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# Racial and ethnic differences in restarting antiplatelet therapy in patients with primary intracranial hemorrhage: a systematic review and meta-analysis

Xuechang Wang<sup>1</sup>, Ting Chen<sup>2</sup>, Junning Zhou<sup>3</sup> and Yuan Qin<sup>4\*</sup>

## Abstract

**Background** There has long been clinical disagreement over the resumption of antiplatelet therapy in patients with primary intracranial hemorrhage (ICH). This meta-analysis aimed to systematically evaluate the efficacy and safety of restarting antiplatelet therapy after ICH among different races and ethnicities.

**Methods** All relevant medical studies involving adults with antiplatelet-associated ICH published in PubMed, The Cochrane Library and Chinese National Knowledge Infrastructure from inception to March 2024 were sourced. Outcome measures were thromboembolic events (stroke and myocardial infarction) and recurrence of ICH. After assessing study heterogeneity and publication bias, we performed a meta-analysis using random-effects model to assess the strength of association between resumption of antiplatelet therapy and our outcomes. The review was not registered and the review protocol was not prepared.

**Results** Thirty-five studies were included, with 9758 ICH patients. Subgroup analysis revealed that restarting antiplatelet therapy was associated with a significantly higher risk of recurrence or aggravation of cerebral hemorrhage in Asians [OR = 1.48, 95% CI (1.13–1.94),  $P = 0.004$ ]; in Caucasians, on the contrary, reinitiation of antiplatelet therapy was not associated with a significantly higher risk of recurrence or aggravation of cerebral hemorrhage [OR = 0.85, 95% CI (0.67–1.06),  $P = 0.149$ ]. Reinitiation of antiplatelet therapy was associated with a significantly lower risk of cerebral infarction [OR = 0.61, 95% CI (0.39–0.96),  $P = 0.033$ ]. Restarting antiplatelet therapy after cerebral hemorrhage was not associated with a higher incidence rate of mortality [OR = 0.79, 95% CI (0.57, 1.08),  $P = 0.138$ ], myocardial infarction [OR = 2.40, 95% CI (0.53, 10.79),  $P = 0.253$ ], hemiparesis [OR = 0.38, 95% CI (0.03, 4.81),  $P = 0.451$ ], neurological deficit [OR = 0.86, 95% CI (0.32, 2.33),  $P = 0.766$ ].

**Conclusion** Reinstitution of antiplatelet therapy after ICH was associated with a lower risk of thromboembolic complications. Resumption of antiplatelet therapy was not associated with a higher incidence of cerebral hemorrhage in Caucasians, but may be associated with a higher risk of cerebral hemorrhage recurrence in Asian populations.

**Keywords** Antiplatelet therapy, Cerebral hemorrhage, Systematic review

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## Background

Intracerebral hemorrhage refers to the nontraumatic rupture and bleeding of small arteries, which causes blood to accumulate in the brain. It is a type of stroke and can be classified as cerebral small vessel disease [1, 2]. It is one of the most common and serious complications in the current antithrombotic treatment process, and its occurrence is often accompanied by high mortality and disability rates. Since high risk factors for ICH (such as advanced age, hypertension, and smoking) are also risk factors for occlusive vascular disease [3], many ICH patients have ischemic stroke or coronary artery disease [4], which has a long-term onset under these conditions and is an important cause of death [5–7]. Antiplatelet therapy is the cornerstone of primary and secondary prevention of ischemic coronary artery disease and stroke; therefore, even after ICH, a considerable number of patients may still need to live antithrombotic treatment for prevention and treatment of occlusal vascular diseases. Among patients with cerebral hemorrhage, as many as 44% are indeed taking antithrombotic drugs [8, 9]. Under normal circumstances, if a patient develops new cerebral hemorrhage or enlarges the hematoma during antithrombotic treatment, the antithrombotic drugs will be stopped immediately. The discontinuation of these drugs is usually permanent. However, the risk of occlusive vascular events may be higher [9], and clinicians are often faced with the challenging decision of whether to restart antithrombotic therapy and, if so, when because of a perceived increased risk of recurrent intracerebral hemorrhage [10]. Nevertheless, we know that in the ten years after the incident, survivors still face a higher risk of death [7]. Therefore, most doctors are reluctant to start antiplatelet therapy in patients with a history of ICH. First, ICH can recur, and previous use of antiplatelet drugs is associated with early hematoma growth in the disease and a higher risk of death [11, 12]. Second, long-term treatment of antiplatelet drugs itself may also increase the incidence of hemorrhagic stroke [13]. To specifically analyze the benefits and safety of patients with ICH after restarting antiplatelet therapy, this article searched relevant studies for a systematic review, which aimed to provide a reference for clinical treatment plans.

## Methods

### Search strategy

We performed comprehensive searches in PubMed, The Cochrane Library, and Chinese National Knowledge Infrastructure from inception to March 2024. Keywords used to query the databases were selected from the MESH Medical Topics Database. Taking the PubMed database as an example, we used the search terms (“intracranial hemorrhages” OR “brain hemorrhages” OR “cerebral hemorrhages”) AND (“antiplatelet”

OR “antithrombotic” OR “anticoagulant” OR “aspirin” OR “clopidogrel” OR “ticlopidine” OR “cilostazol” OR “dipyridamole”) AND (“recurrent intracranial hemorrhage” OR “hematoma expansion” OR “venous thrombosis” OR “arterial thrombosis” OR “myocardial infarction” OR “ischemic stroke” OR “transient ischemic attack”). Articles published in both English and Chinese were included.

### Inclusion and exclusion criteria

The inclusion criteria for our study were as follows: (1) Research design: randomized controlled trials or cohort studies; (2) Research objects: all adult ICH patients  $\geq 18$  years of age; (3) Intervention measures: restart antiplatelet treatment in the experimental group and not reinstate any antithrombotic drugs in the control group; (4) sample size  $\geq 10$  patients to avoid inclusion of case reports or small case series; (5) Outcome indicators: the experimental group and the control group reported recurrence or aggravation of cerebral hemorrhage (a detrimental event of ICH which results in progressive neurologic deteriorations and poor outcomes and defined as an increase in the hematoma volume or CT attenuation value), ischemic stroke, acute coronary syndrome, myocardial infarction and other cardiovascular events, mortality, hemiplegia, and modified Rankin’s scale (mRS) [14]: mRS score  $< 2$  was divided into good functional outcome, while mRS score  $> 2$  was divided into poor outcome. Quality of life (QOL) score, hemiplegia, neurological deficit.

The specific exclusion criteria were as follows: (1) review, case report, letter, commentary, and medical record reports; (2) studies for which the full text was not available or the data provided by the studies could not be converted in specific analysis; and (3) studies with antiplatelet treatment terminated or changed from antiplatelet treatment to other antithrombotic treatment in patients during follow-up.

### Study screening and data extraction

A single investigator (W.X.) had read the title and abstract produced by the initial search and shortlisted articles for further review. These articles were then independently reviewed by 2 investigators (C.T. and Z.J.) and selected based on the inclusion criteria and quality of data. Any disagreements were resolved by a third investigator (Q.Y.). The basic information of the extracted study included author, year, country, age, gender, intervention measures, treatment course, follow-up time limit, etc.

### Study quality evaluation and statistical methods

The quality of studies were evaluated using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) and using the Newcastle–Ottawa Scale (NOS) [15] for non-randomised studies, which was based on the

selection of study groups, comparability of groups and ascertainment of outcome. We used Stata (version 15.0) to perform statistical analysis on the benefits and risks of antiplatelet resumption using the pooled odds ratio (OR) and 95% confidence interval (95% CI) as the effect parameter. The  $I^2$  statistic was used to evaluate heterogeneity (with  $I^2 > 50\%$  indicating significant heterogeneity) as was Cochran's Q P value (with P value  $< 0.05$  indicating significant heterogeneity). To account for heterogeneity, random-effects model was used throughout. Sensitivity analysis was performed to address the influence of each single study on the overall results by removing one study at a time and calculating the combined OR for the remaining studies. Begg's test [16] and Egger's test [17] were conducted to evaluate publication bias. All tests were 2-tailed, and P values  $< 0.05$  were considered significant.

## Results

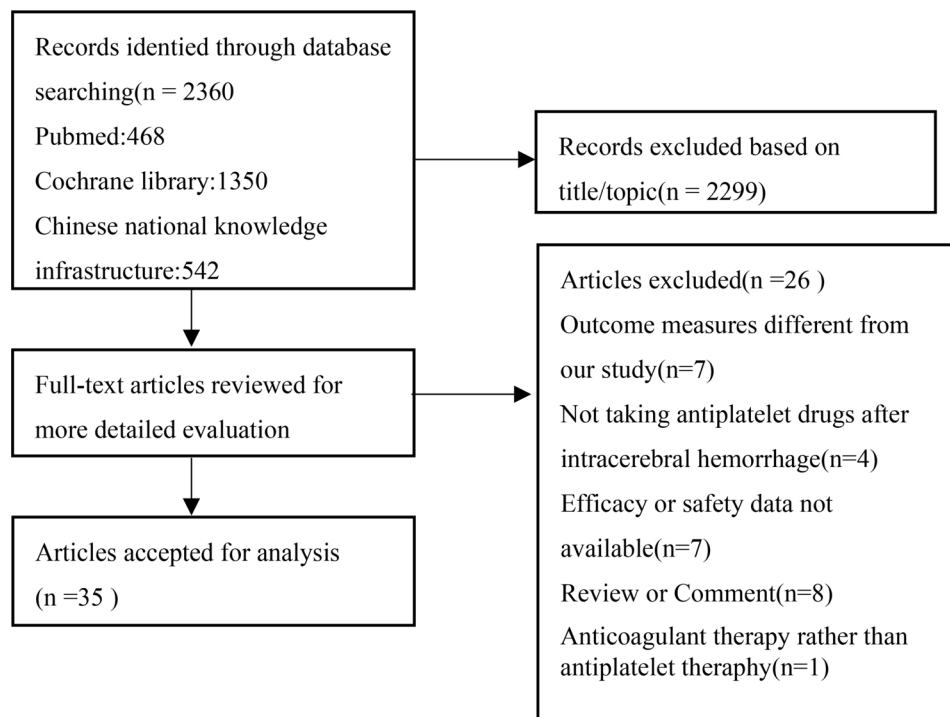
A total of 2360 titles and abstracts were screened, from which 35 studies met the inclusion criteria. The flow chart of study selection was shown in Fig. 1. There were 16 studies [18–34] in Asia, 17 studies [35–51] in Europe or America, a study [52] in Australia.

The 35 studies were published between 1982 and 2024 and included 9758 patients. Among these patients, antiplatelet therapy was restarted in 2971 (30.45%) patients and not restarted in the remaining 6787 patients (69.55%). The mean age of patients, location of ICH, type

of antiplatelet agents, timing of antiplatelet resumption, duration of follow-up, and NOS scores of the cohort study were all shown in Table 1. Quality assessment of included RCTs were shown in Fig. 2.

## Comparison of incidence rate of recurrence or aggravation of ICH

Thirty-five studies [18–52] (9758 patients) reported the effect of antiplatelet therapy on the incidence of recurrence or aggravation of cerebral hemorrhage. The rate of recurrence or aggravation of cerebral hemorrhage in patients on antiplatelet therapy was 13.33% compared with 15.07% for patients not restarted on antiplatelet therapy (Fig. 2). The heterogeneity was detected ( $I^2 = 46.6\%$ ,  $p = 0.002$ ). We performed subgroup analyses by different races and ethnicities. Then there was no heterogeneity within subgroups. In the Asian population, restarting antiplatelet therapy was associated with higher incidence of recurrence or aggravation of cerebral hemorrhage [OR = 1.48, 95% CI (1.13–1.94),  $P = 0.004$ ], and no significant heterogeneity ( $I^2 = 13.0\%$ ,  $P = 0.305$ ) was found between these articles; however, the opposite result appeared in the Caucasian population, restarting antiplatelet therapy was not associated with higher incidence of recurrence or aggravation of cerebral hemorrhage [OR = 0.85, 95% CI (0.67–1.06),  $P = 0.149$ ], with no significant heterogeneity ( $I^2 = 33.5\%$ ,  $P = 0.078$ ), as shown in Fig. 3. A study [51] reported that restarting antiplatelet therapy in patients with non-lobar hemorrhage was



**Fig. 1** Flow chart of study selection

**Table 1** Basic characteristics of the included studies

First author year	Country	Number of patients	Male sex (%)	Age (years)	Location of ICH	Type of antiplatelet therapy	Timing of antiplatelet resumption	Duration of follow-up	Study design	NOS score
Mendelow AD 1982 [35]	Britain	53	43.4	NR	Subarachnoid	Aspirin	NR	NR	RCT	-
Shaw M 1985 [36]	Britain	677	NR	45.4	Subarachnoid	Dipyridamole	3 months	NR	RCT	-
Suzuki S 1989 [18]	Japan	258	41.1	52.3	Subarachnoid	Ozagre	12.2 days	NR	RCT	-
Tokiyo-shi S 1991 [19]	Japan	24	NR	54.2	Subarachnoid	Ozagre	8–14 days	1 month	Cohort study	7
Juvela S 1995 [37]	Finland	291	51.2	45.01	Subarachnoid	Aspirin	NR	1 year	Cohort study	8
Hop JW 2000 [38]	Netherlands	50	26	48.08	Subarachnoid	Aspirin	21 days	4 months	RCT	-
Rust T 2006 [52]	Australia	81	70	NR	Subdural	Aspirin	NR	NR	Cohort study	6
Walter M 2006 [39]	Netherlands	161	21	53	Subarachnoid	Aspirin	14 days	3 months	RCT	-
Torihashi K 2008 [20]	Japan	337	67.66	74.5	Subdural	NR	NR	1 months	Cohort study	7
Lindvall P 2009 [40]	Sweden	71	79	73.9	Subdural	Aspirin/Ticlopidine	14.3 days	12 months	Cohort study	8
Jia WH 2010 [21]	China	268	63.05	62.69	Lobar/Basal ganglia/Brain stem/cerebellum	Aspirin/Clopidogrel	NR	NR	Cohort study	7
Flynn RW 2010 [41]	Britain	417	49.9	69.9	Lobar/Striatum/Thalamus/Cerebellum/Brain stem	Aspirin/Clopidogrel/Dipyridamole	14.8 months	NR	Cohort study	8
Chong BH 2012 [22]	China	440	62.27	59.23	Subarachnoid/Subdural/Lobar	Aspirin/Clopidogrel	NR	62.2 months	Cohort study	8
Chon KH 2012 [23]	South Korea	420	79.52	68.86	Subdural	Aspirin	NR	3 months	Cohort study	7
Okamura A 2013 [24]	Japan	125	69.6	79.62	Subdural	NR	NR	NR	Cohort study	7

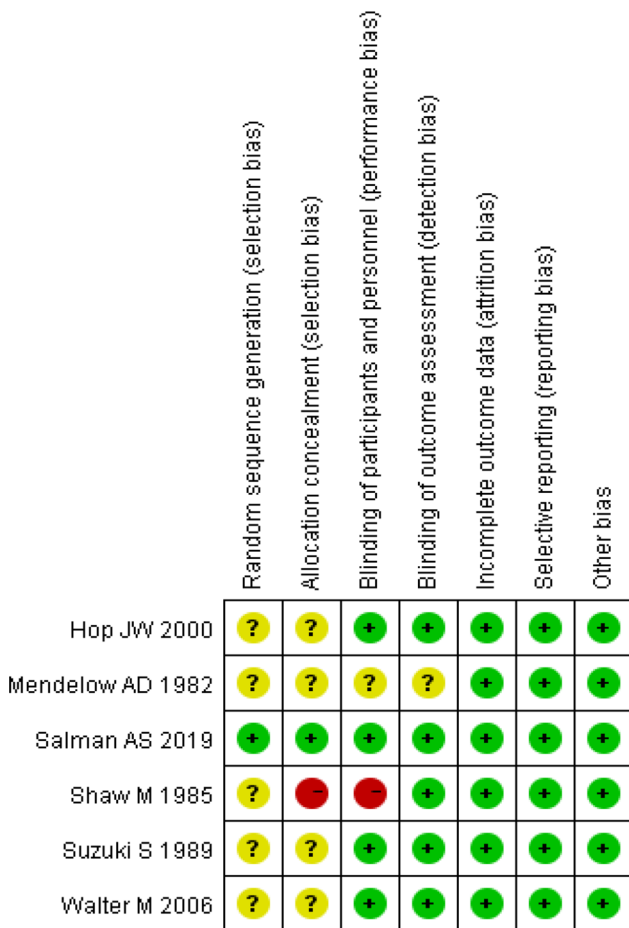
**Table 1** (continued)

First author year	Country	Number of patients	Male sex (%)	Age (years)	Location of ICH	Type of antiplatelet therapy	Timing of anti-platelet resumption	Duration of follow-up	Study design	NOS score
Okano A 2014 [25]	Japan	448	70.1	71.1	Subdural	NR	NR	NR	Cohort study	7
Aspegren OP 2013 [42]	Denmark	239	72	71.8	Subdural	Aspirin/ Clopidogrel/ Dipyridamole	NR	1–71 months	Cohort study	8
Baraniskin A 2014 [43]	Germany	312	57.05	70.9	Subdural	Aspirin/Clopidogrel	NR	NR	Cohort study	7
Teo KC 2014 [26]	China	51	47.1	74.3	Lobar/Deep cerebral/ Cerebellum/Brainstem/ Intraventricular	Aspirin/Clopidogrel	NR	2.5 years	Cohort study	7
Tugcu B 2014 [27]	Turkey	292	68.5	61.9	Subdural	NR	NR	NR	Cohort study	6
Wada M 2014 [28]	Japan	681	66.67	72.9	Subdural	Aspirin/Cilostazol/ Ticlopidine	NR	3 months	Cohort study	8
Mizutani K 2014 [29]	Japan	61	58.06	75.8	Subdural	Aspirin/ Clopidogrel/ Cilostazol	NR	1 month	Cohort study	7
Leroy HA 2015 [44]	France	140	89	75.84	Subdural	NR	NR	3 months	Cohort study	7
Chen T 2015 [30]	China	269	57.9	67.1	NR	Aspirin	NR	NR	Cohort study	6
Nielsen PB 2015 [45]	Denmark	1752	62	78	Lobar/Subdural/ Subarachnoid	Aspirin/ thienopyridines	24 days	5 years	Cohort study	8
Amano T 2016 [31]	Japan	150	71	77	Subdural	Ticlopidine/Aspi- rin/Clopidogrel/ Cilostazol	1 week	NR	Cohort study	7
Guha D 2016 [46]	Canada	479	71.2	72.3	Subdural	Aspirin/Clopidogrel	NR	3.1 months	Cohort study	7
Kuwabara M 2017 [32]	Japan	234	75.2	67.1	Subdural	NR	NR	3 months	Cohort study	7
Kameno-va M 2017 [47]	Switzerland	198	70.2	77.5	Subdural	Aspirin	NR	47 days	Cohort study	7
Brennan PM 2017 [48]	Britain	823	68	77	Subdural	Aspirin/ Clopidogrel/ Dipyridamole	NR	8 months	Cohort study	8

**Table 1** (continued)

First author year	Country	Number of patients	Male sex (%)	Age (years)	Location of ICH	Type of antiplatelet therapy	Timing of antiplatelet resumption	Duration of follow-up	Study design	NOS score
Liang GL 2017 [33]	China	68	60.29	64.25	Ventricle	Aspirin/Clopidogrel	NR	3 years	Cohort study	8
Teo KC 2017 [34]	China	109	66.97	72.75	subarachnoid/subdural	Aspirin	NR	3.5 years	Cohort study	8
Chen CJ 2018 [49]	America	859	61.23	62.44	Infratentorial/Lobar	NR	NR	3 months	Cohort study	7
Ab-boud T 2018 [50]	Germany	158	NR	71.82	Subdural	NR	NR	18.9 months	Cohort study	8
Salman AS 2019 [51]	Britain	537	67.04	76.5	Lobar/non-Lobar	Aspirin/Clopidogrel/Dipyridamole	NR	2 years	RCT	-

NR, not reported

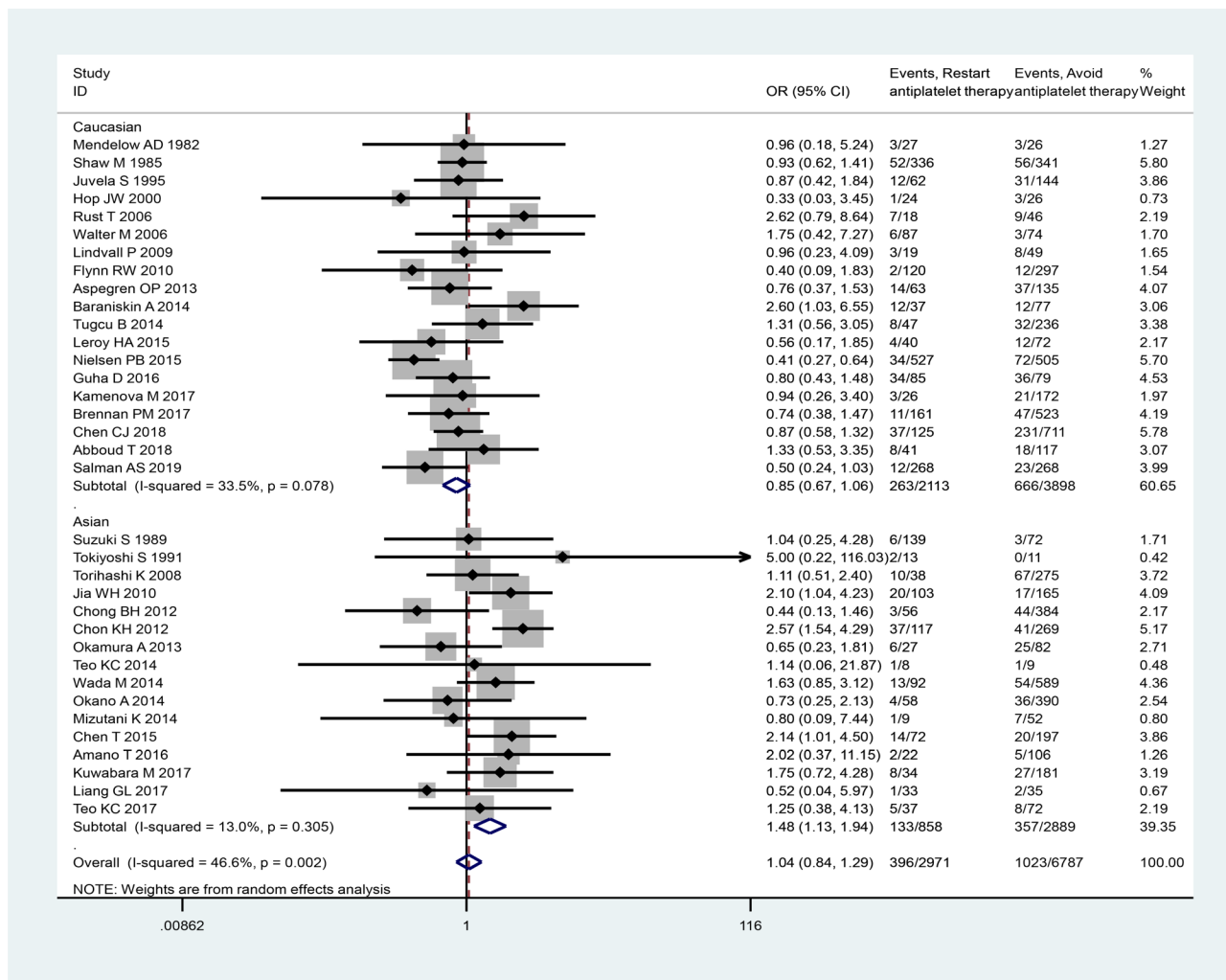


**Fig. 2** Quality assessment of included RCTs

associated with a lower incidence rate of cerebral hemorrhage [OR=0.31, 95% CI (0.10–0.96),  $P=0.047$ ], and restarting antiplatelet therapy in patients with lobar hemorrhage was not associated with a higher incidence of cerebral hemorrhage [OR=0.71, 95% CI (0.28–1.82),  $P=0.480$ ]. We did subgroup analyses according to different study designs. Due to the presence of heterogeneity ( $I^2=53.1%$ ,  $P=0.001$ ), random-effects model was chosen. Both RCTs and cohort studies showed that restarting antiplatelet therapy was not associated with a higher incidence rate of cerebral hemorrhage, as shown in Fig. 4. Subgroup analyses of different locations of the bleed showed that restarting antiplatelet therapy was not associated with a higher incidence rate of cerebral hemorrhage in either subarachnoid subgroup or subdural subgroup or intraparenchymal subgroup, as shown in Fig. 5. Subgroup analysis of different antiplatelet agents showed that aspirin was associated with a higher incidence rate of cerebral hemorrhage, but dipyridamole and ozagrel were not associated with a higher incidence rate of cerebral hemorrhage, as shown in Fig. 6.

**Comparison of incidence rate of ischemic stroke**

Thirteen studies [21, 22, 31, 33, 34, 37–39, 41, 43, 45, 46, 51] (3517 patients) reported the effect of antiplatelet therapy on the incidence rate of cerebral infarction. There was large statistical heterogeneity ( $I^2=60.1%$ ,  $P=0.003$ ). Heterogeneity did not decrease after subgroup division, and the random-effects model was used for analysis. The results showed that restarting antiplatelet treatment after ICH was associated with a lower incidence rate



**Fig. 3** Forest plot of the incidence of recurrence or aggravation of ICH after restarting antiplatelet treatment based on different races and ethnicities

of cerebral infarction [OR=0.61, 95% CI (0.39–0.96),  $P=0.033$ ], as shown in Fig. 7.

#### Comparison of incidence rate of mortality

Eleven studies [19, 21, 29, 34, 37–39, 42, 47, 49, 51] (2448 patients) reported the effect of antiplatelet therapy on mortality, and there was no heterogeneity among studies ( $I^2=0%$ ,  $P=0.888$ ). A random-effect model was used for analysis. The results showed that restarting antiplatelet treatment after ICH was not associated with a higher incidence rate of mortality [OR=0.79, 95% CI (0.57, 1.08),  $P=0.138$ ], as shown in Fig. 8.

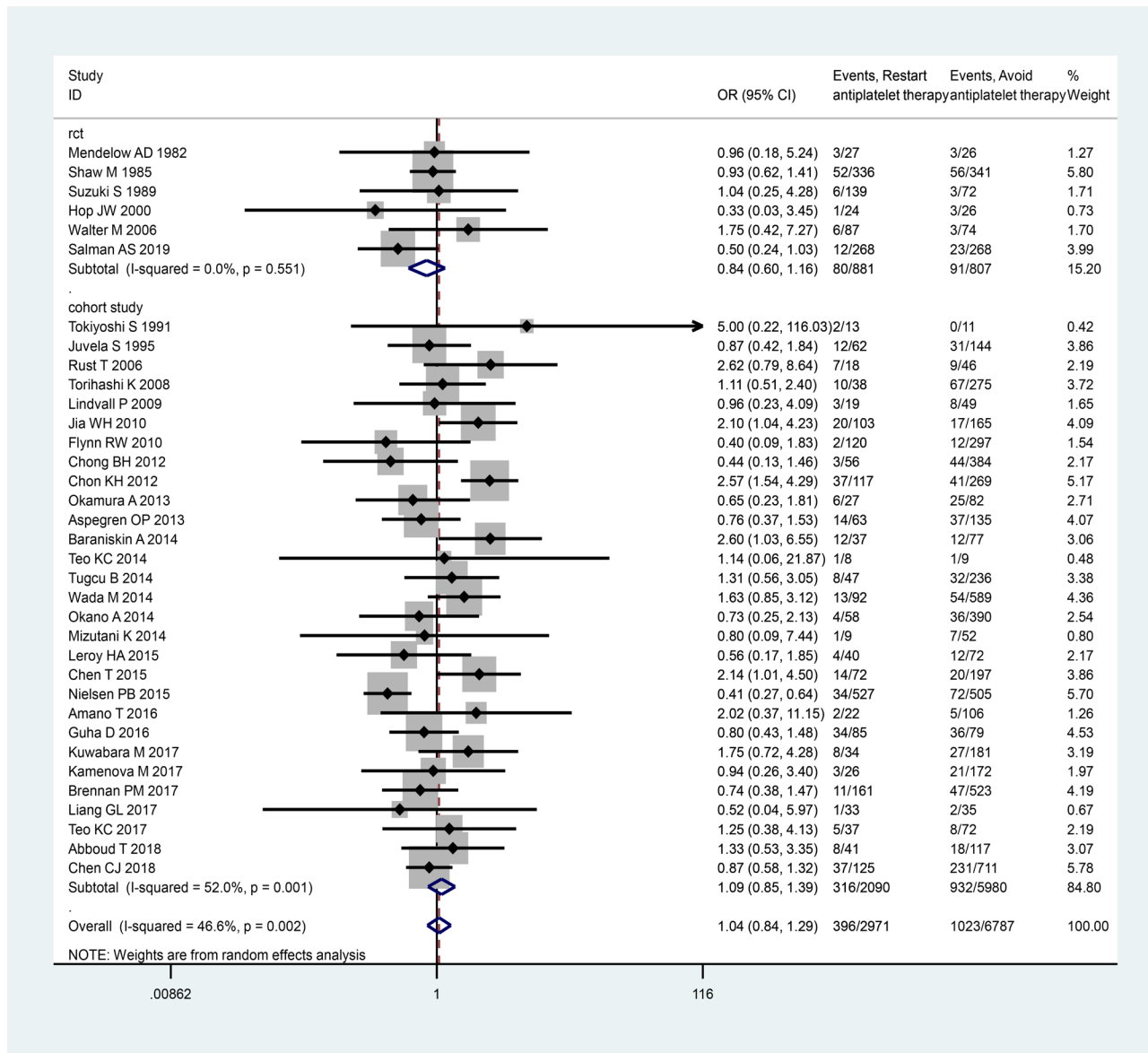
#### Other outcome indicators

The balance of ischemic cardiovascular events and recurrent ICH, among other bleeding complications, may affect functional outcomes and health-related quality of life measures after hospital discharge. In addition, the effect of recurrent ICH in patients taking antiplatelet

therapy on these measures may not be accurately portrayed by the incidence of recurrent ICH alone. So we evaluated the effects of restarting antiplatelet therapy on QOL score, MRS score, neurological deficit, and hemiplegia. Restarting antiplatelet therapy after cerebral hemorrhage was not associated with a higher incidence rates of neurological deficits, cardiovascular events, or hemiparesis. Antiplatelet resumption after cerebral hemorrhage was not associated with lower rates of functional outcome MRS score, QOL score, as shown in Table 2. Due to the small number of included studies and low test power, sensitivity analysis and publication bias evaluation were not performed.

#### Sensitivity analysis

Because of significant heterogeneity when assessing the relationship between resumption of antiplatelet therapy and the incidence of recurrence or aggravation of cerebral hemorrhage, we conducted sensitivity analyses.



**Fig. 4** Forest plot of the incidence of recurrence or aggravation of ICH after restarting antiplatelet treatment based on different study designs

Sensitivity analyses investigating the influence of a single study on the overall risk estimate by omitting one study at each turn yielded a narrow range of ORs from 0.98 (0.81–1.12) to 1.11 (0.92–1.33). In other words, no single study substantially contributed to the heterogeneity across studies.

**Publication bias**

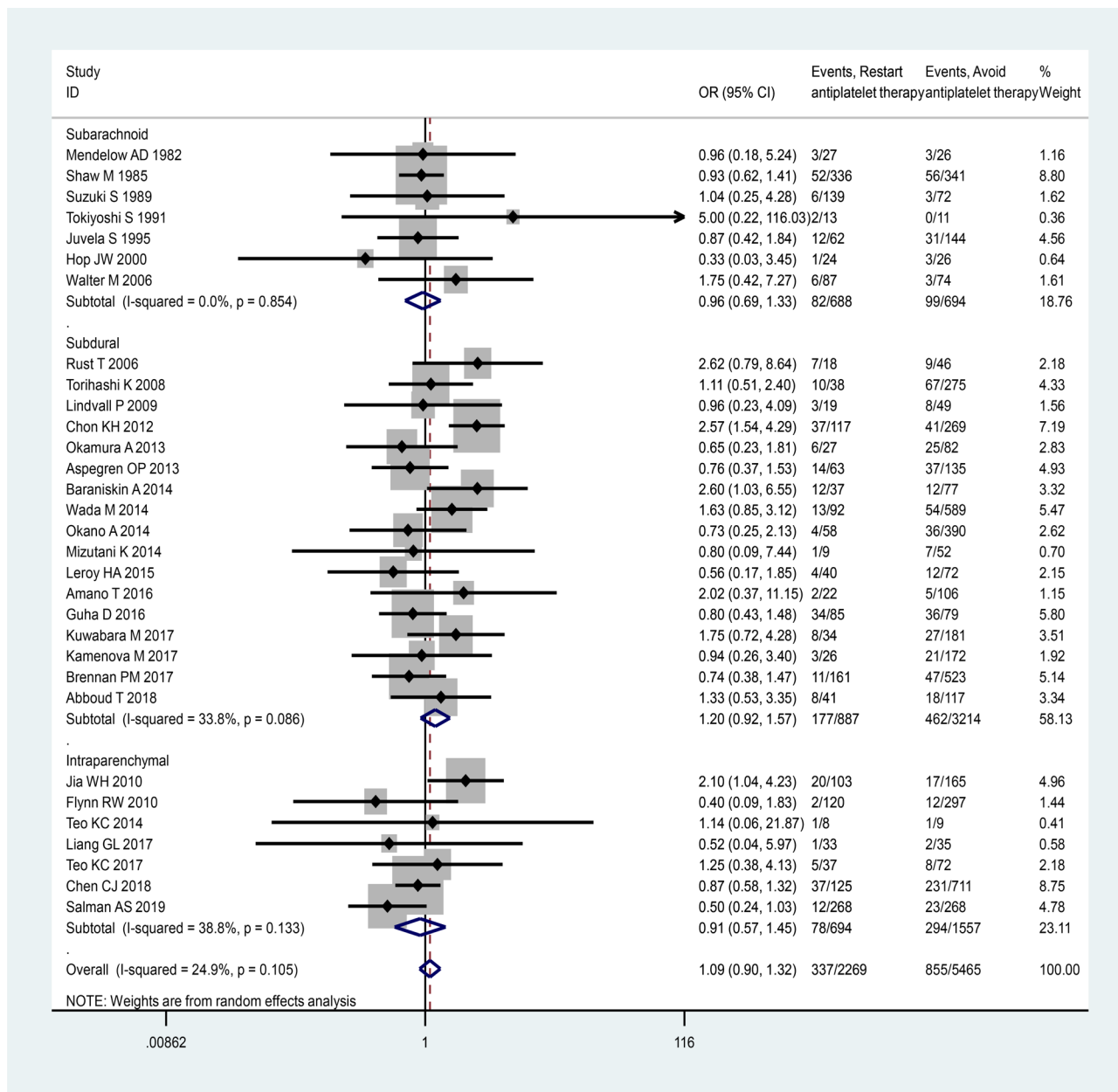
Begg’s test and Egger’s test were performed on the incidence of recurrence or aggravation of cerebral hemorrhage after restarting antiplatelet treatment, and no evidence of publication bias was observed (Egger’s test:  $P=0.55$ ; Begg’s test:  $P=0.98$ ). Therefore, it was the same for ischemic stroke (Egger’s test:  $P=0.83$ ; Begg’s test:

$P=0.86$ ) and mortality (Egger’s test:  $P=0.20$ ; Begg’s test:  $P=0.44$ ).

**Discussion**

Our systematic review results showed that restarting antiplatelet therapy after ICH was associated with a lower risk of ischemic stroke, which was consistent with the research of Blackwell [13] and met clinical expectations. Among patients with ischemic stroke and a history of cardiovascular disease, restarting antiplatelet therapy was not associated with a higher rate of cardiovascular events (myocardial infarction, acute coronary syndrome), although cardiovascular events occurred in 5.71% and 3.27% after restarting or not restarting antiplatelet therapy, respectively. We included a small number of studies



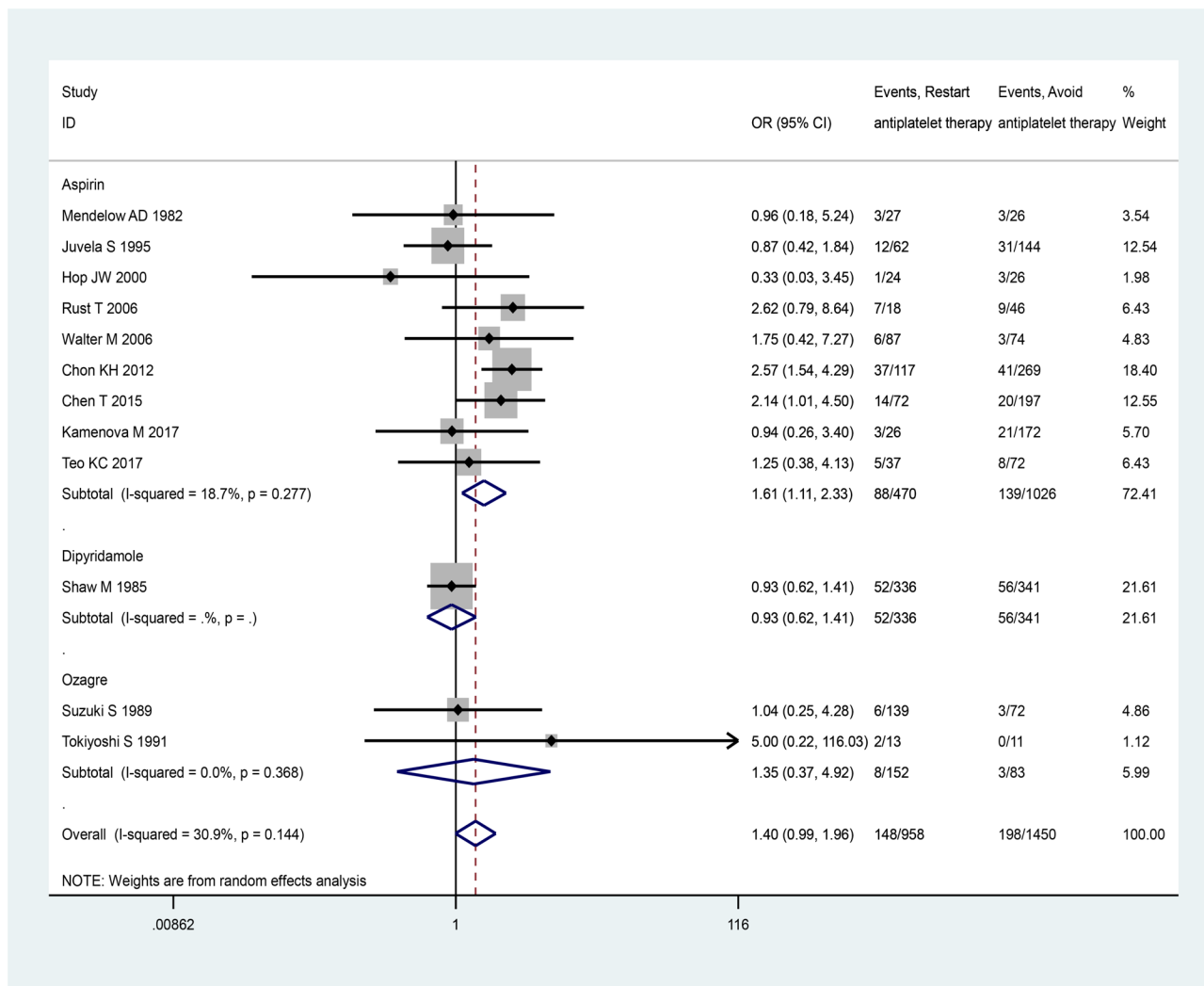


**Fig. 5** Forest plot of the incidence of recurrence or aggravation of ICH after restarting antiplatelet treatment based on different locations of the bleed

(only 3) [22, 47, 51], a total of 1174 patients, and the heterogeneity ( $I^2=84.6\%$ ,  $P=0.002$ ) between studies. thus it's still necessary to carefully read the research results. However, another RCT PICASSO [53], for the prevention of cardiovascular events in Asian patients with ischemic stroke at high risk of cerebral hemorrhage showed that compared with the use of antiplatelet drugs (cilostazol or aspirin) alone, the addition of probucol to antiplatelet therapy (cilostazol or aspirin) was associated with a lower risk of cardiovascular events. It may provide a new choice for Asian patients with ischemic stroke at a high risk of

cerebral hemorrhage in the prevention of cardiovascular events.

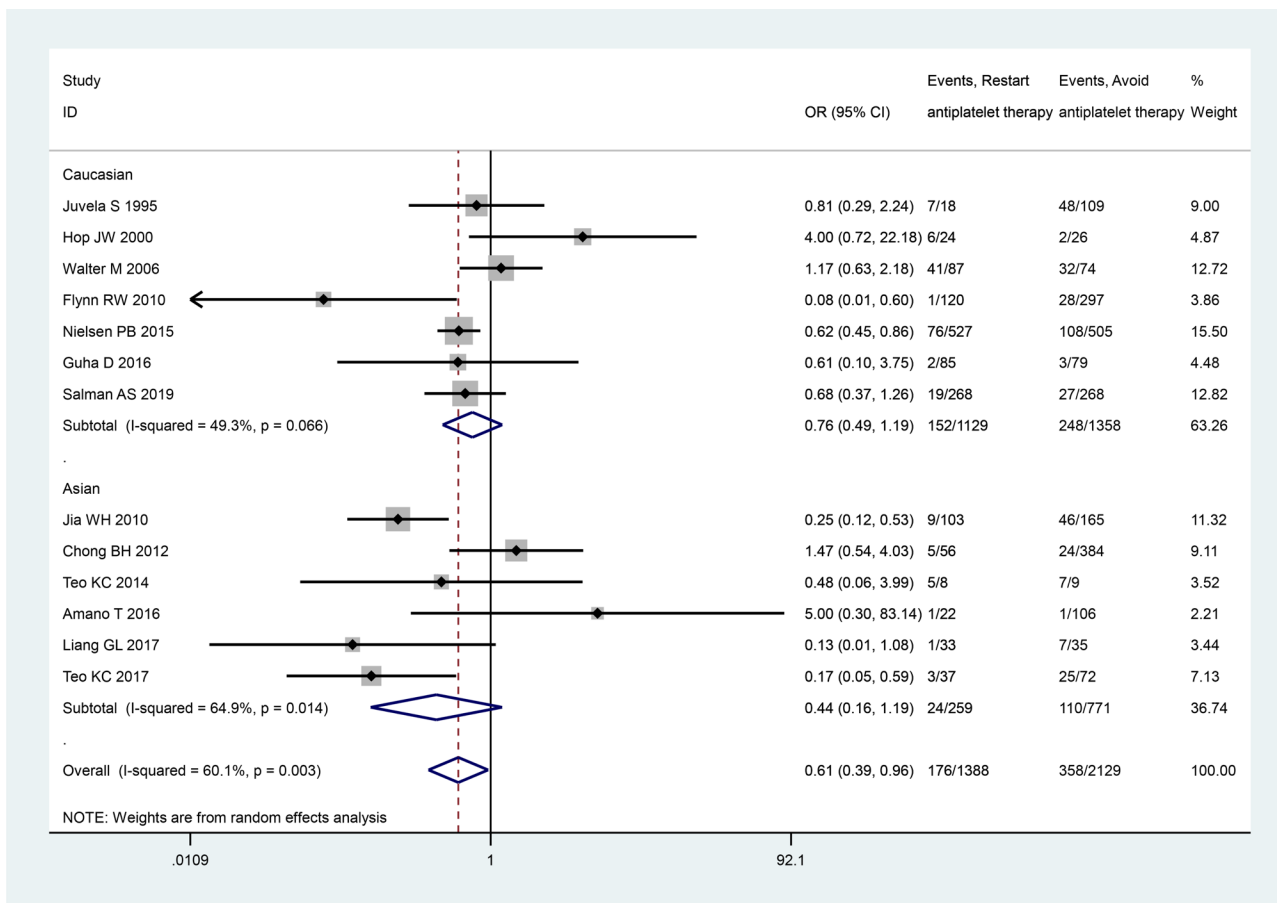
Regarding the risk of restarting antiplatelet therapy after cerebral hemorrhage, some research data could be used as a reference for medical decision-making, but the results between the studies were not consistent [34, 41, 49, 54]. The latest American Heart Association (AHA) guidelines [55] vaguely recommended anticoagulant after non-lobar ICH or antiplatelet monotherapy after any ICH might be considered, particularly when there were strong indications for these agents (class IIb; level of evidence B). In terms of bleeding risk after restarting



**Fig. 6** Forest plot of the incidence of recurrence or aggravation of ICH after restarting antiplatelet treatment based on different antiplatelet drugs

antiplatelet therapy after ICH, we had different results in different subgroups. The incidence of cerebral hemorrhage after restarting antiplatelet treatment (12.45%) is slightly lower than that without restarting antiplatelet treatment (17.09%) in the Caucasian population. This is unexpected because antiplatelet therapy generally seems to be associated with an increased risk of bleeding events. Although random effects cannot be ruled out, the underlying cause of this phenomenon may not be as counterintuitive as it first appears. On the one hand, arterial thrombosis can trigger haemorrhage [56]. On the other hand, more spontaneous intracerebral haemorrhages than expected might be due to haemorrhagic transformation of ischaemic stroke. The RCT RESTART by Salman [51] also found that restarting antiplatelet therapy after cerebral hemorrhage significantly reduced the incidence of cerebral hemorrhage. Therefore, in the Caucasian population, the modest increase in the risk of recurrent ICH with antiplatelet therapy cannot exceed the established

benefits of antiplatelet therapy for secondary prevention [13]. In contrast, in the Asian population, the results of our systematic review showed that the risk of recurrence or aggravation of cerebral hemorrhage was significantly increased after restarting antiplatelet therapy. Several studies [57–59] have shown that certain ethnicities were associated with a greater risk of hemorrhagic strokes. In addition, in a systematic review by van Asch [60], the incidence rate of ICH was 51.8 per 100,000 person-years in Asians, which was significantly higher than the incidence rate in Caucasians of 24.2 per 100,000 person-years. Moreover, compared with Caucasians, Asian populations have a higher ICH incidence rate associated with hypertension and a lower ICH incidence rate associated with cerebral amyloid angiopathy [61, 62]. In the presence of cerebral microbleeds, Asians are at greater risk of ICH. Due to the special epidemiological characteristics, etiology and pathophysiology of ICH among Asian



**Fig. 7** Forest plot of the incidence of ischemic stroke after restarting antiplatelet treatment after ICH

populations, we must strictly and carefully extrapolate the research results to Asian populations.

Among the studies included in our systematic review, Salman's study [51] reported on cerebral lobar hemorrhage and non-lobar hemorrhage: interestingly, in the lobar hemorrhage subgroup, starting antiplatelet therapy did not seem to be associated with a higher rate of recurrent ICH [OR=0.71, 95% CI (0.28–1.82),  $P=0.480$ ]. Although Salman's study found that restoration of anti-thrombotic drugs in patients with lobar hemorrhage would not lead to a significant increase in recurrent ICH, several confounding factors were not considered, such as the number of cortical microbleeds at baseline, the degree of white matter disease/hypertension, and a prior history of cerebral hemorrhage. Another study [63] by Salman concluded that there was no significant difference in the recurrence rate of cerebral hemorrhage after strict lobar microhemorrhage and hemorrhage in other locations. However, it is worth noting that only 7/122 (15%) and 23/132 (29%) patients had severe cortical microbleeds in the restarted antiplatelet therapy experimental group and the non-restarted antiplatelet therapy control group, respectively. Patients with

multiple cortical microbleeds were considered to be at higher risk of recurrent cerebral hemorrhage and were underrepresented in this study. This was contradictory to Biffi's observational study [64] regarding the risk of recurrent ICH in patients with lobar hemorrhage after resuming aspirin. Both randomized controlled trial [65] and pooled analysis [66] of population-based study found that patients with a history of lobar hemorrhage had a higher risk of cerebral hemorrhage than those with non-lobar hemorrhage; meanwhile, patients with lobar ICH without comorbid atrial fibrillation had a risk of recurrent ICH greater than the risk of ischemic stroke. The difference in bleeding location (lobar ICHs and non-lobar ICHs) was fundamentally the reason for the difference in the two different pathophysiological mechanisms. Most lobar hemorrhages in elderly patients may be secondary to amyloid deposits in the distal middle and small arteries near the cortex. Therefore, patients with moderate to severe cerebral amyloid angiopathy must be cautiously initiated antiplatelet therapy. Further studies are needed in this patient population.

In the non-lobar hemorrhage subgroup, the resumption of antiplatelet therapy was associated with a lower

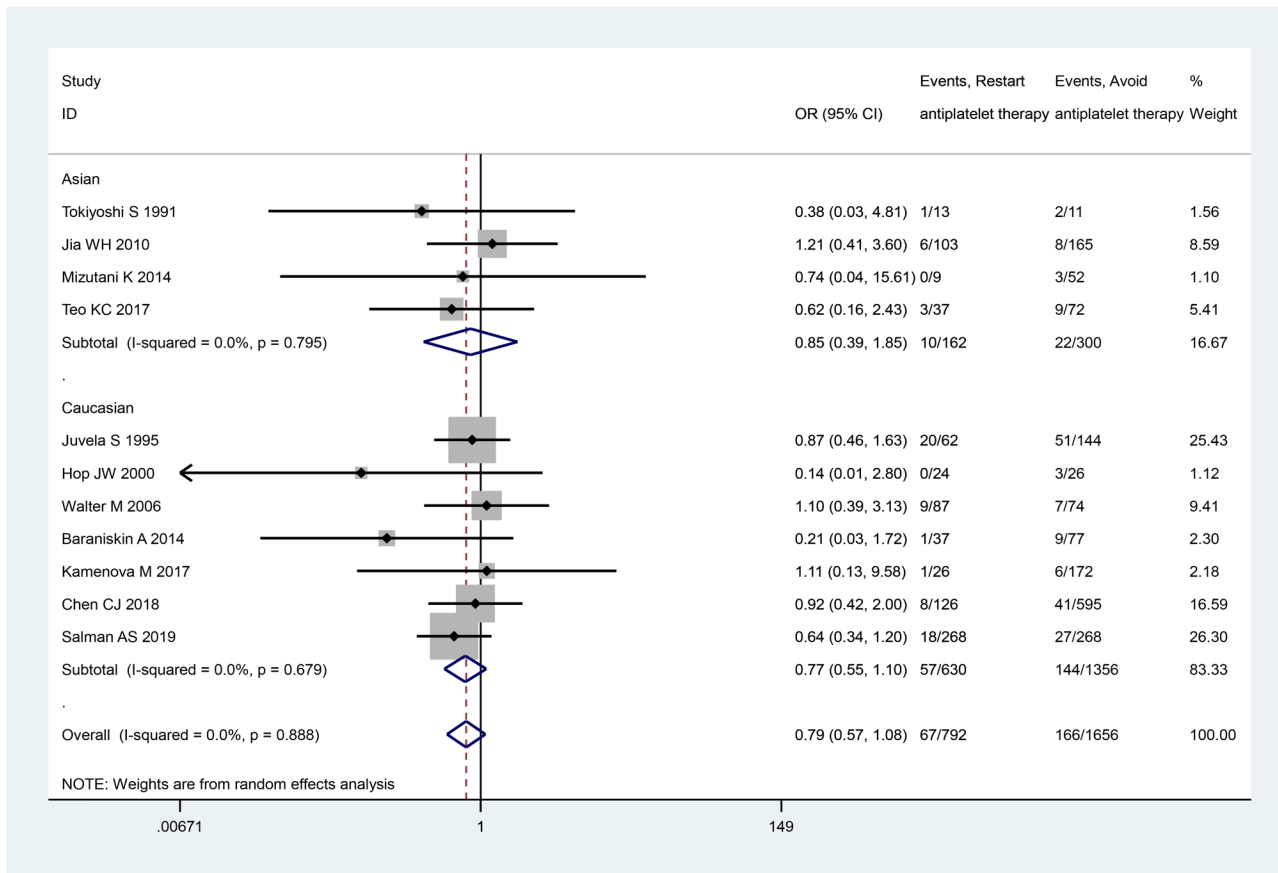


Fig. 8 Forest plot of mortality of patients after restarting antiplatelet treatment after ICH

Table 2 System evaluation results of other outcome indicators

Outcome indicators	Number of studies	Number of patients	Effect model	Results
Neurological deficit	4	396	random	OR=0.86,95 %CI(0.32,2.33),P=0.766
Myocardial infarction	3	1174	Random	OR=2.40,95 %CI(0.53,10.79),P=0.253
MRS score <2	2	882	Random	OR=0.79,95 %CI(0.55,1.15),P=0.214
MRS score >2	2	229	Random	OR=0.82,95 %CI(0.39,1.72),P=0.600
QOL score	1	50	Random	OR=0.52,95 %CI(0.04,6.15),P=0.605
Hemiparesis	1	24	Random	OR=0.38,95 %CI(0.03,4.81),P=0.451

recurrence of ICH. It is generally believed that non-lobar or subcortical cerebral hemorrhage is caused by Charcot-Bouchard affecting the penetrating arterioles secondary to chronic hypertension. The result of a RCT by Banerjee

[65] showed that patients with a history of non-lobar hemorrhage have a lower risk of cerebral hemorrhage than those with lobar hemorrhage. Snyder [67] found that the resumption of antiplatelet therapy after non-lobar hemorrhage did not increase ICH recurrence. After the absorption of hematoma and improvement of secondary tissue damage, patients with hypertension-related non-lobar hemorrhage with no obvious cerebral micro-hemorrhage and strong indications for antiplatelet therapy may safely restart antiplatelet therapy. However, the determination of the optimal timing of resumption and the selection of appropriate types of antiplatelet drugs remain unsolved. The selection of high-risk patients, determination of the optimal timing of resuming treatment, and choice of appropriate antiplatelet agent are issues that remain unresolved in relation to ICH. Nevertheless, the administration of antiplatelet therapy might be as early as possible to prevent new ischemic lesions and subsequent vascular events [68]. A large amount of research is essential to determine the balance time point in the middle.

In addition, several limitations exist in our meta-analysis. First, we included only Chinese and English studies, and language restrictions may cause bias and affect

the applicability of our research results. Second, only a relatively small number of RCTs were included in our systematic review. Third, to obtain as much data as possible, we included not only studies of spontaneous ICH but also subdural hemorrhage and subarachnoid hemorrhage. Hence, there was variability in the selection criteria of individual studies. Fourth, the effect of antiplatelet therapy may depend on the type of drug used. Previous study [69] showed that low-dose aspirin treatment after hemorrhagic stroke was associated with improved survival, but clopidogrel did not have these beneficial effects. Cilostazol had a lower bleeding tendency [53]. Different antiplatelet drugs have different effects. Since most of the studies we included did not separately count the patient's condition after the application of antiplatelet drugs with different mechanisms of action and the time to restart antiplatelet therapy, our study failed to analyze the difference in the efficacy of various antiplatelet agents. Fifth, for some of the outcome indicators, such as neurological deficit, hemiplegia, incidence of cardiovascular events, MRS score, and QOL score, both the number of included studies and patients were small and insufficient, so the conclusion from this part of the analysis is difficult to be convincing. Finally, although our study found a large difference in the incidence of ICH between Asians and Caucasians after restarting antiplatelet therapy, we failed to determine what causes the difference (epidemiology, etiology or pathophysiological variations).

## Conclusion

In summary, reinstatement of antiplatelet therapy after ICH was associated with a lower risk of thromboembolic complications. Resumption of antiplatelet therapy was not associated with a higher incidence of cerebral hemorrhage in Caucasians, but may be associated with a higher risk of cerebral hemorrhage recurrence in Asian populations.

## Abbreviations

ICH	Intracranial hemorrhage
mRS	Modified Rankin's scale
QOL	Quality of life
NOS	Newcastle–Ottawa Scale
OR	Odds ratio
CI	Confidence interval
RCT	Randomized controlled trial
NR	Not reported

## Author contributions

W.X and C.T contributed equally to the study and were co-first authors. W.X and Q.Y contributed to the design, W.X and C.T statistical analysis, participated in most of the study steps. C.T and Q.Y prepared the manuscript. Z.J assisted in designing the study. All authors have read and approved the content of the manuscript.

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## Data availability

Datasets are available through the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

Not declared.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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