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Stroke Prevention With Direct Oral Anticoagulants (Doac) Versus Warfarin In Patients With Non-Valvular Atrial Fibrillation (Nvaf): A Real-World Cohort Meta-Analysis

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Abstract

Atrial fibrillation, particularly NVAF, is a major risk factor for stroke and systemic embolism, yet real-world evidence on the effectiveness and safety of DOACs versus warfarin remains limited. This systematic review and meta-analysis compared the effectiveness and safety outcomes of direct oral anticoagulants (DOACs) vs for stroke prevention in patients with NVAF. This review followed PRISMA guidelines. Cohort studies published in the past 10 years were identified from PubMed, Scopus, and Google Scholar, with study quality assessed using the Newcastle–Ottawa Scale. Pooled hazard ratios for the effectiveness and safety of DOACs versus warfarin in NVAF were calculated using a random-effects model in RevMan 5.4.1. A total of 12 studies were included in this meta-analysis. Compared with warfarin, DOACs significantly reduced the risk of stroke or systemic embolism (HR = 0.76, 95% CI: 0.67–0.87), ischemic stroke (HR = 0.70, 95% CI: 0.54–0.92), and hemorrhagic stroke (HR = 0.62, 95% CI: 0.45–0.86). All-cause mortality was numerically lower with DOACs but not statistically significant (HR = 0.82, 95% CI: 0.66–1.01). For safety outcomes, DOACs were associated with a lower risk of major bleeding (HR = 0.81, 95% CI: 0.65–1.00) and intracranial hemorrhage (HR = 0.57, 95% CI: 0.50–0.65), while gastrointestinal bleeding did not differ significantly between groups (HR = 1.09, 95% CI: 0.62–1.90). Based on real-world cohort evidence, DOACs demonstrate superior effectiveness in reducing stroke and systemic embolism and a more favorable safety profile compared with warfarin in patients with NVAF.

Keywords: Atrial Fibrillation, Direct Oral Anticoagulants, Vitamin K Antagonist, Stroke, Warfarin

INTRODUCTION

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation and ineffective atrial contraction. Atrial fibrillation may occur in patients with or without valvular heart disease, and atrial fibrillation in the absence of valvular abnormalities is defined as non-valvular atrial fibrillation (NVAF) (Joglar et al., 2024).

Non-valvular atrial fibrillation (NVAF) markedly increases the risk of ischemic stroke and systemic embolism, conferring up to a fivefold higher stroke risk and greater stroke severity compared with non–AF-related stroke (Ramagopalan et al., 2019). NVAF accounts for approximately 13–26% of acute ischemic strokes, with prevalence rising with age, and contributes to a substantial proportion of stroke-related mortality. In the United States alone, NVAF is responsible for up to 125,000 stroke events annually, many of which remain undiagnosed or inadequately treated despite established anticoagulation guidelines. Consequently, early and effective prevention of systemic embolization is a cornerstone of NVAF management (Avezum et al., 2015; Song et al., 2025).

Optimal prevention efforts remain the most effective strategy for reducing the burden of stroke (Alberts et al., 2020). Warfarin, a vitamin K antagonist, has been the cornerstone of stroke prevention in patients with NVAF since the 1950s, reducing stroke risk by more than 60% and demonstrating greater efficacy than antiplatelet therapy. More recently, direct oral anticoagulants (DOACs), including apixaban, rivaroxaban, dabigatran, and edoxaban, have been approved for NVAF management (Paschke et al., 2020; Wang et al., 2019). Unlike warfarin, which requires routine INR monitoring, DOACs provide a more convenient option with fewer drug and food interactions for reducing the risk of stroke and systemic embolism (Amin et al., 2017; Gieling et al., 2017).

Although randomized controlled trials provide robust evidence for the efficacy of NOACs, their findings may not fully reflect real-world clinical practice due to differences in patient characteristics.

Real-world evidence comparing the effectiveness and safety of NOACs versus warfarin remains limited, highlighting the need for further evaluation (Bang et al., 2020). Therefore, this meta-analysis aims to assess the efficacy and safety of DOACs compared with warfarin for stroke prevention in patients with non-valvular atrial fibrillation.

RESEARCH METHODS

Literature Search

This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. A comprehensive literature search was performed using the PubMed, Scopus, and Google Scholar databases with the following keywords: (stroke) AND (atrial fibrillation) AND ("direct oral anticoagulant" OR "DOAC" OR "NOAC*" OR "apixaban" OR "rivaroxaban" OR "dabigatran" OR "edoxaban")* AND (warfarin). The publication period was limited to articles published between 2015 and 2025. Duplicate records were removed, and the remaining studies were screened according to predefined inclusion criteria.

Eligibility Criteria

Studies included in this meta-analysis were observational cohort studies (prospective or retrospective) evaluating stroke prevention in patients with non-valvular atrial fibrillation (NVAF) treated with direct oral anticoagulants (DOACs) compared with warfarin. The study population consisted of adult patients (≥18 years) diagnosed with NVAF, defined as atrial fibrillation in the absence of mechanical heart valves or moderate-to-severe mitral stenosis. Outcomes of interest included measures of effectiveness and safety among patients receiving DOACs (apixaban, dabigatran, rivaroxaban, and edoxaban) either analyzed collectively or by individual agent, with warfarin as the comparator.

Exclusion criteria were as follows: (1) studies involving patients with valvular atrial fibrillation, including those with mechanical heart valves or moderate-to-severe mitral stenosis; (2) randomized controlled trials (RCTs), case reports, case series, editorials, letters to the editor, narrative reviews, systematic reviews, or meta-analyses; (3) non-cohort studies (e.g., cross-sectional studies) or studies with duplicate data from the same population; (4) studies that did not report stroke outcomes or did not provide sufficient quantitative data for meta-analysis; and (5) articles not available in full text, not published in peer-reviewed journals, or not written in English.The screening process was conducted independently by two investigators, beginning with title and abstract screening, followed by full-text review to confirm eligibility.

Data Extraction and Study Quality Assessment

Data were independently extracted by two authors using a Microsoft Excel spreadsheet to compile information from eligible studies. Extracted data included first author, year of publication, study design, data collection period, sample size, type of DOAC, mean age, percentage of female participants, duration of follow-up, mean HAS-BLED score, mean CHA_2DS_2-VASc score, and Newcastle–Ottawa Scale (NOS) score. The primary outcomes assessed comprised treatment effectiveness (stroke/systemic embolism (S/SE), all-cause mortality, ischemic stroke, and hemorrhagic stroke) and treatment safety (major bleeding, intracranial hemorrhage, and gastrointestinal bleeding).

Methodological quality and risk of bias for each included study were evaluated using the Newcastle–Ottawa Scale (NOS) for cohort studies. The NOS assesses three main domains: cohort selection, comparability of study groups, and outcome assessment, with a total score ranging from 0 to 9 stars. Based on NOS scores, study quality was classified as good, fair, or poor. Assessments were conducted independently by two authors, and any disagreements were resolved through discussion until consensus was reached. Studies with NOS scores ≥6 were considered high quality and included in the analysis.

Statistical Analysis

Data analysis was performed using Review Manager (RevMan) version 5.4.1. A random-effects model was applied to account for inter-study variability and additional uncertainty among the included studies. Pooled results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The results were presented using forest plots and funnel plots. Heterogeneity was asseRESssed using the Cochran Q (χ^2) test, I^2 statistic, and τ^2. Heterogeneity was considered significant if I^2 exceeded 50% and/or the p-value was <0.05.

RESULTS AND DISCUSSION

Study Selection

The study selection process is shown in the PRISMA flow diagram (**Figure 1**). Of 592 records identified, 491 remained after duplicate removal and were screened. Twenty-eight full-text articles were assessed for eligibility, of which 16 were excluded. Ultimately, 12 cohort studies were included in the qualitative and quantitative synthesis.

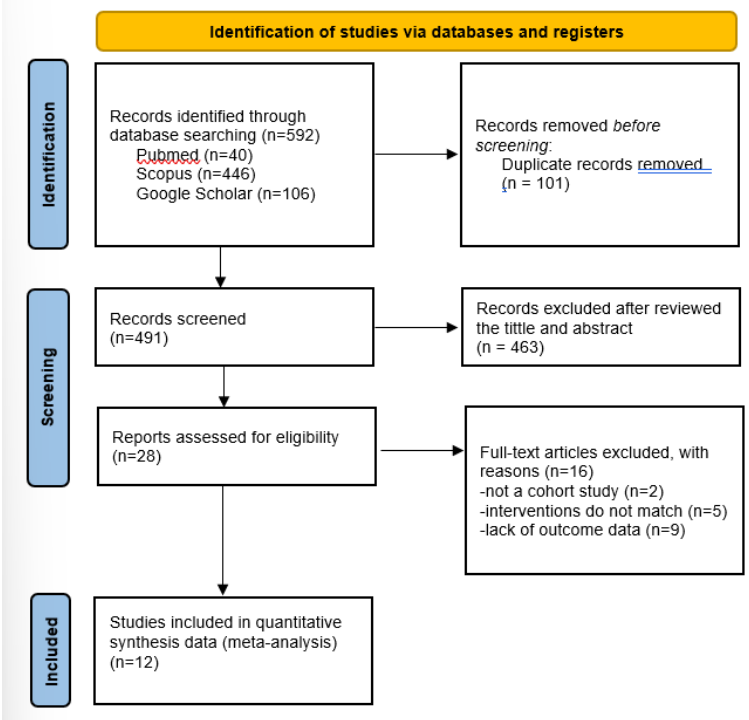

Figure 1. The flowchart of literature retrieval of this meta-analysis

Table 1. Baseline Characteristics

Author (Year)	Study design	Data period	Interverntion & Sample size	Mean age (years)	Female (%)	Follow-up	Mean HAS-BLED	Mean (SD) CHA_2DS_2-VASc	NOS
Alberts et al., 2020(Alberts et al., 2020)	Retrospective cohort	2011 – 2017	Riva/Warfarin 6,876/13,597	75 years	Riva vs Warfarin 10,175 (49%) vs 10,155 (50%)	Riva vs Warfarin 23 (9–36) vs 29 (8–46) mo	Riva vs Warfarin 2.4 (0.9) vs 2.4 (0.9)	Riva vs Warfarin 3.8 (1.2) vs 3.8 (1.3)	**9**
Bang et al., 2020(Bang et al., 2020)	Retrospective cohort	2007 – 2016	Api/Dabi/Riva/Warfarin 10,548/11,414/17,779;/8,648	Api vs Dabi vs Riva vs Warfarin = 71.64 vs 70.68 vs 71.83 vs 71.85	Api vs Dabi vs Riva vs Warfarin = 43.93% vs 41.01% vs 43.15% vs 43.47%	Api vs Dabi vs Riva vs Warfarin (Median (days) 149 vs 171 vs 175 vs 105	Api vs Dabi vs Riva vs Warfarin 3.54 vs 3.50 vs 3.52; vs 3.53	Api vs Dabi vs Riva vs Warfarin 4.52 vs 4.40 vs 4.45 vs 4.49	**9**
Yap et al., 2016(Yap et al., 2016)	Retrospective cohort	2009 – 2013	Dabi/Warfarin 500/500	Dabi vs Warfarin 65.3 ± 11.3 vs 66.8 ± 11.3	Dabi vs Warfarin 38% vs 39.8%	Dabi vs Warfarin 315 ± 280 d vs 355 ± 232 d	Dabi vs Warfarin 1.57 ± 0.96 vs 1.67 ± 0.94	Dabi vs Warfarin 2.69 ± 1.54 vs 3.40 ± 1.54	**8**
Powell et al., 2024(Powell et al., 2024)	Retrospective cohor	2013 – 2019	Api/Warfarin 8,846/8,846	Median 71 (IQR 63–77)	Api vs Warfarin 35.5% vs 36.1%	Api/Warfarin 1.8 y vs 2.2 y	Not reported	NA	**9**
Al-Maawali et al., 2022(Al-Maawali et al., 2022)	Retrospective cohort	2016 – 2018	Riva/Warfarin 96/183	Riva vs Warfarin 61.3 ± 10.9 vs 71.5 ± 11.9	Riva vs Warfarin 46.9% vs 48.6%	Event-based follow-up	Rivaroxaban 2.2 ± 1.0; Warfarin 2.2 ± 0.9	Riva vs Warfarin 2.1 ± 1.1 vs 2.2 ± 1.2	**8**
Lee et al., 2023(H. Lee et al., 2023)	Retrospective cohort	2009 – 2020	All DOAC/Warfarin 2,343/858	All DOAC vs Warfarin 73.44 ± 10.52 vs 70.55 ± 12.43	All DOAC vs Warfarin 49.4% vs 47.2%	All DOAC vs Warfarin 2.4 (IQR 1.2–4.2) y vs	All DOAC vs Warfarin 1.83 ± 0.85 vs 1.87 ± 0.97	All DOAC vs Warfarin 3.59 ± 1.70 vs 3.59 ± 1.84	**8**

						2.3 (IQR 0.8–4.9) y			
de Lusignan et al., 2022(de Lusignan et al., 2022)	Retrospective cohort	2008 – 2019	All DOAC/Warfarin 5,168/7,451	All DOAC/Warfarin ~69–70 vs ~70–71	All DOAC/Warfarin ~44% vs ~42%	Up to 7 years	Not reported	Not reported	**9**
Li et al., 2017(Li et al., 2017)	Retrospective cohort	2008 – 2014	Riva/Dabi/Warfarin 669/467/963	Riva vs Dabi vs Warfarin 73.3 ± 12.1; vs 71.9 ± 11.1 vs 73.9 ± 13.2;	Riva vs Dabi vs Warfarin 40.2%; vs 46,9%; vs 47.0%;	Mean 21.7 ± 13.4 months	Riva vs Dabi vs Warfarin 2.0 ± 0.9; vs 2.0 ± 1.1 vs 2.1 ± 1.0;	Riva vs Dabi vs Warfarin 3.7 ± 1.8 vs 3.6 ± 1.9 vs 3.8 ± 2.0	**8**
Bradley et al., 2020(Bradley et al., 2020)	Retrospective cohort	2012 – 2018	Api/Warfarin 55,038/55,038	Api vs Warfarin 71.3 ± 9.7; vs 71.3 ± 10.6	Api vs Warfarin 39.3%; vs 39.2%	Event-driven	Api vs Warfarin 2.2 ± 1.0; vs 2.2 ± 1.1	Api vs Warfarin 3.2 ± 1.5 vs 3.2 ± 1.5	**9**
Coleman et al., 2016(Coleman et al., 2016)	Retrospective cohort	2012 – 2014	Riva/Warfarin 11,411/11,411	Riva vs Warfarin 70.66 ± 10.99; vs 70.72 ± 11.35	Riva vs Warfarin 46.4%; vs 46.1%	Event-driven	Riva vs Warfarin 1.62 ± 0.69 vs 1.62 ± 0.71	Riva vs Warfarin 3.46 ± 1.37 vs 3.48 ± 1.35	**9**
Forslund et al., 2018(Forslund et al., 2018)	Population-based cohort	2012 – 2015	All NOAC/Warfarin 9,279/12,919	All NOAC vs Warfarin 72.9 ± 11.1; vs 74.1 ± 11.0	All NOAC vs Warfarin 43.5%; vs 44.6%	All NOAC vs Warfarin 1.07 y; vs 1.61 y	Not reported	All NOAC vs Warfarin 3.42 ± 1.91 vs 3.68 ± 1.91	**9**
Milentijevic et al., 2021(Milentijevic et al., 2021)	Retrospective cohort	2011 – 2019	Riva/Warfarin 13,599/39,861	~73	~50	Mean 28 months	Riva vs Warfarin 2.03 ± 1.02; vs 2.04 ± 1.07	Riva vs Warfarin 2.95 ± 0.95 vs 3.10 ± 0.99	**9**

2018

Baseline Characteristics & Study Quality Assessment

The main characteristics and quality of the included studies are summarized in **Table 1.** The studies were conducted in North America, Europe, and Asia and included adult patients with non-valvular atrial fibrillation. Mean participant age ranged from approximately 65 to over 75 years, with women comprising 38%–50% of the study populations, and follow-up durations ranging from several months to more than 7 years. The DOACs evaluated were apixaban, dabigatran, rivaroxaban, and edoxaban, with warfarin as the comparator. Study quality was assessed using the Newcastle–Ottawa Scale, with eight studies rated as high quality and four as moderate quality. Overall, the studies demonstrated moderate to good methodological quality.

Effectiveness outcomes

As shown in **Figure 2**, the pooled results from the random-effects model demonstrated that, compared with warfarin, the use of DOACs was significantly associated with a reduced risk of overall effectiveness outcomes (HR = 0.75, 95% CI: 0.68–0.83). Specifically, DOAC therapy was associated with significantly lower risks of stroke/systemic embolism (SSE) (HR = 0.76, 95% CI: 0.67–0.87), ischemic stroke (HR = 0.70, 95% CI: 0.54–0.92), and hemorrhagic stroke (HR = 0.62, 95% CI: 0.45–0.86). However, there was no statistically significant difference between DOACs and warfarin with respect to all-cause mortality (HR = 0.82, 95% CI: 0.66–1.01).

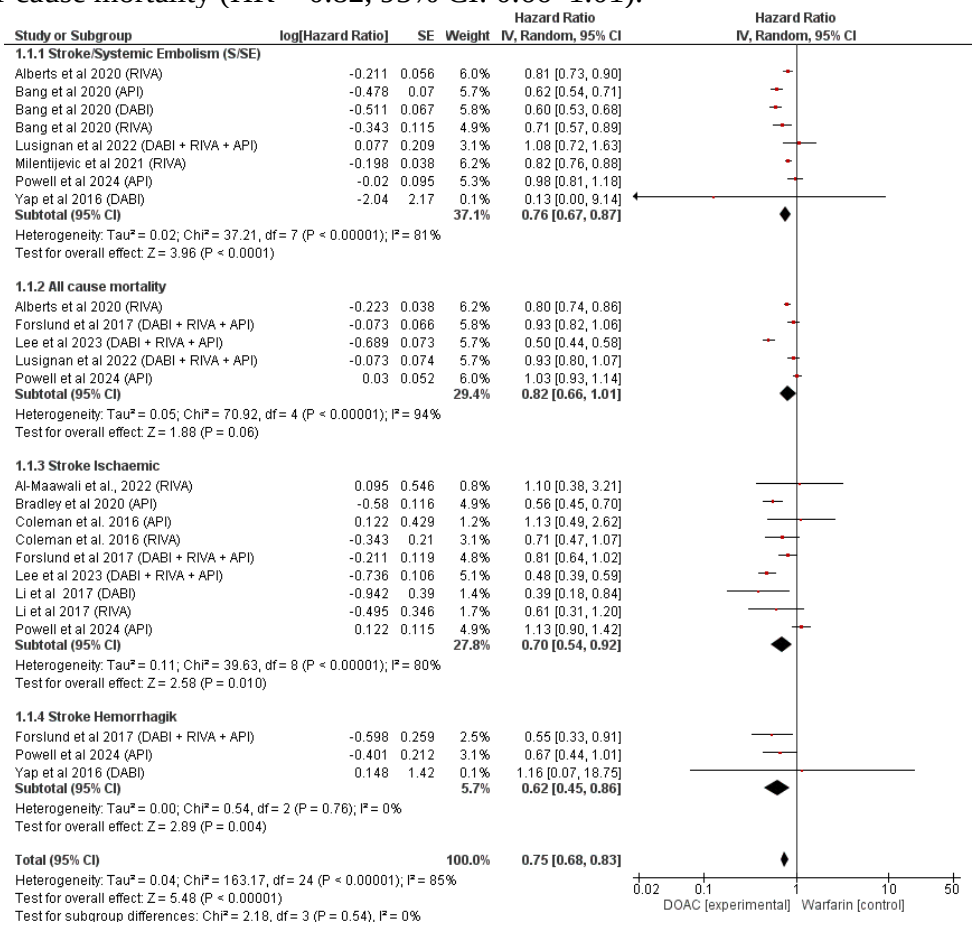

Figure 2. Comparing effectiveness of DOACs with warfarin for stroke prevention in AF patients

Safety outcomes

The safety outcomes are presented in **Figure 3.** Compared with warfarin, DOAC use was associated with a significantly lower risk of overall safety outcomes (HR = 0.72, 95% CI: 0.62–0.85). In subgroup analyses, DOACs significantly reduced the risks of major bleeding (HR = 0.81, 95% CI: 0.65–1.00) and intracranial hemorrhage (HR = 0.57, 95% CI: 0.50–0.65). In contrast, no significant difference was observed in the risk of gastrointestinal bleeding between patients treated with DOACs and those receiving warfarin (HR = 1.09, 95% CI: 0.62–1.90).

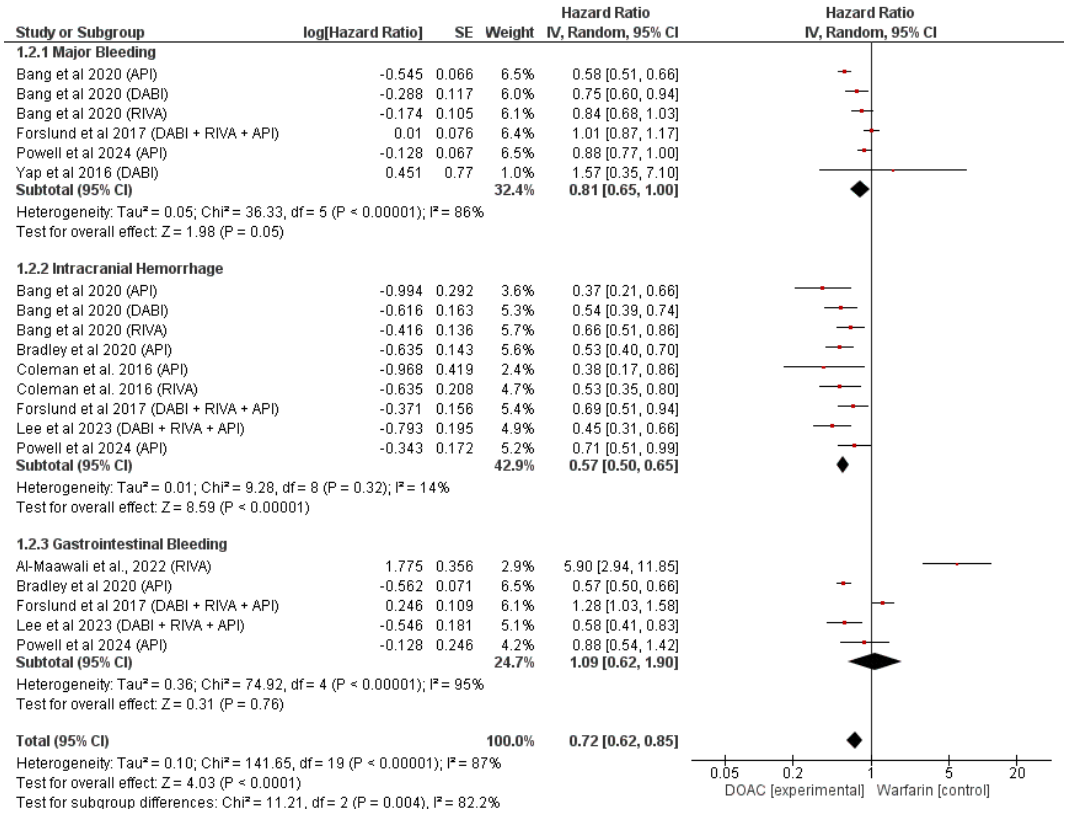

Figure 3. Comparing safety of DOACs with warfarin for stroke prevention in AF patients

Sensitivity Analysis & Publication Bias

Sensitivity analyses comparing fixed-effect and random-effects models demonstrated consistent pooled estimates across all subgroups, indicating that the results were not driven by small-study effects and were robust. Publication bias was assessed using funnel plots for both effectiveness and safety outcomes, including stroke or systemic embolism, ischemic stroke, hemorrhagic stroke, all-cause mortality, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding **(Figures 4 and 5).** The funnel plots showed a generally symmetrical distribution around the pooled estimates, and although some dispersion was observed in outcomes with substantial heterogeneity, no strong evidence of significant publication bias was identified.

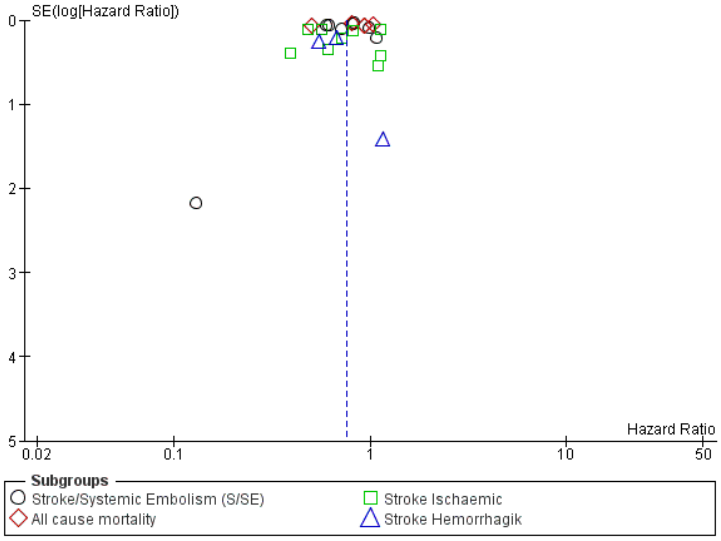

Figure 4. Funnel plot comparing effectiveness of DOACs with warfarin for stroke prevention in AF patients

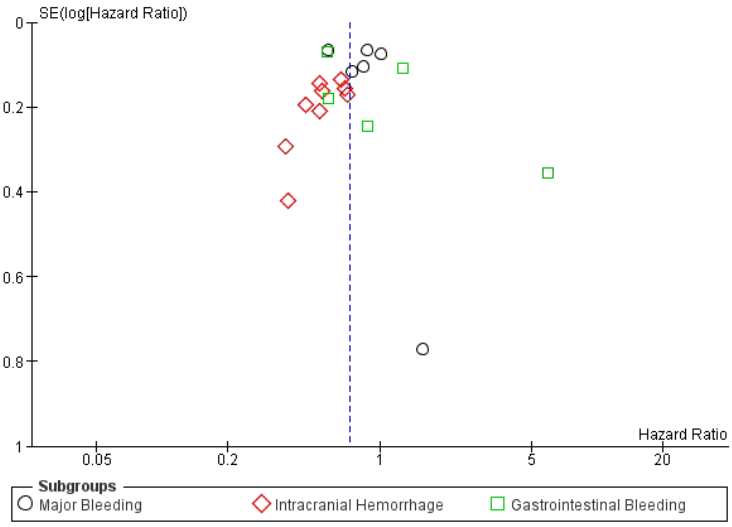

Figure 5. Funnel plot comparing safety of DOACs with warfarin for stroke prevention in AF patients

Discussion

In this meta-analysis, effectiveness outcomes showed that DOACs were associated with a statistically significant reduction in stroke or systemic embolism compared with warfarin in patients with non-valvular atrial fibrillation (NVAF). This benefit was consistently observed for ischemic stroke as well as hemorrhagic stroke. However, no statistically significant difference was found between DOACs and warfarin in all-cause mortality, indicating that although anticoagulant therapy effectively reduces thromboembolic events, overall mortality in AF is largely influenced by non-thrombotic comorbidities. Regarding safety outcomes, DOACs demonstrated a significantly lower risk of major bleeding and intracranial hemorrhage compared with warfarin, while no significant difference was observed in gastrointestinal bleeding, which occurred less frequently in the warfarin group.

Atrial fibrillation increases the risk of ischemic stroke mainly through atrial blood stasis and thrombus formation in the left atrium and left atrial appendage, making oral anticoagulation essential for stroke prevention in non-valvular AF. For decades, warfarin has been the standard anticoagulant and has proven efficacy in reducing AF-related stroke; however, its clinical use is limited by a narrow therapeutic window, frequent INR monitoring, and numerous drug–food interactions, leading to variable anticoagulant control (January et al., 2019)**.** Over the past decade, direct oral anticoagulants have emerged as alternatives that directly inhibit factor Xa or thrombin, offering more predictable pharmacokinetics and fewer interactions. Large randomized trials and real-world studies have demonstrated that DOACs are at least as effective as warfarin, with a lower risk of intracranial hemorrhage, leading to their widespread adoption and recommendation as first-line therapy for stroke prevention in NVAF (Chen et al., 2020)

The superior effectiveness and safety of DOACs observed in this meta-analysis likely reflect their more consistent anticoagulant control compared with warfarin, which depends heavily on maintaining an optimal time in therapeutic range. Evidence indicates that DOACs reduce the risks of stroke or systemic embolism and intracranial hemorrhage across varying levels of warfarin INR control, highlighting how their predictable pharmacokinetics translate into more reliable real-world outcomes than warfarin, which often achieves suboptimal anticoagulation in routine practice (El Moussa et al., 2025; J. J. Lee et al., 2020)**.** The absence of a significant difference in all-cause mortality may reflect competing risks in patients with AF, who often die with rather than from AF, such as heart failure, infection, or malignancy. Although DOACs reduce the most devastating bleeding events, particularly intracranial hemorrhage, gastrointestinal bleeding may remain comparable or even higher in some real-world cohorts, indicating a trade-off related to bleeding site rather than reduced therapeutic effectiveness (Scridon & Balan, 2023).

This meta-analysis has several limitations. All included studies were observational and therefore subject to residual confounding despite statistical adjustment. Substantial heterogeneity across outcomes likely reflected differences in study populations, data sources, follow-up duration, and outcome definitions. Most studies were based on administrative databases, which may be prone to misclassification and incomplete clinical information, including limited reporting of warfarin anticoagulation quality (time in therapeutic range). In addition, the relatively small number of studies limited detailed subgroup analyses by individual DOACs or patient characteristics.

Future studies should prioritize large, high-quality real-world analyses with standardized outcomes, robust confounding adjustment, and detailed reporting of anticoagulant use, including dosing, adherence, renal function, and warfarin TTR. Stratified comparative analyses by individual DOACs, patient subgroups, and healthcare settings, as well as advanced methods such as target trial emulation, are needed to enhance causal inference and generalizability.

CONCLUSIONS

In conclusion, evidence from real-world cohort studies indicates that DOACs provide superior effectiveness compared with warfarin in reducing stroke or systemic embolism, ischemic stroke, and hemorrhagic stroke in patients with non-valvular atrial fibrillation. DOACs are also associated with a lower risk of intracranial hemorrhage and comparable risks of major and gastrointestinal bleeding, while all-cause mortality did not differ significantly. Overall, these findings support the preferential use of DOACs over warfarin for stroke prevention in routine clinical practice, although individualized treatment decisions and further high-quality real-world studies remain necessary.

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