significantly lower initial NIHSS score than the non-PA users. The effect was evident in AT stroke, but not in other subtypes. PA use was independently associated with the decreased risk of END. PA use increased the risk of HT; however, it was only associated with increased risk for asymptomatic HT, not for symptomatic HT. PA use was associated with better functional outcomes (mRS scores ≤2 points) irrespective of stroke subtypes at three months after admission, despite the increased risk of HT.

Conclusions: PA use may reduce initial stroke severity in AT stroke and the risk of END, and can improve functional outcome at three months irrespective of stroke subtypes.

Key words: Prestroke aspirin use, Ischemic stroke, Early neurological deterioration, Hemorrhagic transformation, Outcome

Introduction

Aspirin is well known to prevent primary stroke in high-risk individuals (10-year cardiovascular risk >10%)[1]. However, aspirin use is associated with an increased risk of gastrointestinal bleeding and hemorrhagic stroke, and the benefits of aspirin for primary prevention of stroke in persons with low and medium cardiovascular risk profiles has not been proven[2, 3]. The effects of prestroke aspirin (PA) use on initial severity, hemorrhagic transformation (HT), early neurologic deterioration (END), recurrent ischemic stroke [RIS], and functional outcomes of ischemic stroke (IS) remain controversial. Some studies have demonstrated that PA use

Address for correspondence: Zhao Han, Department of Neurology, Second Affiliated Hospital of Wenzhou Medical College, No 109, College West Road, Wenzhou 325000, Zhejiang, China E-mail: wzhanzhao@aliyun.com

Received: July 21, 2018 Accepted for publication: October 11, 2018

may reduce initial stroke severity and improve overall clinical outcomes[4-7], whereas some others have not shown an association between PA use and stroke severity or clinical outcomes[8-10].

Clinical outcomes and stroke severity may differ in different stroke subtypes. Kim *et al.*[11] reported that the difference in baseline National Institutes of Health Stroke Scale (NIHSS) scores between the PA users and nonusers was significant only in patients with large-artery atherosclerosis, but not in those with cardioembolic (CE) stroke and small-vessel occlusion. However, the study did not analyze bleeding risk and clinical outcomes[11]. Although Park *et al.*[7]. showed that PA use may reduce initial stroke severity in atherothrombotic (AT) stroke and can improve functional outcomes at discharge despite an increase of HT. The study did not investigate the occurrence of RIS or END in PA users and nonusers. Furthermore, a three-month modified Rankin Scale (mRS) is a more generally accepted outcome measure in clinical studies[12]. However, the study only assessed functional outcome of stroke with mRS at discharge instead of at three months[7].

END is a devastating complication and associated with poor prognosis in acute IS[13, 14]. It is very important to prevent END after acute IS. Although our previous efforts have sought to determine reliable predictors and prevention for END in acute IS patients[13, 15-17], the prevention strategies for END are not fully understood. We have previously reported that prestroke concomitant statin and aspirin use is associated with lower END and platelet activity in patients with acute IS, but there was no effect of PA alone use on END and clinical outcomes[18]. However, the previous report had several limitations: it was a small-sized, two-hospital-based study with no stratified-analysis functional outcomes in different stroke subtypes[18].

In the absence of high-level evidence from randomized-controlled clinical trials, observational data from a large-sized, multicenter cohort study can be useful, if confounding (imbalances of baseline variables) can be adequately controlled for in the analysis[19]. Thus, this prospective, multicenter observational study aimed to investigate the effects of PA use on initial stroke severity, clinical outcomes (END, HT, RIS, myocardial infarction [MI], and death) during the three months after admission, and functional outcome (mRS) at three months, according to IS subtypes.

Materials and Methods

Study Populations

This prospective, observational, multicenter cohort study was conducted in the Third Affiliated Hospital of Wenzhou Medical University, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, the People's Hospital of Deyang City, and the Affiliated Hospital of Southwest Medical University between March 2015 and October 2017. The study protocol was reviewed and approved by the Ethics Committee of the above participating hospitals. Each of the participants provided informed consent before participating in this study.

We consecutively enrolled IS patients who experienced their first stroke ever, were admitted to the four participating hospitals within 24 hours of symptom onset, and had relevant cerebral lesions on diffusion weighted magnetic resonance imaging (DWI) consistent with acute IS. All patients underwent a baseline brain computed tomography (CT) scan and magnetic resonance imaging on admission and a follow-up CT within 10−14 days after admission. An additional CT assessment was performed whenever examination deteriorated. CT angiography (CTA) or magnetic resonance angiography of the brain as well as a color duplex ultrasound investigation of the carotid arteries were assessed in all patients. A common electrocardiogram (ECG), 24-hour Holter ECG, and echocardiogram were performed to reveal any possible CE stroke. The inclusion criteria were: (1) age ≥ 40 years old; (2) stroke subtypes were AT, small artery disease (SAD), and CE stroke according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system[20]. Exclusion criteria were: (1) other determined or undetermined etiology of IS; (2) in addition to aspirin, prestroke use of other antiplatelet medication (such as clopidogrel, prasugrel, ticagrelor, or ticlopidine), combination therapy with aspirin and clopidogrel or aspirin-dipyridamole, and warfarin or heparin or new oral anticoagulant within seven days of stroke onset were excluded; (3) history of carotid stent therapy or carotid endoartectomy; (4) fever, hypoxia, or any relevant hemodynamic compromise at admission; (5) asthma, severe cardiovascular, liver, or renal disease; (6) individuals declined to participate in the study; and (7) no information on study variables for the analysis.

The following data were obtained at baseline: (1) age, sex, and systolic and diastolic blood pressures at presentation; (2) history of hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, or coronary artery disease (CAD); and (3) fasting glucose, hemoglobin A1c, fasting total plasma cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C). Hyperlipidemia was defined as TC > 200 mg/dL, TG > 180 mg/dL or use of lipid-lowering medication[13].

Aspirin administration was for the purpose of primary prevention of vascular events in patients with

high cardiovascular risk profiles (10-year cardiovascular risk >10%), including CAD and other high-risk conditions or factors (such as hypertension, diabetes mellitus, cigarette smoking, and hyperlipidemia). PA users were defined as patients who had taken aspirin within seven days before stroke onset to prevent vascular events[7]. Nonusers (non-PA users) were those who had not taken aspirin during the time period.

Stroke Severity and Clinical Outcomes

For each patient, an NIHSS assessment was performed by a member of the stroke team on admission, and subsequently on a daily basis through the period of hospitalization. Initial stroke severity was evaluated by NIHSS score on admission. Functional outcomes were assessed by mRS scores at three months after admission; good functional outcomes were defined as mRS ≤2 points, while poor functional outcomes were mRS >2 points.

Clinical outcomes included: (1) END, where END was defined as an increase of two or more points in NIHSS score during 10 days after admission, while excluding HT of infarct or a new infarct in another vascular territory according to our previous studies[13, 17]; (2) a composite ischemic event of RIS, MI, and death during the 3 months after admission, where RIS was defined as a new focal neurologic deficit of vascular origin lasting at least 24 hours, a DWI-positive lesion corresponded to their clinical symptom and was proven to be nonhemorrhagic, and death was defined as vascular mortality due to MI, IS, or other vascular causes; (3) hemorrhagic episodes, where hemorrhagic episodes were defined as the presence of any of the following: ① HT, where HT was defined as any degree of hyperdensity within the area of low attenuation during two weeks after admission[21]; ② intracerebral hemorrhage (ICH) and extracranial hemorrhages (e.g. gastrointestinal bleeding, hematoma, hematuria, and skin or mucosal bleeding) occurred during the three-month follow-up period.

Statistical Analysis

The power and sample size of the current study were calculated by PASS (Power Analysis and Sample Size) 14.0 software (Beijing HuanZhongRuiChi Technology Co., Ltd, Beijing, China), according to assumed rate of good functional outcome at three months after admission. According to the results of previous studies, the rate of good functional outcome (mRS scores ≤2 points) at three months was approximately 70% in IS patients[13, 15]. We determined that a minimum sample of 1,800 patients would provide 80% power to detect a relative increment of 10% in the percentage of good functional outcomes in PA users, with a two-sided type I error of 0.05, assuming a good functional outcome rate of 70% in non-PA users.

Comparisons of baseline characteristics for study subjects, initial stroke severity, clinical outcomes, and functional outcomes between the PA and non-PA users were made by univariate methods. Categorical variables are presented as percentages and compared using the Chi-square test or Fisher's exact test. Continuous variables are expressed as mean ± standard deviation and compared using the Student's *t*-test if normally distributed; otherwise, rank test was used. Multivariable logistic regression with the proportional odds model was employed to evaluate the effects of the PA use on good functional outcome at three months using variables with $P<0.1$ in univariate analysis[22]. Cox proportional hazard regression analysis was performed to examine the effects of PA use on the presence of HT, END, and reported as the hazard ratio (HR) with the 95% confidence intervals (CI). Variables in Cox proportional-hazards model to adjust for confounding effects were imbalance variables ($P<0.1$) in univariate analysis.

SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. All tests were two sided, and the threshold level of $P<0.05$ denoted statistical significance.

Results

Baseline Characteristics of Study Patients

Between March 2015 and October 2017, a total of 2,511 patients with acute IS were hospitalized within 24 hours of onset with relevant ischemic lesions on DWI in the four participating hospitals. We excluded 649 patients for the following reasons: (1) 381 patients had other determined or undetermined etiology of IS according to TOAST classification; (2) 132 patients were on antithrombotics other than aspirin before stroke onset; (3) 20 patients had histories of carotid endoartectomy or carotid stent therapy; (4) 40 patients had fever, hypoxia, severe cardiovascular, liver, or renal disease; (5) 37 patients declined to participate in the study; and (6) 39 patients were missing glucose, hemoglobin A1c, TC, or LDL-C.

Among the 1,862 patients enrolled in the study, a total of 401 (21.5%) reported aspirin use within seven days before stroke onset, where 315 (16.9%), 1,349 (72.4%), and 522 (28.0%) patients were treated with statin, antihypertensive drugs, and hypoglycemic drug, before stroke onset, respectively, and 183 (9.8%) patients received thrombolysis after admission. The comparisons of baseline characteristics between the PA and non-PA users were shown in **Table 1**. Meaningful imbalance variables (*P* values <0.05) were detected

Table 1. Characteristics of study patients

Characteristics	PA user ($n=401$)	Non-PA user ($n=1461$)	P value
Age (years)	70.8 ± 12.5	68.7 ± 13.4	0.007
Men (n, %)	224 (55.9)	828 (56.7)	0.782
Hypertension (n, %)	325 (81.0)	1078 (73.8)	0.005
Diabetes mellitus (n, %)	153 (38.2)	439 (30.0)	0.007
History of CAD (n, %)	22 (5.5)	33 (2.3)	<0.001
Atrial fibrillation (n, %)	61 (15.2)	145 (9.9)	0.005
Cigarette smoking (n, %)	166 (41.4)	569 (38.9)	0.412
Hyperlipidemia(n, %)	230 (57.4)	716 (49.0)	0.005
Systolic blood pressure (mm Hg)	150.2 ± 17.8	142.6 ± 20.7	<0.001
Diastolic blood pressure (mm Hg)	90.2 ± 14.5	88.9 ± 16.8	0.152
Glucose (mM)	6.9 ± 2.5	6.6 ± 2.8	0.047
Hemoglobin A1c (%)	6.6 ± 1.9	6.2 ± 2.1	<0.001
Onset to admission time (h)	18.8 ± 10.6	19.6 ± 11.3	0.178
Stroke subtype (n, %)			0.008
Atherothrombosis	193 (48.1)	775 (53.0)	
Small artery disease	96 (23.9)	395 (27.0)	
Cardioembolism	112 (27.9)	291 (19.9)	
Prestroke treatment (n, %)			
Previous statins	80 (20.0)	235 (16.1)	0.072
Antihypertensive	297 (74.1)	1052 (72.0)	0.453
Hypoglycemic	119 (29.7)	403 (27.6)	0.451
Antithrombotic therapy in the acute phase (n, %)			
Thrombolysis (n, %)	41 (10.2)	142 (9.7)	0.773
Clopidogrel alone	108 (26.9)	354 (24.9)	0.284
Aspirin alone	81 (20.2)	338 (23.1)	0.247
Clopidogrel plus aspirin	107 (26.7)	371 (25.4)	0.665
Anticoagulants	62 (15.5)	235 (16.1)	0.761

PA, prestroke aspirin; CAD, coronary artery disease.

for age, hypertension, diabetes mellitus, history of CAD, hyperlipidemia, atrial fibrillation, systolic blood pressure, fasting glucose, hemoglobin A1c, and stroke subtype (TOAST classification). There were no significant differences in other risk factors, prestroke statin, and antihypertensive drug or hypoglycemic drug use between the two groups (Table 1). Furthermore, there were also no significant differences in antithrombotic therapy (such as thrombolysis, antiplatelet, and anticoagulants) in the acute phase after admission between the two groups (Table 1).

Initial Stroke Severity in the PA and Non-PA Users

The PA users had a lower initial NIHSS score than the non-PA users ($P<0.001$, Table 2). Specifically, the initial NIHSS score was lower in the PA users than the non-PA users with AT subtype ($P<0.001$), whereas there was no significant difference in the initial NIHSS score between the PA users and non-PA users with SAD or CE subtype ($P>0.001$, Table 2).

Clinical Outcomes in the PA and Non-PA Users

All enrolled IS patients completed a three-month follow-up. Three hundred ninety-two patients (21.1%) experienced END within ten days after admission. Among the 392 patients with END, 60 (15.0%) occurred in the PA users and 332 (22.7%) occurred in the non-PA users. The PA users had a lower incidence of END than the non-PA users ($P=0.002$ for univariate analysis, Table 3). With regard to stroke subtypes, PA use reduced the incidence of END in SAD subtype and AT subtype ($P<0.05$, Table 3), whereas there was no significant difference in the incidence of END between the PA users and non-PA users in the CE subtype ($P>0.05$, Table 3). Cox proportional hazard regression analysis showed that PA use was independently associated with a decreased risk of END after adjusting for confounding variables, including age, hypertension, diabetes mellitus, hyperlipidemia, hemoglobin A1c, previous statins use, NIHSS scores on admission, stroke subtype, and thrombolysis (HR: 0.78;

Table 2. Comparison of NIHSS scores on admission between the PA and non-PA users according to stroke subtypes

	PA user ($n=401$)	Non-PA user ($n=1461$)	P value*
Total	7.6 ± 2.5	8.2 ± 2.9	<0.001
Atherothrombosis	7.2 ± 2.1	8.9 ± 2.7	<0.001
Small artery disease	4.9 ± 1.8	5.1 ± 2.1	0.056
Cardioembolism	11.8 ± 3.6	12.1 ± 4.2	0.146

PA, prestroke aspirin; NIHSS, National Institutes of Health Stroke Scale.

Table 3. The association between PA use and outcomes

	PA user ($n=401$)	Non-PA user ($n=1461$)	P value*
Clincial outcome (n, %)			
END			
Total	60 (15.0)	332 (22.7)	0.002
Atherothrombosis	32 (8.0)	168 (11.5)	0.047
Small artery disease	14 (3.5)	91 (6.2)	0.039
Cardioembolism	14 (3.5)	73 (5.0)	0.198
RIS	16 (4.0)	64 (4.4)	0.621
MI	5 (1.2)	10 (0.7)	0.899
Death	16 (4.0)	16 (1.1)	0.968
Hemorrhagic episodes (n, %)			
HT	50 (12.5)	108 (7.4)	0.002
Asymptomatic HT	40 (10.0)	81 (5.5)	0.003
Symptomatic HT	10 (2.5)	27 (1.8)	0.418
ICH	4 (1.0)	11 (0.8)	0.633
Extracranial bleeding	9 (2.2)	31 (2.1)	0.965
mRS scores ≤2 at 3 months (n, %)			
Total	317 (79.1)	1029 (70.4)	<0.001
Atherothrombosis	151 (37.7)	548 (37.5)	0.039
Small artery disease	81 (20.2)	294 (20.1)	0.044
Cardioembolism	85 (21.2)	187 (12.8)	0.029

PA, prestroke aspirin; END, early neurological deterioration; RIS, recurrent ischemic stroke; MI, myocardial infarction; mRS, modified Rankin Scale; HT, hemorrhagic transformation; ICT, intracerebral hemorrhage.

95% CI: 0.72−0.92; $P=0.002$, **Table 4**).

HT occurred in 158 patients (8.5%) within two weeks after admission, 50 (12.5%) occurred in the PA users, and 108 (7.4%) occurred in the non-PA users. HT was more frequently observed in the PA users compared to the non-PA users ($P=0.002$ for univariate analysis, **Table 3**). However, PA use was only associated with increased risk for asymptomatic HT; there were no significant differences in the percentage of symptomatic HT, ICH, and extracranial bleeding between the PA users and non-PA users. The increased risk of HT with PA use was significant in the Cox proportional hazard regression with additional adjustments for covariates, including age, hypertension, diabetes mellitus, hemoglobin A1c, NIHSS scores on admission, previous statins use, hyperlipidemia, CE subtype, and thrombolysis (HR: 1.38; 95% CI: 1.08-3.04; $P=0.022$, **Table 5**).

Good functional outcomes were defined as mRS scores ≤2 points at three months after admission. The percentage of good functional outcomes was significantly higher in the PA users than the non-PA users (79.1% vs. 70.4%, $P<0.001$ for univariate analysis, **Table 3**). PA users could improve functional outcome at three months despite an increase of HT, irrespective of stroke subtype (**Table 3**). The multivariable logistic regression revealed that PA use was significantly associated with good functional outcomes at three months

Table 4. Cox regression analysis the effect of prestroke aspirin use on early neurological deterioration

Factor	HR	95% CI	*P* value
Age	0.73	0.67−1.28	0.624
Diabetes mellitus	1.82	1.03−4.12	0.026
Hypertension	1.36	0.94−2.68	0.585
Hemoglobin A1C	1.48	0.98−3.27	0.108
Previous statins	0.78	0.72−1.45	0.327
Hyperlipidemia	1.01	0.66−1.62	0.488
NIHSS scores on admission	0.99	0.87−1.57	0.536
Stroke subtype	0.69	0.62−1.36	0.134
Thrombolysis	1.01	0.87−2.15	0.235
Prestroke aspirin	0.78	0.72−0.92	0.002

NIHSS, National Institutes of Health Stroke Scale; HR, hazard ratio; CI, confidence interval.
HR for continuous variables means per 1- Standard Deviation increase.

Table 5. Cox regression analysis the effect of prestroke aspirin use on hemorrhagic transformation

Factor	HR	95% CI	*P* value
Age	0.74	0.62−1.26	0.533
Diabetes mellitus	0.91	0.87−1.69	0.385
Hypertension	1.02	0.97−1.33	0.132
Hemoglobin A1C	0.79	0.61−1.18	0.627
NIHSS scores on admission	1.32	1.01−2.06	0.039
Previous statins	0.88	0.81−1.42	0.624
Hyperlipidemia	0.68	0.85−1.21	0.522
CE subtype	1.41	1.05−2.56	0.016
Thrombolysis	1.44	1.13−3.34	0.011
Prestroke aspirin	1.38	1.08−3.04	0.022

NIHSS, National Institutes of Health Stroke Scale; CE, Cardioembolism; HR, hazard ratio; CI, confidence interval.
HR for continuous variables means per 1- Standard Deviation increase.

after admission after adjusting for covariates (odds ratio: 1.46; 95% CI: 1.12−2.56; $P=0.023$, **Table 6**).

Discussion

The main findings in the present study were: (1) there was a beneficial effect of PA use in relation to the reduction of initial stroke severity according to stroke subtypes. The effect was evident in AT stroke, but not in SAD or CE stroke; (2) PA use was independently associated with the decreased risk of END within ten days after admission; (3) PA use increased the risk of HT. However, it was only associated with increased risk for asymptomatic HT, but not for symptomatic HT; (4) PA use was associated with good functional outcome (mRS scores ≤2 points) at three months after admission irrespective of stroke subtypes, despite the increased risk of HT.

Current guidelines recommend oral administration of aspirin within 48 hours of stroke onset in patients with acute IS to reduce mortality and unfavorable outcomes[23]. However, the effect of PA use on initial stroke severity is controversial. Some studies have demonstrated that strokes are less severe in patients already taking aspirin[4-7], whereas some others have not shown an association between PA use and initial stroke severity[8-11]. Our current results showed that PA use may reduce initial stroke severity. Aspirin may benefit patients with acute IS by improving the microcirculation in the ischemic penumbra through inhibition of platelet-derived vasoconstrictors, such as thromboxane A2 (TXA2)[24, 25]. In addition, aspirin may limit clot size, extent of thrombosis, and subsequent embolism[26]. Anti-inflammatory and neuroprotective effects of aspirin can be expected as other beneficial mechanisms for acute IS[27-29].

Our results also revealed that that the effect of PA use on reducing stroke impairment differed by stroke

Table 6. Logistic regression analysis the effect of prestroke aspirin use on good functional outcome at 3 months after admission

Factor	OR	95% CI	*P* value
Age	0.87	0.68−1.42	0.637
Diabetes mellitus	0.86	0.72−1.17	0.623
Hypertension	1.01	0.92−1.85	0.564
NIHSS scores on admission	0.92	0.80−1.56	0.443
Hemorrhagic transformation	0.77	0.66−1.18	0.211
Early neurological deterioration	0.68	0.61−0.98	0.041
Previous statins	0.81	0.72−1.24	0.556
Stroke subtype	0.75	0.68−1.32	0.266
Thrombolysis	1.54	1.21−2.88	0.016
Prestroke aspirin	1.46	1.12−2.56	0.023

NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.
OR for continuous variables means per 1- Standard Deviation increase.

subtypes: the effect was evident in AT stroke but not in SAD or CE stroke. Different from MI, artery to-artery embolism is a very important mechanism of AT stroke[30]. Aspirin may reduce not only the possibility of embolization from an unstable plaque but also the size of emboli[31]. Thus, antiplatelet therapy may be less beneficial in SAD and CE stroke than AT stroke. Intensive antiplatelet therapy may increase the risk of bleeding in patients with SAD stroke[32]. Atrial fibrillation is the most common cause of CE stroke; a meta-analysis and recent guidelines suggested no or minimal effects of aspirin, especially for primary prevention of stroke[33, 34]. All of these results support our findings that PA use is more beneficial in patients with AT than other stroke subtypes.

END is a devastating complication associated with poor prognosis after acute IS[13, 14]. It is very important to prevent END in acute IS patients. Our previous studies have shown that dual therapy with aspirin and clopidogrel is more effective in reducing END risk in acute IS[15-17]. The present results showed that PA use was associated with the decreased risk of END after acute IS. Platelet activation, thrombus extension, and proinflammatory cytokines play key roles in the pathogenesis of END[35, 36]. Our previous study has demonstrated that PA users may provide greater inhibition of platelet activity than non-PA users[18]. Because of its antithrombotic and anti-inflammatory properties, inhibition of platelet-derived vasoconstrictors, improvement microcirculation in the ischemic penumbra, and neuroprotective effect, aspirin may protect against thrombus extension and subsequent embolism, same-territory recurrent embolization, and reocclusions[25-29, 37]. These potential mechanisms might contribute to reduced incidence of END.

It is well known that HT is expected to worsen clinical outcome in IS patients. Aspirin use is associated with an increased risk of bleeding, including gastrointestinal bleeding, HT, and ICH. Our current results showed PA use was independently associated with increased risk of HT. However, stratified analysis revealed that PA use was only significantly associated with an increased risk of asymptomatic HT, and there was no association between PA use and symptomatic HT. Furthermore, although PA use increased the risk of HT, it was associated with better functional outcomes irrespective of stroke subtypes. These results were consistent with some other studies[7, 38]. Our findings suggest that persons already taking aspirin may have better outcomes associated with acute IS than those who are not already taking aspirin despite increased risk of HT.

Intravenous tissue plasminogen activator (tPA) is known to improve outcomes in acute IS; however, many patients may have been receiving aspirin therapy before acute IS and face an increased risk for bleeding when treated with tPA. Some studies have demonstrated that the risk of symptomatic ICH and HT after intravenous thrombolysis was higher in the PA users compared with the non-PA users; however, the risk was small compared with the benefits of thrombolysis[39, 40]. Among patients with acute IS treated with intravenous tPA, those receiving antiplatelet therapy before the stroke had a higher risk for symptomatic ICH but better functional outcomes than those who were not receiving antiplatelet therapy[39]. These studies agreed with our current results. Thus, PA use prior to tPA-bolus should not be used as a reason to withhold in acute IS patients treated with intravenous thrombolysis[41].

Although prestroke aspirin could ameliorate initial stroke severity only in AT stroke. PA use was asso-

ciated with good functional outcome at three months after admission irrespective of stroke subtype. It is well known that initial stroke severity may be as a predictor of stroke functional outcomes[42]. Apart from initial stroke severity, many other factors may affect functional outcome after IS, such as platelet activation and END[13, 15]. Platelet activation may increase atherogenesis and promote injuries in blood vessel walls and plays a crucial role in thrombus extension[15, 43].

Our previous study has shown that END is fairly common in acute IS and is associated with poor prognosis[13]. The current results showed that PA use reduced the incidence of END in SAD subtype and AT subtype. These may be the reasons that PA use improved functional outcomes in SAD subtype and AT subtype, though there was no significant difference in the incidence of END between the PA users and non-PA users in the CE subtype. PA use was also associated with good functional outcomes at three months after admission. The reasons are unclear. One recent study revealed that preceding antiplatelet therapy was associated with good outcomes in IS patients with atrial fibrillation[44]. This was consistent with our current results. However, further studies are necessary to better understand the relationship.

Our current study has several limitations. First, this is a prospective, multicenter observational, cohort study, and the PA use was not randomized. Baseline characteristics were quite different between the PA and non-PA users, as observed previously[45]. Although we attempted to control confounding using multivariable logistic regression analysis and Cox proportional hazard regression analysis, we could not eliminate bias because of imbalance baseline characteristics. Second, the lack of randomization for PA use still leads to the possibility of unknown sources of biases that may have influenced the findings of this observational study. It is possible that the unmeasured or unknown confounders may influence the results. Third, initial stroke severity was evaluated by NIHSS score on admission in this study. However, we did not assess initial infarct size, as we did not know the association between PA use and initial infarct size. Finally, aspirin has anti-inflammatory and antithrombotic effects. However, platelet activity and inflammatory cytokines were not measured in the present study. Thus, well-designed studies are needed to validate our current findings in future.

In conclusion, this study suggests that PA use may reduce initial stroke severity, at least for AT stroke. The effects of PA use may act differently according to stroke mechanisms on reducing stroke severity. PA use may also decrease the risk of END and improve functional outcomes irrespective of stroke subtypes. Although PA use increased the risk of HT, it was associated with better functional outcomes at three months after admission, suggesting that PA use has a beneficial effect. Further studies should be necessary in the future.

Sources of Funding

This study was supported in part by grants from the Sichuan Science and Technology Agency Research Foundation (Grant No.2018JY0164), Deyang City Science and Technology Research Foundation (Grant No. 2014SZ035) and Scientific Research Foundation of Chengdu University of Traditional Chinese Medicine (Grant No.YYZX1510).

Conflict of Interest

The authors declare no conflicts of interest.

References

1) Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA: Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2014; 45: 3754-3832
2) Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A: Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lance, 2009; 373: 1849-1860
3) Bartolucci AA, Tendera M, Howard G: Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. Am J Cardiol, 2011; 107: 1796-1801
4) Sanossian N, Saver JL, Rajajee V, Selco SL, Kim D, Razinia T, Ovbiagele B: Premorbid antiplatelet use and ischemic stroke outcomes. Neurology, 2006; 66: 319-323
5) Jung JM, Choi J, Eun MY, Seo WK, Cho KH, Yu S, Oh K, Hong S, Park KY: Prestroke antiplatelet agents in first-ever ischemic stroke: clinical effects. Neurology, 2015; 84: 1080-1089
6) O'Donnell M, Oczkowski W, Fang J, Kearon C, Silva J, Bradley C, Guyatt G, Gould L, D'Uva C, Kapral M, Silver F: Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol, 2006; 5: 749-754
7) Park JM, Kang K, Cho YJ, Hong KS, Lee KB, Park TH, Lee SJ, Ko Y, Han MK, Lee J, Cha JK, Kim DH, Kim DE, Kim JT, Choi JC, Yu KH, Lee BC, Lee JS, Lee J, Gorelick PB, Bae HJ: Comparative Effectiveness of Prestroke Aspirin on Stroke Severity and Outcome. Ann Neurol, 2016; 79: 560-568
8) Paciaroni M, Agnelli G, Caso V, Venti M, Alberti A, Milia

P, Silvestrelli G, Biagini S: Prior use of antithrombotic agents and neurological functional outcome at discharge in patients with ischemic stroke. J Thromb Haemost, 2006; 4: 1957-1961
9) Rist PM, Buring JE, Kase CS, Kurth T: Effect of low-dose aspirin on functional outcome from cerebral vascular events in women. Stroke, 2013; 44: 432-436
10) Ricci S, Lewis S, Sandercock P; IST Collaborative Group: Previous use of aspirin and baseline stroke severity: an analysis of 17850 patients in the International Stroke Trial. Stroke, 2006; 37: 1737-1740
11) Kim WJ, Ko Y, Yang MH, Im SH, Park JH, Lee J, Lee J, Han MK, Bae HJ: Differential effect of previous antiplatelet use on stroke severity according to stroke mechanism. Stroke, 2010; 41: 1200-1204
12) Lees KR, Bath PMW, Schellinger PD, Kerr DM, Fulton R, Hacke W, Matchar D, Sehra R, Toni D: Contemporary outcome measures in acute stroke research: choice of primary outcome measure. Stroke, 2012; 43: 1163-1170
13) Yi X, Han Z, Zhou Q, Lin J, Liu P: 20-Hydroxyeicosatetraenoic Acid as a Predictor of Neurological Deterioration in Acute Minor Ischemic Stroke. Stroke, 2016; 47: 3045-3047
14) Vahidy FS, Hicks WJ 2nd, Acosta I, Hallevi H, Peng H, Pandurengan R, Gonzales NR, Barreto AD, Martin-Schild S, Wu TC, Rahbar MH, Bambhroliya AB, Grotta JC, Savitz SI: Neurofluctuation in patients with subcortical ischemic stroke. Neurology, 2014; 83: 398-405
15) Wang C, Yi X, Zhang B, Liao D, Lin J, Chi L: Clopidogrel plus aspirin prevents early neurologic deterioration and improves 6-month outcome in patients with acute large artery atherosclerosis stroke. Clin Appl Thromb Hemost, 2015; 21: 453-461
16) Yi X, Lin J, Wang C, Zhang B, Chi W: A comparative study of dual versus monoantiplatelet therapy in patients with acute large-artery atherosclerosis stroke. J Stroke Cerebrovasc Dis, 2014; 23: 1975-1981
17) Yi X, Wang C, Liu P, Fu C, Lin J, Chen Y: Antiplatelet drug resistance is associated with early neurological deterioration in acute minor ischemic stroke in the Chinese population. J Neurol, 2016; 263: 1612-1629
18) Yi X, Han Z, Wang C, Zhou Q, Lin J: Statin and Aspirin Pretreatment Are Associated with Lower Neurological Deterioration and Platelet Activity in Patients with Acute Ischemic Stroke. J Stroke Cerebrovasc Dis, 2017; 26: 352-359
19) Bufalino VJ, Masoudi FA, Stranne SK, Horton K, Albert NM, Beam C, Bonow RO, Davenport RL, Girgus M, Fonarow GC, Krumholz HM, Legnini MW, Lewis WR, Nichol G, Peterson ED, Rumsfeld JS, Schwamm LH, Shahian DM, Spertus JA, Woodard PK, Yancy CW: The American Heart Association's recommendations for expanding the applications of existing and future clinical registries: a policy statement from the American Heart Association. Circulation, 2011; 123: 2167-2179
20) Han SW, Kim SH, Lee JY, Chu CK, Yang JH, Shin HY, Nam HS, Lee BI, Heo JH: A new subtype classification of ischemic stroke based on treatment and etiologic mechanism. Eur Neurol, 2007; 57: 96-102
21) Toni D, Fiorelli M, Bastianello S, Sacchetti ML, Sette G, Argentino C, Montinaro E, Bozzao L: Hemorrhagic transformation of brain infarcts: predictability in the first 5 hours from stroke onset and influence on clinical outcome. Neurology, 1996; 46: 341-345
22) Scott SC, Goldberg MS, Mayo NE: Statistical assessment of ordinal outcomes in comparative studies. J Clin Epidemiol, 1997; 50: 45-55
23) Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell D: 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 2018; 49: e46-e110
24) Rosenblum WI, El-Sabban F: Platelet aggregation in the cerebral microcirculation: effect of aspirin and other agents. Circ Res, 1977; 40: 320-328
25) Joseph R, D'Andrea G, Oster SB, Welch KM: Whole blood platelet function in acute ischemic stroke. Importance of dense body secretion and effects of antithrombotic agents. Stroke, 1989; 20: 38-44
26) Joseph R, Han E, Tsering C, Grunfeld S, Welch KM: Platelet activity and stroke severity. J Neurol Sci, 1992; 108: 1-6
27) Riepe MW, Kasischke K, Raupach A: Acetylsalicylic acid increases tolerance against hypoxic and chemical hypoxia. Stroke, 1997; 28: 2006-2011
28) Grilli M, Pizzi M, Memo M, Spano P: Neuroprotection by aspirin and sodium salicylate through blockade of NF-jB activation. Science, 1996; 274: 1383-1385
29) Kuhn W, Muller T, Bttner T, Gerlach M: Aspirin as a free radical scavenger: consequences for therapy of cerebrovascular ischemia. Stroke, 1995; 26: 1959-1960
30) Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, Barnett HJ: The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med, 2000; 342: 1693-1700
31) Grotta JC, Lemak NA, Gary H, Fields WS, Vital D: Does platelet antiaggregant therapy lessen the severity of stroke? Neurology, 1985; 35: 632-636
32) The SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA: Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med, 2012; 367: 817-825
33) Hart RG, Pearce LA, Aguilar MI: Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med, 2007; 146: 857-867
34) January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation, 2014; 130: e199-e267
35) Vila N, Castillo J, Davalos A, Chamorro A: Proinflamma-

tory cytokines and early neurological worsening in ischemic stroke. Stroke, 2000; 31: 2325-2329
36) Yi X, Lin J, Wang Y, Zhou J, Zhou Q, Wang C: Response to clopidogrel is associated with early neurological deterioration after acute ischemic stroke. Oncotarget, 2018; 9: 19900-19910
37) Saqqur M, Molina CA, Salam A, Siddiqui M, Ribo M, Uchino K, Calleja S, Garami Z, Khan K, Akhtar N, O'Rourke F, Shuaib A, Demchuk AM, Alexandrov AV: Clinical deterioration after intravenous recombinant tissue plasminogen activator treatment: a multicenter transcranial Doppler study. Stroke, 2007; 38: 69-74
38) Jung JM, Choi J, Eun MY, Seo WK, Cho KH, Yu S, Oh K, Hong S, Park KY: Prestroke antiplatelet agents in first-ever ischemic stroke: clinical effects. Neurology, 2015; 84: 1080-1089
39) Diedler J, Ahmed N, Sykora M, Uyttenboogaart M, Overgaard K, Luijckx GJ, Soinne L, Ford GA, Lees KR, Wahlgren N, Ringleb P: Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset. Stroke, 2010; 41: 288-294
40) Xian Y, Federspiel JJ, Grau-Sepulveda M, Hernandez AF, Schwamm LH, Bhatt DL, Smith EE, Reeves MJ, Thomas L, Webb L, Bettger JP, Laskowitz DT, Fonarow GC, Peterson ED: Risks and Benefits Associated With Prestroke Antiplatelet Therapy Among Patients With Acute Ischemic Stroke Treated With Intravenous Tissue Plasminogen Activator. JAMA Neurol, 2016; 73: 50-59
41) Tsivgoulis G, Katsanos AH, Zand R, Sharma VK, Köhrmann M, Giannopoulos S, Dardiotis E, Alexandrov AW, Mitsias PD, Schellinger PD, Alexandrov AV: Antiplatelet pretreatment and outcomes in intravenous thrombolysis for stroke: a systematic review and meta-analysis. J Neurol, 2017; 264: 1227-1235
42) Wouters A, Nysten C, Thijs V, Lemmens R: Prediction of Outcome in Patients With Acute Ischemic Stroke Based on Initial Severity and Improvement in the First 24 h. Front Neurol , 2018; 9: 308
43) Fateh-Moghadam S, Li Z, Ersel S, Reuter T, Htun P, Plockinger U, Bocksch W, Dietz R, Gawaz M: Platelet degranulation is associated with progression of intima-media thickness of the common carotid artery in patients with diabetes mellitus type 2. Arterioscler Thromb Vasc Biol 2005; 25: 1299-1303
44) Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, Bhatt DL, Smith EE, Olson DM, Maisch L, Hannah D, Lindholm B, Lytle BL, Pencina MJ, Hernandez AF, Peterson ED: Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation. JAMA, 2017; 317: 1057-1067
45) Paciaroni M, Agnelli G, Caso V, Venti M, Alberti A, Milia P, Silvestrelli G, Biagini S: Prior use of antithrombotic agents and neurological functional outcome at discharge in patients with ischemic stroke. J Thromb Haemost, 2006; 4: 1957-1961