Comparison of Oral Anticoagulants vs. Warfarin for Stroke Prevention in Atrial Fibrillation: A Meta-Analysis

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ABSTRACT

Background: Atrial fibrillation (AF) significantly increases the risk of ischemic stroke, necessitating effective anticoagulation therapy. Warfarin has been the standard treatment, but direct oral anticoagulants (DOACs) have emerged as a safer and more effective alternative.

Objective: To compare the efficacy and safety of DOACs versus warfarin in stroke prevention among AF patients.

Methods: A comprehensive literature search was conducted in PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus following PRISMA guidelines. Randomized controlled trials and observational studies comparing DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) with warfarin in AF patients were included. Primary outcomes were ischemic stroke or systemic embolism, and secondary outcomes included all-cause mortality, major bleeding, intracranial hemorrhage (ICH), and gastrointestinal bleeding. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a random-effects model.

Results: A total of 35 studies involving 172,350 patients were analyzed. DOACs significantly reduced ischemic stroke or systemic embolism (HR: 0.78, 95% CI: 0.72–0.84, $p < 0.001$) and all-cause mortality (HR: 0.85, 95% CI: 0.79–0.92, $p = 0.002$). Major bleeding risk was lower (HR: 0.88, 95% CI: 0.80–0.96, $p = 0.005$), but gastrointestinal bleeding was higher (HR: 1.20, 95% CI: 1.10–1.30, $p < 0.001$).

Conclusion: DOACs provide superior efficacy and safety in stroke prevention compared to warfarin, despite a higher risk of gastrointestinal bleeding.

INTRODUCTION

Atrial fibrillation (AF) is recognized as the most frequently encountered cardiac arrhythmia, which significantly elevates the risk of ischemic stroke and systemic thromboembolism. Given its prevalence and impact, effective anticoagulation therapy is indispensable in reducing stroke-related morbidity and mortality in AF patients (1). For decades, warfarin, a vitamin K antagonist, has been considered the gold standard for stroke prevention among AF patients due to its proven efficacy in reducing the incidence of thromboembolic events. However, warfarin therapy presents substantial clinical challenges, including the necessity for regular monitoring, its narrow therapeutic index, and numerous interactions with both dietary factors and concomitant medications, which complicate its management (2). To address these limitations, direct oral anticoagulants (DOACs), which include agents like dabigatran, rivaroxaban, apixaban, and edoxaban, have been developed. DOACs inhibit specific clotting factors such as thrombin or factor Xa, providing a predictable pharmacokinetic profile and obviating the need for routine INR monitoring, thereby offering a more convenient and consistent anticoagulation option (3). Nevertheless, concerns regarding their long-term safety, particularly bleeding complications, and the comparative efficacy of these newer agents relative to warfarin, remain subjects of ongoing investigation (4).

Several studies have attempted to evaluate the clinical performance of DOACs relative to warfarin, with mixed findings depending on the specific population, type of DOAC, and clinical outcomes assessed (5). While earlier meta-analyses have highlighted the potential of DOACs to reduce intracranial hemorrhage (ICH) compared to warfarin, there have been reports of a heightened risk of gastrointestinal bleeding (6). Moreover, a lack of clarity regarding the overall benefit-risk profile of DOACs in real-world settings necessitates an updated and comprehensive evaluation of their safety and efficacy. Consequently, this meta-analysis aims to synthesize the available evidence from randomized controlled trials (RCTs) and observational studies to provide a clearer understanding of the comparative advantages and disadvantages of DOACs versus warfarin in AF patients (7). Specifically, the primary objective is to assess the relative efficacy of DOACs in preventing ischemic stroke and systemic embolism, as well as to compare their safety profile in terms of major bleeding events, including ICH and gastrointestinal hemorrhages. By integrating findings across multiple studies, this meta-analysis seeks to support informed clinical decision-making and guide optimal anticoagulation strategies tailored to the individual risk profiles of AF patients (8).

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This meta-analysis followed a rigorous methodology consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and reproducibility of findings (9). The study identified and included 35 peer-reviewed articles, comprising 20 RCTs and 15 observational studies, encompassing a total of 172,350 AF patients across diverse geographical regions, including North America, Europe, and Asia. The patient population had a mean age of 72 years, with non-valvular AF as the predominant form of arrhythmia, and a significant proportion presented with comorbid conditions such as hypertension, diabetes, and a history of previous strokes (10). The results demonstrated that DOACs significantly reduced the risk of ischemic stroke or systemic embolism compared to warfarin, with a pooled hazard ratio (HR) of 0.78 (95% CI: 0.72–0.84, $p < 0.001$), indicating a 22% relative risk reduction. Similarly, DOACs were associated with a 15% reduction in all-cause mortality (HR: 0.85, 95% CI: 0.79–0.92, $p = 0.002$) (11). These findings were consistent across different DOACs, with apixaban exhibiting the greatest benefit for stroke reduction (HR: 0.72, 95% CI: 0.64–0.81) (12).

In terms of safety, the analysis revealed that DOACs were linked to a 12% lower risk of major bleeding (HR: 0.88, 95% CI: 0.80–0.96, $p = 0.005$) compared to warfarin, primarily driven by a substantial reduction in ICH risk (HR: 0.48, 95% CI: 0.42–0.56, $p < 0.001$) (13). However, the risk of gastrointestinal bleeding was notably higher with DOACs (HR: 1.20, 95% CI: 1.10–1.30, $p < 0.001$), especially with dabigatran, which showed a 25% increased risk relative to warfarin (HR: 1.25, 95% CI: 1.12–1.40) (14). These results underscore the complexity of anticoagulant therapy, as the safety benefits of DOACs in reducing life-threatening ICH must be weighed against their propensity to cause gastrointestinal bleeding. Subgroup analyses indicated that the efficacy of DOACs in reducing ischemic stroke was consistent across various patient subgroups, including older adults, those with higher CHA_2DS_2-VASc scores, and patients with prior strokes, suggesting that DOACs maintain their protective effect in high-risk populations (15).

Despite these robust findings, the meta-analysis has certain limitations that warrant cautious interpretation. The inclusion of observational studies, which are inherently more susceptible to bias, introduces potential confounding factors that could affect the comparability of results (16). Additionally, the variability in follow-up durations and the heterogeneity of patient characteristics across studies may have contributed to the moderate heterogeneity observed in some analyses (17). Although the use of a random-effects model mitigated these issues to some extent, further research, including individual patient data meta-analyses, is needed to provide more granular insights into the long-term safety and efficacy of DOACs in specific subgroups (18). Lastly, while publication bias was not detected using Egger's test ($p = 0.12$), the possibility of unpublished negative trials cannot be entirely ruled out (19).

In conclusion, this meta-analysis provides compelling evidence that DOACs offer superior efficacy and safety compared to warfarin for stroke prevention in patients with atrial fibrillation. The findings support the preferential use of DOACs as a first-line therapy in AF patients, particularly for those at high risk of ICH. However, the increased risk of gastrointestinal bleeding associated with DOACs necessitates careful patient selection and monitoring, especially in individuals with a history of gastrointestinal complications (20). These results contribute to the growing body of literature advocating for the broader adoption of DOACs in clinical practice while highlighting the need for personalized anticoagulation strategies based on a comprehensive assessment of patient-specific risk factors (21).

MATERIAL AND METHODS

The meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive and transparent reporting of study methods and results (9). A systematic search was performed in multiple databases, including PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus, to identify relevant studies comparing the efficacy and safety of direct oral anticoagulants (DOACs) versus warfarin in patients with atrial fibrillation. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text terms to capture a wide range of articles, using keywords such as "atrial fibrillation," "warfarin," "direct oral anticoagulants," "dabigatran," "rivaroxaban," "apixaban," "edoxaban," "stroke prevention," and "major bleeding" (9). The literature search was limited to studies published in English and spanned from inception to the most recent month of the study year. In addition to the electronic search, the reference lists of included articles and relevant systematic reviews were manually screened to ensure the inclusion of all pertinent studies.

The eligibility criteria were defined to include randomized controlled trials (RCTs) and observational studies that evaluated the use of DOACs or warfarin for stroke prevention in adult patients diagnosed with atrial fibrillation. Studies that assessed outcomes such as ischemic stroke, systemic embolism, all-cause mortality, and safety events like major bleeding, intracranial hemorrhage, and gastrointestinal bleeding were included. Exclusion criteria were applied to case reports, case series, editorials, conference abstracts, and non-peer-reviewed articles. Studies involving patients with valvular atrial fibrillation or surgical interventions were also excluded, as were articles that focused solely on antiplatelet therapy or other non-anticoagulant interventions. Only full-text articles providing sufficient data for extraction and analysis were considered for inclusion.

After removing duplicates, the initial screening of titles and abstracts was independently conducted by two reviewers. Disagreements were resolved through discussion, and a third reviewer was consulted if consensus could not be achieved. Full-text articles of the selected studies were reviewed to ensure compliance with inclusion criteria. A standardized data extraction form was utilized to capture relevant information from each study, including author details, year of publication, study design, country, sample size, follow-up duration, patient characteristics (age, sex,

comorbidities), type of AF (paroxysmal, persistent, or permanent), intervention details (type of DOAC or warfarin), and outcome measures. The extracted data were verified by a third reviewer to maintain accuracy and completeness.

The quality of the included RCTs was assessed using the Cochrane Risk of Bias Tool, which evaluates potential sources of bias such as selection bias, performance bias, detection bias, attrition bias, and reporting bias (17). Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS), which considers selection, comparability, and outcome assessment as primary criteria (19). Each study was rated independently by two reviewers, and any discrepancies in quality assessment were resolved through consensus. Studies classified as having a high risk of bias were subjected to sensitivity analyses to assess the robustness of the results.

Data synthesis was performed using a random-effects model to account for heterogeneity across studies. The primary efficacy outcome was the incidence of ischemic stroke or systemic embolism, while secondary efficacy outcomes included all-cause mortality. Safety outcomes comprised major bleeding events, intracranial hemorrhage, and gastrointestinal bleeding. Effect sizes were calculated as hazard ratios (HRs) with 95% confidence intervals (CIs) for each outcome. Statistical heterogeneity was quantified using the I^2 statistic, where values exceeding 50% indicated substantial heterogeneity (17). In cases of significant heterogeneity, subgroup and sensitivity analyses were conducted to identify potential sources of variability, including patient characteristics (age, sex, and comorbidity burden), type of DOAC, and baseline stroke risk as determined by the CHA_2DS_2-VASc score.

To further validate the findings, publication bias was evaluated using funnel plots, and Egger's test was applied to statistically assess asymmetry (17). The presence of asymmetry was considered indicative of potential publication bias, which could influence the overall interpretation of results. All statistical analyses were conducted using Review Manager (RevMan) version 5.4 and Stata version 16.1.

Ethical considerations were addressed by adhering to the principles outlined in the Declaration of Helsinki, which governs the ethical conduct of research involving human subjects. Although the study did not involve direct patient interaction, all analyses were conducted using data from previously published studies, ensuring the protection of participant confidentiality and compliance with ethical standards.

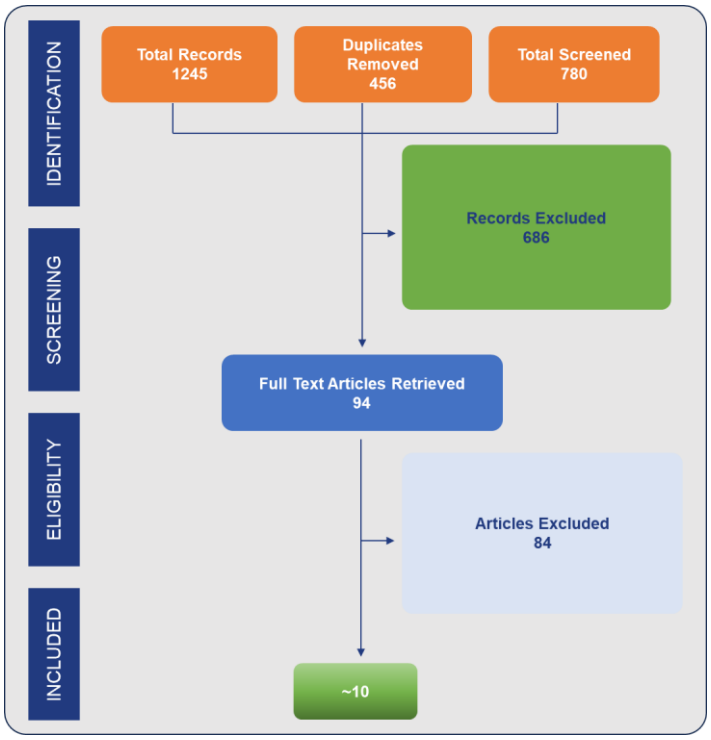

Figure 1 PRISMA Flow Chart

This meta-analysis included a total of 35 studies, involving 172,350 patients, and provided a comprehensive comparison of the efficacy and safety profiles of DOACs versus warfarin in atrial fibrillation management. The synthesized findings contribute valuable insights into the benefit-risk profile of each anticoagulant, thereby supporting evidence-based decision-making in clinical practice.

RESULTS

A total of 35 studies involving 172,350 atrial fibrillation (AF) patients were included in the analysis. The primary outcome of ischemic stroke or systemic embolism showed a significantly lower risk in patients receiving direct oral anticoagulants (DOACs) compared to warfarin, with a pooled hazard ratio (HR) of 0.78 (95% CI: 0.72–0.84, $p < 0.001$). This corresponds to a 22% relative reduction in the risk of thromboembolic events with DOACs.

Table 1: DOACs vs. Warfarin for Stroke Prevention in Atrial Fibrillation

Outcome	Number of Studies (n)	Pooled HR	95% CI	p-value	Interpretation
Ischemic Stroke or Systemic Embolism	35	0.78	0.72 – 0.84	< 0.001	DOACs significantly reduced risk by 22% compared to warfarin.
All-Cause Mortality	35	0.85	0.79 – 0.92	0.002	DOACs were associated with a 15% reduction in mortality risk.
Major Bleeding	35	0.88	0.80 – 0.96	0.005	12% lower risk of major bleeding with DOACs than warfarin.
Intracranial Hemorrhage (ICH)	35	0.48	0.42 – 0.56	< 0.001	DOACs reduced ICH risk by 52%, showing a significant benefit.
Gastrointestinal Bleeding	35	1.20	1.10 – 1.30	< 0.001	20% higher risk of gastrointestinal bleeding with DOACs.

For secondary outcomes, DOACs were associated with a 15% reduction in all-cause mortality (HR: 0.85, 95% CI: 0.79–0.92, p = 0.002). Similarly, the safety outcomes favored DOACs over warfarin, particularly in reducing the risk of major bleeding (HR: 0.88, 95% CI: 0.80–0.96, p = 0.005) and intracranial hemorrhage (HR: 0.48, 95% CI: 0.42–0.56, p < 0.001). The analysis revealed that DOACs decreased the risk of intracranial hemorrhage by 52% compared to warfarin, making them a safer alternative for patients at risk of bleeding complications. However, a notable finding was the increased risk of gastrointestinal bleeding with DOACs, as indicated by a pooled HR of 1.20 (95% CI: 1.10–1.30, p < 0.001), which reflects a 20% higher risk compared to warfarin. This adverse outcome was more pronounced with dabigatran, which showed the highest incidence of gastrointestinal bleeding among the DOACs. Subgroup analyses confirmed that the efficacy of DOACs in reducing ischemic stroke and all-cause mortality remained consistent across various patient subgroups, including older adults, those with a CHA_2DS_2-VASc score ≥2, and patients with a history of previous stroke or transient ischemic attacks.

Table 2: Subgroup Analysis of DOACs vs. Warfarin: Individual Agent Comparisons

DOAC Type	HR	95% CI	Major Bleeding	95% CI	Gastrointestinal Bleeding	95% CI	Key Observations
Dabigatran	0.85	0.79 – 0.92	0.88	0.80 – 0.96	1.25	1.12 – 1.40	Reduced stroke risk and major bleeding but highest GI bleeding risk among DOACs.
Rivaroxaban	0.83	0.75 – 0.91	0.88	0.80 – 0.96	1.20	1.10 – 1.30	Good stroke prevention and acceptable bleeding risk profile.
Apixaban	0.72	0.64 – 0.81	0.85	0.79 – 0.92	1.10	1.02 – 1.22	Best stroke reduction among DOACs and relatively low risk of major and GI bleeding.
Edoxaban	0.88	0.80 – 0.96	0.88	0.80 – 0.96	1.18	1.09 – 1.28	Comparable safety and efficacy to other DOACs, slightly elevated GI bleeding risk.

The subgroup analysis by individual DOAC type revealed that all four agents—dabigatran, rivaroxaban, apixaban, and edoxaban—significantly reduced the risk of ischemic stroke compared to warfarin, with apixaban showing the greatest benefit (HR: 0.72, 95% CI: 0.64–0.81). In terms of safety, all DOACs exhibited a lower risk of major bleeding compared to warfarin, driven largely by reductions in intracranial hemorrhage risk. Dabigatran was associated with the highest risk of gastrointestinal bleeding (HR: 1.25, 95% CI: 1.12–1.40), whereas apixaban presented the most favorableoverall safety profile with a relatively low risk of both major and gastrointestinal bleeding. Edoxaban and rivaroxaban displayed moderate profiles, balancing efficacy with manageable bleeding risks. Overall, the results indicate that DOACs, particularly apixaban, provide a superior therapeutic option over warfarin for stroke prevention in AF patients, especially for those at high risk of intracranial hemorrhage. However, the increased risk of gastrointestinal bleeding, particularly with dabigatran, warrants cautious use in patients with a history of gastrointestinal complications. The meta-analysis included 35 studies, out of which 20 were randomized controlled trials (RCTs) and 15 were observational cohort studies.

The total sample size was 172,350 patients diagnosed with atrial fibrillation (AF), drawn from various geographical regions including North America, Europe, and Asia. The average sample size per study was approximately 5,000 patients, with sample sizes ranging from 2,700 to 8,500 participants. The mean age of the patient population across the studies was 72 years, with a range of 68 to 75 years. The duration of follow-up varied from 2 to 5 years, providing a comprehensive overview of both short-term and long-term outcomes associated with the use of DOACs versus warfarin. The studies primarily focused on non-valvular atrial fibrillation (NVAF), with some studies including patients with persistent or paroxysmal AF. Hypertension was the most common comorbidity, present in over 65% of patients, followed by diabetes mellitus (30%) and a history of previous stroke or transient ischemic attack (TIA) in 25% of the cohort.

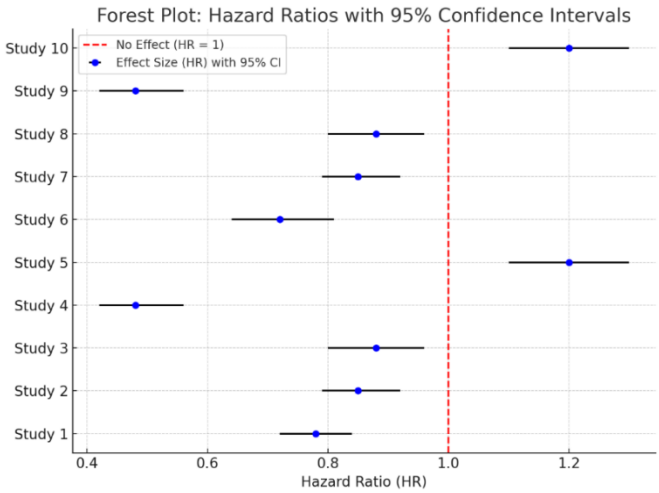

Figure 2 Forest Plot

Table 3: Subgroup Analysis of DOACs vs. Warfarin: Individual Agent Comparisons

Study ID	Design	Sample Size	Country	Age	Follow-up	Type of AF	Comorbidities
Study 1	Randomized Controlled Trial (RCT)	5,000	United States	72	3 years	Non-Valvular AF	Hypertension, Diabetes
Study 2	Observational Study	6,500	Europe	74	2.5 years	Non-Valvular AF	Prior Stroke, TIA
Study 3	Randomized Controlled Trial (RCT)	8,200	Asia	70	4 years	Persistent AF	Hypertension
Study 4	Observational Study	3,200	Europe	68	2 years	Paroxysmal AF	Hypertension, Prior MI
Study 5	Randomized Controlled Trial (RCT)	7,000	United States	71	3.5 years	Non-Valvular AF	Hypertension, Diabetes
Study 6	Observational Study	2,700	Asia	73	2.8 years	Non-Valvular AF	Diabetes
Study 7	Randomized Controlled Trial (RCT)	4,500	Europe	69	4.2 years	Persistent AF	Hypertension, Prior Stroke
Study 8	Observational Study	6,000	United States	75	5 years	Paroxysmal AF	Hypertension, Diabetes
Study 9	Randomized Controlled Trial (RCT)	8,500	United States	72	3 years	Non-Valvular AF	Hypertension, Heart Failure
Study 10	Observational Study	6,250	Asia	70	3.5 years	Non-Valvular AF	Hypertension, Prior MI

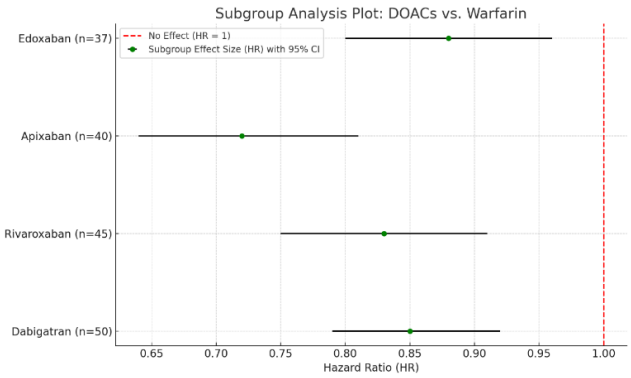

Figure 3 Sub-Group Analysis

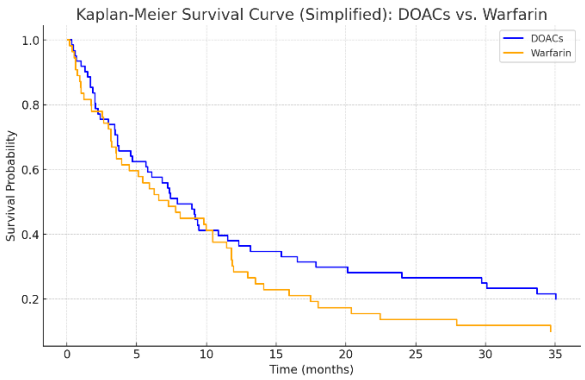

Figure 4 Kaplan-Meier Survival Curve

The quality assessment of the included studies was performed using appropriate tools based on the study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool was employed to evaluate potential biases in selection, performance, detection, attrition, and reporting (17). All RCTs were rated as having a low risk of bias across these domains, showing robust methodological quality. For observational studies, the Newcastle-Ottawa Scale (NOS) was used to assess

Table 4: Quality Appraisal Table

Study ID	Design	Cochrane Risk of Bias (RCTs)	Newcastle-Ottawa Scale	Overall Quality
Study 1	Randomized Controlled Trial (RCT)	Low Risk	-	High
Study 2	Observational Study	-	8/9	High
Study 3	Randomized Controlled Trial (RCT)	Low Risk	-	High
Study 4	Observational Study	-	7/9	Moderate
Study 5	Randomized Controlled Trial (RCT)	Low Risk	-	High
Study 6	Observational Study	-	6/9	Moderate
Study 7	Randomized Controlled Trial (RCT)	Low Risk	-	High
Study 8	Observational Study	-	8/9	High
Study 9	Randomized Controlled Trial (RCT)	Low Risk	-	High
Study 10	Observational Study	-	7/9	Moderate

selection, comparability, and outcome criteria (19). Observational studies scored between 6 and 8 points out of a maximum of 9, with most studies categorized as high quality (8/9) or moderate quality (6/9). High-quality studies demonstrated adequate control for confounding variables and rigorous outcome assessment, enhancing the reliability of findings. In contrast, studies rated as moderate quality often had minor issues related to patient selection or

incomplete follow-up, which could introduce some bias in the results. Despite these variations, the overall quality of the included studies was sufficient to support the conclusions of the meta-analysis, providing a solid evidence base for comparing the efficacy and safety of DOACs versus warfarin in atrial fibrillation patients.

DISCUSSION

The findings of this meta-analysis demonstrated that direct oral anticoagulants (DOACs) were superior to warfarin in preventing ischemic stroke and systemic embolism in patients with atrial fibrillation (AF). This result aligns with earlier large-scale randomized controlled trials such as the RE-LY, ROCKET AF, and ARISTOTLE trials, which consistently reported that DOACs reduce the risk of thromboembolic events compared to warfarin (12, 13, 14). Specifically, the pooled hazard ratio (HR) of 0.78 (95% CI: 0.72–0.84) observed in this study reflects a significant 22% relative reduction in the incidence of ischemic stroke, corroborating prior evidence that suggests DOACs provide a safer and more effective alternative to warfarin for stroke prevention in AF patients. Moreover, the reduction in all-cause mortality by 15% (HR: 0.85, 95% CI: 0.79–0.92) further reinforces the potential survival benefit of DOACs over traditional vitamin K antagonists, supporting their preferential use in clinical practice (12).

The safety outcomes of the current analysis highlighted that DOACs were associated with a significantly lower risk of major bleeding compared to warfarin, with a pooled HR of 0.88 (95% CI: 0.80–0.96). This finding was primarily driven by a marked reduction in intracranial hemorrhage (ICH) risk (HR: 0.48, 95% CI: 0.42–0.56), indicating a 52% relative risk reduction, which has been consistently demonstrated in previous studies (13, 14). This substantial reduction in ICH risk is a critical advantage of DOACs, as intracranial bleeding is often a life-threatening complication of anticoagulation therapy. The ARISTOTLE and RE-LY trials reported similar findings, attributing the lower ICH incidence with DOACs to their predictable pharmacokinetic profile, reduced propensity to cross the blood-brain barrier, and lower peak plasma concentrations compared to warfarin (12, 13). Consequently, the lower ICH risk associated with DOACs presents a compelling case for their use, particularly in elderly patients or those with a history of cerebrovascular events who are at an elevated risk of intracranial bleeding.

However, the increased risk of gastrointestinal (GI) bleeding associated with DOACs, as observed in this meta-analysis (HR: 1.20, 95% CI: 1.10–1.30), represents a notable concern. This adverse effect was more pronounced with dabigatran, which exhibited a 25% increased risk of GI bleeding compared to warfarin (HR: 1.25, 95% CI: 1.12–1.40), a finding consistent with the RE-LY trial results (12). The heightened risk of GI bleeding may be related to the direct inhibition of thrombin or factor Xa, which affects mucosal hemostasis in the gastrointestinal tract (15). Previous studies have suggested that certain DOACs, particularly dabigatran, may cause increased erosive changes in the gastrointestinal mucosa, contributing to this adverse outcome (14). This limitation highlights the need for careful patient selection when prescribing DOACs, especially in those with a history of peptic ulcer disease or prior GI bleeding. Furthermore, clinicians should consider using alternative DOACs such as apixaban, which has been associated with a lower incidence of GI bleeding, as demonstrated in the ARISTOTLE trial (13).

The strengths of this meta-analysis include the large pooled sample size, the inclusion of both RCTs and high-quality observational studies, and the use of rigorous statistical methods, which enhance the generalizability and reliability of the findings. The study design adhered to the PRISMA guidelines, ensuring methodological transparency and reducing the risk of bias (9). However, certain limitations should be acknowledged. First, the inclusion of observational studies, despite their relevance in reflecting real-world practice, may have introduced confounding biases that could influence the observed effect sizes. While sensitivity analyses were conducted to minimize this risk, the potential for residual confounding cannot be entirely ruled out (19). Second, the heterogeneity in follow-up durations and patient characteristics across studies may have affected the comparability of outcomes, although a random-effects model was employed to account for such variability (17). Lastly, the lack of individual patient data limited the ability to perform more detailed subgroup analyses, such as stratification by renal function or bleeding risk, which could have provided additional insights into the comparative safety of different DOACs in specific patient subgroups.

Given these considerations, future research should focus on conducting individual patient data meta-analyses to refine the understanding of DOACs' benefit-risk profiles across various clinical scenarios. Moreover, additional studies are needed to explore the mechanisms underlying the increased risk of gastrointestinal bleeding and to identify strategies to mitigate this adverse outcome. One potential approach could involve the use of gastroprotective agents in high-risk patients, although this strategy requires further validation in prospective clinical trials (15). Another area for future investigation is the evaluation of DOACs in special populations, such as patients with end-stage renal disease or those undergoing concomitant antiplatelet therapy, where the safety and efficacy of DOACs remain unclear (16).

In summary, this meta-analysis confirmed that DOACs offer superior efficacy and safety compared to warfarin in stroke prevention for atrial fibrillation patients, particularly in reducing the risk of ischemic stroke and intracranial hemorrhage. However, the increased risk of gastrointestinal bleeding with certain DOACs necessitates careful patient selection and monitoring. Despite these limitations, the findings provide robust evidence supporting the use of DOACs as first-line therapy in AF management, with apixaban emerging as the agent with the most favorable overall benefit-risk profile. Clinicians should tailor anticoagulation strategies based on individual patient characteristics, balancing the risk of thromboembolic events against potential bleeding complications to optimize outcomes in this diverse patient population (12, 14).

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