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The timing of intraprocedural antiplatelet therapy did not affect outcomes in endovascular treatment of ruptured intracranial aneurysms: a systematic review

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Abstract

Background

Thromboembolic complications (TEC) and perforation are known complication sin patients with ruptured intracranial aneurysms treated with primary coiling. Antiplatelet therapy may reduce TEC; however, crucially, there is no antidote to reverse the antiplatelet effect if an intraprocedural perforation occurs, which is most likely during first-coil deployment. We assessed whether adjunct antithrombotic administration before the procedure or after the first coil offers a better safety–efficacy balance.

Materials and Methods

A PRISMA-based systematic review searched PubMed, Ovid/MEDLINE, and Cochrane CENTRAL to August-2025. Eligible studies reported outcomes of ruptured aneurysm coiling with adjunct anti-thrombotics, excluding stent-assisted/flow diverter cases. The primary outcome was TEC; secondary outcomes were aneurysm perforation and symptomatic intracranial hemorrhage (sICH). Random-effects meta-analyses used logit transformation; subgroup analyses compared pre-procedural versus post–first-coil administration; and leave-one-out sensitivity analyses were performed.

Results

Five studies (n = 526 patients) were included; median Hunt–Hess 2 and Fisher 3. Regimens included aspirin versus no aspirin (3 studies), glycoprotein IIb/IIIa inhibitor versus none (1), and placebo versus clopidogrel versus DAPT (1). Timing: 3 pre-procedural, 2 post–first heterogeneity was modest ($I^2 \approx 30\%$ across outcomes). Adjunct antithrombotics reduced TEC with similar magnitude whether given before the procedure or after the first coil (pooled OR 3.8 [95% CI 1.2–12.5] pre-procedural vs 3.4 [0.9–12.2] post–first-coil) Rates of perforation and sICH did not differ by timing.

Conclusions

In ruptured aneurysm coiling, adjunct anti-platelts lower TEC without increasing perforation or sICH, and their efficacy appears comparable when administered after the first coil. Given the absence of an antiplatelet antidote, post-first-coil administration may offer a pragmatic safety advantage.

Introduction

In 2005, the landmark International Subarachnoid Aneurysm Trial (ISAT) was published[1], which demonstrated the superiority of endovascular coiling over surgical clipping in terms of survival free of disability at 1 year in patients with ruptured brain aneurysms. The AHA/ASA guideline[2] in 2023 confirmed that when possible, primary coiling is the preferred option for securing the aneurysm and preventing rebleeding. The two major complications of primary coiling are procedural rupture and thromboembolic complication[3]. Thromboembolic complications are the most frequent, ranging from 4.7% to 12.5%, with a rate of permanent neurological deficit or death of 3.8% of patients[4]. In contrast, aneurysm perforation occurred in 2%/8.8% of patients, but with more severe outcomes, with permanent neurological deficits from 5% to 63% and death in 20% to 30%[4].

To reduce the risk of TEC complications, some studies have suggested the use of heparin load before the procedure[5, 6]. In particular, heparin load was not associated with an increased risk of bleeding (OR 0.683 [95CI 0.199 – 2.338])[6]. However, some authors have suggested adding antiplatelet therapy to further reduce the risk of TEC. Although this regimen is mandatory in the case of stent placement[7], the use of antiplatelet agents in the treatment of ruptured brain aneurysms with

primary coiling is still a matter of debate. The major problem is the absence of the an antidot for anti-platelet drugs which cannot be revert in case of perforation.

We conducted a systematic review on the impact of different timing of administration of anti-platelet therapy in rupture brain aneurysm treated with primary coiling

Material and Methods

The study protocol is available upon reasonable request from the corresponding author. The data used for the systematic review are publicly available; therefore, IRB approval was not necessary. The review protocol was registered with PROSPERO (ID 1111870). The study was drafted according to the PRISMA guideline[8].

Eligibility Criteria

We included all studies that reported results on the outcomes of patients with subarachnoid hemorrhage due to brain aneurysm rupture treated with adjunctive anti-thrombosis drugs. We did not find any randomized controlled trials. Studies were eligible if they reported one or more of the following outcomes: thromboembolic complications, aneurysm rupture, or artery perforation. The exclusion criteria were case reports, studies in which the aneurysm was treated without primary coiling, studies not reporting the specified outcomes, and articles not published in English. We excluded studies that reported stent-assisted techniques or flow diverter displacement due to the need to use heparin and antiplatelet therapy and the increased difficulties of aneurysm treatment, which may have imbalanced the results.

Searching strategy

A literature review was performed on PubMed, OVID (MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions), and Cochran's CENTRAL from inception to August 2025. The MeSH terms used were: “Subarachnoid Hemorrhage”, “Intracranial Aneurysm”, “Dual Anti-Platelet Therapy”, “Platelet Aggregation Inhibitors”, “Aspirin”, “Clopidogrel”, “Anticoagulants” and “Heparin” with appropiate Boolean operator AND/OR. (The full search is displayed in **the Supplementary Material**.) Initially, an automatic tool for deduplication was used in Ovid, and subsequently, Rayyan (https://www.rayyan.ai) was used for duplication screening[9]. Furthermore, the titles and abstracts were reviewed. All the processes of selection and screening were performed by two neuroradiologists (5 and 15 years of experience), and disagreements were resolved by consensus. The results are shown in Fig. 1. The research aimed to address the PICO question: "For aneurysmal subarachnoid hemorrhage, do the timing of antiplatelet administration provide a better overall balance of fewer clots and no excess bleeding than monotherapy or no therapy regardless the time of administration ?”

Study quality

The methodological index for non-randomized studies (MINORS) was used to evaluate the quality of all studies included in this analysis due to their non-randomized nature (**Table S1**)[10]. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to evaluate the overall body of evidence[11] (**Table S2**). A single reviewer with five years of experience assessed the data quality of the included studies.

Data extraction

The extraction was performed by a neurointerventional radiologist with 5 years of experience. The number of patients and their demographic data, administration of heparin and/or anti-platelet therapy, timing of administration (before or after the

first coil), type of anti-platelet, subarachnoid hemorrhage status (Hunt-Hess[12] and Fisher[13]), and procedural outcomes (thromboembolic complications [TEC], perforation, and symptomatic intracranial hemorrhages [sICH]) were recorded.

Statistical analysis

Ovid was used as a tool for automatic deduplication. Rayyan (https://www.rayyan.ai) was used to screen for duplicates[9]. Data are presented as mean, median, standard deviation, and 95% confidence interval (95% CI), depending on the distribution (Table 1**)**.. I^2 was used for testing heterogeneity. A funnel plot was used to assess publication bias. Due to the low prevalence of events, logit transformation was used. Subgroup analysis was performed comparing the group in which adjunctive therapy plus heparin was administered at different time points: pre-procedural or after the first coil.

Table 1
Articles summary

Authors	years	patients	Age	Gender	Hunt-hess	Comparison	Thromboemboli complication	Perforation	SICH
Ries	2006	184				Aspirine	26 (14.1%)	15 (8.1%)	
Edwards	2017	79	53.8 ± 12.9	59 (74.6%)	3	Aspirine	14 (17.7%)		
Muraoka	2018	100		74 (74%)		Aspirine	18 (18%)	8 (8%)	
Shimamura	2019	30	74 ± 20.1	22 (73.3)		Aspirine	6 (20%)	2 (7.0)	2 2 (7.0%)
Burkle	2024	116	53.8 ± 14.1		2	GIIb/IIIa inhibitors	16 (13.4%)	1 (0.8)	5 (4.3%)

Statistical analyses were performed using two software packages: R-Studio (available from R-project http://www.R-project.org) and OpenMeta version 12.11.[14] (accessible at http://www.cebm.brown.edu/openmeta/index.html).

Results

We retrieved 1704 articles. Rayyan's automatic software for duplication deleted 78/1704 (4.5%). Manual checks removed 1577/1626 (96.9%) records, and the remaining 49 studies were screened using their titles, abstracts, and full texts. After applying the inclusion and exclusion criteria, the final sample size was 5/49 (10.2%) (Fig. 1**)**. .

Five-hundred twenty-six patients were included in this systematic review (87.7 ± 35.0 per study). The median age was 58.7 (95%CI 53.6 to 66.9) years, with a percentage of females ranging from 60.3% to 75%. 1/5 (10.0%) did not report age[15], and 1/5 (10. %) did not report standard deviation of the age[16] and 2/5 (40%)[15, 17] did not show gender balance. The median Hunt-Hess score was 2.0 (95% CI 0.9 to 3.8) and the Fisher grade was 3.0 (95% CI 3 to 3) (Table 1**)**.. The results demonstrated that the anti-platelet/anti-coagulant regimens were very different: 3/5 (60%) compared the use of aspirin vs no-aspirin[15, 18, 19] 1/5 (10%) compared GIIb/IIIa inhibitors vs. no GIIb/IIIa inhibitors[17], 1/5 (14.3%)[16] had three arms comparing placebo vs. clopidogrel vs. DAPT, and 1/5 (14.3%). The treatment was administrated: in 2/5 (40%)[15, 17] after the first coil and remaining 3/5 (60%) before the procedure[16, 18, 19]

The I^2 for thromboembolic complication was 30.1%, for perforation was 29.7% and for symptomatic intracranial hemorrhages was 32.7. This number remained similar after removing Burkle et al[17] (which used GIIb/IIIa inhibitors) 34.01 and 16.81, respectively. The analysis for sICH was not performed in the subgroup of antiplatelet therapy because Ries et al[15] did not report this outcome. The funnel plot is shown in Fig. 2. demonstrated no significant publication bias.

There was a similar probability of reducing TEC if the drugs were administered before the procedure or after the first coil; however, the odds ratio in the latter was not significant in terms of general reduction (OR 3.8 [95% CI 1.2 to 12.5] vs. OR 3.4 [95% CI 0.9 to 12.2], respectively). This datum remain similar after removing Burkle et al[17] which administrated GIIb/IIIa inhibitor (OR 3.8 [95% CI 1.2 to 12.5] vs OR 2.2 [95% CI 1.0 to 5.2], respectively) (Fig. 3. **and 4.**)

There were no differences in the probability of perforation or sICH considering both possible timings of administration. Figure 3. **and 4.**

Discussion

The present systematic review showed that in patients with ruptured brain aneurysms treated with primary coiling, the rates of TEC, perforation, or sICH were similar if the drugs (either antiplatelet or GIIb/IIIa inhibitors) were administered before the procedure or after the first coils.

TEC is reported as the most common complication in primary coiling for brain aneurysms, both unruptured and ruptured, but with different frequencies (5.9% and 12.5%, respectively)[20–22], probably due to a mix of reasons, including vasospasm and hypercoagulability[23]. A similar pattern was found in terms of intra-procedural rupture for ruptured aneurysms and for unruptured aneurysms (4.1% vs. 0.5%; P < 0.001, respectively) with the worst composite outcome (permanent neurologic disability and death 38% vs. 29%, respectively)[24].

To partially reduce the burden of thromboembolic complications, some authors[6, 15] have suggested the administration of heparin. However, the risk of rebleeding from an already ruptured aneurysm remain a challenge to face[2]. In addition, although TEC are more frequent than aneurysm rupture, their impact on outcomes is less important. However, all studies included in this systematic review reported the use of heparin to reduce TEC, although its effectiveness has not yet been proven. In fact, in a case-control study in2021, Choi et al[6] showed that TEC did not significantly differ with or without heparin load (1.3% vs. 3.3%, p = 0.463, respectively) without any effect on rebleeding. However, a brut difference of 2% may not be clinically irrelevant and may suggest insufficient power to detect statistical significance.

Diffuse-weighted imaging (DWI) lesions were frequently observed following endovascular treatment for cerebral aneurysms[25] (47.0% [95% CI, 39.6%–55.8%]). Therefore, some authors have suggested adding antiplatelet therapy to reduce TEC. In 2022, Takase et al[26] demonstrated the same results as our systematic review: antiplatelet therapy reduced the risk of TEC (OR 3.42; 95% CI 1.77 to 6.61, p < 0.001). However, a very significant point is missing: heparin has an antidote, but antiplatelet therapy does not. This fundamental clue is important in the management of the devastating complications of endovascular treatment: aneurysm perforation. During an iatrogenic rupture of the aneurysm, it is possible to revert heparin with protamine sulfate, but there is no possible action for anti-platelet therapy.

Aneurysm perforation is more frequent during the first coil deployment[27]; in addition, because of the absence of any protection on the aneurysm sac, the clinical consequences are more severe[28]. Therefore, in this systematic review, we tested the effect of antithrombotic drugs at two different time points: before the procedure and after the first coil. The idea behind The second approach has the advantage of a safer profile (the aneurysm is more protected) and less TEC (antithrombotic agents). This systematic review demonstrated that the TEC rate was similar whether antiplatelet therapy was administered before the procedure or after the first coil. This is a crucial aspect because there is no antidote for antiplatelet drugs, and the possibility of administering it after the first coil with a more secured aneurysm aids in maintaining the benefit of antiplatelet treatment while reducing its drawbacks.

This systematic review has several limitations. First, very few studies have reported this specific topic with a retrospective nature. Second, the outcomes considered are uncommon, although clinically impactful, and therefore prone to sample bias. Thirdly, the anti-platelet regimen was very various limited the analysis. Finally, while study heterogeneity and varying quality may limit broad generalizations, this systematic review represents one of the first attempts to address this clinical question.

The nature of the setting (focusing on emergency scenarios and rare complications) inherently constrained the feasibility of a more homogenous study design.

In conclusion, the timing of anti-platelet therapy administration did not affect the known effect of decreasing the TEC rate with similar percentages of perforation and sICH. This allows for the administration of antithrombotic drugs immediately after the first coil deployment, reducing the risk of rupture and maintaining the benefit of the drugs.

Declarations

Human Ethics and Consent to Participate declarations: not applicable

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IRB approval was not necessary

Author Contribution

Conceptualization GDR, Data Curation AT, LB, , Formal Analysis GDR , Funding Acquisition NA, Investigation GDR LS, Methodology GDR LS, Project Administration NA, Resources NA, Software, GDR Supervision SF, RR, EP, LS, Validation SF, RR, EP, LS, Visualization GDR, Writing – Original Draft GDR, and Writing – Review & Editing SF, RR, EP, LS

References

1. Molyneux AJ, Kerr RSC, Yu L-M et al (2005) International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 366:809–817
2. Hoh BL, Ko NU, Amin-Hanjani S et al (2023) 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke 54:e314–e70
3. van Rooij WJ, Sluzewski M, Beute GN, Nijssen PC (2006) Procedural Complications of Coiling of Ruptured Intracranial Aneurysms: Incidence and Risk Factors in a Consecutive Series of 681 Patients. Am J Neuroradiol 27:1498
4. Orrù E, Roccatagliata L, Cester G, Causin F, Castellan L (2013) Complications of endovascular treatment of cerebral aneurysms. Eur J Radiol 82:1653–1658
5. Egashira Y, Yoshimura S, Enomoto Y, Ishiguro M, Asano T, Iwama T (2013) Ultra-early endovascular embolization of ruptured cerebral aneurysm and the increased risk of hematoma growth unrelated to aneurysmal rebleeding: Clinical article. J Neurosurg JNS 118:1003–1008
6. Choi J, Koo Y, Whang K, Cho S, Kim J (2021) Safety of heparin loading during endovascular embolization in patients with aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 201:106453
7. Li L, Huang Q-H, Shao Q-J et al (2024) Different antiplatelet regimens for stenting versus coiling for acutely-ruptured cerebral aneurysms. Sci Rep 14:30331
8. Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. Syst Reviews 5:210
10. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 73:712–716

11. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011; 64: 383 – 94
12. Hunt WE, Hess RM (1968) Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 28:14–20
13. Fisher CM, Kistler JP, Davis JM (1980) Relation of Cerebral Vasospasm to Subarachnoid Hemorrhage Visualized by Computerized Tomographic Scanning. Neurosurgery. ; 6
14. O'Brien SF, Yi QL (2016) How do I interpret a confidence interval? Transfusion 56:1680–1683
15. Ries T, Buhk J-H, Kucinski T et al (2006) Intravenous Administration of Acetylsalicylic Acid During Endovascular Treatment of Cerebral Aneurysms Reduces the Rate of Thromboembolic Events. Stroke 37:1816–1821
16. Muraoka K, Sato Y, Hosomoto K et al (2018) Effectiveness of antiplatelet drug loading before acute-phase coil embolization of ruptured cerebral aneurysms. J Neuroendovascular Therapy 12:75–80
17. Bürkle F, Weyland CS, Hasan D et al (2024) Propensity score-adjusted analysis on early tirofiban administration to prevent thromboembolic complications during stand-alone coil embolization of ruptured aneurysms. Sci Rep 14:26350
18. Shimamura N, Naraoka M, Matsuda N et al (2020) Use of Preprocedural, Multiple Antiplatelet Medications for Coil Embolization of Ruptured Cerebral Aneurysm in the Acute Stage Improved Clinical Outcome and Reduced Thromboembolic Complications without Hemorrhagic Complications. World Neurosurg 133:e751–e6
19. Edwards NJ, Jones WH, Sanzgiri A, Corona J, Dannenbaum M, Chen PR (2017) Antiplatelet therapy for the prevention of peri-coiling thromboembolism in high-risk patients with ruptured intracranial aneurysms. J Neurosurg 127:1326–1332
20. Pierot L, Cognard C, Anxionnat R, Ricolfi F (2010) Ruptured intracranial aneurysms: factors affecting the rate and outcome of endovascular treatment complications in a series of 782 patients (CLARITY study). Radiology 256:916–923
21. Pierot L, Spelle L, Leclerc X, Cognard C, Bonafé A, Moret J (2009) Endovascular treatment of unruptured intracranial aneurysms: comparison of safety of remodeling technique and standard treatment with coils. Radiology 251:846–855
22. De Rubeis G, Fabiano S, Bertaccini L, Ricciuti R, Saba L, Pampana E (2025) Setting benchmark for brain aneurysm treated endovascularly: a systematic review and meta-analysis. Neurosurg Rev 48:411
23. Altay T, Kang HI, Woo HH et al (2011) Thromboembolic events associated with endovascular treatment of cerebral aneurysms. J neurointerventional Surg 3:147–150
24. Cloft HJ, Kallmes DF (2002) Cerebral aneurysm perforations complicating therapy with Guglielmi detachable coils: a meta-analysis. AJNR Am J Neuroradiol 23:1706–1709
25. Habtezghi AB, Ghozy S, Bilgin C, Kobeissi H, Kadirvel R, Kallmes DF (2023) DWI-Detected Ischemic Lesions after Endovascular Treatment for Cerebral Aneurysms: An Updated Systematic Review and Meta-analysis. Am J Neuroradiol 44:1256
26. Takase H, Tatezuki J, Salem MM et al (2022) Antiplatelet therapy for standalone coiling of ruptured intracranial aneurysms: a systematic review and meta-analysis. J neurointerventional Surg 14:1207–1212
27. Santillan A, Gobin YP, Greenberg ED et al (2012) Intraprocedural aneurysmal rupture during coil embolization of brain aneurysms: role of balloon-assisted coiling. AJNR Am J Neuroradiol 33:2017–2021
28. Murayama Y, Nien YL, Duckwiler G et al (2003) Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg 98:959–966

Figures

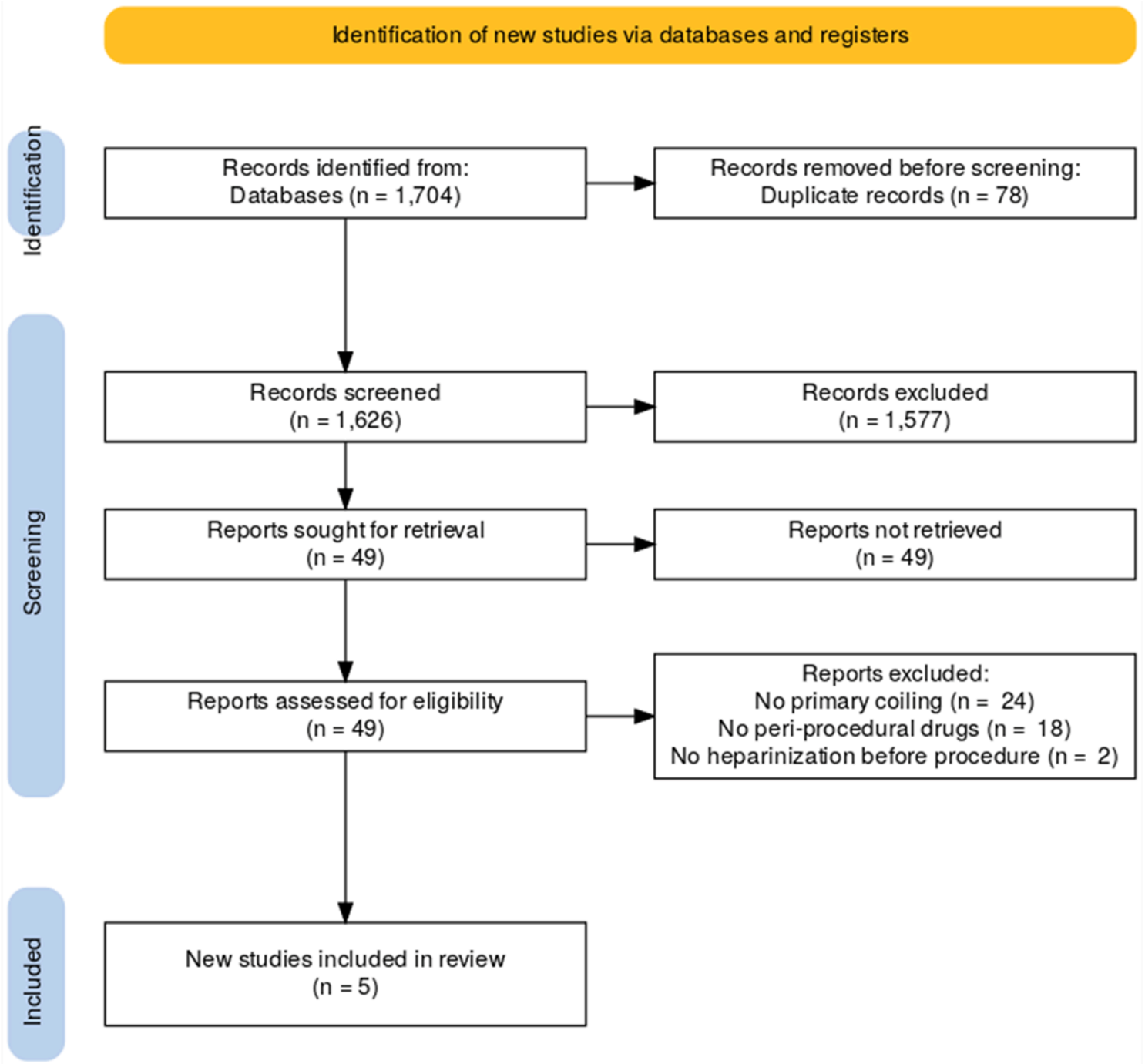


Figure 1

Flowchart of the systematic review

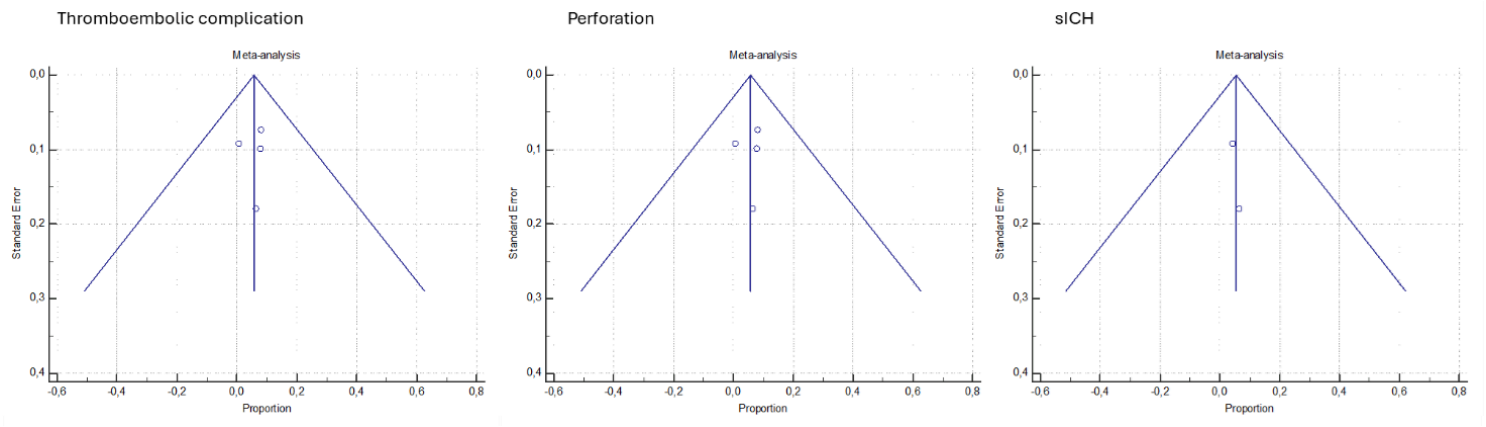


Figure 2

Funnel plot

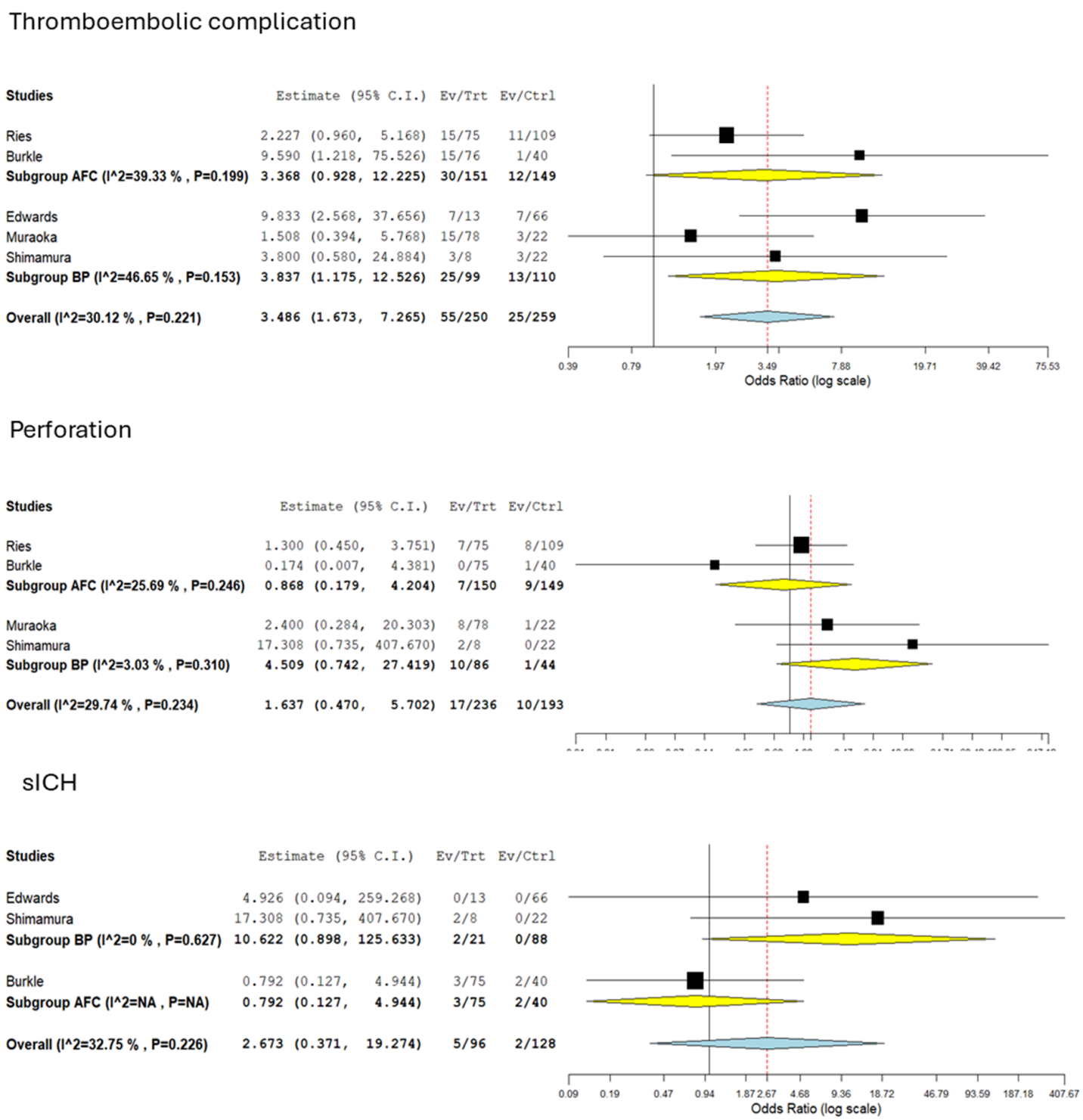


Figure 3

The meta-regressions comparing the three outcomes between after the first coil (AFC) and before procedure (BP) which demonstrate no statistical differences

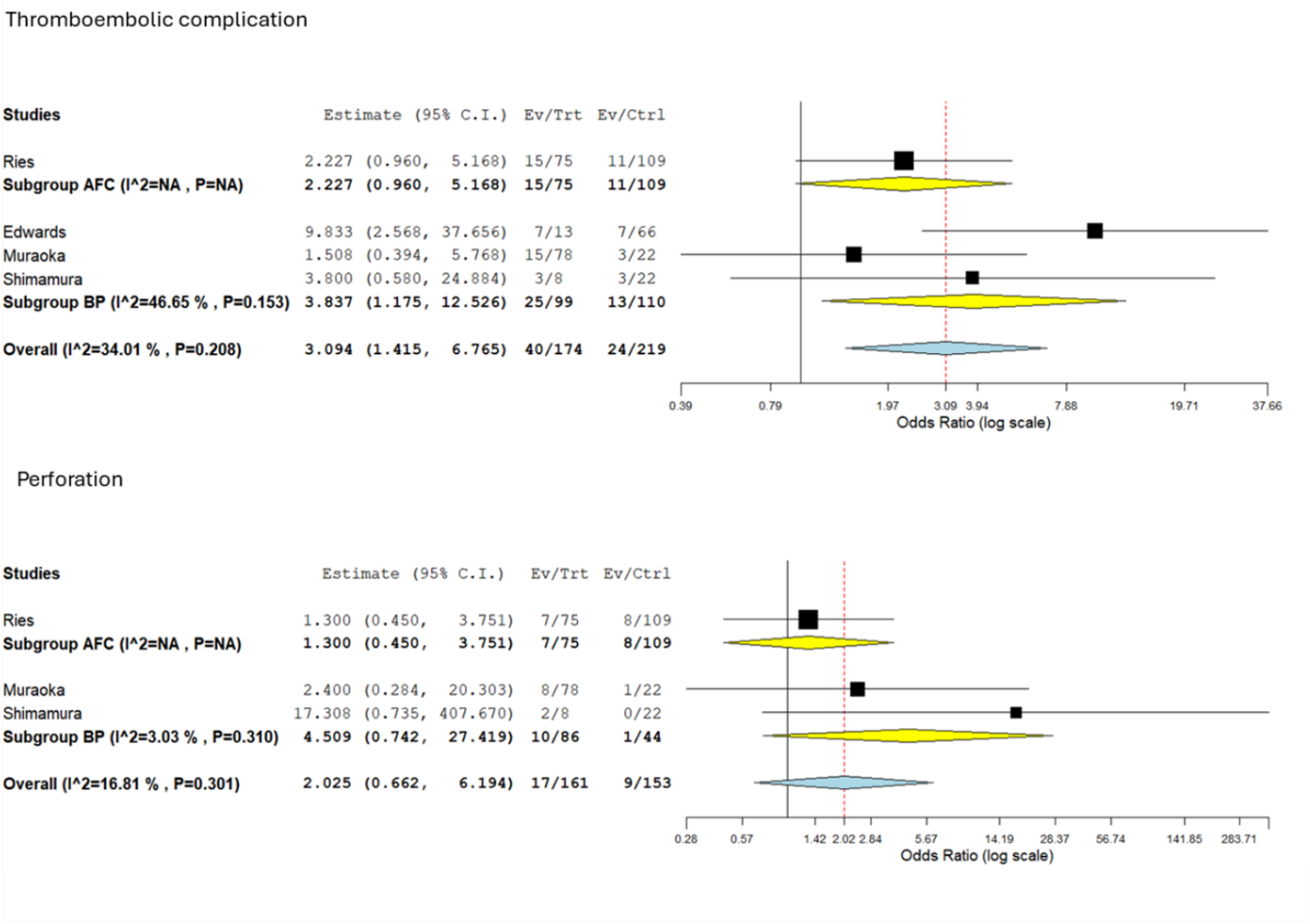


Figure 4

The leave-one-out meta-analysis demonstrate no significant sign of heterogeneity

Supplementary Files

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