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Risk and benefit of reinitiating antiplatelet therapy after spontaneous intracerebral hemorrhage: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This study aimed to assess the risks and benefits of reinitiating antiplatelet therapy after spontaneous intracerebral hemorrhage (ICH) through a systematic review and meta-analysis. The reinitiation of antiplatelet therapy is commonly used to reduce major vascular events in patients with occlusive vascular diseases, but its use in ICH patients may increase the risk of bleeding.

MATERIALS AND METHODS: A comprehensive search was conducted on databases including MEDLINE, Embase, Cochrane Library, clinicaltrials.gov, and the International Standard Randomized Controlled Trial Number Register (ISRCTN). Randomized controlled trials and cohort studies that investigated the use of reinitiation of antiplatelet therapy after hemorrhagic stroke were included. Data on ICH recurrence, major bleeding events, major occlusive cerebrovascular events, ischemic stroke, and all-cause mortality were extracted and analyzed using R software.

RESULTS: The study included a total of 10 studies with 6,340 participants. The control group consisted of 2,964 patients who did not receive antiplatelet therapy, while the study group included 1,285 patients who received antiplatelet therapy without restrictions on the specific drug type. The meta-analysis showed that antiplatelet therapy significantly reduced the risk of ICH recurrence (RR=0.72, 95% CI: 0.59, 0.87), had no significant impact on the risk of severe bleeding events (RR=0.93, 95% CI: 0.80, 1.08), significantly lowered the risk of major occlusive cerebrovascular events (RR=0.59, 95% CI: 0.46, 0.77), had no significant effect on the risk of ischemic stroke (RR=0.77, 95% CI: 0.53, 1.12), and did not significantly influence the risk of all-cause mortality (RR=0.75, 95% CI: 0.45, 1.15).

CONCLUSIONS: Based on the findings, reinitiating antiplatelet therapy after spontaneous ICH appears to be generally safe. However, the benefits in terms of reducing the risk of all-cause mortality are not evident and require confirmation through large-scale, long-term, prospective, randomized controlled trials.

Key Words:
Reinitiation of antiplatelet therapy, Spontaneous intracerebral hemorrhage, Systematic Review, Meta-analysis.

Introduction

Spontaneous intracerebral hemorrhage (ICH), also known as hemorrhagic stroke, refers to the rupture of cerebral blood vessels without trauma, resulting in the accumulation of blood within the brain tissue. It is often associated with changes in blood pressure or other vascular abnormalities[1]. ICH is a common type of stroke, second only to ischemic stroke, and accounts for approximately 10-20% of all strokes[2]. ICH is characterized by high morbidity, with a 30-day mortality rate ranging from 35% to 52%, and only about 20% of patients achieving independent living after the event[3]. Compared to ischemic stroke, ICH has higher rates of mortality and disability, and currently, there are no proven interventions to improve clinical outcomes after ICH[4].

The treatment of post-ICH primarily focuses on controlling bleeding, maintaining cerebral perfusion, and preventing complications. Early cessation of antithrombotic medications is necessary due to the increased risk of bleeding and re-bleeding after ICH. However, discontinuing these medications may lead to an elevated risk of occlusive vascular events[5]. Platelets play a crucial role in normal blood clotting by adhering to and aggregating at the site of injury, contributing to vascular repair. ICH patients often require antiplatelet therapy (APT) to prevent thrombus formation, but the use of APT after ICH remains a topic of debate. On one hand, APT drugs like aspirin and clopidogrel can inhibit platelet aggregation, preventing thrombus formation and reducing the occurrence of cardiovascular and cerebrovas-

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cular events. On the other hand, APT treatment may increase the risk of bleeding by interfering with normal platelet function and reducing the blood's ability to clot. Since ICH shares common risk factors with ischemic stroke and myocardial infarction, such as aging and uncontrolled hypertension, anticoagulation and antiplatelet therapy are often required[6]. Population-based studies[7] have shown a significantly higher risk of ischemic cerebrovascular diseases, such as ischemic stroke, transient ischemic attacks, and myocardial infarction, with unfavorable outcomes among survivors of ICH.

The safety of reinitiation of APT treatment after ICH remains a clinical challenge, with conflicting findings in different studies. This meta-analysis aims to evaluate the impact of reinitiation of APT on cardiovascular and cerebrovascular events after ICH, providing an assessment of patient outcomes.

Materials and Methods

Search Strategy

This comprehensive systematic review and meta-analysis was performed based on the PRISMA guidelines. Our registration number is INPLASY202410031 (INPLASY.COM).

To identify relevant studies, comprehensive computer searches were conducted on several databases up to December 1, 2023. The databases searched included MEDLINE, Embase, Cochrane Library, clinicaltrials.gov, and the International Standard Randomized Controlled Trial Number Register (ISRCTN). The search terms used were: ("intracranial hemorrhages" OR "ICH" OR "cerebral hemorrhages") AND ("stroke") AND ("antiplatelet"). This search strategy aimed to retrieve articles that assessed the efficacy of antiplatelet therapy (APT) post-ICH. To avoid duplication, in cases where a study had multiple publications with overlapping patient group results, only the largest available published dataset was included in the analysis.

This meta-analysis was conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist. Its registration number is INPLASY 202410031.

Criteria for Literature Selection

The studies were selected based on the following inclusion criteria:

- Study types – Prospective or retrospective observational cohort studies, case-control studies, and randomized controlled trials.
- Participant types – Surviving patients diagnosed with spontaneous intracerebral hemorrhage (ICH) through CT or MRI.
- Intervention measures – Application of at least one antiplatelet (APT) drug.
- Outcome measures – Severe vascular events, including ischemic stroke, myocardial infarction, other major ischemic events, ICH, cerebral hemorrhage, and vascular death during planned follow-up.

The exclusion criteria were:

- Participants with specified comorbidities in addition to ICH.
- Reviews, cohort studies, animal experiments, case studies, basic research, cross-sectional studies, case reports, etc.
- Literature with outcome measures that did not meet the inclusion criteria.
- Inaccessible full-text literature.
- Literature with unextractable data, incomplete original data, or unsuccessful data retrieval.
- Literature with a sample size of fewer than 15 cases.

Literature Collection and Data Extraction

Two review authors independently screened the titles and abstracts of the retrieved literature for relevance, excluding obviously unrelated articles. Additionally, a secondary search of the references of collected literature was conducted to avoid any omissions. Any disagreements during the screening process were resolved through discussion, with consultation from a third review author if necessary.

Data extraction was performed independently by two review authors using a predefined data collection form. The extracted data included information such as the first author, publication year, country, study design type, sample size, age, gender, ICH location, APT drugs used, APT initiation time, follow-up time, and other relevant details. Any discrepancies in data extraction were resolved through discussion, with consultation from a third review author if needed.

Quality Assessment of Literature

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The NOS involves scoring for population selection, comparability, and exposure/outcome, with

a maximum of 2 stars for comparability and 1 star for the remaining items. The total score ranged from 0 to 9 stars, with higher scores indicating higher study quality.

Statistical Analysis

For the meta-analysis, the R language meta-package was employed (The R Foundation for Statistical Computing, Vienna, Austria). Risk ratios (RR) and 95% confidence intervals (CI) were used for analyzing binary variables, while standard mean differences (SMD) and 95% CIs were used for continuous variables. The heterogeneity between studies was analyzed using the I^2 test. An I^2 value of 0% indicated no observed heterogeneity while increasing values indicated greater heterogeneity. If $I^2 > 50\%$, indicating significant heterogeneity, subgroup analysis or analysis using a random-effects model was performed. For $I^2 \leq 50\%$, indicating no significant heterogeneity, a fixed-effects model was used for analysis. A significance level of $\alpha = 0.05$ was considered for statistical significance.

Results

Literature Selection Results

A total of 563 articles were initially obtained from the computer search and imported into Endnote. After removing 54 duplicate articles, the titles and abstracts of the remaining 509 articles were reviewed. Among them, 438 articles were excluded, including 216 non-clinical studies (reviews, conference reports, commentaries), 121 studies with unspecified intervention methods, and 101 studies unrelated to the research topic. The full texts of the remaining 71 articles were read, leading to the exclusion of 36 articles due to the inability to extract specified data and 25 articles due to non-specified study subjects. Finally, 10 studies were included in the analysis. Figure 1 shows the flowchart of the literature selection.

Basic Characteristics and Quality of Included Studies

Among the 10 included studies, one was a prospective randomized controlled trial[11], four were

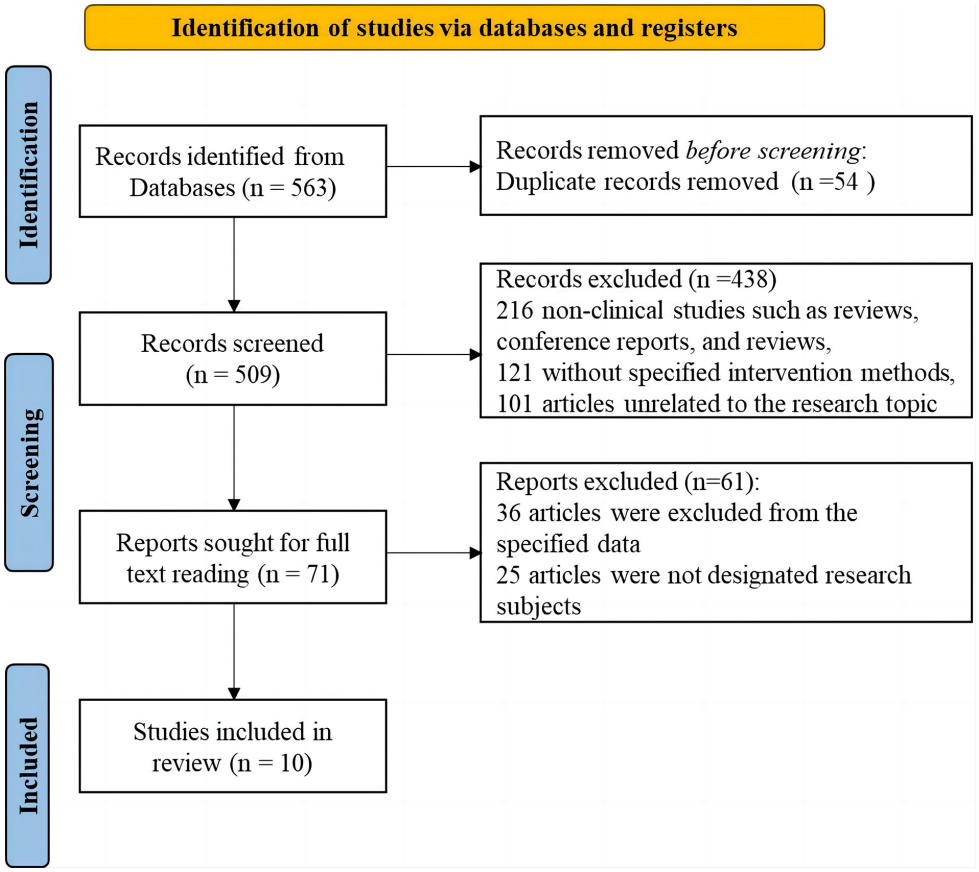

Figure 1. Literature retrieval flowchart.

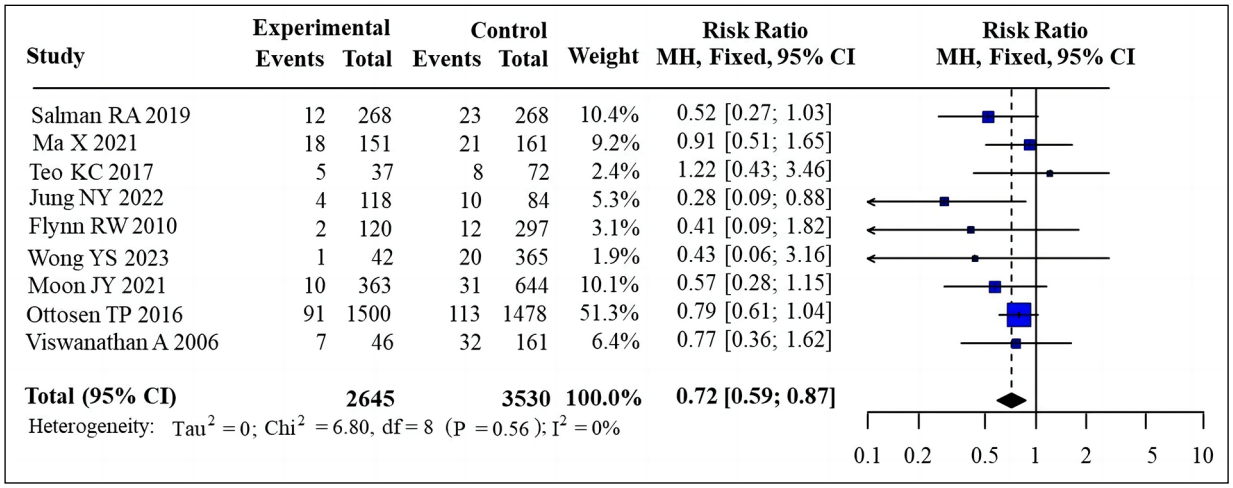

Figure 2. Forest plot for risk of ICH recurrence.

prospective cohort studies[6,17-19], and five were retrospective cohort studies[12-16]. The control group in these studies did not receive reinitiation of APT and consisted of a total of 2,964 patients, while the treatment group received reinitiation of APT without specifying the type of medication, totaling 1,285 patients. The quality of the literature was assessed using the NOS score, which ranged from 4 to 8, indicating generally high-quality literature. Table I presents the basic characteristics and quality of the included studies.

Analysis Results

Hemorrhagic event meta-analysis

Out of the 10 included studies, nine[6,11-16,18,19] reported the recurrence of intracranial hemorrhage (ICH) after treatment, as shown in Figure 2. Two studies[17,18] reported the occurrence of severe bleeding events, as shown in Figure 3. Heterogeneity analysis of the nine literature reports on ICH recurrence showed an I^2 value of 0%, indicating no heterogeneity among studies, and a fixed-effects model was used for analysis. The statistical analysis results indicated that APT treatment significantly reduced the risk of ICH recurrence (risk ratio [RR] = 0.72, 95% confidence interval [CI]: 0.59, 0.87). Heterogeneity analysis of the two literature reports on the occurrence of severe bleeding events showed an I^2 value of 12%, indicating mild heterogeneity among studies, and a fixed-effects model was used for analysis. The statistical analysis results indicated that APT treatment had no significant impact on the risk of severe bleeding (RR = 0.93, 95% CI: 0.80, 1.08). A funnel plot was used to assess publication bias, as shown in Figure 4.

Major occlusive vascular events meta-analysis

Out of the 10 included studies, four[11-14] reported the incidence of major occlusive vascular events after treatment, as shown in Figure 5. Three studies[6,11,16] reported the occurrence of ischemic stroke, as shown in Figure 6. Heterogeneity analysis of the four literature reports[11-14] on major occlusive vascular events showed an I^2 value of 36%, indicating mild heterogeneity among studies, and a fixed-effects model was used for analysis. The statistical analysis results indicated that APT treatment significantly reduced the risk of major occlusive vascular events (RR = 0.59, 95% CI: 0.46, 0.77). Heterogeneity analysis of the three literature reports[6,11,16] on the occurrence of ischemic stroke showed an I^2 value of 61%, indicating significant heterogeneity among studies, and a random-effects model was used for analysis. The statistical analysis results indicated that APT treatment had no significant impact on the risk of ischemic stroke (RR = 0.77, 95% CI: 0.53, 1.12). A funnel plot was used to assess publication bias, as shown in Figure 7.

Death event meta-analysis

Out of the 10 included studies, five reported all-cause mortality rates, as shown in Figure 8. Heterogeneity analysis of the five literature reports on all-cause mortality showed an I^2 value of 84%, indicating significant heterogeneity among studies, and a random-effects model was used for

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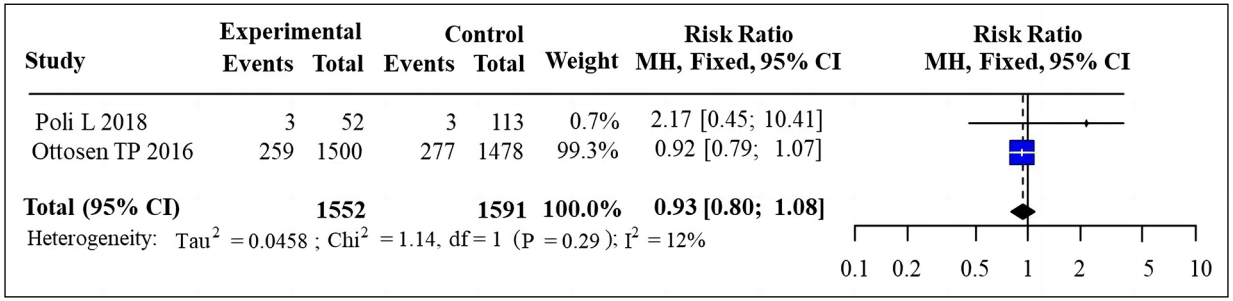

Figure 3. Forest plot for severe bleeding events.

Table I. Basic characteristics and quality assessment of included studies.

Authors	Publication date	Study types	Cases of no APT	Cases of APT	APT drugs	Follow-up time (median or mean)	Literature quality (NOS)
RESTART Collaboration[11]	2019	RCT	268	268	Aspirin/dipyridamole/clopidogre[l]	2.0 years	4
Ma et al[12]	2021	R-CS	161	151	Aspirin/clopidogrel	4.0 years	7
Teo et al[13]	2017	R-CS	72	37	Aspirin/clopidogrel	3.5 years	7
Jung and Cho[14]	2022	R-CS	84	118	Unspecified	47.0 months	6
Flynn et al[6]	2010	P-CS	297	120	Aspirin	19.5 months	7
Wong et al[15]	2023	R-CS	365	42	Unspecified	4-years	7
Moon et al[16]	2021	R-CS	644	363	Unspecified	2.5 years	7
Poli et al[17]	2018	P-CS	113	52	Aspirin/thienepyrimidine	4.0 years	7
Ottosen et al[18]	2016	P-CS	1,478	1,500	Aspirin/clopidogrel	2.3 years	8
Viswanathan et al[19]	2006	P-CS	161	46	Aspirin	19.5 months	7

RCT = randomized controlled study, P-CS = prospective cohort study, R-CS = retrospective cohort study.

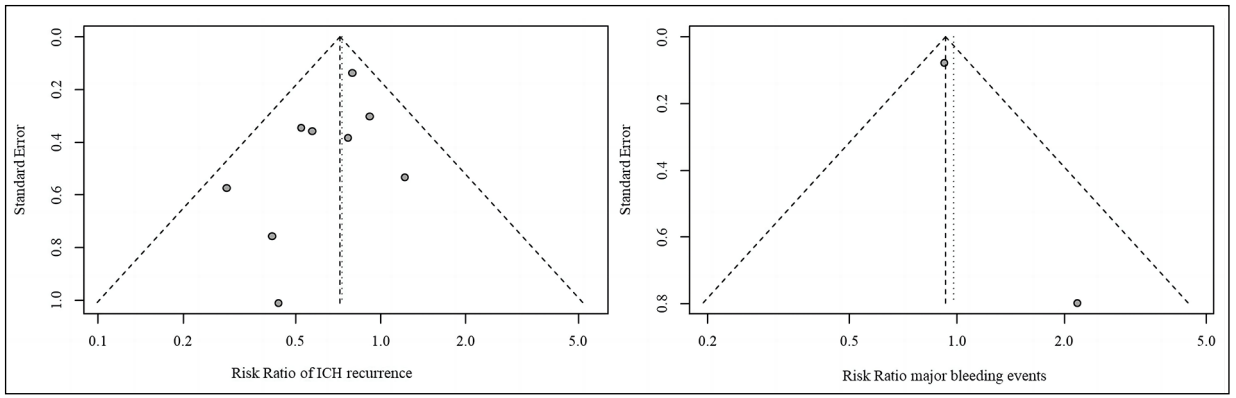

Figure 4. Funnel plot of publication bias for ICH recurrence and major bleeding events.

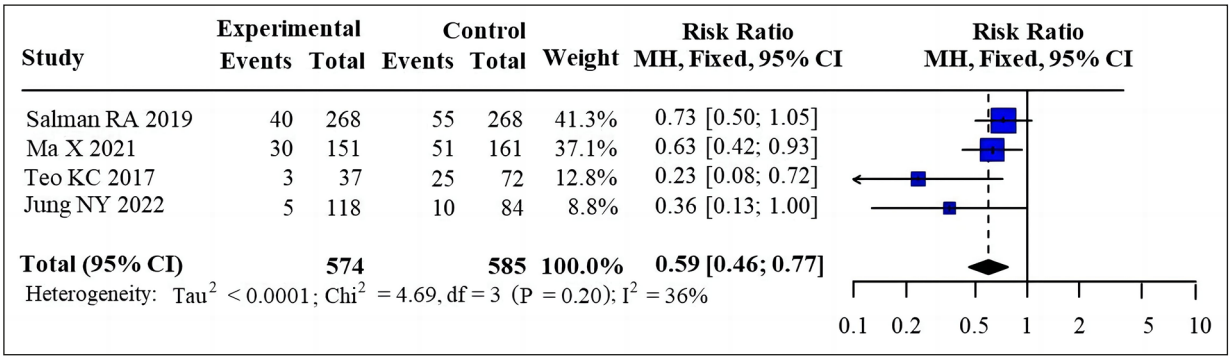

Figure 5. Forest plot for risk of major occlusive vascular events.

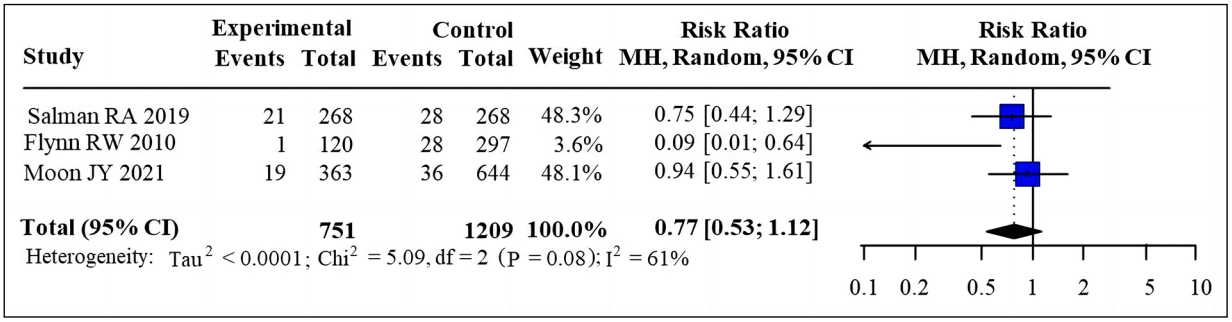

Figure 6. Forest plot for incidence of ischemic stroke.

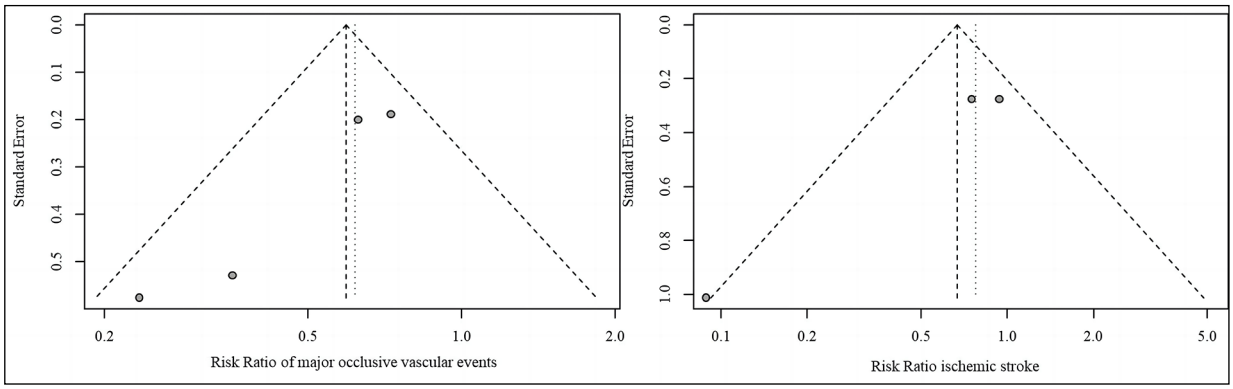

Figure 7. Funnel plot of publication bias for major occlusive vascular events and ischemic stroke.

analysis. The statistical analysis results indicated that APT treatment had no significant impact on the overall risk of death (RR = 0.75, 95% CI: 0.45, 1.15). A funnel plot and Egger's test were used to assess publication bias, as shown in Figure 9.

Discussion

ICH is a type of stroke associated with high mortality and disability rates, often accompanied by pathological changes indicating underlying ischemic vascular diseases. Studies[20,21] have shown that a significant proportion of ICH patients, approximately 44%, have a history of or are currently receiving anticoagulant and antiplatelet therapy. Furthermore, survivors of ICH are at a substantially elevated risk of occlusive diseases such as ischemic stroke and myocardial infarction, which are associated with poor prognoses[22]. APT is widely employed for primary and secondary prevention of ischemic stroke and coronary

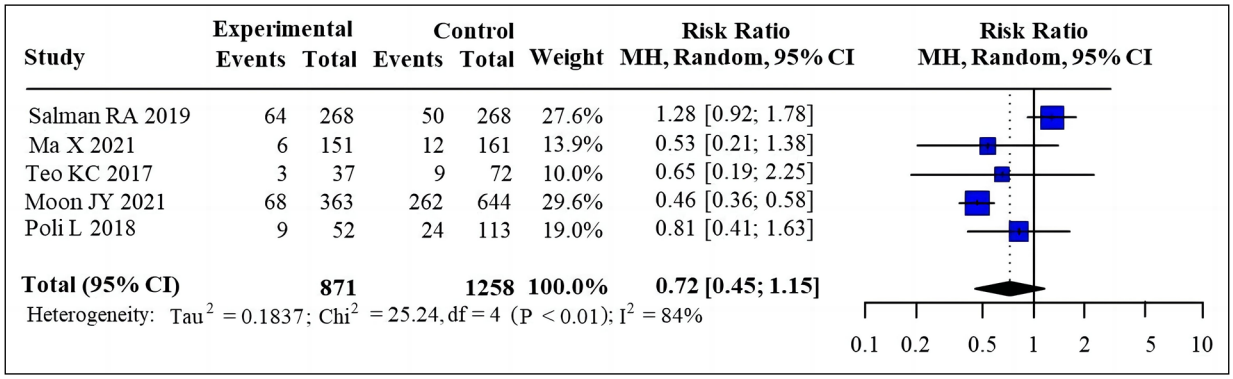

Figure 8. Forest plot for all-cause mortality rate.

artery diseases. However, in the context of ICH, there exists a delicate balance between the risk of recurrent bleeding and the occurrence of ischemic vascular events[23]. Several studies[24,25] have indicated that the incidence of ischemic vascular events is higher than that of recurrent bleeding following cerebral hemorrhage, underscoring the heightened risk of ischemic vascular events in patients with ICH. Consequently, a greater emphasis should be placed on preventing ischemic vascular events in post-ICH patients, and the reinitiation of APT is considered crucial for improving overall prognosis[26].

This study employed a meta-analysis to investigate the benefits and risks associated with reinitiation of APT in individuals experiencing spontaneous intracerebral hemorrhagic stroke. The findings demonstrated that APT treatment significantly reduced the recurrence rate of ICH and the occurrence of major occlusive vascular events while not exerting a significant impact on major bleeding events or all-cause mortality. Long-term observational studies[27] included in the meta-analysis indicated that restarting APT treatment after cerebral hemorrhage was associated with a reduced incidence of occlusive vascular events compared to not reinitiating APT therapy, without an increased risk of recurrent bleeding events such as subarachnoid hemorrhage, cerebral parenchymal hemorrhage, or subdural hematoma. Population studies[28] have suggested an annual recurrence risk of bleeding in survivors of cerebral hemorrhage ranging

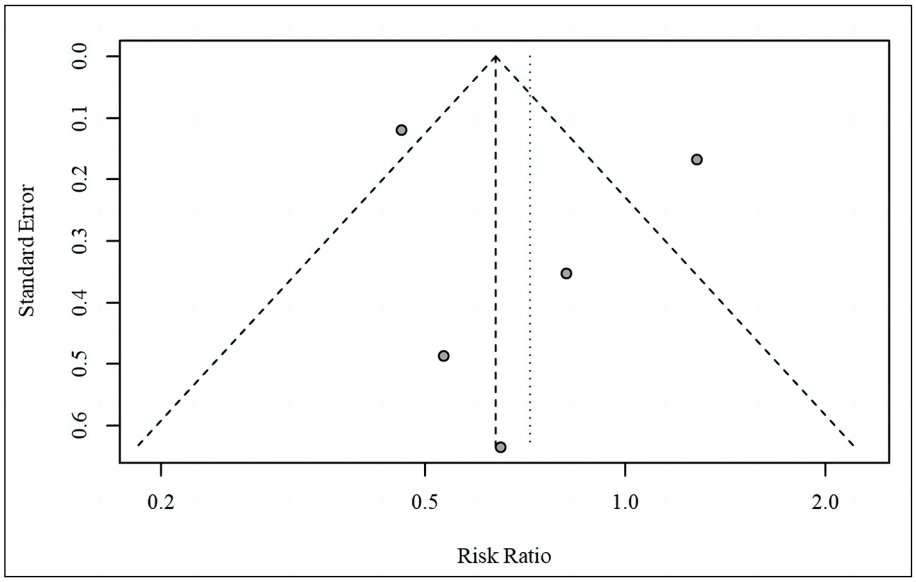

Figure 9. Funnel plot of publication bias for all-cause mortality rate.

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from 2% to 3%, with an approximate 1% recurrence risk within the first three months following the initial hemorrhagic event. Furthermore, research[29] has shown that cerebral lobe hemorrhages involving the cerebral cortex display a significantly higher recurrence rate compared to hemorrhages occurring in other locations, with recurrence rates of up to 21% within a two-year timeframe. Certain cohort and retrospective studies[30] have indicated that APT treatment does not increase the risk of recurrent cerebral hemorrhage, and initiating APT therapy within three months after cerebral hemorrhage does not worsen patient outcomes. Consequently, careful consideration is necessary before recommencing APT treatment.

Among the literature reviewed in this study, Viswanathan et al[19] published the earliest results of a cohort study investigating the initiation of APT treatment in survivors of ICH in 2006. Their findings revealed a higher incidence of recurrent lobar ICH, but initiating APT therapy did not increase the risk of ICH recurrence, thus providing evidence-based support for the reinitiation of APT in survivors of ICH. Results from Teo et al[13] indicated that reinitiating APT did not elevate the risk of a recurrent cerebral hemorrhage. However, systolic blood pressure exceeding 140 mmHg and the presence of cerebral amyloid angiopathy were identified as risk factors for recurrent cerebral hemorrhage. Biffi et al[31] analyzed 104 survivors clinically diagnosed with cerebral amyloid angiopathy and observed an increased risk of cerebral hemorrhage associated with the reinitiation of APT. Due to differences in subject diagnosis between this study and others, the findings from Biffi's research were not included in the meta-analysis. One prospective randomized controlled trial was incorporated into this study, demonstrating that restarting APT treatment 76 days after ICH did not heighten the risk of ICH recurrence over a two-year follow-up period[11], similar to Xu et al[32] results. The RESTART trial[33], the most important trial to date, reinitiation of APT may reduce the risk of recurrent intracerebral hemorrhage and is strongly associated with bleeding due to arterial thrombosis, hemorrhagic transformation in ischemic stroke, and inflammation. A Phase 3 ASPIRING[34] (International Randomized Trial of Secondary Prevention of Antiplatelets after Intracerebral Hemorrhage) is currently being prepared, which aims to enroll 4,000 patients with intracerebral hemorrhage and provide high-quality evidence-based evidence for the reinitiation of APT.

Limitations

However, despite the valuable results obtained, this study is subject to certain limitations. Firstly, only one prospective randomized controlled trial was included, with the remaining studies being cohort studies, thus introducing inevitable selection bias. Secondly, inconsistencies in the timing of APT reinitiation and the duration of follow-up introduced reporting biases in outcome events. Thirdly, the management of blood pressure, lipid levels, and risk factors for ischemic vascular diseases are crucial considerations for assessing outcome events, yet these indicators were not consistently evaluated across the included studies.

Conclusions

In conclusion, reinitiating APT treatment in patients with spontaneous ICH generally appears to be safe, albeit with no significant benefits in terms of all-cause mortality risk. Larger-scale, long-term prospective randomized controlled studies are needed to corroborate these findings and provide more robust evidence.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and Informed Consent

Not applicable.

Data Availability

The datasets generated during and/or analyzed during the current study are available in the manuscript.

Funding

None.

Authors' Contribution

Jiawei Zhang conceived the structure of the paper, designed the research method, consulted the literature, collected the data. Jianxu Zhao analyzed the data, screened it, and made the charts. Gangfeng Yin reviewed and edited the manuscript, and all the authors read and finalized the manuscript.

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