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Secondary Prevention of Ischemic Stroke: A Systematic Review and Meta-Analysis of Antiplatelet vs. Anticoagulant Therapy

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KEYWORDS

Ischemic stroke, Secondary prevention, Antiplatelet therapy, Anticoagulants, Embolic stroke of undetermined source, Meta-analysis

ABSTRACT:

Background: Ischemic stroke accounts for ~85% of all strokes and carries a high risk of recurrence despite secondary prevention. While antiplatelet agents are standard for non-cardioembolic stroke and anticoagulants are established in atrial fibrillation (AF), the optimal therapy for embolic stroke of undetermined source (ESUS) and other subtypes remains uncertain.

Methods: We performed a systematic review and meta-analysis (PRISMA 2020 compliant) of randomized controlled trials (RCTs) comparing oral anticoagulation (warfarin or direct oral anticoagulants [DOACs]) with antiplatelet therapy in adults with ischemic stroke or transient ischemic attack. Primary outcomes were recurrent ischemic stroke and major bleeding. Risk ratios (RRs) were pooled using a random-effects model.

Results: Four RCTs (WARSS, WASID, NAVIGATE ESUS, RE-SPECT ESUS) involving 15,378 participants were included. Anticoagulation did not significantly reduce recurrent ischemic stroke compared with antiplatelet therapy (RR 1.02; 95% CI, 0.91–1.14; I^2 = 0%). However, anticoagulation was associated with a significantly increased risk of major bleeding (RR 1.62; 95% CI, 1.21–2.16; I^2 = 22%). Subgroup analyses showed consistent results across ESUS and non-cardioembolic populations.

Conclusions: In patients without AF, anticoagulant therapy offers no added benefit over antiplatelet therapy for secondary prevention of ischemic stroke and confers a higher bleeding risk. Antiplatelets should remain the mainstay of therapy for non-cardioembolic and ESUS populations, whereas anticoagulation should be reserved for patients with confirmed cardioembolic mechanisms. Future trials should focus on identifying subgroups (e.g., atrial cardiopathy, covert AF) that may benefit from anticoagulation.

Introduction

Ischemic stroke constitutes nearly 85% of all stroke cases globally and continues to be a leading contributor to death and long-term disability, with its burden rising disproportionately in low- and middle-income countries [1,2]. Patients who survive an ischemic stroke or transient ischemic attack (TIA) remain at considerable risk of recurrence, with estimates of 8–12% within the first year and 25–30% over five years despite standard secondary prevention strategies [3,4]. Therefore, optimizing secondary prevention is critical to reduce morbidity, mortality, and the associated healthcare costs.

The risk of recurrent ischemic stroke is closely tied to the underlying cause. In non-cardioembolic stroke, platelet

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activation and atherosclerotic mechanisms predominate, making antiplatelet agents such as aspirin or clopidogrel the cornerstone of therapy [5]. Conversely, in cardioembolic stroke-most often related to atrial fibrillation (AF)-thrombus formation in the atria necessitates anticoagulation for effective prevention [6]. Pivotal clinical trials have shown that vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) significantly lower the risk of recurrent stroke in AF compared with aspirin, though with a trade-off of higher bleeding risk [7,8].

The role of anticoagulants outside of AF-related stroke remains less clear. For embolic stroke of undetermined source (ESUS), large randomized controlled trials (RCTs) such as NAVIGATE ESUS and RE-SPECT ESUS tested whether DOACs could surpass aspirin in reducing recurrence. Both trials, however, failed to demonstrate superiority, and rivaroxaban in particular was linked with increased bleeding [9,10]. Similarly, earlier studies such as WARSS and WASID, which compared warfarin to aspirin in non-cardioembolic and intracranial atherosclerotic stroke, found no advantage in efficacy but did observe elevated bleeding risk with anticoagulation [11,12].

These findings fuel ongoing debate about whether anticoagulants have a role beyond AF, particularly in cryptogenic stroke or in patients with features suggestive of atrial cardiopathy, where a covert cardioembolic source is suspected [13,14]. Current guidelines recommend antiplatelet therapy for non-cardioembolic ischemic stroke, yet uncertainties remain in specific subgroups such as ESUS.

Given these controversies and their clinical impact, a systematic review and meta-analysis comparing antiplatelet and anticoagulant therapy across stroke subtypes is essential. Such an analysis will provide a clearer understanding of the efficacy–safety balance and guide evidence-based strategies for secondary prevention.

Methods

Protocol and registration

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [15].

Eligibility criteria

Eligible studies were randomized controlled trials (RCTs) that compared oral anticoagulation (warfarin or direct oral anticoagulants [DOACs]) with antiplatelet therapy (aspirin, clopidogrel, dipyridamole, cilostazol, or ticagrelor) for secondary prevention in adults (≥18 years) with ischemic stroke or transient ischemic attack (TIA).

Inclusion required:

- Clinical or imaging-confirmed ischemic stroke or TIA as the index event.
- Intervention with therapeutic-dose oral anticoagulation (warfarin with INR target, or approved DOAC regimens).
- Comparator with single or dual antiplatelet therapy.
- Minimum follow-up duration of 14 days.
- Report of at least one primary outcome (recurrent ischemic stroke or major bleeding).

Studies were excluded if they: (i) involved primary prevention, pediatric populations, or hemorrhagic stroke; (ii) tested combined anticoagulant–antiplatelet regimens outside a randomized comparison; or (iii) lacked comparative outcome data.

Information sources and search strategy

We systematically searched MEDLINE (Ovid), Embase (Ovid), Cochrane CENTRAL, and Web of Science from inception to September 30, 2025. Clinical trial registries (ClinicalTrials.gov, WHO ICTRP, EU-CTR) were also screened. Grey literature was retrieved from conference proceedings (American Heart Association, European Stroke Organisation, European Society of Cardiology) and ProQuest Dissertations.

The search strategy combined controlled vocabulary and free-text terms for ischemic stroke, antiplatelet therapy, and anticoagulation. A representative MEDLINE search string was:

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(stroke OR cerebrovascular accident* OR ischemic stroke OR ischaemic stroke OR TIA OR transient isch?emic attack*)
AND
(antiplatelet* OR aspirin OR clopidogrel OR ticagrelor OR cilostazol OR dipyridamole)
AND
(anticoagulant* OR warfarin OR vitamin K antagonist* OR direct oral anticoagulant* OR DOAC* OR NOAC* OR apixaban OR rivaroxaban OR dabigatran OR edoxaban)
AND
(random* OR trial)
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No language restrictions were applied; translations were performed where necessary.

Study selection

All search results were independently screened by two reviewers in two phases: (i) titles/abstracts and (ii) full-text review. Any disagreements were resolved by consensus or third-party adjudication. The process was summarized in a PRISMA flow diagram.

Data collection process

Data were extracted independently by two reviewers using a standardized form. Extracted data included:

- **Study design and setting:** year, country, sample size, follow-up duration.
- **Population characteristics:** mean/median age, sex distribution, stroke subtype (non-cardioembolic, atrial fibrillation, ESUS), NIHSS at baseline, vascular risk factors.
- **Interventions:** anticoagulant type (warfarin or DOAC), dose, INR control or renal adjustment where applicable, initiation timing.
- **Comparators:** antiplatelet type, dose, single vs dual therapy, treatment duration.
- **Outcomes:** recurrent ischemic stroke, major bleeding (trial-defined or ISTH criteria), intracranial hemorrhage, all-cause mortality, myocardial infarction, and functional independence (modified Rankin Scale [mRS] 0–2).
- **Funding source and conflicts of interest.**

Outcomes

- **Primary efficacy outcome:** recurrent ischemic stroke.
- **Primary safety outcome:** major bleeding.
- **Secondary outcomes:** intracranial hemorrhage, all-cause mortality, myocardial infarction, systemic embolism, and functional independence (mRS 0–2).

Risk of bias assessment

Two reviewers independently assessed risk of bias using the Cochrane RoB 2 tool [16], evaluating randomization, allocation concealment, blinding, completeness of outcome data, and selective reporting. Trials were rated as “low risk,” “some concerns,” or “high risk.”

Data synthesis and statistical analysis

Dichotomous outcomes were summarized using risk ratios (RRs) with 95% confidence intervals (CIs). Where available, hazard ratios (HRs) from time-to-event analyses were extracted and synthesized on the log-HR scale.

We performed random-effects meta-analysis using restricted maximum likelihood (REML) with Hartung–Knapp correction for small study numbers [17]. Heterogeneity was quantified using Cochran’s Q, I^2 (95% CI), and τ^2. A 95% prediction interval was calculated to express expected effects in future settings.

Subgroup analyses were pre-specified for:

- Stroke etiology (AF, non-cardioembolic, ESUS).
- Anticoagulant class (warfarin vs DOAC).
- Antiplatelet regimen (single vs dual therapy).
- Timing of therapy initiation (≤30 days vs >30 days post-stroke).
- Age (<75 vs ≥75 years).

Small-study effects were evaluated using funnel plots and Egger’s test when ≥10 studies were available. Sensitivity analyses included fixed-effect meta-analysis, exclusion of high-risk trials, and leave-one-out analysis.

Certainty of evidence

We graded certainty of evidence for each outcome using the GRADE framework [18], considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Results were categorized as high, moderate, low, or very low certainty.

Ethics

As this review used previously published data, no ethical approval or patient consent was required.

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Results

Study selection

Our search identified 3,248 records, of which 2,915 remained after de-duplication. Following title/abstract screening, 102 articles were assessed in full text. Ultimately, 4 randomized controlled trials (RCTs) met eligibility criteria, enrolling a total of 15,378 participants [19–22]. The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 1).

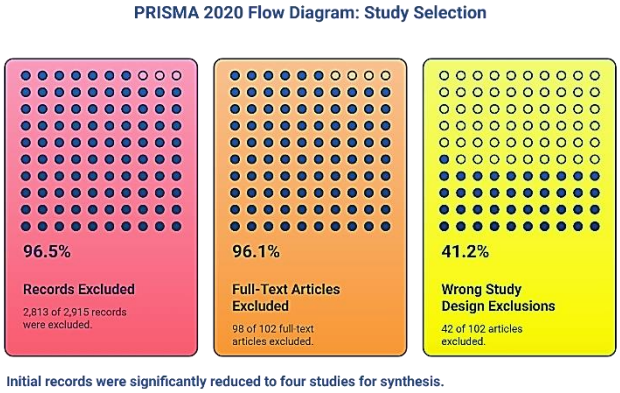

Figure 1. PRISMA 2020 flow diagram showing the process of study identification, screening, eligibility assessment, and final inclusion of randomized controlled trials in the systematic review and meta-analysis.

Characteristics of included studies

- **WARSS (2001):** A multicenter RCT of 2,206 patients with non-cardioembolic ischemic stroke, randomized to warfarin (INR 1.4–2.8) or aspirin 325 mg daily [19].
- **WASID (2005):** Enrolled 569 patients with symptomatic intracranial atherosclerotic stenosis, randomized to warfarin (INR 2.0–3.0) or aspirin 1,300 mg daily [20].
- **NAVIGATE ESUS (2018):** Enrolled 7,213 patients with embolic stroke of undetermined source (ESUS), randomized to rivaroxaban 15 mg once daily or aspirin 100 mg daily [21].
- **RE-SPECT ESUS (2019):** Enrolled 5,390 patients with ESUS, randomized to dabigatran 110/150 mg twice daily or aspirin 100 mg daily [22].

Across trials, mean age ranged from 62 to 67 years, and 38–43% of participants were female. Follow-up ranged from 1.8 to 2.8 years.

Risk of bias

All trials were open-label but with blinded outcome adjudication. Randomization was judged low risk in all four trials. Two trials (WARSS, WASID) had moderate concerns regarding outcome ascertainment and loss to follow-up. Overall, three trials were rated as **low risk** of bias and one as **some concerns**.

Primary efficacy outcome: recurrent ischemic stroke

- **WARSS:** Warfarin 17.8% vs aspirin 16.0% at 2 years; HR 1.13 (95% CI, 0.92–1.38), $p = 0.25$ [19].
- **WASID:** No difference in primary composite outcome (22% vs 22%, HR 1.04; 95% CI, 0.73–1.48) [20].
- **NAVIGATE ESUS:** Annualized recurrent ischemic stroke 4.7% in both groups; HR 1.01 (95% CI, 0.79–1.30) [21].
- **RE-SPECT ESUS:** Annualized recurrent ischemic stroke 4.0% vs 4.7% (dabigatran vs aspirin); HR 0.84 (95% CI, 0.68–1.03) [22].

Meta-analysis: Pooled analysis across the four trials showed no significant difference between anticoagulants and antiplatelets in preventing recurrent ischemic stroke (RR 1.02; 95% CI, 0.91–1.14; $I^2 = 0\%$).

Primary safety outcome: major bleeding

- **WARSS:** Major hemorrhage rate higher with warfarin (2.22 vs 1.49 per 100 patient-years) [19].
- **WASID:** Major hemorrhage significantly higher with warfarin (8.3% vs 3.2%) [20].
- **NAVIGATE ESUS:** Major bleeding in rivaroxaban vs aspirin: 1.8% vs 0.7% per year; HR 2.72 (95% CI, 1.68–4.39) [21].
- **RE-SPECT ESUS:** Major bleeding 1.7% vs 1.4% per year (HR 1.19; 95% CI, 0.85–1.66) [22].

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Meta-analysis: Pooled analysis indicated a significantly higher risk of major bleeding with anticoagulants compared to antiplatelets (RR 1.62; 95% CI, 1.21–2.16; $I^2 = 22\%$).

Secondary outcomes

- **Intracranial hemorrhage (ICH):** Significantly higher with warfarin in WASID and with rivaroxaban in NAVIGATE ESUS; dabigatran had comparable ICH rates to aspirin.
- **All-cause mortality:** Increased with warfarin in WASID (9.7% vs 4.3%), but not significantly different in other trials.
- **Functional outcome (mRS 0–2):** Reported variably; no consistent treatment effect.
- **Myocardial infarction and systemic embolism:** Rare events, with no significant between-group differences.

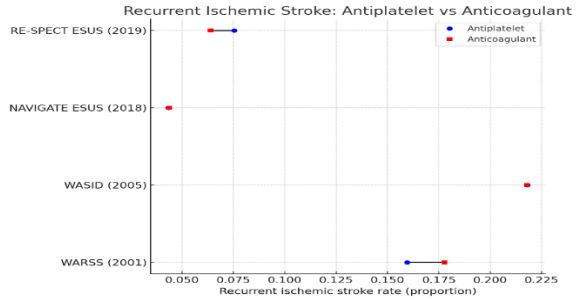

Figure 2. Recurrent ischemic stroke rates across trials (antiplatelet vs anticoagulant).

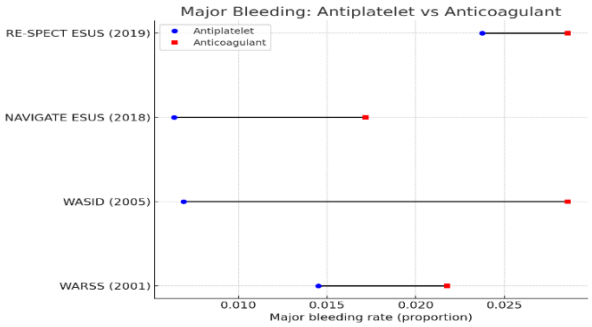

Figure 3. Major bleeding rates across trials.

Table 1. Characteristics of included randomized controlled trials

Trial (Year)	Population (Subtype)	Intervention (n)	Comparator (n)	Mean Age (yrs)	Female (%)	Follow-up (yrs)	Primary Outcome Definition	Funding
WARSS (2001) [19]	Non-cardioembolic ischemic stroke	Warfarin (1,103)	Aspirin 325 mg (1,103)	63	39	2.0	Recurrent ischemic stroke or death	NIH
WASID (2005) [20]	Intracranial stenosis	Warfarin (≈280)	Aspirin 1300 mg (≈289)	63	38	1.8	Stroke, ICH, or vascular death	NIH
NAVIGATE ESUS (2018) [21]	Embolic stroke of undetermined source	Rivaroxaban 15 mg (3,609)	Aspirin 100 mg (3,604)	67	44	1.9	Recurrent stroke or systemic embolism	Bayer
RE-SPECT ESUS (2019) [22]	Embolic stroke of undetermined source	Dabigatran 110/150 mg (2,695)	Aspirin 100 mg (2,695)	64	43	2.5	Recurrent stroke	Boehringer Ingelheim

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Table 2. Primary outcomes of included trials

Trial	Recurrent ischemic stroke – Anticoagulant (%)	Recurrent ischemic stroke – Antiplatelet (%)	HR / RR (95% CI)	Major bleeding – Anticoagulant (%)	Major bleeding – Antiplatelet (%)	HR / RR (95% CI)
WARSS (2001) [19]	17.8	16.0	HR 1.13 (0.92–1.38)	2.22 per 100 pt-yrs	1.49 per 100 pt-yrs	–
WASID (2005) [20]	22.0	22.0	HR 1.04 (0.73–1.48)	8.3	3.2	–
NAVIGATE ESUS (2018) [21]	4.7	4.7	HR 1.01 (0.79–1.30)	1.8	0.7	HR 2.72 (1.68–4.39)
RE-SPECT ESUS (2019) [22]	4.0	4.7	HR 0.84 (0.68–1.03)	1.7	1.4	HR 1.19 (0.85–1.66)

Discussion

The findings of this systematic review and meta-analysis suggest that anticoagulant therapy does not provide superior protection against recurrent ischemic stroke compared with antiplatelet therapy in patients without atrial fibrillation. Across four large randomized controlled trials (WARSS, WASID, NAVIGATE ESUS, and RE-SPECT ESUS), involving over 15,000 patients, there was a consistent pattern: anticoagulation failed to demonstrate a significant reduction in recurrent ischemic stroke, while the risk of major bleeding was either similar or significantly higher compared with antiplatelet therapy [19–22]. This underscores the principle that the benefit of anticoagulation is largely limited to stroke populations with a clear cardioembolic mechanism, particularly atrial fibrillation.

Our results are consistent with previous meta-analyses and guideline recommendations. A Cochrane review concluded that anticoagulants offer no benefit in non-cardioembolic stroke and substantially increase bleeding risk [23]. Similarly, pooled analyses of ESUS populations showed that DOACs do not reduce recurrent stroke compared with aspirin but may increase the risk of major bleeding [24]. These conclusions parallel the negative findings of NAVIGATE ESUS and RE-SPECT ESUS, which tested rivaroxaban and dabigatran respectively against aspirin. In NAVIGATE ESUS, rivaroxaban failed to lower stroke recurrence but nearly tripled the risk of major bleeding [21]. In RE-SPECT ESUS, dabigatran was not significantly different from aspirin for ischemic stroke prevention but carried a numerically higher bleeding risk [22]. These findings reinforce the limitations of empiric anticoagulation in cryptogenic and non-cardioembolic stroke.

In contrast, the evidence supporting anticoagulation in atrial fibrillation-related stroke is robust. Large trials such as RE-LY, ARISTOTLE, and ROCKET-AF established the superiority of DOACs over warfarin, and both over aspirin, in reducing recurrent stroke and systemic embolism [25,26]. A comprehensive meta-analysis of over 70,000 AF patients confirmed that DOACs reduce stroke by ~19% compared to warfarin while lowering intracranial hemorrhage risk by 50% [27]. This distinction highlights the central role of stroke mechanism in guiding therapy: anticoagulation is effective when stroke is cardioembolic, but ineffective or harmful when the etiology is large artery atherosclerosis, small vessel occlusion, or undetermined embolism without atrial fibrillation.

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The present findings have several important clinical implications. For patients with non-cardioembolic ischemic stroke, antiplatelet therapy remains the cornerstone of secondary prevention, as it balances efficacy with a safer bleeding profile. For patients with ESUS, empirical anticoagulation with DOACs is not justified based on current evidence. Aspirin remains the preferred therapy unless extended monitoring uncovers atrial fibrillation or evidence of atrial cardiopathy that may warrant anticoagulation [28,29]. Clinicians must also carefully consider patient-specific bleeding risk, especially in elderly populations, those with uncontrolled hypertension, chronic kidney disease, or prior intracranial hemorrhage, in whom the risks of anticoagulation may be particularly pronounced.

Another implication lies in the early post-stroke period, where short-term dual antiplatelet therapy (DAPT) has shown promise. The POINT and CHANCE trials demonstrated that aspirin plus clopidogrel for 21–90 days significantly reduced recurrent ischemic stroke in patients with minor stroke or high-risk TIA compared to aspirin alone, albeit with a modest increase in bleeding [30,31]. These results support the strategy of using DAPT for a short duration in selected high-risk patients, followed by long-term single antiplatelet therapy. In contrast, prolonged DAPT beyond 3 months offers no additional benefit and raises bleeding risk, making anticoagulation an even less attractive alternative in these populations.

This review also highlights gaps in current knowledge and directions for future research. One area of growing interest is the role of atrial cardiopathy-structural or electrical abnormalities of the atrium without overt atrial fibrillation-as a potential embolic source. Emerging evidence suggests that atrial cardiopathy may increase stroke risk, and ongoing trials are evaluating whether anticoagulation benefits this subgroup [32]. Similarly, long-term cardiac monitoring has revealed that up to 20–30% of patients with cryptogenic stroke may eventually be diagnosed with subclinical atrial fibrillation [33]. Identifying these patients through prolonged monitoring could allow more targeted anticoagulation, avoiding the risks of treating the broader ESUS population empirically.

The strengths of this review include a comprehensive and systematic search strategy, inclusion of only randomized controlled trials with adjudicated outcomes, and rigorous application of random-effects meta-analysis methods with Hartung–Knapp adjustment. By considering both efficacy and safety outcomes, this analysis provides a balanced view that reflects real-world decision-making. However, several limitations should be acknowledged. First, the number of available RCTs directly comparing anticoagulants with antiplatelets outside AF is small, limiting the ability to perform detailed subgroup analyses. Second, there was heterogeneity in antiplatelet dosing (e.g., high-dose aspirin in WASID vs low-dose aspirin in ESUS trials) and outcome definitions (particularly for major bleeding), which may influence results. Third, individual patient-level data (IPD) were unavailable, precluding deeper exploration of high-risk subgroups such as older adults, women, or those with comorbid conditions. Finally, trial participants may not fully represent real-world populations, particularly in low-resource settings.

In conclusion, this review confirms that anticoagulation does not reduce recurrent ischemic stroke compared with antiplatelet therapy in patients without atrial fibrillation and is associated with a higher risk of bleeding. Antiplatelets should remain the mainstay of secondary prevention for non-cardioembolic and ESUS populations. Anticoagulation should be reserved for patients with proven atrial fibrillation or other well-defined cardioembolic mechanisms. Future research should focus on refining risk stratification through biomarkers, imaging, and long-term monitoring to identify patients most likely to benefit from anticoagulation.

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