Prior antiplatelet therapy, excluding phosphodiesterase inhibitor is associated with poor outcome in patients with spontaneous intracerebral haemorrhage

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Abstract

There is conflicting results on whether prior antiplatelet therapy (APT) is associated with poor outcome in spontaneous intracerebral haemorrhage (ICH) patients. To determine whether prior APT is associated with spontaneous ICH, and whether there is a difference between the different types of APT, including cyclooxygenase inhibitor (COX-I), adenosine diphosphate receptor inhibitor (ADP-I), and phosphodiesterase inhibitor (PDE-I). A retrospective study of patients with ICH diagnosed between 2001 and 2013 in the National Health Insurance Research Database. Baseline unbalance between APT and non-APT groups was solved by multivariable adjustment (primary analysis) and propensity score matching (sensitivity analysis). Patients with prior APT had a higher rate of in-hospital death (odds ratio [OR], 1.16; 95% confidence interval [CI], 1.09–1.23) compared to non-APT group. Compared to non-APT group, there was a greater rate of in-hospital death with spontaneous ICH with ADP-I (OR, 1.49; 95% CI, 1.24–1.79), and COX-I (OR, 1.17; 95% CI, 1.09–1.25). PDE-I exhibited no difference in in-hospital death with spontaneous ICH (OR, 1.03; 95% CI, 0.91–1.16) compared to non-APT group. Remarkably, the in-hospital mortality rate was significantly higher in the ADP-I group than in the PDE-I group (hazard ratio, 1.45; 95% CI, 1.17–1.80). In this study, ADP-I and COX-1, but not PDE-I is the most likely contributors to the association of APT with poor outcome with spontaneous ICH patients. These findings suggest the complexity of the different mechanism of actions of prior APT can alter the outcome in spontaneous ICH.

Introduction

Platelets are essential for normal haemostasis, but can also be involved in thrombosis. Antiplatelet therapy (APT) has recently gained popularity due to its reported beneficial effects in cardiovascular and cerebrovascular diseases. However, platelet dysfunction as measured by platelet function assays has been associated with hematoma expansion and worse clinical outcome [1].

Recent studies have suggested that there is a higher risk factor for intracerebral haemorrhage (ICH) patients under APT treatment associated with poor clinical outcome in the setting of both spontaneous [2] as well as traumatic ICH [3, 4]. Furthermore, several studies have revealed higher rates of progression of initial ICH in patients on APT [5]. However, the association of APT with ICH outcome from these studies remains controversial, possibly due to differences in sample size, demographics, methodology, and statistical analysis [6, 7]

Interestingly, given there are several forms of APT, few studies have investigated the type of antiplatelet agents to the clinical outcomes. Studies assessing the impact of APT in this cohort of patients generally have grouped all the antiplatelet mediations into one group without considering the different types of antiplatelet medications. However, the different mechanism of action of the different antiplatelet agents may cause variable outcomes. Therefore, we proposed to study the association of prior use of different groups of APT on patients with ICH in a real world setting, using Taiwan's National Health Insurance Research Database (NHIRD).

Methods

Data source

A nationwide population-based cohort study using Taiwan's National Health Insurance Research Database (NHIRD) was conducted. It consisted of standard computerized claims document that covers nearly 100% of the 23.7 million residents of Taiwan [8]. This is a comprehensive health-related database for each patient include demographic characteristics, medical diagnoses, surgical procedure, blood transfusion, and details of all prescriptions. Accuracy and validation of NHIRD data are based on regular auditing claims by the National Health Insurance Bureau. Personal identities have been encrypted for privacy protection, but all data sets could be linked with anonymous identifiers created for research purpose. Therefore, the study was completely exempt from ethics review by the ethics institutional review board of Chang Gung Memorial Hospital (Taiwan).

Study population

In this study, eligible patients was screened from hospitalization records by principal diagnosis, which was recorded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9 CM) codes. Eligible patients from the NHIRD were identified as those admitted for first event of cerebrovascular accident from January 1, 2001 and December 31, 2013 (ICD-9 CM codes, 430–437) (Supplemental Table 1). Within this cohort of patients with cerebrovascular accident, we excluded patients with incomplete medical record and were admitted without the diagnosis of spontaneous intracerebral haemorrhage (ICH). We also excluded the comorbidities where the conditions can possibly interfere with coagulation conditions, such as coagulopathy, liver cirrhosis, malignancy and autoimmune disease predating the index date. In order to compare the effect of different type single antiplatelet regiment on ICH patients, we retrieved the patient's claim data from outpatient clinics or refilling prescription at pharmacies 3 months before the index admission. According to prescription record system, we excluded the patients who were under anticoagulant or with combined APT treatment. Overall, 97,335 patients with ICH qualified for this study.

Exposure of antithrombotic therapy

The study population was divided into APT and non-APT groups according to prescription record system. According to different pharmacological effect of antiplatelet agents, eligible patients were further divided into three groups (i) irreversible cyclooxygenase inhibitors (COX-

I): Aspirin, (ii) Adenosine diphosphate receptor inhibitor (ADP-I): clopidorgrel or ticlopidine, (iii) Phosphodiesterase inhibitor (PDE-I): dipyridamole or cilostazol.

Comorbidities and outcome measurement

We extracted the baseline patient's characteristics, including gender age, hospital level, monthly income, and urbanization level. We also obtained medical records before the index admission to track their history of comorbidities and major events. Charlson comorbidity index (CCI) scores were used to determinate overall systemic health [9]. Estimated National Institute of Health Stroke Scale (NIHSS) was applied to access the severity of haemorrhagic stroke, which was validated in a previous NHIRD study [10]. To identify neurosurgical procedures and in-hospital events, ICD-9-CM and NHI reimbursement codes during the index hospitalization were used. Accuracy of ICD-9-CM, NHI reimbursement codes and identification of comorbidity of NHIRD have been validated in patients with cerebrovascular events [11, 12]. The outcomes of interest in this study included antiplatelet related complication, in-hospital mortality, and long-term outcome including all-cause mortality, recurrent ICH and ischemic stroke within 6 months after the index hospitalization. Patients were followed from their index admission date to date of event occurrence, or December 31 2013, or death.

Statistical analysis

Risks of in-hospital outcomes among the study groups were compared using logistic regression analyses. Risks of time to event outcomes during a 6-month follow up among groups were compared using Cox proportional hazard models. The regression analyses were adjusted for all the covariates, including sex, age, hospital level, income and urbanization level, seven coexisting diseases, prior ischemic stroke, prior myocardial infarction and stroke severity index via NIHSS, four neurosurgical procedures during the index hospitalization, and the index year. There were seven pairwise comparisons among the study groups (APT vs. Non-APT; and the six pairwise comparisons among the non-APT and different APT groups), therefore to avoid type 1 errors, a Bonferroni adjustment with a statistical significance $p < 0.0071$ (0.05/7) was used.

To assess the robustness of the primary analysis, we additionally conducted propensity score matching (PSM) as the sensitivity analysis. The propensity score was the predicted probability of being in the APT group given the values of all the aforementioned covariates. Each patient in the APT group was matched with a counterpart in the non-APT group. We adopted a greedy nearest neighbour algorithm and the caliper was set as 0.2 times the standard deviation of

the logit of propensity score [13]. The quality of matching was checked using the absolute standardized mean difference (ASMD) between the groups after matching, where a value less than 0.1 was considered to have a non-substantially difference between the groups [14]. Risks of in-hospital outcomes or time to event outcomes during a 6-month follow up between the APT and non-APT groups were compared using univariate logistic regression or univariate Cox model in which robust standard error was used to account for the outcome dependency within the same matching pairs. Additional adjustment of covariates due to possible imbalance of covariates was carried out when comparing the non-APT and different APT groups. Data analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of study population

After applying a series of exclusion criteria, a total of 97,355 patients with ICH were identified of whom 11,351 received APT and 86,004 received non-APT prior accident (Figure 1). Patients under APT treatment were divided into three groups according to the different types of APT prescribed before onset of ICH. Patients with APT treatment were either under COX-I (aspirin), ADP-I (clopidogrel or ticlopidine), or PGE-I (dipyridamole or cilostazol). The number of APT users were 8,282, 741 and 2,328 patients in the COX-I, ADP-I and PDE-I groups, respectively.

Within the 86,004 ICH patients without APT, the mean age (± SD) was 61.4 (14.8) years, and 64.4% were male (Table 1). However, the patients who received APT were generally older (mean age ± SD) in age (COX-I: 68.5 ± 12.1, ADP-1 71.8 ± 11.3, PDE-1: 70.0 ± 12.5), slightly more females, and had a substantial higher prevalence of many comorbidities than non-APT patients (Table 1). Among the 11,351 patients under APT, the patients received ADP-I were older than the other two groups (COX-I and PDE-I) (Table 1). Furthermore, the prevalence of hypertension, diabetes, dyslipidaemia, coronary artery disease, arterial fibrillation was substantially higher in the ADP-I group compared to other two APT groups. The PDE-I group had a higher prevalence of peripheral arterial disease than did the other two APT group. Furthermore, based on NIHSS, the severity of neurologic deficit was higher, and required surgical intervention after admission in the patients with prior ADP-I treatment compared to the other two groups (Table 1).

Events during index hospitalization

The event number and rate of various outcomes during index hospitalization in non-APT and different APT groups were studied (Supplemental Table 2). Patients under prior APT treatment had significantly higher in-hospital mortality rate than those without APT (odds ratio [OR], 1.16; 95% confidence interval [CI], 1.09–1.23) when the covariates listed in Table 1 were adjusted (Table 2). In comparison with non-APT group, significantly higher in-hospital mortality was noted in patients that had received COX-I (OR, 1.17; 95% CI, 1.09–1.25) or ADP-I (OR, 1.49; 95% CI, 1.24–1.79), but not with PDE-I (OR, 1.03; 95% CI, 0.91–1.16) (Table 2). Remarkably, the in-hospital mortality rate was significantly higher in the ADP-I group than in the PDE-I group (hazard ratio, 1.45; 95% CI, 1.17–1.80) (Table 2). Furthermore, a higher risk of in-hospital mortality was observed for the ADP-I group when compared to the COX-I group

(OR, 1.28; 95% CI, 1.06–1.54), but was not statistically significant (*P* = 0.012) after Bonferroni adjustment (Table 2).

In comparison to the non-APT group, patients with APT treatment appeared to have significantly higher risk to develop an ischemic stroke (OR, 1.18; 95% CI, 1.07–1.30) during hospitalization, especially those with COX-I treatment (OR, 1.17; 95% CI, 1.05–1.31) (Table 2). In addition, no significant difference in the risk of perioperative gastrointestinal bleeding among the groups was observed.

Follow-up outcomes of ICH

The event number and rate of various follow-up outcomes of ICH in each group were studied (Supplemental Table 2). No significant difference in risk of 6-month all-cause mortality was found between the APT and non-APT groups (Supplemental Table 2). Of note, the ADP-I group had a higher risk of mortaliy compared to the non-APT (hazard ratio [HR], 1.18; 95% CI, 1.05–1.33], and a non-significant trend compared to COX-I (HR, 1.14; 95% CI, 1.01–1.29, p=0.037), and PDE-I (HR, 1.19; 95% CI, 1.04–1.37, p=0.011) after Bonferroni adjustment (Supplemental Table 3). In contrast, comparison of all four groups did not significantly show difference in the risk of new occurrence ischemic or haemorrhagic stroke during the six-month follow-up (Supplemental Table 3).

Sensitivity analysis

After PSM, the 11,285 patients in both APT and non-APT groups showed no significant difference (ASMD < 0.1) in all the demographic and comorbidities such as gender, ages, morbidities, hospital level, patient income, or urbanization level (Table 3). Furthermore, the APT group did not received more surgical intervention compared to the non-APT group (Table 3). Baseline characteristics of ICH patients (Supplemental Table 4), and event number and rate (Supplemental Table 5) in the non-APT and difference APT groups were analysed. Comparison between all the groups showed no differences with in-hospital outcomes or 6-months follow-up outcomes (Supplemental Table 4 & 5). The results of propensity score matching were less statistically significant due to the smaller sample size after matching (Table 4 and Supplemental Table 6).

Discussion

Primary result

Our study involving 22,702 ICH patients in Taiwan demonstrated significant increase in-hospital mortality and adverse event at 6-months follow-up outcome in those ICH patients with prior APT compared to those without prior APT. Therefore, these results support the hypothesis that APT treatment prior ICH contribute to poor clinical outcome. However, the different types of prior APT treatment has various impact on the ICH patients' poor outcome and mortality.

Prior APT treatment associated with ICH

Recently, APT treatment is often prescribed for both primary and secondary prevention of atherothrombotic vascular events, myocardial infarction, and vascular death. The correlation of prior APT treatment on ICH outcomes has been debated extensively based on inconsistent results. Some studies has demonstrated that APT plays a role in worsening of neurologic outcome and progression of haemorrhage size [15], but others have found that only combined APT contribute to poor clinical outcome [2]. It has been suggested that the differences in the outcomes could be associated with sample size, demographics, methodology, exclusion criteria and statistical analysis in study design [16]. However, we suggest there are two main possibilities that may explain the heterogeneous results across studies. First, the underlying disease in patients receiving APT, and second, the various mechanism of actions of the different APT. The mechanism of action for COX-I, such as aspirin is to irreversibly inhibit cyclooxygenase required for prostaglandin H2 formation, which promote blood clotting [17]. Another popular group of APT is the ADP-I, such as clopidogrel and ticlopidine, which irreversibly inhibits the P2Y12 subtype of ADP receptor, resulting in inhibition of platelet activation and fibrin cross-linking [18]. The third group of APT is the PDE-I, such as cilostazol and dipyridamole, which inhibit platelet aggregation due to increase cAMP via inhibition of phosphodiesterase [19]. Therefore, in our study, we minimized the risk of confounding by determining baseline characteristics of all ICH patients and using PSM to adjust for differences in the comparison groups. Furthermore, since different type of APT have different mechanism of action that may pose different level of ICH risk, we compared the clinical outcome among different types of APT. To date, this current study is the only national-base study, which analysis the risk of different types of prior APT used in ICH patients.

Several randomized studies have tried to determine if prehospital APT use is correlated with clinical outcome and ICH volume [6, 26]. In these studies, the use of any antiplatelet medication was considered as one research arm. However, it is unlikely that different antiplatelet medication with different mechanism of actions mentioned previously will have the same risk in ICH patients. Patients taking COX-I accounts for the largest group of APT user in previous studies. Another popular antiplatelet agent is ADP-I, which is often used in conjunction with COX-I, aspirin in patients with at high risk for ischemic events or patients with allergies or intolerances to aspirin [27]. Another group of APT is PDE-I, such as cilostazol or dipyridamole, which has been approved for use as a vasodilation antiplatelet drug. Cilostazol has been reported to be more effective than COX-I in the secondary prevention of all types of stroke, especially secondary haemorrhagic stroke in a clinical trial [31]. Also, a recent study also showed Cilostazol was non-inferior to aspirin for the prevention of cardiovascular events in patients with ischemic stroke [32].

In our study, we assessed the effects of prior administration of various types of APT on patients with ICH, which yielded several important results. First, COX-I and ADP-I group, but not PDE-I group have significantly higher in-hospital mortality rate compared with non-APT group. These results appear to be consistent with those of clinical studies suggesting that ADP-I is associated with poor neurologic outcome in ICH patients (refs). The absence in poor outcome with PDE-I could be due to the additional beneficial effects of inhibiting the phosphodiesterase enzyme. Apart from blocking platelet aggregation, PDE-I can also inhibit cellular reuptake of adenosine into erythrocytes, resulting in an increase in extracellular adenosine [33]. Adenosine is clinically used in supraventricular tachycardia management and recently have been shown to have neuroprotective properties in stroke [34]. Second, our result also suggested the significant increased mortality risk is confined to patients receiving ADP-I treatment in comparison with COX-I and PDE-I groups. Recently, several studies have focus on the ADP-I effect on the intracranial haemorrhage. Wong and colleagues demonstrated higher rates of progression in patients on clopidogrel therapy in comparison with aspirin (COX-I) and warfarin (deplete vitamin K required for synthesis of active clotting factor) therapy [35]. Interestingly, aspirin exhibited more hematoma expansion and higher in-hospital mortality rates at 3 months in one retrospective study [36]. Third, although overall mortality has no difference between APT and non-APT treatments during 6-months follow-up in our study, the ICH patients receiving prior ADP-I had significantly higher mortality rate than non-APT ICH patients. All these results appear to be consistent in suggesting that the ADP-I is

associated with a poor neurologic outcome in ICH patients. Although the reason for this is not known, a possible explanation is that platelet functional recovery is stable after COX-I is withdrawn for 5 days, but, there is variable platelet function recovery in patients with ADP-I treatment [37]. Fourth, a reduced mortality of survivors during the index hospitalization of prior COX-I treatment compared to the other groups was observed. This finding was unexpected and the reason for this is unknown. However, this could be due to COX-I have the additional benefits of anti-inflammation, analgesia and reduction in fever [38].

Limitations

We acknowledge that our study also has several limitations. First, the health insurance database that we used was developed for administrative purposes rather than from direct data collection. The NHIRD does not contain information of ICH details, such as severity, amount of bleeding, bleeding area, and size, which may bias the estimates. However, the CCI scores and estimated NIHSS were used to partially address this limitation. Second, the database only provided information on the frequency and classes of prescribed medications and did not provide detailed clinical information, so, we could only estimate the indication of drug administration. Third, the database did not contain information on various lifestyle risk factors for haemorrhagic stroke, such as physical activity, alcohol consumption, smoking, body mass index, socioeconomic status and diet, which could have a negative impact on the ICH were not included in the analysis. Although we adjusted the potential covariates, such as co-morbidities and the use of other medications, the misclassification of these covariates could still have some impact on our results. Fifth, a majority of the patients were of Chinese origin in this study. The pharmacodynamics and pharmacokinetics of clopidogrel have interpatient variability related to ethic background, so this could limit their correlative value to non-Chinese background patients [39].

Conclusion

Our findings indicate that prior use of APT treatment is likely to be associated with higher in-hospital mortality after ICH, especially patients under prior ADP-I, such as clopidogrel and ticlopidine treatment. Furthermore, in 6-months follow-up, prior ADP-I treatment significantly

increased over-all mortality in ICH patients. Our data suggest that the various effects observed are contributed by the various mechanism of actions of the antiplatelet agents. Future studies must address APT as individual drug types and not combine into a single entity.

Figure legends

Figure 1

Flow chart of the study patient selection. Patients with cerebrovascular accident admitted for hemorrhage stroke were included after relevant exclusions. After PSM 1:1 matching, patients without prior APT was selected. Spontaneous ICH patients receiving APT were further divided into three groups (COX-I, ADP-I, and PDE-I) according to the prior different medication treatment.

Abbreviation: PSM, propensity score matching; APT, anti-platelet therapy; ICH, intracerebral hemorrhage; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, irreversible cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor.

Compliance with Ethical Standards

The authors declare that they have no competing financial interests. This work was supported by the Chang Gung Memorial Hospital (CMRPG3H1061, CMRPG3G1002) grant number This study was exempt from approval requirements by the Institutional Review Board of Chang Gung Memorial Hospital in Taiwan (IRB number, 201601518B0) and without permission of patient's consent, given that it was an epidemiology study with no definable patient information.

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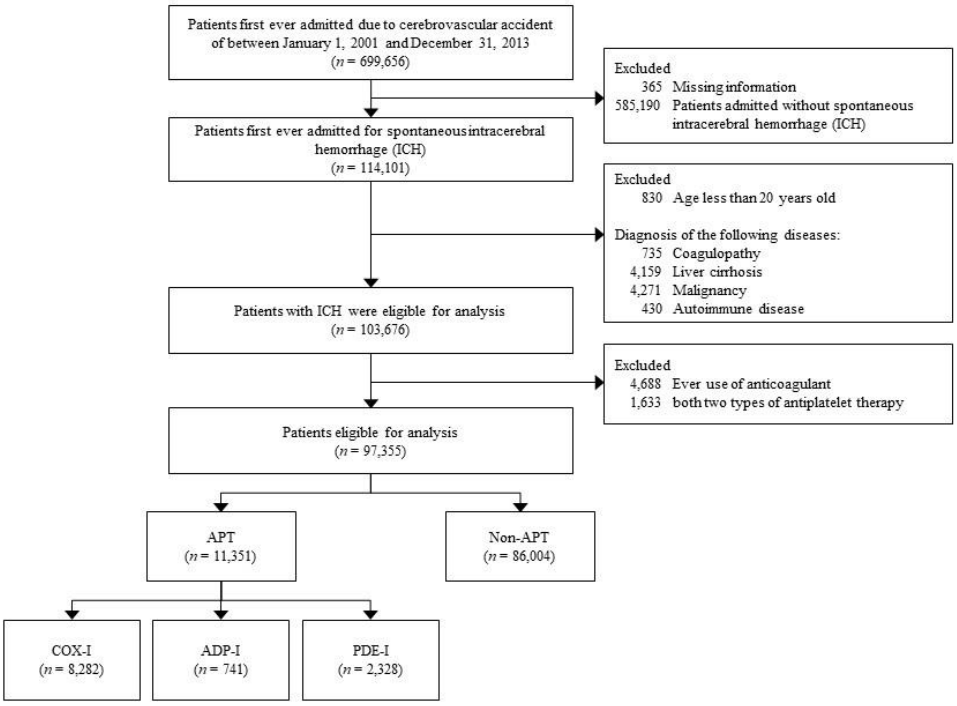

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Table 1. Baseline characteristics of ICH patients that had received prior APT and non-APT treatment.

Variable	Non-APT (n = 86,004)	COX-I (n = 8,282)	ADP-I (n = 741)	PDE-I (n = 2,328)
Sex				
Male	55,416 (64.4)	5,001 (60.4)	439 (59.2)	1,247 (53.6)
Female	30,588 (35.6)	3,281 (39.6)	302 (40.8)	1,081 (46.4)
Age (years)	61.4±14.8	68.5±12.1	71.8±11.3	70.0±12.5
Age group				
20-39	5,949 (6.9)	91 (1.1)	4 (0.5)	35 (1.5)
40-59	35,850 (41.7)	1,976 (23.9)	118 (15.9)	483 (20.7)
60-79	33,831 (39.3)	4,722 (57.0)	423 (57.1)	1,285 (55.2)
≥ 80	10,374 (12.1)	1,493 (18.0)	196 (26.5)	525 (22.6)
Operation in teaching hospital	31,245 (36.3)	3,067 (37.0)	291 (39.3)	795 (34.1)
Income, NTD				
≤ 17880	37,470 (43.6)	3,863 (46.6)	384 (51.8)	1,063 (45.7)
17881–22800	33,312 (38.7)	3,273 (39.5)	285 (38.5)	1,040 (44.7)
> 22800	15,222 (17.7)	1,146 (13.8)	72 (9.7)	225 (9.7)
Urbanization level				
Low	10,755 (12.5)	993 (12.0)	85 (11.5)	325 (14.0)
Moderate	26,479 (30.8)	2,476 (29.9)	215 (29.0)	757 (32.5)
High	29,701 (34.5)	2,891 (34.9)	259 (35.0)	764 (32.8)
Very high	19,069 (22.2)	1,922 (23.2)	182 (24.6)	482 (20.7)
Coexisting disease				
Hypertension	25,308 (29.4)	6,302 (76.1)	572 (77.2)	1,544 (66.3)
Diabetes mellitus	8,038 (9.3)	2,514 (30.4)	257 (34.7)	663 (28.5)
Dyslipidemia	3,876 (4.5)	1,509 (18.2)	167 (22.5)	282 (12.1)
Coronary artery disease	6,401 (7.4)	2,836 (34.2)	305 (41.2)	645 (27.7)
Atrial fibrillation	1,254 (1.5)	474 (5.7)	75 (10.1)	95 (4.1)
Peripheral arterial disease	882 (1.0)	277 (3.3)	29 (3.9)	119 (5.1)
Chronic kidney disease or dialysis	3,968 (4.6)	643 (7.8)	126 (17.0)	392 (16.8)
History of major event				
Ischemic stroke	3,430 (4.0)	1,021 (12.3)	190 (25.6)	206 (8.8)
Myocardial infarction	712 (0.8)	341 (4.1)	67 (9.0)	41 (1.8)
Charlson Comorbidity Index	1.9±1.3	2.5±1.6	3.1±1.9	2.9±1.8
Estimated NIHSS	17.0±7.2	16.8±7.7	18.4±7.2	16.6±7.6
Estimated NIHSS group				
≤ 5	6,451 (7.5)	906 (10.9)	53 (7.2)	242 (10.4)
5 < NIHSS ≤ 13	21,315 (24.8)	1,916 (23.1)	125 (16.9)	558 (24.0)
> 13	58,238 (67.7)	5,460 (65.9)	563 (76.0)	1,528 (65.6)
Neurosurgical procedure during the index hospitalization				
Craniotomy	17,317 (20.1)	1,427 (17.2)	137 (18.5)	347 (14.9)
Craniectomy	1,597 (1.9)	136 (1.6)	15 (2.0)	30 (1.3)
EVD or ICP	18,480 (21.5)	1,630 (19.7)	156 (21.1)	404 (17.4)
Aspiration	1,390 (1.6)	85 (1.0)	8 (1.1)	20 (0.9)
Follow up years	3.8±3.7	3.4±3.6	2.4±3.1	3.4±3.7

Abbreviation: ICH, intracerebral hemorrhage; APT, anti-platelet therapy; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor; NTD, New Taiwan Dollar; NIHSS, National Institute of Health Stroke Scale; EVD, external ventricular drain; ICP, intracranial pressure.

Table 2. In-hospital outcome

Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
In-hospital death				
APT vs. Non-APT	1.29 (1.23–1.36)	<0.001	1.16 (1.09–1.23)	<0.001†
COX-I vs. Non-APT	1.25 (1.18–1.32)	<0.001	1.17 (1.09–1.25)	<0.001†
ADP-I vs. Non-APT	2.03 (1.73–2.38)	<0.001	1.49 (1.24–1.79)	<0.001†
PDE-I vs. Non-APT	1.24 (1.12–1.37)	<0.001	1.03 (0.91–1.16)	0.658
ADP-I vs. COX-I	1.63 (1.38–1.92)	<0.001	1.28 (1.06–1.54)	0.012
PDE-I vs. COX-I	0.99 (0.88–1.11)	0.870	0.88 (0.77–1.004)	0.057
ADP-I vs. PDE-I	1.64 (1.36–1.98)	<0.001	1.45 (1.17–1.80)	<0.001†
Gastrointestinal bleeding				
APT vs. Non-APT	1.01 (0.93–1.09)	0.896	0.95 (0.87–1.04)	0.227
COX-I vs. Non-APT	0.95 (0.86–1.04)	0.285	0.92 (0.83–1.02)	0.125
ADP-I vs. Non-APT	1.30 (0.99–1.70)	0.056	1.05 (0.79–1.38)	0.744
PDE-I vs. Non-APT	1.12 (0.95–1.31)	0.191	0.99 (0.84–1.18)	0.919
ADP-I vs. COX-I	1.37 (1.03–1.81)	0.029	1.14 (0.85–1.52)	0.386
PDE-I vs. COX-I	1.17 (0.98–1.41)	0.088	1.08 (0.89–1.30)	0.454
ADP-I vs. PDE-I	1.17 (0.85–1.59)	0.335	1.06 (0.77–1.45)	0.735
Ischemic stroke				
APT vs. Non-APT	1.36 (1.24–1.48)	<0.001	1.18 (1.07–1.30)	0.001†
COX-I vs. Non-APT	1.36 (1.23–1.50)	<0.001	1.17 (1.05–1.31)	0.005†
ADP-I vs. Non-APT	1.57 (1.16–2.12)	0.003	1.25 (0.92–1.70)	0.161
PDE-I vs. Non-APT	1.28 (1.06–1.54)	0.011	1.18 (0.97–1.43)	0.091
ADP-I vs. COX-I	1.16 (0.84–1.58)	0.368	1.07 (0.78–1.46)	0.694
PDE-I vs. COX-I	0.94 (0.76–1.16)	0.558	1.01 (0.82–1.25)	0.929
ADP-I vs. PDE-I	1.23 (0.87–1.75)	0.250	1.06 (0.74–1.50)	0.765

Abbreviation: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; APT, anti-platelet therapy; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor;

* Adjusted for sex, age, hospital level, income and urbanization level, seven coexisting diseases, prior ischemic stroke, prior myocardial infarction and stroke severity index (NIHSS), four neurosurgical procedures during the index hospitalization and the index year;

† Statistical significance after Bonferroni adjustment (*P* <0.0071).

Table 3. Baseline characteristics of the study patients according to APT before and after propensity score matching.

	Before matching			After matching		
Variable	APT (n = 11,351)	Non-APT (n = 86,004)	ASMD	APT (n = 11,285)	Non-APT (n = 11,285)	ASMD
Sex						
Male	6,687 (58.9)	55,416 (64.4)	0.114	6,647 (58.9)	6,517 (57.7)	0.023
Female	4,664 (41.1)	30,588 (35.6)	0.114	4,638 (41.1)	4,768 (42.3)	0.023
Age (years)	69.1±12.1	61.4±14.8	0.568	69.0±12.2	69.4±12.2	0.031
Age group						
20-39	130 (1.1)	5,949 (6.9)	0.297	130 (1.2)	98 (0.9)	0.028
40-59	2,577 (22.7)	35,850 (41.7)	0.415	2,577 (22.8)	2,507 (22.2)	0.015
60-79	6,430 (56.6)	33,831 (39.3)	0.352	6,386 (56.6)	6,436 (57.0)	0.009
≥ 80	2,214 (19.5)	10,374 (12.1)	0.205	2,192 (19.4)	2,244 (19.9)	0.012
Operation in teaching hospital	4,153 (36.6)	31,245 (36.3)	0.005	4,131 (36.6)	4,081 (36.2)	0.009
Income, NTD						
≤ 17880	5,310 (46.8)	37,470 (43.6)	0.065	5,267 (46.7)	5,200 (46.1)	0.012
17881–22800	4,598 (40.5)	33,312 (38.7)	0.036	4,579 (40.6)	4,705 (41.7)	0.023
> 22800	1,443 (12.7)	15,222 (17.7)	0.139	1,439 (12.8)	1,380 (12.2)	0.016
Urbanization level						
Low	1,403 (12.4)	10,755 (12.5)	0.004	1,396 (12.4)	1,471 (13.0)	0.020
Moderate	3,448 (30.4)	26,479 (30.8)	0.009	3,432 (30.4)	3,493 (31.0)	0.012
High	3,914 (34.5)	29,701 (34.5)	0.001	3,890 (34.5)	3,804 (33.7)	0.016
Very high	2,586 (22.8)	19,069 (22.2)	0.015	2,567 (22.7)	2,517 (22.3)	0.011
Coexisting disease						
Hypertension	8,418 (74.2)	25,308 (29.4)	1.001	8,352 (74.0)	8,688 (77.0)	0.069
Diabetes mellitus	3,434 (30.3)	8,038 (9.3)	0.544	3,383 (30.0)	3,267 (28.9)	0.023
Dyslipidemia	1,958 (17.2)	3,876 (4.5)	0.418	1,920 (17.0)	1,816 (16.1)	0.025
Coronary artery disease	3,786 (33.4)	6,401 (7.4)	0.679	3,722 (33.0)	3,411 (30.2)	0.059
Atrial fibrillation	644 (5.7)	1,254 (1.5)	0.229	626 (5.5)	534 (4.7)	0.037
Peripheral arterial disease	425 (3.7)	882 (1.0)	0.179	417 (3.7)	378 (3.3)	0.019
Chronic kidney disease or dialysis	1,161 (10.2)	3,968 (4.6)	0.215	1,144 (10.1)	1,151 (10.2)	0.002
History of major event						
Ischemic stroke	1,417 (12.5)	3,430 (4.0)	0.313	1,390 (12.3)	1,369 (12.1)	0.006
Myocardial infarction	449 (4.0)	712 (0.8)	0.206	434 (3.8)	372 (3.3)	0.030
Charlson Comorbidity Index	2.6±1.7	1.9±1.3	0.476	2.6±1.7	2.6±1.6	0.011
Estimated NIHSS	16.9±7.6	17.0±7.2	0.019	16.9±7.6	16.8±7.5	0.011
Estimated NIHSS group						
≤ 5	1,201 (10.6)	6,451 (7.5)	0.108	1,191 (10.6)	1,219 (10.8)	0.008
5 < NIHSS ≤ 13	2,599 (22.9)	21,315 (24.8)	0.044	2,587 (22.9)	2,628 (23.3)	0.009
> 13	7,551 (66.5)	58,238 (67.7)	0.025	7,507 (66.5)	7,438 (65.9)	0.013
Neurosurgical procedure during the index hospitalization						
Craniotomy	1,911 (16.8)	17,317 (20.1)	0.085	1,901 (16.8)	1,856 (16.4)	0.011
Craniectomy	181 (1.6)	1,597 (1.9)	0.020	181 (1.6)	201 (1.8)	0.014
EVD or ICP	2,190 (19.3)	18,480 (21.5)	0.054	2,178 (19.3)	2,123 (18.8)	0.012
Aspiration	113 (1.0)	1,390 (1.6)	0.055	112 (1.0)	104 (0.9)	0.007
Follow up years	3.4±3.6	3.8±3.7	0.135	3.4±3.6	3.4±3.6	0.012

Abbreviation: APT, anti-platelet therapy; ASMD, absolute standardized mean difference; NTD, New Taiwan Dollar; NIHSS, National Institute of Health Stroke Scale; EVD, external ventricular drain; ICP, intracranial pressure.

Table 4. In-hospital outcomes in the propensity score matched cohort (sensitivity analysis).

	Unadjusted model		Fully-adjusted model*	
Outcome / contrast	OR (95% CI)	*P*	aOR (95% CI)	*P*
In-hospital death				
APT vs. Non-APT	1.12 (1.05–1.19)	0.001	1.12 (1.05–1.19)#	0.001†
COX-I vs. Non-APT	1.08 (1.01–1.16)	0.035	1.13 (1.05–1.23)	0.002†
ADP-I vs. Non-APT	1.73 (1.47–2.05)	<0.001	1.40 (1.16–1.69)	<0.001†
PDE-I vs. Non-APT	1.07 (0.96–1.20)	0.231	0.99 (0.87–1.12)	0.884
ADP-I vs. COX-I	1.61 (1.36–1.90)	<0.001	1.24 (1.02–1.49)	0.029
PDE-I vs. COX-I	0.99 (0.89–1.11)	0.886	0.87 (0.77–0.99)	0.043
ADP-I vs. PDE-I	1.62 (1.34–1.96)	<0.001	1.41 (1.14–1.75)	0.002†
Gastrointestinal bleeding				
APT vs. Non-APT	0.92 (0.83–1.03)	0.137	0.92 (0.83–1.03)#	0.137
COX-I vs. Non-APT	0.87 (0.78–0.98)	0.022	0.89 (0.79–0.99)	0.049
ADP-I vs. Non-APT	1.21 (0.92–1.59)	0.177	1.04 (0.79–1.39)	0.764
PDE-I vs. Non-APT	1.02 (0.85–1.21)	0.850	0.96 (0.80–1.15)	0.631
ADP-I vs. COX-I	1.39 (1.05–1.84)	0.023	1.18 (0.88–1.57)	0.268
PDE-I vs. COX-I	1.17 (0.97–1.40)	0.103	1.08 (0.89–1.30)	0.439
ADP-I vs. PDE-I	1.19 (0.87–1.62)	0.275	1.09 (0.79–1.50)	0.590
Ischemic stroke				
APT vs. Non-APT	1.19 (1.05–1.34)	0.006	1.19 (1.05–1.34)#	0.006†
COX-I vs. Non-APT	1.18 (1.04–1.35)	0.011	1.16 (1.02–1.32)	0.026
ADP-I vs. Non-APT	1.40 (1.03–1.92)	0.033	1.31 (0.96–1.80)	0.093
PDE-I vs. Non-APT	1.13 (0.92–1.38)	0.255	1.19 (0.97–1.46)	0.105
ADP-I vs. COX-I	1.19 (0.87–1.62)	0.288	1.13 (0.82–1.55)	0.452
PDE-I vs. COX-I	0.95 (0.77–1.17)	0.636	1.02 (0.83–1.26)	0.833
ADP-I vs. PDE-I	1.25 (0.88–1.77)	0.219	1.10 (0.77–1.58)	0.586

Abbreviation: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; APT, anti-platelet therapy; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor;

* Adjusted for sex, age, hospital level, income and urbanization level, seven coexisting diseases, prior ischemic stroke, prior myocardial infarction and stroke severity index (NIHSS), four neurosurgical procedures during the index hospitalization and the index year;

The study group (APT vs. Non-APT) was the only explanatory variable without additional adjustment;

† Statistical significance after Bonferroni adjustment (P <0.0071).

488 Suppl.1

Supplement Table 1. ICD-9-CM code used in the current study

Variable	Code
Cerebrovascular accident	430.xx–437.xx
Intracerebral hemorrhage	431.xx
Coagulopathy	286.0–286.9, 287.1, 287.3–287.5, 289.81–289.82
Liver cirrhosis	571.2, 571.5, 571.6
Malignancy	140.xx–208.xx (Catastrophic illness card)
Autoimmune disease	710.0, 710.1, 714.0, 710.4, 710.3, 446.0, 446.2, 446.4, 446.5, 443.1, 446.7, 136.1, 694.4, 710.2, 555.xx, 556.xx, 714.30–714.33
Hypertension	401.xx–405.xx
Diabetes mellitus	250.xx
Dyslipidemia	272.xx
Coronary artery disease	410.xx–414.xx
Atrial fibrillation	427.31
Peripheral arterial disease	440.0x, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x, 444.22, 444.8x, 447.8x, 447.9x
Chronic kidney disease	580.xx–589.xx, 403.xx–404.xx, 016.0x, 095.4x, 236.9x, 250.4x, 274.1x, 442.1x, 447.3x, 440.1x, 572.4x, 642.1x, 646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Dialysis	585.xx (Catastrophic illness certificate)
Ischemic stroke	433.xx–435.xx
Myocardial infarction	410.xx
Gastrointestinal bleeding	530.21, 530.7, 530.82, 531.xx–534.xx, 535.xx, 537.83, 537.84, and 578.xx

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

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492 Suppl. 2

Supplemental Table 2. Event rate of in-hospital and long-term outcomes

	Number of event (%)				
Outcome	Non-APT (n = 86,004)	APT (n = 11,351)	COX-I (n = 8,282)	ADP-I (n = 741)	PDE-I (n = 2,328)
In-hospital outcome					
In-hospital death	14,876 (17.3)	2,417 (21.3)	1,717 (20.7)	221 (29.8)	479 (20.6)
Gastrointestinal bleeding	5,375 (6.2)	713 (6.3)	493 (6.0)	59 (8.0)	161 (6.9)
Ischemic stroke	3,484 (4.1)	614 (5.4)	449 (5.4)	46 (6.2)	119 (5.1)
Long-term outcome§					
All-cause mortality	20,316 (23.6)	3,340 (29.4)	2,343 (28.3)	295 (39.8)	702 (30.2)
Intracerebral hemorrhage	12,541 (14.6)	1,523 (13.4)	1,132 (13.7)	91 (12.3)	300 (12.9)
Ischemic stroke	3,417 (4.0)	570 (5.0)	416 (5.0)	37 (5.0)	117 (5.0)

§ 6-month follow up;

Abbreviation: APT, anti-platelet therapy; COX-I, cyclooxygenase inhibitor; ADP-I, adenosine diphosphate receptor inhibitor; PDE-I, phosphodiesterase inhibitor.

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495 Suppl. 3

Supplemental Table 3. Time to event outcomes during a 6-month follow up

	Unadjusted model		Fully-adjusted model*	
Outcome / contrast	HR (95% CI)	*P*	aHR (95% CI)	*P*
All-cause mortality				
APT vs. Non-APT	1.27 (1.22, 1.31)	<0.001	1.04 (0.998–1.08)	0.062
COX-I vs. Non-APT	1.21 (1.16, 1.27)	<0.001	1.04 (0.99–1.09)	0.097
ADP-I vs. Non-APT	1.78 (1.59, 2.00)	<0.001	1.18 (1.05–1.33)	0.005†
PDE-I vs. Non-APT	1.30 (1.20, 1.40)	<0.001	0.99 (0.92–1.07)	0.819
ADP-I vs. COX-I	1.47 (1.30, 1.66)	<0.001	1.14 (1.01–1.29)	0.037
PDI vs. COX-I	1.07 (0.98, 1.16)	0.133	0.95 (0.88–1.04)	0.267
ADP-I vs. PDE-I	1.38 (1.20, 1.58)	<0.001	1.19 (1.04–1.37)	0.011
Recurrent intracerebral hemorrhage				
APT vs. Non-APT	0.93 (0.88, 0.98)	0.009	0.97 (0.92–1.03)	0.371
COX-I vs. Non-APT	0.95 (0.89, 1.01)	0.075	0.98 (0.92–1.05)	0.624
ADP-I vs. Non-APT	0.89 (0.72, 1.09)	0.249	0.94 (0.76–1.15)	0.537
PDE-I vs. Non-APT	0.89 (0.80, 1.00)	0.049	0.95 (0.85–1.07)	0.382
ADP-I vs. COX-I	0.94 (0.76, 1.16)	0.544	0.95 (0.77–1.18)	0.652
PDE-I vs. COX-I	0.94 (0.83, 1.07)	0.357	0.97 (0.85–1.10)	0.585
ADP-I vs. PDE-I	0.99 (0.79, 1.26)	0.958	0.99 (0.78–1.25)	0.909
Ischemic stroke				
APT vs. Non-APT	1.33 (1.22, 1.45)	<0.001	1.08 (0.98–1.19)	0.139
COX-I vs. Non-APT	1.32 (1.19, 1.46)	<0.001	1.08 (0.97–1.21)	0.168
ADP-I vs. Non-APT	1.47 (1.07, 2.04)	0.019	1.18 (0.85–1.64)	0.329
PDE-I vs. Non-APT	1.32 (1.10, 1.59)	0.003	1.04 (0.86–1.25)	0.701
ADP-I vs. COX-I	1.12 (0.80, 1.56)	0.524	1.09 (0.78–1.53)	0.615
PDE-I vs. COX-I	1.000 (0.82, 1.23)	0.996	0.96 (0.78–1.18)	0.700
ADP-I vs. PDE-I	1.12 (0.77, 1.61)	0.564	1.14 (0.78–1.65)	0.502

Abbreviation: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; APT, anti-platelet therapy; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor;

* Adjusted for sex, age, hospital level, income and urbanization level, seven coexisting diseases, prior ischemic stroke, prior myocardial infarction and stroke severity index (NIHSS), four neurosurgical procedures during the index hospitalization and the index year;

† Reached statistical significance after Bonferroni adjustment (*P* <0.0071).

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Supplemental Table 4. Baseline characteristics of ICH patients that had received prior APT and non-APT treatment in the propensity score matched cohort.

Variable	Non-APT (*n* = 11,285)	COX-I (*n* = 8,236)	ADP-I (*n* = 729)	PDE-I (*n* = 2,320)
Sex				
Male	6,517 (57.7)	4,971 (60.4)	433 (59.4)	1,243 (53.6)
Female	4,768 (42.3)	3,265 (39.6)	296 (40.6)	1,077 (46.4)
Age (years)	69.4±12.2	68.5±12.1	71.8±11.3	70.0±12.5
Age group				
20-39	98 (0.9)	91 (1.1)	4 (0.5)	35 (1.5)
40-59	2,507 (22.2)	1,976 (24.0)	118 (16.2)	483 (20.8)
60-79	6,436 (57.0)	4,689 (56.9)	416 (57.1)	1,281 (55.2)
≥ 80	2,244 (19.9)	1,480 (18.0)	191 (26.2)	521 (22.5)
Operation in teaching hospital	4,081 (36.2)	3,051 (37.0)	286 (39.2)	794 (34.2)
Income, NTD				
≤ 17880	5,200 (46.1)	3,834 (46.6)	375 (51.4)	1,058 (45.6)
17881–22800	4,705 (41.7)	3,258 (39.6)	282 (38.7)	1,039 (44.8)
> 22800	1,380 (12.2)	1,144 (13.9)	72 (9.9)	223 (9.6)
Urbanization level				
Low	1,471 (13.0)	987 (12.0)	84 (11.5)	325 (14.0)
Moderate	3,493 (31.0)	2,467 (30.0)	211 (28.9)	754 (32.5)
High	3,804 (33.7)	2,874 (34.9)	255 (35.0)	761 (32.8)
Very high	2,517 (22.3)	1,908 (23.2)	179 (24.6)	480 (20.7)

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Variable	Non-APT (*n* = 11,285)	COX-I (*n* = 8,236)	ADP-I (*n* = 729)	PDE-I (*n* = 2,320)
Coexisting disease				
Hypertension	8,688 (77.0)	6,256 (76.0)	560 (76.8)	1,536 (66.2)
Diabetes mellitus	3,267 (28.9)	2,476 (30.1)	248 (34.0)	659 (28.4)
Dyslipidemia	1,816 (16.1)	1,482 (18.0)	159 (21.8)	279 (12.0)
Coronary artery disease	3,411 (30.2)	2,792 (33.9)	293 (40.2)	637 (27.5)
Atrial fibrillation	534 (4.7)	464 (5.6)	69 (9.5)	93 (4.0)
Peripheral arterial disease	378 (3.3)	272 (3.3)	28 (3.8)	117 (5.0)
Chronic kidney disease or dialysis	1,151 (10.2)	633 (7.7)	121 (16.6)	390 (16.8)
History of major event				
Ischemic stroke	1,369 (12.1)	1,001 (12.2)	188 (25.8)	201 (8.7)
Myocardial infarction	372 (3.3)	332 (4.0)	63 (8.6)	39 (1.7)
Charlson Comorbidity Index	2.6±1.6	2.5±1.6	3.1±1.9	2.9±1.8
Estimated NIHSS	16.8±7.5	16.8±7.7	18.4±7.1	16.6±7.6
Estimated NIHSS group				
≤ 5	1,219 (10.8)	898 (10.9)	51 (7.0)	242 (10.4)
5 < NIHSS ≤ 13	2,628 (23.3)	1,906 (23.1)	125 (17.1)	556 (24.0)
> 13	7,438 (65.9)	5,432 (66.0)	553 (75.9)	1,522 (65.6)
Neurosurgical procedure during the index hospitalization				
Craniotomy	1,856 (16.4)	1,423 (17.3)	133 (18.2)	345 (14.9)
Craniectomy	201 (1.8)	136 (1.7)	15 (2.1)	30 (1.3)

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Variable	Non-APT (*n* = 11,285)	COX-I (*n* = 8,236)	ADP-I (*n* = 729)	PDE-I (*n* = 2,320)
EVD or ICP	2,123 (18.8)	1,623 (19.7)	153 (21.0)	402 (17.3)
Aspiration	104 (0.9)	84 (1.0)	8 (1.1)	20 (0.9)
Follow up years	3.4±3.6	3.4±3.6	2.5±3.2	3.4±3.7

Abbreviation: ICH, intracerebral hemorrhage; APT, anti-platelet therapy; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor; NTD, New Taiwan Dollar; NIHSS, National Institute of Health Stroke Scale; EVD, external ventricular drain; ICP, intracranial pressure.

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Supplemental Table 5. Event rate of in-hospital and long-term outcomes in the propensity score matched cohort.

	Number of event (%)				
Outcome	Non-APT (n = 11,285)	APT (n = 11,285)	COX-I (n = 8,236)	ADP-I (n = 729)	PDE-I (n = 2,320)
In-hospital outcome					
In-hospital death	2,193 (19.4)	2,392 (21.2)	1,701 (20.7)	215 (29.5)	476 (20.5)
Gastrointestinal bleeding	766 (6.8)	711 (6.3)	492 (6.0)	59 (8.1)	160 (6.9)
Ischemic stroke	517 (4.6)	608 (5.4)	443 (5.4)	46 (6.3)	119 (5.1)
Long-term outcome§					
All-cause mortality	3,220 (28.5)	3,309 (29.3)	2,323 (28.2)	288 (39.5)	698 (30.1)
Intracerebral hemorrhage	1,565 (13.9)	1,516 (13.4)	1,127 (13.7)	90 (12.3)	299 (12.9)
Ischemic stroke	549 (4.9)	567 (5.0)	413 (5.0)	37 (5.1)	117 (5.0)

§ 6-month follow up;

Abbreviation: APT, anti-platelet therapy; COX-I, cyclooxygenase inhibitor; ADP-I, adenosine diphosphate receptor inhibitor; PDE-I, phosphodiesterase inhibitor.

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Supplemental Table 6. Time to event outcomes during a 6-month follow up in the propensity score matched cohort.

	Unadjusted model		Fully-adjusted model*	
Outcome / contrast	HR (95% CI)	*P*	aHR (95% CI)	*P*
All-cause mortality				
APT vs. Non-APT	1.03 (0.99, 1.08)	0.153	-	-
COX-I vs. Non-APT	0.99 (0.94, 1.05)	0.736	1.02 (0.97–1.08)	0.450
ADP-I vs. Non-APT	1.45 (1.29, 1.64)	<0.001	1.16 (1.03–1.31)	0.016
PDE-I vs. Non-APT	1.06 (0.98, 1.15)	0.175	0.97 (0.89–1.05)	0.446
ADP-I vs. COX-I	1.47 (1.30, 1.66)	<0.001	1.14 (1.01–1.29)	0.042
PDI vs. COX-I	1.07 (0.98, 1.16)	0.128	0.95 (0.87–1.03)	0.229
ADP-I vs. PDE-I	1.37 (1.20, 1.58)	<0.001	1.20 (1.04–1.38)	0.011
Recurrent intracerebral hemorrhage				
APT vs. Non-APT	0.97 (0.91, 1.04)	0.432	-	-
COX-I vs. Non-APT	0.99 (0.92, 1.07)	0.760	0.98 (0.91–1.06)	0.610
ADP-I vs. Non-APT	0.93 (0.75, 1.15)	0.506	0.92 (0.75–1.14)	0.464
PDE-I vs. Non-APT	0.93 (0.82, 1.05)	0.250	0.94 (0.83–1.06)	0.301
ADP-I vs. COX-I	0.94 (0.76, 1.17)	0.583	0.94 (0.76–1.17)	0.587
PDE-I vs. COX-I	0.94 (0.83, 1.07)	0.351	0.96 (0.84–1.09)	0.487
ADP-I vs. PDE-I	1.001 (0.79, 1.27)	0.996	0.99 (0.78–1.25)	0.908
Ischemic stroke				
APT vs. Non-APT	1.05 (0.93, 1.18)	0.428	-	-
COX-I vs. Non-APT	1.04 (0.91, 1.18)	0.558	1.06 (0.93–1.20)	0.408
ADP-I vs. Non-APT	1.18 (0.85, 1.65)	0.327	1.20 (0.86–1.68)	0.278
PDE-I vs. Non-APT	1.05 (0.86, 1.28)	0.663	0.99 (0.81–1.21)	0.943
ADP-I vs. COX-I	1.14 (0.81, 1.59)	0.455	1.14 (0.81–1.60)	0.447
PDE-I vs. COX-I	1.01 (0.82, 1.24)	0.953	0.94 (0.76–1.16)	0.563
ADP-I vs. PDE-I	1.13 (0.78, 1.64)	0.517	1.21 (0.84–1.76)	0.311

Abbreviation: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; APT, anti-platelet therapy; ADP-I, adenosine diphosphate receptor inhibitor; COX-I, cyclooxygenase inhibitor; PDE-I, phosphodiesterase inhibitor;

* Adjusted for sex, age, hospital level, income and urbanization level, seven coexisting diseases, prior ischemic stroke, prior myocardial infarction and stroke severity index (NIHSS), four neurosurgical procedures during the index hospitalization and the index year;

The study group (APT vs. Non-APT) was the only explanatory variable without additional adjustment;

† Reached statistical significance after Bonferroni adjustment (*P* <0.0071).

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