RESEARCH ARTICLE

Anticoagulation Strategies Following Breakthrough Ischemic Stroke While on Direct Anticoagulants

A Meta-Analysis

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Abstract

Background and Objectives

The management of anticoagulation after ischemic stroke while on direct oral anticoagulants (DOACs) is controversial. We performed an aggregate-data meta-analysis to compare anticoagulation strategies against each other to define the effect of switch to warfarin, switch to another DOAC, change in dosage, and add-on antiplatelet for the prevention of recurrent stroke, intracranial hemorrhage (ICH), any stroke, and mortality.

Methods

The study protocol was deposited with PROSPERO (CRD42025639057). We systematically searched MEDLINE, Scopus, and the Cochrane Library—all studies reporting on anticoagulation strategies after a stroke while on DOAC up to January 31, 2025. We included randomized controlled clinical studies and cohort studies with sample size ≥50 that (1) enrolled adult patients who experienced ischemic stroke while on DOACs, (2) assessed modifications to anticoagulation therapy, and (3) reported on at least one of the outcomes. Main outcome was recurrent ischemic stroke; secondary outcomes were ICH, all-cause mortality, and any stroke. We pooled estimates by random-effects modelling, reporting risk ratio (RR) with 95% CIs comparing anticoagulation strategies against each other.

Results

We retrieved 2,171 results, with 8 observational studies reaching quantitative synthesis (n = 14,307 patients, mean age = 75 years, 48% female). Switching to warfarin was associated with a higher risk of ischemic stroke compared with keeping the same DOAC (RR 1.80, 95% CI 1.42–2.29, I^2 = 0%, $n_{studies}$ = 5) or changing DOAC dosage (RR 1.72, 95% CI 1.20–2.45, I^2 = 0%, $n_{studies}$ = 4). Switching to warfarin was also associated with higher ICH rates compared with keeping the same DOAC (RR 2.90, 95% CI 2.01–4.18, I^2 = 0%, $n_{studies}$ = 5) and DOAC-to-DOAC switch (RR 3.25, 95% CI 2.13–4.96, I^2 = 0%; $n_{studies}$ = 5). Keeping the same DOAC and switching to another DOAC, independently from mechanism, had similar rates of primary and secondary outcomes.

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Glossary

AF = atrial fibrillation; **DOAC** = direct oral anticoagulant; **ICH** = intracranial hemorrhage; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-analyses; **RCT** = randomized controlled clinical trial; **RR** = risk ratio; **VKA** = vitamin K antagonist.

Discussion

Our meta-analysis indicates that switching to warfarin after a stroke while on DOAC seems less effective and safe in stroke recurrence prevention, ICH, and mortality compared with DOAC-based strategies.

Introduction

Ischemic stroke in patients with atrial fibrillation (AF) taking oral anticoagulants represents a significant clinical challenge, posing a dilemma for secondary prevention strategies.[1] Despite advances in stroke management and the widespread adoption of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs, including warfarin) for thromboembolism prevention, breakthrough stroke can still occur,[2] leaving clinicians with limited evidence to guide adjustments to anticoagulation regimens. Current guidelines from leading cardiovascular and neurologic societies do not offer clear recommendations for these scenarios, reflecting a gap in evidence-based recommendations.[3]

The urgency of this issue is underscored by the increasing prevalence of ischemic stroke and the potential risks associated with modifying anticoagulation therapy, including recurrent thrombotic events, major and minor bleeding complications.[4] Although individual studies have examined various strategies—ranging from dose adjustments to switching anticoagulant classes—these studies are often underpowered, making it difficult to draw definitive conclusions.[1,5]

This systematic review and meta-analysis aims to synthesize existing evidence to identify optimal anticoagulation strategies following ischemic stroke while on DOACs. By pooling data from available studies, this study seeks to determine the relative efficacy and safety of different interventions, focusing on critical outcomes including recurrent ischemic stroke, intracranial hemorrhage (ICH), and all-cause mortality.

Methods

Protocol and Search Strategy

This systematic review and aggregate-data meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[6] The protocol was preregistered in the PROSPERO database (CRD42025639057). Protocol and findings are reported according to the Meta-analysis Of Observational Studies in Epidemiology recommendations.[7] A comprehensive search was conducted in MEDLINE, Scopus, and the Cochrane Library from inception to January 31, 2025. Search terms included variations of anticoagulation, ischemic stroke, direct oral anticoagulants, novel oral anticoagulants, non-vitamin K oral anticoagulants, and related Medical Subject Headings terms. Boolean operators and filters were applied to exclude irrelevant study designs. Alerts for newly published studies were set to capture relevant literature during the review process.

We selected studies that (1) enrolled adult patients who experienced ischemic stroke while on DOACs; (2) assessed interventions involving modifications to anticoagulation therapy, including dosage adjustments, switching to VKA or another DOAC, with a similar or a different (e.g., from anti-Xa inhibitors to direct thrombin inhibitors or vice versa), or combination with antiplatelet therapy; and (3) reported on at least one of the primary (recurrent ischemic stroke) or secondary outcomes (ICH, any stroke, and all-cause mortality). We included randomized controlled clinical trials (RCTs), cohort and observational studies comparing at least 2 anticoagulation strategies. Exclusion criteria included sample size (<50 patients), insufficient outcome data, reviews, case reports, and studies involving pediatric populations. Two independent reviewers screened titles and abstracts for eligibility (M.R., N.M.). Studies meeting inclusion criteria were subjected to full-text review. Discrepancies were resolved by consensus or consultation with a third reviewer (M.P.).

Data Extraction

Data were extracted independently by 2 reviewers using a standardized template (M.R., N.M.). The following information was recorded: study characteristics, including author, year, design, setting, and sample size; participant demographics, including age, sex, race, cardiovascular risk scores, and baseline NIH Stroke Scale-score; interventions, including type and modification of anticoagulation therapy; and outcomes, including recurrent ischemic stroke, intracranial hemorrhage, all-cause mortality, and any stroke. Any disagreements were resolved by discussion with a third reviewer (M.P.) and/or the senior author (G.T.). In all cases of uncertain data, the authors of the studies were asked to share subgroup data to allow for multiple comparison of treatment strategies.

Risk of Bias Assessment

The Cochrane Risk of Bias 2.0 tool was used for RCTs, while the Risk of Bias in Non–Randomized Studies of Interventions was applied for observational studies. Assessments were conducted independently by 2 reviewers (M.R., N.M.), with discrepancies resolved by a third reviewer (M.P.) and/or the senior author (G.T.). Publication bias was planned with the funnel plot whenever more than 10 studies were available.

Statistical Analysis

A meta-analysis was conducted to calculate pooled estimates of risk ratios (RRs) for binary outcomes, with 95% CIs, of the primary outcome comparing strategies one vs another. The presence of heterogeneity was assessed using Cochran Q test and quantified using the I^2 statistic. Random-effects models were applied in the presence of significant heterogeneity (I^2 > 50%) or in all cases of possible heterogeneity arising from differences in study population and setting. Meta-regression analyses were conducted to explore the effect of sex, age, and vascular risk scores on the pooled estimates. In case of unavailable raw data, plots were analyzed with Python for data mining, back-constructing data from ratios and 95% CI. Analyses were performed using R, version 3.5.1, with metafor, meta, ggplot packages, and in-house built packages/functions (MR).

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was registered with PROSPERO (CRD42025639057) and did not require institutional review board approval given the meta-analytic nature.

Data Availability

This meta-analysis used data from available literature. Data can be retrieved from original publications.

Results

The systematic review retrieved 2,171 papers; 8 observational studies reached the final stage of quantitative synthesis[1,8-14] (eFigure 1 for the PRISMA flowchart), totalling 14,307 patients. Mean ± SD age was 75 ± 7 years, and 48.4% were women (5,102/10,548 available cases). Only 2 derived from prospectively collected registry data[1,8] (Table 1; eTable 1). Five studies were single-center or restricted to 1 country, while 3 studies were multicenter international studies.[1,8,12] Overall, studies had moderate quality and no publication bias, with comprehensive risk of bias ranging low to high, mainly in relation to bias regarding confounding, cohort selection, and intervention (Figure 1; eTable 2).

Ischemic Stroke Recurrence

Six studies provided data on ischemic stroke recurrence rates.[1,9-11,13,14] Switching to warfarin was associated with a higher risk of recurrent ischemic stroke compared with keeping the same DOAC (RR 1.80, 95% CI 1.42–2.29, I^2 = 0%, $n_{studies}$ = 5) or changing DOAC dosage (RR 1.72, 95% CI 1.20–2.45, I^2 = 0%, $n_{studies}$ = 4; Figure 2; eFigure 2 for treatment by comparator detailed meta-analysis; eTable 3 for summary results). Warfarin was associated with a nonsignificant trend toward an increase in recurrent ischemic stroke compared with DOAC to DOAC switch (RR 1.60, 95% CI 0.93–2.76, I^2 = 66%, $n_{studies}$ = 4). Keeping the prestroke DOAC was associated with a nonsignificant trend toward reduction in recurrent ischemic stroke compared with adding an antiplatelet to the DOAC (RR 0.76, 95% CI 0.56–1.02, I^2 = 0%, $n_{studies}$ = 3). No critical differences were found comparing the remaining strategies (Figure 2). The number of studies included did not allow for meta-regression analysis.

Intracranial Hemorrhage

Switching to warfarin was associated with a higher risk of ICH compared with keeping the same DOAC (RR 2.90, 95% CI 2.01–4.18, I^2 = 0%, $n_{studies}$ = 5), DOAC dosage change (RR 2.95, 95% CI 1.68–5.00, I^2 = 0%, $n_{studies}$ = 4), and DOAC to DOAC switch (RR 3.25, 95% CI 2.13–4.96, I^2 = 0%; $n_{studies}$ = 5, Figure 3; eFigure 3 for treatment by comparator detailed meta-analysis). Keeping the prestroke DOAC was associated with similar rates of ICH compared with adding an antiplatelet to DOAC and switching to another DOAC, independently from the change in DOAC mechanism (Figure 3).

Any Stroke

Switching to warfarin increased the risk of any stroke compared with keeping the prestroke DOAC (RR 2.02, 95% CI 1.59–2.57, I^2 = 0%, $n_{studies}$ = 5), changing DOAC dosage (RR 2.08, 95% CI 1.57–2.75, I^2 = 0%, $n_{studies}$ = 4), and DOAC to DOAC switch (RR 1.83, 95% CI 1.10–3.07, I^2 = 0%, $n_{studies}$ = 5), particularly for DOAC to DOAC switch toward a DOAC with a similar mechanism (RR 2.28, 95% CI 1.31–3.99, I^2 = 0%, $n_{studies}$ = 2; Figure 4; eFigure 4 for treatment by comparator detailed meta-analysis). Keeping the prestroke DOAC seemed to have a marginally nonsignificant reduction in any stroke compared with adding an antiplatelet to DOAC (RR 0.77, 95% CI 0.59–1.01, I^2 = 0%, $n_{studies}$ = 3), while a nonsignificant increase in any stroke risk was found for DOAC dosage change vs DOAC to DOAC switch (RR 1.21, 95% CI 0.95–1.53, I^2 = 0%, $n_{studies}$ = 5; Figure 4).

Mortality

Compared with adding an antiplatelet to DOAC, switching to warfarin was associated with a significant increase in mortality risk (RR 1.47, 95% CI 1.09–2.00, I^2 = 0%, $n_{studies}$ = 2; Figure 5; eFigure 5 for treatment by comparator detailed meta-analysis). No critical differences emerged from the comparison between other strategies, although estimates trends were nonsignificantly against switching to warfarin compared with DOAC-based strategies (Figure 5). The number of studies included did not allow for meta-regression analysis for secondary outcomes.

Discussion

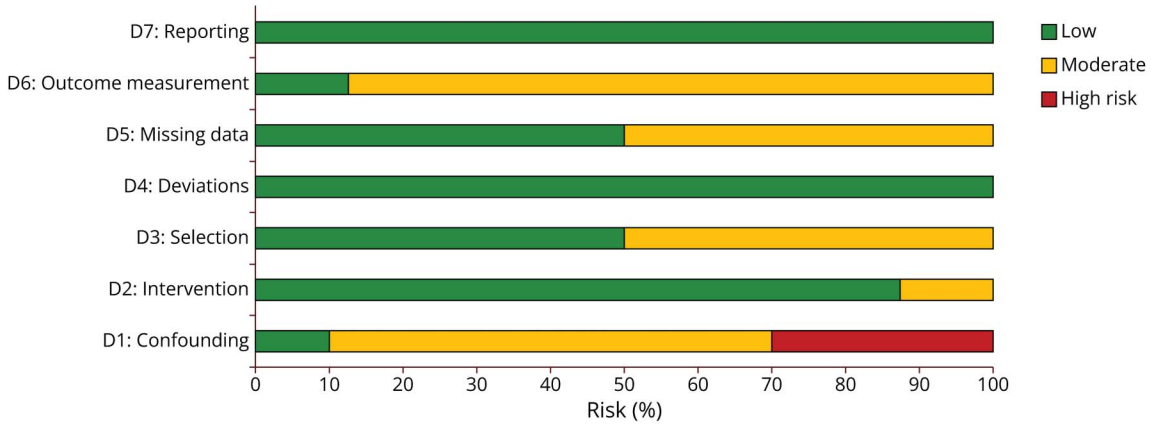
In this meta-analysis, we compared anticoagulation strategies in people with ischemic stroke while on anticoagulation with

Table 1 Characteristics of the Included Studies

Study	Country	Setting	Sample	Age, mean	Female, n (%)	Follow-up, mo	Ethnic group	NIHSS	IVT, n (%)	EVT, n (%)	CHA_2DS_2VASc	Competing etiology, n (%)	Nonadherence before index event, n (%)	Indication for anticoagulation	Low anticoagulant activity, n (%)
Duong et al., 2023[11]	Canada	Inpatient, emergency, outpatient	985	80	457 (46.4)	21	NA	NA	NA	NA	1.7 (1)	NA	445 (45)	NVAF	NA
Grifoni et al., 2024[10]	Italy	Inpatient	169	83	90 (53.3)	12	White	NA	NA (3.5)	NA (8.3)	5 (1.2)	34 (20.1)	NA	NVAF	NA
Hsieh et al., 2023[13]	Taiwan	Inpatient	3,759	62	NA	NA	Asian	NA	NA	NA	5.2 (2.1)	NA	NA	AF	NA
Ip et al., 2023[9]	Hong Kong	Inpatient	2,337	79	1,234 (52.8)	16	Asian	NA	NA	NA	4.6 (1.7)	257 (10.9)	NA	NVAF	NA
Lin et al., 2024[14]	Taiwan	Inpatient, outpatient	1,979	77	939 (47.5)	13	Asian	NA	NA	NA	3.8 (2.6)	NA	NA	NVAF	NA
Paciaroni et al., 2022[1]	Multicenter (Europe, USA)	Inpatient, outpatient	1,240	72	574 (46.3)	15	Mixed (largely white)	NA	NA	NA	4.7 (2.0)	320 (25.8)	NA	AF	NA
Polymeris et al., 2022[12]	Multicenter (Switzerland, Germany, USA)	Inpatient	2,946	81	1,404 (47.7)	3	Mixed (largely white)	6 (2.1)	351 (11.9)	787 (26.8)	NA	713 (24.2)	934 (31.7)	NVAF	220 (7.5)
Seiffge et al., 2020[8]	Multicenter (Europe, Asia, North America)	Inpatient, outpatient	892	67	404 (45.3)	≥3	Mixed (largely white)	5.8 (7.3)	1,085 (20.5)	189 (3.8)	5.0 (2.2)	NA	NA	NVAF	NA

Abbreviations: AF = atrial fibrillation; EVT = endovascular thrombectomy; IVT = IV thrombolysis; NA = not available; NIHSS = NIH Stroke Scale; NVAF = nonvalvular atrial fibrillation.

Figure 1 Risk of Bias in Included Studies

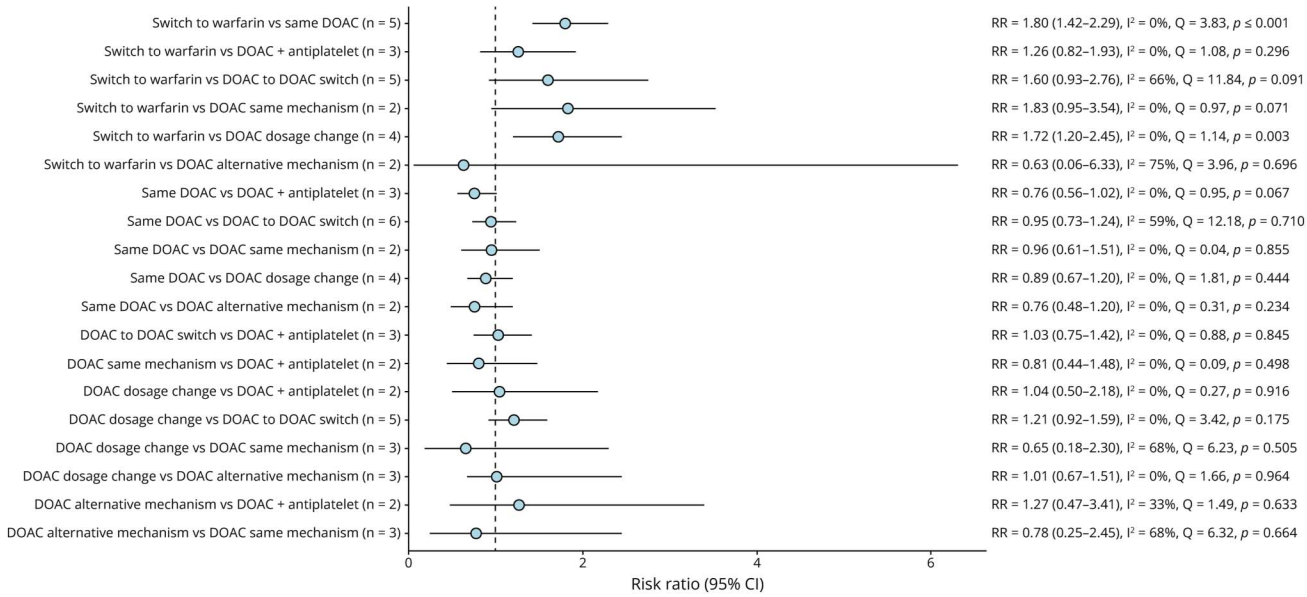


Risk of bias according to the Cochrane Risk of Bias for Non–Randomized Studies of Interventions. D1 = risk of bias due to confounding; D2 = risk of bias in classification of interventions; D3 = risk of bias in selection of participants into the study (or into the analysis); D4 = risk of bias due to deviations from intended interventions; D5 = risk of bias due to missing data; D6 = risk of bias arising from measurement of the outcome; D7 = risk of bias in selection of the reported result.

DOACs. Our results indicate that switching to warfarin is associated with significantly increased rates of ischemic stroke recurrence and ICH compared with keeping the prestroke DOAC. DOAC to DOAC switch and keeping the prestroke DOAC have a favorable profile compared with switching to warfarin in any stroke prevention, supporting that DOACs should be considered in preference to warfarin when reassessing patients after ischemic stroke while on anticoagulation. The addition of an antiplatelet on top of the DOAC does not seem to carry any benefit in stroke recurrence and ICH prevention while being potentially detrimental compared with maintaining prestroke DOAC for the prevention of any recurrent stroke. Finally, in the context of DOAC to DOAC switch, the results of this meta-analysis do not suggest any effect in ischemic stroke recurrence, ICH, or any stroke between switching to a different DOAC mechanism as compared with switching to another DOAC with a similar mechanism.

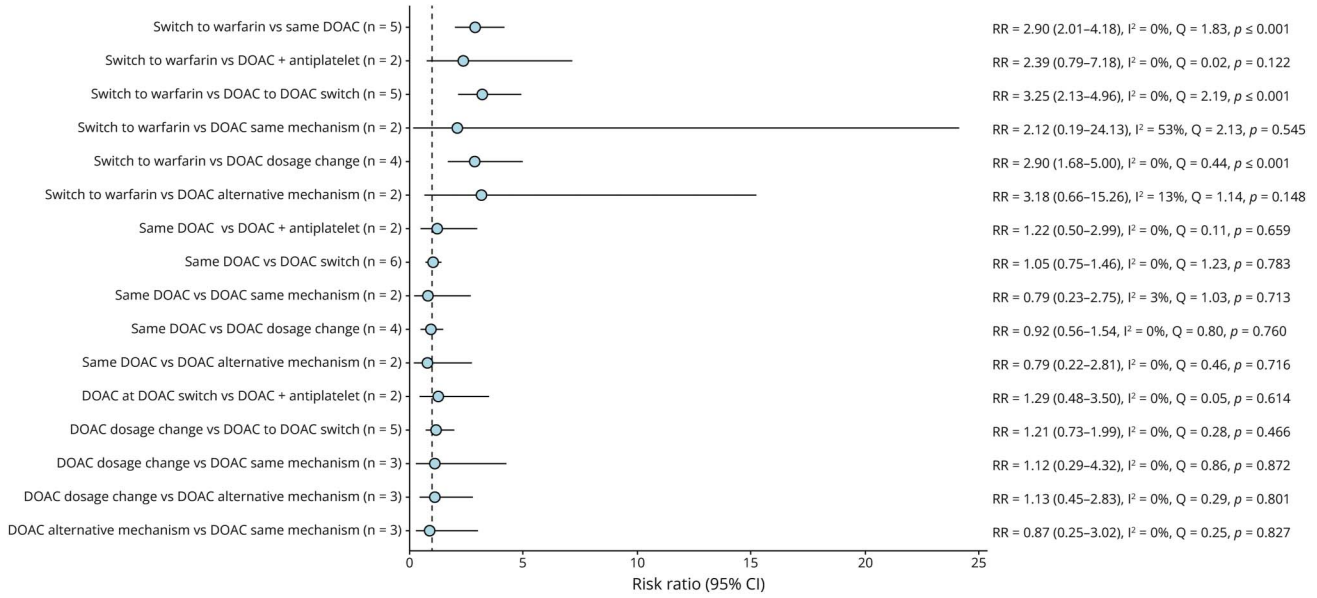
To this extent, our results suggest the need to tailor the treatment to the patient in all cases of stroke while on DOACs. Simply changing to a different DOAC, changing or

Figure 2 Ischemic Stroke Recurrence Pooled Estimates for Treatment Comparison



DOAC = direct oral anticoagulant; n = number of studies included in the meta-analysis; RR = risk ratio. The forest plot for each meta-analysis summarized here is available in eFigure 2.

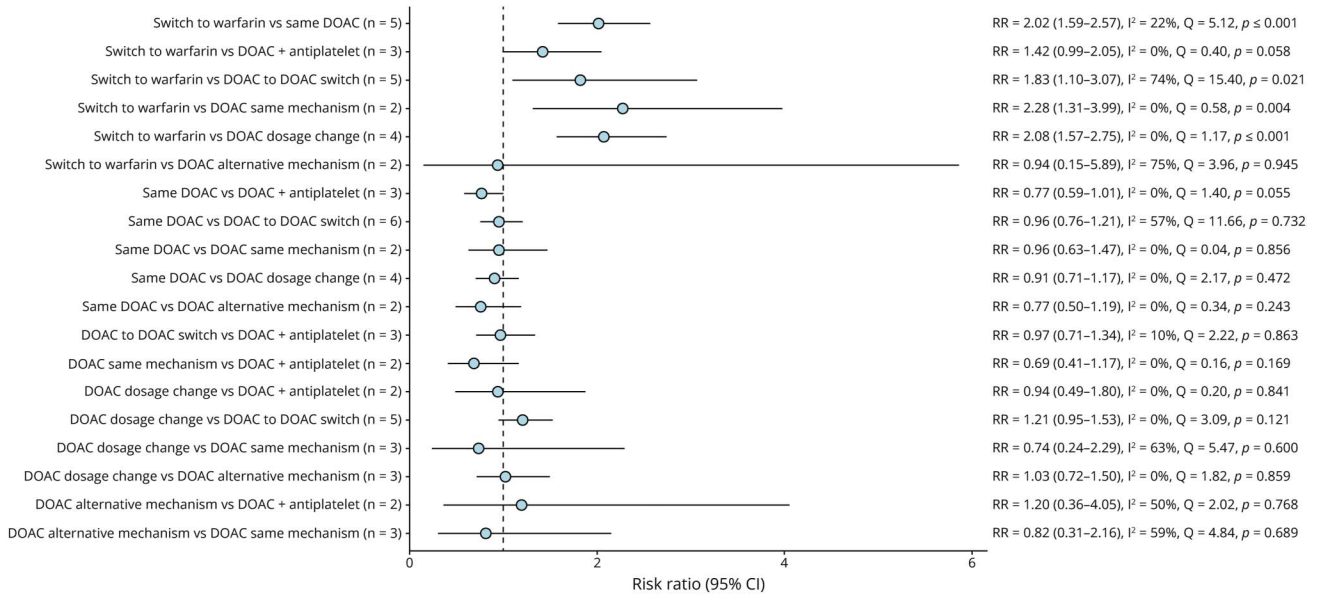
Figure 3 Intracranial Hemorrhage Pooled Estimates for Treatment Comparison



DOAC = direct oral anticoagulant; n = number of studies included in the meta-analysis; RR = risk ratio. The forest plot for each meta-analysis summarized here is available in eFigure 3.

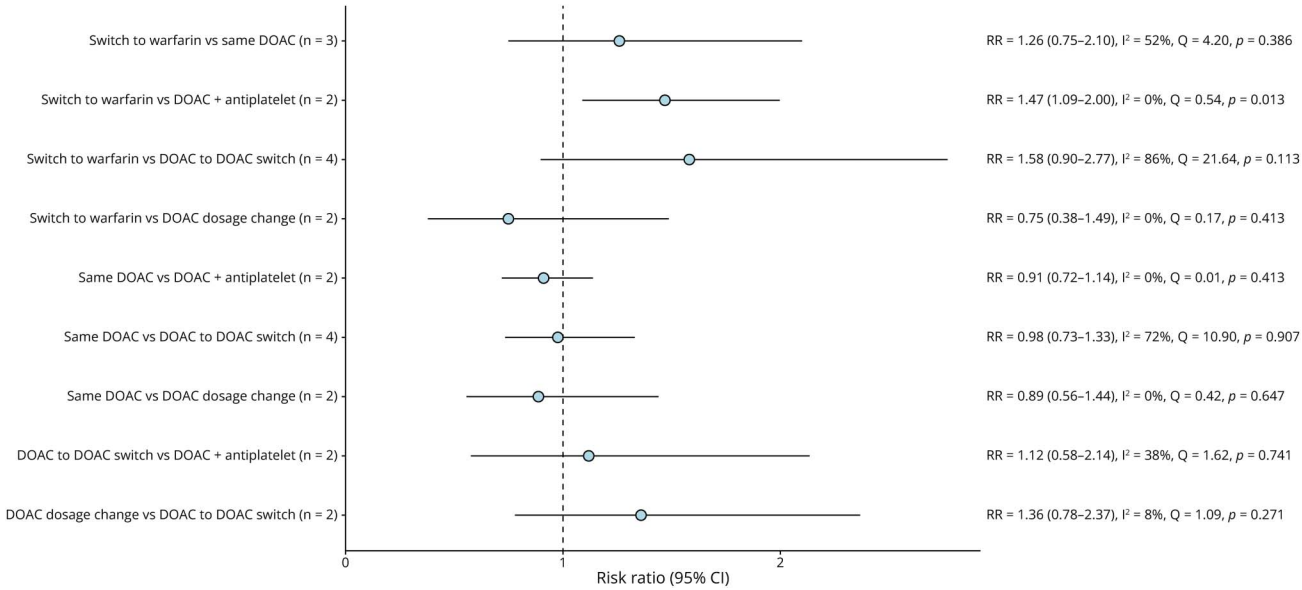
adjusting the dose does not clearly reduce the risk of another stroke. At the same time, the addition of an antiplatelet may even be detrimental in any stroke prevention. Therefore, checking for adherence issues, inappropriate dosage, pharmacologic interactions, and whether the stroke was truly attributable to AF rather than another competing etiology seems paramount.[12,15] Inappropriate dosing has been described in up to 20% of cases of DOAC prescription, particularly in the context of elderly population,[16] and may take part in the effect of DOAC dosage change on recurrent events after a stroke while on anticoagulants. Individualized treatment should take into account the potential comedications interacting with DOACs, as well as the comorbid conditions, such as kidney failure or gastric surgery, that may potentially

Figure 4 Pooled Estimates for Any Stroke for Treatment Comparison



DOAC = direct oral anticoagulant; n = number of studies included in the meta-analysis; RR = risk ratio. The forest plot for each meta-analysis summarized here is available in eFigure 4.

Figure 5 Pooled Estimates for Mortality for Treatment Comparison



DOAC = direct oral anticoagulant; n = number of studies included in the meta-analysis; RR = risk ratio. The forest plot for each meta-analysis summarized here is available in eFigure 5.

limit the absorption and adversely affect DOAC metabolism.[17-20] To this extent, antiseizure medications, statins, and previous gastric surgery should be carefully considered because they all may affect the absorption, metabolism, and bioavailability of DOACs.[17-19]

Evaluation for other potential stroke etiologies seems important for people with AF who experience ischemic stroke while taking oral anticoagulation.[12,21] Implementing an accurate screening, including cardiac and vascular imaging, may allow the early recognition of alternative sources of embolism, shortening the time to diagnosis and treatment.[22,23] Cancer-related coagulopathy or specific cardiac features may increase the risk of stroke, therefore calling for a patient-centered revision of the antithrombotic strategy.[24-26] Patients experiencing a stroke while on DOACs present with several cardiovascular comorbidities and potential competing etiologies,[21,27] therefore implying the need for tailored treatment and comprehensive care. Optimizing the rhythm control may contribute to lowering the risk of ischemic stroke recurrence,[28] with a synergic action with DOACs in cutting the risk of recurrent stroke.

Finally, optimal compliance with anticoagulation strategy should be prioritized. The nonadherence rate before the index stroke among the included studies was as high as 45%,[11] also suggesting a potential effect of patient sensitization to compliance issues after the event. As the rate of compliance can be extremely variable across studies,[12,29,30] clinicians should ensure that patients are well informed and understand that adherence is needed for an effective DOAC-based cardiovascular prevention.

There are limitations to this meta-analysis. First, the clinical heterogeneity of the studies and their limited number prevented from further subgroup or meta-regression analysis for both the primary and secondary outcomes, particularly regarding the etiology of the recurrent event (eTable 1). Second, data were lacking for some outcomes of interest, particularly those related to the switch to a different mechanism of action. Such strategy needs further investigations to highlight the potential benefit in specific switch paradigms. To this extent, our analysis was limited to the study-level aggregate data because adjusted estimates from each study critically differed for covariates, potentially introducing unquantifiable heterogeneity. Third, data on DOAC subtypes were not available for all studies, and data were lacking for adherence and drug metabolism in each group, therefore limiting the interpretation of transition from one DOAC to the other. In addition, all analyses are based on observational (and in the majority of studies retrospective) data, with a risk, albeit low, of overlap between studies (eTable1). Fourth, there may have been factors, such as severe heart failure or mitral stenosis, that increase the risk of stroke and justify the decision to switch from DOAC to VKA. Further studies are needed to follow these subgroups over the long-term. Furthermore, there is limited information regarding acute reperfusion therapies in patients suffering from stroke while on DOAC therapy, and this may potentially affect the switch from one DOAC to another.[31,32] Finally, there are no data on the timing of DOAC switch. We may assume that a switch happens once only and soon after the index event, but this represents a further limitation to the interpretation of the results.

The findings of this meta-analysis support DOAC-based strategies over warfarin for recurrent stroke prevention in

people with AF who have an ischemic stroke while on anticoagulation with DOACs. Moreover, the results suggest that there are no differences in any of the primary and secondary outcomes between patients switching DOACs and patients keeping the same DOAC as secondary prevention strategies. Ongoing RCTs, including Carotid Implants for PreveNtion of STrokE ReCurrEnce from Large Vessel Occlusion in Atrial Fibrillation Patients Treated with Oral Anticoagulation (NCT05723926), Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy (NCT05976685), The Fourth Left Atrial Appendage Occlusion Study (NCT05963698), and TAILored anticoagulation SWITCHing in people with stroke while on anticoagulants (TAILSWITCH, NCT pending),[33] will provide additional information, especially regarding alternative measures and tailored treatment when an ischemic stroke occurs despite DOAC therapy in patients with AF.

Author Contributions

M. Romoli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Paciaroni: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. N. Marrone: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. L. Palaiodimou: drafting/revision of the manuscript for content, including medical writing for content. V. Tudisco: drafting/revision of the manuscript for content, including medical writing for content. C. Faini: drafting/revision of the manuscript for content, including medical writing for content. A.H. Katsanos: drafting/revision of the manuscript for content, including medical writing for content. M. Rubiera: drafting/revision of the manuscript for content, including medical writing for content. P. Eusebi: drafting/revision of the manuscript for content, including medical writing for content. G. Merlino: drafting/revision of the manuscript for content, including medical writing for content. S. Giacomozzi: drafting/revision of the manuscript for content, including medical writing for content. L. D'Anna: drafting/revision of the manuscript for content, including medical writing for content. F. Giammello: drafting/revision of the manuscript for content, including medical writing for content. F. Diana: drafting/revision of the manuscript for content, including medical writing for content. F.N. Sepe: drafting/revision of the manuscript for content, including medical writing for content. L. Barba: drafting/revision of the manuscript for content, including medical writing for content. S. Abu-Rumeileh: drafting/revision of the manuscript for content, including medical writing for content. S. Diamanti: drafting/revision of the manuscript for content, including medical writing for content. E. Grifoni: drafting/revision of the manuscript for content, including medical writing for content. L. Masotti: drafting/revision of the manuscript for content, including medical writing for content. A. Toscano: drafting/revision of the manuscript for content, including medical writing for content. G. Defazio: drafting/revision of the manuscript for content, including medical writing for content. A. Zini: drafting/revision of the manuscript for content, including medical writing for content. M. Longoni: drafting/revision of the manuscript for content, including medical writing for content. C.A. Molina: drafting/revision of the manuscript for content, including medical writing for content. A.C. Cameron: drafting/revision of the manuscript for content, including medical writing for content. A. Shoamanesh: drafting/revision of the manuscript for content, including medical writing for content. U. Fischer: drafting/revision of the manuscript for content, including medical writing for content. M. Petruzzellis: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. L.A. Sposato: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. G. Tsivgoulis: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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