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Antiplatelet Therapy Following Endovascular Treatment of Intracranial Aneurysms with Flow Diversion or Stent-Assisted Coiling: Protocol for an Umbrella Review of Systematic Reviews and Meta-Analyses

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ADMINISTRATIVE INFORMATION

Support - No support.

Review stage at the time of initial registration - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 November 2026 and was last updated on 6 November 2026.

INTRODUCTION

Review question / Objective The objective is to map, appraise and reconcile the systematic review evidence on antiplatelet management in endovascular aneurysm treatment, and to derive a research agenda. Four questions will be addressed.
Q1. Which decision dimensions of antiplatelet management are covered by existing systematic reviews, and with what primary-study base?
Q2. What is the degree of overlap within each dimension and across dimensions?
Q3. What is the methodological quality of each review, and what is the certainty of evidence for each outcome within each dimension?
Q4. Where are the gaps, and which primary studies would close them?.

Condition being studied Intracranial aneurysms are focal dilations of the cerebral arterial wall that are usually asymptomatic until they rupture, at which point they cause subarachnoid haemorrhage with high morbidity and mortality. They are increasingly treated by endovascular means: either by coil embolisation supported by a stent (stent-assisted coiling), or by deploying a flow-diverting stent across the aneurysm neck so that the parent artery is reconstructed and inflow into the sac is redirected. Both device types are thrombogenic and therefore obligate antiplatelet therapy, in practice usually dual therapy with aspirin plus a P2Y12 inhibitor, continued for a period that varies from several months to indefinite. The condition of interest in this review is accordingly not the unruptured or ruptured aneurysm in isolation, but the iatrogenic state created by its endovascular treatment: a patient maintained on antiplatelet therapy in whom under-treatment produces device thrombosis, thromboembolism and ischaemic stroke, while over-treatment produces intracranial or extracranial haemorrhage, and in whom the duration, intensity, choice of P2Y12 inhibitor and individualisation of that therapy all remain unresolved.A preliminary scoping search (Europe PMC, 6 November 2026) identified six systematic reviews with meta-analyses, each anchored on a different decision dimension. Their principal

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characteristics are summarised in Table 2. The duration question has been addressed directly by one review of seven studies and 17,380 patients, which pooled one randomised trial with six retrospective cohorts and compared short-term (six months or less) with long-term (more than six months) dual antiplatelet therapy, finding no difference in thromboembolic events (RR 1.18, 95% CI 0.42 to 3.30, I-squared 60.5 per cent) and fewer major bleeds with the shorter regimen (RR 0.54, 95% CI 0.32 to 0.91).

METHODS

Participant or population Adults aged 18 years or older with one or more intracranial aneurysms, ruptured or unruptured, who have undergone endovascular treatment with a flow-diverting stent or with stent-assisted coiling and who receive, or are planned to receive, antiplatelet therapy. No restriction by sex, ethnicity, aneurysm location or morphology (saccular, fusiform, blister-like or dissecting), aneurysm size, device generation, or whether the device is bare metal or surface modified. Patients treated by surgical clipping, by coiling without a stent, by parent-vessel occlusion, or by any strategy without antiplatelet therapy will be excluded, as will paediatric patients and patients treated for non-aneurysmal indications such as arteriovenous fistulae, carotid stenosis or extracranial atherosclerotic disease. Because this is an umbrella review, the unit of analysis is the published systematic review, but the population is specified at patient level so that every candidate review can be judged against a single standard.

Intervention Antiplatelet therapy given during and after endovascular treatment of an intracranial aneurysm with a flow-diverting stent or with stent-assisted coiling, defined at the level of the treatment strategy rather than the individual drug. Four dimensions will be mapped: (1) duration, covering short versus long, or fixed versus extended, regimens; (2) intensity, covering single antiplatelet therapy, dual antiplatelet therapy and triple or otherwise intensified regimens; (3) choice of agent, in particular clopidogrel versus ticagrelor or prasugrel, and the use of glycoprotein IIb/IIIa inhibitors such as tirofiban as bridging therapy; and (4) individualisation, meaning adjustment of the regimen according to platelet function testing or pharmacogenetic testing, together with alternative routes and timing of administration. Surface-modified flow-diverting devices designed to permit single antiplatelet therapy are included as a device-contingent variant of dimension 2. Both periprocedural and post-discharge strategies are eligible, and combination strategies that vary more than one dimension at once are retained rather than excluded.

Comparator Any alternative antiplatelet strategy against which the intervention is contrasted within an included review, differing in at least one of the four dimensions set out above. This comprises in practice: a longer against a shorter duration, or continued against discontinued therapy; dual or triple therapy against single therapy; one P2Y12 inhibitor against another, most often clopidogrel against ticagrelor or prasugrel; a platelet-function-testing-guided regimen against a fixed standard regimen; and bridging glycoprotein IIb/IIIa inhibition against oral antiplatelet therapy alone. Two conditions apply. First, no comparator is constructed by the review team: a systematic review qualifies only if it performs its own internal comparison, so pooled single-arm rates under one regimen are not accepted as evidence of a comparative effect. Second, where a review contrasts more than two strategies, every pairwise contrast it reports is recorded and tagged by the dimension it varies, so that a duration contrast and a drug contrast are never placed in the same cell of the evidence map.

Study designs to be included Systematic reviews and meta-analyses, including network meta-analyses, of quantitative studies in which two or more antiplatelet strategies are compared. Eligible syntheses may pool randomised trials, non-randomised comparative studies, or both; no restriction is placed on the underlying primary study designs, on the risk-of-bias instrument used, or on whether the synthesis was prospectively registered. A review must report a reproducible search strategy, an explicit eligibility statement and a quantitative synthesis of the strategies of interest. Two tiers are distinguished. Tier A comprises.

Eligibility criteria Additional criteria not already covered by the preceding items are as follows. (a) Publication status: peer-reviewed systematic reviews and meta-analyses are included; preprints are included only if they report a completed synthesis and carry a permanent identifier, and are flagged as such in the appraisal; conference abstracts, editorials and protocols without results are excluded. (b) Date: no lower limit; the search closes on 31 October 2026. (c) Language: no restriction. (d) A review addressing a broader population than endovascular aneurysm treatment remains eligible if it reports a subgroup matching the criteria above; the subgroup data are used and the review is flagged. (e) Where a review has been updated, the most recent version is used and the

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earlier version recorded but not counted separately. (f) No minimum methodological quality threshold is applied at inclusion; quality is appraised after inclusion so that the distribution of quality can itself be reported, which is one of the objectives of this review. (g) Overlap is measured, not used as an exclusion criterion; syntheses whose evidence base is wholly contained within another are presented as a single evidence node in the synthesis rather than excluded at screening. (h) Reviews published within the same calendar year, addressing the same dimension and reporting identical included-study lists, are examined for redundant publication and reported accordingly. (i) Tier assignment: a synthesis is assigned to the comparative tier if it generates at least one effect estimate between antiplatelet strategies, and to the single-arm tier if it reports only pooled rates under one strategy; where both are reported, it enters both tiers and the tier of each extracted estimate is recorded.

Information sources Bibliographic databases: PubMed/MEDLINE, Embase, Web of Science Core Collection, the Cochrane Database of Systematic Reviews within the Cochrane Library, and Scopus, each searched from inception to 31 October 2026. Verification and citation tracking: Europe PMC is used to confirm publication status, PMID and PMCID for every candidate record, and to perform forward citation tracking on reviews with overlapping evidence bases. Registers: PROSPERO and INPLASY are searched to identify ongoing and completed protocols and to check for duplicate or overlapping registrations; ClinicalTrials.gov is searched to identify the randomised trials that candidate reviews rely on, so that the completeness of the randomised component of the evidence base can be judged. Supplementary material: supplementary files of candidate reviews are retrieved and screened as information sources in their own right, because included-study lists, overlap-relevant tables and certainty assessments are frequently reported only in supplementary files. Author contact: corresponding authors are contacted where an included-study list or a subgroup result is not available in the accessible material, and any response is recorded as a source. Grey literature: conference abstracts, dissertations and preprint servers are not searched systematically and conference abstracts are excluded by protocol; abstracts already cited within an included review are noted but not used as evidence.

Main outcome(s) Two co-primary outcomes, chosen to reflect the net-benefit framing of the review. (1) Thromboembolic events, defined as ischaemic stroke, transient ischaemic attack, or in-stent or device-related thrombosis, occurring between the procedure and the longest follow-up reported by each review, with 30 days as a secondary extraction window where reported. (2) Major haemorrhage, defined as intracranial haemorrhage including parenchymal, subarachnoid and subdural bleeding, gastrointestinal or other extracranial major bleeding, or bleeding requiring intervention, transfusion or discontinuation of antiplatelet therapy, over the same windows. For each outcome in each included review the following are recorded: the definition used by that review, the number of contributing studies, the reported pooled effect measure with its 95 per cent confidence interval (risk ratio, odds ratio or risk difference, preserved as reported rather than converted), the heterogeneity statistic, the certainty rating where the review applied one, and whether the estimate derives from a comparative or a single-arm synthesis. No new effect estimate is generated for either co-primary outcome; the primary output is the distribution of estimates, definitions and certainty ratings across reviews, together with the degree to which the same outcome has been estimated repeatedly from the same primary studies.

Quality assessment / Risk of bias analysis Two co-primary outcomes reflecting the net-benefit framing: (1) thromboembolic events, defined as ischaemic stroke, transient ischaemic attack or in-stent or device-related thrombosis, from the procedure to the longest follow-up reported by each review, with 30 days as a secondary window; and (2) major haemorrhage, defined as intracranial, gastrointestinal or other extracranial major bleeding, or bleeding requiring intervention, transfusion or antiplatelet discontinuation, over the same windows. For each outcome and each review we record that review's own definition, the number of contributing studies, the pooled effect measure with 95 per cent confidence interval preserved as reported (risk ratio, odds ratio or risk difference), the heterogeneity statistic, any certainty rating, and whether the estimate is comparative or single-arm. No new pooled estimate is generated; the output is the distribution of estimates, definitions and certainty across reviews, and the extent to which one outcome has been estimated repeatedly from the same studies.

Strategy of data synthesis Statistical pooling of the meta-analyses themselves will not be performed: reviews are not independent units of evidence, and pooling them would compound precisely the duplication that this review is

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designed to quantify. The synthesis proceeds in four layers. First, a structured evidence map is constructed with the decision dimension on one axis (duration, intensity, choice of agent, individualisation) and the outcome on the other (thromboembolic events, major haemorrhage and the secondary outcomes); each cell records the contributing reviews, the number of unique primary studies, the pooled effect estimate where reported, the AMSTAR-2 rating and the certainty rating. Second, overlap is quantified with the corrected covered area, computed as (N minus r) divided by (r times c minus r), where N is the number of study entries, r the number of unique primary studies and c the number of reviews being compared; the value is computed for every pair of reviews within a dimension and for the whole set, and is reported beside the raw counts so that the calculation can be reproduced. Third, where one review's evidence base is wholly contained within another, the two are collapsed into a single evidence node with an explicit note, and the map is re-reported on that basis. Fourth, disagreement between reviews that share an evidence base is described qualitatively by comparing their definitions, time windows, effect measures and interpretive framing, since a difference in conclusion drawn from identical data is itself a finding. Certainty is carried forward from contributing reviews where GRADE was applied and appraised at review level where it was not; certainty is never upgraded as a result of aggregation.

Subgroup analysis Subgroup analyses are planned at the level of the reviews and of the primary studies they summarise, and will be presented as stratified descriptions rather than as re-pooled estimates, for the reasons stated for the synthesis strategy. Five strata are planned. (1) Rupture status: ruptured versus unruptured aneurysms, because the antiplatelet rationale differs and the consequences of haemorrhagic complications are not comparable between the two. (2) Device: flow diversion versus stent-assisted coiling, and within flow diversion, surface-modified or coated versus bare-metal devices, since coated devices are the principal setting in which single antiplatelet therapy is used. (3) Duration cut-point: the definition of the short arm adopted by each review (one, three, six, nine or twelve months), which differs across reviews and cannot be harmonised without discarding the meaning of the contrast. (4) Type of synthesis: comparative syntheses versus single-arm rate syntheses, so that effect estimates and absolute rates remain distinguishable. (5) Origin of evidence: reviews and primary studies from Chinese centres compared with those from other countries, since the primary literature is concentrated in a small number of high-volume centres and this concentration bears on the generalisability of the pooled estimates. Where a review does not report the relevant subgroup, the absence is recorded rather than filled by inference.

Sensitivity analysis Four sensitivity analyses are planned, each interrogating a different dependency of the analysis. (1) Appraisal instrument: the quality appraisal is repeated with R-AMSTAR and the resulting ranking compared with that obtained from AMSTAR-2, to test whether the ordering of reviews is an artefact of the instrument used. (2) Quality threshold: the evidence map is reproduced restricting to reviews rated moderate or high confidence on AMSTAR-2, showing what the map would look like if only the better conducted syntheses were considered. (3) Overlap exclusion: the corrected covered area is recomputed after removing reviews whose evidence base is wholly contained within another, quantifying how much of the global overlap estimate depends on that single containment. (4) Search currency: the map is reproduced restricting first to reviews published within the preceding three years and then to reviews whose search end date is later than the earliest review addressing the same dimension, to test whether current conclusions are being carried by superseded searches. Where a sensitivity analysis cannot be performed because the underlying data are not reported, this is stated explicitly rather than approximated by inference.

Country(ies) involved China.

Keywords intracranial aneurysm; flow diversion; stent-assisted coiling; antiplatelet therapy; dual antiplatelet therapy; P2Y12 inhibitor; clopidogrel; umbrella review.

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