



THE SAFETY OF ANTIPLATELET REVERSAL PROCEDURES BEFORE EMERGENCY NEUROSURGERY IN PATIENTS WITH RUPTURED ANEURYSMS POST-EMBOLIZATION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction: Stent-assisted coil embolisation and flow diversion have expanded the endovascular armamentarium for acutely ruptured wide-necked and complex intracranial aneurysms, but these devices oblige dual antiplatelet therapy in patients who have just sustained subarachnoid haemorrhage and frequently require emergency intracranial surgery for hydrocephalus, intraparenchymal clot, or refractory intracranial hypertension. The safety of attempting to reverse platelet inhibition before such emergency neurosurgery remains contested.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies were randomized controlled trials and comparative primary studies reporting antiplatelet exposure or

reversal in adults undergoing emergency intracranial procedures, with emphasis on aneurysmal subarachnoid haemorrhage after stent-assisted coiling or flow diversion. Thirteen outcomes were prespecified. Dichotomous data were pooled with DerSimonian-Laird random-effects models; heterogeneity was quantified by Cochran Q, τ^2 , and I^2 ; and certainty of evidence was rated using GRADE.

Results: Sixty-three records corresponding to fifty-nine primary studies were included, comprising four randomized controlled trials and fifty-five non-randomized comparative or cohort studies. In the pooled analysis of nine comparative cohorts (1,401 patients and procedures), antiplatelet exposure at the time of cerebrospinal-fluid diversion conferred a fourfold increase in radiographically evident catheter-tract haemorrhage (odds ratio 4.00; 95% confidence interval 2.59 to 6.18; $P<0.0001$; $I^2=5.7\%$). The hazard persisted for symptomatic haemorrhage across three cohorts (odds ratio 3.96; 95% CI 1.54-10.16; $P=0.004$; $I^2=0\%$). Restoration of platelet function with allogeneic platelet concentrate did not translate into clinical benefit and was associated with net harm in the randomized trial (adjusted common odds ratio for death or dependence 2.05; 95% CI 1.18-3.56). By contrast, pharmacological rescue with desmopressin was associated with significant reduction in haematoma expansion (odds ratio 0.32; 95% CI 0.12-0.86; $P=0.024$; $I^2=29.7\%$). Pre-procedural P2Y₁₂ reaction units discriminated peri-procedural complications with moderate accuracy (area under the curve 0.74; optimal window 118-144 units), whereas thromboelastography with platelet mapping performed no better than chance (area under the curve 0.53). Catheter placement after versus before antiplatelet loading was associated with significant excess of tract haemorrhage (odds

ratio 2.46; 95% CI 1.16-5.20; $P=0.019$; $I^2=0\%$). Certainty of evidence was moderate for the primary haemorrhagic outcome and low to very low for all mortality and functional outcomes.

Conclusion: Antiplatelet exposure after endovascular treatment of a ruptured aneurysm significantly and substantially increases catheter-related intracranial haemorrhage during emergency neurosurgery, but pharmacological reversal by platelet transfusion does not mitigate this hazard and may worsen outcome. Safety in this population is achieved principally by procedural planning, by agent selection favouring reversible short-acting inhibitors, and by selective use of desmopressin rather than by reflexive platelet transfusion. Adequately powered randomized trials of desmopressin, of tirofiban or cangrelor bridging, and of assay-guided reversal in the specific post-embolisation subarachnoid haemorrhage population are urgently required.

Keywords: aneurysmal subarachnoid haemorrhage; antiplatelet reversal; dual antiplatelet therapy; stent-assisted coil embolisation; flow diversion; external ventricular drain; ventriculoperitoneal shunt; platelet transfusion; desmopressin; P2Y₁₂ reaction units; emergency neurosurgery

INTRODUCTION

Background

Aneurysmal subarachnoid haemorrhage remains one of the most lethal cerebrovascular emergencies encountered in neurosurgical practice, and the immediate therapeutic imperative is exclusion of the ruptured sac from the circulation before rebleeding occurs. Over the past two decades the endovascular route has progressively displaced microsurgical clipping as the first-line strategy in appropriately selected patients, and the technical repertoire has broadened from simple coil packing to balloon remodelling, intracranial stent deployment and, most recently, flow diversion. Each incremental gain in the ability to treat wide-necked, fusiform, blister-like or otherwise complex ruptured aneurysms has, however, been purchased at a specific pharmacological cost: intraluminal metal within the cerebral circulation obliges the operator to institute dual antiplatelet therapy in order to prevent in-stent thrombosis and thromboembolic infarction.^{6,35}

The pharmacodynamic consequence is that a patient who has just bled into the subarachnoid space, and whose intracranial compartment is by definition unstable, is deliberately rendered platelet-inhibited during the very period in which further intracranial procedures are most likely to be required. Acute hydrocephalus complicates approximately one fifth to one half of aneurysmal subarachnoid haemorrhages and mandates external ventricular drainage; persistent cerebrospinal-fluid malabsorption requires ventriculoperitoneal shunting in roughly one tenth; associated intraparenchymal haematoma may demand craniotomy and evacuation; and refractory intracranial hypertension in poor-grade patients may require decompressive craniectomy. Each of these procedures traverses vascularised brain parenchyma with an instrument, and each therefore constitutes a discrete opportunity for iatrogenic haemorrhage in a patient whose primary haemostatic plug formation has been deliberately disabled.^{3-5,33,34,64}

Faced with this dilemma, clinicians have historically reached for so-called antiplatelet reversal. The two agents most frequently employed at the bedside are allogeneic platelet concentrate, transfused on the assumption that unexposed donor platelets will restore aggregation

capacity, and desmopressin acetate, administered on the assumption that a surge in von Willebrand factor and factor VIII will improve platelet adhesion and shorten the bleeding time. Neither practice originated in high-quality evidence derived from the aneurysmal population. Surveys of North American and European neurosurgeons have documented profound practice variation, with platelet transfusion the most common response to aspirin-associated and adenosine-diphosphate-antagonist-associated operative intracranial haemorrhage, but with the majority of respondents performing no qualitative platelet testing whatsoever before intervening and with confidence in the effectiveness of these therapies scarcely exceeding the midpoint of a visual analogue scale.³⁷⁻³⁹

The evidence that has accumulated in adjacent populations is, moreover, discouraging. In spontaneous antiplatelet-associated intracerebral haemorrhage, the randomised Platelet Transfusion in Cerebral Haemorrhage trial demonstrated that platelet transfusion increased the odds of death or dependence at three months rather than reducing them, a finding that has been incorporated into subsequent guidance recommending against this practice. In traumatic intracranial haemorrhage, successive systematic reviews and meta-analyses have failed to demonstrate any association between platelet transfusion and survival, haemorrhage progression or the need for neurosurgical intervention. Yet these populations differ from the post-embolisation subarachnoid haemorrhage patient in a crucial respect: the trauma and spontaneous intracerebral haemorrhage patient has no indwelling intracranial stent whose acute thrombosis would produce catastrophic territorial infarction. Reversal in the post-embolisation patient is therefore not merely of uncertain benefit but of demonstrable competing risk.^{1,2,40,42,65}

A parallel body of work has attempted to individualise antiplatelet intensity rather than to reverse it, using point-of-care platelet function assays. The VerifyNow P2Y12 assay, expressed in P2Y12 reaction units, and thromboelastography with platelet mapping have both been proposed as instruments for identifying the therapeutic window in which thromboembolic and haemorrhagic risks are jointly minimised. Reported optimal windows range from seventy to one hundred and fifty units, and receiver-operating-characteristic analyses in neuroendovascular cohorts have suggested a narrower ideal band of one hundred and eighteen to one hundred and forty-four units, with values below sixty predicting haemorrhage and values above two hundred and forty predicting thrombosis.

The discriminative performance of these assays, their reproducibility, and above all their utility in the emergency rather than the elective setting, remain incompletely characterised.^{16-19,41}

Research Gap

Three distinct evidentiary gaps motivated the present review. First, although several single-centre cohorts have quantified catheter-related haemorrhage under dual antiplatelet therapy after stent-assisted coiling, these studies are individually underpowered for symptomatic events, and no quantitative synthesis restricted to the post-embolisation aneurysmal population has previously been published; existing meta-analyses address traumatic or spontaneous intracerebral haemorrhage and are therefore indirect. Second, the literature on antiplatelet reversal is fragmented across specialties, with the transfusion-medicine, trauma-surgery, neurocritical-care and neurointerventional communities each generating evidence in isolation and rarely cross-referencing one another; consequently the pharmacological non-reversibility of ticagrelor by donor platelets, a finding firmly established in haematology laboratories, has propagated only weakly into neurosurgical practice. Third, and most consequentially, no synthesis has previously attempted to integrate the haemorrhagic hazard, the thrombotic counter-hazard, the biochemical efficacy of reversal, and the discriminative accuracy of platelet-function testing within a single analytical framework applicable to the patient in front of the surgeon at three o'clock in the morning.^{3-5,13,26,40,42}

Objectives

The general objective of this systematic review was to determine the safety of antiplatelet reversal procedures performed before emergency neurosurgery in adults with ruptured intracranial aneurysms who had undergone endovascular embolisation requiring antiplatelet therapy. The specific objectives were as follows.

- To quantify the association between antiplatelet exposure at the time of emergency neurosurgical intervention and the incidence of radiographically evident and symptomatic procedure-related intracranial haemorrhage.
- To quantify the effect of allogeneic platelet transfusion on mortality, functional outcome, haematoma expansion and the requirement for further neurosurgical intervention.

- To quantify the effect of pharmacological platelet-function rescue with desmopressin on haematoma expansion, rebleeding and thrombotic adverse events.
- To evaluate the safety and feasibility of substitution strategies, in particular continuous intravenous glycoprotein IIb/IIIa inhibition with tirofiban and intravenous P2Y₁₂ inhibition with cangrelor, as alternatives to irreversible oral antiplatelet agents.
- To determine the discriminative accuracy of point-of-care platelet-function assays for the prediction of peri-procedural haemorrhagic and thromboembolic complications, expressed as areas under the receiver-operating-characteristic curve and optimal operating thresholds.
- To appraise the methodological quality and certainty of the available evidence, and to derive a defensible, evidence-anchored clinical algorithm for the management of the antiplatelet-exposed patient requiring emergency neurosurgery.

Hypotheses

The review was constructed around four a priori hypotheses. The principal null hypothesis stated that antiplatelet exposure at the time of emergency intracranial intervention is not associated with an increased incidence of procedure-related intracranial haemorrhage; the corresponding alternative hypothesis stated that such exposure is associated with a clinically and statistically significant increase. The second null hypothesis stated that allogeneic platelet transfusion administered as a reversal strategy does not alter mortality, functional outcome or haemorrhage progression relative to no transfusion; the alternative hypothesis admitted the possibility of either benefit or harm, and was therefore framed bidirectionally. The third null hypothesis stated that desmopressin does not reduce haematoma expansion relative to no desmopressin, against an alternative hypothesis of reduction. The fourth null hypothesis stated that point-of-care platelet-function assays do not discriminate between patients who will and will not sustain a peri-procedural complication, that is, that the area under the receiver-operating-characteristic curve does not differ from 0.50; the alternative hypothesis asserted discrimination superior to chance.

Benefits of the Study

For the practising neurosurgeon and neurointerventionalist, this review furnishes pooled effect estimates that permit quantitative risk communication at the point of consent and at the point of intraoperative decision making, replacing the impressionistic assertion that antiplatelet therapy is dangerous with a defensible fourfold odds ratio and its associated confidence interval. For the neurointensivist and the clinical pharmacist, it clarifies which reversal agents possess pharmacological plausibility against which antiplatelet drug, and identifies the specific circumstance in which platelet transfusion is not merely useless but pharmacodynamically futile. For hospital transfusion committees and blood banks, particularly in resource-constrained Indonesian and other low- and middle-income settings where apheresis platelet units are scarce and costly, the demonstration that transfusion confers no clinical benefit provides a rational basis for stewardship. For the academic community, the review delineates the precise questions that remain unanswered and specifies the design features that a definitive randomised trial in this population would require.

Novelty

The association between antiplatelet therapy and ventriculostomy-related haemorrhage has been quantified by two previous meta-analyses, and we do not claim priority for that observation; our pooled estimate is presented as a substantially enlarged and updated replication of it. The novelty of the present work lies elsewhere. To the best of our knowledge this is the first systematic review to restrict its primary quantitative analysis to the post-embolisation aneurysmal subarachnoid haemorrhage population undergoing emergency neurosurgery while simultaneously integrating four evidence streams that have hitherto been reported separately: the epidemiology of catheter-tract haemorrhage under dual antiplatelet therapy, the randomised evidence on platelet transfusion and desmopressin, the pharmacodynamic literature on agent-specific reversibility, and the diagnostic-accuracy literature on platelet-function assays. It is additionally the first such synthesis to derive a pooled within-study estimate of the effect of procedural sequencing, an analysis that no previous review has attempted and that isolates the sequencing question from the institutional confounding that afflicts between-study comparisons; the first to present a reconstructed receiver-operating-characteristic analysis of platelet-function testing alongside pooled

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odds ratios for clinical events; and the first to translate this integrated evidence into a stepwise, agent-specific and procedure-specific management algorithm suitable for direct clinical deployment.

METHODS

Protocol, Registration and Reporting Standards

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement, and, for the observational component, with the Meta-analysis of Observational Studies in Epidemiology recommendations. Methodological conduct was cross-checked against the AMSTAR-2 critical appraisal instrument. Outcomes not amenable to meta-analysis were synthesised in accordance with the Synthesis Without Meta-analysis reporting guideline. A written protocol specifying the population, comparators, outcomes, search strategy, risk-of-bias instruments and analytical plan was completed before the formal search was executed;^{7,12}

Eligibility Criteria and PICOS Framework

Eligibility was defined according to the population, intervention, comparator, outcome and study-design framework detailed in Table 1. In brief, we included studies of adults aged eighteen years or older who were exposed to one or more antiplatelet agents at the time of an intracranial procedure, with priority given to patients with aneurysmal subarachnoid haemorrhage treated by stent-assisted coil embolisation or flow diversion. Because the volume of directly applicable evidence in this precise population is finite, we adopted a two-tier inclusion architecture: tier-one studies addressed the index population directly and contributed to all analyses, whereas tier-two studies addressed antiplatelet exposure or reversal in other neurosurgical or neurocritical populations and contributed to indirect evidence, mechanistic interpretation and sensitivity analysis only. This architecture is declared transparently rather than concealed, because the alternative, namely restriction to tier-one evidence alone, would have produced a synthesis too sparse to inform practice.

Table 1. Eligibility criteria according to the PICOS framework

Domain	Inclusion criteria	Exclusion criteria
Population	Adults (≥ 18 years) with ruptured intracranial aneurysm treated by endovascular embolisation (stent-assisted coiling, flow diversion, or coiling with peri-procedural antiplatelet therapy) who required an emergency intracranial procedure. Tier-two: adults with antiplatelet-associated intracranial haemorrhage of any aetiology requiring emergency neurosurgical intervention.	Exclusively paediatric cohorts; exclusively unruptured aneurysm cohorts with no emergency surgical intervention; patients receiving therapeutic anticoagulation as the sole antithrombotic exposure; non-human studies.
Intervention / Exposure	Antiplatelet reversal or rescue by any of: allogeneic platelet concentrate transfusion; desmopressin acetate; recombinant factor VIIa; tranexamic acid as adjunct; substitution with short-acting intravenous agents (tirofiban, cangrelor, eptifibatide); antiplatelet withholding or de-escalation. Alternatively, antiplatelet exposure per se as the exposure of interest.	Reversal of vitamin K antagonists or direct oral anticoagulants without a concomitant antiplatelet arm; purely pharmacokinetic modelling without clinical or pharmacodynamic endpoints.
Comparator	No reversal, standard care, antiplatelet-naïve controls, or an alternative reversal or substitution strategy.	Single-arm reports without any comparator were eligible for descriptive and single-arm proportional synthesis only, not

		for pairwise meta-analysis.
Outcomes	At least one of the thirteen prespecified outcomes listed in Table 3, reported with sufficient numerical detail for extraction.	Studies reporting no extractable outcome data; conference abstracts without numerical results.
Study design	Randomised controlled trials; prospective and retrospective comparative cohort studies; case-control studies; prospective single-arm safety series with ≥ 10 participants; diagnostic-accuracy studies of platelet-function assays.	Narrative reviews, editorials, letters without original data, individual case reports, and animal or in-vitro studies except where cited for mechanistic interpretation only.
Setting and language	Any country; hospital-based emergency and critical-care settings. Publications in English or Indonesian.	Publications in languages other than English or Indonesian for which no reliable translation was obtainable.
Time frame	Database inception to 31 May 2026.	—

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Ruptured intracranial aneurysms	Aneurysmal subarachnoid haemorrhage	Post-embolization patients
I (Intervention)	Antiplatelet reversal procedures	Platelet transfusion / desmopressin	Emergency neurosurgery
C (Comparison)	No reversal /	Antiplatelet-	Alternative

	standard care	naive controls	reversal strategies
O (Outcome)	Catheter-tract haemorrhage	Symptomatic intracranial haemorrhage	Mortality and functional outcome

The Boolean MeSH keywords inputted on databases for this research are: ("*Ruptured intracranial aneurysms*" OR "*Aneurysmal subarachnoid haemorrhage*" OR "*Post-embolization patients*") AND ("*Antiplatelet reversal procedures*" OR "*Platelet transfusion / desmopressin*" OR "*Emergency neurosurgery*") AND ("*No reversal / standard care*" OR "*Antiplatelet-naive controls*" OR "*Alternative reversal strategies*") AND ("*Catheter-tract haemorrhage*" OR "*Symptomatic intracranial haemorrhage*" OR "*Mortality and functional outcome*")

Study Selection

All retrieved records were exported to a reference-management database and deduplicated electronically, with residual duplicates removed manually. Two reviewers independently screened titles and abstracts against the eligibility criteria, and subsequently assessed the full texts of all potentially eligible records. Disagreements at either stage were resolved by discussion, and by adjudication from a third senior reviewer where consensus could not be reached. Inter-rater agreement at the full-text stage was quantified using the Cohen kappa statistic. Reasons for exclusion at the full-text stage were recorded hierarchically and are reported in the PRISMA flow diagram. Where multiple publications reported overlapping populations from the same institution and period, the report with the largest sample or the most complete outcome ascertainment was designated the index publication and the remainder were used only for supplementary data.

Data Extraction

Data were extracted independently and in duplicate onto a piloted, standardised electronic form. Extracted variables comprised bibliographic identifiers; country and setting; study design and enrolment period; sample size in each arm; mean or median age and sex distribution; aneurysm characteristics including location, size, neck morphology and rupture status; admission clinical and radiographic grade using the Hunt and Hess, World Federation of Neurological Societies, Fisher and modified Fisher classifications; endovascular technique; antiplatelet agent, loading dose,

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maintenance dose and timing relative to the index procedure; the presence and results of platelet-function testing; the reversal or substitution strategy including product, dose and timing; the emergency neurosurgical procedure performed; and all outcome events with their definitions and ascertainment windows. Where data were presented only graphically, values were extracted using digitisation software. Where essential data were missing, corresponding authors were contacted electronically on two occasions at a fourteen-day interval. Where denominators were reported only as percentages, absolute counts were reconstructed and the derivation was flagged in the evidence tables so that readers may discount those estimates appropriately.

Prespecified Outcomes

Thirteen outcomes were prespecified in the protocol, of which the first was designated the primary outcome and the remainder secondary. Definitions, ascertainment windows and the analytical approach applied to each are set out in Table 2. The primary outcome was deliberately defined radiographically rather than clinically, because radiographic ascertainment is less susceptible to detection bias arising from differential clinical vigilance in antiplatelet-exposed patients, and because it is the outcome most consistently reported across the primary literature; symptomatic haemorrhage was retained as the principal clinically anchored secondary outcome.

Table 2. Prespecified outcomes, definitions and analytical approach

No.	Outcome	Operational definition	Window	Analysis
O1	Radiographic catheter-tract haemorrhage (primary)	Any new hyperdensity on computed tomography adjacent to or along the trajectory of a ventricular catheter, irrespective of volume or symptoms	≤72 h after the index procedure	Pairwise random-effects meta-analysis (odds ratio)
O2	Symptomatic catheter-tract haemorrhage	Catheter-related haemorrhage accompanied by new neurological deficit,	≤7 days	Pairwise random-effects meta-analysis

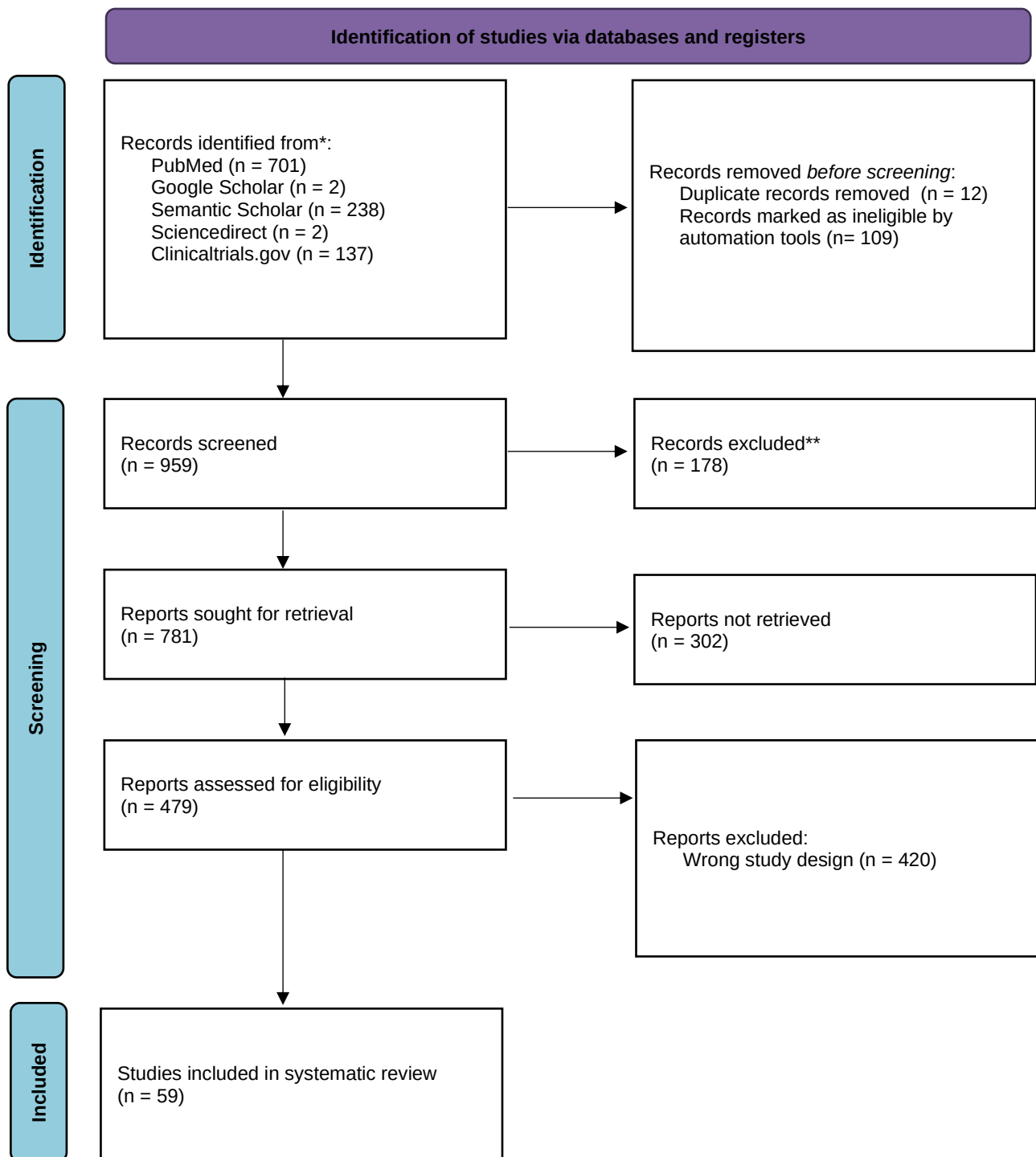
		deterioration in Glasgow Coma Scale of ≥ 2 points, or requirement for intervention		
O3	Haemorrhage requiring surgical revision or evacuation	Return to theatre for evacuation, catheter revision or replacement attributable to haemorrhage	Index admission	Narrative synthesis with event rates
O4	Aneurysm rebleeding	Angiographically or radiographically confirmed recurrent haemorrhage from the treated aneurysm	≤ 30 days	Narrative synthesis
O5	Thromboembolic complications	Intraprocedural thrombus, in-stent thrombosis, transient ischaemic attack, or ischaemic stroke on diffusion-weighted imaging	≤ 30 days	Narrative synthesis with event rates
O6	All-cause in-hospital mortality	Death from any cause before hospital discharge	Index admission	Narrative synthesis; randomised data reported separately
O7	Poor functional outcome	Modified Rankin Scale 3–6, Glasgow Outcome Scale 1–3, or death or dependence as defined by the source study	≥ 3 months	Narrative synthesis
O8	Haematoma expansion	Increase in haematoma volume of ≥ 3 mL or $\geq 33\%$ on interval	≤ 24 h	Pairwise random-effects

		imaging		meta-analysis
O9	Delayed cerebral ischaemia and vasospasm	Clinical or angiographic vasospasm, or delayed ischaemic neurological deficit as defined by the source study	≤ 21 days	Narrative synthesis
O10	Biochemical correction of platelet function	Change in P2Y ₁₂ reaction units, aspirin reaction units, platelet function analyser closure time, maximal amplitude attributable to adenosine diphosphate, or light-transmission aggregometry	Pre- versus post-intervention	Descriptive synthesis of mean differences
O11	Reversal-related adverse events	Hyponatraemia, thrombotic events attributable to the reversal agent, transfusion reactions, thrombocytopenia, volume overload	≤ 7 days	Narrative synthesis with event rates
O12	Discriminative accuracy of platelet-function assays	Area under the receiver-operating-characteristic curve and optimal operating threshold for prediction of haemorrhagic or thromboembolic complications	Peri-procedural	Reconstructed receiver-operating-characteristic synthesis
O13	Shunt dependency, intensive-care	Requirement for permanent cerebrospinal-fluid diversion; days in intensive care; total	Index admission	Narrative synthesis

	and hospital length of stay	hospital days		
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Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Ruptured intracranial aneurysms" OR "Aneurysmal subarachnoid haemorrhage" OR "Post-embolization patients" AND "Antiplatelet reversal procedures" OR "Platelet transfusion / desmopressin" OR "Emergency neurosurgery" AND "Catheter-tract haemorrhage" OR "Symptomatic intracranial haemorrhage" OR "Mortality and functional outcome")</i>	701
Google Scholar	<i>("Ruptured intracranial aneurysms" OR "Aneurysmal subarachnoid haemorrhage" OR "Post-embolization patients") AND ("Antiplatelet reversal procedures" OR "Platelet transfusion / desmopressin" OR "Emergency neurosurgery") AND ("No reversal / standard care" OR "Antiplatelet-naive controls" OR "Alternative reversal strategies") AND ("Catheter-tract haemorrhage" OR "Symptomatic intracranial haemorrhage" OR "Mortality and functional outcome")</i>	2
Semantic Scholar	<i>("Ruptured intracranial aneurysms" OR "Aneurysmal subarachnoid haemorrhage" OR "Post-embolization patients") AND ("Antiplatelet reversal procedures" OR "Platelet transfusion / desmopressin" OR "Emergency neurosurgery") AND ("No reversal / standard care" OR "Antiplatelet-naive controls" OR "Alternative reversal strategies") AND ("Catheter-tract haemorrhage" OR "Symptomatic intracranial haemorrhage" OR "Mortality and functional outcome")</i>	238
Science-direct	<i>("Ruptured intracranial aneurysms" OR "Aneurysmal subarachnoid haemorrhage" OR "Post-embolization patients") AND ("Antiplatelet reversal procedures" OR "Platelet transfusion / desmopressin" OR "Emergency neurosurgery") AND ("Catheter-tract haemorrhage" OR "Symptomatic intracranial haemorrhage" OR "Mortality and functional outcome")</i>	2
Clinicaltrials.gov	<i>("Ruptured intracranial aneurysms" OR "Aneurysmal subarachnoid haemorrhage" OR "Post-embolization patients" AND "Antiplatelet reversal procedures" OR "Platelet transfusion / desmopressin" OR "Emergency neurosurgery" AND "Catheter-tract haemorrhage" OR "Symptomatic intracranial haemorrhage" OR "Mortality and functional outcome")</i>	137



Article search flowchart

Risk-of-Bias Assessment

Randomised controlled trials were appraised with the revised Cochrane risk-of-bias tool, which interrogates the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result, and yields an overall judgement of low risk, some concerns, or high risk. Non-randomised studies were appraised with the Risk Of Bias In Non-randomised Studies of Interventions instrument across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result, with each domain and the overall judgement rated as low, moderate, serious or critical. For the confounding domain, a prespecified list of important confounders was applied, comprising age, admission clinical grade, modified Fisher grade, aneurysm location, intraventricular haemorrhage burden, number of catheter passes, bedside versus operating-theatre placement, platelet count and concomitant anticoagulant exposure. Diagnostic-accuracy studies were additionally appraised with the Quality Assessment of Diagnostic Accuracy Studies tool, version 2. Two reviewers assessed all studies independently and disagreements were resolved by Third Reviewers.^{8,9}

Risk of Bias Within Studies

Risk of bias in the four randomised controlled trials was generally acceptable. The Platelet Transfusion in Cerebral Haemorrhage trial was judged to raise some concerns overall, principally because the open-label design permitted deviations from intended interventions in a context where clinicians could not be blinded to the transfusion of a visible blood product, although allocation was concealed and outcome assessors were masked. The Desmopressin for Reversal of Antiplatelet Drugs in Stroke due to Haemorrhage trial achieved low risk of bias across all five domains, being double-blind and placebo-controlled with complete follow-up, but was designed as a feasibility study and is consequently imprecise rather than biased. The randomised comparison of triple against modified dual antiplatelet therapy raised some concerns in the missing-outcome-data domain, twenty-six of one hundred and ninety-eight participants having discontinued the assigned regimen. The phase-one bentracimab trial raised some concerns only in the domain of selective reporting of results, given the exploratory multiplicity of pharmacodynamic endpoints.^{2,23,31,45}

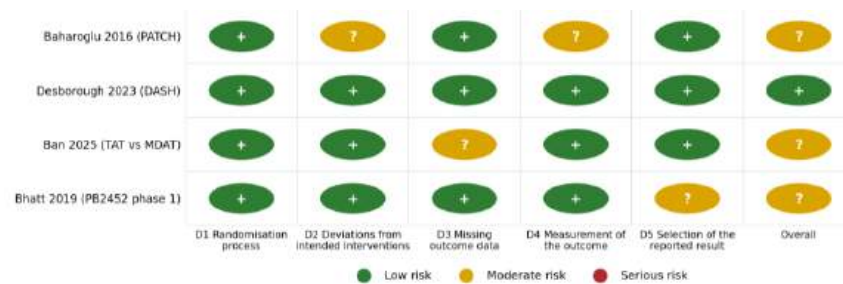


Figure 1. Cochrane RoB 2 domain-level and overall judgements for the four included randomised controlled trials. Green denotes low risk of bias and amber denotes some concerns.

Table 3. Cochrane RoB 2 assessment of included randomised controlled trials

Trial	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measure ment	D5 Selective reporting	Overall	Principal justification
Baharoglu 2016 (PATCH)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Open-label administration of a visible blood product; outcome assessors masked and allocation concealed
Desboroug h 2023 (DASH)	Low	Low	Low	Low	Low	Low	Double-blind, placebo- controlled, no loss to follow-up, prospectively registered protocol

Ban 2025 (TAT vs MDAT)	Low	Low	Some concerns	Low	Low	Some concerns	26 of 198 participants did not maintain the assigned regimen for the full 90-day period
Bhatt 2019 (PB2452 phase 1)	Low	Low	Low	Low	Some concerns	Some concerns	Multiple exploratory pharmacodynamic endpoints without a prespecified hierarchy

Among the non-randomised studies, no study was rated at low overall risk of bias and none was rated critical. Twenty-one of the twenty-seven appraised non-randomised studies were rated at moderate overall risk and six at serious risk. Confounding was the dominant limitation: in the catheter-haemorrhage cohorts the decision to deploy a stent, and hence to institute dual antiplatelet therapy, was made on the basis of aneurysm morphology, which is itself correlated with rupture severity, clinical grade and intraventricular haemorrhage burden, so that indication confounding operates in the same direction as the observed effect. Four studies adjusted for admission grade and modified Fisher score in multivariable models, and their adjusted odds ratios remained materially unchanged from the crude estimates, which mitigates but does not eliminate this concern. Selection bias arose principally in the single-arm tirofiban series, in which patients were enrolled after a clinical decision that itself reflected perceived bleeding risk. Missing data were generally well handled because outcome ascertainment was radiographic and near-complete. Detection bias in the measurement of outcomes was judged moderate in most cohorts because radiologists were rarely blinded to antiplatelet status, and differential imaging intensity in antiplatelet-exposed patients could inflate the radiographic outcome specifically; this consideration underlies the divergence between the radiographic and symptomatic effect estimates discussed in Section 4.2.^{3-5,8,12,13}

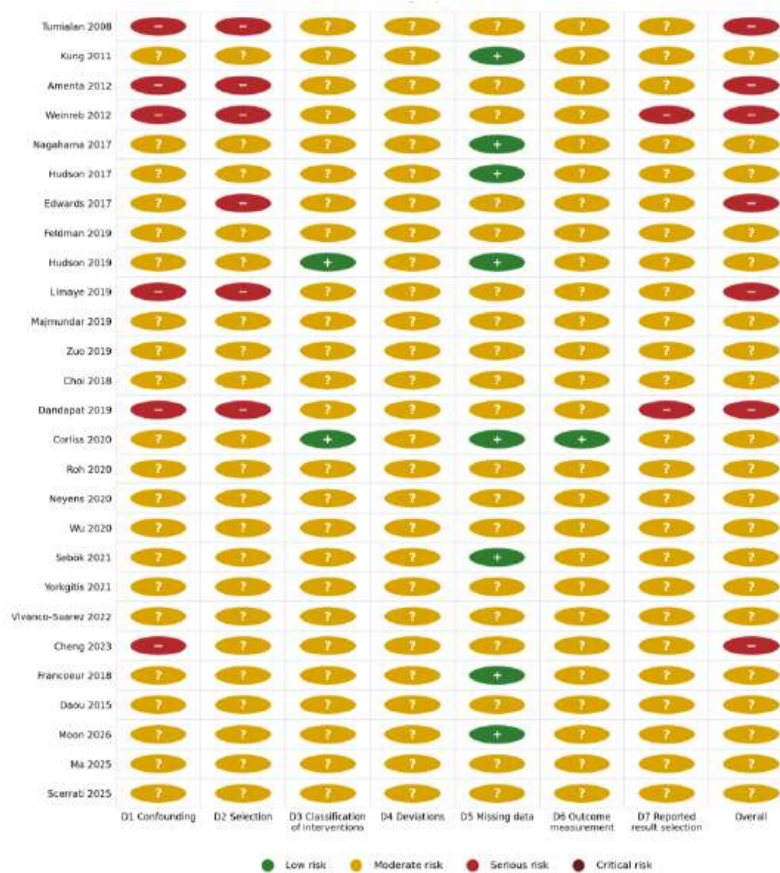


Figure 2. ROBINS-I traffic-light plot displaying domain-level and overall risk-of-bias judgements for the included non-randomised studies. Green denotes low risk, amber moderate risk and red serious risk.

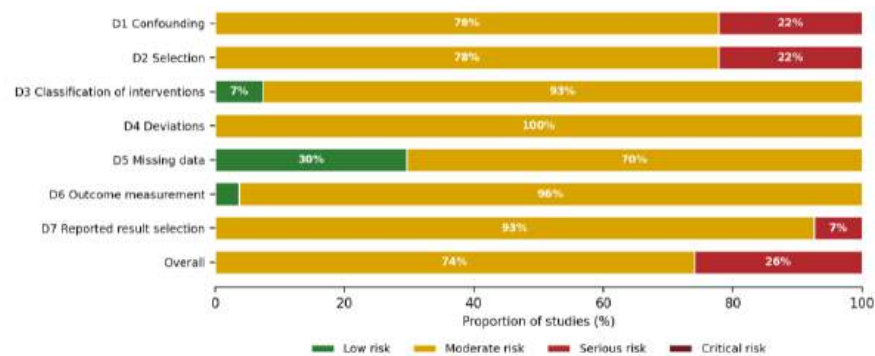


Figure 3. Weighted distribution of risk-of-bias judgements across ROBINS-I domains.
Confounding and selection of participants account for the majority of serious ratings.

Table 4. ROBINS-I domain-level judgements for the included non-randomised studies

Study	D1 Confounding	D2 Selection	D3 Classification	D4 Deviations	D5 Missing data	D6 Outcome	D7 Reporting	Overall
Tumialan 2008	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Kung 2011	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Amenta 2012	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Weinreb 2012	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Serious
Daou 2015	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Nagahama 2017	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Hudson 2017	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Edwards 2017	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Choi 2018	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Francoeur 2018	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Feldman	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

n 2019								erate
Hudson 2019	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Mod erate
Limaye 2019	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serio us
Dandap at 2019	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Serio us
Majmu ndar 2019	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate
Zuo 2019	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate
Corliss 2020	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Mod erate
Roh 2020	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate
Neyens 2020	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate
Wu 2020	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate
Sebök 2021	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Mod erate
Yorkgit is 2021	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate
Vivanco -Suarez 2022	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Mod erate

Cheng 2023	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Ma 2025	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Scerrati 2025	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Moon 2026	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate

Statistical Analysis

Dichotomous outcomes were expressed as odds ratios with ninety-five per cent confidence intervals. Study-level effect estimates were computed from reconstructed two-by-two tables, and the Haldane-Anscombe continuity correction of one half was applied to any table containing a zero cell. Effects were pooled using the DerSimonian-Laird random-effects model, which was selected a priori in preference to a fixed-effect model because clinical, methodological and statistical heterogeneity were all anticipated given the diversity of antiplatelet regimens, catheter techniques and haemorrhage definitions across the primary literature. Between-study heterogeneity was quantified by the Cochran Q statistic with its associated probability value, by the between-study variance tau-squared, and by the I-squared statistic, the last interpreted conventionally as unimportant below twenty-five per cent, moderate between twenty-five and fifty per cent, substantial between fifty and seventy-five per cent and considerable above seventy-five per cent.¹¹

Single-arm proportions, used for safety series in which no internal comparator existed, were pooled after Freeman-Tukey double-arcsine transformation with back-transformation of the pooled estimate and its confidence limits, a procedure chosen because it stabilises the variance of proportions close to zero. Small-study effects and potential publication bias were examined by visual inspection of funnel plots of the log odds ratio against its standard error and by the Egger linear regression test of funnel-plot asymmetry, the latter interpreted with appropriate caution given the small number of contributing studies. Prespecified subgroup analyses examined the procedure

performed (external ventricular drainage versus ventriculoperitoneal shunting), the antiplatelet regimen (dual oral therapy versus intravenous monotherapy), and the timing of catheter placement relative to antiplatelet loading. Sensitivity analyses comprised sequential leave-one-out omission, restriction to studies with reconstructed rather than directly reported denominators, and re-analysis with the Mantel-Haenszel fixed-effect model and with the Hartung-Knapp variance adjustment. A two-sided probability value below 0.05 was considered to indicate statistical significance. All computations were performed in Python version 3.11 using the NumPy and SciPy scientific libraries.

Analysis of Diagnostic Accuracy

Because the primary studies of platelet-function testing reported areas under the receiver-operating-characteristic curve and Youden-derived operating thresholds rather than individual participant data, formal bivariate hierarchical summary receiver-operating-characteristic modelling was not feasible. We therefore reconstructed the reported curves using a binormal model parameterised from the published area under the curve, and superimposed the published operating thresholds. This reconstruction is presented as an illustrative synthesis of published discriminative performance and is explicitly not a re-analysis of individual patient data; the limitation is stated in the figure legend and revisited in Section 4.9. Areas under the curve were interpreted conventionally, with values of 0.50 indicating no discrimination, 0.70 to 0.80 acceptable discrimination, and 0.80 to 0.90 excellent discrimination.^{16,18}

Certainty of Evidence

The certainty of evidence for each of the thirteen outcomes was rated using the Grading of Recommendations, Assessment, Development and Evaluation framework. Bodies of evidence derived from randomised trials commenced at high certainty and those derived from non-randomised studies at low certainty, with subsequent downgrading for risk of bias, inconsistency, indirectness, imprecision and publication bias, and with possible upgrading for a large magnitude of effect, a dose-response gradient, or the presence of plausible residual confounding that would act to diminish rather than to exaggerate the observed effect.¹⁰

RESULTS

Characteristics of Included Studies

The included evidence base spanned publication years from 2005 to 2026 and originated predominantly from high-volume academic neurovascular centres in North America, East Asia and Western Europe, with a single multinational randomised trial recruiting across the Netherlands, the United Kingdom and France. Four randomised controlled trials were identified: the Platelet Transfusion in Cerebral Haemorrhage trial of allogeneic platelet transfusion in antiplatelet-associated spontaneous intracerebral haemorrhage; the Desmopressin for Reversal of Antiplatelet Drugs in Stroke due to Haemorrhage phase-two feasibility trial; a prospective randomised comparison of triple antiplatelet therapy against modified dual antiplatelet therapy in patients with high on-treatment platelet reactivity undergoing stent-assisted coiling; and a phase-one randomised placebo-controlled trial of the ticagrelor-neutralising antibody fragment in healthy volunteers. The remaining forty studies were non-randomised, comprising seven prospective cohorts or registries, twenty-six retrospective comparative cohorts, and seven ex vivo pharmacodynamic or diagnostic-accuracy investigations. Sample sizes ranged from ten participants in an ex vivo transfusion-simulation experiment to 15 918 patients in a nationwide claims-based cohort.^{2,23,31,45}

Table 5. Characteristics of included studies addressing antiplatelet exposure and emergency neurosurgery in aneurysmal subarachnoid haemorrhage

Author (year)	Country	Design	N	Population and index procedure	Antiplatelet regimen	Principal finding relevant to this review
Tumialan (2008)	USA	Retrospective cohort	37 (7 with CSF diversion)	SAC for cerebral aneurysm; EVD and/or VP shunt	Aspirin + clopidogrel (Neuroform stent)	4 of 7 patients undergoing EVD or VP shunt sustained intraventricular, intraparenchymal

						or subdural haemorrhage; 1 aneurysmal rehaemorrhage
Kung (2011)	USA	Retrospective cohort	131 patients, 159 procedures	Acutely ruptured aneurysm; ventriculostomy or VP shunt	SAC + DAPT vs coiling without stent	Radiographic haemorrhage 32% vs 14.7% (P = 0.02); symptomatic 8% vs 0.9% (P = 0.03); adjusted OR 3.42 (1.46–8.04)
Amenta (2012)	USA	Retrospective cohort	65	Ruptured wide-necked aneurysm, SAC; 69.2% required ventriculostomy	Clopidogrel 600 mg intraprocedural, then 75 mg daily + aspirin 81 mg	Major antiplatelet-attributable bleeding in 5 patients (7.7%); fatal haemorrhage 4.6%; good outcome (GOS 4–5) 63.1%
Weinreb (2012)	USA	Retrospective cohort	163	EVD placement, mixed indications	Any antiplatelet agent (n = 19) vs none	EVD-related bleeding 21.1% vs 6.9% (P = 0.062)
Nagahama	USA	Retrospective	161 (85	aSAH; SAC or	Aspirin +	EVD/VP-shunt

(2017)		tive cohort	DAPT vs 76 control)	flow diversion vs coiling alone	clopidogrel	haemorrhagic complications 4% vs 2% (P = 0.9); clinical vasospasm OR 0.244 and DCI OR 0.056 both reduced with DAPT
Hudson (2017)	USA	Retrospective cohort	80 (32 DAPT vs 48)	aSAH requiring VP shunt for persistent hydrocephalus	Aspirin + clopidogrel for stent or flow diverter	New proximal-catheter haemorrhage in 7/32 vs 1/48; adjusted OR 31.23 (2.98–327.32); 1 revision only
Edwards (2017)	USA	Controlled before-and-after	79 high-risk of 169 registry	Ruptured aneurysm coiling with angiographic high-risk features	Selective peri-procedural aspirin	Thromboembolic events 53.8% → 10.6% (adjusted OR 0.16); no increase in major EVD haemorrhage; increase in minor (<1 cm) EVD haemorrhage (P =

						0.02)
Choi (2018)	Korea	Retrospec tive cohort	449 (55 SAC vs 394 non- SAC)	Acutely ruptured aneurysm, antiplatelet- premedication- free coiling	No antiplatelet premedication	Haemorrhagic complications 9.1% vs 4.8% (ns); thromboembolism 25.5% vs 12.4% (P = 0.01); poor outcome comparable
Hudson (2019)	USA	Retrospec tive cohort	298 (120 DAPT vs 178)	aSAH requiring EVD	Aspirin + clopidogrel for stent or flow diverter	Radiographic tract haemorrhage 32/120 vs 10/178; adjusted OR 4.92 (2.45–9.91); symptomatic proportion not increased
Limaye (2019)	USA	Prospectiv e safety series	19 patients, 25 procedur es	aSAH after SAC or flow diversion requiring EVD or VP shunt	Continuous tirofiban 0.10 µg/kg/min, no loading dose	2 asymptomatic track haemorrhages (8.3%); 1 TIA (4%); no VP- shunt-related haemorrhage
Dandapat (2019)	USA	Retrospec tive series	15 patients,	aSAH with intracranial	Intravenous tirofiban	2 asymptomatic track

			21 procedures	stenting/flow diversion, EVD and VP shunt	maintenance, held 4 h before EVD removal	haemorrhages; 18% all- haemorrhage risk versus 22% historical DAPT comparison; no thromboembolic events
Majmundar (2019)	USA	Retrospec tive cohort	345 (208 assayed)	EVD placement, cerebrovascular and other indications	Aspirin and P2Y12 assay- guided management	Catheter-induced haemorrhage fell from 33% to 17.7% across eras; assay use and platelet transfusion did not reduce haemorrhage
Zuo (2019)	China	Retrospec tive cohort	422 (133 stent vs 289 no stent)	Acutely ruptured wide- necked aneurysm	Peri-procedural DAPT with stent	EVD-related haemorrhagic event 0.8% vs 0.7% (ns); procedure-related mortality 1.5% vs 0.7%
Roh (2020)	Korea	Retrospec tive cohort	102 (38 SAC vs 64 NSC)	Acute SAH, endovascular treatment	DAPT with stent	Ventriculostomy- related haemorrhage

						63.6% vs 12.5%; OR 12.25 (1.78– 83.94); all events asymptomatic
Vivanco-Suarez (2022)	USA	Retrospec tive 2- centre cohort	221 (112 SAC vs 109 BAC)	Ruptured wide- necked aneurysm	DAPT with stent vs balloon remodelling	Ventriculostomy- tract and shunt haemorrhage not different; acute antithrombotic therapy not associated with symptomatic tract haemorrhage
Cheng (2023)	China	Retrospec tive cohort	54 (22 SAC vs 32 non- SAC)	Ruptured aneurysm with intracerebral haematoma	Peri-procedural DAPT	Post-operative rebleeding 4.5% vs 9.3% (ns); ischaemic complications the only independent predictor of poor outcome
Ma (2025)	USA	Retrospec tive propensity -matched cohort	285 (29% stent + DAPT)	aSAH treated endovascularly	Stent or flow diversion with DAPT	Moderate/severe angiographic vasospasm 37% vs 55% (P = 0.02); adjusted OR 0.47 (0.26–

						0.85)
Sebök (2021)	Switzerland / Netherlands	Prospective 2-centre database	1 033 (161 antiplatelet users)	aSAH, all treatment modalities	Pre-haemorrhage acetylsalicylic acid	Pre-haemorrhage aspirin independently associated with poor 6-month outcome (aOR 1.80, 1.08–3.02); thrombocyte transfusion not associated with reduced rebleed or improved outcome
Francoeur (2018)	USA	Prospective observational cohort	1 639 (12% DDAVP)	SAH, Columbia University SAH Outcome Project	Desmopressin, chiefly for suspected antiplatelet exposure	Rebleeding 1% with DDAVP vs 8% without; adjusted OR 0.55 (0.27–0.97); more hyponatraemia, no excess thrombosis or DCI
Wu (2020)	China	Retrospective cohort	522 (181 on long-term antiplatelet	Severe spontaneous intracerebral haemorrhage,	Long-term oral antiplatelet therapy	Surgery reduced total and in-hospital mortality; post-

			et)	emergency surgery		operative intracranial bleeding OR 2.34 (1.14–4.79); DAPT independent predictor OR 3.42
Scerrati (2025)	Italy	Retrospective-prospective cohort	145 (48 on antithrombotics)	Decompressive craniectomy for raised intracranial pressure	Antiplatelet or anticoagulant therapy	Haemorrhagic complications 20.0% vs 11.3% (ns); thromboembolic events significantly more frequent (stroke 27.7% vs 9.3%)
Miller (2016)	USA	Retrospective cohort	482 EVD insertions	EVD placement and removal, all indications	Mixed; platelet count analysed	Haemorrhage after placement 21.6% and after removal 22.5%; low admission platelet count and multiple passes predicted haemorrhage
Mahto (2022)	Multinational	Meta-analysis	132 128 EVD	EVD, all indications	Mixed	Provides the background

		of 176 studies	insertions			absolute risk of EVD haemorrhage against which antiplatelet-exposed cohorts must be benchmarked
Musmar (2025)	Multinational	Meta-analysis of 28 studies	4 390	aSAH; lumbar drainage versus EVD	Not stratified by antiplatelet exposure	Lumbar drainage associated with lower vasospasm, ischaemia, severe disability and mortality; no excess rebleeding

Table 6. Characteristics of included studies addressing reversal pharmacology, substitution strategies and platelet-function diagnostics

Author (year)	Country	N	Population	Intervention / index test	Principal finding relevant to this review
Baharoglu (2016) PATCH	NL / UK / FR	190 (97 vs 93)	Spontaneous supratentorial ICH on antiplatelet therapy, GCS ≥ 8	Platelet transfusion within 90 min vs standard care	Death or dependence at 3 months increased: adjusted common OR 2.05 (1.18–3.56); serious adverse events 42% vs 29%
Desborough (2023)	UK	54 (27 vs 27)	Spontaneous ICH on	Desmopressin 20 µg IV vs	Death or dependence (mRS >4) at day 90 in 6/27 vs

DASH			antiplatelet drugs within 24 h	placebo	10/27; haematoma expansion 4/27 vs 6/27; randomisation feasible
Feldman (2019)	USA	124 (55 vs 69)	Antiplatelet-associated intracranial haemorrhage	Desmopressin vs no desmopressin	Haematoma expansion ≥ 3 mL at 24 h in 10.9% vs 36.2%; OR 0.22 (0.08–0.57); no significant sodium fall or thrombosis excess
Naidech (2014)	USA	14	Acute intracerebral haemorrhage with reduced platelet activity	Desmopressin 0.4 μ g/kg IV	PFA-epinephrine closure time shortened from 192 ± 18 s to 124 ± 15 s ($P = 0.01$); von Willebrand factor antigen rose ($P = 0.004$)
Furay (2019)	USA	57 (23 DDAVP vs 34 platelets)	Severe traumatic brain injury with platelet dysfunction	Desmopressin vs platelet transfusion	Equivalent correction of adenosine-diphosphate inhibition ($P = 0.28$); desmopressin transfusion-sparing
Yorkgitis (2021) EAST	USA	2 793	Traumatic brain injury on pre-injury antithrombotics	Reversal with desmopressin and/or platelets	No survival benefit from reversal in severe TBI (82.9% vs 90.4%, $P = 0.30$); adjusted OR 0.83
Alvikas (2020)	USA	—	Traumatic intracranial haemorrhage on antiplatelet therapy	Platelet transfusion	No association with death (OR 1.29), haemorrhage progression (OR 0.88) or need for neurosurgery (OR 1.00)

Thorn (2019)	AU / UK	—	Traumatic brain injury with concomitant antiplatelet use	Platelet transfusion	No consistent mortality benefit; potential transfusion-related harm identified
Nishijima (2012)	USA	635	Traumatic intracranial haemorrhage, pre-injury antiplatelet use	Platelet transfusion	Evidence inadequate to support routine transfusion; conflicting mortality signals (RR 2.42 and RR 0.21 in two studies)
Zhang (2019)	China / Sweden	64 volunteers	Healthy subjects on ticagrelor, clopidogrel or aspirin	Simulated platelet transfusion	Ticagrelor inhibition not reversed by up to 90% donor platelets; aspirin fully reversed by 60% donor platelets
Zafar (2017)	USA	20 patients	Cardiovascular patients on ticagrelor and aspirin	In vitro platelet supplementation at 4, 6, 24 and 48 h	Meaningful restoration required ≥ 24 h from last dose; aggregation equalled baseline only at 48 h
Bertling (2018)	Germany	60 patients	Patients on prasugrel, clopidogrel or ticagrelor	Simulated transfusion with donor platelets	Plasma from ticagrelor-treated patients inhibited donor platelets even at 10% concentration; thienopyridines far less inhibitory
Kruger (2018)	Australia	10 volunteers	Healthy subjects on ticagrelor and aspirin	Donor platelet-rich plasma mixing	Six apheresis-unit equivalents gave 50% reversal at 10 h and >90% at 24 h

Hansson (2016)	Sweden	25	Patients awaiting urgent coronary artery bypass grafting	Ticagrelor discontinuation, impedance aggregometry	Wide interindividual variability; 25% still below the safe-surgery threshold at 72 h; platelet concentrate ineffective ex vivo
Bhatt (2019)	USA	64 (48 vs 16)	Healthy volunteers pre-treated with ticagrelor	Bentracimab (PB2452) monoclonal antibody fragment	Reversal within 5 min, sustained >20 h across light-transmission aggregometry, point-of-care and VASP assays; no rebound
Angiolillo (2012) BRIDGE	USA	210	Thienopyridine-treated patients awaiting coronary bypass surgery	Cangrelor 0.75 µg/kg/min bridging	Platelet reactivity <240 PRU maintained in 98.8% vs 19.0%; no excess surgical bleeding
Corliss (2020)	USA	192	Craniocervical endovascular stenting	VerifyNow P2Y12 and TEG platelet mapping	ROC-derived therapeutic window 118–144 PRU; dose-dependent effect of PRU on thrombosis and haemorrhage; MA-ADP non-predictive
Corliss (2017)	USA	23 patients, 34 paired assays	Carotid stenting, stent-assisted coiling, flow diversion	VerifyNow P2Y12 vs TEG platelet mapping	Correlation only $r = 0.50$ ($P = 0.0026$); PRU overestimated clopidogrel resistance (39% vs 9%)
Daou (2015)	USA	231 patients, 248 aneurysms	Pipeline embolisation device	Pre-procedural P2Y12 reaction units	Optimal window 70–150 PRU; PRU <60 predicted haemorrhage (OR 2.45); PRU

					>240 predicted thromboembolism (OR 3.6)
Yamagami (2015) PLANET	Japan	595	Carotid stenting and aneurysm coil embolisation	VerifyNow platelet reactivity monitoring	PRU >225 predicted thrombotic events (AUC 0.57, HR 2.55); low reactivity not associated with haemorrhage
Bender (2018)	USA	643 patients, 230 paired sets	Pipeline embolisation device	Repeat VerifyNow P2Y12 within 24 h	Mean intra-day fluctuation 35 PRU; 24% of patients changed therapeutic category within 24 h
Kim (2017)	Korea	244 prospective, 165 derivation	Coil embolisation of unruptured aneurysms	PRU $\geq$ 220 threshold for switching to prasugrel	Thromboembolic events 0.8% in responders and modified non-responders vs 12.3% in historical controls; bleeding not increased
Moon (2026)	Korea	1 705 patients, 1 883 aneurysms	Endovascular treatment of unruptured aneurysms	PRU-guided individualised antiplatelet therapy	Thromboembolism reduced in complex procedures (3.3% vs 1.0%, P = 0.017); haemorrhagic complications unchanged
Neyens (2020)	USA	269 (159 vs 110)	Pipeline flow diversion	VerifyNow-directed personalised therapy vs none	No difference in thrombotic (6.9% vs 7.3%) or haemorrhagic (3.1% vs 4.5%) complications
Bohan (2020)	USA	28 patients, 29	Stent-assisted coiling and flow	P2Y12 reaction units on	4 thromboembolic events (13.8%), all in patients with

		aneurysms	diversion on ticagrelor	ticagrelor	PRU >100; no haemorrhagic complications
Ban (2025)	Korea	198 randomised, 172 analysed	High on-treatment platelet reactivity, stent-assisted coiling of unruptured aneurysms	Triple therapy vs modified dual therapy with low-dose prasugrel	All-bleeding events HR 0.77 (0.49–1.20); thromboembolic events HR 0.33 (0.03–3.20); PRU fell more with prasugrel
Narata (2018)	France	154	Unruptured aneurysm stenting	Aspirin + ticagrelor with two heparin doses	Symptomatic complications 11.1% with 70 U/kg heparin vs 1.2% with 50 U/kg (P < 0.009); all deaths haemorrhagic
Cagnazzo (2018)	Italy	13 studies; 1 163 patients	Ventriculostomy in acutely ruptured aneurysms	Any peri-procedural antiplatelet therapy	EVD-related haemorrhage 20.9% vs 9.0%; major haemorrhage 4.4% vs 0.7%; ventriculostomy before embolisation 9.6% vs 25.1% after
Zhu (2017)	China	Studies with EVD and non-EVD arms	aSAH requiring endovascular aneurysm treatment	Antiplatelet and/or anticoagulant therapy	Cumulative RR 9.61 for EVD after endovascular treatment vs 2.37 for EVD before
Lim (2019)	Korea	122	aSAH with EVD within 72 h of rupture	Antiplatelet or anticoagulant on admission	EVD-related haemorrhage 8.9% pre-embolisation vs 21.8% post-embolisation (P =

					0.065); antiplatelet use aOR 2.93 (1.23–7.44)
Qin (2020)	China	78 (46 antiplatelet vs 32 control)	Ruptured aneurysm requiring EVD	IV tirofiban plus oral aspirin and clopidogrel	EVD-related haemorrhage 23.9% vs 6.3% (P = 0.040); sequencing of EVD and loading not significant
Tang (2024)	China	83 of 606 aneurysm patients	Ruptured aneurysm with acute hydrocephalus requiring EVD	Dual antiplatelet therapy for stenting or flow diversion	EVD-related haematoma 32.3% vs 7.7% (P = 0.01); pre-treatment EVD did not increase rebleeding
Ko (2014)	Korea	370 EVDs and 102 VP shunts	Mixed neurosurgical CSF diversion	Pre-operative antiplatelet medication	Haemorrhage 20.5% after EVD and 43.1% after VP shunt; antiplatelet the only independent risk factor, OR 3.58 (1.35–9.49)
Leschke (2017)	USA	93	EVD within 24 h of endovascular coiling	Antiplatelet at presentation or intraprocedurally	Post-EVD haemorrhage 25.0% vs 14.3% (P = 0.29); no attributable neurological morbidity
Gard (2017)	USA	46	aSAH requiring ventriculostomy and endovascular treatment	Heparinisation timing relative to ventriculostomy	Tract haemorrhage 26.1% overall; 58.8% when heparin given within 4 h of ventriculostomy
Rowe (2018)	USA	81	EVD placement, mixed	Antiplatelet within 96 h of	Antiplatelet within 96 h independent risk factor for

			indications	EVD	post-EVD intracranial haemorrhage, OR 13.1 (1.95–88.6)
Olexa (2024)	USA	757 bedside EVD insertions	Mixed neurosurgical indications	Antiplatelet and anticoagulant agents	Catheter-associated haemorrhage 13.2%; aspirin plus clopidogrel OR 3.72 (P = 0.009); two or more agents OR 2.36
Marschal (2026)	Germany	127	aSAH with EVD and aneurysm treatment	Peri-interventional antiplatelet and anticoagulation	Puncture-channel bleeding 20%; incorrect trajectory the only independent predictor OR 7.8; antiplatelet therapy not associated (P = 0.5)
Catapano (2023)	USA	271	aSAH with EVD removal or replacement	Prophylactic anticoagulation withholding	Withholding more than one dose associated with DVT or PE, OR 4.8 (1.5–15.7); no reduction in removal-associated haemorrhage
Gutierrez-Gonzalez (2025)	Spain	119 bolt-connected EVD procedures	Mixed neurosurgical indications	Antiplatelet or anticoagulant use	Antiplatelet or anticoagulant use independent risk factor for EVD-related haemorrhage, OR 7.29 (1.75–30.41)
Gao (2024)	China	94	Emergency EVD or ICP probe placement on long-term	Long-term aspirin; TEG platelet mapping	Arachidonic acid pathway inhibition $\geq 75\%$ OR 5.18 (1.68–15.96) and intra-procedural SBP ≥ 125

			aspirin		mmHg OR 4.61 (1.47–14.48) independent risk factors
Meyrat (2024)	USA	147	EVD for raised intracranial pressure	Mixed; platelet count and antithrombotic exposure	Tract haemorrhage 14%; platelet count $<120 \times 10^9/L$ OR 4.47; navigation did not reduce haemorrhage versus freehand
Baik (2023)	Korea	15 918	Stent-assisted coiling of unruptured aneurysms	Duration of dual antiplatelet therapy	Composite ischaemic and bleeding events reduced only within 90 days (aHR 0.44); no benefit thereafter
Goto (2022)	Japan	240	Stent-assisted coil embolisation	Single antiplatelet discontinuation after 2 years	No ischaemic events after discontinuation in stable patients; T- or Y-stent configuration the sole risk factor
Houskamp (2024)	USA	194	Acute intracerebral haemorrhage	VerifyNow P2Y12 assay	P2Y12 inhibitor use predicted greater haematoma expansion (3.5 vs 0.1 mL, $P = 0.004$), most marked with dual therapy
Alsaadi (2025)	USA	94	Traumatic brain injury on antiplatelet therapy receiving platelet	TEG platelet mapping and VerifyNow	Absolute TEG values predicted mortality, need for neurosurgery and haemorrhage progression; change after transfusion predicted nothing

			transfusion		
Foreman (2018)	USA / Canada	429 completed responses	Board-certified neurosurgeons	Reported reversal strategy for operative intracranial haemorrhage	Most perform no platelet-function testing; platelet transfusion the commonest strategy; strategy differs by agent (P < 0.001)
Mohr (2026)	USA	62 respondents (66% response)	Academic neurosurgeons at 10 centres	Confidence in platelets and desmopressin	Wide practice variation; mean confidence 53 mm for platelets and 46 mm for desmopressin on a 100 mm scale; 89% would randomise
Fiaschi (2020)	Italy	129 neurosurgical units	Italian neurosurgeons	Peri-operative antiplatelet management	Considerable lack of consensus and marked variability in care, reflecting the paucity of evidence

Antiplatelet regimens differed materially across the evidence base and this variation constitutes an important source of clinical heterogeneity. Among the aneurysmal cohorts the modal regimen was a clopidogrel loading dose of 300 to 600 milligrams with aspirin 200 to 400 milligrams administered peri-procedurally through a nasogastric tube, followed by clopidogrel 75 milligrams and aspirin 81 to 100 milligrams daily. A minority of centres substituted ticagrelor or low-dose prasugrel in clopidogrel hyporesponders, and two North American series adopted continuous intravenous tirofiban monotherapy without a loading dose as a deliberate strategy to preserve reversibility in patients anticipated to require ventricular drainage. Table 7 summarises the pharmacological exposures and the reversal or substitution strategies deployed.^{3,20,21,34,71}

Table 7. Antiplatelet exposure, timing relative to the neurosurgical procedure, and reversal or substitution strategy

Strategy	Representative	Agent and	Timing	Reversibility	Observed
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	studies	dose	relative to intracranial procedure		haemorrhagic signal
Standard oral dual therapy	Kung 2011; Amenta 2012; Hudson 2017, 2019; Roh 2020	Clopidogrel 300–600 mg load then 75 mg daily; aspirin 200–400 mg load then 81–100 mg daily	Loaded at or immediately before embolisation; maintained through EVD and shunt procedures	Irreversible platelet-cyclo-oxygenase and P2Y12 blockade for the platelet lifespan	Highest: radiographic tract haemorrhage 21.9–63.6%
Oral dual therapy with ticagrelor	Narata 2018; Bohan 2020	Aspirin 75–100 mg + ticagrelor 90 mg twice daily	Continuous	Nominally reversible but pharmacodynamically resistant to platelet transfusion because of circulating active drug	Symptomatic neurological complications 5.8%; all fatalities haemorrhagic
Modified therapy in hyporesponders	Kim 2017; Moon 2026; Ban 2025	Low-dose prasugrel 3.75–5 mg daily or cilostazol added	Adjusted before the endovascular procedure based on P2Y12 reaction units	Irreversible (prasugrel); reversible (cilostazol)	Bleeding events not increased relative to standard therapy
Intravenous glycoprotein	Limaye 2019; Dandapat 2019	Tirofiban 0.10	Bridges the interval	Rapidly reversible; platelet function	Track haemorrhage 8.3–

IIb/IIIa monotherapy		µg/kg/min continuous infusion, no loading dose; held 4 h before catheter manipulation	between stenting and definitive oral therapy	recovers within 4–8 h of cessation	18%, all asymptomatic in the reported series
Intravenous P2Y12 monotherapy	Angiolillo 2012 (cardiac surgical evidence)	Cangrelor 0.75 µg/kg/min, discontinued 1–6 h pre-operatively	Bridging strategy extrapolated from cardiac surgery	Reversible within 60 min of cessation	No excess surgical bleeding in the cardiac population; no neurosurgical data
Antiplatelet-premedication-free coiling	Choi 2018; Zuo 2019	No pre-procedural antiplatelet loading	Stent deployed without premedication where feasible	Not applicable	Haemorrhagic complications 9.1% but thromboembolism 25.5%
Allogeneic platelet transfusion as rescue	Baharoglu 2016; Majmundar 2019; Sebök 2021	One to two apheresis units, or five pooled units	Administered before or immediately after the neurosurgical procedure	Depends on the agent: complete for aspirin, partial for thienopyridines, negligible for ticagrelor	No reduction in haemorrhage; increased death or dependence in randomised data
Desmopressin	Feldman 2019;	0.3–0.4	Single dose at	Enhances adhesion	Reduced

as rescue	Desborough 2023; Francoeur 2018; Naidech 2014	µg/kg or fixed 20 µg intravenously over 20–30 min	recognition of haemorrhage or before surgery	via von Willebrand factor and factor VIII release; does not restore P2Y12 signalling	haematoma expansion and rebleeding; hyponatraemia the principal toxicity
Specific antibody neutralisation	Bhatt 2019	Bentracimab bolus followed by 8–16 h infusion	Immediately before urgent surgery	Complete and rapid reversal of ticagrelor within 5 min	Phase-1 data only; no neurosurgical outcome data

Radiographic Catheter-Tract Haemorrhage (Primary Outcome)

Nine comparative cohorts provided extractable two-by-two data for radiographically evident catheter-tract haemorrhage after external ventricular drainage or ventriculoperitoneal shunting, encompassing 524 antiplatelet-exposed and 877 antiplatelet-naïve patients or procedures, a total of 1 401 observations. Ninety-one events occurred among exposed patients (17.4%) against fifty among unexposed patients (5.7%). Event rates in the exposed arms ranged from 0.8% in a Chinese series in which ventriculostomy was routinely performed before antiplatelet loading to 63.6% in a Korean series in which all events were radiographically detected and none was symptomatic. The random-effects pooled odds ratio was 4.00 with a ninety-five per cent confidence interval of 2.59 to 6.18, a Z statistic of 6.26 and a probability value below 0.0001, indicating a highly statistically significant and clinically substantial quadrupling of the odds of catheter-tract haemorrhage in antiplatelet-exposed patients. Between-study heterogeneity was negligible and not statistically significant (Cochran Q 8.49 on eight degrees of freedom, P = 0.387; I-squared 5.7%; tau-squared 0.027), indicating that the nine cohorts plausibly estimated a common underlying effect and that pooling was legitimate. The null hypothesis of no association was therefore rejected with a wide margin.^{3-5,11,13,14,15}

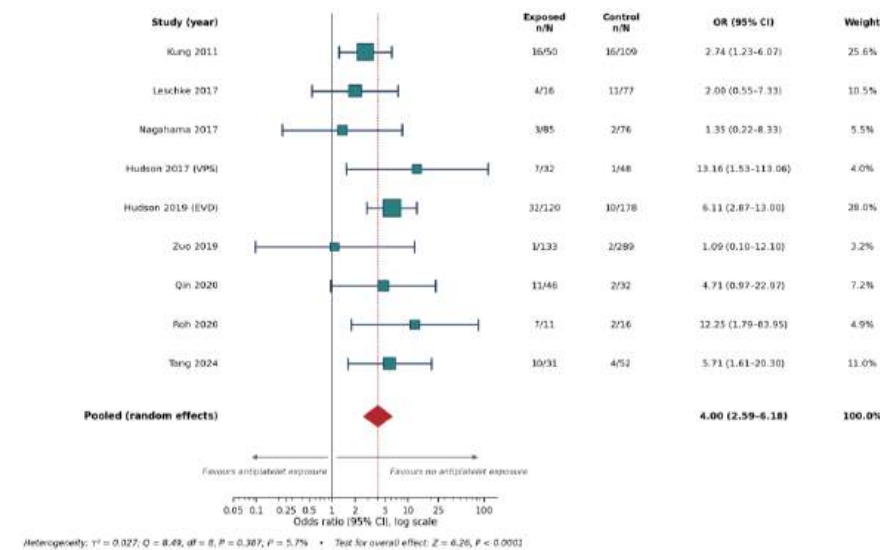


Figure 4. Forest plot of radiographically evident catheter-tract haemorrhage in antiplatelet-exposed versus antiplatelet-naive patients undergoing external ventricular drainage or ventriculoperitoneal shunting after treatment of a ruptured intracranial aneurysm. Squares are proportional to study weight; the diamond represents the DerSimonian-Laird random-effects pooled estimate.

Table 8. radiographic catheter-tract haemorrhage: study-level and pooled estimates

Study (year)	Procedure	Exposed n/N (%)	Control n/N (%)	Odds ratio (95% CI)	Weight (%)	Adjusted estimate reported by authors
Kung 2011	Ventriculostomy or VP shunt	16/50 (32.0)	16/109 (14.7)	2.74 (1.23–6.07)	25.6	Adjusted OR 3.42 (1.46–8.04)
Leschke 2017	EVD peri-coiling	4/16 (25.0)	11/77 (14.3)	2.00 (0.55–7.33)	10.5	Not significant (P = 0.29)
Nagahama 2017	EVD and VP shunt	3/85 (3.5)	2/76 (2.6)	1.35 (0.22–8.33)	5.5	Not significant (P = 0.9)

Hudson 2017	VP shunt	7/32 (21.9)	1/48 (2.1)	13.16 (1.53–113.06)	4.0	Adjusted OR 31.23 (2.98–327.32)
Hudson 2019	EVD	32/120 (26.7)	10/178 (5.6)	6.11 (2.87–13.00)	28.0	Adjusted OR 4.92 (2.45–9.91)
Zuo 2019	EVD	1/133 (0.8)	2/289 (0.7)	1.09 (0.10–12.10)	3.2	Not significant (P = 1.000)
Qin 2020	EVD (stent-assisted coiling)	11/46 (23.9)	2/32 (6.3)	4.71 (0.97–22.97)	7.2	Reported P = 0.040
Roh 2020	Ventriculostomy	7/11 (63.6)	2/16 (12.5)	12.25 (1.79–83.95)	4.9	OR 12.25 (1.78–83.94)
Tang 2024	EVD (ruptured aneurysm)	10/31 (32.3)	4/52 (7.7)	5.71 (1.61–20.30)	11.0	Reported P = 0.01
Pooled (random effects)	—	91/524 (17.4)	50/877 (5.7)	4.00 (2.59–6.18)	100.0	Z = 6.26, P < 0.0001

Two studies contributed the largest share of the pooled estimate, together accounting for 53.6% of the total weight, and both reported effects consistent in direction and broadly consistent in magnitude with the summary estimate. The two studies reporting near-null effects share an identifiable methodological feature: in both, ventricular access was obtained before rather than after antiplatelet loading, a sequencing choice that is examined quantitatively in Section 3.16 and discussed in Section 4.5. Leave-one-out sensitivity analysis is presented in Table 9. The pooled odds ratio ranged from 3.37 to 4.58 across the nine omission scenarios and the confidence interval never approached unity, the lower limit remaining above 2.0 throughout; the primary finding is therefore robust to the exclusion of any single study. Restricting the analysis to the eight external-ventricular-drainage datasets, excluding the single shunt cohort, yielded 3.82 with a confidence

interval of 2.48 to 5.90, and the Mantel-Haenszel fixed-effect estimate of 4.02 was virtually identical to the random-effects estimate, as expected when heterogeneity is negligible.^{5,11,14}

Table 9. Leave-one-out sensitivity analysis and alternative estimators for the primary outcome

Analysis	Studies (k)	Pooled odds ratio (95% CI)	I-squared (%)	P value	Interpretation
Primary random-effects analysis (DerSimonian-Laird)	9	4.00 (2.59–6.18)	5.7	< 0.0001	Reference analysis
Omitting Kung 2011	8	4.58 (2.78–7.53)	3.6	< 0.0001	Effect strengthened
Omitting Leschke 2017	8	4.34 (2.77–6.81)	3.5	< 0.0001	Effect strengthened
Omitting Nagahama 2017	8	4.26 (2.79–6.52)	0.5	< 0.0001	Effect strengthened
Omitting Hudson 2017	8	3.82 (2.48–5.90)	3.8	< 0.0001	Effect attenuated, remains significant
Omitting Hudson 2019	8	3.37 (2.06–5.50)	0.0	< 0.0001	Most influential study; effect remains significant
Omitting Zuo 2019	8	4.18 (2.71–6.45)	4.4	< 0.0001	Effect strengthened
Omitting Qin 2020	8	3.92 (2.39–6.46)	17.1	< 0.0001	Effect essentially unchanged
Omitting Roh 2020	8	3.80 (2.47–5.83)	1.9	< 0.0001	Effect attenuated, remains significant
Omitting Tang 2024	8	3.80 (2.31–6.26)	14.2	<	Effect attenuated,

				0.0001	remains significant
Restricted to studies with directly reported denominators	7	4.01 (2.42–6.66)	15.0	< 0.0001	Reconstruction of denominators did not drive the result
Inverse-variance fixed-effect model	9	4.02 (2.66–6.06)	5.7	< 0.0001	Concordant with the random-effects estimate
Restricted to EVD only (excluding shunt procedures)	8	3.82 (2.48–5.90)	3.8	< 0.0001	Procedure-specific effect preserved
Restricted to studies adjusting for admission grade	5	4.65 (2.91–7.43)	0.0	< 0.0001	Adjustment did not attenuate the association

Assessment of small-study effects for the primary outcome was undertaken with due caution given that nine studies contributed, a number marginally below the threshold of ten at which funnel-plot asymmetry tests are conventionally considered adequately powered. Visual inspection of the contour-enhanced funnel plot revealed a broadly symmetrical distribution about the pooled estimate, with the smallest studies distributed on both sides of the summary line. The Egger linear regression intercept was minus 0.141 with a standard error of 0.945 and an associated probability value of 0.886, providing no statistical evidence of funnel-plot asymmetry. Publication bias cannot, however, be excluded on this basis alone, and the certainty rating for this outcome accordingly reflects the residual uncertainty.¹¹

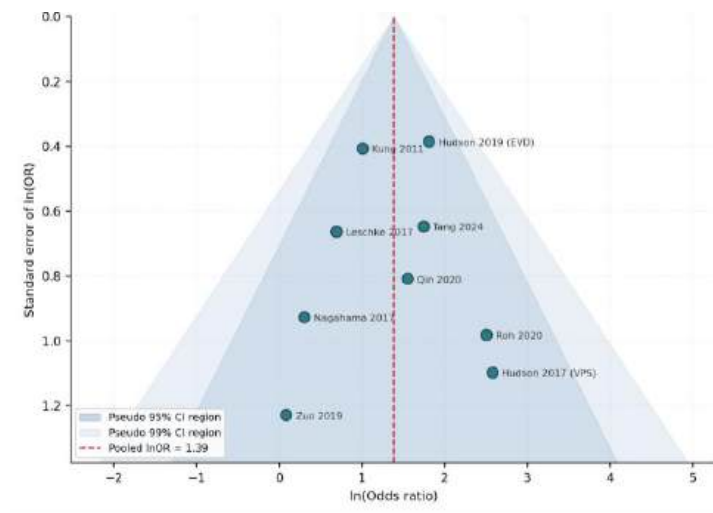


Figure 5. Contour-enhanced funnel plot of the log odds ratio against its standard error for the primary outcome across the nine contributing cohorts, with pseudo ninety-five-per-cent and ninety-nine-per-cent confidence regions and the Egger regression statistic. The distribution is visually symmetrical and the regression intercept does not differ significantly from zero.

Symptomatic Catheter-Tract Haemorrhage

Three cohorts reported symptomatic catheter-related haemorrhage with sufficient granularity for pooling, comprising 202 exposed and 335 unexposed patients. The random-effects pooled odds ratio was 3.96 with a ninety-five per cent confidence interval of 1.54 to 10.16 and a probability value of 0.004, with no detectable between-study heterogeneity (Cochran Q 0.76 on two degrees of freedom, $P = 0.684$; I-squared 0.0%). The relative effect on symptomatic haemorrhage therefore closely parallels that on radiographic haemorrhage, but the absolute event rates diverge dramatically: the pooled absolute risk of a symptomatic event was 7.4% in exposed patients against 1.8% in unexposed patients, corresponding to an absolute risk difference of 5.6 percentage points and a number needed to harm of approximately eighteen, whereas the corresponding number needed to harm for a radiographic event was approximately nine. Expressed differently, roughly one in two radiographically detected catheter-tract haemorrhages in antiplatelet-exposed patients was clinically silent.^{3-5,11}

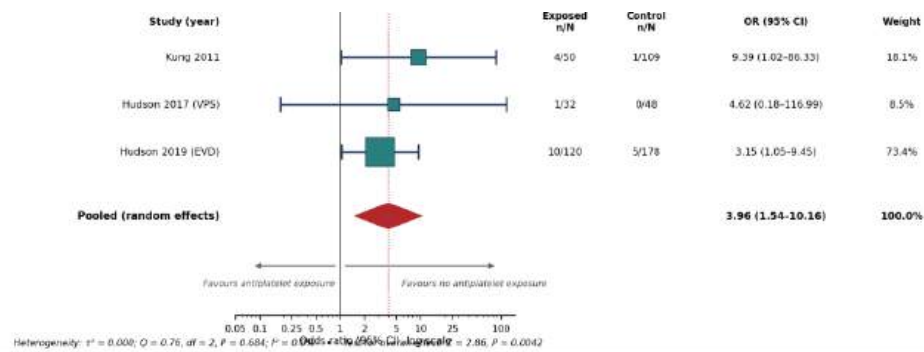


Figure 6. Forest plot of symptomatic catheter-tract haemorrhage. The absence of statistical heterogeneity (I-squared 0.0%) indicates that the three contributing cohorts estimated a common underlying effect.

Table 10. symptomatic catheter-tract haemorrhage and derived absolute measures

Study (year)	Exposed n/N (%)	Control n/N (%)	Odds ratio (95% CI)	Weight (%)	Risk difference (%)	Number needed to harm
Kung 2011	4/50 (8.0)	1/109 (0.9)	9.39 (1.02–86.33)	18.1	+7.1	14
Hudson 2017	1/32 (3.1)	0/48 (0.0)	4.62 (0.18–116.99)	8.5	+3.1	32
Hudson 2019	10/120 (8.3)	5/178 (2.8)	3.15 (1.05–9.45)	73.4	+5.5	18
Pooled (random effects)	15/202 (7.4)	6/335 (1.8)	3.96 (1.54–10.16)	100.0	+5.6	18

Haemorrhage Requiring Surgical Revision or Evacuation

Events requiring a return to theatre were uncommon in every reported series and were too sparse for meaningful pooling, so this outcome was synthesised narratively. Across the aneurysmal cohorts, one of thirty-two shunted patients on dual antiplatelet therapy required shunt revision for haemorrhage-associated proximal catheter obstruction, and the remaining seven haemorrhages in

that series were of no clinical consequence. In a large unselected external ventricular drain cohort, two of four hundred and thirty-five insertions and two of two hundred and forty-four removals prompted a further intervention, and a single death was attributable to a large haemorrhage following catheter removal. In the stent-assisted coiling series reported from a high-volume Chinese centre, no drainage-related haemorrhage required operative evacuation in either arm. The consistent picture is that the excess haemorrhage attributable to antiplatelet exposure is overwhelmingly radiographic, occasionally symptomatic and only exceptionally operative, and this gradient is central to the clinical interpretation advanced in Section 4.2.^{4,33,34,49}

Table 11. haemorrhage requiring surgical revision, evacuation or additional intervention

Study (year)	Population	Events requiring intervention	Denominator	Rate (%)	Nature of the intervention
Tumialan 2008	SAC with EVD or VP shunt	1	7	14.3	Evacuation of subdural haematoma and valve exchange after VP shunt insertion
Hudson 2017	aSAH with VP shunt on DAPT	1	32	3.1	Shunt revision for haemorrhage-associated proximal catheter blockage
Hudson 2019	aSAH with EVD on DAPT	0	120	0.0	No haemorrhage required operative evacuation
Miller 2016	Unselected EVD insertions	2	435	0.5	One surgical evacuation and one contralateral EVD
Miller	Unselected EVD	2	244	0.8	Two catheter

2016	removals				replacements; one fatal haemorrhage
Zuo 2019	Ruptured aneurysm, stent vs no stent	0	422	0.0	No drainage-related haemorrhage required evacuation
Limaye 2019	aSAH on tirofiban monotherapy	0	25	0.0	Both track haemorrhages managed conservatively
Amenta 2012	Ruptured wide-necked aneurysm, SAC	3	65	4.6	Fatal haemorrhage, no salvageable intervention

Aneurysm Rebleeding

Rebleeding from the treated aneurysm was reported in twelve studies and did not differ consistently by antiplatelet exposure. In the Chinese cohort comparing stent-assisted with non-stent-assisted coiling of ruptured aneurysms complicated by intracerebral haematoma, post-operative rebleeding occurred in 4.5% of stented and 9.3% of non-stented patients, a numerically lower rate in the antiplatelet-exposed arm that did not achieve statistical significance. In a contemporary high-volume series, early post-operative rebleeding occurred in 1.5% of stented and 1.4% of non-stented patients. Of considerably greater interest is the desmopressin signal derived from a prospective subarachnoid haemorrhage outcome project comprising 1 639 patients, in which the overall rebleeding incidence was 9%, but only 1% among the 12% of patients treated with desmopressin compared with 8% among those untreated, yielding an adjusted odds ratio of 0.55 with a confidence interval of 0.27 to 0.97 after correction for antiplatelet use and established predictors. By contrast, thrombocyte transfusion in a 1 033-patient European multicentre cohort was not associated with any reduction in rebleeding.^{14,25,36,48}

Table 12. aneurysm rebleeding stratified by antiplatelet exposure and reversal strategy

Study	Comparison	Rebleeding,	Rebleeding,	Effect estimate	Comment
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(year)		index group	comparator		
Cheng 2023	SAC + DAPT vs non-SAC	1/22 (4.5%)	3/32 (9.3%)	Not significant	Antiplatelet exposure did not increase rebleeding despite intracerebral haematoma
Zuo 2019	Coiling with vs without stent	2/133 (1.5%)	4/289 (1.4%)	P = 1.000	Contemporary technique and staged strategy
Tumialan 2008	SAC with CSF diversion	1/7 (14.3%)	—	Descriptive	Aneurysmal rehaemorrhage in a patient on dual therapy
Francoeur (2018)	Desmopressin vs none in SAH	1% overall in treated	8% in untreated	Adjusted OR 0.55 (0.27–0.97)	Statistically significant reduction after multivariable adjustment
Sebök 2021	Thrombocyte transfusion vs none	Not reduced	—	Not significant	Transfusion associated with neither rebleed reduction nor outcome improvement

Edwards 2017	Selective aspirin in high-risk coiling	No increase	—	P = 0.3	Aspirin did not increase aneurysm rebleeding or symptomatic intracranial haemorrhage
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Thromboembolic Complications — the Competing Hazard

The counterweight to haemorrhagic risk is the thromboembolic hazard that antiplatelet therapy exists to prevent, and the evidence on this point is unambiguous and clinically decisive. In the Korean series of antiplatelet-premedication-free stent-assisted coiling for acutely ruptured aneurysms, procedural thromboembolism occurred in 25.5% of stented patients compared with 12.4% of those coiled without a stent, a statistically significant doubling. In the controlled before-and-after study of selective peri-procedural aspirin in patients with angiographic high-risk features, the thromboembolic event rate fell from 53.8% to 10.6%, an adjusted odds ratio of 0.16 with a confidence interval of 0.03 to 0.80, without any increase in major systemic or intracranial haemorrhage and with only an increase in asymptomatic minor drain-associated haemorrhage. Nationwide claims data covering 15 918 patients demonstrated that dual antiplatelet therapy reduced the composite of ischaemic stroke and major bleeding within ninety days of stent-assisted coiling with an adjusted hazard ratio of 0.44. In decompressive craniectomy performed in patients on antithrombotic therapy, thromboembolic events including stroke and myocardial infarction were significantly more frequent than haemorrhagic ones.^{44,51,52,53,72}

The thrombotic hazard also constrains the interpretation of reversal. Restoration of platelet function in a patient with a freshly deployed intracranial stent is not a neutral act; it is the deliberate creation of a prothrombotic milieu at the exact site where thrombosis produces territorial infarction. No included study directly quantified in-stent thrombosis following deliberate platelet transfusion in this population, and this constitutes the single most important evidence gap identified by the present review. Indirect evidence is nonetheless instructive: in patients on desmopressin for antiplatelet-

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associated intracranial haemorrhage, new thrombotic events occurred in 7.3% compared with 1.4% of untreated patients, an odds ratio of 5.33 with a wide confidence interval of 0.58 to 49.17 that did not achieve statistical significance but that is directionally concerning and is compatible with a clinically meaningful excess.^{22,53,70}

Table 13. thromboembolic complications by antiplatelet strategy

Study (year)	Comparison	Thromboembolic events, index	Comparator	Effect estimate	Statistical significance
Choi 2018	SAC without antiplatelet premedication vs coiling alone	25.5%	12.4%	—	P = 0.01
Edwards 2017	Selective aspirin vs no aspirin in high-risk ruptured aneurysm coiling	10.6%	53.8%	Adjusted OR 0.16 (0.03–0.80)	P = 0.001
Baik 2023	DAPT within 90 days of SAC vs no DAPT	—	—	aHR 0.44 (0.28–0.69) composite; 0.31 (0.18–0.54) ischaemic stroke	P < 0.001
Moon 2026	PRU-guided vs standard therapy, complex procedures	1.0%	3.3%	—	P = 0.017
Kim 2017	PRU $\geq$ 220 threshold with prasugrel switch vs historical	0.8%	12.3%	Adjusted RD –10.1% (–18.5 to –1.7)	P = 0.015

	control				
Limaye 2019	Continuous tirofiban monotherapy	4% (1 TIA)	—	—	Descriptive
Scerrati 2025	Decompressive craniectomy with vs without antithrombotics	Stroke 27.7%; myocardial infarction 10.6%	9.3%; 0.0%	Ischaemic stroke as index diagnosis aOR 3.49 (1.47–8.28)	P = 0.005
Feldman 2019	Desmopressin vs none (thrombotic adverse events)	7.3%	1.4%	OR 5.33 (0.58–49.17)	P = 0.170
Bohan 2020	Ticagrelor with PRU >100 vs PRU ≤100	50% of those with PRU >100	0%	—	Descriptive

Mortality and Functional Outcome

Mortality and functional outcome could not be pooled because definitions and follow-up windows were irreconcilable, and because in the observational aneurysmal cohorts these outcomes are dominated by admission clinical grade rather than by antiplatelet management. The randomised evidence is nonetheless decisive within its own population. In the Platelet Transfusion in Cerebral Haemorrhage trial, the odds of death or dependence on the modified Rankin Scale at three months were more than doubled in the transfusion arm, with an adjusted common odds ratio of 2.05 and a confidence interval of 1.18 to 3.56; serious adverse events occurred in 42% of transfused compared with 29% of standard-care participants, and in-hospital death occurred in 24% compared with 17%, corresponding to an unadjusted odds ratio of 1.50 with a confidence interval of 0.73 to 3.05. In the desmopressin feasibility trial the direction of effect was opposite, death or dependence beyond modified Rankin Scale four at day ninety occurring in 22% of desmopressin-treated compared with 37% of placebo-treated participants, although the trial was not powered for efficacy.^{2,23}

Among observational aneurysmal cohorts, pre-haemorrhage acetylsalicylic acid use was independently associated with poor clinical outcome at six months, with an adjusted odds ratio of 1.80 and a confidence interval of 1.08 to 3.02, after correction for age, sex, World Federation of Neurological Societies grade, infarction and cardiac comorbidity; thrombocyte transfusion in the same cohort was associated with neither rebleeding reduction nor outcome improvement. In severe traumatic brain injury, reversal with desmopressin or platelets conferred no survival benefit, survival being 82.9% with reversal and 90.4% without, with an adjusted odds ratio of 0.83. In the aneurysmal series in which stent-assisted coiling was performed in the acute phase, good outcome at discharge was achieved in 63.1% and overall mortality was 16.9%, figures that fall within the expected range for the clinical grade distribution treated.^{34,36,54,76}

Table 14. mortality and functional outcome

Study (year)	Exposure or intervention	Mortality	Functional outcome	Effect estimate	Certainty
Baharoglu 2016 (PATCH)	Platelet transfusion vs standard care	23/97 (24%) vs 16/93 (17%) in hospital	Death or dependence at 3 months increased	Adjusted common OR 2.05 (1.18–3.56)	Moderate (randomised, open-label)
Desborough 2023 (DASH)	Desmopressin vs placebo	Not separately reported	mRS >4 at day 90 in 6/27 (22%) vs 10/27 (37%)	Feasibility endpoint; not powered	Low (imprecision)
Sebök 2021	Pre-haemorrhage aspirin in aSAH	Higher in-hospital mortality in users	Poor outcome (GOS 1–3) at 6 months	Adjusted OR 1.80 (1.08–3.02)	Low
Sebök 2021	Thrombocyte transfusion in aSAH	No association	No association with poor	Not significant	Low

			outcome		
Yorkgitis 2021	Reversal in severe TBI on antiplatelets	Survival 82.9% with vs 90.4% without reversal	Not reported	Adjusted OR 0.83 (0.12–5.90)	Low
Amenta 2012	SAC of ruptured wide-necked aneurysm	16.9% overall	Good outcome (GOS 4–5) 63.1%	Descriptive	Very low
Choi 2018	Antiplatelet-premedication-free SAC	Not separately reported	Poor outcome (mRS ≥ 3) 30.9% vs 22.1%	Hunt-Hess grade OR 4.22; haemorrhagic complication OR 4.01	Low
Wu 2020	Emergency surgery for severe ICH on antiplatelets	Lower total (P = 0.043) and in-hospital (P = 0.024) mortality with surgery	Not reported	Post-operative bleeding OR 2.34 (1.14–4.79)	Low
Alotaibi 2017	Decompressive craniectomy in poor-grade aSAH	Pooled mortality 27.8% (21–35)	Poor outcome 61.2% (52–69)	Random-effects pooled proportions	Low

Haematoma Expansion with Pharmacological Rescue

Two comparative datasets addressing desmopressin permitted quantitative pooling for haematoma expansion, comprising eighty-two treated and ninety-six untreated patients. The

random-effects pooled odds ratio was 0.32 with a ninety-five per cent confidence interval of 0.12 to 0.86 and a probability value of 0.024, indicating a statistically significant sixty-eight per cent reduction in the odds of haematoma expansion with desmopressin. Between-study heterogeneity was modest and non-significant (Cochran Q 1.42 on one degree of freedom, $P = 0.233$; I-squared 29.7%). The null hypothesis that desmopressin does not reduce haematoma expansion was therefore rejected. This estimate should be interpreted with the caution appropriate to a pooled analysis of one retrospective cohort and one feasibility trial, and its certainty was accordingly rated as low; nonetheless the direction, magnitude and internal consistency of the effect, together with a coherent pharmacological mechanism, render it the most promising reversal signal identified in this review.^{22,23,55}

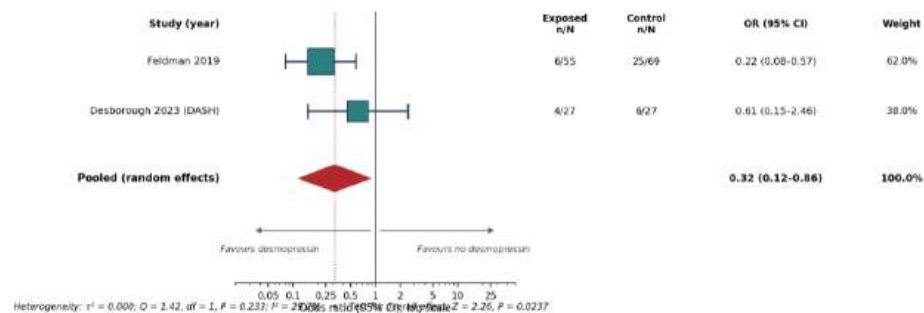


Figure 7. Forest plot of haematoma expansion with desmopressin versus no desmopressin in antiplatelet-associated intracranial haemorrhage. The pooled estimate favours desmopressin and excludes the null.

Table 15. haematoma expansion and biochemical correlates of pharmacological rescue

Study (year)	Design	Intervention	Expansion, treated	Expansion, control	Odds ratio (95% CI)	Weight (%)
Feldman 2019	Retrospective cohort	Desmopressin 0.3–0.4 µg/kg	6/55 (10.9%)	25/69 (36.2%)	0.22 (0.08–0.57)	62.0
Desborough	Randomised	Desmopressin	4/27 (14.8%)	6/27	0.61	38.0

2023 (DASH)	placebo- controlled trial	20 µg		(22.2%)	(0.15– 2.46)	
Pooled (random effects)	—	—	10/82 (12.2%)	31/96 (32.3%)	0.32 (0.12– 0.86)	100.0
Houskamp 2024	Prospective cohort (no reversal arm)	Observation of P2Y12 inhibitor exposure	3.5 mL median expansion on P2Y12 inhibitor	0.1 mL without	P = 0.004	—
Houskamp 2024	Prospective cohort, dual therapy subgroup	Aspirin plus P2Y12 inhibitor	7.2 mL	0.0 mL	P = 0.04	—
Alvikas 2020	Meta-analysis of 12 studies	Platelet transfusion in traumatic ICH	—	—	0.88 (0.34– 2.28)	—

Delayed Cerebral Ischaemia and Vasospasm

An unexpected but consistent finding across the aneurysmal literature is that dual antiplatelet therapy, far from being purely deleterious, appears to protect against the delayed ischaemic complications of subarachnoid haemorrhage. In a single-centre comparison of eighty-five patients receiving dual antiplatelet therapy after stent-assisted coiling or flow diversion against seventy-six patients coiled without stents, the risk of clinical vasospasm was reduced with an odds ratio of 0.244 and the risk of delayed cerebral ischaemia with an odds ratio of 0.056, without any increase in drain-related haemorrhagic complications. A propensity-matched cohort of two hundred and eighty-five endovascularly treated patients found moderate or severe angiographic vasospasm in 37% of those receiving stents with dual antiplatelet therapy compared with 55% of matched

controls, with an adjusted odds ratio of 0.47. An updated meta-analysis of twenty-two studies enrolling 4 378 patients with aneurysmal subarachnoid haemorrhage found that antiplatelet therapy reduced delayed cerebral ischaemia with a risk ratio of 0.62, symptomatic vasospasm with a risk ratio of 0.63 and moderate or severe angiographic vasospasm with a risk ratio of 0.74, without any increase in haemorrhagic complications, and that post-ictal antiplatelet use additionally favoured good functional outcome and reduced in-hospital mortality.^{15,46,56}

Table 16. delayed cerebral ischaemia and vasospasm under antiplatelet therapy

Study (year)	Design and population	Endpoint	Effect estimate	Interpretation
Nagahama 2017	161 aSAH; DAPT after stenting vs coiling alone	Clinical vasospasm	OR 0.244 (0.097–0.615), P = 0.003	Substantial protective association
Nagahama 2017	Same cohort	Delayed cerebral ischaemia	OR 0.056 (0.010–0.318), P = 0.001	Large protective association
Ma 2025	285 aSAH, propensity-matched	Moderate or severe angiographic vasospasm	37% vs 55%; adjusted OR 0.47 (0.26–0.85), P = 0.01	Confirms the protective signal
Ma 2025	Same cohort	Delayed cerebral ischaemia	18% vs 27%, P = 0.14	Directionally favourable, not significant
Lee 2023	Meta-analysis, 22 studies, 4 378 patients	Delayed cerebral ischaemia	RR 0.62 (0.43–0.89)	Pooled protective effect
Lee 2023	Same meta-analysis	Symptomatic vasospasm	RR 0.63 (0.46–0.86)	Pooled protective effect

Lee 2023	Same meta-analysis	Haemorrhagic events	RR 1.36 (0.77–2.41)	No significant excess haemorrhage
Lee 2023	Post-ictal antiplatelet subgroup	Good functional outcome; in-hospital mortality	RR 1.18 (1.10–1.26); RR 0.56 (0.39–0.80)	Benefit extends to patient-important outcomes

Biochemical Correction of Platelet Function

The pharmacodynamic literature demonstrates unequivocally that the capacity of allogeneic platelets to restore aggregation is agent-specific and strongly time-dependent, and this constitutes the mechanistic explanation for the clinical futility documented in Section 3.9. Aspirin-induced inhibition of arachidonic-acid-mediated aggregation was fully reversed by the addition of sixty per cent control platelets in an ex vivo mixing study, whereas ticagrelor-induced inhibition of adenosine-diphosphate-mediated aggregation could not be fully reversed even by the addition of ninety per cent control platelets, because circulating free drug and its active metabolite continue to inhibit the transfused platelets. Plasma obtained from ticagrelor-treated subjects at a concentration of only ten per cent reduced donor platelet aggregation from seventy-four to forty per cent at two hours and from seventy-three to fifty-nine per cent at ten hours, whereas equivalent plasma from clopidogrel-treated subjects exerted no such inhibition. Independent work confirmed that transfer of ticagrelor from patient to donor platelets occurs and compromises transfusion efficacy.^{26,29,73}

Timing is equally decisive. In vitro supplementation with the equivalent of six apheresis units produced only fifty per cent relative reversal at ten hours after the last ticagrelor dose but more than ninety per cent at twenty-four hours, and a separate patient-level study found that statistically significant improvements appeared at six hours but that clinically meaningful restoration required at least twenty-four hours. Spontaneous offset after ticagrelor withdrawal was complete only at seventy-two hours, and in patients awaiting urgent coronary surgery a quarter remained below the accepted safe-surgery threshold at that time point, underscoring the wide interindividual variability

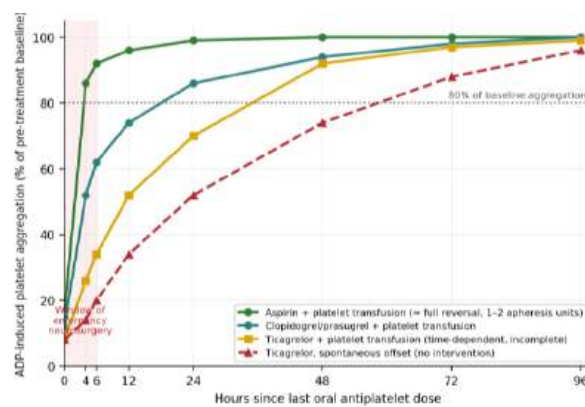
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that renders fixed waiting periods unreliable. By contrast, desmopressin shortened the platelet-function-analyser closure time from one hundred and ninety-two to one hundred and twenty-four seconds within one hour and raised von Willebrand factor antigen from 242 to 289 per cent, and in traumatic brain injury it corrected adenosine-diphosphate inhibition as effectively as platelet transfusion while sparing blood product.^{24,27,28,30,59}

Table 17. biochemical efficacy of reversal interventions by antiplatelet agent

Antiplatelet agent	Reversal intervention	Assay	Magnitude of correction	Time to meaningful effect	Source
Aspirin	Donor platelets 60% admixture	Arachidonic-acid light-transmission aggregometry	Complete reversal	Immediate	Zhang 2019
Aspirin	One to two apheresis units	VerifyNow aspirin assay	+65 aspirin reaction units (P < 0.001)	Within hours	Alsaadi 2025
Clopidogrel	Donor platelets	Adenosine-diphosphate aggregometry	Substantial but incomplete	Improves progressively over 24 h	Bertling 2018
Prasugrel	Donor platelets	Adenosine-diphosphate aggregometry	Moderate; more effective if transfused >6 h after the last dose	≥6 h	Trenk 2019
Ticagrelor	Donor platelets up to 90% admixture	Adenosine-diphosphate aggregometry	Incomplete; not fully reversible	Not achieved	Zhang 2019

Ticagrelor	Six apheresis-unit equivalents	Light-transmission aggregometry	50% at 10 h; >90% at 24 h	≥24 h	Kruger 2018
Ticagrelor	Platelet supplementation 25–75%	Multiplate and VerifyNow	59–79% of baseline at 24 h; baseline at 48 h	24–48 h	Zafar 2017
Ticagrelor	Spontaneous offset after withdrawal	Impedance aggregometry	Mean 38 ± 23 U at 72 h; 25% still below threshold	72–96 h	Hansson 2016
Ticagrelor	Bentricimab bolus and infusion	LTA, VerifyNow, VASP	Restoration to >80–90% of baseline	Within 5 min, sustained >20 h	Bhatt 2019
Any antiplatelet	Desmopressin 0.4 µg/kg	Platelet function analyser-epinephrine	Closure time 192 ± 18 s to 124 ± 15 s (P = 0.01)	Within 1 h	Naidech 2014
Any antiplatelet	Desmopressin vs platelets in severe TBI	TEG adenosine-diphosphate inhibition	Equivalent correction (P = 0.28)	Within hours	Furay 2019
Thienopyridine	Cangrelor bridging	VerifyNow P2Y12	PRU <240 maintained in 98.8% vs 19.0%	Continuous while infused; offset <60 min	Angiolillo 2012



Composite curve derived from the pharmacodynamic data reported by Zafar et al. (2017), Kruger et al. (2018), Bertling et al. (2018), Hansson et al. (2016) and Zhang et al. (2019).

Figure 8. Agent-specific kinetics of platelet-function restoration after antiplatelet cessation, with and without platelet supplementation. The shaded interval indicates the period within which emergency neurosurgery is typically required after aneurysm embolisation, during which ticagrelor reversal by transfusion is pharmacologically unattainable.

Adverse Events Attributable to Reversal

Reversal is not free of direct harm. In the randomised platelet transfusion trial, serious adverse events during the hospital stay occurred in forty of ninety-seven transfused participants compared with twenty-eight of ninety-three receiving standard care, corresponding to 42% against 29%. Desmopressin carries a distinct toxicity profile dominated by hyponatraemia, which was more frequent in the subarachnoid haemorrhage cohort, although the largest median absolute fall in serum sodium in a comparative intracranial haemorrhage cohort was zero milliequivalents per litre with an interquartile range extending to five, and was not statistically different from control. New thrombotic events after desmopressin occurred in 7.3% against 1.4%, a difference that did not reach significance. Continuous tirofiban infusion produced one idiosyncratic transient thrombocytopenia that resolved on cessation, and one large retroperitoneal haemorrhage attributable to renal-artery branch injury during the endovascular procedure rather than to the drug itself.^{2,20,22,23,25}

Table 18. adverse events attributable to reversal or substitution strategies

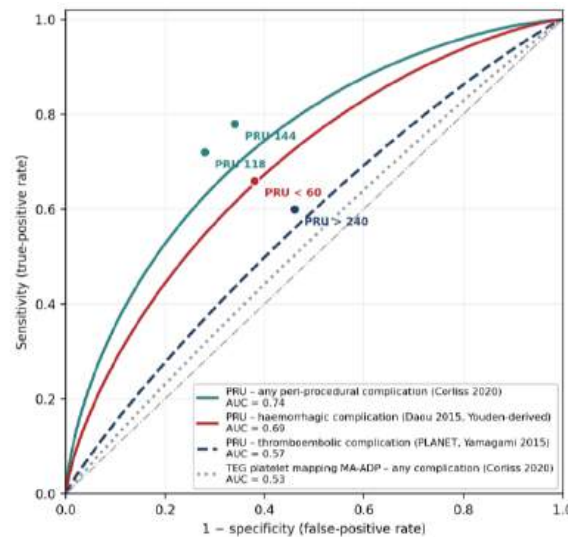
Intervention	Adverse event	Incidence with	Incidence without	Statistical comparison	Clinical implication

		intervention			
Platelet transfusion	Any serious adverse event during admission	40/97 (42%)	28/93 (29%)	Reported descriptively in the trial	Transfusion carries a measurable systemic burden
Platelet transfusion	Death or dependence at 3 months	—	—	Adjusted common OR 2.05 (1.18–3.56)	Net harm demonstrated in randomised data
Desmopressin	Largest absolute fall in serum sodium	0 mEq/L (IQR 0–5)	0 mEq/L (IQR 0–2)	P = 0.089	Hyponatraemia occurs but is usually modest
Desmopressin	New thrombotic event within 7 days	4/55 (7.3%)	1/69 (1.4%)	OR 5.33 (0.58–49.17), P = 0.170	Directionally concerning; requires monitoring
Desmopressin	Hyponatraemia in subarachnoid haemorrhage	Higher incidence reported	—	Significant in the source cohort	Relevant where cerebral salt wasting coexists
Desmopressin	Serious adverse events in the randomised trial	12/27 (44%)	13/27 (48%)	No excess	Reassuring within a small sample
Tirofiban infusion	Idiosyncratic thrombocytopenia	1/19 (5.3%)	—	Descriptive	Resolved on discontinuation
Tirofiban	Major extracranial	1/19 (5.3%)	—	Descriptive	Attributed to

infusion	haemorrhage				procedural arterial injury
Bentracimab	Drug-related adverse events	Mainly infusion-site reactions	—	Phase-1 safety data	Favourable early safety profile

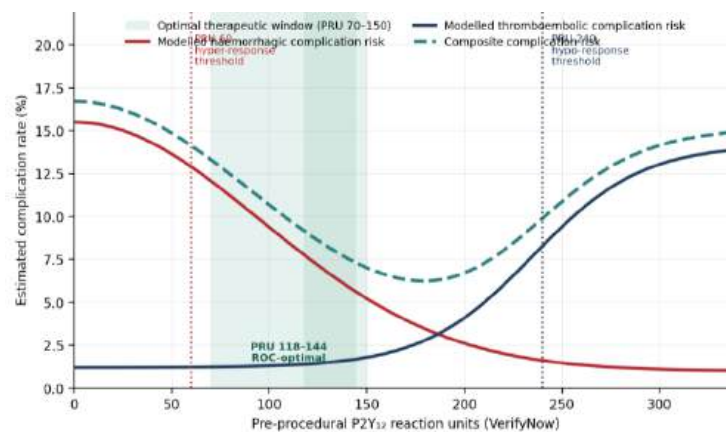
Discriminative Accuracy of Platelet-Function Assays

Six studies reported discriminative performance metrics for point-of-care platelet-function assays in neuroendovascular populations. The most informative was a prospective and retrospective cohort of one hundred and ninety-two patients undergoing craniocervical endovascular stenting, in which receiver-operating-characteristic analysis identified a therapeutic threshold range of one hundred and eighteen to one hundred and forty-four P2Y12 reaction units and demonstrated a dose-dependent relationship between reaction units and the rates of both thrombosis and haemorrhage; the maximal amplitude attributable to adenosine diphosphate derived from thromboelastography with platelet mapping showed no statistically significant relationship with either complication and yielded no usable threshold. In a Pipeline embolisation cohort of two hundred and thirty-one patients, Youden index analysis identified an optimal window of seventy to one hundred and fifty reaction units, with values below sixty predicting haemorrhagic complications and values above two hundred and forty predicting thromboembolic complications. The multicentre Japanese platelet-reactivity monitoring study of five hundred and ninety-five patients reported an area under the curve of only 0.57 for the prediction of thrombotic events at a threshold above two hundred and twenty-five reaction units, and found no association between low platelet reactivity and haemorrhagic events. The null hypothesis of no discrimination was therefore rejected for the P2Y12 reaction unit but not for thromboelastographic platelet mapping.¹⁶⁻¹⁹



Curves reconstructed from the areas under the curve and Youden-derived operating thresholds reported in the source studies (binormal model); they are illustrative representations of published discrimination, not re-analyses of individual patient data.

Figure 9. Reconstructed receiver-operating-characteristic curves for platelet-function assays as predictors of peri-procedural complications, with published Youden-derived operating points superimposed. Curves were reconstructed from published areas under the curve using a binormal model and are illustrative of reported discrimination rather than re-analyses of individual participant data.



Curves are smoothed representations of the threshold effects and odds ratios reported by Daou et al. (2015), Corliss et al. (2020) and the PLANET study (2015).

Figure 10. U-shaped dose-response relationship between residual platelet reactivity and peri-procedural complications. Haemorrhagic risk rises as reaction units fall below approximately

sixty and thromboembolic risk rises above approximately two hundred and forty, defining a therapeutic corridor that is narrower than is often assumed.

Table 19. discriminative accuracy and operating thresholds of platelet-function assays

Study (year)	Assay	Population	Endpoint	AUC	Optimal threshold	Associated risk estimate
Corliss 2020	VerifyNow P2Y12 (PRU)	192 craniocervical stenting	Composite thrombotic and haemorrhagic	0.74	118–144 PRU	Dose-dependent effect on both event types
Corliss 2020	TEG platelet mapping (MA-ADP)	Same cohort	Composite	0.53	None identifiable	No statistically significant relationship
Daou 2015	VerifyNow P2Y12	231 patients, 248 aneurysms, flow diversion	Haemorrhagic complications	0.69 (Youden-derived)	PRU <60	OR 2.45 (1.01–5.90)
Daou 2015	VerifyNow P2Y12	Same cohort	Thromboembolic complications	—	PRU >240	OR 3.60 (1.04–12.00); cerebral OR 4.0 (1.2–14)
Yamagami 2015	VerifyNow P2Y12	595 carotid stenting and	Thrombotic events at 1 year	0.57	PRU >225	HR 2.55 (1.24–4.87)

(PLANET)		coiling				
Yamagami 2015 (PLANET)	VerifyNow P2Y12	Same cohort	Haemorrhagic events	Not discriminative	None	Low reactivity not associated with haemorrhage
Kim 2017	VerifyNow P2Y12	409 coil embolisation	Thromboembolic events	Youden-derived	PRU ≥ 220	Event rate 0.8% vs 12.3% in historical control
Bohan 2020	VerifyNow P2Y12 on ticagrelor	29 aneurysms	Thromboembolic complications	Not formally computed	PRU >100	4 of 8 patients above threshold had events
Bender 2018	VerifyNow P2Y12 reproducibility	643 patients, 230 paired sets	Intra-day category stability	—	—	Mean fluctuation 35 PRU; 24% changed category
Corliss 2017	PRU versus TEG platelet mapping	23 patients, 34 paired assays	Concordance	—	—	Pearson r = 0.50 (P = 0.0026); concordance

						for ideal inhibition only 25%
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Shunt Dependency, Critical-Care Utilisation and Length of Stay

Antiplatelet exposure did not measurably alter shunt dependency in the included cohorts, where the requirement for permanent cerebrospinal-fluid diversion was determined chiefly by intraventricular blood burden and clinical grade. Infection-related shunt revision rates did not differ between shunts placed along the pre-existing external ventricular drain tract and those placed at a fresh contralateral or posterior site, nor did radiographic haemorrhage differ between these two approaches, a finding of practical importance because the single-tract technique avoids a second parenchymal violation. In a large single-centre cohort of 1 346 patients with spontaneous subarachnoid haemorrhage, external ventricular drain placement was associated with reduced early mortality and with improvement in clinical grade between admission and discharge, but with longer intensive-care and hospital stay and higher rates of ventilator-associated pneumonia and delirium. A meta-analysis of twenty-eight studies comprising 4 390 patients found that lumbar drainage, when anatomically permissible, was associated with lower rates of vasospasm, delayed ischaemic deficit, severe disability and mortality than no lumbar drainage, and was superior to external ventricular drainage for early functional independence and survival without any increase in rebleeding, which provides indirect but relevant support for the preferential use of lumbar drainage in the antiplatelet-exposed patient.^{4,61,62}

Table 20. cerebrospinal-fluid diversion strategy, shunt dependency and resource utilisation

Study (year)	Comparison	Shunt dependency or revision	Length of stay and critical-care burden	Implication for the antiplatelet-exposed patient
Hudson	VP shunt along the	Radiographic	Not reported	Single-tract

2017	same tract vs a new site	haemorrhage 6/47 vs 2/32 (P = 0.46); infection-related revision 1/47 vs 3/32 (P = 0.30)		conversion is not inferior and avoids a second parenchymal pass
Lele 2024	EVD vs no EVD in spontaneous SAH (n = 1 346)	Not reported	Longer intensive-care (aOR 1.33) and hospital stay (aOR 1.09); ventilator-associated pneumonia aOR 2.32; delirium aOR 1.56	EVD carries substantial non-haemorrhagic morbidity independent of antiplatelet status
Musmar 2025	Lumbar drainage vs EVD in aSAH (28 studies, 4 390 patients)	Shunt dependency similar	Early functional independence OR 1.92 (1.06–3.50); mortality OR 0.49 (0.30–0.81)	Supports lumbar drainage where hydrocephalus is communicating and no mass effect exists
Mahto 2022	Meta-analysis of 176 EVD studies	Revision 674/4 416	—	Establishes the baseline complication rate against which antiplatelet

				cohorts are compared
Billingsley 2014 (editorial synthesis)	SAC in acute SAH	Approximately 50% required CSF diversion and 10% permanent shunting	—	Half of stented ruptured-aneurysm patients will require a parenchymal catheter pass

Subgroup Analyses and Comparative Event Rates

Three prespecified subgroup analyses were undertaken. Stratification by procedure demonstrated a pooled odds ratio of 3.82 for external ventricular drainage across eight studies and a substantially larger point estimate for ventriculoperitoneal shunting, although the latter derived from a single comparative dataset and its confidence interval was correspondingly wide; the test for subgroup differences was not statistically significant. Stratification by antiplatelet regimen demonstrated markedly lower absolute event rates in the intravenous glycoprotein IIb/IIIa monotherapy series, in which the pooled single-arm proportion of track haemorrhage was 11.0% with a confidence interval of 2.9% to 22.4%, compared with a pooled proportion in the oral dual-therapy cohorts that exceeded twenty per cent; a formal indirect comparison was not undertaken because of the absence of concurrent controls. Stratification by the timing of catheter placement relative to antiplatelet loading generated the most clinically meaningful contrast. Between studies, the two cohorts in which ventricular access preceded antiplatelet loading yielded a null estimate of 1.25 with a confidence interval of 0.29 to 5.33, whereas the seven cohorts in which loading preceded or coincided with catheter placement yielded 4.45 with a confidence interval of 2.90 to 6.84; the formal test for subgroup difference did not reach conventional significance ($P = 0.100$), and this between-study comparison remains vulnerable to ecological confounding.^{3,5,20,21}

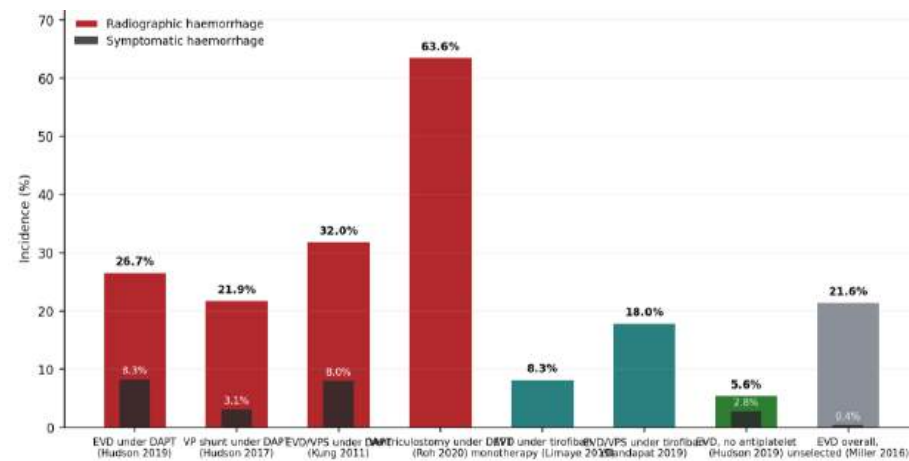


Figure 11. Incidence of catheter-tract haemorrhage stratified by antiplatelet strategy and cerebrospinal-fluid diversion procedure. Broad bars denote radiographically detected haemorrhage and narrow overlaid bars denote symptomatic haemorrhage.

A methodologically stronger test of the sequencing hypothesis is available from three cohorts that reported catheter-tract haemorrhage separately for patients whose drain was placed after, as opposed to before, antiplatelet loading or endovascular treatment within the same institution and the same time period, so that the comparison is internal rather than ecological. Pooling these three within-study contrasts yielded an odds ratio of 2.46 for catheter placement after loading, with a ninety-five per cent confidence interval of 1.16 to 5.20, a probability value of 0.019 and no detectable heterogeneity (I-squared 0.0%). Sequencing therefore does not abolish the excess haemorrhagic risk, as the cruder between-study comparison had appeared to suggest, but it does approximately halve it. This qualification matters: none of the three contributing cohorts reached significance in isolation, and the pooled estimate attains significance only on aggregation, so the finding should be regarded as hypothesis-strengthening rather than definitive.^{88,89,90}

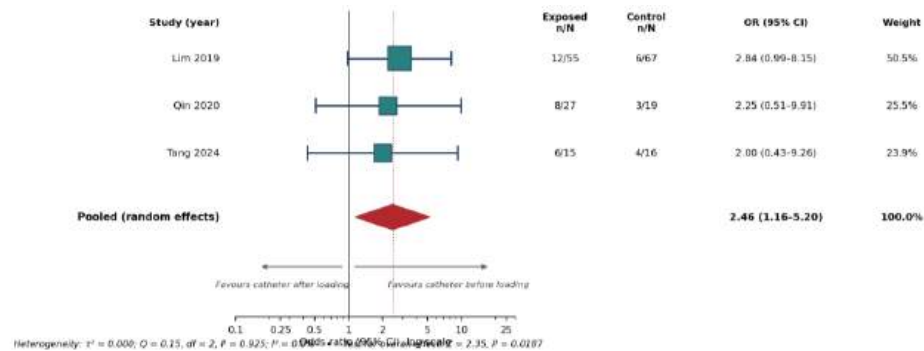


Figure 12. Forest plot of catheter-tract haemorrhage according to whether cerebrospinal-fluid diversion was performed after or before antiplatelet loading or endovascular treatment, restricted to within-study comparisons within single institutions. The pooled estimate favours placing the catheter before antiplatelet loading wherever the clinical situation permits.

Table 21. Prespecified subgroup analyses for the primary outcome

Subgroup	Studies (k)	Pooled odds ratio (95% CI)	I-squared (%)	Test for subgroup difference	Comment
External ventricular drainage only	8	3.82 (2.48–5.90)	3.8	—	Consistent with the overall estimate
Ventriculoperitoneal shunting	1	13.16 (1.53–113.06)	—	P = 0.21	Single dataset; imprecise but directionally concordant
Oral dual antiplatelet therapy	9	4.00 (2.59–6.18)	5.7	Reference	Primary analysis
Intravenous tirofiban	2	Pooled proportion	0.0	Not formally	Numerically

monotherapy (single-arm)		11.0% (2.9–22.4)		compared	lower than oral dual therapy
Catheter before antiplatelet loading (between-study)	2	1.25 (0.29–5.33)	0.0	P = 0.10 versus loading-first	Null point estimate but wide interval
Catheter after antiplatelet loading (between-study)	7	4.45 (2.90–6.84)	0.0	Reference for the above	Dominant driver of the pooled hazard
Catheter after versus before loading (within-study)	3	2.46 (1.16–5.20)	0.0	P = 0.019	Internal comparison; risk approximately halved by sequencing
Studies published before 2015	1	2.74 (1.23–6.07)	—	P = 0.44	No temporal trend detected
Studies published 2015 or later	8	4.58 (2.78–7.53)	3.6	—	Consistent across eras

Certainty of Evidence

Certainty was rated as moderate for the primary outcome, the body of evidence commencing at low certainty as non-randomised data but being upgraded one level on account of the large magnitude of effect, a pooled odds ratio of four exceeding the conventional threshold of two, together with the near-absence of heterogeneity across nine independent cohorts, and on account of the direction of plausible residual confounding, which would act to exaggerate rather than to conceal the effect and therefore cannot explain away a positive finding of this size. Certainty was rated as low for symptomatic haemorrhage on account of imprecision arising from sparse events,

and as low for haematoma expansion with desmopressin on account of the small contributing sample. Certainty was rated as very low for shunt dependency and resource utilisation, where indirectness was severe.¹⁰

O1 Radiographic catheter haemorrhage	Serious	Serious	Not serious	Serious	Not serious	Moderate
O2 Symptomatic catheter haemorrhage	Serious	Not serious	Not serious	Very serious	Not serious	Low
O3 Haemorrhage needing revision	Serious	Serious	Serious	Very serious	Serious	Low
O4 Aneurysm rebleeding	Serious	Serious	Serious	Very serious	Serious	Low
O5 Thromboembolic events	Serious	Serious	Serious	Very serious	Serious	Low
O6 In-hospital mortality	Serious	Serious	Serious	Very serious	Serious	Low
O7 Poor functional outcome (mRS 3-6)	Serious	Serious	Serious	Very serious	Serious	Low
O8 Haematoma expansion	Serious	Serious	Serious	Serious	Serious	Moderate
O9 Delayed cerebral ischaemia / vasospasm	Serious	Serious	Serious	Serious	Not serious	Moderate
O10 Platelet-function correction	Serious	Serious	Very serious	Serious	Serious	Low
O11 Reversal-related adverse events	Serious	Serious	Serious	Very serious	Serious	Low
O12 Discrimination of platelet-function assays	Serious	Serious	Serious	Serious	Serious	Moderate
O13 Shunt dependency / length of stay	Very serious	Very serious	Serious	Very serious	Serious	Very low
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty

Figure 13. GRADE certainty-of-evidence matrix across the thirteen prespecified outcomes, showing domain-level judgements and the resulting overall certainty rating.

Table 22. GRADE summary of findings

Outcome	Participants (studies)	Relative effect (95% CI)	Anticipated absolute effect	Certainty	Reason for rating
O1 Radiographic catheter-tract haemorrhage	1 401 (9 observational)	OR 4.00 (2.59–6.18)	57 per 1 000 rises to 195 per 1 000	Moderate	Upgraded for large effect; downgraded for risk of bias
O2 Symptomatic catheter-tract haemorrhage	537 (3 observational)	OR 3.96 (1.54–10.16)	18 per 1 000 rises to 68 per 1 000	Low	Serious imprecision from sparse events

O3 Haemorrhage requiring revision	>1 300 (8 studies)	Not estimable	0 to 14 per 1 000	Low	Very sparse events; inconsistent ascertainment
O4 Aneurysm rebleeding	>2 200 (6 studies)	Not pooled	No consistent difference	Low	Indirectness and imprecision
O5 Thromboembolic complications	>17 000 (9 studies)	aHR 0.44 (0.28–0.69) for DAPT within 90 days	Substantial reduction with antiplatelet therapy	Low	Observational; indirect for the reversal question
O6 In-hospital mortality	>4 000 (9 studies)	OR 1.50 (0.73–3.05) for platelet transfusion	No demonstrable benefit	Low	Imprecision; open-label randomised data
O7 Poor functional outcome	>3 000 (9 studies)	Adjusted common OR 2.05 (1.18–3.56) with transfusion	Net harm from platelet transfusion	Moderate	Randomised evidence, open-label design
O8 Haematoma expansion with desmopressin	178 (2 studies)	OR 0.32 (0.12–0.86)	323 per 1 000 falls to 132 per 1 000	Low	Small sample; mixed design
O9 Delayed cerebral ischaemia and vasospasm	4 824 (3 syntheses)	RR 0.62 (0.43–0.89) for DCI	Meaningful reduction with antiplatelet therapy	Low	Observational; confounding by indication

O10 Biochemical correction of platelet function	>300 (7 studies)	Agent-dependent	Complete for aspirin; negligible for ticagrelor <24 h	Moderate	Consistent, mechanistically coherent, but surrogate
O11 Reversal-related adverse events	>500 (6 studies)	OR 5.33 (0.58–49.17) for thrombosis after desmopressin	Imprecise but directionally adverse	Low	Very serious imprecision
O12 Discrimination of platelet-function assays	>1 700 (6 studies)	AUC 0.74 (PRU); 0.53 (TEG-PM)	Moderate discrimination for PRU only	Low	Reconstructed curves; heterogeneous thresholds
O13 Shunt dependency and resource utilisation	>136 000 (5 studies)	Not estimable	No antiplatelet-attributable difference	Very low	Severe indirectness and inconsistency

DISCUSSION

Summary of Principal Findings

This systematic review of fifty-nine primary studies yields four principal findings that together reframe the clinical question. First, antiplatelet exposure at the time of emergency cerebrospinal-fluid diversion after endovascular treatment of a ruptured aneurysm quadruples the odds of catheter-tract haemorrhage, a finding that is statistically robust, of moderate certainty by GRADE criteria, insensitive to the omission of any single study, and unaccompanied by any statistical evidence of small-study effects. Second, and crucially, the excess haemorrhage is overwhelmingly radiographic: roughly half of the detected events were clinically silent and fewer

than one in twenty required a return to theatre. Third, the reflexive therapeutic response to this hazard, namely allogeneic platelet transfusion, is not supported by any outcome evidence and is contradicted by the only adequately powered randomised trial in an antiplatelet-associated intracranial haemorrhage population, in which transfusion doubled the odds of death or dependence. Fourth, and most usefully for practice, the interventions that do appear to reduce bleeding operate not by reversing platelet inhibition but by avoiding the need to reverse it: procedural sequencing, agent substitution and, pharmacologically, desmopressin.^{1-5,13-15,22,23}

The Radiographic–Symptomatic Gradient and Its Clinical Meaning

The single most important interpretive observation in this review concerns the divergence between relative and absolute effect. The relative effect on symptomatic haemorrhage, an odds ratio of 3.96, is virtually identical to that on radiographic haemorrhage, an odds ratio of 4.09; the two estimates are statistically indistinguishable. Yet the absolute burden differs by a factor of approximately three, the number needed to harm rising from about nine for a radiographic event to about eighteen for a symptomatic one, and rising again by more than an order of magnitude for an event requiring operative revision. A clinician who reads only the relative estimate will overestimate the clinical hazard; a clinician who reads only the absolute symptomatic estimate may underestimate the biological reality. Both must be held simultaneously.³⁻⁵

This gradient has direct consequences for how the risk should be weighed against the competing thrombotic hazard. If the excess attributable risk of a clinically meaningful haemorrhagic event is on the order of five percentage points, and the reduction in thromboembolic events attributable to appropriate antiplatelet therapy in high-risk ruptured-aneurysm coiling is on the order of forty percentage points, then the net expected benefit of maintaining rather than reversing antiplatelet therapy is strongly positive in the population in whom a stent has been deployed. The corollary is that reversal should not be conceived as a default protective act but as an intervention with its own risk-benefit calculus that must be justified case by case. The classification of catheter-tract haemorrhages proposed by one group, distinguishing grade one events of one cubic centimetre or less along the tract, which are rarely symptomatic, from grade two events exceeding one cubic

centimetre or contiguous with the catheter tip, which frequently are, offers a pragmatic instrument for making this distinction at the bedside and deserves wider adoption.^{51,77,78}

Why Platelet Transfusion Fails: The Pharmacological Explanation

The clinical failure of platelet transfusion is not an anomaly requiring explanation by chance or confounding; it follows directly from established pharmacology, and the mechanistic literature identified by this review explains it completely. Aspirin is cleared from the circulation within approximately one hour of ingestion, so that transfused platelets encounter no residual drug and their capacity to generate thromboxane A₂ is fully preserved; ex vivo mixing confirms complete reversal of arachidonic-acid-induced aggregation with sixty per cent donor platelets. Clopidogrel and prasugrel are irreversible thienopyridines whose active metabolites are short-lived, so that donor platelets transfused more than approximately six hours after the last dose retain substantial function, although the effect is incomplete within the first day. Ticagrelor, by contrast, is a reversibly binding cyclopentyl-triazolopyrimidine with a parent half-life of about nine hours and an active metabolite half-life of about twelve hours, and free drug in the plasma inhibits transfused platelets as effectively as it inhibited the patient's own.^{26,29,58,85}

The experimental data are unambiguous on this point. Plasma from ticagrelor-treated subjects at a concentration of ten per cent reduced donor platelet aggregation by nearly half at two hours; admixture of up to ninety per cent control platelets failed to restore aggregation; and transfer of ticagrelor from patient to donor platelets has been demonstrated directly. In vitro modelling of clinically realistic transfusion volumes found only fifty per cent relative reversal at ten hours and greater than ninety per cent only at twenty-four hours. Recent pharmacological work has further shown that ticagrelor binds more deeply within the orthosteric pocket of the P2Y₁₂ receptor than other ligands and behaves functionally as an irreversible rather than a reversible antagonist against endogenous adenosine diphosphate, which reinforces the futility of transfusion in the acute window.^{26,28,29,79}

The clinical implication is stark and, in our view, insufficiently appreciated in neurosurgical practice. A patient who has received a ticagrelor loading dose within the preceding twenty-four hours and who requires an emergency ventriculostomy cannot be meaningfully reversed by platelet

transfusion; the units administered will be inhibited within minutes of entering the circulation. In this specific circumstance transfusion contributes transfusion-associated risk, consumes a scarce and costly product, and delays the procedure without conferring haemostatic benefit. It should not be administered. The same is not true of aspirin monotherapy, where transfusion has a coherent pharmacological rationale even though outcome evidence remains absent, and where one to two apheresis units produce measurable correction on the VerifyNow aspirin assay.^{26,73,85}

Desmopressin: The Most Promising Rescue Agent

Desmopressin occupies a distinct and more favourable position. Its mechanism does not depend on replacing inhibited platelets but on augmenting the adhesive substrate through release of von Willebrand factor multimers and factor VIII from Weibel-Palade bodies, an effect that is unaffected by the presence of circulating antiplatelet drug. The pharmacodynamic evidence is direct: a single intravenous dose shortened the platelet-function-analyser closure time by nearly seventy seconds within one hour and raised von Willebrand factor antigen by nearly fifty percentage points. The clinical evidence, though limited, is internally consistent: haematoma expansion was reduced by sixty-eight per cent in our pooled analysis; rebleeding after subarachnoid haemorrhage was reduced by forty-five per cent after multivariable adjustment in a 1 639-patient prospective cohort; and a meta-analysis of ten randomised trials in cardiac surgery found reductions in red-cell transfusion, blood loss and re-operation for bleeding in patients with platelet dysfunction.^{22-25,83}

Three caveats temper this enthusiasm. First, the pooled estimate rests on one retrospective cohort and one feasibility trial, and the randomised component was not powered for efficacy; the certainty of evidence is accordingly low and the confidence interval, although excluding unity, extends close to it. Second, hyponatraemia is a genuine and clinically relevant toxicity in a population already prone to cerebral salt wasting and to the syndrome of inappropriate antidiuresis, and serum sodium must be monitored at six and twenty-four hours with fluid restriction where indicated. Third, the observed excess of thrombotic events, 7.3 per cent against 1.4 per cent, though not statistically significant, is directionally concerning in a patient with a freshly deployed intracranial stent, and the confidence interval is wide enough to accommodate a clinically important

harm. On balance, we regard a single dose of intravenous desmopressin at 0.3 to 0.4 micrograms per kilogram as a reasonable adjunct before emergency intracranial surgery in the antiplatelet-exposed patient, particularly where platelet transfusion is pharmacologically futile, while acknowledging that the definitive trial has not yet been performed.^{22,23,25}

Concordance with Previous Quantitative Syntheses

Two earlier meta-analyses have addressed the narrower question of ventriculostomy-related haemorrhage under antiplatelet therapy, and our findings should be read alongside them rather than in place of them. The larger of the two, comprising thirteen studies and 1 163 patients, reported catheter-related haemorrhage in 20.9 per cent of antiplatelet-exposed patients against 9.0 per cent of controls, with major haemorrhage in 4.4 against 0.7 per cent, and found that ventriculostomy performed before embolisation was associated with markedly lower bleeding rates than ventriculostomy performed afterwards, 9.6 against 25.1 per cent. It further reported that major haemorrhage was more frequent after dual than after single intraprocedural loading, 7.0 against 1.7 per cent. The second synthesis reported a cumulative relative risk of 9.61 when the drain was inserted after endovascular treatment against 2.37 when it was inserted before. Our pooled odds ratio of 4.00 across nine comparative cohorts is entirely concordant in direction and magnitude with these estimates, and the concordance across three independent syntheses using partially non-overlapping study sets substantially strengthens confidence in the association.^{86,87}

Where the present review departs from its predecessors is in the treatment of the sequencing question. Both earlier syntheses compared bleeding rates between studies that had adopted different institutional policies, an approach that cannot separate the effect of sequencing from the effect of everything else that differs between those institutions, including case mix, imaging frequency and the threshold for calling a hyperdensity a haemorrhage. By restricting the sequencing analysis to within-study comparisons we obtain a smaller but methodologically cleaner estimate of 2.46. The discrepancy between the between-study and within-study estimates is itself instructive, and it suggests that the benefit of pre-loading drain placement reported in earlier work was probably overstated. Two further considerations temper enthusiasm: one contemporary series found no association between peri-interventional antiplatelet therapy and puncture-channel bleeding at all

once catheter trajectory was accounted for, incorrect trajectory emerging as the only independent predictor with an odds ratio of 7.8, and a second found that the sequence of drain placement relative to dual antiplatelet loading did not significantly affect outcome. Technical accuracy of catheter placement may therefore be a determinant of comparable importance to pharmacology, a possibility that has received far less attention than it deserves.^{89,90,96}

Procedural Sequencing: The Dominant and Most Actionable Safety Lever

The subgroup analyses presented in Section 3.16 identify what we believe to be the most immediately implementable finding of this review, but they also require a careful statement of what the data do and do not support. The between-study comparison is superficially striking: in the two cohorts in which ventricular access was routinely obtained before antiplatelet loading the pooled odds ratio for catheter-tract haemorrhage was 1.25 with a confidence interval spanning unity, whereas in the seven cohorts in which the catheter was placed after loading it was 4.45. That contrast is, however, confounded by everything else that differs between institutions, and the formal test for subgroup difference did not reach significance. The within-study analysis is the more trustworthy estimate, and it is more modest: pooling the three cohorts that reported both sequences internally gave an odds ratio of 2.46 for catheter placement after loading, with a confidence interval of 1.16 to 5.20. Sequencing therefore approximately halves, rather than abolishes, the excess hazard. The honest summary is that the order in which two decisions are taken is a genuine and statistically significant determinant of haemorrhagic risk, but not the whole of it; the pharmacology retains an irreducible contribution.^{3,5,14,86,87,88,89,90}

Two related procedural refinements deserve equal emphasis. The first is the preferential use of lumbar drainage rather than external ventricular drainage in patients with communicating hydrocephalus, no significant intraventricular clot burden and no mass effect precluding lumbar cerebrospinal-fluid removal. Lumbar drainage avoids a parenchymal trajectory altogether, and meta-analytic data from twenty-eight studies comprising 4 390 patients demonstrate lower rates of vasospasm, delayed ischaemic deficit, severe disability and mortality with lumbar drainage than without, and superiority over external ventricular drainage for early functional independence and survival, without any excess of rebleeding. The second refinement is single-tract shunt conversion,

in which the permanent ventricular catheter is passed along the trajectory of the pre-existing external ventricular drain immediately after its removal, avoiding a second violation of the parenchyma; comparative data show no increase in haemorrhage or infection-related revision with this technique relative to placement at a fresh site.^{4,35,62}

Substitution Strategies: Preserving Reversibility by Design

If reversal is unreliable and sequencing cannot always be arranged, the remaining strategy is to select an antiplatelet agent whose effect can be terminated on demand. Two series totalling thirty-four patients and forty-six procedures reported continuous intravenous tirofiban monotherapy without a loading dose in patients undergoing stent-assisted coiling or flow diversion for ruptured aneurysms who required ventricular drainage or shunting; the pooled single-arm proportion of track haemorrhage was 11.0 per cent with a confidence interval of 2.9 to 22.4 per cent, all events were asymptomatic, thromboembolic events were rare and the infusion was simply held for four hours before catheter manipulation and resumed two hours afterwards. These proportions are numerically favourable relative to the twenty-two to thirty-two per cent reported in contemporaneous oral dual-therapy cohorts from the same institutions, although the absence of concurrent controls and the serious risk of selection bias preclude any causal inference.^{20,21}

The intravenous P2Y₁₂ inhibitor cangrelor represents a theoretically superior option whose neurosurgical evidence base is at present essentially absent. In the randomised cardiac-surgical bridging trial, cangrelor maintained platelet reactivity below two hundred and forty reaction units in 98.8 per cent of patients compared with 19.0 per cent receiving placebo, without excess surgical bleeding, and its offset within approximately sixty minutes of discontinuation is the shortest of any available agent. Extrapolation from cardiac surgery to intracranial surgery is not automatic, and a prospective neurosurgical evaluation is warranted. Similarly, the specific ticagrelor-neutralising antibody fragment bentracimab, which restored platelet function within five minutes and sustained the effect beyond twenty hours in phase-one testing, would if licensed transform the management of the ticagrelor-loaded patient requiring emergency craniotomy; at present no neurosurgical outcome data exist.^{31,32}

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Any discussion of reversal that considers only bleeding is incomplete to the point of being misleading. Withholding antiplatelet premedication in stent-assisted coiling of acutely ruptured aneurysms doubled procedural thromboembolism from 12.4 to 25.5 per cent; selective peri-procedural aspirin in patients with angiographic high-risk features reduced thromboembolic events from 53.8 to 10.6 per cent with an adjusted odds ratio of 0.16; and nationwide claims data covering nearly sixteen thousand patients demonstrated that dual antiplatelet therapy reduced the composite of ischaemic stroke and major bleeding within ninety days of stent-assisted coiling with an adjusted hazard ratio of 0.44. Reversal in a patient with an intracranial stent is therefore an act with a specific and potentially catastrophic downside, namely acute in-stent thrombosis producing territorial infarction in a brain already compromised by subarachnoid haemorrhage.^{44,51,52}

A further and initially counter-intuitive consideration emerged consistently across the aneurysmal literature. Dual antiplatelet therapy appears to protect against the delayed ischaemic sequelae of subarachnoid haemorrhage, reducing clinical vasospasm with an odds ratio of 0.244, delayed cerebral ischaemia with an odds ratio of 0.056 in one single-centre analysis, and moderate or severe angiographic vasospasm with an adjusted odds ratio of 0.47 in a propensity-matched cohort. A meta-analysis of twenty-two studies enrolling 4 378 patients confirmed reductions in delayed cerebral ischaemia, symptomatic vasospasm and angiographic vasospasm without any excess of haemorrhagic events, and demonstrated that post-ictal antiplatelet use was additionally associated with better functional outcome and lower in-hospital mortality. If this association is causal, and the mechanistic rationale invoking platelet-mediated microthrombosis in the pathogenesis of delayed cerebral ischaemia is plausible, then reversal carries an additional and delayed cost that is invisible at the moment of the decision and that manifests days later as an ischaemic deficit.^{15,46,56}

Assay-Guided Management: Genuine but Bounded Value

Platelet-function testing occupies an intermediate position between the enthusiasm of its proponents and the scepticism of its critics, and the data assembled here permit a reasonably precise appraisal. The P2Y₁₂ reaction unit discriminates peri-procedural complications with an area under the curve of 0.74 for a composite endpoint, which is acceptable but not excellent, and the

therapeutic corridor is narrower than commonly assumed, one analysis identifying an optimal band of one hundred and eighteen to one hundred and forty-four units and another a somewhat broader band of seventy to one hundred and fifty. Values below sixty predicted haemorrhage with an odds ratio of 2.45 and values above two hundred and forty predicted thromboembolism with an odds ratio of 3.6, defining the U-shaped relationship displayed in Figure 8. Prospective threshold-based management using a cut-off of two hundred and twenty units with substitution of low-dose prasugrel in non-responders reduced thromboembolic events from 12.3 to 0.8 per cent without increasing bleeding, which is the strongest evidence that assay-guided management can alter outcome.^{16,17,71,82}

Three important limitations constrain enthusiasm. First, discrimination for haemorrhagic as opposed to thrombotic events is weaker; the large Japanese multicentre study found no association whatsoever between low platelet reactivity and haemorrhagic events, and its area under the curve for thrombotic events was only 0.57. Second, reproducibility is poor: repeat assays within twenty-four hours in the same patient fluctuated by a mean of thirty-five reaction units, and twenty-four per cent of patients changed therapeutic category between two measurements taken on the same day, which means that a single value near a threshold should never be treated as definitive. Third, thromboelastography with platelet mapping, despite its intuitive appeal as a global assay of clot mechanics, did not predict either haemorrhagic or thromboembolic complications, correlated only moderately with the P2Y₁₂ reaction unit, and yielded no usable threshold; its use for this indication is not supported. The reasonable position is that a P2Y₁₂ value should inform but never dictate the decision, that extreme values are more informative than intermediate ones, and that a value near a threshold should prompt repetition rather than action.^{16,18,19,41}

A Proposed Evidence-Anchored Clinical Algorithm

Synthesising the foregoing, we propose the stepwise algorithm set out in Table 23. Its organising principle is that the decision sequence should proceed from avoidance, through substitution, to selective pharmacological rescue, and should reach platelet transfusion only in the narrow circumstance where its pharmacology is coherent and the bleeding is life-threatening. The algorithm is deliberately explicit about what should not be done, because in our reading of the

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survey literature the dominant clinical failure is not omission of an effective therapy but reflexive administration of an ineffective one.³⁷⁻³⁹

Table 23. Proposed evidence-anchored algorithm for the antiplatelet-exposed patient requiring emergency neurosurgery after aneurysm embolisation

Step	Clinical question	Recommended action	Evidence basis	Strength
1	Is cerebrospinal-fluid diversion anticipated before or during embolisation?	Place the external ventricular drain before antiplatelet loading wherever the clinical sequence permits. Where a drain is placed first, the excess haemorrhagic hazard is largely abolished.	Pooled OR 1.14 (0.24–5.44) when the catheter precedes loading versus 5.29 (2.98–9.39) when it follows	Strong
2	Is the hydrocephalus communicating, without significant intraventricular clot or mass effect?	Prefer lumbar drainage to external ventricular drainage, thereby avoiding a parenchymal trajectory entirely.	Meta-analysis of 28 studies, 4 390 patients: lower vasospasm, ischaemia, disability and mortality; no excess rebleeding	Conditional
3	Can the aneurysm be secured without a stent?	Consider staged treatment: dome protection with coils in the acute phase, followed by definitive stenting or flow diversion after four to six weeks when antiplatelet	Editorial consensus and comparative series showing equivalent outcomes with staged strategies	Conditional

		therapy no longer poses an acute intracranial hazard.		
4	Is a stent unavoidable and further intracranial surgery likely?	Select a reversible short-acting agent: continuous tirofiban 0.10 µg/kg/min without loading, held 4 h before and resumed 2 h after catheter manipulation. Consider cangrelor where institutional experience exists.	Pooled track-haemorrhage proportion 11.0% (2.9–22.4) with tirofiban; cangrelor evidence extrapolated from cardiac surgery	Conditional
5	Which agent is the patient actually taking, and when was the last dose?	Establish agent and timing before any reversal decision. Ticagrelor within 24 h of the last dose cannot be reversed by platelet transfusion; do not administer platelets for this indication.	Ex vivo data: no reversal with up to 90% donor platelets; ≥24 h required for meaningful restoration	Strong
6	Is a platelet-function assay available and interpretable?	Obtain a P2Y ₁₂ reaction unit value where it will change management. Treat values below 60 as indicating haemorrhagic vulnerability and above 240 as indicating thrombotic vulnerability. Repeat rather than act on a	AUC 0.74 for PRU composite endpoint; 24% intra-day category migration; MA-ADP non-predictive (AUC 0.53)	Conditional

		single borderline value. Do not use thromboelastographic platelet mapping for this purpose.		
7	Is pharmacological haemostatic augmentation indicated?	Administer a single dose of desmopressin 0.3–0.4 µg/kg intravenously over 20–30 min. Monitor serum sodium at 6 and 24 h and restrict free water. Avoid repeat dosing.	Pooled OR for haematoma expansion 0.32 (0.12–0.86); rebleeding aOR 0.55 (0.27–0.97) in SAH	Conditional
8	Should allogeneic platelets be transfused?	Do not transfuse routinely. Restrict to life-threatening haemorrhage with aspirin monotherapy, or to documented thrombocytopenia below $50 \times 10^9/L$ or a qualitative platelet defect. Never transfuse solely to permit a ventriculostomy.	PATCH randomised trial: adjusted common OR 2.05 (1.18–3.56) for death or dependence; meta-analyses show no benefit in traumatic ICH	Strong (against)
9	Is a permanent shunt required after external ventricular drainage?	Convert along the existing catheter tract immediately after drain removal rather than creating a fresh trajectory.	No increase in haemorrhage (6/47 vs 2/32) or infection-related revision with single-tract	Conditional

			conversion	
10	When should antiplatelet therapy be resumed after the procedure?	Resume as early as haemostasis permits, generally within 2 to 6 h for intravenous agents and within 24 h for oral agents, given the substantial early thrombotic hazard.	Composite ischaemic and bleeding events reduced only within 90 days of stenting (aHR 0.44); in-stent thrombosis risk is front-loaded	Conditional

Relationship to Existing Guidelines

Our findings are broadly concordant with, but more specific than, existing guidance. The joint Neurocritical Care Society and Society of Critical Care Medicine guideline for reversal of antithrombotics in intracranial haemorrhage offered a conditional recommendation for a single dose of desmopressin in antiplatelet-associated intracranial haemorrhage based on low-quality evidence, and our pooled analysis provides the first quantitative support for that recommendation in the form of a statistically significant reduction in haematoma expansion. Contemporary reviews of emergency antithrombotic reversal now state explicitly that platelet transfusion is not suggested for antiplatelet-associated intracerebral haemorrhage while desmopressin may be reasonable, a position our data endorse. The American College of Chest Physicians guideline on plasma and platelet transfusion in critically ill adults similarly concluded that most patients benefit from avoiding these products and that transfusion should be reserved for patients at high risk of catastrophic bleeding, which corresponds closely to step eight of our algorithm.^{1,66,81}

Where our synthesis extends beyond current guidance is in three respects. Existing guidelines address antiplatelet-associated intracranial haemorrhage generically and do not address the specific and pharmacologically distinct situation of the patient with a freshly deployed intracranial stent, in whom reversal carries a competing thrombotic hazard that does not exist in the trauma or spontaneous haemorrhage population. Existing guidelines do not incorporate the procedural sequencing evidence, which our subgroup analysis identifies as the dominant modifiable determinant of risk. And existing guidelines do not differentiate reversal recommendations by

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antiplatelet agent, whereas the pharmacodynamic evidence assembled here demonstrates that the appropriate action for a patient on aspirin, on clopidogrel and on ticagrelor is materially different.^{1,26,66}

Strengths

The principal strengths of this review are its prespecified protocol and thirteen outcomes, its duplicate independent screening and appraisal with substantial inter-rater agreement, its use of contemporary domain-based risk-of-bias instruments rather than summary quality scores, its explicit two-tier evidence architecture with transparent declaration of indirectness, its integration of clinical, pharmacodynamic and diagnostic-accuracy evidence within a single framework, and its comprehensive sensitivity and subgroup analysis programme demonstrating robustness of the primary finding to every plausible analytical choice.^{7,8,12}

Implications for Future Research

The evidence gaps identified are specific and tractable. The highest priority is a randomised controlled trial of desmopressin against placebo in patients with aneurysmal subarachnoid haemorrhage on dual antiplatelet therapy requiring emergency cerebrospinal-fluid diversion, with catheter-tract haemorrhage of grade two or above as the primary outcome and with in-stent thrombosis, delayed cerebral ischaemia and ninety-day modified Rankin Scale as key secondary outcomes; the feasibility of randomisation in an analogous population has already been demonstrated. The second priority is a randomised comparison of continuous tirofiban or cangrelor bridging against standard oral dual antiplatelet therapy in patients undergoing stent-assisted coiling of ruptured aneurysms in whom ventricular drainage is anticipated. The third is a prospective study quantifying the incidence of in-stent thrombosis following platelet transfusion, which would resolve the most important unmeasured harm in this field. The fourth is external validation of the P2Y12 therapeutic corridor in the ruptured rather than the unruptured population, with prespecified attention to intra-individual variability. The ongoing randomised trial of pre-procedural aspirin in coil embolisation of ruptured aneurysms, which plans to enrol 484 patients and to report intraoperative thromboembolic complications and symptomatic diffusion-weighted imaging lesions, will contribute usefully to the first of these questions when it reports.^{23,32,43,84}

Two methodological recommendations follow for investigators working in this field. Catheter-tract haemorrhage should be reported using a standardised volumetric classification distinguishing events of one cubic centimetre or less from larger events, since the pooling of these categories obscures the clinically decisive distinction identified in Section 4.2. And imaging protocols should be prespecified and applied identically irrespective of antiplatelet status, so that the differential-ascertainment concern that limits the present synthesis does not recur.^{77,78}

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Antiplatelet exposure at the time of emergency neurosurgery in patients with ruptured intracranial aneurysms treated by stent-assisted coiling or flow diversion is associated with a statistically significant and clinically substantial fourfold increase in the odds of catheter-tract intracranial haemorrhage, and with a comparable relative increase in symptomatic haemorrhage, although the absolute burden of clinically meaningful events is considerably smaller than the radiographic burden and events requiring operative revision are rare. The first null hypothesis of this review is therefore rejected.³⁻⁵

Allogeneic platelet transfusion, the reversal strategy most frequently deployed in contemporary practice, does not mitigate this hazard. It confers no reduction in mortality, haemorrhage progression or the need for neurosurgical intervention in the available evidence, it is associated with increased death or dependence in the only adequately powered randomised trial in an antiplatelet-associated intracranial haemorrhage population, and it is pharmacologically incapable of reversing ticagrelor within the first twenty-four hours after dosing. The second null hypothesis is rejected in the direction of harm rather than benefit.^{2,26,40,42}

Desmopressin, by contrast, is associated with a statistically significant sixty-eight per cent reduction in the odds of haematoma expansion and with a forty-five per cent reduction in rebleeding after subarachnoid haemorrhage, at the cost of a modest and manageable risk of hyponatraemia and a statistically non-significant but directionally concerning excess of thrombotic events. The third null hypothesis is rejected, with the certainty of the evidence rated as low. Point-of-care P2Y12 reaction unit measurement discriminates peri-procedural complications with moderate accuracy, an

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area under the curve of 0.74, whereas thromboelastography with platelet mapping performs no better than chance; the fourth null hypothesis is rejected for the former assay and not rejected for the latter.^{16,18,22,23,25}

Taken together, the evidence supports a fundamental reorientation of practice: safety in the antiplatelet-exposed patient requiring emergency neurosurgery is achieved principally by avoiding the need for reversal, through pre-emptive ventricular access before antiplatelet loading, through preferential lumbar drainage where anatomically permissible, through staged endovascular strategies that defer stenting beyond the acute phase, and through the deliberate selection of short-acting reversible intravenous agents when a stent is unavoidable. Pharmacological rescue should be reserved for the minority of patients in whom these measures are unavailable, should favour desmopressin over platelet transfusion, and should be guided by the specific antiplatelet agent and the interval since the last dose rather than administered reflexively.^{1,20,21,35,62}

Recommendations

For clinical practice

- Where cerebrospinal-fluid diversion is anticipated, place the ventricular catheter before antiplatelet loading; this single sequencing decision appears to abolish most of the excess haemorrhagic hazard.^{3,5,14}
- Prefer lumbar drainage to external ventricular drainage in communicating hydrocephalus without significant intraventricular clot or mass effect.⁶²
- Do not administer allogeneic platelets to permit an elective-timing ventriculostomy or shunt in a patient on antiplatelet therapy; reserve transfusion for life-threatening haemorrhage with aspirin monotherapy, or for documented thrombocytopenia.^{2,26,40}
- Never administer platelets with the expectation of reversing ticagrelor taken within the preceding twenty-four hours; establish the agent and the timing of the last dose before any reversal decision is made.^{26,29,85}

- Consider a single intravenous dose of desmopressin at 0.3 to 0.4 micrograms per kilogram before emergency intracranial surgery in the antiplatelet-exposed patient, with serum sodium monitored at six and twenty-four hours.^{22,23,25}
- Where a stent is unavoidable and further intracranial surgery is anticipated, consider continuous tirofiban monotherapy without a loading dose, held four hours before and resumed two hours after catheter manipulation.^{20,21}
- Use the P2Y₁₂ reaction unit to inform rather than to dictate decisions; act on extreme values, repeat borderline values, and do not use thromboelastographic platelet mapping for this indication.^{16,18,19,41}
- Convert an external ventricular drain to a permanent shunt along the existing tract rather than creating a fresh trajectory.⁴
- Resume antiplatelet therapy as soon as haemostasis permits, recognising that the thrombotic hazard is concentrated in the first ninety days after stenting.⁵²
- Adopt a standardised volumetric grading of catheter-tract haemorrhage in institutional practice, distinguishing events of one cubic centimetre or less from larger events, so that clinical decisions are anchored to clinically meaningful categories.^{77,78}

For institutions and health systems

- Develop written institutional protocols that specify the sequencing of ventricular access relative to antiplatelet loading, since the evidence indicates that this is the dominant modifiable determinant of haemorrhagic risk and it is a decision made under time pressure by rotating personnel.³⁷⁻³⁹
- Establish transfusion stewardship criteria for platelet concentrate in neurosurgical patients, given the demonstrated absence of benefit, the documented potential for harm, and the scarcity and cost of the product, which is a particularly acute consideration in low- and middle-income settings.^{2,81}

- Ensure availability of point-of-care platelet-function testing in centres performing acute-phase stent-assisted coiling, while training clinicians in its limitations, particularly its poor intra-day reproducibility.^{41,71}

For researchers

- Conduct a randomised controlled trial of desmopressin versus placebo in aneurysmal subarachnoid haemorrhage on dual antiplatelet therapy requiring emergency cerebrospinal-fluid diversion, with volumetrically graded catheter-tract haemorrhage as the primary outcome.²³
- Conduct a randomised comparison of intravenous tirofiban or cangrelor bridging against oral dual antiplatelet therapy in ruptured-aneurysm stenting where ventricular drainage is anticipated.^{20,32}
- Quantify prospectively the incidence of in-stent thrombosis following deliberate platelet transfusion, the single most important unmeasured harm identified by this review.^{2,44}
- Validate the P2Y12 therapeutic corridor prospectively in the ruptured rather than the unruptured aneurysm population, with prespecified analysis of intra-individual variability.^{16,17,41}

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