

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

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40

41 **Abstract**

42

43 There is conflicting results on whether prior antiplatelet therapy (APT) is associated with poor
44 outcome in spontaneous intracerebral haemorrhage (ICH) patients. To determine whether
45 prior APT is associated with spontaneous ICH, and whether there is a difference between the
46 different types of APT, including cyclooxygenase inhibitor (COX-I), adenosine diphosphate
47 receptor inhibitor (ADP-I), and phosphodiesterase inhibitor (PDE-I). A retrospective study of
48 patients with ICH diagnosed between 2001 and 2013 in the National Health Insurance
49 Research Database. Baseline unbalance between APT and non-APT groups was solved by
50 multivariable adjustment (primary analysis) and propensity score matching (sensitivity
51 analysis). Patients with prior APT had a higher rate of in-hospital death (odds ratio [OR], 1.16;
52 95% confidence interval [CI], 1.09–1.23) compared to non-APT group. Compared to non-APT
53 group, there was a greater rate of in-hospital death with spontaneous ICH with ADP-I (OR,
54 1.49; 95% CI, 1.24–1.79), and COX-I (OR, 1.17; 95% CI, 1.09–1.25). PDE-I exhibited no
55 difference in in-hospital death with spontaneous ICH (OR, 1.03; 95% CI, 0.91–1.16) compared
56 to non-APT group. Remarkably, the in-hospital mortality rate was significantly higher in the
57 ADP-I group than in the PDE-I group (hazard ratio, 1.45; 95% CI, 1.17–1.80). In this study, ADP-
58 I and COX-1, but not PDE-I is the most likely contributors to the association of APT with poor
59 outcome with spontaneous ICH patients. These findings suggest the complexity of the
60 different mechanism of actions of prior APT can alter the outcome in spontaneous ICH.

61

62 **Introduction**

63

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

69

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

76

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

85

86

87 **Methods**

88 **Data source**

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

99 **Study population**

100 In this study, eligible patients was screened from hospitalization records by principal diagnosis,
101 which was recorded according to the International Classification of Disease, Ninth Revision,
102 Clinical Modification (ICD-9 CM) codes. Eligible patients from the NHIRD were identified as
103 those admitted for first event of cerebrovascular accident from January 1, 2001 and December
104 31, 2013 (ICD-9 CM codes, 430–437) (Supplemental Table 1). Within this cohort of patients
105 with cerebrovascular accident, we excluded patients with incomplete medical record and
106 were admitted without the diagnosis of spontaneous intracerebral haemorrhage (ICH). We
107 also excluded the comorbidities where the conditions can possibly interfere with coagulation
108 conditions, such as coagulopathy, liver cirrhosis, malignancy and autoimmune disease
109 predating the index date. In order to compare the effect of different type single antiplatelet
110 regiment on ICH patients, we retrieved the patient's claim data from outpatient clinics or
111 refilling prescription at pharmacies 3 months before the index admission. According to
112 prescription record system, we excluded the patients who were under anticoagulant or with
113 combined APT treatment. Overall, 97,335 patients with ICH qualified for this study.

114 **Exposure of antithrombotic therapy**

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

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

120 **Comorbidities and outcome measurement**

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

134 **Statistical analysis**

135 Risks of in-hospital outcomes among the study groups were compared using logistic
136 regression analyses. Risks of time to event outcomes during a 6-month follow up among
137 groups were compared using Cox proportional hazard models. The regression analyses were
138 adjusted for all the covariates, including sex, age, hospital level, income and urbanization level,
139 seven coexisting diseases, prior ischemic stroke, prior myocardial infarction and stroke
140 severity index via NIHSS, four neurosurgical procedures during the index hospitalization, and
141 the index year. There were seven pairwise comparisons among the study groups (APT vs. Non-
142 APT; and the six pairwise comparisons among the non-APT and different APT groups),
143 therefore to avoid type 1 errors, a Bonferroni adjustment with a statistical significance $p <$
144 0.0071 ($0.05/7$) was used.

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

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

159

160

161 **Results**

162 **Characteristics of study population**

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

169 Within the 86,004 ICH patients without APT, the mean age (\pm SD) was 61.4 (14.8) years, and
170 64.4% were male (Table 1). However, the patients who received APT were generally older
171 (mean age \pm SD) in age (COX-I: 68.5 ± 12.1 , ADP-I 71.8 ± 11.3 , PDE-I: 70.0 ± 12.5), slightly
172 more females, and had a substantial higher prevalence of many comorbidities than non-APT
173 patients (Table 1). Among the 11,351 patients under APT, the patients received ADP-I were
174 older than the other two groups (COX-I and PDE-I) (Table 1). Furthermore, the prevalence of
175 hypertension, diabetes, dyslipidaemia, coronary artery disease, arterial fibrillation was
176 substantially higher in the ADP-I group compared to other two APT groups. The PDE-I group
177 had a higher prevalence of peripheral arterial disease than did the other two APT group.
178 Furthermore, based on NIHSS, the severity of neurologic deficit was higher, and required
179 surgical intervention after admission in the patients with prior ADP-I treatment compared to
180 the other two groups (Table 1).

181 **Events during index hospitalization**

182 The event number and rate of various outcomes during index hospitalization in non-APT and
183 different APT groups were studied (Supplemental Table 2). Patients under prior APT treatment
184 had significantly higher in-hospital mortality rate than those without APT (odds ratio [OR],
185 1.16; 95% confidence interval [CI], 1.09–1.23) when the covariates listed in Table 1 were
186 adjusted (Table 2). In comparison with non-APT group, significantly higher in-hospital
187 mortality was noted in patients that had received COX-I (OR, 1.17; 95% CI, 1.09–1.25) or ADP-
188 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).
189 Remarkably, the in-hospital mortality rate was significantly higher in the ADP-I group than in
190 the PDE-I group (hazard ratio, 1.45; 95% CI, 1.17–1.80) (Table 2). Furthermore, a higher risk of
191 in-hospital mortality was observed for the ADP-I group when compared to the COX-I group

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

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

199 **Follow-up outcomes of ICH**

200 The event number and rate of various follow-up outcomes of ICH in each group were studied
201 (Supplemental Table 2). No significant difference in risk of 6-month all-cause mortality was
202 found between the APT and non-APT groups (Supplemental Table 2). Of note, the ADP-I group
203 had a higher risk of mortality compared to the non-APT (hazard ratio [HR], 1.18; 95% CI, 1.05–
204 1.33], and a non-significant trend compared to COX-I (HR, 1.14; 95% CI, 1.01–1.29, $p=0.037$),
205 and PDE-I (HR, 1.19; 95% CI, 1.04–1.37, $p=0.011$) after Bonferroni adjustment (Supplemental
206 Table 3). In contrast, comparison of all four groups did not significantly show difference in the
207 risk of new occurrence ischemic or haemorrhagic stroke during the six-month follow-up
208 (Supplemental Table 3).

209

210 **Sensitivity analysis**

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

221

222

223 **Discussion**

224 **Primary result**

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

231

232 **Prior APT treatment associated with ICH**

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

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

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

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

295

296 **Limitations**

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

313

314

315 **Conclusion**

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

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

322

323 **Figure legends**

324 **Figure 1**

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

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

333

334 **Compliance with Ethical Standards**

335 The authors declare that they have no competing financial interests. This work was supported
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339 patient's consent, given that it was an epidemiology study with no definable patient
340 information.

341

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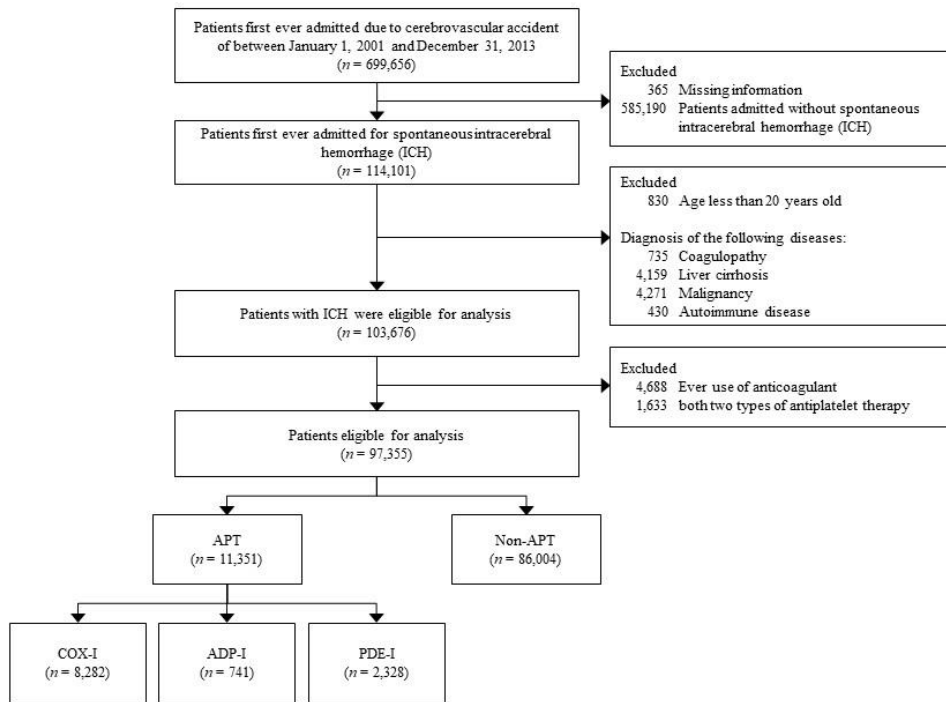
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464 Fig. 1



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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.

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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

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Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	OR (95% CI)	P	aOR (95% CI)	P
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 ($P < 0.0071$).

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

Variable	Before matching			After matching		
	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

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Variable	Before matching			After matching		
	APT (n = 11,351)	Non-APT (n = 86,004)	ASMD	APT (n = 11,285)	Non-APT (n = 11,285)	ASMD
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						

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Variable	Before matching			After matching		
	APT (n = 11,351)	Non-APT (n = 86,004)	ASMD	APT (n = 11,285)	Non-APT (n = 11,285)	ASMD
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.

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

Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	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

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Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	OR (95% CI)	P	aOR (95% CI)	P
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 ($P < 0.0071$).

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

Outcome	Number of event (%)				
	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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Supplemental Table 3. Time to event outcomes during a 6-month follow up

Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	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

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Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	HR (95% CI)	P	aHR (95% CI)	P
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.

Outcome	Number of event (%)				
	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.

Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	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

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Outcome / contrast	Unadjusted model		Fully-adjusted model*	
	HR (95% CI)	P	aHR (95% CI)	P
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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