Stroke

CLINICAL AND POPULATION SCIENCES

Early Antiplatelet Resumption and the Risks of Major Bleeding After Intracerebral Hemorrhage

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BACKGROUND: The appropriate timing of resuming antithrombotic therapy after intracerebral hemorrhage (ICH) remains unclear. The aim of this study was to compare the risks of major bleeding between early and late antiplatelet resumption in ICH survivors.

METHODS: Between 2008 and 2017, ICH patients were available in the National Health Insurance Research Database. Patients with a medication possession ratio of antiplatelet treatment ≥50% before ICH and after antiplatelet resumption were screened. We excluded patients with atrial fibrillation, heart failure, under anticoagulant or hemodialysis treatment, and developed cerebrovascular events or died before antiplatelet resumption. Finally, 1584 eligible patients were divided into EARLY (≤30 days) and LATE groups (31–365 days after the index ICH) based on the timing of antiplatelet resumption. Patients were followed until the occurrence of a clinical outcome, end of 1-year follow-up, death, or until December 31, 2018. The primary outcome was recurrent ICH. The secondary outcomes included all-cause mortality, major hemorrhagic events, major occlusive vascular events, and ischemic stroke. Cox proportional hazard model after matching was used for comparison between the 2 groups.

RESULTS: Both the EARLY and LATE groups had a similar risk of 1-year recurrent ICH (EARLY versus LATE: 3.12% versus 3.27%; adjusted hazard ratio [AHR], 0.967 [95% CI, 0.522–1.791]) after matching. Both groups also had a similar risk of each secondary outcome at 1-year follow-up. Subgroup analyses disclosed early antiplatelet resumption in the patients without prior cerebrovascular disease were associated with lower risks of all-cause mortality (AHR, 0.199 [95% CI, 0.054–0.739]) and major hemorrhagic events (AHR, 0.090 [95% CI, 0.010–0.797]), while early antiplatelet resumption in the patients with chronic kidney disease were associated with a lower risk of ischemic stroke (AHR, 0.065 [95% CI, 0.012–0.364]).

CONCLUSIONS: Early resumption of antiplatelet was as safe as delayed antiplatelet resumption in ICH patients. Besides, those without prior cerebrovascular disease or with chronic kidney disease may benefit more from early antiplatelet resumption.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: antiplatelet ■ antiplatelet resumption ■ intracerebral hemorrhage ■ ischemic stroke ■ major bleeding

Stroke is one of the leading causes of death worldwide. Both ischemic stroke (IS) and intracerebral hemorrhage (ICH) patients have high recurrence rates in long-term follow-up. The use of antiplatelet agent prior to acute ICH is associated with an increased bleeding risk and poor outcomes,[1,2] and therefore discontinuing antithrombotic agent during acute ICH is generally recommended.[3,4] In addition to the risk of recurrent ICH, the risks of ischemic cerebrovascular events were 3.0% per year and 2.8 per 100 person-years in patients without atrial fibrillation (AF),[5,6] while the risk of ischemic stroke/systemic embolism and all-cause mortality could reach 27.3 per 100 person-years in patients with AF.[7] The mortality rate of ICH survivors could be as high as

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AHR	adjusted hazard ratio
CCI	Charlson comorbidity index
CKD	chronic kidney disease
CVD	cerebrovascular disease
ICH	intracerebral hemorrhage
IS	ischemic stroke
MI	myocardial infarction
MPR	medication possession ratio
NHIRD	National Health Insurance Research Database
PSM	propensity score matching
SSI	stroke severity index

21.7 per 100 person-years if there was occurrence of arterial ischemic event.[8]

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However, restarting antiplatelet therapy after the episode of ICH is a clinical dilemma: the resumption of antiplatelet may increase the risk of recurrent ICH, but deferring the use of antiplatelet may increase the risk of ischemic events. An observational study[9] and the recent RESTART trial (Restart or Stop Antithrombotics Randomized Trial)[10–12] demonstrated that resuming antiplatelet could be safe with a minor risk of recurrent ICH, which might not outweigh the benefits of antiplatelet therapy for the prevention of occlusive vascular disease.

The timing of antithrombotic resumption should therefore consider the risk of recurrent ICH and ischemic events. The risk of acute IS is known to be the highest within the first month after ICH.[13] However, in clinical practice, only 5% of patients received antiplatelet therapy within 1 month after ICH.[14] To date, there is no recommendation regarding the appropriate time interval between the presentation of ICH and the resumption of antiplatelet. Using the national cohort database in Taiwan, the aim of this study was to compare the safety outcome between early (≤30 days) and late (31–365 days) antiplatelet resumption in ICH survivors to fill this gap.

METHODS

Data Source and Patient Identification

The ICH patients were recruited from the National Health Insurance Research Database (NHIRD) released by Health and Welfare Data Science Center in Taiwan. The accuracy of diagnoses in the NHIRD has been validated in several diseases including diabetes,[15] stroke,[16] and acute myocardial infarction (MI).[17] International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM [2008–2015] and ICD-10-CM [2016–2017]) codes were used for all outpatient and hospitalization diagnoses. Patients aged 20 years or older who were admitted to hospital due to spontaneous ICH were identified using the codes ICD-9-CM 431 and ICD-10-CM I61 between January 1, 2008 and December 31, 2017. Two medication possession ratios (MPRs) were used to assess the adherence to antiplatelet treatment. MPR1 was calculated by dividing the number of days that the antiplatelet was prescribed within 3 months before ICH by 90 days, whereas MPR2 was calculated by dividing the number of antiplatelet prescription days within 3 months after antiplatelet resumption by 90 days. To ascertain the persistence of antiplatelet use before and after ICH, eligible patients were defined if both MPR1 and MPR2 were ≥50%. Patients were excluded if there was missing demographic information in the NHIRD. We focused on the resumption of antiplatelet treatment after ICH, and therefore patients were excluded if there was a history of AF, heart failure, or anticoagulant use. Anticoagulants are frequently used in patients undergoing dialysis treatment, and therefore patients under hemodialysis were also excluded. As we aimed to study the safety outcome of antiplatelet resumption, we excluded the patients who did not receive antiplatelet before ICH (de novo initiation). We also excluded patients who developed cardiovascular events or died before antiplatelet resumption. The detailed patient selection flow chart is shown in Figure 1. This study was approved by the institutional review board of the National Health Research Institutes (EC1060704-E) and the Ethics Institutional Review Board of Linkou Chang Gung Memorial Hospital (No. 202101079B0). For privacy protection, all data from the NHIRD were deidentified before the release for research; therefore, the need for informed consent was waived. This cohort study was conducted following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines. The STROBE checklist is available in the Supplemental Material.

Exposure to the Study Drugs

We used a pseudo-placebo comparison group rather than an active comparator design. We divided the eligible patients into 2 groups based on the timing of antiplatelet resumption after the index ICH: (1) early antiplatelet user (EARLY) group and (2) late antiplatelet user (LATE) group. We extracted data on antiplatelet medication from the outpatient claims or pharmacy refills for chronic illnesses. The EARLY group was defined if antiplatelet was prescribed within 30 days after the index ICH and was used continuously for >3 months at outpatient visits or pharmacy refills. The LATE group was defined if they received antiplatelet from 31 to 365 days after the index ICH. Cohort entry was defined as the time when the patients were first prescribed with antiplatelet after the index ICH.

Covariates

The covariates included age, sex, year of ICH patients' entry into the cohort, and comorbidities such as MI, chronic kidney disease (CKD), ischemic heart disease, dyslipidemia, diabetes, hypertension, and prior cerebrovascular disease (CVD).

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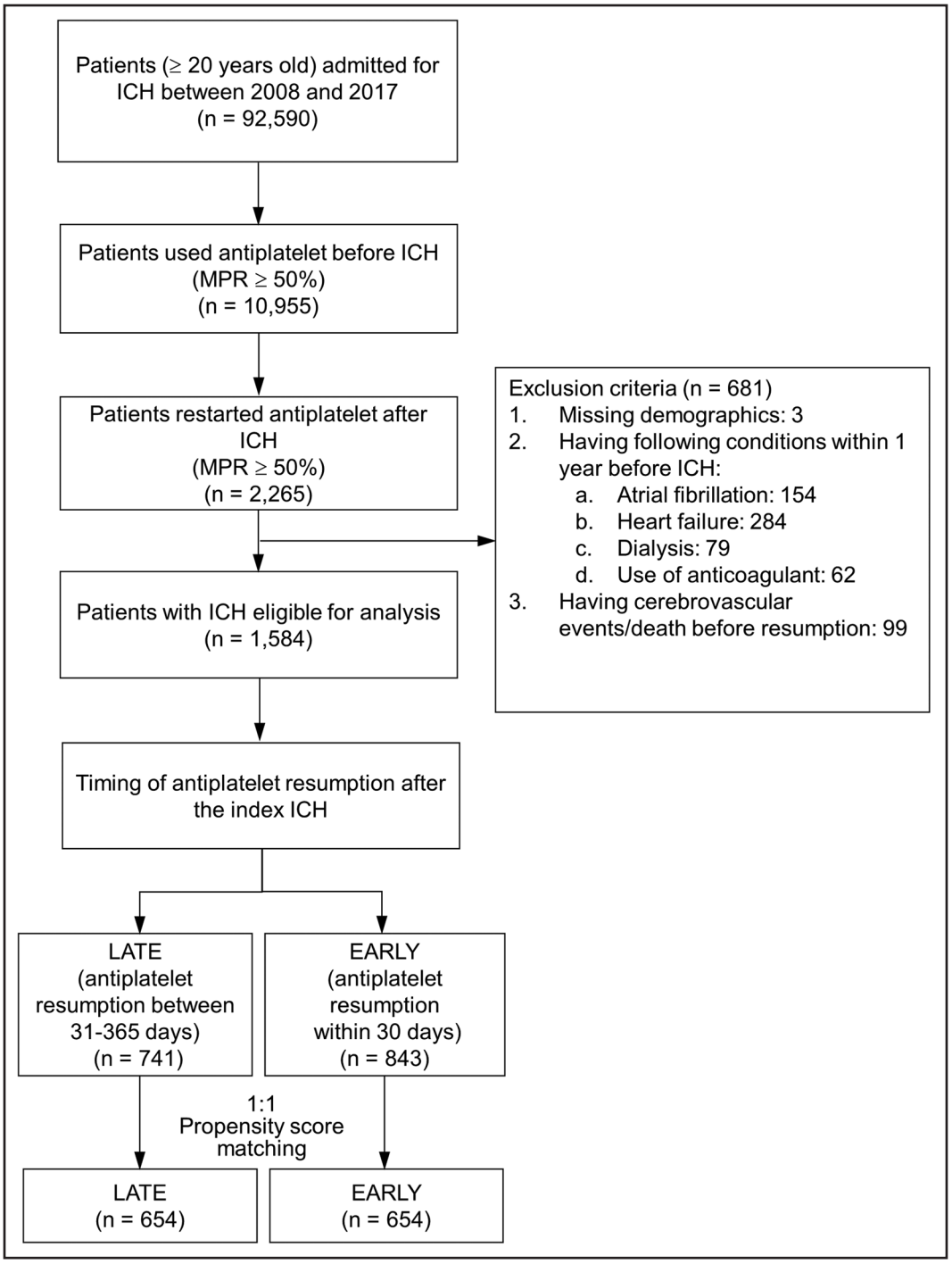

Figure 1. Flow chart for the inclusion of study patients.
ICH indicates intracerebral hemorrhage; and MPR, medication possession ratio.

We extracted the patients' baseline characteristics from the claim database and traced their diagnostic codes within 1 year before the index ICH to define the presence of major comorbidities. Comorbidities were defined if the patients had at least an inpatient diagnosis or 2 outpatient diagnoses of the disease, and prior CVD and MI were defined by any inpatient diagnosis. The diagnostic codes for these events and comorbidities have been validated previously[18] and are listed in Table S1. Charlson Comorbidity Index (CCI) and stroke severity index (SSI) scores were also calculated in the 2 groups. The CCI score represents a patient's overall systemic health status.[19] The claim-based SSI for ICH was validated in a previous NHIRD study.[20]

Outcome Measurements

The primary outcome was recurrent ICH, which was identified by the hospitalization with an ICD-9-CM code of 431 or ICD-10-CM code of I61 during the follow-up period. The secondary

outcomes included all-cause mortality, major hemorrhagic events, major occlusive vascular events, and IS. Major hemorrhagic events included intracranial hemorrhage and major gastrointestinal hemorrhage. Major occlusive vascular events included IS, MI, ischemic heart disease, and peripheral vascular disease. IS was defined when patients were admitted primarily due to IS. The definitions of major hemorrhagic events, MI, ischemic heart disease, IS, and all-cause mortality were the same as those used in our previous NHIRD studies (Table S1).[21,22] The patients were followed from cohort entry until the occurrence of a primary/secondary outcome, the end of 1-year follow-up, death, or until December 31, 2018, whichever occurred first.

Statistical Analysis

Propensity score matching (PSM) was used to balance the distribution of baseline characteristics between the 2 study groups. The covariates used to calculate the propensity score included age, sex, year of ICH patients' entry into the cohort, comorbidities, CCI scores, and SSI scores. The greedy nearest neighbor matching algorithm was used for the 8-to-1-digit of the PSM. Replacement after matching was not allowed, and we randomly selected 1 control if >1 matched control were identified. A 1:1 matching ratio was used.[23] The risk of all-cause mortality was compared between the 2 groups using a Cox proportional hazard model with robust sandwich standard error estimates. The risk of investigated events other than mortality was compared using the Fine and Gray subdistribution hazard model, which considered all-cause mortality as a competing risk. The study groups (EARLY versus LATE) were the only explanatory variables in the survival analysis. Subgroup analyses for recurrent ICH were conducted on 5 pre-specified variables, including age, hypertension, diabetes, CKD, and prior CVD. The EARLY group was further divided into 2 subgroups (antiplatelet resumption 1–14 days and 15–30 days after the index ICH). Outcomes were compared between these subgroups after PSM. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was set at $P<0.05$.

RESULTS

Study Patients

A total of 92 590 patients admitted due to ICH were available in the NHIRD. Of these patients, 10 955 had an antiplatelet MPR1≥50%, but only 2265 continued antiplatelet therapy with an MPR2≥50%. Three patients with missing information, 154 with AF and 284 with heart failure were excluded. In addition, 79 patients with a history of dialysis, 62 who underwent anticoagulant therapy, and 99 who had cerebrovascular events or died before antiplatelet resumption were also excluded. Finally, 1584 ICH patients were eligible for analysis, including 843 in the EARLY group and 741 in the LATE group (Figure 1).

Baseline Characteristics

Before PSM (Table 1), the EARLY group had an older age (EARLY versus LATE: 71.28±11.97 versus 70.06±11.71 years; $P=0.0414$) and a higher frequency of acute MI (6.17% versus 3.24%; $P=0.0065$). The frequencies of comorbidities including hypertension, diabetes, CKD, prior CVD, ischemic heart disease, dyslipidemia, and the CCI scores as well as the proportion of antihypertensive medication use were not different between the 2 groups. There was a higher SSI score in the LATE group (EARLY versus LATE: 9.91±5.62 versus11.67±5.76, $P<0.0001$). The EARLY group had a higher frequency of prior dual antiplatelet use before the index ICH (12.34% versus 6.61%; $P=0.0001$), but both groups had nonsignificant difference of dual antiplatelet use after resumption (4.74% versus 3.37%; $P=0.1699$). After PSM (Table S2), all baseline characteristics were well balanced between these groups.

Table 1. Characteristics of the Study Patients Before Propensity Score Matching

Demographic characteristic	LATE group (n = 741)	EARLY group (n = 843)	*P* value
Men, n (%)	475 (64.10)	547 (64.89)	0.7446
Age, mean±SD	70.06±11.71	71.28±11.97	0.0414
<50 y	27 (3.64)	36 (4.27)	0.0921
50–64 y	218 (29.42)	202 (23.96)	
65–74 y	201 (27.13)	255 (30.25)	
≥75 y	295 (39.81)	350 (41.52)	
Comorbidity, n (%)			
Hypertension	602 (81.24)	668 (79.24)	0.3190
Diabetes	327 (44.13)	395 (46.86)	0.2769
Chronic kidney disease	96 (12.96)	134 (15.90)	0.0975
Prior CVD	619 (83.54)	681 (80.78)	0.1541
Ischemic heart disease	258 (34.82)	311 (36.89)	0.3906
Acute myocardial infarction	24 (3.24)	52 (6.17)	0.0065
Dyslipidemia	322 (43.45)	357 (42.35)	0.6572
CCI score, mean±SD	1.89±1.65	1.95±1.69	0.5271
0	186 (25.10)	218 (25.86)	0.7000
1	154 (20.78)	161 (19.10)	
≥2	401 (54.12)	464 (55.04)	
SSI score, mean±SD	11.67±5.76	9.91±5.62	<0.0001
0–5	137 (18.49)	278 (32.98)	<0.0001
6–10	259 (34.95)	280 (33.21)	
11–15	142 (19.16)	131 (15.54)	
≥16	203 (27.40)	154 (18.27)	
HTN medication, n (%)	637 (85.96)	723 (85.77)	0.9093
Prior antiplatelet use before ICH			
SAPT	692 (93.39)	739 (87.66)	0.0001
DAPT	49 (6.61)	104 (12.34)	
Antiplatelet use after ICH			
SAPT	716 (96.6)	803 (95.3)	0.1699
DAPT	25 (3.37)	40 (4.74)	

Statistics: Student *t* test or χ^2 test with $P<0.05$ indicating significance. CCI indicates Charlson Comorbidity Index; CVD, cerebrovascular disease; DAPT, dual antiplatelet; HTN, hypertension; SAPT, single antiplatelet; SD, standard deviation; and SSI, stroke severity index.

Primary Outcome: Recurrent ICH

Compared with the LATE group, the EARLY group had a similar risk of 1-year recurrent ICH before (EARLY versus LATE: 4.63% versus 3.37%; adjusted hazard ratio [AHR], 1.415 [95% CI, 0.854–2.347]; Table S3) and after PSM (3.12% versus 3.27%; AHR, 0.967 [95% CI, 0.522–1.791]; Table 2). There was a similar cumulative probability of event-free survival for the recurrent ICH in both groups (P=0.9414; Figure 2).

Secondary Outcomes

The risks of all-cause mortality (EARLY versus LATE: 9.17% versus 7.19%; AHR, 1.364 [95% CI, 0.916–2.031]), major hemorrhagic events (4.86% versus 6.11%; AHR, 0.780 [95% CI, 0.482–1.260]), major occlusive vascular events (8.02% versus 9.12%; AHR, 0.829 [95% CI, 0.567–1.212]), and IS (4.80% versus 4.18%; AHR, 1.147 [95% CI, 0.689–1.909]) had no significant difference between the 2 groups at 1-year follow-up (Table 2).

Subgroup Analyses

After PSM, subgroup analyses of recurrent ICH defined by 4 baseline features did not disclose any significant difference to the observed effect of early antiplatelet use (Figure 3A). In addition, there was no significant difference to the observed effect of early antiplatelet use in the age subgroups of primary and secondary outcomes (Table S4). However, EARLY group without prior CVD was associated with significantly lower risks of all-cause mortality (AHR, 0.199 [95% CI, 0.054–0.739]; Figure 3B) and major hemorrhagic events (AHR, 0.090 [95% CI, 0.010–0.797]; Figure 3C and Table S5). Besides, EARLY group with CKD was associated with a lower risk of IS (AHR, 0.065 [95% CI, 0.012–0.364]; Figure 3E). There was also an observed interaction between diabetes and IS ($P_{interaction}$=0.0355). However, the risks of IS were not different between the EARLY and LATE groups in patients with (AHR, 2.030 [95% CI, 0.916–4.501]) or without (AHR, 0.584; 95% CI [0.267–1.277]) a history of diabetes (Figure 3D and Table S5). There was no significance regarding the 1-year outcomes among patients resuming antiplatelet 1–14, 15–30, or 31–365 days after ICH before PSM (Table S6). After PSM, there was a lower risk of all-cause mortality if antiplatelet was resumed within 14 days (1–14 versus 15–30 days: 4.53% versus 9.06%; AHR, 0.422; 95% CI, 0.205–0.868; Table S7).

DISCUSSION

In this study, we found that EARLY group with the resumption of antiplatelet therapy within 30 days after ICH had similar risks of recurrent ICH, all-cause mortality, major hemorrhagic events, major occlusive vascular events, and IS compared with the LATE group. However, our subgroup analyses showed ICH patients without prior CVD could benefit more from early antiplatelet resumption

Table 2. Hazard Ratios of 1-Year Outcomes in the Late Versus Early Groups After Propensity Score Matching

(Patient number)	Events, n (%)	Crude HR [95% CI]	Adjusted HR [95% CI]	*P* value
Primary outcome				
Recurrent ICH				
Late (642)	21 (3.27)	1.00 [reference]	1.00 [reference]	
Early (642)	20 (3.12)	0.977 [0.531–1.800]	0.967 [0.522–1.791]	0.9145
Secondary outcomes				
All-cause mortality				
Late (654)	47 (7.19)	1.00 [reference]	1.00 [reference]	
Early (654)	60 (9.17)	1.318 [0.901–1.929]	1.364 [0.916–2.031]	0.1266
Major hemorrhagic events				
Late (638)	39 (6.11)	1.00 [reference]	1.00 [reference]	
Early (638)	31 (4.86)	0.809 [0.505–1.295]	0.780 [0.482–1.260]	0.3094
Major occlusive vascular events				
Late (636)	58 (9.12)	1.00 [reference]	1.00 [reference]	
Early (636)	51 (8.02)	0.879 [0.603–1.280]	0.829 [0.567–1.212]	0.3331
Ischemic stroke				
Late (646)	27 (4.18)	1.00 [reference]	1.00 [reference]	
Early (646)	31 (4.80)	1.167 [0.696–1.958]	1.147 [0.689–1.909]	0.5975

Adjusted by age, sex, year of ICH patients' entry into the cohort, hypertension, diabetes, chronic kidney disease, prior stroke, ischemic heart disease, acute myocardial infarction, dyslipidemia, Charlson Comorbidity Index score, and stroke severity index score. Adjusted HR with death as the competing risk. HR indicates hazard ratio; and ICH, intracerebral hemorrhage.

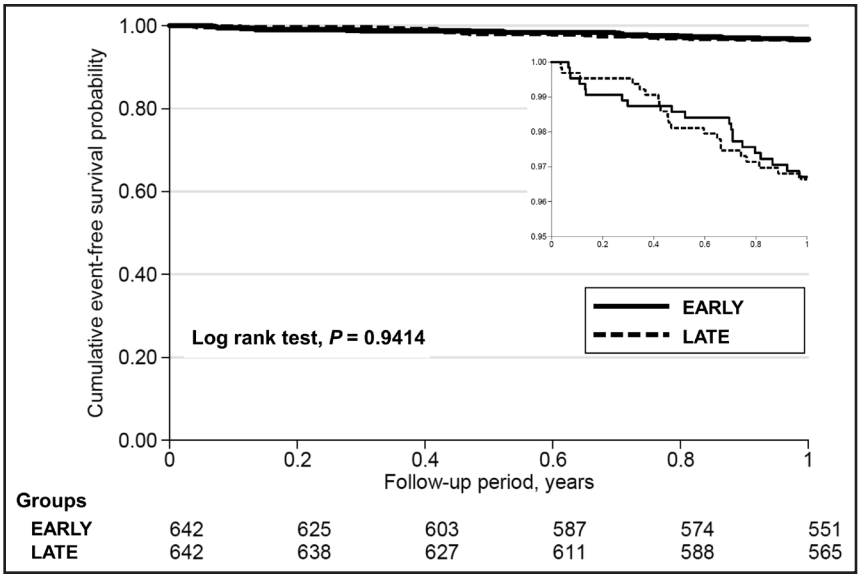

Figure 2. Comparison of the cumulative probability of recurrent intracerebral hemorrhage-free between the EARLY and LATE groups in the propensity score matched cohort.
The curves show a similar cumulative probability of event-free between the 2 groups. The adjusted hazard ratios consider mortality as a competing risk.

due to the lower risks of major hemorrhagic events and all-cause mortality. Also, ICH patients with prior CKD may benefit more from early antiplatelet resumption due to the lower risk of ischemic stroke.

A recent study demonstrated that ICH could be a novel risk factor for arterial thrombotic events,[24] and elderly ICH survivors have been reported to have an increased risk of death after a subsequent IS or MI.[8] Anticoagulant resumption is recommended 4–8 weeks after ICH in patients with AF.[25] The SoSTART and APACHE-AF trials investigated the advanced resumption of anticoagulant ≥1 and 7–90 days after ICH, respectively, and found that the resumption of anticoagulant at median 104 and 45 days after ICH, respectively, did not increase the risk of hemorrhagic events.[26,27] Compared with anticoagulant, antiplatelet is associated with a lower risk of bleeding complications.[28] It is therefore reasonable that antiplatelet could be resumed earlier than anticoagulants. Our results suggest the early resumption of antiplatelet within 30 days after ICH could be a safe strategy.

Asians have a high incidence of small vessel disease such as ICH, cerebral microbleed, and lacunar infarction.[29,30] The major concerns with early antiplatelet resumption in ICH patients are the risks of hematoma enlargement and recurrent bleeding,[31,32] which are related to multifocal microscopic and macroscopic bleeding into the peri-hematoma area.[32] Local tissue distortion, blood-brain barrier breakdown, and secondary inflammatory reactions are the possible mechanisms responsible for hematoma enlargement.[32–34] Prior antiplatelet use is a risk factor for hematoma enlargement or early evacuation.[1,35] However, platelet transfusion has not been shown to improve clinical outcomes in ICH patients with prior antiplatelet treatment.[36,37] Previous study reported that antithrombotic, particularly antiplatelet, could be used safely after ICH and may not be associated with neurological deterioration or aggravation of hematoma.[38] Other studies demonstrated that blood-brain barrier can be repaired and recovered 7–14 days after ICH, and suggested an insufficient evidence to preclude antiplatelet resumption within 1 month after ICH.[39,40] Our results may help support the resumption of antiplatelet within 1 month after ICH.

Patients with multiple cerebral microbleeds are at risk of ICH and IS,[41] and aspirin is suggested to be used 4–6 weeks after ICH in these patients.[42] However, the limitation of NHIRD is the lack of image data, which precludes the examination of cerebral microbleeds in patients with antiplatelet resumption. The types of antiplatelet could also be a contributing factor to the clinical outcomes in ICH patients. One previous study using NHIRD showed that the use of phosphodiesterase inhibitor prior to ICH may be associated with lower in-hospital mortality when compared with the use of cyclooxygenase inhibitors or adenosine diphosphate receptor inhibitors.[43] However, whether switching antiplatelets is associated with a better clinical outcome after ICH deserves further investigation.

In Kaplan-Meier survival analysis of the 99 patients with cerebrovascular events or mortality prior to antiplatelet resumption, 43.4% of the event or death occurred within the first 60 days after index ICH (Figure S1). In real-world practice, physicians tend to add antiplatelet agent earlier to patients with a high thrombotic risk but low stroke severity and bleeding risk in order to reduce the occurrence of ischemic diseases. These could be the possible reasons to explain why in our study, the patients resuming antiplatelet within 14 days had a trend of lower all-cause mortality than those restarting antiplatelet 15–30 days after the index ICH. CKD is a known risk factor associated with high risks of stroke recurrence and suboptimal treatment in acute stroke,[44] and our study revealed ICH patients with CKD might have a lower risk of IS if antiplatelet was resumed early.

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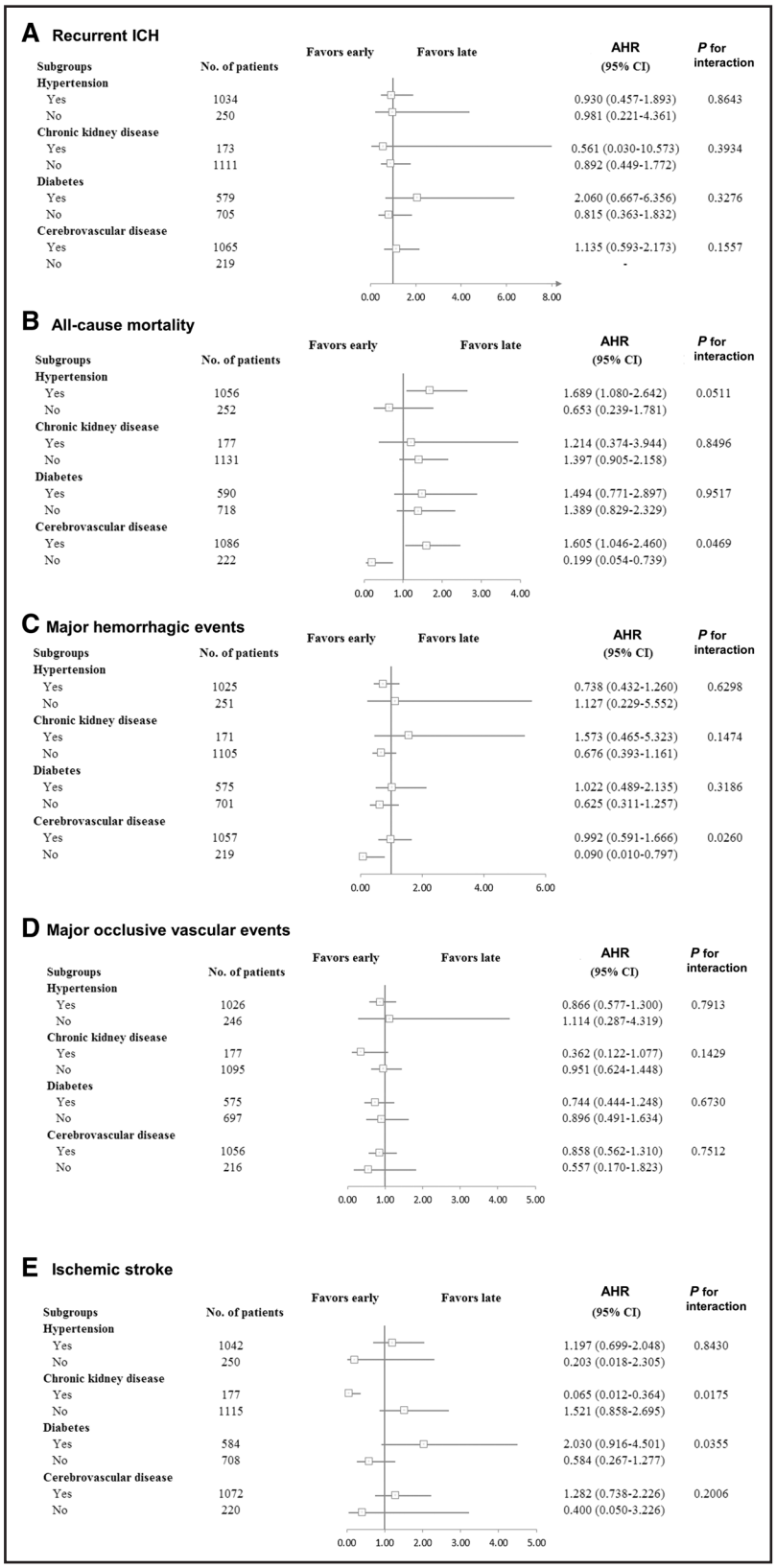

Figure 3. Subgroup analyses of primary and secondary outcomes. **A**, Subgroup analyses of recurrent intracerebral hemorrhage do not disclose significant differences to the observed effect of early antiplatelet use. **B**, Patients without previous cerebrovascular disease have lower risks of all-cause mortality (adjusted hazard ratio [AHR], 0.199 [95% CI, 0.054–0.739]). **C**, Major hemorrhagic events (AHR, 0.090 [95% CI, 0.010–0.797]) in the EARLY group. **E**, In ischemic stroke (IS) analysis, patients with chronic kidney disease (AHR, 0.065 [95% CI, 0.012–0.364]) are associated with a lower risk of IS in the EARLY group. Although there is also an observed interaction between diabetes and IS ($P_{interaction}$=0.0355), the risks of IS are not different between the EARLY and LATE groups in patients with or without a history of diabetes (**D**). Statistical significance for interaction of subgroup analyses is set at P<0.05.

Our data also demonstrated relatively lower risks of all-cause mortality and major bleeding in EARLY group without prior CVD. Although patients with prior stroke may potentially gain benefit from antiplatelet resumption, previous stroke is also a well-known risk factor for ICH occurrence and may be associated with a higher bleeding risk after antithrombotic use.[45] This may offset the net benefit of antiplatelet resumption in the ICH patients

with prior CVD. Furthermore, previous study showed significantly higher risks of all-cause mortality, and cardiac death in coronary artery disease patients with a history of stroke.[46] Coronary artery disease is another main reason for antiplatelet use before ICH, and these patients may have an increased risk of acute coronary syndrome when antiplatelet is discontinued.[47] These may also explain why our EARLY group patients without prior CVD were associated with a lower risk of mortality.

There are several limitations to the present study. First, although the NHIRD contains administrative data, several risk factors such as lifestyle, laboratory results, smoking and physical activity are not recorded. The degree of medication adherence may also not be reflected by the recorded prescription pattern. To overcome this inherent limitation, we used MPR≥50% to select eligible patients under antiplatelet treatment. Second, the NHIRD lacks image data. So, the effects of cerebral microbleeds, hematoma size and location cannot be evaluated to correlate with the stroke severity and clinical outcomes. Third, clinicians may consider the timing of antiplatelet resumption after ICH based on ICH severity and clinical comorbidities to prevent from recurrent ICH. Such decision could be the major confounding factor affecting the resumption of antiplatelets after ICH. Before PSM, the EARLY group had lower SSI but higher CCI scores. It is likely that in real-world practice, physicians tend to resume antiplatelet earlier for patients with high vascular comorbidities but low stroke severity to prevent major occlusive-ischemic events, which could also lead to attribution bias. However, NHIRD includes >99.5% population in Taiwan, which could mitigate the influence of attribution bias. Randomized trial in the future is warranted to confirm or dispute our findings. It is also possible that our findings could be biased due to the differences in baseline characteristics and confounded by indication after matching. Fourth, poor blood pressure control is known to be a predictor of hematoma enlargement after ICH and is also a risk factor for ICH in patients receiving antiplatelet.[32,48] Data on blood pressure were also not available in the NHIRD, we could not investigate the impact of blood pressure control on antiplatelet resumption. Finally, the generalizability of our findings to another ethnicity remains uncertain.

CONCLUSIONS

The early resumption of antiplatelet within 30 days was not associated with an increased risk of recurrent ICH and was as safe as late antiplatelet resumption after ICH. Our results may help mitigate the concern of early antiplatelet resumption in patients at risk of thrombo-embolic disease, and help provide evidence on the suitable timing of antiplatelet resumption after ICH.

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Disclosures

None.

Supplemental Material

STROBE checklist
Table S1–S7
Figure S1

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