

Oral Anticoagulation with or without Antiplatelet Therapy for Secondary Stroke Prevention in Patients with Atrial Fibrillation and Atherosclerosis: A Systematic Review and Meta-Analysis

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Research Article

Keywords: Ischemic stroke, Antiplatelet therapy, Atrial fibrillation, Atherosclerosis, Oral anticoagulation, Antithrombotic therapy, Secondary prevention, Meta-analysis

Posted Date: August 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10630015/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Patients with ischemic stroke (IS), atrial fibrillation (AF), and atherosclerosis have an increased risk of recurrent ischemic events. Addition of antiplatelet therapy (APT) to oral anticoagulant therapy (OAC) may offer additional protection against these events, at the cost of an increased risk of bleeding. This systematic review and meta-analysis aimed to compare the efficacy and safety of combined antithrombotic therapy versus OAC alone in this population.

Methods

PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from inception through October 2025 for randomized controlled trials and observational studies comparing OAC plus APT versus OAC alone in adults with IS, AF, and atherosclerosis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using random-effects models. Risk of bias was assessed with RoB 2 and ROBINS-I. The protocol was registered in PROSPERO (CRD420251164174).

Results

Seven studies (4 retrospective, 2 prospective, 1 randomized trial; $n = 10,985$) were included. Combined therapy was not associated with a reduction in vascular composite outcome (HR 1.10, 95% CI 0.76–1.58), recurrent IS (HR 1.03, 95% CI 0.95–1.12), major bleeding (HR 1.17, 95% CI 0.94–1.46), or all-cause mortality (HR 0.90, 95% CI 0.68–1.21). In the subgroup with intracranial or extracranial atherosclerosis, combined therapy was associated with a significantly higher vascular composite risk (HR 1.67, 95% CI 1.17–2.37).

Conclusions

Combined antithrombotic therapy with OAC plus APT was not associated with a reduction in recurrent IS, vascular composite outcome, major bleeding, or all-cause mortality in patients with IS, AF, and atherosclerosis. In patients with intracranial or extracranial atherosclerosis, combined therapy was associated with a higher vascular composite risk. These findings suggest that the addition of APT to OAC should be approached with caution in this population, and may be best reserved for select clinical contexts.

1. INTRODUCTION

Atrial fibrillation (AF) is one of the leading causes of ischemic stroke (IS), accounting for 20% to 30% of cases and being associated with up to a fivefold increased risk of both recurrence and mortality.^{1,2} In patients with non-valvular atrial fibrillation (NVAf), oral anticoagulation (OAC) is the recommended therapy for primary and secondary prevention of IS.^{3–5} Even with appropriate OAC, a residual annual risk of recurrent stroke persists, ranging from 0.7% to 2.3% per year.^{6–9}

The cause of these recurrences is often unclear, and many factors may be associated, including competing etiology mechanisms (e.g., large artery or small vessel atherosclerosis), suboptimal anticoagulation due to non-compliance, persistent cardioembolism despite therapeutic anticoagulation levels, or thrombogenic left atrial appendage anatomy.^{10–14} Nevertheless, most recurrent events appear to be related to AF-driven cardioembolism even under adequate anticoagulation.^{12,15,16}

Concomitant atherosclerosis is particularly relevant, as it is estimated that up to one-third of patients with IS and NVAf have atherosclerotic disease, contributing to an even higher thromboembolic risk.^{16,17} This overlap further complicates the choice of the optimal antithrombotic regimen for preventing recurrent IS. In this context, combining OAC with single antiplatelet therapy (SAPT) has been considered in clinical practice for patients with IS and concurrent NVAf and atherosclerosis, although there are concerns about increased risk of major bleeding and intracranial hemorrhage.^{16,18,19}

Recently, the randomized ATIS-NVAf trial found no net clinical benefit from adding an antiplatelet agent to anticoagulation in this population, with an increased bleeding risk.²⁰ A network meta-analysis by Ibrahim et al. likewise found OAC monotherapy to be the most favorable strategy.²¹ However, their network combined randomized and observational studies, a practice the Cochrane Handbook generally advises against.²² Given the remaining uncertainty about the comparative effectiveness between OAC in monotherapy versus its combination with SAPT for this population, the present study seeks to synthesize the best available evidence to clarify the risk of IS recurrence, mortality, major bleeding, and other clinically relevant outcomes.

2. METHODS

This systematic review and meta-analysis were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^{23,24} The protocol was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) database under protocol number CRD420251164174.

2.1 Eligibility criteria

Studies were eligible for inclusion if they met all of the following criteria: (1) randomized controlled trials (RCTs) or observational studies (retrospective or prospective cohorts); (2) included adult patients (≥ 18 years); (3) reported a diagnosis of IS, AF and atherosclerosis; (4) compared combined antithrombotic therapy (Anticoagulant therapy and Antiplatelet agent) against OAC monotherapy; and (5) assessed at least one outcome of interest, such as risk of major bleeding, vascular composite outcome, stroke recurrence, or mortality. Studies were excluded if they were published only as conference abstracts, review articles, editorials, or case reports; did not include a comparator group of patients treated with anticoagulant therapy alone; or did not report at least one outcome of interest. When an overlap was identified between studies, we included the study with the largest sample size for that specific outcome.

2.2 Study selection and data extraction

We conducted a systematic search in PubMed, Embase, and the Cochrane Central Register of Controlled Trials from database inception to October 2025. The search strategy included combinations of the following terms: "atrial fibrillation", "AF", "ischemic stroke", "brain infarction", "cerebral infarction", "cerebrovascular accident", "atherosclerosis", "coronary artery disease", "carotid artery stenosis", "intracranial stenosis", "peripheral artery disease", "antiplatelet". The complete search strategies for each database are presented in **Supplementary Table S1**.

Additionally, we manually screened the reference lists of all included studies, as well as relevant systematic reviews and meta-analyses, to identify potentially eligible publications. Two authors (V.H.P.L. and G.N.M.) independently screened titles and abstracts for relevance and subsequently assessed full-text articles against predefined eligibility criteria. Any disagreements were resolved through discussion and consensus. Data extraction was performed independently by three additional authors (V.H.P.L., J.L., and L.G.C.F.) for all outcomes of interest and individual characteristics of included studies (first author, study design, sex distribution, mean age, follow-up time, comorbidities, and CHA₂DS₂-VASc score).

2.3 Outcomes and subanalysis

Primary efficacy outcome included vascular composite outcome, as defined by the individual studies. The secondary efficacy outcome was IS. Safety outcomes were major bleeding and all-cause mortality. When multiple definitions were reported across studies, outcomes were harmonized by grouping conceptually similar endpoints, while preserving study-specific definitions. Definitions of major bleeding and vascular composite outcome, as reported in the included studies, are provided in **Supplementary Table S2**.

The individual components of vascular composite outcome are also detailed to allow comparison across studies. When studies reported outcomes at multiple time points, the longest available follow-up was used for the primary analysis. A prespecified subanalysis was conducted in individuals with intracranial or extracranial atherosclerosis, according to study-specific definitions. Definitions used for this subgroup are detailed in **Supplementary Table S3**.

2.4 Risk-of-Bias Assessment

We assessed the risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized studies and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for observational studies.^{25,26} Two independent authors (V.H.P.L. and A.M.P.S.) completed the risk of bias assessment. Disagreements were resolved through consensus. Publication bias was not assessed by funnel plot analysis due to the small number of studies included.²³

2.5 Statistical Analysis

We pooled hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs). Estimates were combined using an inverse-variance method under random-effects models. All analyses were conducted using restricted maximum likelihood (REML) to account for between-study heterogeneity, in line with Cochrane recommendations.²³ Heterogeneity was assessed using Cochran's Q test and quantified with the I² statistic. P-values < 0.05 were considered statistically significant. Heterogeneity was assessed using the Q test and its p-value, with the magnitude evaluated by I² values: 0–40% indicating low, 40–60% moderate, and $> 60\%$ high heterogeneity, following Higgins et al.²³ To address high heterogeneity, sensitivity analyses were conducted, systematically excluding one study at a time and recalculating the pooled estimates.²⁷ All statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria), with statistical significance set at $p < 0.05$.²⁸

3. RESULTS

3.1 Study selection

A total of 2,045 records were identified from databases. After removing 223 duplicates, 1,822 records remained for title and abstract screening. Of these, 40 articles were retrieved for full-text assessment. Ultimately, seven studies met the inclusion criteria and were included.^{20,29–34} The reasons for exclusion after full-text review are summarized in Fig. 1.

3.2 Baseline characteristics of the included studies and patients

Across the included studies, four were retrospective^{29–32}, two were prospective^{33,34}, and one was an RCT²⁰, encompassing a total of 10,985 patients, of whom 4,467 participants were assigned to OAC plus APT and 6,518 to OAC alone. Follow-up times ranged from 3 months to 4 years. The mean age varied from 72.5 to 83.6 years between studies. Female sex ranged from 0% to 68%. The most prevalent comorbidities were hypertension (68.1% to 96.1%) and diabetes mellitus (25.2% to 54.5%). The prevalence of coronary disease (encompassing coronary artery disease, ischemic heart disease, and coronary heart disease as defined in the original reports) varied substantially, ranging from 9.9% to 79.3%. Where reported, mean CHA₂DS₂-VASc scores were generally ≥ 3 . Other baseline characteristics are detailed in Table 1.

Table 1
Baseline characteristics of included studies.

Study	Group	Study design	Number of patients	Female, n (%)	Age, years*	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)	Smoking, n (%)	Coronary Disease, n (%)†	CHA2DS2-VASc
ATIS-NVAF trial	OAC + APT	RCT	159	46 (29)	76.8 ± 7.5	140 (88)	49 (31)	116 (73)	19 (12)	23 (15)	155 (9)
	OAC		157	44 (28)	77.7 ± 7.3	140 (89)	47 (30)	105 (67)	18 (12)	24 (15)	151 (9)
Choi et al, 2019	OAC + APT	Retrospective cohort	97	NA	NA	NA	NA	NA	NA	NA	NA
	OAC		290	NA	NA	NA	NA	NA	NA	NA	NA
Harrison et al, 2024	NOAC + APT	Retrospective cohort	1401	540 (38.5)	74.2 ± 9.9	973 (69.5)	550 (39.3)	NA	NA	692 (49.4)	NA
	NOAC		1628	760 (46.7)	75.0 ± 10.4	1187 (72.9)	543 (33.4)	NA	NA	726 (44.6)	NA
	Warfarin + APT		1436	662 (47.1)	73.9 ± 11.7	1380 (96.1)	782 (54.5)	NA	NA	1139 (79.3)	NA
	Warfarin		1243	533 (42.9)	73.4 ± 11.6	1172 (94.3)	625 (50.3)	NA	NA	847 (68.1)	NA
Heo et al, 2024	OAC + APT	Retrospective cohort	149	55 (36.9)	76 (51.0)*	135 (90.6)	60 (40.3)	65 (22.0)	22 (14.8)	106 (71.1)	NA
	OAC		296	126 (42.6)	131 (44.3)*	246 (83.1)	105 (35.5)	33 (22.1)	38 (12.8)	172 (58.1)	NA
Kim et al, 2020	OAC + APT	Retrospective cohort	540	261 (48.3)	72.5 ± 10.0	413 (76.5)	175 (32.4)	145 (26.9)	94 (17.4)	135 (25.0)	5 [4–6]
	OAC		2013	1005 (49.9)	72.5 ± 10.1	1371 (68.1)	508 (25.2)	539 (26.8)	337 (16.7)	200 (9.9)	5 [4–6]
Koyanagi et al, 2022	OAC + APT	Prospective cohort	13	0 (0)	76 [70–81]	NA	NA	NA	NA	NA	2 [2–3]
	OAC		41	28 (68)	84 [79–88]	NA	NA	NA	NA	NA	3 [3–4]
McGrath et al, 2014	OAC + APT	Prospective cohort	672	359 (53.4)	77.0 ± 10.1	502 (74.7)	289 (43.0)	NA	NA	NA	NA
	OAC		850	492 (57.9)	77.6 ± 10.2	600 (70.6)	334 (39.3)	NA	NA	NA	NA

Abbreviations: APT = Antiplatelet Therapy; CHA2DS2-VASc = Congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke or transient ischemic attack; n = number; NA = Not Available; NOAC: Novel oral

anticoagulant; OAC: Oral Anticoagulant; RCT = Randomized controlled trial.

*Mean ± standard deviation or median [interquartile range]

†Age > 75 years, n (%)

‡Included: Coronary Artery Disease; Ischemic Heart Disease; Coronary Heart Disease

‡CHA2DS2-VASc ≥ 3, n(%)

3.3 Efficacy outcomes

Five studies compared the hazard of vascular composite outcome between combined therapy and OAC alone.^{20,31–34} There was no significant difference between groups (HR 1.10; 95% CI 0.76–1.58; $p = 0.62$; $I^2 = 64.8\%$; Fig. 2A). Regarding IS, time-to-event analysis was reported by five studies,^{20,29–31,34} with no significant difference between treatments (HR 1.03; 95% CI 0.95–1.12; $p = 0.51$; $I^2 = 0\%$; Fig. 2B).

3.4 Safety outcomes

Regarding major bleeding, the hazard between combined therapy and OAC alone was not significantly different (HR 1.17; 95% CI 0.94–1.46; $p = 0.17$; $I^2 = 55\%$; Fig. 3A) according to three studies.^{20,30,34} Likewise, four studies reported no significant difference between combined therapy and OAC alone in the hazard of mortality (HR 0.90; 95% CI 0.68–1.21; $p = 0.50$; $I^2 = 71\%$; Fig. 3B).^{20,30,31,34}

3.5 Intracranial and extracranial atherosclerosis

Three studies reported time-to-event analysis of vascular composite outcome for patients with intracranial and extracranial atherosclerosis. There was a significant difference between groups (HR 1.67; 95% CI 1.17–2.37; $p < 0.01$; $I^2=0\%$; Fig. 4) for vascular composite outcome.^{20,32,33}

3.6 Sensitivity analysis

The leave-one-out analysis showed moderate heterogeneity (64.8% to 44.6%) after removal of Kim et al. (2020) for vascular composite outcome.³² Regarding major bleeding, our sensitivity analyses showed a significant effect when removing the warfarin-based comparison from Harrison et al. (2024), with no heterogeneity observed (55% to 0%).³⁰ Furthermore, we also obtained moderate heterogeneity in the risk of mortality (71% to 47%) after the removal of McGrath et al. (2014).³⁴ The sensitivity analyses are presented in **Supplementary Figure S1**.

3.7 Quality assessment

One observational study was judged as having a serious risk of bias, primarily due to residual confounding and limitations in intervention classification.²⁹ Only one study was assessed using RoB 2.0, and was judged to have some concerns overall, mainly related to potential bias from deviations from intended interventions in an open-label design (Fig. 5).²⁰ Detailed risk of bias assessment is presented in **Supplementary Tables S4-S5**. Publication bias was not assessed by funnel plot analysis due to the small number of studies included.

4. DISCUSSION

In this systematic review and meta-analysis of studies including patients with IS, AF, and concomitant atherosclerosis, we evaluated the efficacy and safety of combined antithrombotic therapy versus OAC alone. The synthesized evidence indicated a lack of meaningful reduction in recurrent ischemic events with the addition of SAPT to anticoagulation, alongside an absence of clear effect in overall mortality or bleeding profiles. A notable signal emerged in patients documented with intracranial or extracranial atherosclerosis, where combined therapy was associated with heightened vascular risks. The relevance of this systematic review and meta-analysis resides in consolidating fragmented evidence into a comprehensive synthesis, establishing the limited role of routine combination therapy in this population, and providing a framework for refined patient selection and targeted management in future research and clinical practice.

The absence of IS reduction with combined therapy may stem from the predominant role of AF-mediated embolism in recurrence, where anticoagulation effectively mitigates thrombus formation in the left atrial appendage, overshadowing any supplementary antiplatelet effects on atherosclerotic plaques.^{35,36} In anticoagulated patients with AF, platelet activation appears less central to residual stroke risk, as competing etiologies like atherothrombosis may not sufficiently drive events to warrant dual pathway inhibition. Instead, cardioembolic mechanisms persist as the primary driver, with atherothrombotic contributions often secondary or coincidental.³⁷ This aligns with pathophysiological insights distinguishing friable, red thrombi in atrial stasis from white, platelet-rich thrombi in arterial shear stress, suggesting that adding antiplatelet agents may not address the root cardioembolic propensity.³⁸ Findings from the AFIRE trial, which demonstrated noninferiority of rivaroxaban monotherapy in AF with stable coronary disease, support this interpretation, as do broader coronary literature emphasizing OAC monotherapy for reducing ischemic events without excess harm.³⁹ Some meta-analyses in AF populations confirm no consistent efficacy gain from combining OACs with SAPT, reinforcing that residual risk in these patients is unlikely to be predominantly platelet-mediated.⁴⁰ At the same time, there is evidence that Xa factor inhibitors also act on atherosclerosis-related pathophysiological pathways, which may explain no significant effects of combining OAC with antiplatelets.⁴¹

In terms of safety, although major bleeding differences did not reach statistical thresholds, a consistent directional increase with combined therapy highlights potential harm, compounded by wide confidence intervals that may obscure true effects in underpowered analyses.⁴² Observational data introduce confounding, such as preferential assignment of combination regimens to higher-risk patients, while biological plausibility arises from additive inhibition of hemostatic pathways, elevating hemorrhage susceptibility without proportional ischemic protection.⁴³ From a net clinical benefit standpoint, this imbalance favors monotherapy, as any marginal efficacy gains are offset by safety concerns, particularly in older populations with polypharmacy. Supporting evidence from randomized trials and meta-analyses, including network evaluations of antithrombotic strategies in AF post-percutaneous intervention, consistently shows elevated bleeding with dual or triple therapy, advocating de-intensification where feasible.^{42,44}

In the subgroup with intracranial or extracranial atherosclerosis, the observed elevation in the hazard of vascular composite outcome with combined therapy displayed consistency with minimal heterogeneity, suggesting a more reliable signal of increased risk. This could arise from confounding by indication, wherein clinicians escalate to combination therapy for perceived higher atherosclerotic burden, introducing therapeutic escalation bias that inflates event rates in the treated group. Such patients may inherently face amplified vascular risks due to progressive plaque instability, independent of antithrombotic choice, thus limiting causal inferences from these data.

These findings suggest that routine addition of SAPT to anticoagulation in patients with AF, IS, and atherosclerosis lacks supportive evidence and may introduce unnecessary risks. Combination approaches should be limited to select contexts, such as recent coronary stenting or acute coronary syndrome, where short-term dual therapy mitigates stent thrombosis while transitioning to monotherapy.⁴⁵ De-escalation strategies, including timely antiplatelet discontinuation after procedural needs, align with this cautious stance to optimize safety. This interpretation is consistent with current cardiology and stroke guidelines, which prioritize OAC monotherapy for AF-related stroke prevention, reserving combinations for comorbid coronary indications and emphasizing individualized risk-benefit assessment.^{46,47}

Future research should prioritize dedicated randomized trials in patients with AF, recent IS, and confirmed intracranial stenosis to delineate optimal regimens. Stratification by advanced plaque imaging characteristics, such as vulnerability assessed via high-resolution magnetic resonance or computed tomography angiography, could refine subgroups benefiting from intensified therapy. Incorporating biomarkers of thrombosis and inflammation, like D-dimer or high-

sensitivity C-reactive protein, may further personalize approaches. Additionally, evaluating left atrial appendage morphology through echocardiography or computed tomography could identify cardioembolic predominance, while advanced vascular imaging might highlight atherothrombotic contributions, guiding precision antithrombotic strategies. Such efforts may enable a more precise, mechanism-guided approach to antithrombotic therapy. Until then, current evidence favors cautious restraint over routine therapeutic intensification in this challenging clinical scenario.

Limitations

Finally, it is important to acknowledge that the present study has limitations that must be considered while interpreting its results. First, the evidence base was composed predominantly of retrospective observational studies, rendering the findings susceptible to selection bias, residual confounding, and indication bias, particularly given the nonrandomized allocation of combination therapy to potentially higher-risk patients. Secondly, substantial clinical and methodological heterogeneity (stemming from differences in patient populations, definitions, and severity of atherosclerosis, anticoagulant and antiplatelet regimens, and follow-up duration) persisted despite subgroup analyses, limiting the interpretability and generalizability of the results. Additionally, risk-of-bias assessments identified at least moderate concerns across studies, including deviations from intended interventions and incomplete data, and the possibility of publication bias cannot be excluded. Finally, with only one randomized trial contributing data, the overall certainty of evidence remains limited, underscoring the need for adequately powered prospective trials to define optimal therapy in this population.

5. CONCLUSION

In patients with IS, AF, and concomitant atherosclerotic disease, the addition of SAPT to OAC regimen was not associated with a reduction in recurrent ischemic events or mortality and did not confer a clear safety advantage compared with OAC alone. Although subgroup analyses suggested a signal toward worse composite outcomes among patients with intracranial or extracranial atherosclerosis receiving combination therapy, these findings should be interpreted cautiously, given the predominance of observational data and potential confounding. Overall, the available evidence does not support routine therapeutic intensification beyond anticoagulation in this population outside established indications such as recent acute coronary syndrome or coronary stenting. Until adequately powered randomized trials provide more definitive guidance, treatment decisions should be individualized, balancing ischemic and hemorrhagic risks within a net clinical benefit framework.

Declarations

Acknowledgments

None.

Conflicting interests

The authors have no conflicts of interest to declare.

Funding

There were no external funding sources for this study.

Ethics approval

Not applicable. This is a secondary analysis of previously published data.

Data availability

All data included in this review are available in the published articles referenced in the manuscript.

Contributorship: V.H.P.L (protocol register, conception and design, study selection, data acquisition, data analysis, risk of bias assessment, tables, editing, writing the initial draft); A.M.P.S (conception and design, data acquisition, data analysis, risk of bias assessment, tables, editing, writing the initial draft), L.J.C.C (data analysis, editing, writing the initial draft); G.N.M (study selection, data analysis, writing the initial draft); L.G.C.F (data acquisition, tables, writing the initial draft); O.R.G (data analysis, writing the initial draft), L.M.V (data analysis, writing the initial draft); J.L.L (data acquisition, writing the initial draft), C.D.S.A (data analysis, review), M.K.I (data analysis, editing, and review); J.P.M.T (conception and design, editing, and review).

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Figures

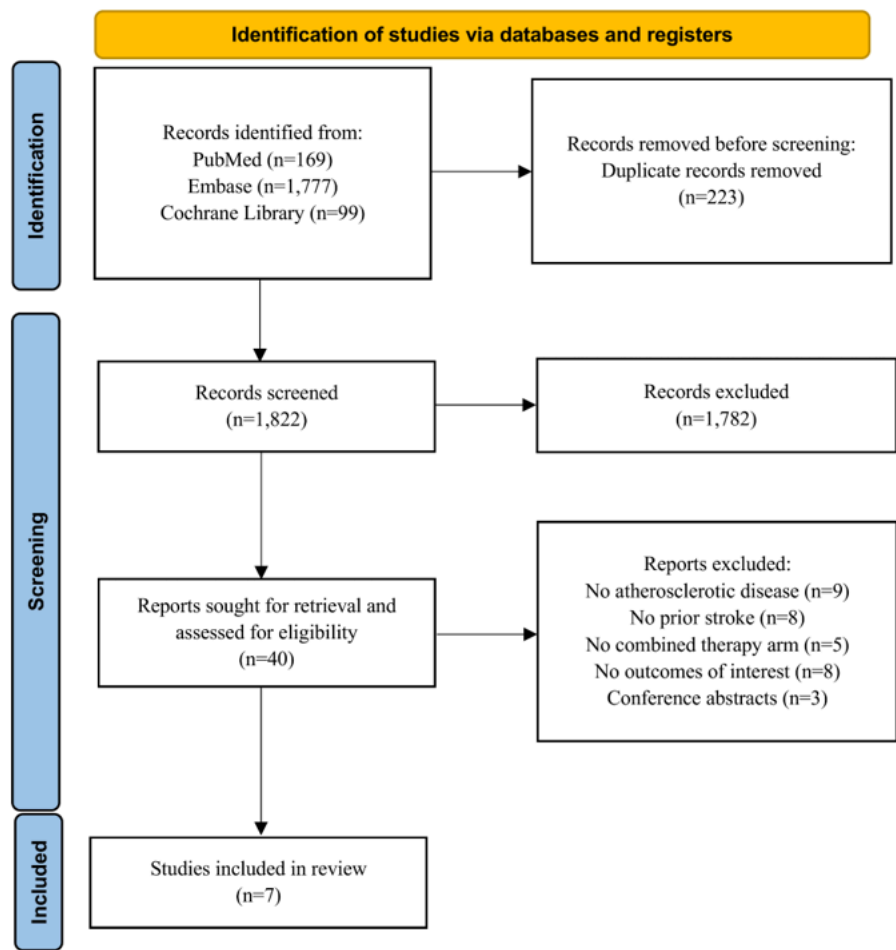
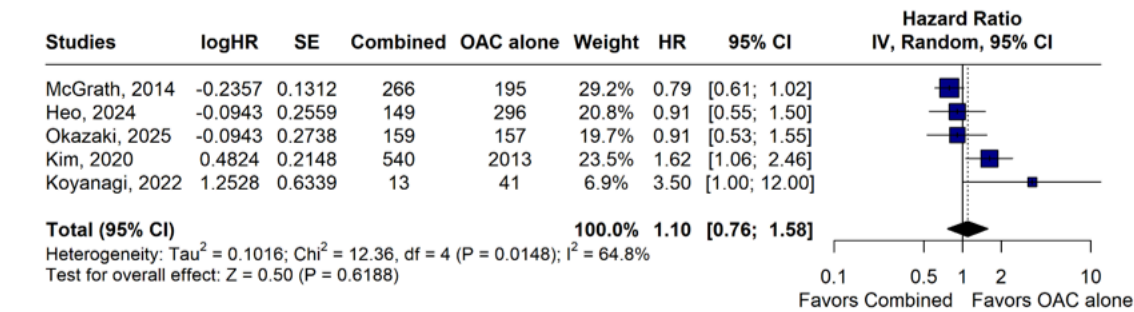


Figure 1

Flowchart of literature search and selection.

A



B

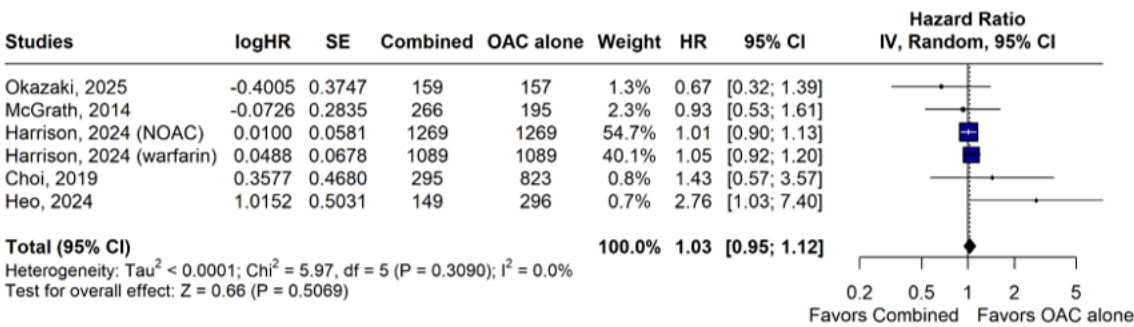
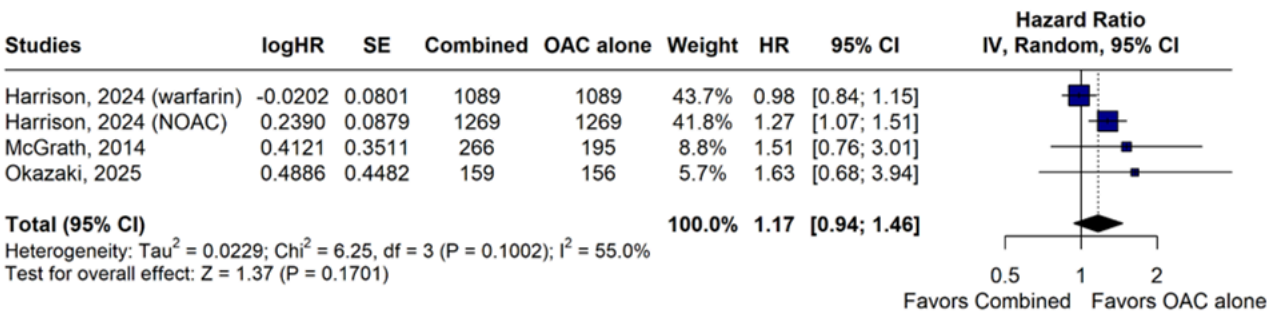


Figure 2

Forest plots of efficacy outcomes regarding hazard of (A) vascular composite outcome, and (B) ischemic stroke.

A



B

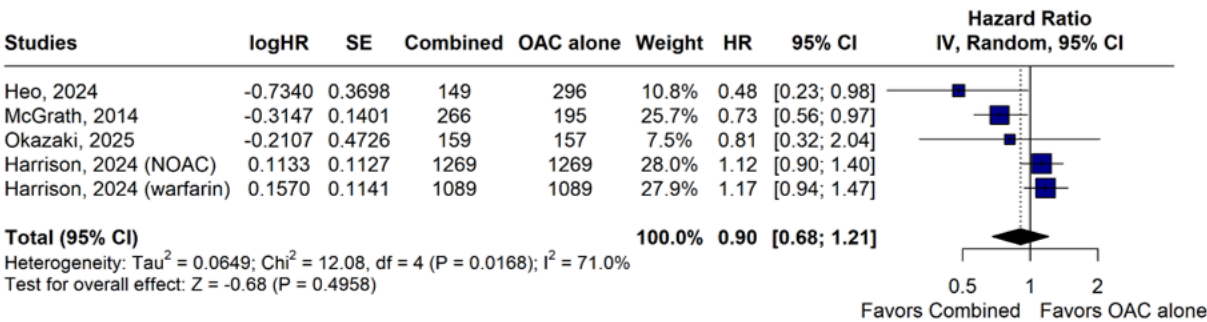


Figure 3
Forest plots of safety outcomes regarding hazard of (A) major bleeding, and (B) mortality.

A

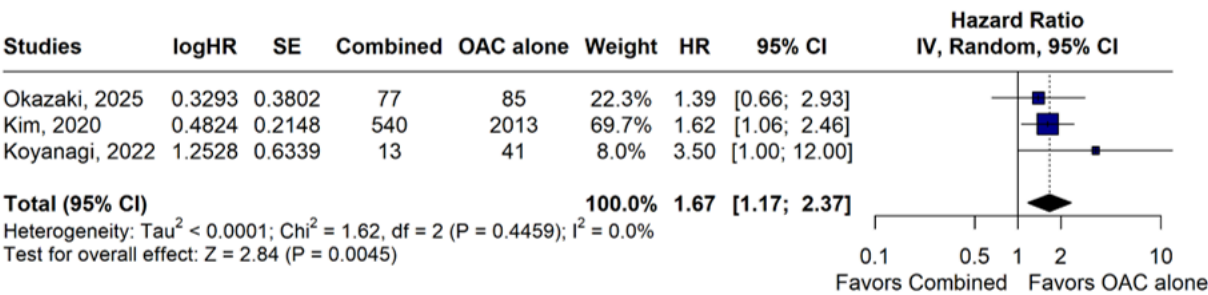
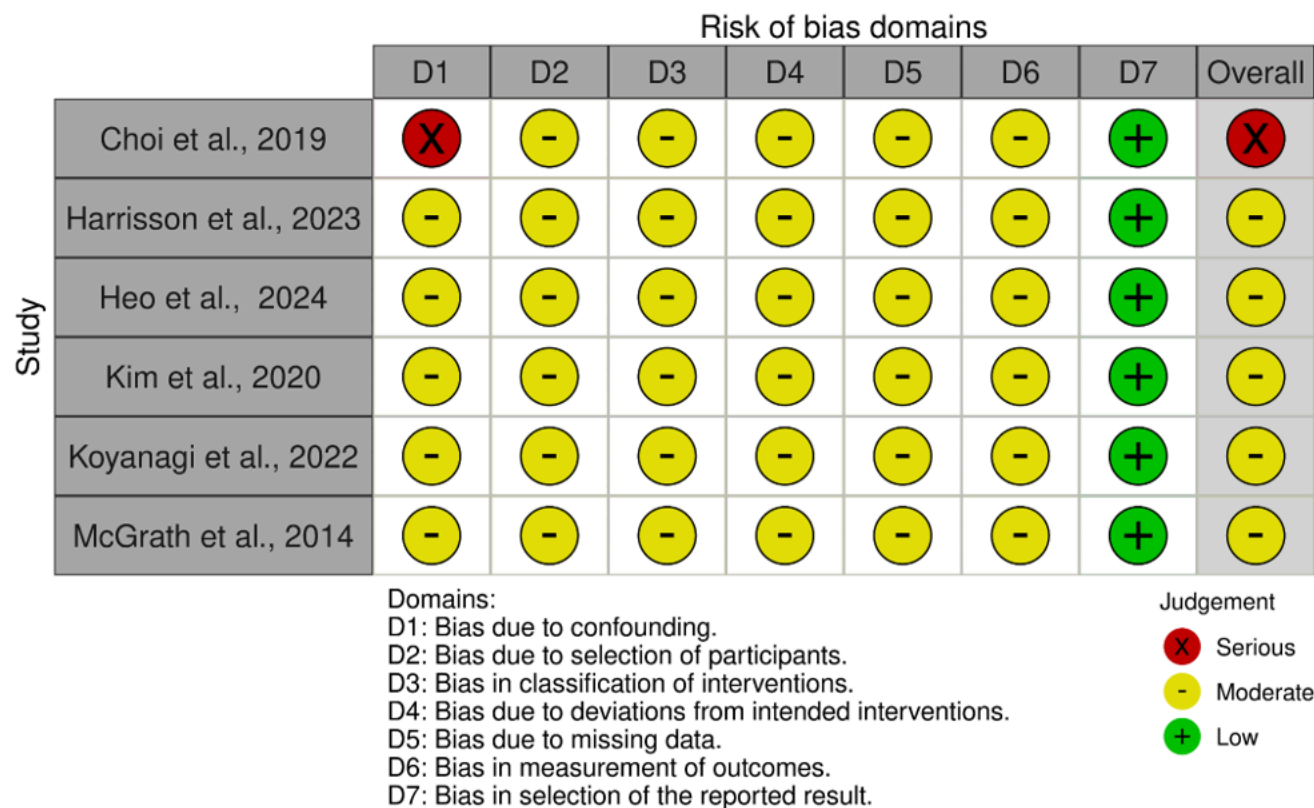


Figure 4
Forest plot of intracranial and extracranial atherosclerosis subanalysis regarding hazard of vascular composite outcome.

A



B

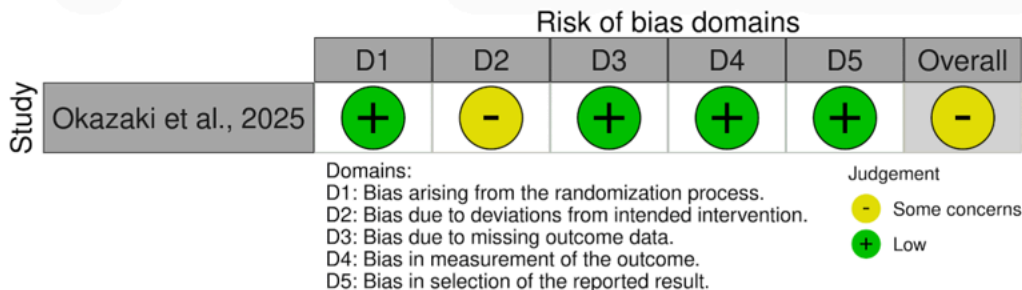


Figure 5
Risk of bias assessment for (A) observational studies and (B) randomized clinical trials.

Supplementary Files

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