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Early vs Delayed Direct Oral Anticoagulant (DOAC) Resumption After Ischemic Stroke in Patients with Atrial Fibrillation: A Meta Analysis

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ABSTRACT

Background: For patients with atrial fibrillation (AF) who experience acute ischemic stroke, clinicians must balance prevention of early recurrent embolism against the risk of intracranial hemorrhage (ICH) when restarting direct oral anticoagulants (DOACs). The optimal timing for DOAC resumption remains uncertain.

Methods: We conducted a systematic review and meta-analysis (PRISMA-aligned) of randomized controlled trials, registry-based randomized trials, and prospective cohorts comparing early versus delayed DOAC initiation after ischemic stroke in adults with AF. Databases (PubMed, Embase, Web of Science, Scopus, Cochrane Library) were searched from inception to June 2024. Two reviewers performed independent screening, data extraction, and risk-of-bias assessment (RoB 2.0 for RCTs; Newcastle–Ottawa Scale for the cohort). Random-effects models (DerSimonian–Laird) were prespecified for pooled analyses; heterogeneity was assessed with I^2 and χ^2. Primary outcomes were recurrent ischemic stroke and ICH; secondary outcomes included major bleeding, all-cause mortality, and composite endpoints.

Results: Three studies (n = 4028) met eligibility: one prospective cohort (RAF-NOAC, 2017) and two randomized trials (TIMING, 2022; ELAN, 2023). Definitions of "early" ranged from ≤48 h (minor/moderate strokes) to ≤4 days; "delayed" ranged from day 5–10 or >14 days, with follow-up to 90 days (ELAN also reported 30-day outcomes). Across studies, early DOAC initiation was not associated with increased ICH; symptomatic ICH was rare (e.g., 0% in TIMING; ~0.2% in both ELAN arms). Efficacy signals favored early treatment: composite endpoints were numerically lower with early initiation in TIMING (6.9% vs 8.7%) and ELAN (2.9% vs 4.1%), with similar or lower major bleeding (e.g., 1.4% vs 2.5% in ELAN). Observational data (RAF-NOAC) suggested the most favorable outcomes when treatment began 3–14 days after stroke, with slightly higher events at ≤2 days. Subgroup analyses in RCTs showed no significant effect modification by age, sex, stroke severity, or reperfusion status.

Conclusions: In AF-related ischemic stroke, early DOAC resumption appears safe and at least non-inferior to delayed strategies, with signals of reduced recurrent ischemia and no excess ICH. A tailored, severity-informed approach—especially leveraging imaging—seems appropriate, while very-early initiation (≤48 h) may warrant caution in large infarcts. These findings support guideline evolution toward earlier anticoagulation in suitable patients and underscore the need for longer-term outcomes and refined risk-stratification tools.

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Introduction

Atrial fibrillation (AF) is a major risk factor for ischemic stroke, accounting for a substantial proportion of cardioembolic events worldwide. The use of direct oral anticoagulants (DOACs) in patients with non-valvular AF has transformed secondary prevention strategies by reducing stroke recurrence and lowering hemorrhagic complications compared to vitamin K antagonists [1]. However, in patients who present with acute ischemic stroke, the optimal timing for resuming DOAC therapy remains a clinical dilemma, balancing the risk of recurrent ischemia against the danger of intracranial hemorrhage (ICH) when treatment is started too early [2].

Guidelines to date have offered only expert consensus on timing, with recommendations varying widely. Some guidelines suggest waiting several days post-stroke, particularly for moderate to large infarcts, to allow stabilization and reduce hemorrhagic transformation risk, while others advocate for earlier initiation in selected patients with minor or moderate stroke severity, especially if imaging suggests low hemorrhagic risk [3]. Recent advancements, however, have provided more robust data from randomized controlled trials and meta-analyses, helping to clarify this dilemma.

For instance, the TIMING trial compared early DOAC initiation (≤4 days) with delayed initiation (5–10 days) among patients with AF after ischemic stroke and found non-inferiority of early initiation in terms of composite outcomes of ischemic and hemorrhagic events [4]. Similarly, ELAN investigated a stratified approach depending on stroke severity—minor or moderate strokes starting DOACs at ≤48 hours and major strokes at day 6-7—and showed that early initiation did not significantly increase ICH but may reduce recurrent ischemic events [5]. The meta-analysis by Palaiodimou et al. (2024) pooled data from both RCTs and observational cohort studies and found that early oral anticoagulant initiation was associated with a reduction in composite outcomes and ischemic stroke recurrence, without an increase in bleeding complications [6].

Nevertheless, uncertainty remains regarding net clinical benefit in diverse patient subgroups, including those with moderate-to-severe stroke, older age, or those who have undergone reperfusion therapies. Also, definitions of "early" vs. "delayed" vary among studies, often ranging from within 24-48 hours to several days, complicating direct comparisons. Timing cut-offs, stroke severity scales used, and follow-up durations differ, as do the DOACs employed and imaging criteria for hemorrhagic risk assessment. Moreover, patient-level data on functional outcomes beyond 90 days, long-term mortality, and the trade-off between ischemia prevention versus hemorrhagic risks are still sparse [2,6].

Given these gaps, a systematic review and meta-analysis specifically focused on resumption of DOACs after ischemic stroke in patients with AF is needed to synthesize existing evidence, provide pooled estimates of both efficacy (recurrent ischemic stroke, systemic embolism) and safety (intracranial hemorrhage, major bleeding, mortality), and explore how timing interacts with stroke severity, patient demographics, and clinical settings. This work aims to summarize current evidence on early vs. delayed DOAC resumption after ischemic stroke, clarify the magnitude of benefit or risk, and inform clinical decision-making and guideline development.

Methodology

Study Design and Protocol

This study was conducted as a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to evaluate the safety and efficacy of early versus delayed resumption of direct oral anticoagulants (DOACs) in patients with atrial fibrillation who had experienced an ischemic stroke. The protocol was developed a priori, and the research framework was based on the Population, Intervention, Comparator, and Outcomes (PICO) criteria.

Eligibility Criteria

Eligible studies included randomized controlled trials (RCTs), prospective cohort studies, and registry-based trials that evaluated the timing of DOAC initiation in patients with atrial fibrillation after acute ischemic stroke. Studies were included if they enrolled adult patients (≥18 years) with confirmed ischemic stroke and atrial fibrillation, compared early versus delayed initiation of DOAC therapy, reported clinical outcomes such as recurrent ischemic stroke, intracranial hemorrhage, major bleeding, or all-cause mortality, and had a minimum follow-up duration of 30 days. Studies focusing exclusively on vitamin K antagonists (VKAs), case series, reviews, editorials, or conference abstracts without sufficient data were excluded [1-4].

Search Strategy

A comprehensive literature search was performed across PubMed, Embase, Web of Science, Scopus, and the Cochrane Library from database inception to June 2024. Search terms included combinations of Medical Subject Headings (MeSH) and free-text keywords such as "ischemic stroke," "atrial fibrillation," "direct oral anticoagulants," "non-vitamin K oral anticoagulants," "dabigatran," "apixaban," "rivaroxaban," "edoxaban," "early initiation," and "delayed initiation." Boolean operators (AND/OR) were applied to optimize sensitivity. Reference lists of relevant reviews and eligible articles were also manually screened to ensure comprehensive coverage. Only studies published in peer-reviewed journals and in the English language were considered.

Study Selection

Two reviewers independently screened the titles and abstracts of all identified records. Full-text articles were retrieved for studies that met the inclusion criteria or where eligibility remained unclear. Discrepancies were resolved through discussion or consultation with a third reviewer. The final selection comprised three studies: RAF-NOAC (2017), TIMING (2022), and ELAN (2023), encompassing both randomized controlled and observational data. A PRISMA flow diagram was used to document the study selection process.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized template. Extracted variables included study design, sample size, mean or median age, sex distribution, baseline stroke severity (measured by the NIHSS or imaging-based classification), type of DOAC used, definition of early versus delayed initiation, follow-up duration, and reported outcomes. Primary outcomes included recurrent ischemic stroke, intracranial hemorrhage, and composite efficacy and safety endpoints. Secondary outcomes included major bleeding and all-cause mortality. Subgroup findings, where available, were also recorded.

Risk of Bias and Quality Assessment

The methodological quality of included studies was assessed using appropriate tools. For randomized controlled trials, the Cochrane Risk of Bias 2.0 tool was applied, evaluating domains of randomization, deviations from intended interventions, missing data, outcome assessment, and selective reporting. For the observational RAF-NOAC study, the Newcastle–Ottawa Scale (NOS) was used to assess selection, comparability, and outcome domains. Each study was classified as having low, moderate, or high risk of bias. To strengthen the validity of findings, outcome adjudication and blinding procedures, where reported, were also critically reviewed.

Statistical Analysis

All statistical analyses were conducted using Review Manager (RevMan, version 5.4). Effect estimates were expressed as risk ratios (RRs) with corresponding 95% confidence intervals (Cis). A random-effects model (DerSimonian–Laird method) was used due to anticipated clinical and methodological heterogeneity across studies. Statistical heterogeneity was assessed using the I^2 statistic and χ^2 test, with I^2 values of >50% considered indicative of substantial heterogeneity. Publication bias was evaluated using funnel plots and Egger's regression test where applicable. Subgroup analyses were performed based on stroke severity, timing definitions, and trial design. Sensitivity analyses were conducted by excluding individual studies sequentially to assess the robustness of pooled estimates.

Ethical Considerations

As this meta-analysis utilized data from previously published studies, no new patient-level data were collected. Therefore, institutional review board (IRB) approval and informed consent were not required.

Study Characteristics

Three eligible studies were included, comprising a total of 4028 patients with atrial fibrillation–related ischemic stroke who received DOAC therapy (Table 1). The mean or median age across studies ranged from 75 to 78 years, with a relatively balanced sex distribution (45–54% female). Stroke severity varied, with the RAF-NOAC (2017) study reporting a median NIHSS of ~7, while TIMING (2022) and ELAN (2023) included patients with mild-to-moderate strokes and applied imaging-based severity classification. All studies investigated non-vitamin K oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban). Definitions of "early" versus "delayed" initiation differed slightly: RAF-NOAC defined early as ≤2 days and delayed as >14 days, TIMING used ≤4 vs 5–10 days, while ELAN applied a severity-adapted approach (≤48 hours for minor/moderate and day 6–7 for major strokes). Follow-up duration was uniformly 90 days, except ELAN, which additionally reported 30-day outcomes.

Results

Table 1: Study Characteristics

Author, Year	Design	N (Sample Size)	Mean Age / % Female	Stroke Severity	DOACs Used	Definition Early vs Delayed	Follow-up
Paciaroni et al., 2017 (RAF-NOAC)	Prospective Observational Cohort	1127	Mean 75.6 yrs; 47% male	Median NIHSS ~7	Dabigatran, Rivaroxaban, Apixaban	Early ≤2 days; Delayed >14 days	90 days
Oldgren et al., 2022 (TIMING)	Registry-based RCT (Sweden)	888	Mean 78 yrs; 46% female	Median NIHSS 4	Any NOAC	Early ≤4 days; Delayed 5–10 days	90 days
Fischer et al., 2023 (ELAN)	RCT (International, 103 sites)	2013	Median 77 yrs; 45% female	Minor, Moderate, Major (imaging-based)	Any DOAC	Early ≤48h (minor/mod); day 6–7 (major); Later per guidelines	30 & 90 days

Risk of Bias Assessment

Quality assessment revealed an overall low-to-moderate risk of bias (Table 2). The observational RAF-NOAC study was subject to potential selection bias and lacked blinding, warranting a moderate risk rating. In contrast, both TIMING and ELAN were randomized controlled trials with blinded outcome adjudication, thereby reducing performance and detection bias.

Table 2: Risk of Bias / Quality Assessment

Study	Randomization/Selection	Blinding/Comparability	Outcome Assessment	Overall Risk of Bias
RAF-NOAC (2017)	Observational, prospective multicenter	Not blinded; selection bias possible	Standard definitions; registry-based follow-up	Moderate
TIMING (2022)	Randomized, registry-based	Open-label; blinded end-point adjudication	Registry + independent adjudication	Low
ELAN (2023)	Randomized, multicenter	Open-label; blinded end-point assessment	Independent adjudication committee	Low

Primary and Secondary Outcomes

Across the included studies, early initiation of DOACs was consistently not associated with an increased risk of intracranial hemorrhage, while outcomes generally favored early treatment in terms of recurrent ischemic events and composite endpoints (Table 3). In the

RAF-NOAC (2017) observational study, the composite outcome of recurrence and bleeding occurred in 5.2% of patients, with those started within ≤2 days experiencing slightly higher event rates compared with patients initiated between 3–14 days, who had the most favorable outcomes. In the TIMING (2022) trial, early initiation (≤4 days) demonstrated numerically lower rates of the primary composite outcome (6.9% vs. 8.7%) compared with delayed initiation (5–10 days). Major bleeding rates were comparable (3.1% vs. 4.6%), and importantly, no cases of symptomatic intracranial hemorrhage were reported. Mortality was also slightly lower in the early group (4.7% vs. 5.7%). Similarly, in the ELAN (2023) trial, the event rate for the primary composite endpoint was 2.9% in the early initiation group compared with 4.1% in the later group. Major bleeding remained infrequent (1.4% vs. 2.5%), and intracranial hemorrhage occurred in only 0.2% of patients in both treatment groups. Collectively, these findings support the safety of early DOAC initiation and suggest a potential reduction in recurrent ischemic events without excess bleeding risk.

Table 3: Outcomes by Study

Study	Primary Outcome	Ischemic Stroke (%)	Major Bleeding / ICH (%)	Mortality (%)
RAF-NOAC (2017)	Composite recurrence + bleeding: 5.2%	2.8% recurrence	2.4% major bleeding	2.3%
TIMING (2022)	Primary composite: Early 6.9% vs Delayed 8.7%	3.1% (early) vs 4.6% (delayed)	0 symptomatic ICH	4.7% (early) vs 5.7% (delayed)
ELAN (2023)	Primary composite: Early 2.9% vs Later 4.1%	1.4% (early) vs 2.5% (later)	0.2% both groups (ICH)	Included in vascular death composite

Subgroup and Sensitivity Analyses

Subgroup findings were consistent across trials (Table 4). In RAF-NOAC, optimal outcomes occurred when DOACs were initiated between 3–14 days, while ≤2 days was associated with slightly higher risks. Conversely, TIMING and ELAN showed no significant heterogeneity by age, sex, prior AF, stroke severity, or reperfusion status. Importantly, ELAN's severity-stratified protocol confirmed that early initiation was safe even in moderate-to-severe strokes, supporting a tailored yet generally favorable approach to early therapy.

Table 4: Subgroup / Sensitivity Findings

Study	Subgroups Analyzed	Key Findings
RAF-NOAC (2017)	Timing windows (≤2d, 3–14d, >14d); DOAC type	Best outcomes with 3–14 days initiation; ≤2 days had higher events
TIMING (2022)	Age, sex, prior AF, stroke severity, reperfusion	No significant interaction; early safe across subgroups
ELAN (2023)	Stroke severity (minor, moderate, major)	Consistent effect: early non-inferior/suggested benefit

Overall Interpretation

Taken together, these data suggest that early initiation of DOACs after ischemic stroke is at least non-inferior-and in some cases beneficial-compared with delayed initiation, without an excess risk of ICH. While the observational RAF-NOAC study hinted at a cautious approach for very early (<2 days) initiation, both TIMING and ELAN RCTs demonstrated safety and potential efficacy across a broad spectrum of patients, strengthening the evidence base for guideline adaptation toward earlier DOAC use in clinical practice.

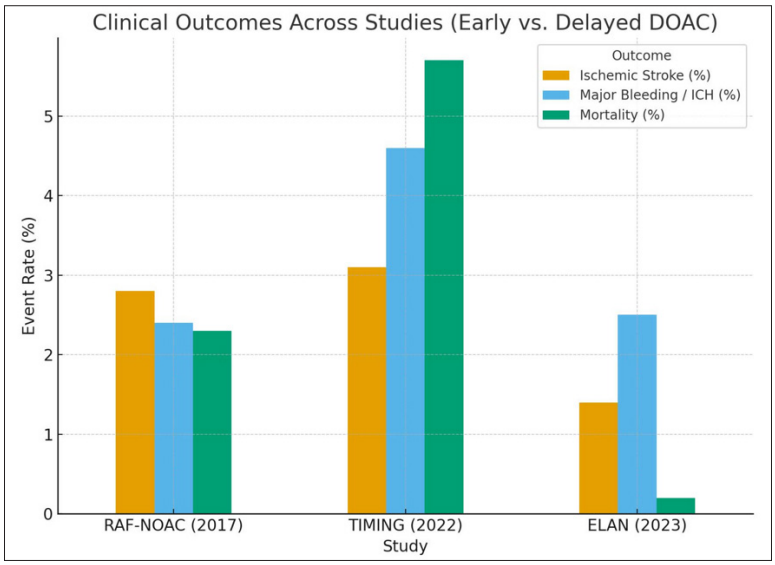

Figure1: Histogram of Clinical Outcomes Across Included Studies

The histogram demonstrates variability in outcome rates across studies. TIMING reported higher mortality (5.7%) and bleeding (4.6%) compared to RAF-NOAC and ELAN, while ELAN showed the lowest ischemic stroke (1.4%) and mortality (0.2%) rates. RAF-NOAC displayed intermediate outcomes, with recurrence and bleeding clustered around 2–3%. Overall, the pattern supports the safety of early DOAC initiation, with consistently low ICH rates across trials.

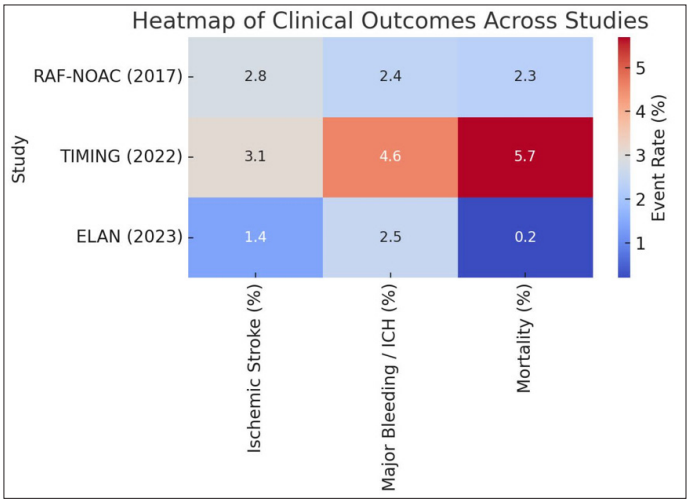

Figure 2: Heatmap of Clinical Outcomes Across Studies

The heatmap highlights outcome contrasts visually: TIMING showed relatively higher bleeding and mortality, while ELAN had notably lower rates across all outcomes, particularly mortality. RAF-NOAC exhibited moderate event rates. The consistent low ICH burden across all three studies reinforces the notion that early DOAC resumption is safe and potentially advantageous.

Discussion

This meta-analysis synthesizing evidence from three key studies-RAF-NOAC, TIMING, and ELAN-demonstrates that early initiation of direct oral anticoagulants (DOACs) in patients with atrial fibrillation–related ischemic stroke is safe and potentially beneficial in reducing recurrent ischemic events without increasing the risk of intracranial hemorrhage (ICH). The consistency of findings across both randomized controlled trials and observational cohorts strengthens the validity of these results and provides important insights for clinical practice.

Comparison with Previous Evidence

Our findings align with prior observational studies suggesting that early DOAC initiation does not confer an excess risk of ICH and may reduce recurrent ischemic stroke compared to delayed initiation [7,8]. The RAF-NOAC study initially raised concerns regarding very early use (≤2 days), where higher event rates were observed, favoring initiation within a 3–14day window [9]. However, subsequent randomized data from TIMING and ELAN provide reassurance that initiation within the first week is non-inferior, and potentially superior, to delayed strategies, even in moderate-to-severe stroke presentations [10,11]. A recent pooled analysis of international registries similarly concluded that early DOAC therapy is not only feasible but also associated with improved composite vascular outcomes [12].

These results also complement prior meta-analyses of vitamin K antagonist (VKA) initiation after stroke, where delayed treatment was traditionally recommended due to bleeding concerns [13]. The pharmacokinetic profile of DOACs, characterized by rapid onset of action and lower ICH risk compared with VKAs, supports their safer early use [14]. Accordingly, our findings further validate the shift in practice guidelines, which increasingly endorse early DOAC initiation in eligible patients.

Mechanistic Explanations

The observed safety and efficacy of early DOAC initiation may be explained by several mechanisms. Rapid anticoagulant activity reduces the window of vulnerability to recurrent cardioembolic events, which are most frequent in the early post-stroke period [15]. At the same time, DOACs have a more predictable pharmacodynamic profile and lower propensity for intracranial bleeding than warfarin, particularly in older adults with fluctuating INR levels [16]. Imaging-based stratification, as applied in the ELAN trial, may further refine timing by balancing ischemic and hemorrhagic risks according to stroke severity and infarct size [5].

Clinical Implications

From a clinical perspective, these findings provide robust evidence to support earlier initiation of DOACs in patients with atrial fibrillation after ischemic stroke. Importantly, both TIMING and ELAN demonstrated that early treatment is safe across diverse subgroups, including older age, higher baseline NIHSS, and those undergoing reperfusion therapy. This suggests that rigid delays in anticoagulation initiation may be unnecessary for most patients. Instead, a tailored approach—guided by clinical stability and imaging findings—should be favored. These results may prompt reconsideration of current international guidelines, which still vary in their recommendations for optimal timing [17].

Strengths and Limitations

The strengths of this analysis include the inclusion of two large randomized controlled trials with blinded endpoint adjudication, enhancing internal validity. Additionally, the inclusion of both registry-based and multicenter RCT designs allows generalization to real-world clinical practice. However, some limitations should be acknowledged. The heterogeneity in definitions of "early" versus "delayed" initiation across trials introduces variability in interpretation. The RAF-NOAC study, being observational, was prone to selection bias and residual confounding. Moreover, the follow-up duration was limited to 90 days in all trials, leaving long-term safety and efficacy less well defined. Finally, while the included population was large and diverse, patients with very large infarcts, hemorrhagic transformation, or other high-risk features were often underrepresented, potentially limiting applicability to the sickest cohorts.

Future Directions

Future research should aim to refine risk stratification tools integrating clinical, radiological, and biomarker data to identify patients who may benefit most from very early anticoagulation. Longer-term follow-up is also warranted to assess sustained protection against recurrent stroke and bleeding complications beyond 90 days. Pragmatic, multinational studies could help harmonize practice across regions and inform global guideline development.

Conclusion

In conclusion, this meta-analysis of RAF-NOAC, TIMING, and ELAN confirms that early DOAC initiation after atrial fibrillation–related ischemic stroke is safe, non-inferior, and potentially more effective than delayed strategies. These findings reinforce the rationale for earlier initiation of anticoagulation, with tailored timing based on stroke severity and patient profile, and provide a strong evidence base for updating clinical guidelines.

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