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Restarting antiplatelet therapy after spontaneous intracerebral hemorrhage

Functional outcomes

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Abstract

Objective

To compare the functional outcomes and health-related quality of life metrics of restarting vs not restarting antiplatelet therapy (APT) in patients presenting with intracerebral hemorrhage (ICH) in the ERICH (Ethnic/Racial Variations of Intracerebral Hemorrhage) study.

Methods

Adult patients aged 18 years and older who were on APT before ICH and were alive at hospital discharge were included. Patients were dichotomized based on whether or not APT was restarted after hospital discharge. The primary outcome was a modified Rankin Scale score of 0–2 at 90 days. Secondary outcomes were excellent outcome (modified Rankin Scale score 0–1), mortality, Barthel Index, and health status (EuroQol–5 dimensions [EQ-5D] and EQ-5D visual analog scale scores) at 90 days.

Results

The APT and no APT cohorts comprised 127 and 732 patients, respectively. Restarting APT was associated with lower rates of good functional outcome (36.5% vs 40.8%; $p = 0.021$) and lower Barthel Index scores at 90 days ($p = 0.041$). The 2 cohorts were then matched in a 1:1 ratio, and the matched cohorts each comprised 107 patients. No difference in primary outcome was observed between restarting vs not restarting APT (35.5% vs 43.9%; $p = 0.105$). There were also no differences between the secondary outcomes of the 2 cohorts.

Conclusion

Restarting APT in patients with ICH of mild to moderate severity after acute hospitalization is not associated with worse functional outcomes or health-related quality of life at 90 days. In patients with significant cardiovascular risk factors who experience an ICH, restarting APT remains the decision of the treating practitioner.

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ERICH coinvestigators are listed at links.lww.com/WNL/A551.

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Glossary

APT = antiplatelet therapy; **CAD** = coronary artery disease; **CI** = confidence interval; **DAPT** = dual antiplatelet therapy; **EQ-5D** = EuroQol–5 dimensions; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **EVD** = external ventricular drain; **GCS** = Glasgow Coma Scale; **HR** = hazard ratio; **HRQoL** = health-related quality of life; **ICH** = intracerebral hemorrhage; **MI** = myocardial infarction; **mRS** = modified Rankin Scale; **OR** = odds ratio; **VAS** = visual analog scale.

Despite its effectiveness in primary and secondary myocardial infarction (MI) and stroke prevention, antiplatelet therapy (APT) is associated with an increased risk of spontaneous intracerebral hemorrhage (ICH).[1,2] Patients with ICH taking APT, particularly dual APT (DAPT), have higher rates of in-hospital mortality.[3,4] In patients with ICH who were on APT and remain alive at the time of hospital discharge, clinicians are frequently faced with the decision of whether or not to restart APT. APT after ICH has been found to be associated with a decreased incidence of ischemic cardiovascular events, without an elevated risk of recurrent ICH.[5–7] The balance of ischemic cardiovascular events and recurrent ICH, among other bleeding complications, may affect functional outcomes and health-related quality of life (HRQoL) measures after hospital discharge. In addition, the effect of recurrent ICH in patients taking APT on these measures may not be accurately portrayed by the incidence of recurrent ICH alone. Therefore, the aim of this multicenter, retrospective matched cohort study was to compare the functional outcomes and HRQoL metrics of restarting vs not restarting APT in patients with ICH.

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board at each respective site, and written informed consent was obtained from all patients (or guardians of patients) participating in the study. Patient data were deidentified and then pooled for analysis. In this study, we followed the guidelines set forth by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Data sources and restarting APT

The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study methods have been previously described in detail.[8] Briefly, ERICH is a multicenter, prospective, case-control study designed to recruit 1,000 non-Hispanic white, 1,000 non-Hispanic black, and 1,000 Hispanic participants with spontaneous ICH, along with matched ICH-free controls for the identification of genetic and epidemiologic risk factors for ICH and outcomes after ICH. Participants were recruited from 19 US sites comprising 42 hospitals. All participants or designated proxies underwent a standardized data collection protocol, including a personal interview and medical chart abstraction.

Patients included in the present study were derived from the spontaneous ICH case cohort of the ERICH study. The inclusion criteria for this study were (1) age 18 years or older, (2) patients taking APT before presentation with ICH, and (3) alive at the time of hospital discharge. The exclusion criteria were (1) thrombocytopenia (platelet count <150,000/μL) on admission, (2) patients on anticoagulation (heparin, low-molecular-weight heparin, warfarin, or non-vitamin K antagonist oral anticoagulants) before presentation with ICH, and (3) patients who were designated comfort care at hospital discharge.

Baseline demographic medical history data included age, sex, smoking status, TIA, ischemic stroke, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease (CAD), MI, atrial fibrillation, angina, congestive heart failure, carotid artery disease, peripheral vascular disease, heart valve replacement, coronary artery angioplasty or stent placement, carotid artery angioplasty or stent placement, carotid endarterectomy, and coronary artery bypass grafting. Laboratory data obtained on admission included platelet count, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. Data regarding APT or DAPT before ICH were derived from directed chart review and comprehensive interviews.

Clinical, radiologic, and treatment data included Glasgow Coma Scale (GCS) score on admission, ICH volume, presence of intraventricular hemorrhage, ICH location (categorized as lobar, deep, and infratentorial), surgical evacuation of ICH, external ventricular drain (EVD) placement, intracranial pressure monitor placement, CSF shunt placement, intubation, platelet transfusion, ICH score on admission, and initiation of anticoagulation at hospital discharge.[9,10] The resumption of APT, or lack thereof, at hospital discharge was determined from directed chart review, and APT status at 90-day follow-up was derived from interviews. For patients who were alive at follow-up, resumption of APT after ICH was defined as being on APT at 90 days. For patients who died prior to 90-day follow-up, resumption of APT was defined as inclusion of APT on the discharge medications list.

Outcomes

The primary outcome was a modified Rankin Scale (mRS) score of 0–2 (i.e., functional independence) at 90 days.[11,12] The secondary outcomes were excellent outcome (mRS score 0–1), mortality, Barthel Index (on a scale of 0–100, with higher scores indicating less disability), and HRQoL, as

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measured by the EuroQol–5 dimensions (EQ-5D) (on a scale of −0.11 to 1, with higher values indicating better HRQoL), and EQ-5D visual analog scale (VAS) (on a scale of 0–100, with higher values indicating better HRQoL) self-report questionnaires.[13]

Statistical analysis

All statistical analyses were performed using Stata version 14.2 (StataCorp LP, College Station, TX). Patients who satisfied the inclusion and exclusion criteria were dichotomized into 2 cohorts (no APT and APT) based on resumption of APT after ICH, or lack thereof. Baseline, clinical, radiologic, and treatment characteristics were compared between the 2 cohorts. Continuous variables were compared using Student *t* or Mann-Whitney *U* tests, as appropriate. Categorical variables were compared using Pearson χ^2 or Fisher exact tests, as appropriate. Univariable logistic and linear regression analyses were performed on the cohorts to assess the relationship between the resumption of APT and the primary and secondary outcomes. The findings from the logistic and linear regression analyses were adjusted for covariates of the cohorts with $p < 0.10$. In the subsequent analysis, to adjust for baseline differences, the 2 cohorts were matched, without replacement, in a 1:1 ratio with a caliper of 0.2 using propensity scores derived from baseline characteristics comparisons with $p < 0.10$. The matching was performed using the PSMATCH2 package developed for Stata.[14] Reduction in standardized absolute bias for each covariate is provided in table e-1 (links.lww.com/WNL/A550) and figure e-1 (links.lww.com/WNL/A549). Univariable logistic and linear regression analyses were performed on the matched cohorts to assess the relationship between the resumption of APT and the primary and secondary outcomes. The findings from the logistic and linear regression analyses were adjusted for covariates of the matched cohorts with $p < 0.10$. The covariates were tested for multicollinearity using tolerance and variance inflation factor. Statistical significance was defined as $p < 0.05$, and all tests were 2-tailed. Missing data were not imputed.

Data availability

The data from the ERICH study, including interview, chart abstraction, and imaging findings for cases and controls are now made publicly available both through direct request from the ERICH study principal investigator (D.W. at daniel.woo@uc.edu) or the National Institute of Neurological Disorders and Stroke.

Results

Characteristics of matched cohorts

Of the 3,000 patients with spontaneous ICH enrolled in the ERICH study, 2,141 patients were excluded from the present study based on the inclusion and exclusion criteria. The remaining 859 patients comprised 127 patients who were restarted on APT and 732 patients who were not restarted on APT after ICH (figure 1).

Table 1 shows a comparison of the baseline, clinical, radiologic, and treatment characteristics between patients who were restarted on APT vs those who were not restarted on APT, prior to matching. Patients who were restarted on APT were older ($p = 0.021$) and were more likely to have diabetes mellitus ($p = 0.005$), CAD ($p < 0.001$), previous MI ($p = 0.001$), atrial fibrillation ($p = 0.005$), congestive heart failure ($p = 0.001$), previous coronary angioplasty or stent placement ($p < 0.001$), carotid artery disease ($p = 0.011$), previous carotid angioplasty or stent placement ($p = 0.020$), peripheral vascular disease ($p = 0.001$), and a history of smoking ($p < 0.001$); they were also more likely to be on DAPT (22.1% vs 6.8%; $p < 0.001$). Patients who were restarted on APT had higher GCS scores ($p = 0.018$) and were less likely to have intraventricular hemorrhage ($p = 0.014$), had EVD ($p = 0.004$), CSF shunt ($p = 0.012$), intracranial pressure monitor placement ($p = 0.029$), or intubation ($p = 0.002$). Patients who were restarted on APT also had smaller ICH volume ($p = 0.023$) and lower ICH scores ($p = 0.047$).

The 2 cohorts were matched in a 1:1 ratio using propensity scores based on significant baseline characteristics. The matched APT and no APT cohorts each comprised 107 patients. Table 2 shows a comparison of the patient, clinical, radiologic, and treatment characteristics between the matched cohorts. EVD (15.9% vs 6.5%) and CSF shunt (6.5% vs 0.9%) placement were more common in the no APT cohort. There were no differences between the matched cohorts in the remainder of the variables.

Primary outcome

The primary outcome was observed in 36.5% vs 40.8% of the APT vs no APT cohorts, respectively (table 3 and figure 2). Restarting APT was associated with lower rates of good functional outcome at 90 days on multivariable analysis (adjusted odds ratio [OR] = 0.55 [95% confidence interval, CI 0.33–0.91]; $p = 0.021$). In the matched cohort analysis, the primary outcome was observed in 35.5% vs 43.9% of the APT vs no APT cohorts, respectively (table 4 and figure 2). The difference in the rate of the primary outcome was not significant between the matched cohorts in the univariate analysis (OR = 1.42 [95% CI 0.82–2.47]; $p = 0.209$) and remained nonsignificant after adjustments for platelet count, history of carotid endarterectomy, EVD placement, and CSF shunt placement (adjusted OR = 1.62 [95% CI 0.90–2.91]; $p = 0.105$).

Secondary outcomes

Excellent outcome at 90 days was observed in 19.1% and 23% of the APT and no APT cohorts, respectively (OR = 0.79 [95% CI 0.49–1.28]; $p = 0.331$; table 3 and figure 2). No difference was found between the cohorts in the rate of excellent outcome, even after adjustment (adjusted OR = 0.68 [95% CI 0.38–1.22]; $p = 0.195$). There were also no differences, either before or after adjustment, between the APT and no APT cohorts in mortality (6.4% vs 6.9%; adjusted OR = 0.94 [95% CI 0.34–2.60]; $p = 0.908$), EQ-5D scores (median

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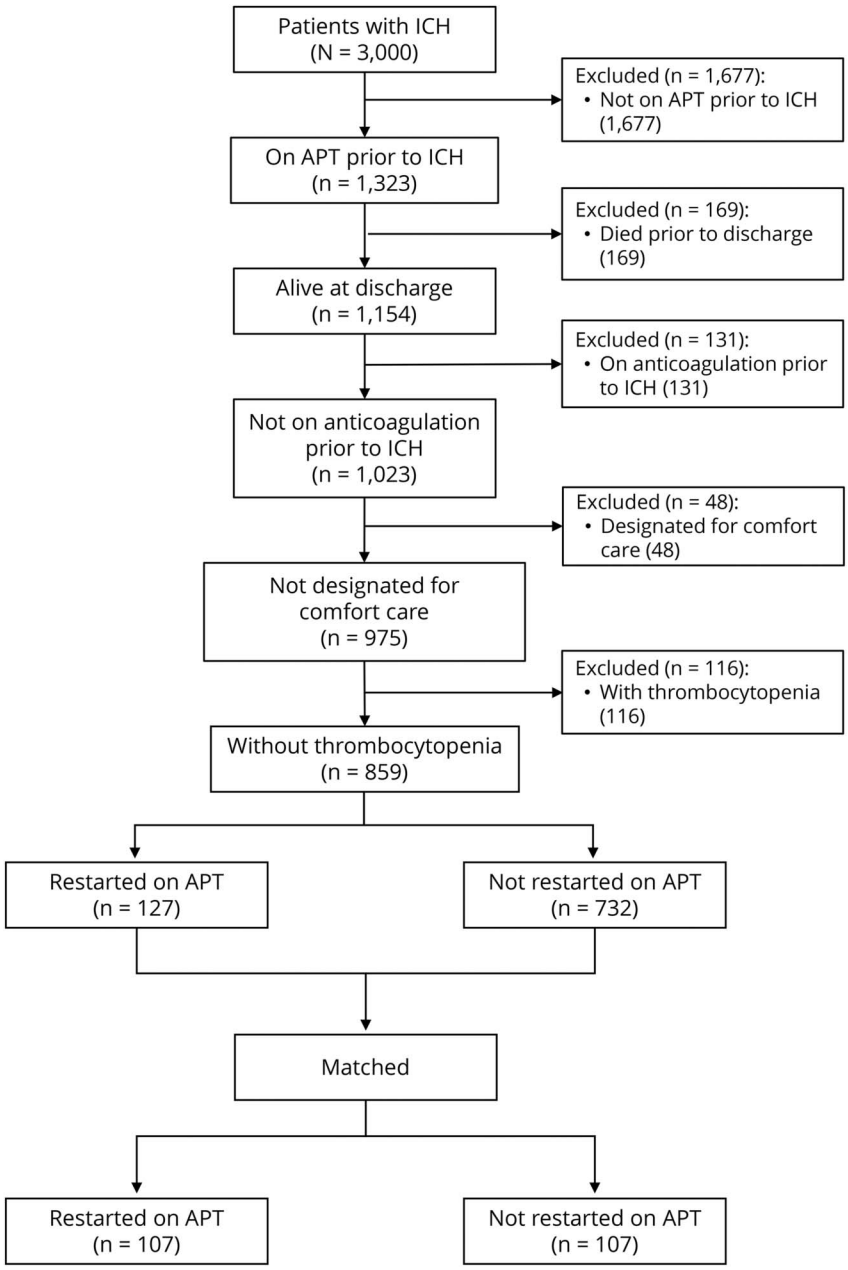
Figure 1 Flow diagram showing the patient selection process



APT = antiplatelet therapy; ICH = intracerebral hemorrhage.

0.71 vs 0.71; adjusted β = −0.04 [95% CI −0.11 to 0.03]; p = 0.244), or EQ-5D VAS scores (median 60 vs 65; adjusted β = −5.54 [95% CI −11.11 to 0.03]; p = 0.051). Restarting APT was associated with lower Barthel Index scores at 90 days after adjustments (adjusted β = −6.88 [95% CI −13.47 to 0.29]; p = 0.041). In the matched cohort analysis, excellent outcome at 90 days was observed in 17.8% and 22.4% of the APT and no APT cohorts, respectively (OR = 1.34 [95% CI 0.68–2.62]; p = 0.395; table 4 and figure 2). No difference was found between the matched cohorts in the rate of excellent outcome, even after adjustment (adjusted OR = 1.52 [95% CI 0.76–3.06]; p = 0.239). There were also no differences, either before or after adjustment, between the APT and no APT cohorts in mortality (5.6% vs 5.6%; adjusted OR = 1.01 [95% CI 0.29–3.56]; p = 0.989), Barthel Index scores (median 85 vs 85; adjusted β = 5.39 [95% CI −3.63 to 14.41]; p = 0.240), EQ-5D scores (median 0.71 vs 0.71; adjusted β = 0.029 [95% CI −0.068 to 0.126]; p = 0.555), or EQ-5D VAS scores (median 60 vs 67.5; adjusted β = 3.43 [95% CI −3.78 to 10.63]; p = 0.349).

Discussion

Although platelets are essential to achieving hemostasis, platelet aggregation in the setting of atherosclerosis can lead to thromboembolic complications.[15] The effectiveness of

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Table 1 Comparison of baseline, clinical, radiologic, and treatment characteristics between patients who were restarted on APT vs those who were not restarted on APT

Characteristic	Resumption of APT (n = 127)	No resumption of APT (n = 732)	*p* Value
Age, y	65.0 (57.0–74.0)	62.0 (53.5–73.0)	0.021[a]
Sex, male	85/127 (66.9)	441/732 (60.3)	0.154
History of TIA	18/127 (14.2)	79/730 (10.8)	0.271
History of ischemic stroke	15/124 (12.1)	84/716 (11.7)	0.907
Hypertension	115/127 (90.6)	659/731 (90.2)	0.888
Diabetes mellitus	58/127 (45.7)	214/732 (32.9)	0.005[a]
Hyperlipidemia	80/125 (64.0)	434/728 (59.6)	0.355
Coronary artery disease	46/127 (36.2)	147/730 (20.1)	<0.001[a]
History of myocardial infarction	25/127 (19.7)	72/731 (9.9)	0.001[a]
Atrial fibrillation	25/127 (19.7)	80/732 (10.9)	0.005[a]
Angina	11/127 (8.7)	37/732 (5.1)	0.102
CHF	22/127 (17.3)	55/711 (7.7)	0.001[a]
History of heart valve replacement	1/127 (0.8)	3/725 (0.4)	0.476
History of CABG	7/127 (5.5)	32/732 (4.4)	0.569
History of coronary angioplasty/stent placement	26/127 (20.5)	54/732 (7.4)	<0.001[a]
Carotid artery disease	13/127 (10.2)	34/731 (4.7)	0.011[a]
History of CEA	3/127 (2.4)	26/730 (3.6)	0.789
History of carotid angioplasty/stent placement	4/126 (3.2)	4/726 (0.6)	0.020[a]
Peripheral vascular disease	10/124 (8.1)	14/708 (2.0)	0.001[a]
History of smoking	74/121 (61.2)	297/676 (43.9)	<0.001[a]
Current smoker	28/74 (37.8)	127/292 (43.5)	0.379
DAPT before ICH	28/127 (22.1)	50/732 (6.8)	<0.001[a]
Platelet count, k/μL[b]	228 (191–281)	228 (191–271)	0.396
Total cholesterol, mg/dL[b]	165 (145–198)	171 (139–196)	0.764
HDL, mg/dL[b]	46 (35–57)	44 (36–54)	0.952
LDL, mg/dL[b]	95 (76–123)	100 (72–122)	0.695
Triglycerides, mg/dL[b]	102.5 (75.5–172.5)	103 (72–149)	0.868
GCS score[b]	15 (14–15)	15 (12–15)	0.018[a]
Surgical evacuation of ICH	8/127 (6.3)	57/732 (7.8)	0.558
EVD placement	8/127 (6.3)	119/732 (16.3)	0.004[a]
CSF shunt placement	1/127 (0.8)	46/732 (6.3)	0.012[a]
ICP monitor placement	10/127 (7.9)	111/732 (15.2)	0.029[a]
Intubation	19/127 (15)	204/732 (27.9)	0.002[a]
Platelet transfusion	25/127 (19.7)	124/731 (17)	0.455
ICH volume, mL[b]	6.6 (2.1–16.9)	9.6 (3.9–23)	0.023[a]
IVH	35/124 (28.2)	280/702 (39.9)	0.014[a]
Infratentorial hemorrhage	17/125 (13.6)	81/711 (11.4)	0.479

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Table 1 Comparison of baseline, clinical, radiologic, and treatment characteristics between patients who were restarted on APT vs those who were not restarted on APT *(continued)*

Characteristic	Resumption of APT (n = 127)	No resumption of APT (n = 732)	*p* Value
Lobar hemorrhage	37/125 (29.6)	231/711 (32.5)	0.523
ICH score			0.047[a]
0	47/122 (38.5)	212/687 (30.9)	
1	54/122 (44.3)	268/687 (39)	
2	17/122 (13.9)	129/687 (18.8)	
3	4/122 (3.3)	62/687 (9)	
4	0/122 (0)	14/687 (2)	
5	0/122 (0)	2/687 (0.3)	
Anticoagulant use at/after discharge	5/127 (3.9)	30/732 (4.1)	0.932

Abbreviations: APT = antiplatelet therapy; CABG = coronary artery bypass grafting; CEA = carotid endarterectomy; CHF = congestive heart failure; DAPT = dual antiplatelet therapy; EVD = external ventricular drain; GCS = Glasgow Coma Scale; HDL = high-density lipoprotein; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; k = ×1,000; LDL = low-density lipoprotein.
Data represent median (interquartile range) or n/n (%).
[a] Statistically significant.
[b] On admission.

APT in both primary and secondary prevention of ischemic CAD and stroke has resulted in an increase in the number of patients receiving APT.[16–21] Despite the overall benefit of APT in preventing the thromboembolic sequelae of atherosclerosis, its use may elevate the risk of spontaneous ICH.[1,2,22,23] In addition, APT use before ICH is associated with hematoma expansion, increased mortality, and worse outcomes.[3,24–26] For patients who survive the initial ICH, recurrent ICH incurs the risk of further morbidity and mortality, and its incidence has been reported to range between 2.0 and 4.0 per 100 patient-years.[6,27–31] Risk factors for recurrent ICH include lobar ICH location, advanced age, hypertension, and previous ischemic stroke.[27,31]

Despite the increased cardiovascular risks associated with APT withdrawal, some clinicians are reluctant to restart APT after ICH because of a perception that doing so will subject the patient to an elevated risk of recurrent ICH. Since thrombotic diseases and ICH share many common risk factors, ICH survivors are frequently at risk of both ischemic cardiovascular disease and recurrent ICH. The decision to restart APT after ICH in the posthospitalization setting represents a major challenge, not only for clinicians who manage these patients during the acute hospitalization but also for primary care physicians who encounter these patients after discharge. Prior studies have not shown that restarting APT increases the risk of recurrent ICH.[5–7,31,32] However, the effect of APT resumption in patients with ICH on functional outcomes and HRQoL has not been previously assessed. In this multicenter, retrospective matched cohort study, we report the first analysis of functional outcomes and HRQoL after restarting vs withholding APT in patients with ICH following acute hospitalization. In the initial analysis using the entire cohort, we found restarting APT was associated with lower rates of good functional outcome and lower Barthel Index scores at 90 days. However, after adjusting for differences in baseline characteristics using matched cohort analysis, we did not find a difference in functional outcomes between patients with ICH who restarted APT vs those who did not, including comparable rates of good (mRS score 0–2) and excellent (mRS score 0–1) outcomes at 90 days. Furthermore, the HRQoL metrics and mortality rates were not different between the 2 matched cohorts.

Flynn et al.[7] found higher rates of ischemic stroke/MI compared to recurrent ICH (28.7 vs 9.7 per 1,000 patient-years) among the 417 ICH survivors in the Tayside Stroke Cohort. The authors reported recurrent ICH and ischemic stroke rates of 9.4 and 5.1 per 1,000 patient-years for the APT cohort, respectively. In the non-APT cohort, the recurrent ICH and ischemic stroke rates were 9.8 and 23.1 per 1,000 patient-years, respectively. No differences in recurrent ICH (hazard ratio [HR] = 1.07 [95% CI 0.24–4.84]) and ischemic stroke (HR 0.23 [95% CI 0.03–1.68]) rates between the APT and non-APT cohorts in the study were found. In addition, no differences in other endpoints, including MI (HR = 1.77 [95% CI 0.49–6.49]), ischemic stroke/MI (HR = 0.72 [95% CI 0.25–2.02]), and serious vascular events (HR = 0.73 [95% CI 0.42–1.28]), were observed. It should be noted that only 33% of patients who received APT after discharge were on APT before presenting with ICH. Viswanathan et al.[31] studied 207 patients with ICH and found no association between APT and either lobar (HR = 0.8 [95% CI 0.3–2.3]; $p = 0.73$) or deep (HR = 1.2 [95% CI 0.1–14.3]; $p = 0.88$) ICH recurrence in

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Table 2 Comparison of patient, clinical, radiologic, and treatment characteristics between the matched cohorts

Characteristic	Resumption of APT (n = 107)	No resumption of APT (n = 107)	*p* Value
Age, y, mean (SD)	65.3 (11.1)	65.6 (11.8)	0.881[a]
Sex, male	72/107 (67.3)	65/107 (60.8)	0.319
History of TIA	15/107 (14.0)	16/107 (15.0)	0.846
History of ischemic stroke	13/106 (12.3)	21/107 (19.6)	0.142
Hypertension	97/107 (90.7)	101/107 (94.4)	0.299
Diabetes mellitus	47/107 (43.9)	48/107 (44.9)	0.891[a]
Hyperlipidemia	64/105 (61.0)	76/107 (71.0)	0.121
Coronary artery disease	35/107 (32.7)	31/107 (29.0)	0.554[a]
History of myocardial infarction	18/107 (16.8)	16/107 (15.0)	0.708[a]
Atrial fibrillation	19/107 (17.8)	17/107 (15.9)	0.715[a]
Angina	8/107 (7.5)	8/107 (7.5)	1.000
CHF	16/107 (15.0)	17/107 (15.9)	0.850[a]
History of heart valve replacement	1/107 (0.9)	1/107 (0.9)	1.000
History of CABG	3/107 (2.8)	8/107 (7.5)	0.122
History of coronary angioplasty/stent placement	19/107 (17.8)	14/107 (13.1)	0.344[a]
Carotid artery disease	7/107 (6.5)	8/107 (7.5)	0.789[a]
History of CEA	3/107 (2.8)	9/107 (8.4)	0.075
History of carotid angioplasty/stent placement	1/107 (0.9)	2/107 (1.9)	0.561[a]
Peripheral vascular disease	5/107 (4.7)	7/107 (6.5)	0.552[a]
History of smoking	63/107 (58.9)	67/107 (62.6)	0.576[a]
Current smoker	27/63 (42.9)	19/67 (28.4)	0.084
DAPT before ICH	18/107 (16.8)	18/107 (16.8)	1.000[a]
Platelet count, k/μL[b]	232 (191–284)	221 (189–256)	0.094
Total cholesterol, mg/dL[b]	169 (145–204)	162 (139–194)	0.237
HDL, mg/dL[b]	46 (35–58)	46 (36–53)	0.797
LDL, mg/dL[b]	95 (73–125)	93 (65–117)	0.282
Triglycerides, mg/dL[b]	103 (73–174)	92 (65–134)	0.436
GCS score[b]	15 (14–15)	15 (13–15)	0.270
Surgical evacuation of ICH	7/107 (6.5)	6/107 (5.6)	0.775
EVD placement	7/107 (6.5)	17/107 (15.9)	0.030[c]
CSF shunt placement	1/107 (0.9)	7/107 (6.5)	0.031[c]
ICP monitor placement	9/107 (8.4)	15/107 (14.0)	0.194
Intubation	17/107 (15.9)	23/107 (21.5)	0.293
Platelet transfusion	19/107 (17.8)	24/107 (22.6)	0.375
ICH volume, mL[b]	8.3 (2.0–17.2)	7.4 (2.6–18.3)	0.646
IVH	32/105 (30.5)	39/106 (36.8)	0.332
Infratentorial hemorrhage	11/105 (10.5)	18/106 (17.0)	0.170
Lobar hemorrhage	30/105 (28.6)	39/106 (36.8)	0.203

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Table 2 Comparison of patient, clinical, radiologic, and treatment characteristics between the matched cohorts *(continued)*

Characteristic	Resumption of APT (n = 107)	No resumption of APT (n = 107)	*p* Value
ICH score			0.250
0	42/104 (40.4)	33/102 (32.4)	
1	44/104 (42.3)	39/104 (38.2)	
2	14/104 (13.5)	22/104 (21.6)	
3	4/104 (3.9)	6/104 (5.9)	
4	0/104 (0)	2/104 (2.0)	
5	0/104 (0)	0/104 (0)	
Anticoagulant use at/after discharge	8/107 (7.5)	9/107 (8.4)	0.800

Abbreviations: APT = antiplatelet therapy; CABG = coronary artery bypass grafting; CEA = carotid endarterectomy; CHF = congestive heart failure; DAPT = dual antiplatelet therapy; EVD = external ventricular drain; GCS = Glasgow Coma Scale; HDL = high-density lipoprotein; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; k = ×1,000; LDL = low-density lipoprotein.
Data represent n/n (%) or median (interquartile range) unless otherwise indicated.
[a] Matched covariates.
[b] On admission.
[c] Statistically significant.

the subgroup of 46 patients who were prescribed APT during the follow-up period. Chong et al.[6] also reported comparable risks of recurrent ICH between patients who were prescribed aspirin (n = 56) vs those who were not (n = 384) after ICH (22.7 vs 22.4 per 1,000 patient-years; $p = 0.70$). However, in their subgroup analysis of patients with standard indications

Table 3 Comparison of primary and secondary outcomes between patients who were restarted on APT and those who were not restarted on APT

Outcome	Resumption of APT (n = 127)	No resumption of APT (n = 732)	Effect variable	Unadjusted value (95% CI)	*p* Value	Adjusted value (95% CI)[a]	*p* Value
Primary outcome							
mRS 0–2 at 90 d, n (%)	46/126 (36.5)	243/595 (40.8)	OR	0.833 (0.560 to 1.240)	0.368	0.549 (0.331 to 0.912)	0.021[b]
Secondary outcomes							
mRS 0–1 at 90 d, n (%)	24/126 (19.1)	137/595 (23.0)	OR	0.787 (0.485 to 1.276)	0.331	0.683 (0.384 to 1.215)	0.195
Mortality at 90 d, n (%)	8/126 (6.4)	41/595 (6.9)	OR	0.916 (0.419 to 2.005)	0.826	0.942 (0.342 to 2.595)	0.908
Barthel Index at 90 d, median (IQR)[c]	85 (35–100)	80 (35–100)	β	1.603 (−5.544 to 8.750)	0.660	−6.884 (−13.474 to −0.294)	0.041[b]
EQ-5D score at 90 d, median (IQR)[d]	0.71 (0.33–0.83)	0.71 (0.38–0.84)	β	−0.013 (−0.083 to 0.056)	0.705	−0.042 (−0.112 to 0.029)	0.244
EQ-5D VAS score at 90 d, median (IQR)[e]	60 (40–80)	65 (50–80)	β	−1.900 (−7.379 to 3.577)	0.496	−5.538 (−11.106 to 0.029)	0.051

Abbreviations: APT = antiplatelet therapy; CI = confidence interval; EQ-5D = EuroQol–5 dimensions; IQR = interquartile range; mRS = modified Rankin Scale; OR = odds ratio; VAS = visual analog scale.
[a] Values were adjusted for age, diabetes mellitus, coronary artery disease, history of myocardial infarction, atrial fibrillation, congestive heart failure, history of cardiac angioplasty/stent placement, history of carotid angioplasty/stent placement, peripheral vascular disease, history of smoking, dual APT prior to intracerebral hemorrhage (ICH), Glasgow Coma Scale score, external ventricular drain placement, intracerebral pressure monitor placement, CSF shunt placement, ICH volume, intubation, and ICH score.
[b] Statistically significant.
[c] The Barthel Index is an ordinal 10-item scale for measuring performance of activities of daily living. Score ranges from 0 to 100, with 0 indicating severe disability and 100 indicating no disability that interferes with daily activities.
[d] The EQ-5D self-report questionnaire is a standardized instrument for the measurement of generic health status in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from −0.11 to 1.00, with higher scores indicating better health and death indicated by score of 0.
[e] The EQ-5D visual analog scale is the second part of the EQ-5D questionnaire, in which the patient is asked to mark their health status on a 20-cm vertical scale with endpoints of 0 ("the worst health you can imagine") and 100 ("the best health you can imagine").

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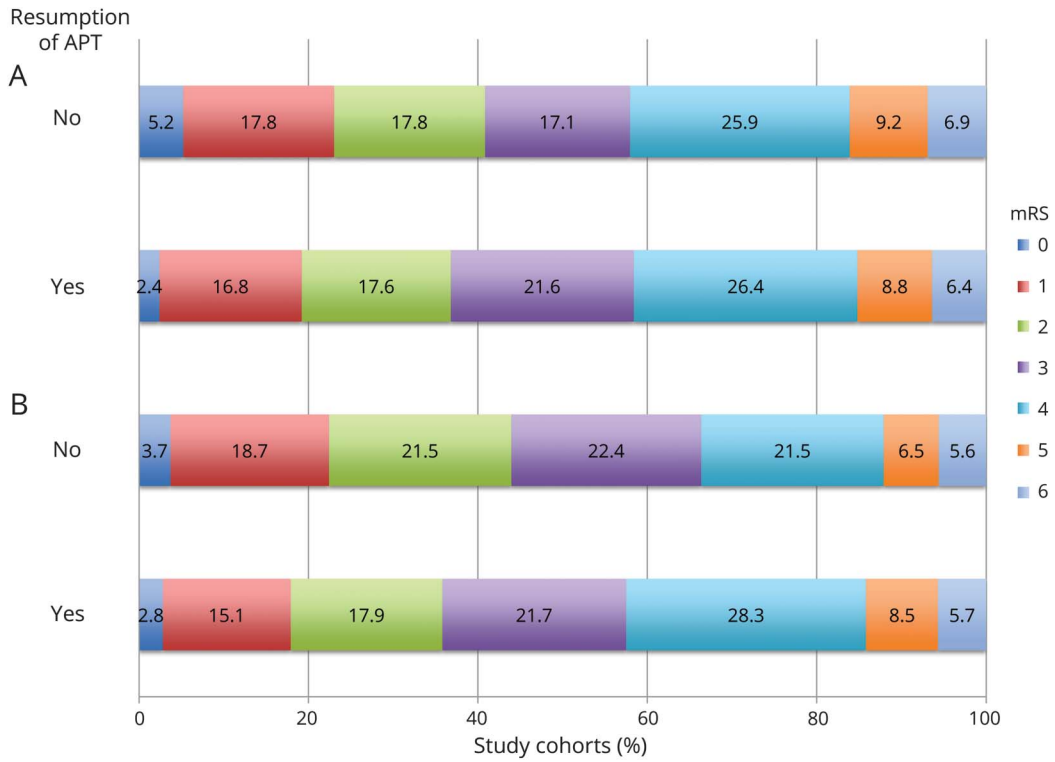
Figure 2 Comparisons of functional outcomes at 90 days



Bar chart comparing the functional outcomes at 90 days for (A) the resumption of APT vs no resumption of APT cohorts, and (B) the matched resumption of APT vs no resumption of APT cohorts, as measured by the mRS. APT = antiplatelet therapy; mRS = modified Rankin Scale.

for aspirin, the incidence of combined vascular events (recurrent ICH, ischemic stroke, and acute coronary syndrome) was lower in patients prescribed aspirin (52.4 vs 112.8 per 1,000 patient-years; $p = 0.04$). In a recent study examining the effects of antithrombotic therapy use in Danish patients with a history of ICH, Ottosen et al.[5] reported that APT in patients with appropriate indications was not associated with recurrent ICH (HR = 1.33 [95% CI 0.93–1.92]), mortality (HR = 0.96 [95% CI 0.80–1.15]), thromboembolic events (HR = 0.99 [95% CI 0.75–1.31]), or major bleeding events (HR = 0.89 [95% CI 0.68–1.16]). Although the data collected in the ERICH study does not include cardiovascular events or recurrent ICH in the posthospitalization period, the results of our analysis concur with prior studies, and they provide additional, clinically relevant findings that were not previously available.

We acknowledge that our study has several limitations. Our results are contingent on the accuracy and reliability of medication documentation on admission, at discharge, and during follow-up, which were based on patient self-report and family members of patients who were incapacitated. Therefore, this study is subject to reporting and recall biases. In addition, balancing of both measured and unmeasured variables between the cohorts may be limited by the small dataset available for propensity score matching. Hence, results from both the unmatched and matched analyses were presented in this study. The timing of restarting APT during the follow-up period could not be determined. Hence, no recommendation regarding the appropriate time interval between presentation with ICH and the resumption of APT can be derived from our findings. Although the major clinical indications for APT were included in the baseline variables, there may be other indications that were not accounted for. The specific indication for APT use in each patient could not be differentiated, since it was not a part of the ERICH questionnaire. We acknowledge that the results may be confounded by indication for restarting APT. Furthermore, detailed data regarding indications for DAPT rather than antiplatelet monotherapy, differences in specific APT medications, and APT dosage were not available. Since only 1.6% of patients with ICH were restarted on DAPT after hospitalization, a comparison among patients restarted on DAPT, single APT, and no APT could not be performed. Because the ERICH study was not specifically designed to evaluate outcomes associated with restarting APT in the post-ICH setting, data regarding recurrent ICH, bleeding complications, cardiovascular events, and thromboembolic complications after discharge were not recorded. Lastly, the findings of this study may not be generalizable to all patients with ICH, as most patients presented with relatively low ICH scores, high GCS scores, and small ICH volumes.

In patients who were taking APT before presenting with a spontaneous ICH of mild to moderate severity, restarting

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Table 4 Comparison of primary and secondary outcomes between the matched cohorts

Outcomes	Resumption of APT (n = 107)	No resumption of APT (n = 107)	Effect variable	Unadjusted value (95% CI)	*p* Value	Adjusted value (95% CI)[a]	*p* Value
Primary outcome							
mRS score 0–2 at 90 d, n (%)	38/107 (35.5)	47/107 (43.9)	OR	1.422 (0.821 to 2.465)	0.209	1.622 (0.904 to 2.907)	0.105
Secondary outcomes							
mRS score 0–1 at 90 d, n (%)	19/107 (17.8)	24/107 (22.4)	OR	1.339 (0.684 to 2.624)	0.395	1.521 (0.757 to 3.057)	0.239
Mortality at 90 d, n (%)	6/107 (5.6)	6/107 (5.6)	OR	1.000 (0.312 to 3.205)	1.000	1.009 (0.286 to 3.558)	0.989
Barthel Index score at 90 d, median (IQR)[b]	85 (35–100)	85 (50–100)	β	4.019 (−5.433 to 13.471)	0.403	5.389 (−3.626 to 14.405)	0.240
EQ-5D score at 90 d, median (IQR)[c]	0.71 (0.33–0.83)	0.71 (0.38–0.84)	β	0.026 (−0.069 to 0.120)	0.594	0.029 (−0.068 to 0.126)	0.555
EQ-5D VAS score at 90 d, median (IQR)[d]	60 (42.5–77.5)	67.5 (50–80)	β	2.952 (−4.155 to 10.060)	0.414	3.428 (−3.778 to 10.634)	0.349

Abbreviations: APT = antiplatelet therapy; CI = confidence interval; EQ-5D = EuroQol–5 dimensions; IQR = interquartile range; mRS = modified Rankin Scale; OR = odds ratio; VAS = visual analog scale.
[a] Values were adjusted for platelet count, history of carotid endarterectomy, external ventricular drain placement, and shunt placement.
[b] The Barthel Index is an ordinal 10-item scale for measuring performance of activities of daily living. Score ranges from 0 to 100, with 0 indicating severe disability and 100 indicating no disability that interferes with daily activities.
[c] The EQ-5D self-report questionnaire is a standardized instrument for the measurement of generic health status in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from −0.11 to 1.00, with higher scores indicating better health.
[d] The EQ-5D visual analog scale is the second part of the EQ-5D questionnaire, in which the patient is asked to mark their health status on a 20-cm vertical scale with endpoints of 0 ("the worst health you can imagine") and 100 ("the best health you can imagine").

APT after acute hospitalization does not appear to be associated with worse functional outcomes or HRQoL. However, without detailed data regarding ischemic vs hemorrhagic cerebrovascular and cardiovascular events, we were unable to attribute our findings to restarting APT. In patients with significant cardiovascular risk factors, restarting APT in the posthospitalization setting remains the decision of the treating practitioner. Future prospective studies are necessary to ascertain the long-term benefits and risks of restarting APT after ICH.

Author contributions

Ching-Jen Chen: design of study, acquisition of data, data analysis and interpretation, drafting of manuscript, critical revision of the manuscript for important intellectual content. Dale Ding: design of study, data interpretation, drafting of manuscript, critical revision of the manuscript for important intellectual content. Thomas Buell: data interpretation, drafting of manuscript, critical revision of the manuscript for important intellectual content. Fernando Testai: data interpretation, critical revision of the manuscript for important intellectual content. Sebastian Koch: data interpretation, critical revision of the manuscript for important intellectual content, study supervision. Daniel Woo: data interpretation, critical revision of the manuscript for important intellectual content, study supervision. Bradford Worrall: data interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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