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Original Article

Combined Oral Anticoagulant and Antiplatelet for Atrial Fibrillation and Cerebral Atherosclerosis: A Meta-Analysis

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Background and Purpose Patients with ischemic stroke with both atrial fibrillation (AF) and large artery atherosclerosis (LAA) represent therapeutic challenges, and the optimal antithrombotic regimen remains uncertain. We conducted a meta-analysis comparing oral anticoagulant (OAC) monotherapy with OAC plus antiplatelet therapy in this population.

Methods PubMed and EMBASE were searched through June 30, 2025, for studies enrolling patients with ischemic stroke and evidence of both AF and LAA. Outcomes included recurrent ischemic stroke, major bleeding, all-cause mortality, and a composite outcome. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Peto method, with random-effects sensitivity analyses, stratified by short-term (<3 months) and long-term (≥1 year) follow-up.

Results Eight cohort studies were analyzed. In the short-term, combination therapy was associated with a reduced risk of recurrent ischemic stroke (OR, 0.37; 95% CI, 0.14–0.97; *P*=0.043), without a significant increase in major bleeding, although this association did not persist under random-effects sensitivity analysis (OR, 0.37; 95% CI, 0.13–1.07; *P*=0.067). Conversely, long-term combination therapy was associated with higher risks of major bleeding (OR, 1.25; 95% CI, 1.08–1.45; *P*=0.002), all-cause mortality (OR, 1.25; 95% CI, 1.01–1.54; *P*=0.039), and composite outcome (OR, 1.49; 95% CI, 1.27–1.74; *P*<0.001), without reducing recurrent ischemic stroke (OR, 1.12; 95% CI, 1.00–1.26; *P*=0.054).

Conclusions While long-term OAC plus antiplatelet therapy increases bleeding risk without preventing recurrent stroke, short-term combination therapy may offer benefits in selected patients with concomitant LAA, though this early efficacy signal should be interpreted with caution.

Keywords Atrial fibrillation; Atherosclerosis; Stroke; Anticoagulant; Antiplatelet

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Introduction

Identifying the cause of ischemic stroke and prescribing appropriate secondary prevention therapies are critical in reducing the risk of recurrence. Many patients with stroke present with well-defined etiologies, such as large artery atherosclerosis (LAA) or cardioembolism, enabling clinicians to tailor preventive strategies accordingly.[1] However, a significant proportion of patients still present with undetermined stroke mechanisms, complicating the delivery of optimal management strategies.[2,3] Among them, a notable and increasingly recognized subgroup consists of individuals with both atrial fibrillation (AF) and LAA. This group

continues to grow with the aging population and wider use of prolonged cardiac monitoring.[4-7]

This clinical overlap has prompted ongoing investigations into whether a combination of oral anticoagulants (OACs) with antiplatelet agents, typically indicated for AF and LAA, respectively, may improve outcomes in patients presenting with both cardioembolic and atherosclerotic stroke risk factors. Several observational studies investigating the role of combination therapy (OAC plus antiplatelets) in stroke patients with AF and LAA have reported contradictory results regarding both efficacy and safety.[8-15] A related clinical question has been addressed in patients with AF and coexisting coronary artery occlusive disease (CAOD), for which recent randomized trials and a meta-analysis have shown that OAC monotherapy may offer comparable protection against thrombotic events, while significantly lowering bleeding risk.[16-19] However, there is a lack of both randomized controlled trials and comprehensive systematic reviews or meta-analyses directly comparing OAC monotherapy with combination therapy involving antiplatelet agents for stroke patients with AF and LAA.

Therefore, we conducted a systematic review and meta-analysis to compare the efficacy and safety of combination therapy with OAC and antiplatelet agents with those of OAC alone in ischemic stroke patients with both AF and LAA as causes of stroke. We further examined whether the impact of combination therapy differed according to treatment duration, with the goal of informing individualized therapeutic strategies for this patient population.

Methods

Search strategy and study selection

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20] Two authors (H.L. and Y.D.K.) independently designed and executed a comprehensive literature search using the PubMed and EMBASE databases, searching from inception to June 30, 2025. Only studies published in English were included, while editorials, reviews, case reports, conference abstracts, and animal studies were excluded. The following search terms were used: ("stroke" OR "cerebral infarction") AND ("atherosclerosis" OR "LAA" OR "stenosis") AND ("atrial fibrillation" OR "AFib" OR "NVAF" OR "cardioembolism"). Two reviewers (H.L. and J.H.) independently screened all titles and abstracts, followed by full-text reviews of articles deemed potentially relevant. Disagreements were resolved by consensus or arbitration by a third reviewer (Y.D.K.). Studies that investigated stroke patients with evidence of both AF and LAA were included. Studies were deemed eligible if they compared the outcomes of patients receiving OAC monotherapy and those treated with a combination of OAC and antiplatelet agents. Only observational cohort studies were included, because no randomized controlled trials were identified. As the primary aim of this study was to compare the efficacy and safety of OAC plus antiplatelet therapy versus OAC alone in patients with ischemic stroke who had both AF and LAA, we included studies that reported clinical outcomes, such as recurrent ischemic stroke, major bleeding, all-cause mortality, or a composite outcome, with raw event data to allow for the calculation of odds ratios (ORs).

Outcome of interest

The primary efficacy and safety outcomes were recurrent ischemic stroke and major bleeding, respectively. The secondary outcomes included a composite outcome and all-cause mortality. To assess how treatment effects may vary over time, outcomes were stratified into short-term (<3 months) and long-term (≥1 year) periods, allowing for the direct evaluation of temporal differences in both efficacy and safety. The composite outcomes were defined based on the criteria used in the original studies. For studies lacking a predefined composite outcome, we utilized an endpoint comprising all-cause mortality, ischemic heart disease, and stroke. The definitions of ischemic heart disease, stroke, and major bleeding were also considered, as reported in individual studies.

Data extraction

The following data were extracted from each of the included studies: study design; cohort description; baseline characteristics, including mean or median age; percentage of males; geographic location; type of OAC used; and, when available, the prevalence of cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia. The definition of the LAA used in each study was also recorded. The duration of follow-up was noted, and when studies reported event rates for different periods, short-term (<3 months) and long-term (≥1 year) outcomes were extracted separately. For each study, the event rates for recurrent ischemic stroke, major bleeding, all-cause mortality, and the composite outcome were collected. The ORs and 95% confidence intervals (CIs) were calculated based on raw event data.

Study quality assessment

Study quality was assessed using the Newcastle–Ottawa Scale, which examines selection, comparability, and outcome domains, with a maximum score of 9 points. All included studies scored 7 or higher, indicating an overall moderate-to-high quality (Sup-

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plementary Figure 1).

Statistical analysis

All outcomes were analyzed using a fixed-effects model based on the Peto one-step odds ratio method, given its robustness in the setting of low event rates.[21] Analyses were conducted separately for short-term (<3 months) and long-term (≥1 year) follow-up periods. For sensitivity analysis, the Mantel–Haenszel method with a random-effects model was applied to evaluate the consistency of the pooled estimates. Effect sizes are reported as ORs with corresponding 95% CIs. Statistical heterogeneity was evaluated using Cochran's Q test and I^2 statistic. I^2 values were interpreted as follows: low (25%–50%), moderate (50%–75%), and high (>75%) heterogeneity. Funnel plots were used to assess publication bias. Statistical significance was set at $P<0.05$. R version 4.3.3 (http://www.R-project.org; R Core Team, Vienna, Austria) was used for all statistical analyses.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Results

Literature review, study selection and patient characteristics

The search strategy yielded 3,537 articles. After removing seven duplicates, the titles and abstracts of 3,530 articles were screened, of which 3,509 were excluded. Following a full-text review of 21 articles, 13 were excluded owing to a lack of relevant outcomes or insufficient data. Ultimately, 8 observational cohort studies were included in the meta-analysis (Figure 1). Of the included studies, 6 (75.0%) were conducted in Asia and 2 (25.0%) were conducted in North America. In one enrolled study, conducted by our group,[9] the original dataset included patients with systemic atherosclerosis. For this meta-analysis, we reanalyzed the dataset and extracted only those patients with cerebral or cervical atherosclerosis and AF, in accordance with the eligibility criteria of this study. In one study by Kim et al.[10] that reported results separately for patients with moderate-to-severe stenosis and complete occlusion, we only included data from patients with moderate-to-severe stenosis in the present analysis. Of the included studies, six (75.0%) enrolled patients treated with either warfarin or direct oral anticoagulants (DOACs), while two (25.0%) enrolled DOAC-only cohorts. Notably, none of these studies exclusively investigated a specific DOAC. Non-valvular AF was explicitly defined in three studies (37.5%), whereas the remaining five studies (62.5%) included patients with any type of AF. The definition of LAA varied, with six studies (75.0%) considering both intracranial artery stenosis (ICAS) and extracranial artery stenosis (ECAS), and two studies (25.0%) restricting inclusion to ECAS only. Sample sizes ranged from fewer than 500 participants in four studies (50.0%) to over 1,000 participants in two studies (25.0%) (Table 1). Supplementary Tables 1-3 summarize the baseline characteristics of the study populations. A descriptive comparison of baseline variables across short-term and long-term cohorts showed broadly similar distributions of

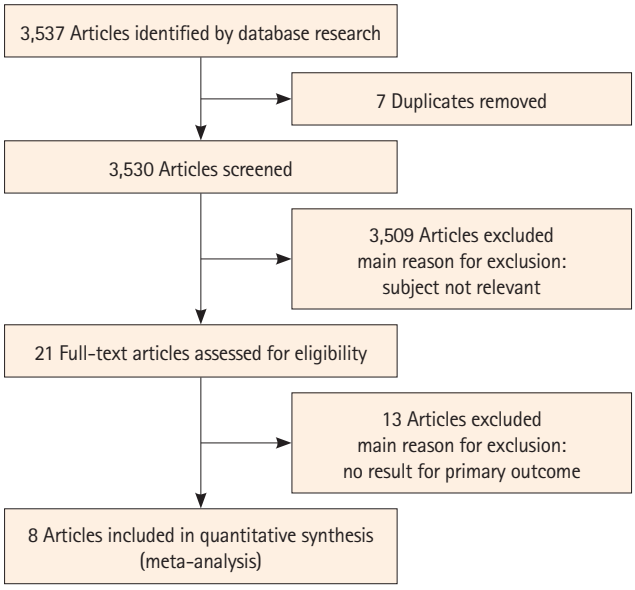

Figure 1. PRISMA flow diagram of study selection for the meta-analysis.

Table 1. Summary of baseline characteristics of the included studies

	Study number, n (%)
Region	
Asia	6 (75.0)
North America	2 (25.0)
Type of OAC	
Warfarin+DOAC	6 (75.0)
DOAC only	2 (25.0)
Type of AF	
Non-valvular AF	3 (37.5)
Any AF	5 (62.5)
Definition of LAA	
Extracranial artery stenosis	2 (25.0)
Intra-/extracranial artery stenosis	6 (75.0)
Sample size	
<500	4 (50.0)
500–1,000	2 (25.0)
>1,000	2 (25.0)

OAC, oral anticoagulant; DOAC, direct oral anticoagulant; AF, atrial fibrillation; LAA, large artery atherosclerosis.

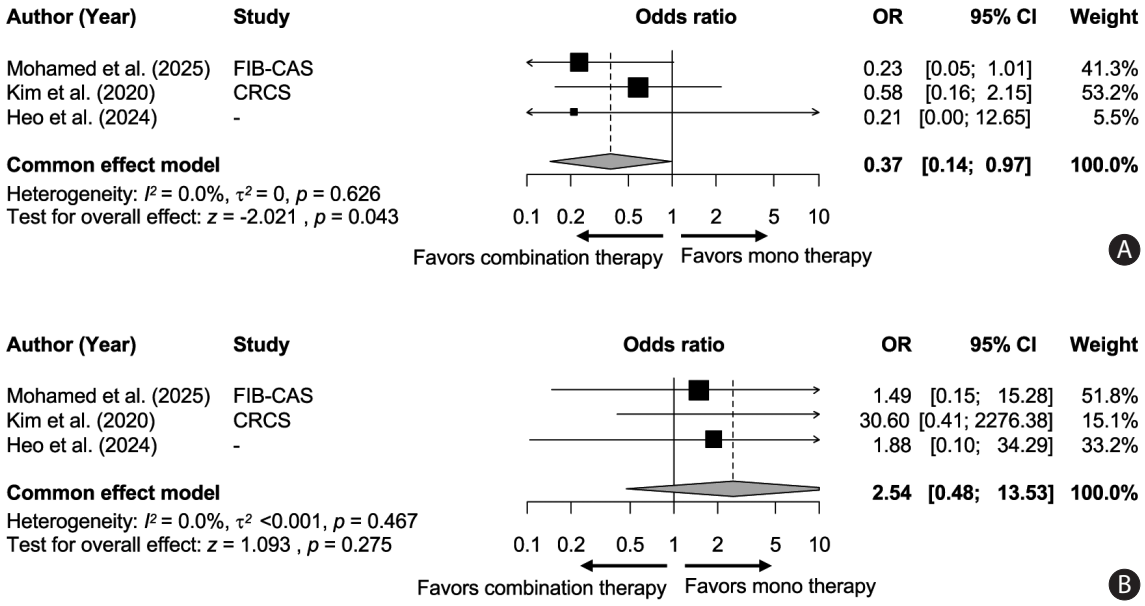

Figure 2. Forest plots showing short-term outcomes comparing OAC plus antiplatelet therapy versus OAC alone in patients with atrial fibrillation and large artery atherosclerosis. (A) Recurrent ischemic stroke. (B) Major bleeding. OR, odds ratio; CI, confidence interval; OAC, oral anticoagulant.

age and diabetes mellitus, whereas long-term studies tended to include a higher proportion of male participants and patients with hypertension (Supplementary Table 4). Visual inspection of the funnel plots revealed no clear evidence of publication bias across the evaluated outcomes (Supplementary Figures 2 and 3).

Short-term outcomes

Short-term outcomes were reported in three studies that provided data on both recurrent ischemic stroke and major bleeding within 3 months of the index event. For recurrent ischemic stroke, combination therapy was found to be associated with a significantly lower risk than OAC monotherapy (OR, 0.37 [95% CI, 0.14–0.97]; *P*=0.043; I^2=0.0%) (Figure 2A). For major bleeding, the odds were higher in the combination therapy group (OR, 2.54 [95% CI, 0.48–13.53]; *P*=0.275; I^2=0.0%); however, this difference was not statistically significant (Figure 2B). In addition, two studies reported short-term outcomes for all-cause mortality and the composite outcome. For all-cause mortality, only one study by Kim et al.[10] observed events, revealing a non-significant trend favoring combination therapy (OR, 0.44 [95% CI, 0.15–1.30]; *P*=0.136). For the composite outcome, the pooled estimate from both studies showed no significant difference between groups (OR, 0.73 [95% CI, 0.33–1.62]; *P*=0.438; I^2=0.0%) (Supplementary Figure 4).

Long-term outcomes

Long-term outcomes for recurrent ischemic stroke and major bleeding were reported in six studies. For recurrent ischemic stroke, combination therapy showed a trend towards a higher risk compared to OAC monotherapy (OR, 1.12 [95% CI, 1.00–1.26]; *P*=0.054) with moderate heterogeneity observed (I^2=71.1%) (Figure 3A). The risk of major bleeding was also higher with combination therapy (OR, 1.25 [95% CI, 1.08–1.45]; *P*=0.002), with moderate heterogeneity across studies (I^2=61.2%) (Figure 3B). Long-term all-cause mortality and the composite outcome were reported in four and five studies, respectively. For all-cause mortality, combination therapy was associated with a higher risk than OAC monotherapy (OR, 1.25 [95% CI, 1.01–1.54]; *P*=0.039; I^2=71.6%) (Supplementary Figure 5A). For the composite outcome, combination therapy was also associated with a higher risk (OR, 1.49 [95% CI, 1.27–1.74]; *P*<0.001; I^2=55.9%) (Supplementary Figure 5B).

Sensitivity analysis

For sensitivity analysis, we re-estimated the pooled effects using the Mantel–Haenszel random-effects model. For short-term outcomes, the direction of effect for recurrent ischemic stroke was consistent with the primary Peto analysis, favoring combination therapy, but did not reach statistical significance (OR, 0.37 [95% CI, 0.13–1.07]; *P*=0.067; I^2=0.0%). Major bleeding likewise did not differ between the groups (OR, 2.39 [95% CI, 0.48–11.81]; *P*=0.286; I^2=0.0%). All-cause mortality (OR, 0.34 [95% CI, 0.08–1.50]; *P*=0.154) and the composite endpoint (OR, 0.72 [95% CI, 0.30–1.72]; *P*=0.456; I^2=0.0%) were also not significantly different. For long-term outcomes (≥1 year), the effect estimates were directionally consistent with those of the primary Peto analysis. Recurrent ischemic stroke (OR, 1.17 [95% CI, 0.86–1.59]; *P*=0.326; I^2=70.7%), major bleeding (OR, 1.73 [95% CI,

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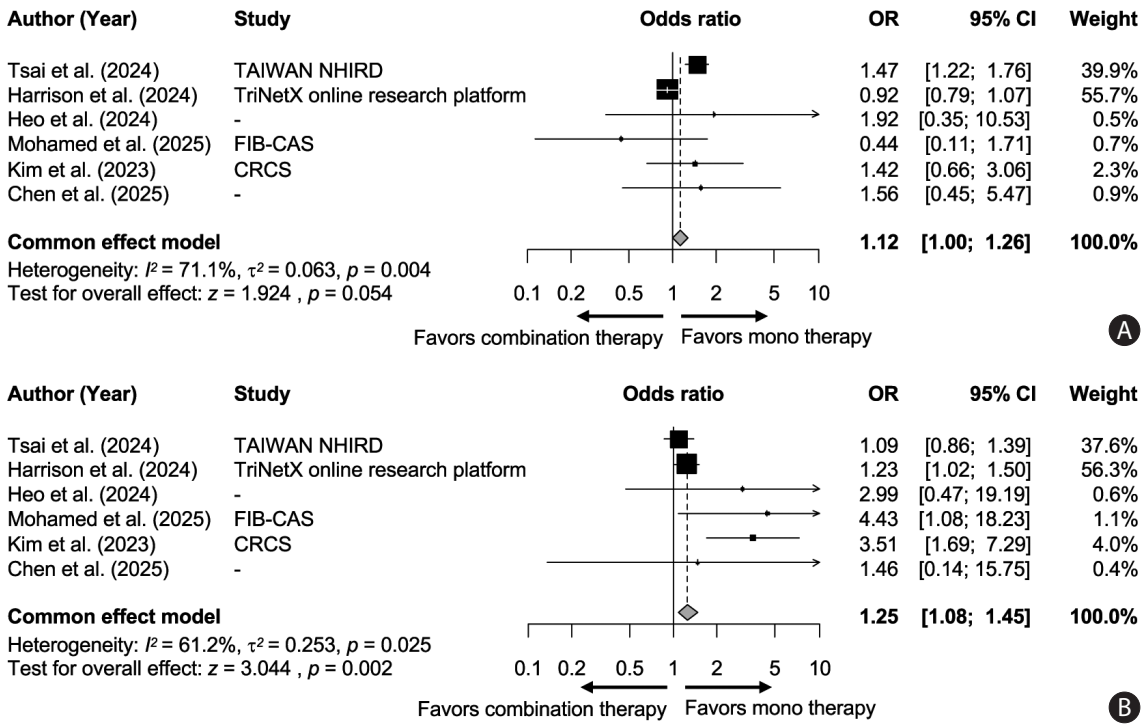

Figure 3. Forest plots showing long-term outcomes comparing OAC plus antiplatelet therapy versus OAC alone in patients with atrial fibrillation and large artery atherosclerosis. (A) Recurrent ischemic stroke. (B) Major bleeding. OR, odds ratio; CI, confidence interval; OAC, oral anticoagulant.

1.00–2.99]; *P*=0.050; I^2=56.9%), and all-cause mortality (OR, 1.32 [95% CI, 0.67–2.60]; *P*=0.146; I^2=69.9%) showed no significant differences between groups, whereas the composite endpoint remained significantly higher with combination therapy (OR, 1.67 [95% CI, 1.15–2.42]; *P*=0.007; I^2=52.8%) (Supplementary Figures 6 and 7).

Subgroup analysis

Subgroup analyses based on the modality used to define large-artery stenosis showed consistent effect directions across International Classification of Diseases (ICD)-based and imaging-confirmed cohorts. For long-term recurrent ischemic stroke, the two ICD-based studies demonstrated effect estimates aligned with the pooled effect of imaging-confirmed studies (all requiring >50% stenosis on angiography). For long-term major bleeding, the overall direction of effect also remained consistent across subgroups, although the test for subgroup differences was statistically significant (*P*=0.001), reflecting a more pronounced bleeding risk in imaging-based studies (Supplementary Figure 8).

Discussion

The coexistence of AF and cerebral atherosclerosis constitutes a uniquely high-risk stroke population, reflecting the combined impact of two major stroke etiologies: cardioembolism and LAA. Patients with both conditions are increasingly encountered in clinical practice, particularly in aging populations, where both AF and the atherosclerotic burden are increasing.[4,5,22] However, there is a substantial lack of high-quality data to guide antithrombotic management in this group. In contrast to CAOD, in which dozens of randomized trials have defined the optimal timing and duration of combination antithrombotic regimens,[23,24] evidence in stroke patients with overlapping etiologies remains sparse.[25] Current clinical guidelines recommend administering OAC monotherapy in patients with AF, as adding antiplatelet therapy provides little benefit, but increases bleeding risk.[26] However, in patients with potentially symptomatic ICAS or ECAS, evidence to guide treatment decisions is insufficient. The present meta-analysis addresses this gap by evaluating the efficacy and safety of combination therapy with OAC and antiplatelet agents (vs. OAC monotherapy) in stroke patients with AF and LAA.

The pooled results in this meta-analysis demonstrated that long-term combination therapy with OAC and antiplatelet agents failed to significantly reduce the rate of recurrent ischemic stroke compared to OAC monotherapy. However, this strategy is associated with a substantially increased risk of major bleeding, including intracranial hemorrhage. These findings are consistent with large-scale data in cardiology, where prolonged combination therapy has been found to increase bleeding complications without proportional ischemic benefit.[24,26] However, direct extrapolation from AF populations with coronary artery disease

should be approached with caution because the therapeutic context of cerebrovascular atherosclerosis differs fundamentally from that of coronary artery disease. Coronary lesions are frequently treated with percutaneous revascularization, and antithrombotic therapy in that setting is primarily directed toward preventing stent-related thrombosis during a defined healing period. By contrast, cerebrovascular plaques remain persistently stenotic without structural correction, generating different hemodynamic environments, patterns of plaque instability, and embolic mechanisms. These mechanistic differences underscore the need for cerebrovascular-specific evidence rather than reliance on data derived from AF with coronary artery disease. In particular, the risk of intracranial hemorrhage is notably higher in Asian populations, which are more vulnerable to bleeding complications under antithrombotic therapy regimens.[13,27,28] These findings reinforce current guideline recommendations favoring OAC monotherapy as the standard of care for secondary prevention in stroke patients with concomitant AF and cerebral atherosclerosis, and caution against the routine use of combination therapy beyond specific, time-limited indications.

While long-term combination therapy appears detrimental, our analysis indicates that the short-term use of OAC plus antiplatelet therapy, typically within the first 3 months (i.e., 30–90 days) after the index stroke, may reduce the risk of early recurrent ischemic events, particularly in patients in whom LAA is a contributing mechanism. This early vulnerability period is characterized by vascular inflammation, active platelet aggregation, and plaque instability.[29,30] These pathophysiologic changes may transiently increase the risk of artery-to-artery embolism, particularly among patients with high-grade symptomatic stenosis or ulcerated plaques. Evidence from stroke trials, such as the Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials strongly supports the use of short-term dual antiplatelet therapy in non-cardioembolic stroke, where dual antiplatelet therapy for a short period (<21 days) reduced early recurrence with an acceptable safety profile.[31] Although these trials did not enroll patients with AF, the biological rationale may extend to AF patients with mixed etiologies, particularly in the acute phase.

The potential benefits of short-term combination therapy may be particularly relevant among patients with stroke, which is more plausibly attributable to atherosclerotic mechanisms than to cardioembolism. Such considerations highlight that antithrombotic strategies should not be uniform across all AF patients with stroke, but should instead be determined by the individualized underlying stroke mechanism and adapted through time-dependent therapy adjustment. Patients with symptomatic atherosclerotic lesions or unstable plaques may derive short-term benefits from the addition of an antiplatelet agent, provided that this is followed by timely de-escalation to OAC monotherapy.[31] This is analogous to the transient use of dual antiplatelet therapy following coronary or carotid stenting,[26] which may help balance the efficacy and safety of the use of OAC with antiplatelets.

Taken together, our findings provide a practical treatment framework for this patient group, showing that chronic OAC monotherapy is the safest and most effective long-term treatment option for patients with AF and coexisting LAA. However, short-term combination therapy may be justified in selected patients with high-risk atherothrombotic features. Such decisions should be guided by careful assessment of the bleeding risk, individualized patient characteristics, and informed shared decision-making. Importantly, the duration of combination therapy should be limited to the early post-stroke period, with de-escalation to monotherapy once the high-risk window has passed. Ethnic and regional differences in susceptibility to bleeding must also be considered when applying these strategies to diverse patient populations.

Further, this meta-analysis highlights the urgent need for prospective, well-powered, randomized controlled trials to guide antithrombotic strategies in patients with AF and significant cerebrovascular atherosclerosis. Future trials should clearly define treatment duration, drug classes, and endpoints and incorporate centralized adjudication of ischemic and hemorrhagic events. Mechanism-driven subgroup stratification and modern imaging are critical for patient selection. Several important studies in this field are currently at different stages of investigation, including the completed ADD-ON trial (adding antiplatelets during edoxaban treatment in stroke patients with nonvalvular atrial fibrillation [NCT04010955]) and ATIS-NVAF trial (optimal antithrombotic therapy in ischemic stroke patients with nonvalvular atrial fibrillation and atherothrombosis [NCT03062319]), the ongoing ALLY trial (combination of antiplatelet and anticoagulation for AIS patients with concomitant NVAF and extracranial/intracranial artery stenosis [NCT06058130]), and the planned BEACON-AA trial (Benefits of Apixaban and Clopidogrel On stroke prevention in patients with Atrial fibrillation and cerebral Atherosclerosis). These studies vary in their designs, particularly regarding treatment duration and primary endpoints, thereby addressing different therapeutic windows. The BEACON-AA and ALLY trials focus on the high-risk acute-to-subacute phase by administering combination therapy for 1 month and 3 months, respectively, in patients with symptomatic intracranial or extracranial stenosis. In contrast, the ADD-ON study and ATIS-NVAF trials were designed to evaluate the safety and efficacy of long-term combination therapy ranging from 1.5 to 2

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years. Notably, the recently published ATIS-NVAF randomized trial reported that long-term combination therapy did not reduce ischemic cardiovascular events but significantly increased major and clinically relevant non-major bleeding, underscoring the safety concerns associated with prolonged dual therapy.[28] Furthermore, regarding endpoints, BEACON-AA utilizes recurrent ischemic lesions on magnetic resonance imaging as a surrogate marker to detect early efficacy, whereas the other trials assess composite clinical events. Highlighting these differences clarifies how short-term intensification may complement long-term maintenance strategies in future guidelines (Supplementary Table 5). These trials will provide essential data to support evidence-based guidelines. However, until such results are available, clinicians must rely on the best available evidence and clinical judgment, applying time-limited combination therapy only in strictly defined high-risk situations with an emphasis on de-escalation and safety monitoring.

Despite the consistent patterns observed, our analysis had important limitations. Most of the included studies were retrospective cohort analyses or registry-based studies, with inherent risks of selection bias and confounding factors. Given that the meta-analysis incorporated crude event counts from observational cohorts, unmeasured confounding and treatment-selection bias are unavoidable. These methodological constraints limit causal inference, and the conclusions should therefore be viewed as exploratory pending confirmation in randomized studies. Significant heterogeneity was identified in the antithrombotic regimens, including differences in the OAC type (vitamin K antagonists [VKAs] vs. DOACs), choice of antiplatelet agent, treatment duration, and outcome definition. Notably, the definition of composite outcomes varied substantially across the included studies. While some studies used predefined composite endpoints combining ischemic stroke, myocardial infarction, and all-cause mortality, others incorporated major bleeding or systemic embolism into their composite measures. This heterogeneity limits the clinical interpretability of the pooled composite outcome and underscores that these results should be considered exploratory rather than definitive. However, the ability to perform detailed stratified analyses was limited by the underlying data. Only one study provided DOAC-exclusive outcomes, and most cohorts included mixed VKA+DOAC populations, preventing a separate DOAC-only meta-analysis. In addition, P2Y12 inhibitor–specific results were not available in the included studies, precluding antiplatelet class–specific analyses that would reflect contemporary practice. Accordingly, the findings of this meta-analysis should not be generalized to specific contemporary regimens such as DOAC plus P2Y12 inhibitor combinations, which were not specifically evaluated in the included studies. These constraints arise from limitations in the existing evidence base rather than the analytic approach and highlight the need for standardized reporting in future studies. Additionally, much of the data was sourced from East Asian populations, where ICAS is more prevalent and bleeding risk under dual antiplatelet therapy is known to be higher.[27] Thus, while this analysis provides clinically valuable insights for these patients, this limits generalizability to Western populations with different risk profiles and genetic backgrounds. In addition, two included studies defined large-artery stenosis using ICD-9/10 diagnostic codes rather than imaging-based confirmation, which risks introducing misclassification of LAA status due to the lower specificity of administrative coding. However, in exploratory subgroup analyses stratified by stenosis ascertainment modality, the overall direction of the treatment effect remained generally consistent between imaging-based and ICD-based cohorts. Although these findings should be interpreted with caution, this suggests that differences in tools to define LAA did not appear to have substantially influenced the main conclusions of our analysis. Detailed information on antiplatelet agent subtype, lesion location, including distinctions between intracranial and extracranial atherosclerosis, and stenosis severity was also not consistently available, which limited further stratified analyses. These variables likely represent important sources of heterogeneity. Moreover, the real-world attribution of stroke mechanisms is often imprecise, particularly when patients harbor both AF and atherosclerotic lesions. Future studies should incorporate high-resolution vessel wall imaging, advanced cardiac monitoring, and standardized endpoint adjudication to improve the precision of the mechanism-specific patient classification.

Taken together, these sources of clinical and methodological heterogeneity indicate that the findings of this meta-analysis should be interpreted as hypothesis-generating rather than prescriptive for clinical practice. Although consistent patterns emerged across observational cohorts, the absence of randomized evidence, coupled with limitations in treatment definitions and drug-specific reporting, constrains the strength of any causal inference. Notably, since most included studies enrolled mixed populations treated with VKA and DOAC, these findings should not be directly extrapolated to current DOAC-based antithrombotic strategies. Accordingly, practice-changing recommendations should await rigorously designed randomized trials that apply standardized criteria, contemporary DOAC-based regimens, and clearly defined antiplatelet subclasses.

Conclusions

This analysis showed that while long-term OAC plus antiplate-

let therapy increases bleeding risk without preventing recurrent stroke, short-term combination therapy (<3 months) may offer benefits. Randomized controlled trials are required to confirm the efficacy and safety of these therapeutic strategies.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2025.04609.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: Young Dae Kim. Study design: Hyungwoo Lee, Young Dae Kim. Methodology: Hyungwoo Lee, Young Dae Kim. Data collection: Hyungwoo Lee, JoonNyung Heo, Young Dae Kim. Investigation: Hyungwoo Lee, JoonNyung Heo, Young Dae Kim. Statistical analysis: Hyungwoo Lee, Young Dae Kim. Writing—original draft: Hyungwoo Lee, Young Dae Kim. Writing—review & editing: all authors. Funding acquisition: Young Dae Kim. Approval of final manuscript: all authors.

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Supplementary Table 1. Overview of the eight included studies

Author/year	Study name	Region	Design	Outcome	Definition of composite outcome	Included patients	Anticoagulant	Antiplatelet	Duration of antiplatelet
Harrison et al.[8] /2024	TriNetX online research platform	North America	Cross-sectional National Retrospective	Ischemic stroke (short/long-term) Bleeding (long-term) Mortality (long-term)	N/A	Ischemic stroke patient with carotid disease and AF	DOAC	Dipyridamole, clopidogrel, or aspirin	N/A
Heo et al.[9] /2024	-	Asia	Cross-sectional Local Retrospective	Ischemic stroke (short/long-term) Bleeding (short/long-term) Mortality (short/long-term) Composite (short/long-term)	Composite of ischemic stroke, hemorrhagic stroke, major bleeding, myocardial infarction, and all-cause mortality	Ischemic stroke with newly diagnosed non-valvular AF and having large artery moderate to severe stenosis	VKA or DOAC	N/A	N/A
Kim et al.[10] /2020	CRCS	Asia	Cross-sectional National Retrospective	Ischemic stroke (short-term) Bleeding (short-term) Mortality (short-term) Composite (short-term)	Composite of ischemic stroke, hemorrhagic stroke, myocardial infarction, and all-cause mortality	Ischemic stroke patient with AF and concomitant large artery moderate to severe stenosis	VKA or DOAC	N/A	N/A
Kim et al.[11] /2023	CRCS	Asia	Cross-sectional National Retrospective	Ischemic stroke (long-term) Bleeding (long-term) Mortality (long-term) Composite (long-term)	Composite of ischemic stroke, intracranial hemorrhage, myocardial infarction, and all-cause mortality	Ischemic stroke patient with AF and TOAST UT (LAA+AF)	VKA or DOAC	N/A	N/A
Mohamed et al.[12] /2025	FIB-CAS	North America	Cross-sectional Local Retrospective	Ischemic stroke (short/long-term) Bleeding (short/long-term)	N/A	Ischemic stroke patient with AF and symptomatic ICAS or symptomatic ECAS	VKA or DOAC	Aspirin or P2Y12 inhibitor	N/A
Tsai et al.[13] /2024	TAIWAN NHIRD	Asia	Cross-sectional National Retrospective	Ischemic stroke (long-term) Bleeding (long-term) Composite (long-term)	Ischemic stroke and major bleeding	AF patients who experienced ischemic stroke and survived for at least 90 days and having ECAS	VKA (53.7%) or DOAC (46.3%)	N/A	N/A
Koyanagi et al.[14] /2023	ALVO	Asia	Cross-sectional National Retrospective	Composite (long-term)	Composite of all-cause death, major bleeding, ischemic stroke, acute coronary syndrome, acute myocardial infarction, and systemic embolism	Ischemic stroke patient with non-valvular AF and concomitant intra-/extra-cranial artery stenosis >50% who initiated apixaban	DOAC (apixaban)	Aspirin (70%) or clopidogrel (14%) or cilostazol (12%) or others (6%)	More than 90 days after the onset of the initial stroke or continued until the onset of any clinical events
Chen et al.[15] /2025	-	Asia	Cross-sectional Local Retrospective	Ischemic stroke (long-term) Bleeding (long-term) Mortality (long-term) Composite (long-term)	Composite of ischemic stroke, intracranial hemorrhage, myocardial infarction, gastrointestinal bleeding, and all-cause death	Ischemic stroke patient with non-valvular AF and LAA	VKA (0.8%) or DOAC (rivaroxaban 87.8%, dabigatran 11.4%)	N/A	N/A

"-" indicates no formal study name reported.
N/A, not available; AF, atrial fibrillation; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UT, undetermined type; LAA, large artery atherosclerosis; ICAS, intracranial atherosclerotic stenosis; ECAS, extracranial atherosclerotic stenosis; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant.

Supplementary Table 2. Baseline characteristics of included studies

Author/year	Sample size	Age (mean or median, yr)	Male (%)	Hypertension (%)	Diabetes mellitus (%)	Dyslipidemia (%)
Harrison et al.[8]/2024	3,029	74.2	56.3	82.6	36.1	N/A
Heo et al.[9]/2024	129	74.3	62.0	68.6	39.5	24.0
Kim et al.[10]/2020	585	73.7	52.3	75.2	39.4	29.1
Kim et al.[11]/2023	693	72.6	58.4	82.8	34.3	28.4
Mohamed et al.[12]/2025	69	74	56.5	91.3	39.1	N/A
Tsai et al.[13]/2024	2,404	75.8	62.4	89.3	40.7	N/A
Koyanagi et al.[14]/2023	54	81	48	31	5.6	N/A
Chen et al.[15]/2025	474	76	70.7	81	9.4	7.0

N/A, not available.

Supplementary Table 3. Definitions of cerebral artery stenosis in the included studies

Author/year	Cerebral artery stenosis	Definition of stenosis	Modality used to assess stenosis
Harrison et al.[8]/2024	Carotid artery disease	ICD-10-CM	ICD-based identification
Heo et al.[9]/2024	Relevant artery stenosis	Stenosis >50%	CTA or MRA or DSA
Kim et al.[10]/2020	Concomitant large artery moderate to severe stenosis	Stenosis >50%	CTA or MRA
Kim et al.[11]/2023	Relevant artery stenosis	Stenosis >50%	Diagnostic criteria for LAA (TOAST classification)
Mohamed et al.[12]/2025	Symptomatic ICAS or symptomatic ECAS	Stenosis >50%	CTA or MRA or doppler or DSA
Tsai et al.[13]/2024	ECAS	ICD-9-CM	ICD-based identification
Koyanagi et al.[14]/2023	Concomitant intra-/extra-cranial artery stenosis	Stenosis >50%	CTA or MRA or DSA
Chen et al.[15]/2025	Large artery moderate to severe stenosis	Stenosis >50%	CTA or MRA or DSA

ICAS, intracranial atherosclerotic stenosis; ECAS, extracranial atherosclerotic stenosis; ICD, International Classification of Diseases; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography; LAA, large artery atherosclerosis; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Supplementary Table 4. Descriptive comparison of baseline characteristics between short-term and long-term follow-up cohorts for each cardiovascular outcome

Outcome	Follow-up cohort (No. of studies)	Age (yr)	Male (%)	Hypertension (%)	Diabetes mellitus (%)
Ischemic stroke	Short-term (3)	74.7	48.4	68.7	30.7
	Long-term (6)	74.7	60.7	83.6	32.8
Major bleeding	Short-term (3)	74.7	48.4	68.7	30.7
	Long-term (6)	74.7	60.7	83.6	32.8
All-cause mortality	Short-term (2)	75.1	44.4	57.4	26.5
	Long-term (4)	74.6	61.4	80.2	29.2
Composite outcome	Short-term (2)	75.1	44.4	57.4	26.5
	Long-term (5)	76.1	59.8	74.0	25.4

Values represent the mean of study-level reported ages (means or medians, depending on individual study reporting).

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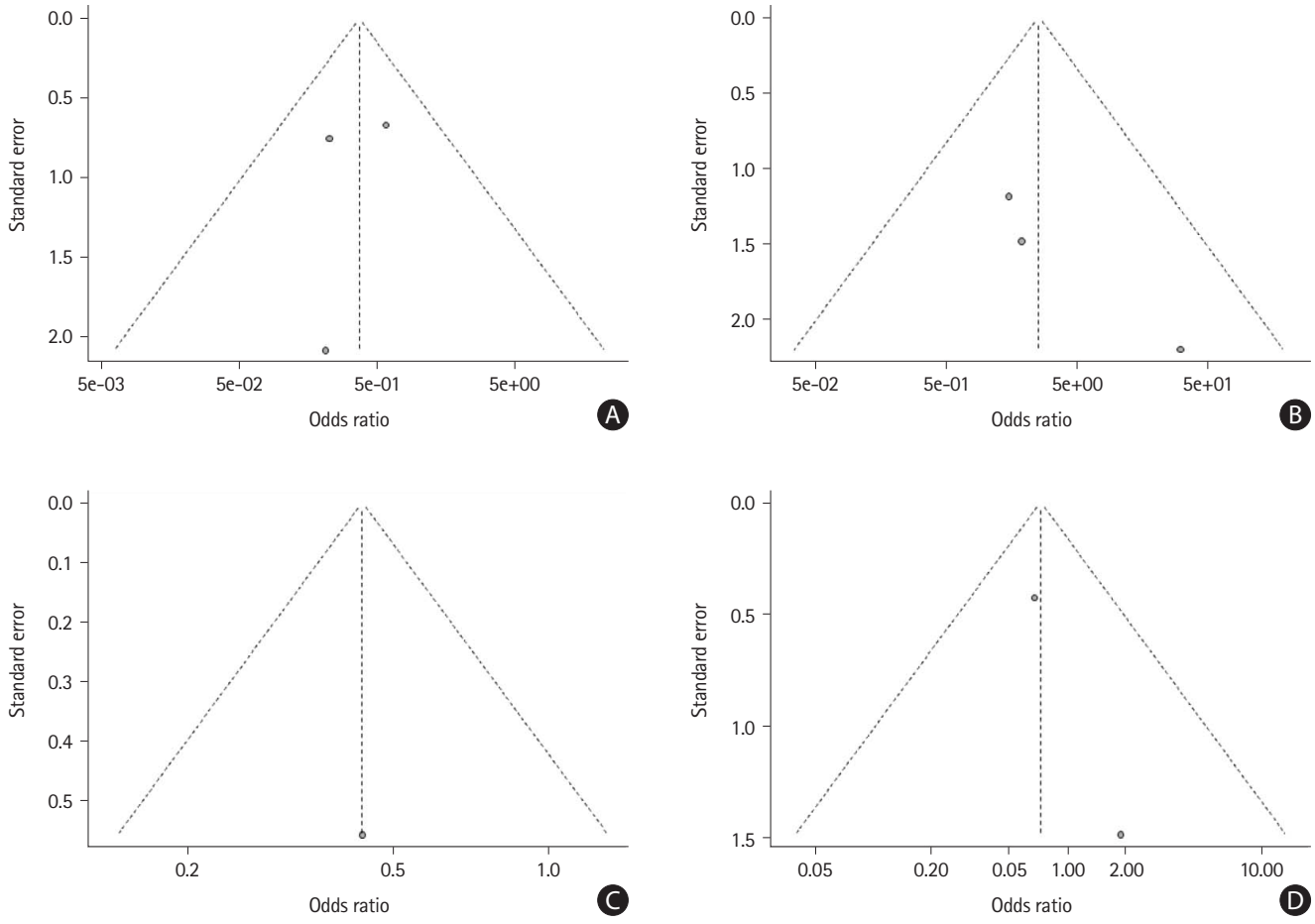
Supplementary Table 5. Key characteristics of randomized controlled trials evaluating combination therapy in patients with AF and concomitant atherosclerosis

Study name (NCT number)	Target population (key inclusion criteria)	Intervention arms (experimental vs. control)	Treatment duration (combination therapy)	Primary endpoint	Status
BEACON-AA (NCT07237308)	Acute ischemic stroke patients with AF and symptomatic intracranial or extracranial atherosclerosis	Apixaban + clopidogrel vs. apixaban alone	30 days	Incidence of recurrent ischemic lesions on brain MRI (DWI/FLAIR) at 30 days	Planned
ALLY (NCT06058130)	Acute ischemic stroke patients with concomitant NVAF and extracranial/intracranial artery stenosis (>50%)	Anticoagulation + antiplatelet vs. anticoagulation alone	90 days	Composite of ischemic stroke, hemorrhagic stroke, MI, systemic embolism, major bleeding, and vascular death at 3 months	Ongoing
ADD-ON (NCT04010955)	Stroke patients with NVAF and significant atherosclerosis (intracranial, extracranial, coronary, or peripheral)	Edoxaban + antiplatelet vs. edoxaban alone	Long-term (approx. 18 mon)	Major adverse cardiovascular events (MACE: ischemic stroke, hemorrhagic stroke, MI, vascular death)	Completed
ATIS-NVAF[28] (NCT03062319)	Ischemic stroke/TIA patients with NVAF and atherothrombotic disease	OAC + antiplatelet vs. OAC alone	Long-term (up to 2 yr)	Net clinical benefit (composite of ischemic cardiovascular events and major bleeding)	Published

AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation; TIA, transient ischemic attack; OAC, oral anticoagulant; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MI, myocardial infarction; MACE, major adverse cardiovascular events.

	Selection				Compatibility		Outcome		
Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohort	Total Quality score
Harrison et al.[8]		★	★	★	★	★	★	★	7
Heo et al.[9]		★	★	★	★	★	★	★	7
Kim et al.[10]	★	★	★	★	★	★	★	★	8
Kim et al.[11]	★	★	★	★	★	★	★	★	8
Mohamed et al.[12]		★	★	★	★	★	★	★	7
Tsai et al.[13]		★	★	★	★	★	★	★	7
Koyanagi et al.[14]	★	★	★	★	★	★	★	★	8
Chen et al.[15]		★	★	★	★	★	★	★	7

Supplementary Figure 1. Quality assessment of included studies using the Newcastle–Ottawa Scale.



Supplementary Figure 2. Funnel plots of short-term outcomes. (A) Recurrent ischemic stroke. (B) Major bleeding. (C) All-cause mortality. (D) Composite outcome.

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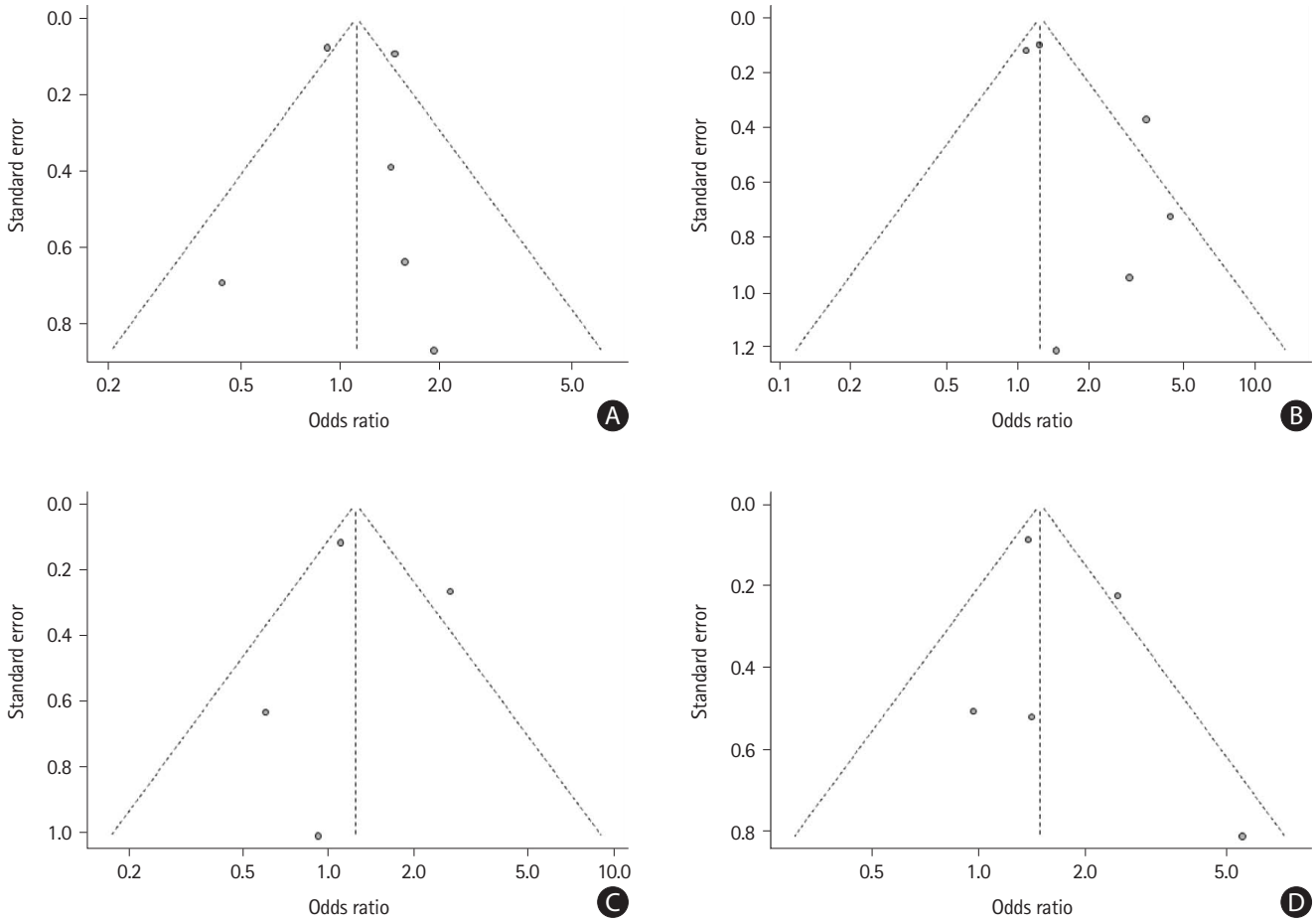
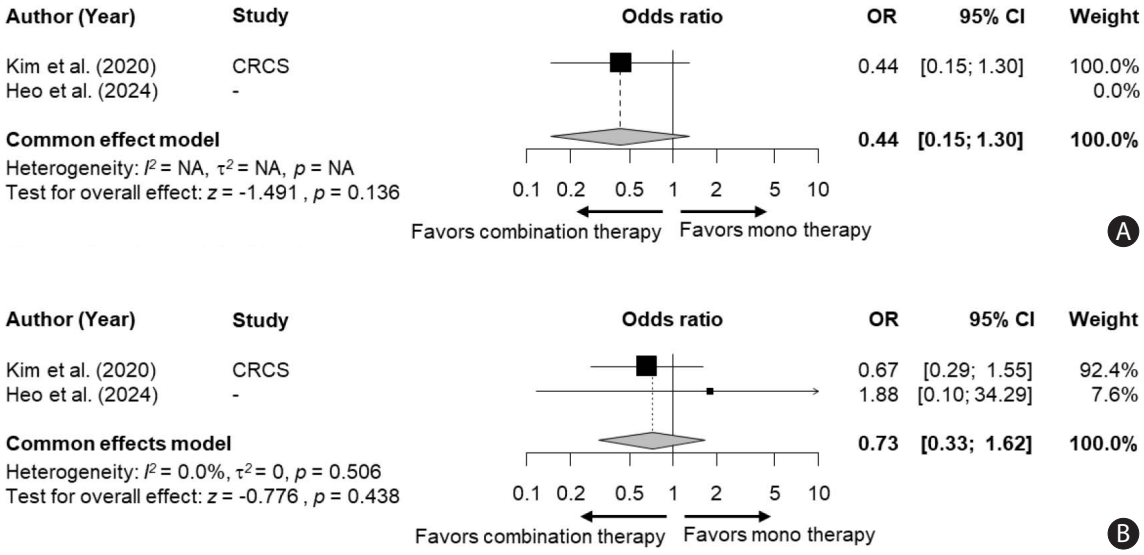
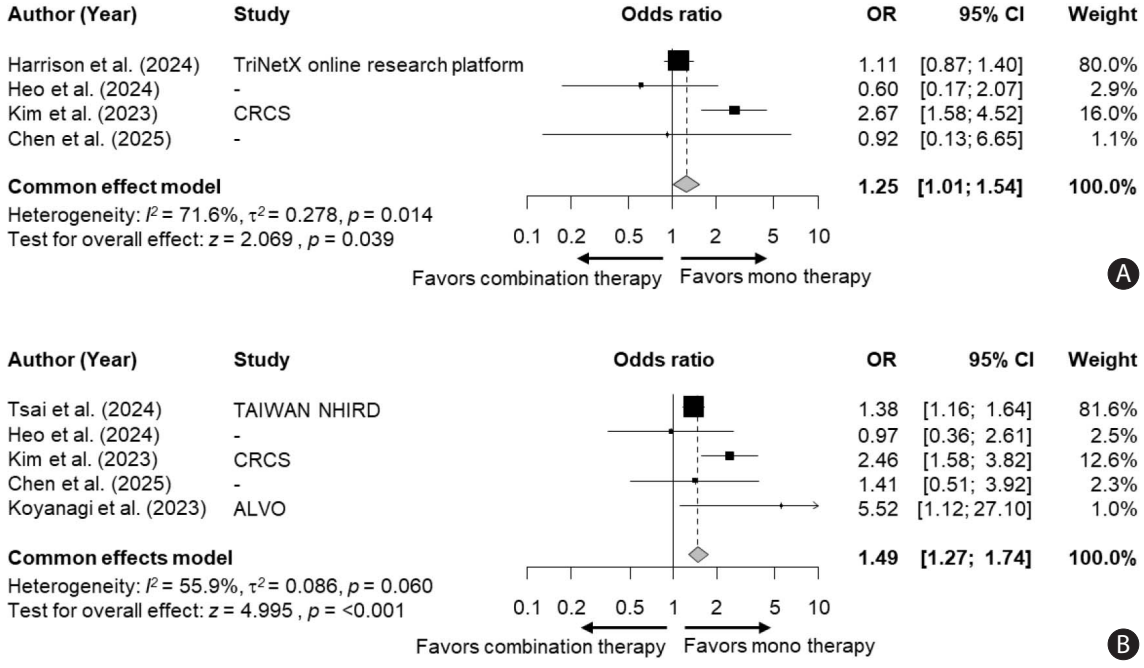


Supplementary Figure 3. Funnel plots of long-term outcomes. (A) Recurrent ischemic stroke. (B) Major bleeding. (C) All-cause mortality. (D) Composite outcome.



Supplementary Figure 4. Short-term outcomes comparing OAC plus antiplatelet therapy versus OAC alone in patients with atrial fibrillation and large artery atherosclerosis. (A) All-cause mortality. (B) Composite outcome. OR, odds ratio; CI, confidence interval; OAC, oral anticoagulant.



Supplementary Figure 5. Long-term outcomes comparing OAC plus antiplatelet therapy versus OAC alone in patients with atrial fibrillation and large artery atherosclerosis. (A) All-cause mortality. (B) Composite outcome. OR, odds ratio; CI, confidence interval; OAC, oral anticoagulant.

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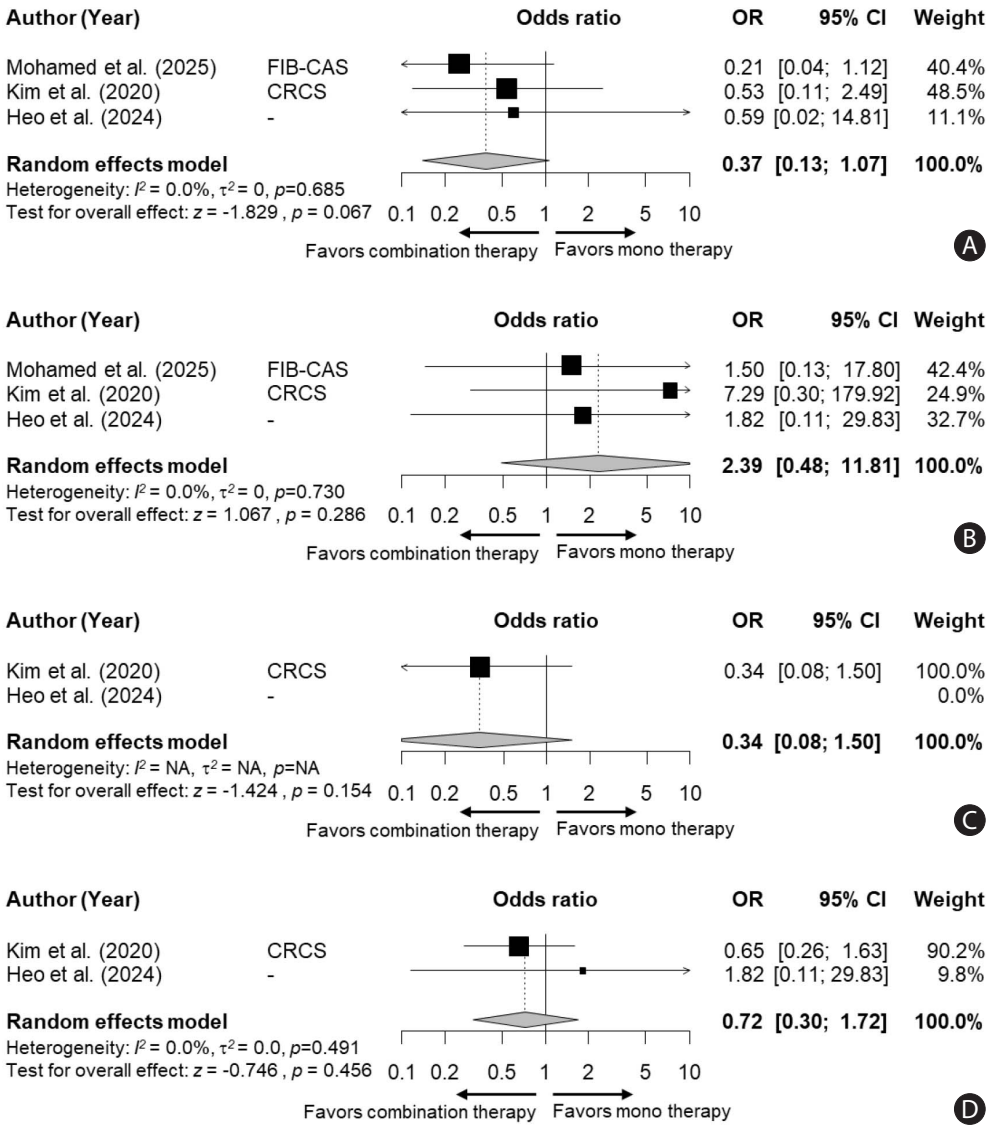
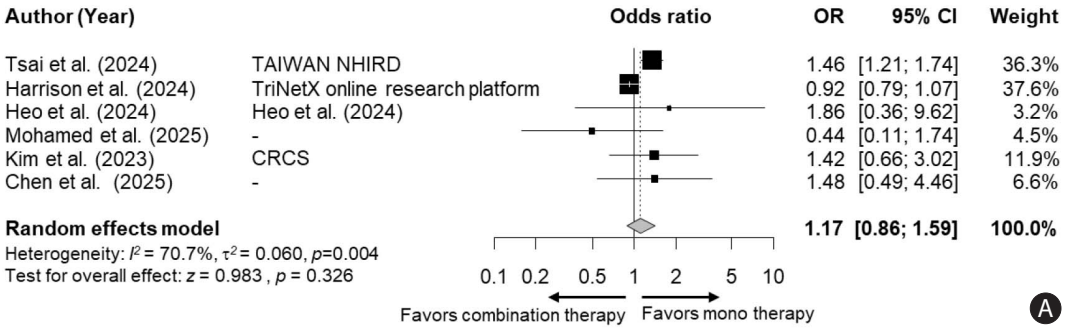
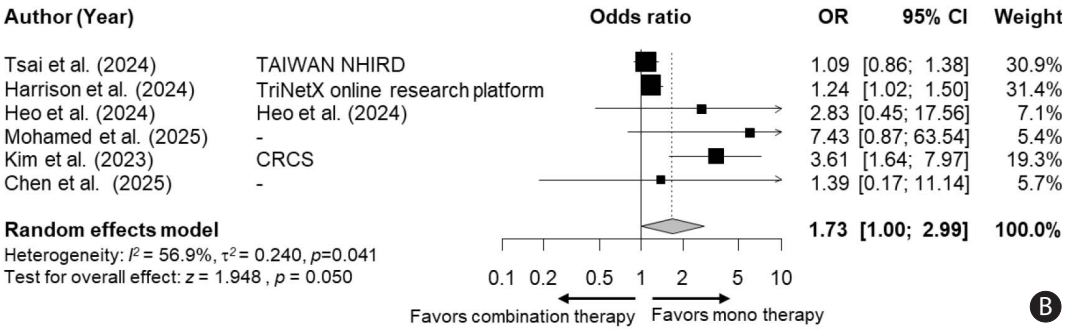
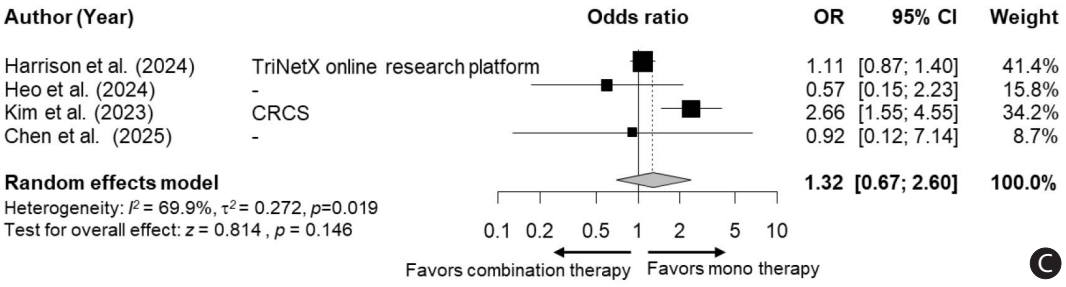
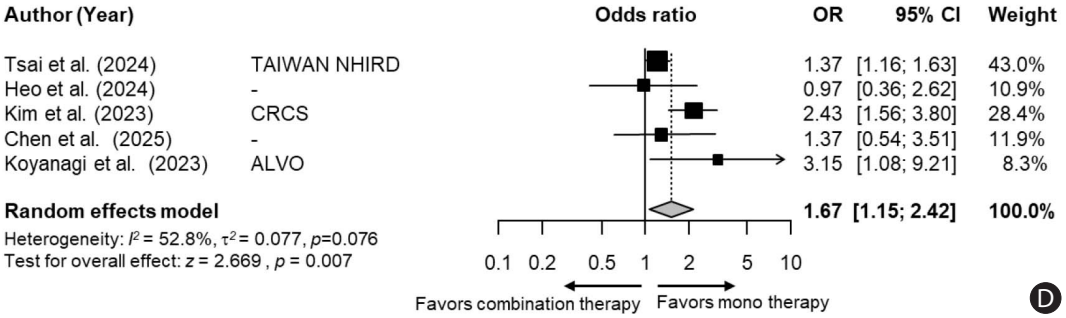


Supplementary Figure 6. Mantel–Haenszel random-effects sensitivity analysis for short-term outcomes. (A) Recurrent ischemic stroke. (B) Major bleeding. (C) All-cause mortality. (D) Composite outcome. OR, odds ratio; CI, confidence interval.









Supplementary Figure 7. Mantel–Haenszel random-effects sensitivity analysis for long-term outcomes. (A) Recurrent ischemic stroke. (B) Major bleeding. (C) All-cause mortality. (D) Composite outcome. OR, odds ratio; CI, confidence interval.

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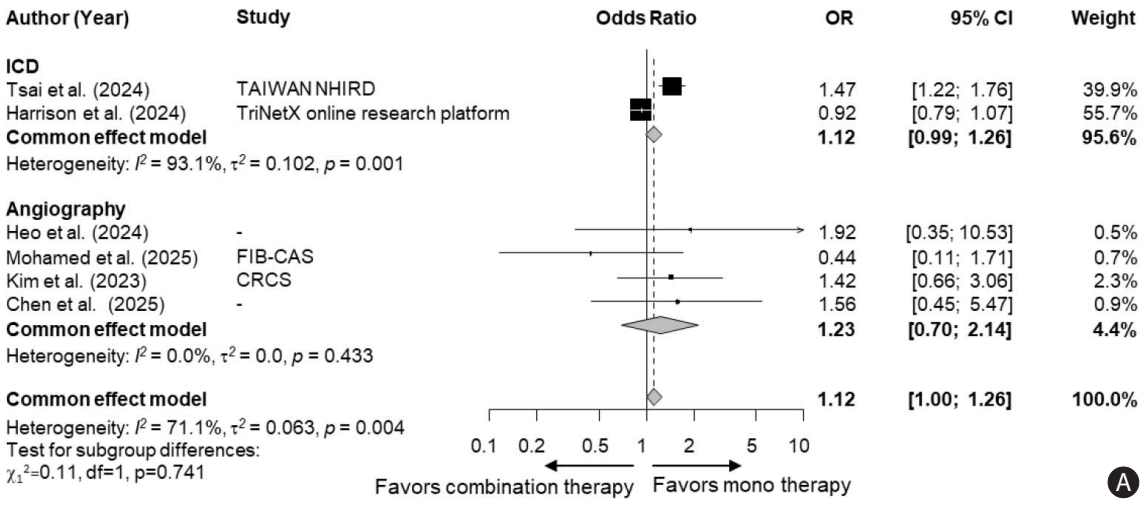

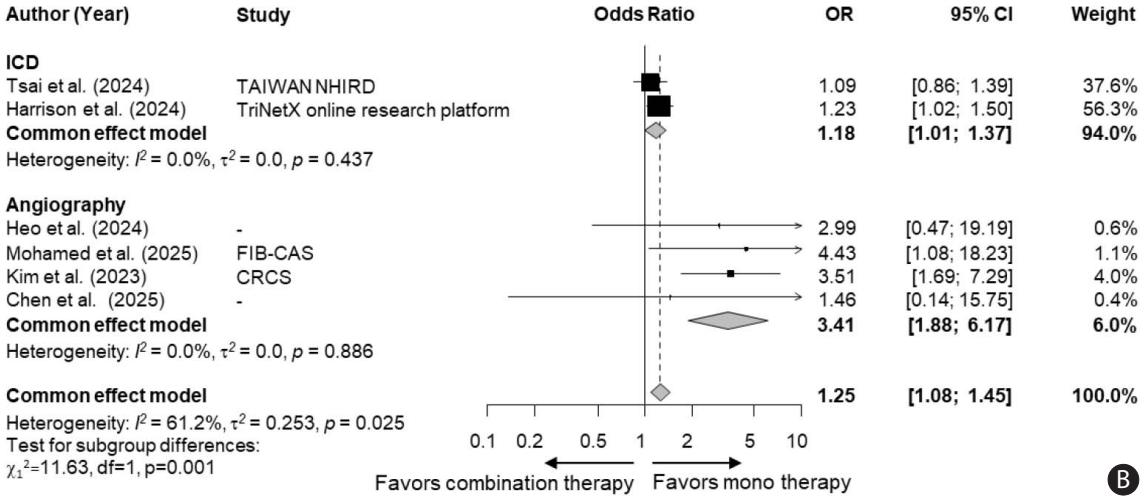

Supplementary Figure 8. Subgroup analysis of long-term cardiovascular outcome according to modality used to define large artery atherosclerosis (image-based vs. ICD-code). (A) Recurrent ischemic stroke. (B) Major bleeding. OR, odds ratio; CI, confidence interval; ICD, International Classification of Diseases.