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Antiplatelet Therapy and Outcomes after Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis

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Abstract

Background: The efficacy of antiplatelet therapy (APT) after aneurysmal subarachnoid hemorrhage (aSAH) remains unclear. We performed a systematic review and meta-analysis to summarize the associations of APT use after aSAH with outcomes.

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Study supervision: Murthy.

Credit Author Statement

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Methods: We searched published medical literature to identify cohort studies involving adults with aSAH. The exposure was APT use after aSAH. Outcome measures were good functional outcome (modified Rankin Score 0-2 or Glasgow Outcome Scale 4-5), delayed cerebral ischemia (infarcts on neuroimaging), and intracranial hemorrhage. After assessing study heterogeneity and publication bias, we performed a meta-analysis using random-effects models to assess the strength of association between APT and SAH outcomes.

Results: A total of 14 studies with 4,228 aSAH patients were included. APT after aSAH was associated with good functional outcome (pooled relative risk, 1.08; 95% confidence interval, [CI], 1.02-1.15; I^2 = 45%, p for heterogeneity = 0.04), but there was no relationship with delayed cerebral ischemia (pooled relative risk, 0.80; 95% confidence interval, [CI], 0.63-1.02; I^2 = 61%, p for heterogeneity <0.01) or intracranial hemorrhage (pooled relative risk, 1.50; 95% confidence interval, [CI], 0.98-2.31; I^2 = 0, p for heterogeneity =0.71). In additional analyses, APT resulted in good functional outcomes in endovascularly-treated patients. When stratified by type of medication, aspirin, clopidogrel, and ticlopidine were associated with good functional outcomes.

Conclusions: APT after aSAH was associated with a modest improvement in functional outcome, but there was no relationship with delayed cerebral ischemia or intracranial hemorrhage.

Keywords

Subarachnoid hemorrhage; intracranial aneurysm; antiplatelet therapy; disability; delayed cerebral infarction

Introduction

Non-traumatic subarachnoid hemorrhage (SAH) accounts for 5 to 10% of all strokes in the United States, and in 80% of cases occurs from the rupture of an intracranial aneurysm.[1] A major cause of death and disability after SAH is delayed cerebral ischemia (DCI), a clinical syndrome of focal neurologic deficits that develops in one third of patients in the first two weeks after aneurysm rupture. [2] Patients with aneurysmal SAH (aSAH) tend to be younger than those affected by other stroke subtypes, which results in a greater loss of productive life.[3] Additionally, the course of illness, including treatment of DCI, incurs higher healthcare costs than other forms of stroke.[4,5] However, despite technological advances in the surgical treatment of aneurysms, breakthroughs in the prevention of DCI have significantly lagged behind. Current guidelines recommend the use of oral nimodipine, a calcium channel blocker, to improve neurological outcomes should vasospasm occur, and maintenance of euvolemia to prevent vasospasm and subsequent DCI.[6,7]

Several medical therapies such as statins, magnesium, nicardipine, cilostazol, and clazosentan have been studied as potential interventions to improve SAH outcomes.[8-11] With the exception of cilostazol, a medication used primarily for peripheral arterial disease in the U.S., the other therapies have failed to show benefit. DCI and downstream complications of aSAH are purported to result from neuroinflammation and micro-thrombosis, both potential mechanistic targets for antiplatelet therapy (APT).[12,13] However, earlier trials and studies of APT found no significant benefit, but these studies were performed at a time when surgical clipping was the mainstay of aneurysm treatment.[14,15] In fact, a prior meta-analysis that

assessed APT in aSAH patients who mostly underwent surgical clipping, suggested a trend toward better outcome with APT.[16] Endovascular therapy is now increasingly preferred for securing ruptured aneurysms with a favorable anatomy[17], which sometimes requires APT even in the acute phase of SAH. Emerging single-center observational data suggest that APT may be associated with lower rates of DCI and disability in SAH patients treated with coiling or stenting.[18,19] We therefore sought to perform a systematic review and meta-analysis of published literature to first, evaluate the relationship between APT and SAH outcomes, and second, assess if this relationship varies by aneurysm treatment strategy and APT regimen.

Methods

We performed this study in accordance with the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[20] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[21] statements. We also prospectively registered our study protocol on the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42021252189). This study was exempt from approval by the Weill Cornell Medicine Institutional Review Board since the analyses entailed publicly available, de-identified published data.

Data Sources and Searches

We performed comprehensive searches in Ovid MEDLINE, Ovid Embase, and the Cochrane Library from the inception of each database to March 31, 2021. An English language filter was not applied. Following the initial search in Ovid MEDLINE, the search was extended to other databases. Keywords used to query the databases included: ‘subarachnoid hemorrhage’ and a combination of ‘aneurysm’, ‘coiling’, ‘clipping’, ‘antiplatelet’, ‘aspirin’, ‘clopidogrel’, ‘delayed cerebral ischemia’, ‘outcome’, and ‘functional outcome’. Details of the search methodology are listed in the online-only Data Supplement.

Study Selection

We included studies evaluating initiation or resumption of APT during hospitalization for SAH. The inclusion criteria for our study were: (1) studies with aneurysmal SAH as the primary inclusion criteria; (2) studies with documented outcomes of DCI and functional outcomes in the follow-up period; (3) studies with clear documentation of the use of antiplatelet medications; (4) adult patients ≥18 years of age; and (5) sample size ≥10 patients to avoid inclusion of case reports or small case series. In this systematic review, we only included peer-reviewed publications in scientific journals, and not conference proceedings or abstracts since the latter typically do not provide the level of detail needed of rigorous data extraction. In case of multiple publications from a single cohort of patients or institutional database, the study with the largest cohort of patients was selected to avoid duplication of data. The search methodology has been outlined in the online only data supplement.

Data Extraction and Quality Assessment

Two investigators (A.G and K.B) read the title and abstract produced by the initial search, shortlisted articles, reviewed them, and selected articles based on the inclusion criteria and

quality of data. Any disagreements were resolved by a third investigator (S.B.M). Data were extracted using a pre-specified collection template. The following study characteristics were extracted: first author, journal of publication, year of publication, and study design. We also collected patient demographics including age, sex, and stroke comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and smoking history. Additionally, we obtained information about the type of antiplatelet medication and type of definitive aneurysm treatment. Outcome data included cases of DCI and functional outcome in the follow-up period.

We adapted risk of bias assessments in previously published meta-analyses on stroke risk, and generated eight specific questions to evaluate for potential selection, detection, reporting, and confounding bias.[22,23] Two readers assessed for risk of bias using this questionnaire, with disagreements in assessment resolved by a third tie-breaking evaluator.

Definitions of Outcomes

The main outcomes were (i) good functional outcome, defined as a modified Rankin Score (mRS) 0-2 or a Glasgow Outcome Scale (GOS) 4-5, (ii) DCI, defined as evidence of infarction on neuroimaging (computed tomography of the head or magnetic resonance imaging of the brain), and (iii) any intracranial hemorrhage. DCI was diagnosed during the course of SAH hospitalization, while functional outcomes were ascertained between 2 and 12 months. In the International Subarachnoid Aneurysm Trial (ISAT), rates of good functional outcome in endovascularly treated patients were 74.6% at 2 months and 76.3% at 12 months, suggesting that variation in the timing of disability assessments should have a minimal confounding effect on the relationship between APT and outcomes.[24]

Data Synthesis and Analysis

We performed a meta-analysis to assess the association between APT and SAH outcomes using the pooled relative risk (RR) as the effect parameter. We used a random-effects (DerSimonian-Laird) model to calculate the pooled RR, and generated forest plots to display the individual study RR and pooled RR.[25] The rationale of using the more conservative random-effects model was to account for the variability in effect sizes, design, and follow-up between the individual studies. We assessed heterogeneity using the I^2 statistic.[26] The presence of publication bias was evaluated using the Begg-Mazumdar rank correlation test. We performed pre-specified subgroup analyses by type of aneurysm treatment, antiplatelet medication, and type of study design, anticipating significant heterogeneity since the studies spanned over 3 decades. Statistical analyses were performed using Stata, version 15 (StataCorp) and R, version 3.6.3 (R Project for Statistical Computing). All tests were two-tailed and p values <0.05 were considered significant.

Results

Study Selection and Characteristics

We screened a total of 752 titles and abstracts, and 14 met criteria for inclusion (Supplemental Figure I). The study from the Magnesium and Acetylsalicylic acid in Subarachnoid Haemorrhage (MASH) trial reported comparisons between APT and no APT

groups in the coiling and clipping subgroups.[15] We therefore considered the two aneurysm treatment arms as different studies in our analyses. Of the various antiplatelet medications, 8 studies evaluated aspirin monotherapy[18,27-32], while 3 studies assessed dual APT.[19,32,33] Among aneurysm treatment modalities, predominantly surgical clipping was done in 9 studies, while endovascular treatment was favored in 5 cohorts[18,19,27,32,33], and both done equally in 1 study.[30] Dual APT was used in 3 studies[19,32,33], while the rest preferred antiplatelet monotherapy. Among the included studies, three were from Germany[18,27,32], three from the Netherlands[15,28,30], two each from the USA[31,33] and Japan[34,35], and one each from England[14], Finland[29], and South Korea.[19]

Association between APT and Good Functional Outcome

We included 12 studies with 3,904 patients with aSAH. APT was started in 1,493 (38.2%), and not initiated in 2,385 (61.8%) patients. Good functional outcome was observed in 1,067 (71.4%) with APT compared with 1,618 (67.1%) in patients not on APT. In the random effects model, APT was significantly associated with good functional outcome (pooled RR, 1.08; 95% confidence interval, [CI], 1.02-1.15) (Figure 1). There was statistically significant heterogeneity (I^2 = 45%; p for heterogeneity = 0.04) but no publication bias (p value for Begg-Mazumdar test = 0.27). The funnel plot for assessment of publication bias is shown in Supplemental Figure II.

Association between APT and DCI

A total of 11 studies were eligible for the meta-analysis on the relationship between APT and DCI. These studies included 3,381 patients with aSAH, of whom 1,303 (38.5%) were started on APT. DCI was observed in 314 (24.1%) patients on APT and 621 (30.6%) who were not started on APT. In the fixed effects model, APT was associated with a lower risk of DCI (pooled RR, 0.85; 95% confidence interval, [CI], 0.75-0.95). However, there was no difference in the risk of DCI in the random effects model (pooled RR, 0.80; 95% CI, 0.63-1.02) (Figure 1). There was significant heterogeneity (I^2 = 61%; p for heterogeneity <0.01) but no publication bias was noted (p value for Begg-Mazumdar test = 0.63) (Supplemental Figure III).

Association between APT and intracranial hemorrhage

Ten studies reported intracranial hemorrhage, which included a total of 2166 aSAH patients, of whom 1162 (53.6%) were started on APT (Supplemental Table I). In the random effects model, there was no significant relationship between APT and intracranial hemorrhage (pooled RR, 1.50; 95% confidence interval, [CI], 0.98-2.31) (Figure 1). There was statistically significant heterogeneity (I^2 = 0; p for heterogeneity = 0.71) but no publication bias (p value for Begg-Mazumdar test = 0.134). The funnel plot for assessment of publication bias is shown in Supplemental Figure IV.

Subgroup Analysis

In pre-specified subgroup analyses by type of aneurysm treatment, APT was associated with favorable functional outcome (RR, 1.12; 95% CI, 1.03-1.22, I^2 = 17%, p value for heterogeneity = 0.31), but not with DCI (RR, 0.66; 95% CI, 0.40-1.07, I^2 = 73%, p value for

heterogeneity <0.01) or intracranial hemorrhage (pooled RR, 1.50; 95% CI, 0.84-2.69, I^2 = 19%, *p* value for heterogeneity 0.30) among patients treated with endovascular interventions (Figures 1-3). However, among SAH patients treated with surgical clipping, APT was not associated with functional outcome, DCI, or intracranial hemorrhage.

In the subgroup analysis stratified by type of APT, administration of aspirin, clopidogrel, and ticlopidine were associated with favorable functional outcome, while dipyridamole, ozagrel, and OKY-046 were not (Supplemental Figure V). Similarly, ticlopidine was associated with a lower risk of DCI, while aspirin and clopidogrel usage suggested no benefit for DCI (Supplemental Figure VI). There was no relationship between type of APT and intracranial hemorrhage (Supplemental Figure VII).

Finally, in the subgroup analysis stratified by study design, retrospective studies were associated with favorable functional outcomes and lower risk of DCI, but not with intracranial hemorrhage. Prospective studies and randomized clinical trials did not relate to any of the outcomes (Supplemental Figures VIII-X).

Assessment of the Quality of Included Studies

The results from the quality assessment questionnaire are shown in Supplemental Table II. Selection bias was minimized in seven studies through random selection of patients in the setting of a clinical trial. [14,15,28,31,34,36] A majority of the studies adjusted for covariate risk factors in assessing the relationship between APT and aSAH outcomes (Supplemental Table I).

Discussion

In this systematic review and meta-analysis of nearly 4,500 patients with aSAH, initiation of APT was associated with a modestly lower risk of major disability or death, and there was a trend toward a decreased risk of DCI, compared to patients not on APT.

APT has been posited to reduce the risk of aneurysm formation and rupture in healthy subjects, and decrease the risk of embolic events in the periprocedural period in patients undergoing aneurysm treatment, presumably due to anti-inflammatory properties.[37] However, data on the efficacy of APT in improving aSAH outcomes is divided. While a few prior studies including randomized trials have shown equivocal benefit of APT for reducing vasospasm and DCI in patients with aSAH undergoing surgical treatment, recent data in primarily endovascularly-treated patients seems to suggest a benefit.[8,18] In the context of these conflicting results, our meta-analysis showed a possible benefit for APT after aSAH.

Clinicians may be hesitant to initiate APT after an acute aSAH since majority of these patients require an external ventriculostomy drain (EVD).[38] In the secondary analysis of the Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III) trial, prior APT use in the setting of intraventricular alteplase administration only resulted in small, clinically inconsequential EVD tract hemorrhages.[39] The APT regimen however appears to influence this bleeding risk. For instance, anecdotal data indicate that flow diversion of ruptured aneurysms in the acute phase of aSAH, an

intervention that requires dual APT, is associated with a higher incidence of intracranial hemorrhage, compared to antiplatelet monotherapy.[40] The trend toward an increased risk of intracranial hemorrhage in our meta-analysis may have also been driven by dual APT regimen utilized in some of the studies. This is not surprising since several clinical trials in ischemic stroke have demonstrated a higher risk of major bleeding events with dual APT compared to a single agent.[41,42] A parallel line of research has suggested that patients with aSAH have a heightened risk of arterial ischemic events such as ischemic stroke, myocardial infarction, and overall cardiovascular mortality, both short- and long-term, further supporting the exploration of APT in these patients.[43,44]

We observed a trend toward lower DCI risk with APT, particularly in endovascularly treated patients, where this relationship was significant in the fixed-effects model, but not in the random-effects analysis. While symptomatic vasospasm is a more common and reversible complication of aSAH, the definition is subjective and therefore subject to more variation. In the present meta-analysis, some studies used angiographic vasospasm as an outcome, even in the absence of clinical symptoms. To minimize heterogeneity in the definition of vasospasm, we therefore opted to include only DCI, where there was clear evidence of infarction on neuroimaging. From a mechanistic standpoint, APT may help alleviate the severity of vasospasm by targeting neuroinflammation and micro-thrombosis, two pathways believed to result in vasospasm.[12,13] Interestingly, ticlopidine appeared to decrease the risk of DCI in our analyses, while the other antiplatelet medications did not. In the Ticlopidine Aspirin Stroke Study, there was a nearly 2-fold reduction in the risk of recurrent stroke in the first year, compared to aspirin among patients with a completed minor stroke.[45] Although it is unclear if one type of APT is superior to others in aSAH, further study and careful consideration of the individual antiplatelet medications is warranted. From a mechanistic standpoint, APT may have a role in mitigating DCI. Although the pathophysiology of DCI is not clearly understood, it is purported to involve activation of inflammatory and coagulation cascades, increased platelet aggregation, and endothelial dysfunction, which collectively lead to the formation of microthrombi eventually resulting in infarcts.[12,46] APT, particularly aspirin, inhibits platelet aggregation and potentially even decreases vasoconstriction by inhibiting proline-rich tyrosine kinase 2 in vascular smooth muscle cells.[47,48] An ongoing clinical trial evaluating the relationship between APT and cognition after SAH may shed more light on the role of APT in future.[49]

Our meta-analysis has several noteworthy limitations. First, the studies included were published over nearly four decades during which practice changes such as the emergence of endovascular treatment, and improvement in intensive care management changed, and presumably introduced heterogeneity and influenced our results. However, we tried to mitigate this issue by performing subgroup analyses by type of surgical intervention and APT regimen. Second, the follow up period for good functional outcomes varied between studies, ranging from 1-12 months, but rates of good functional outcome in endovascularly treated patients were 74.6% at 2 months and 76.3% at 12 months in the ISAT trial, suggesting that variation in the timing of disability assessments should have had a minimal confounding effect on the relationship between APT and outcomes.[24] Third, the findings in this study should be interpreted with caution given the confounding by indication in that SAH severity factors such as presence of a parenchymal hematoma, severe modified Fischer

score, and surgical decompression may have influenced clinicians to consider starting or not starting antiplatelet therapy. Fourth, the dose and duration of APT was not available in all studies; therefore, it is unknown whether a specific APT regimen should be targeted in these patients. Additionally, the timing of initiation of APT was also not provided in all studies, which may have influenced outcomes, particularly DCI. Fifth, since some studies evaluated vasospasm regardless of clinical symptoms (i.e. asymptomatic spasm), we chose to use DCI as an outcome, which is objectively easier to diagnose. That said, the diagnosis and treatment of DCI varied across studies and likely introduced bias. Lastly, data on platelet transfusions, a practice shown to potentially worsen outcomes in patients with intracerebral hemorrhage, were not available.[50]

Conclusion

In this meta-analysis of 14 studies, APT after aSAH was associated with favorable functional outcomes, with a trend toward decreased delayed cerebral ischemia. Increasing use of APT in the context of endovascular therapy for ruptured aneurysms warrants re-exploration of this low-cost intervention to improve outcomes after aSAH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- In this meta-analysis of nearly 4,500 aSAH patients, initiation of APT was associated with a modestly lower risk of major disability or death.
- There was a trend toward a decreased risk of DCI with the use of APT.
- APT was associated with favorable functional outcomes among patients with aneurysms treated with endovascularly compared to those who had surgical clipping.

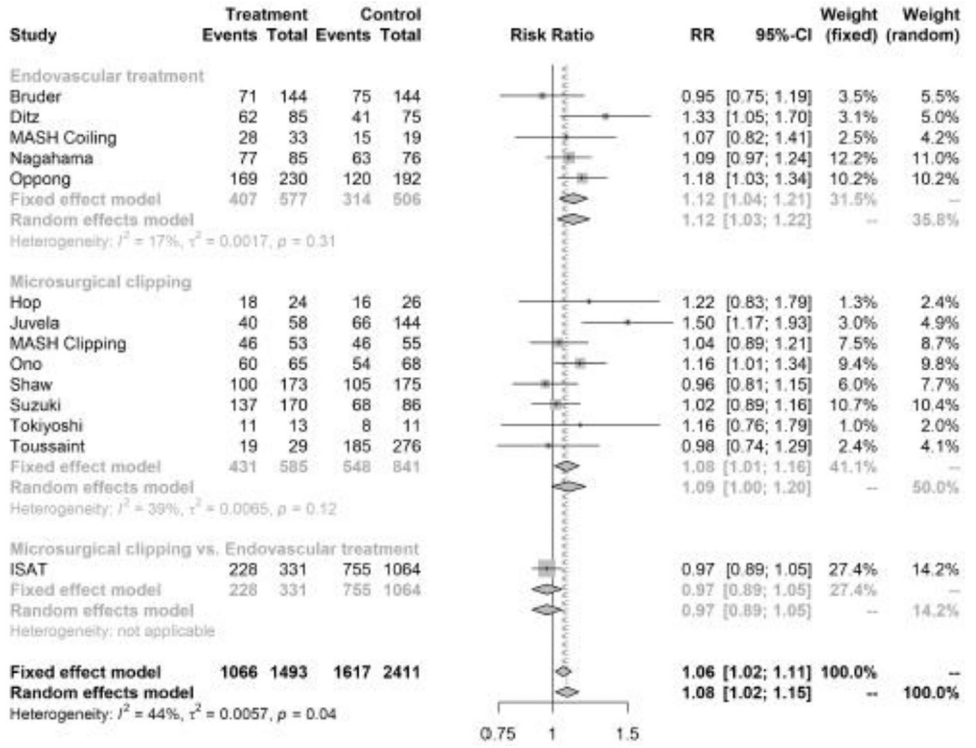

Figure 1.

Forest plot of the association between antiplatelet therapy and good functional outcome after aneurysmal subarachnoid hemorrhage, stratified by type of aneurysm treatment. The meta-analysis was calculated using a random-effects model, with the pooled relative risk shown in the forest plot. Each square represents the point estimate of any given study's effect size. The size of the squares is proportional to the inverse of the variance of the estimate, while the horizontal lines represent each study's 95% confidence intervals. The diamond represents the pooled estimate with the width of the diamond representing the pooled 95% confidence intervals.

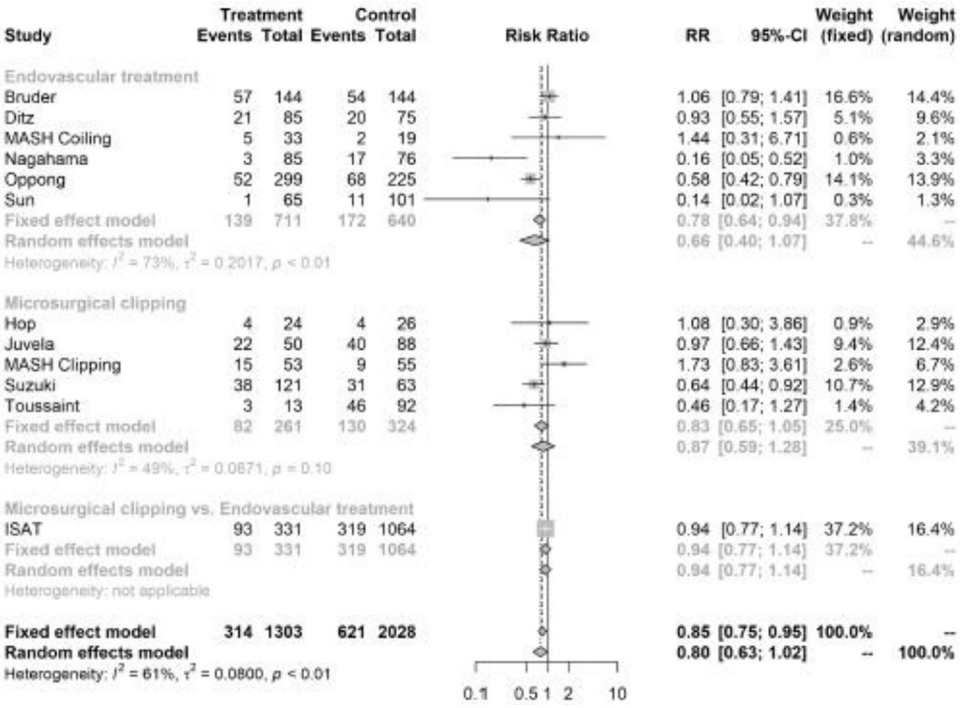

Figure 2.

Forest plot of the association between antiplatelet therapy and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage, stratified by type of aneurysm treatment. The meta-analysis was calculated using a random-effects model, with the pooled relative risk shown in the forest plot.

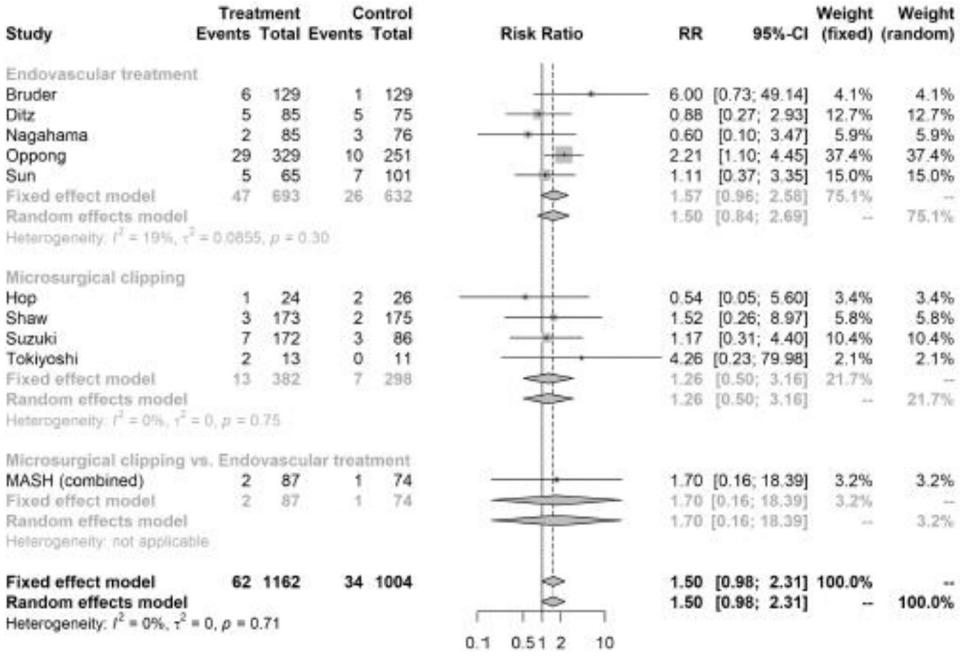

Figure 3.

Forest plot of the association between antiplatelet therapy and intracranial hemorrhage after aneurysmal subarachnoid hemorrhage, stratified by type of aneurysm treatment. The meta-analysis was calculated using a random-effects model, with the pooled relative risk shown in the forest plot.

Table 1:

Overview of the Characteristics of Studies Included in the Meta-Analysis

Study	Design	Major Inclusion Criteria	Number of Subjects	Mean/ Median Follow-up (Mo)	Type of APT	Outcomes
Bruder (2018)[27]	Prospective cohort	Aneurysmal SAH	288	6	ASA	Good outcome-mRS 0-2; vasospasm; DCI
Ditz (2021)[32]	Retrospective cohort	Aneurysmal SAH, endovascular aneurysm treatment only	160	3	Single and dual APT	Good outcome-mRS 0-2; angiographic vasospasm; DCI
Hop (2000)[28]	RCT	Aneurysmal SAH; early surgical clipping	50	4	ASA	Functional outcome; DCI
ISAT (2009)[30]	Secondary analysis of RCT	Aneurysmal SAH; randomized to surgical clipping vs. endovascular coiling	1395	2 and 12	Not specified	Good outcome-mRS 0-2; DCI
Juvela (1995)[29]	Prospective	Aneurysmal SAH	291	12	NSAIDs, ASA	Functional outcome; cerebral ischemia; DCI
MASH Clipping (2009)[15]	RCT	Aneurysmal SAH	108	N/A	ASA	Good outcome-mRS 0-2; DCI
MASH Coiling (2009))[15]	RCT	Aneurysmal SAH	52	N/A	ASA	Good outcome-mRS 0-2; DCI
Nagahama (2018)[33]	Retrospective cohort	Aneurysmal SAH	161	6 weeks	DAPT	Good outcome-mRS 0-2; vasospasm; DCI
Ono (1984)[36]	RCT	Aneurysmal SAH;	135	3	Ticlopidine	Functional outcome; angiographic vasospasm; mortality
Oppong (2019)[18]	Retrospective case-control	Aneurysmal SAH; endovascular coiling only	580	6	ASA	Good outcome-mRS 0-2; DCI
Shaw (1985)[14]	RCT	Any SAH	677	3	Dipyridamole	Functional outcome; postoperative complications
Sun (2020)[19]	Retrospective cohort	Aneurysmal SAH	166	None	DAPT	Vasospasm; DCI
Suzuki (1989)[34]	RCT	Aneurysmal SAH	258	3	OKY-046 (Ozagrel)	Functional outcome; DCI; intracerebral hemorrhage
Tokiyoshi (1991)[35]	Prospective cohort	Aneurysmal SAH; Hunt Hess ≤4	24	1	Cataclot	Functional outcome; vasospasm
Toussaint (2004)[31]	Retrospective cohort	Aneurysmal SAH	305	16.4	ASA	Good outcome-GOS ≤3; vasospasm; permanent deficit; rebleeding

Abbreviations: ASA, acetyl salicylic acid (aspirin); APT, antiplatelet therapy; DAPT, dual antiplatelet therapy; DCI, delayed cerebral ischemia; GOS, Glasgow Outcome Scale; Mo, months; mRS, modified Rankin Scale; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomized clinical trial.

Table 2.

Rates of Good Functional Outcome and Delayed Cerebral Infarction

Study (Year)	Antiplatelet Therapy			No Antiplatelet Therapy		
	Good Outcome (%)	DCI (%)	Total Population	Good Outcome (%)	DCI (%)	Total Population
Bruder (2018)[27]	71 (49.3)	57 (39.5)	144	75 (52.1)	54 (37.5)	144
Ditz (2021)[32]	62 (72.9)	21 (24.7)	85	41 (54.7)	20 (26.7)	75
Hop (2000)[28]	18 (75.0)	4 (16.7)	24	16 (61.5)	4 (15.4)	26
ISAT (2009)[30]	228 (68.9)	93 (28.0)	331	755 (71.0)	319 (30.0)	1064
Juvela (1995)[29]	40 (68.9)	22/50 (44.0)	58	66 (45.8)	40/88 (45.4)	144
MASH Clipping (2009)[15]	46 (87.0)	15 (28.0)	53	46 (84.0)	9 (16.0)	55
MASH Coiling (2009))[15]	28 (85)	5 (15.0)	33	15 (79.0)	2 (11.0)	19
Nagahama (2018)[33]	77 (90.6)	3 (3.5)	85	63 (82.9)	17 (22.4)	76
Ono (1984)[36]	60 (92.3)	N/A	65	54 (79.4)	N/A	68
Oppong (2019)[18]	169/230 (73.5)	52/299 (17.4)	329	120/192 (62.5)	68/225 (30.2)	251
Shaw (1985)[14]	100(58.0)	N/A	173	105 (60.0)	N/A	175
Sun (2020)[19]	N/A	1	65	N/A	11	101
Suzuki (1989)[34]	138 (81.2)	38/121 (31.4)	170	69 (80.2)	31/63 (49.2)	86
Tokiyoshi (1991)[35]	11 (84.6)	N/A	13	8 (72.7)	N/A	11
Toussaint (2004)[31]	19 (65.5)	3/13 (23.0)	29	185 (67.0)	46/92 (50.0)	276
Total Events	**1067/1493**	**314/1303**	**1657**	**1618/2411**	**621/2028**	**2571**

Abbreviations: DCI, delayed cerebral infarction; N/A, not available.