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Comprehensive systematic review and meta-analysis on anticoagulants and aspirin for stroke prevention in non-valvular atrial fibrillation patients

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Abstract. – OBJECTIVE: Non-valvular atrial fibrillation (NVAF) is a common manifestation of cardiac arrhythmia, whose significance is heightened in the context of an aging global population and changing lifestyles, leading to an increased incidence. Stroke prevention in NVAF is a complex challenge that requires a comprehensive exploration of interventions. The emergence of Direct Oral Anticoagulants (DOACs) is a potential treatment, necessitating a thorough evaluation of their safety and efficacy. As the quest for the best strategy for thrombotic risk in these patients continues, the interaction between DOAC and aspirin has become the focus of research.

MATERIALS AND METHODS: With a rigorous methodological approach, we conducted a thorough search of scientific databases up to August 2023. The methodology involved meticulous screening, careful data extraction, and rigorous assessment of trial quality, all conducted by two independent investigators. The results were synthesized through standardized mean differences, accompanied by 95% confidence intervals.

RESULTS: DOACs demonstrated significant enhancements in stroke prevention for NVAF, which was indicated by favorable outcomes in bleeding (RR = 4.04, 95% CI: 3.96, 4.12), coronary artery disease (RR = 2.45, 95% CI: 2.42, 2.48), mortality (RR = 0.49, 95% CI: 0.43, 0.56), myocardial infarction (RR = 1.85, 95% CI: 1.81, 1.88), and stroke (RR = 1.50, 95% CI: 1.47, 1.54). Notably, DOACs demonstrated optimal efficacy for NVAF patients with stroke.

CONCLUSIONS: DOACs may be potentially effective for preventing stroke after NVAF.

Key Words:
Non-valvular atrial fibrillation, Stroke prevention, Anticoagulants, Aspirin, Meta-analysis.

Introduction

Atrial fibrillation (AF) stands as the prevailing cardiac arrhythmia in clinical practice, afflicting a current global population of 335 million individuals, resulting in an overall prevalence rate of 2.9%. This escalating burden of AF is underscored by its well-established role as a risk factor for ischemic stroke (IS)[1,2]. AF patients face an annual risk of IS of about 5%, five times higher compared to the general population[3]. Notably, AF contributes to nearly 15-20% of all stroke cases, with AF-related strokes characterized by high mortality and sustained disability compared to other causes[4]. Thrombosis and embolism constitute the primary challenges of AF, with patients experiencing non-valvular atrial fibrillation (NVAF), with a 5% annual incidence of embolic events, responsible for 15-20% of cerebral embolisms[5,6]. Consequently, the threat of death and disability posed by NVAF far exceeds fivefold. As a fundamental approach to counteracting IS, clinical guidelines underscore the importance of anticoagulation for NVAF patients[7].

Oral anticoagulants have demonstrated significant effectiveness in preventing IS and improving outcomes for patients affected by NVAF. However, before initiating anticoagulation, the crucial and primary step involves assessing the risk of stroke, a foundational measure aimed at optimizing the benefits of anticoagulant treatment[8]. The primary goal of clinicians is to identify individuals with a higher predisposition to IS while stratifying patients with reduced IS risk, thereby tailoring the application of anticoagulation to better suit clinical practice[9]. Over the past five decades, the use of oral anticoagulants (OACs) has been recommended by guidelines[10] for managing NVAF, including the well-established warfarin, widely prevalent, and the more efficient direct-acting oral anticoagulants (DOACs). A wealth of empirical evidence underscores that the utilization of OACs in the context of NVAF yields

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a notable diminution of stroke risks[11]. Studies[12] emphasize the capacity of anticoagulant therapies to decrease stroke incidence by a substantial 50%, concurrently preventing the recurrence of this serious cardiovascular event.

In normal physiological circumstances, the coagulation process in the human body unfolds like a cascading enzymatic waterfall. The core principle underlying anticoagulant pharmaceuticals is to intercept this cascade sequence, achieved through the direct or indirect inhibition of one or more key components within the coagulation process[13]. This intervention aims to prevent the occurrence of thrombotic events. Vitamin K antagonists (VKAs) exert their anticoagulant effect by non-specifically and indirectly inhibiting clotting factors (including factors X, IX, VIII, VII, and II)[14]. Among VKAs, warfarin, a multi-faceted oral anticoagulant derived from coumarin, operates by intricately influencing vitamin K metabolism[15]. It acts on critical coagulation factors (VII, IX, and X) at the early stages of the coagulation cascade, impeding the generation of thrombin and the activation of factor II[16]. It is worth noting that this approach does not affect the synthesis of clotting factors at the protein level; instead, it operates by impeding their carboxylation process. Therefore, this mechanism does not impact clotting factors that have already been activated in the physiological environment[17]. Contrarily, DOACs, distinguished by their pronounced specificity, exert their anticoagulant effects by directly interdicting the activities of coagulation factors Xa and IIa.

The central focus of managing NVAF and mitigating its associated complications resides in the use of prolonged anticoagulant therapy. Presently, four DOACs – namely dabigatran, rivaroxaban, apixaban, and edoxaban – have emerged as the preferred options, offering improved safety and efficacy outcomes[18]. Notably, within the scope of National Health Services practices in the UK in 2019, DOACs constituted a substantial proportion, accounting for 74% of all prescribed anticoagulants[19]. The past era has witnessed the combination of warfarin, a vitamin K antagonist, with antiplatelet therapy, aimed at treating conditions such as atrial fibrillation, venous thromboembolism, and atherosclerosis[20]. The increasing use of DOACs has generated a substantial body of empirical data supporting their effectiveness in managing NVAF, reinforced by their favorable safety profile for patients. Recent evidence[21] leans toward DOACs over vitamin K antagonists, primarily due to their superior safety profile. Nonetheless, the therapeutic landscape is not without potential challenges, including the risk of gastrointestinal hemorrhage and the concerning possibility of fatal intracranial hemorrhage. Such potential adverse effects may impact the implementation of preventive strategies[22]. The specter of major bleeding, a tangential consequence, adds intricate complexities to patient management, necessitating a pressing search for an anticoagulant regimen that harmonizes both efficacy and safety considerations.

This study has constructed a meta-analysis to explore the impact of DOACs on the risk of stroke following NVAF, contrasting relevant randomized controlled trials. In this analytical domain, DOACs may emerge as effective medications in preventing stroke after NVAF. Figure 1 illustrates the process of literature screening.

Materials And Methods

Search Strategy

This study strictly adhered to the established guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) for conducting a meta-analysis. Computer searches were conducted in databases including Cochrane Library, Embase, Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), and Wanfang Database. The English search keywords were "dabigatran, rivaroxaban, apixaban, betrixaban, and Warfarin". In addition, keywords related to the condition were "Non-valvular atrial fibrillation" and "Stroke". Taking the Pubmed database as an example, the search strategy is outlined in Table I. Furthermore, we conducted a thorough manual exploration of the titles and contents of the included studies, supplemented with an objective summary assessment, ultimately identifying other relevant literature.

Table I. Search strategy in PubMed.

#1	(dabigatran[Title/Abstract]) OR (rivaroxaban[Title/Abstract])) OR (apixaban[Title/Abstract] OR (betrixaban[Title/Abstract] OR (Warfarin[Title/Abstract]
#2	(Non-valvular atrial fibrillation [Title/Abstract]) OR (Stroke[Title/Abstract]))
#3	#1 AND #2

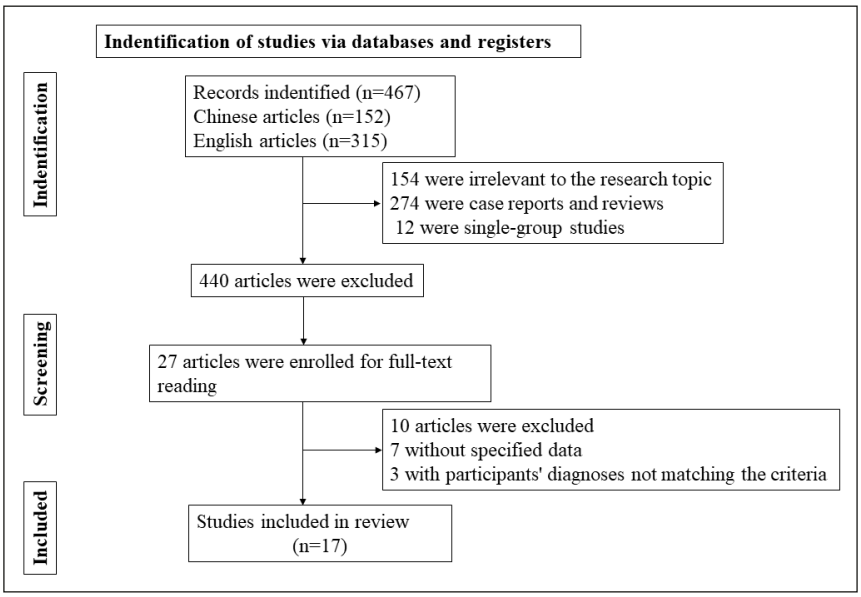

Figure 1. Flowchart of literature screening.

Inclusion Criteria

The criteria for inclusion, fortified by a resonance spanning seven thematic dimensions, seamlessly converged to establish a robust threshold of scholarly importance. The imperatives of our inclusion criteria were guided by distinct directives: (a) the realm of publication encompassed randomized controlled trials (RCTs) or observational studies; (b) a demographic scope of adult patients (≥18 years) was required, with a follow-up period of at least 3 months; (c) a meticulous comparison between DOAC alone and DOAC plus aspirin was sought, with a focus on safety and efficacy outcomes; (d) a comprehensive array of pivotal outcomes was explicitly reported, including major bleeding, myocardial infarction (MI), major adverse cardiac events (MACE), hospitalizations, all-cause mortality, stroke, or composite permutations thereof. (e) The study was conducted with a scientifically sound research design and adhered to standardized protocols. Follow-up data and other relevant information were comprehensively documented and completed.

Exclusion Criteria

(1) Case reports; (2) Studies lacking extractable relevant outcome measures, such as incidence rates; (3) Studies including patients with comorbid cross diseases

Quality Assessment Criteria and Data Extraction

Two independent reviewers conducted the literature screening, data extraction, and quality assessment. Any discrepancies were resolved by a third reviewer. The data extracted in this study encompassed study design, study population, inclusion and exclusion criteria, intervention measures, treatment methods for the control group, and outcomes. Continuous data were extracted as means ± standard deviations (SD). For randomized controlled trials, the Jadad scale was used for quality assessment, while cohort studies and case-control studies were assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment.

Statistical Analysis

Review Manager 5.3 (RevMan 5.3, https://community.cochrane.org/help/tools-and-software/revman-5) was used for analysis: (1) Binary variables were analyzed using odds ratios (OR) with a 95% confidence interval (CI). Heterogeneity was tested using Q and I^2. When heterogeneity was low, a fixed-effect model was selected. When heterogeneity was high, a random-effects model (RE) was used for analysis, and a reevaluation of the literature was conducted to identify and analyze the sources of heterogeneity. Subgroup analysis was performed if there was significant heterogeneity and statistical differences in characteristics. If the source of heterogeneity could not be identified, descriptive analysis was conducted. $p < 0.05$ was considered as significantly different.

Results

Characteristics of Included Studies

Within the timeframe from 2019 to August 2023, after meticulous research, a total of 732 relevant

articles were obtained. After removing duplicate literature, 467 articles remained, including 315 in English and 152 in Chinese. Following a preliminary screening based on titles and abstracts, 440 articles were excluded, of which 154 were irrelevant to the research topic, 274 were case reports and reviews, and 12 were single-group studies. After the initial screening, 27 articles were included. After reading the full texts, 10 articles were excluded, including 7 without specified data and 3 with participants' diagnoses not matching the criteria. Finally, 17 articles[23-39] were included. Encompassing a DOAC cohort comprising 751,355 participants, this compilation encompassed 473,577 individuals within the Warfarin group. Furthermore, the identification of literature bias risk provides a multifaceted perspective on the heterogeneity of the components. The flowchart of the included literature screening process is presented in Figure 1. The basic information of the included literature is shown in Table II.

Quality Assessment of Included Literature

Among the 17 studies[24-40] included in this article, 16[24,26-40] were case-control studies, and 1[25] was a retrospective case-control study. The quality of randomized controlled trials was evaluated using the Jadad scale, with appropriate random sequence generation (2 points), unclear allocation concealment (1 point), lack of blinding (0 points), and lack of description of withdrawals or dropouts (0 points), resulting in a Jadad score of 3 points, indicating low-quality literature. Please refer to Table III and Figure 2.

Bleeding

15[24,25,27-32,34-40] of the articles conducted detailed studies on bleeding. The results of the heterogeneity

Table II. Basic information of included literature.

Authors	Research Type	Number of Participants	Treatment	Outcome measures
Tinkham et al[24], 2019	Case-Control Study	407	DOAC *vs.* Warfarin	a, b, c
Elvira et al[25], 2019	Unspecified	2,361	DOAC *vs.* Warfarin	a, c, d, e
Alberts et al[26], 2019	Case-Control Study	365,950	DOAC *vs.* Warfarin	b, c, e
Amin et al[27], 2021	Case-Control Study	198,171	DOAC *vs.* Warfarin	a, b, d, e
Wanat et al[40], 2019	Case-Control Study	20,378	DOAC *vs.* Warfarin	a, e
Coleman et al[28], 2020	Case-Control Study	6,744	DOAC *vs.* Warfarin	a, b, d, e
Coleman et al[29], 2019	Case-Control Study	103,511	DOAC *vs.* Warfarin	a, b, d, e
Deitelzweig et al[30], 2020	Case-Control Study	448,944	DOAC *vs.* Warfarin	a, e
Graham et al[31], 2019	Case-Control Study	41,001	DOAC *vs.* Warfarin	a, b, d, e
Gupta et al[32], 2019	Case-Control Study	128	DOAC *vs.* Warfarin	a, b, d, e
Kido et al[34], 2019	Case-Control Study	30,820	DOAC *vs.* Warfarin	a, e
Kjerpeseth et al[35], 2019	Case-Control Study	116,803	DOAC *vs.* Warfarin	a, b, d, e
Lee et al[36], 2019	Case-Control Study	21,562	DOAC *vs.* Warfarin	a, d, e
Lin et al[37], 2019	Case-Control Study	27,962	DOAC *vs.* Warfarin	a, b, d, e
Martinez et al[38], 2019	Case-Control Study	7,126	DOAC *vs.* Warfarin	a, b, d, e
Peterson et al[39], 2019	Case-Control Study	20,473	DOAC *vs.* Warfarin	a, b, d, e
Jung et al[33], 2019	Case-Control Study	2,459	DOAC *vs.* Warfarin	b, e

a: Bleeding; b: Coronary artery disease; c: Mortality; d: Myocardial infarction; e: Stroke

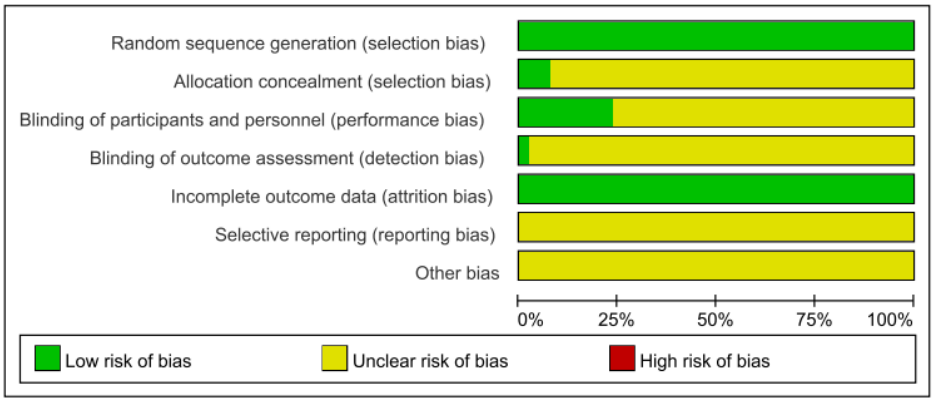

Figure 2. Quality evaluation chart of the included studies.

Table III. Newcastle-Ottawa Scale (NOS) scores of the included literature.

Authors	Case Selection	Comparability	Outcome	NOS scores
Tinkham et al[24], 2019	4	2	1	7
Elvira et al[25], 2019	3	2	1	6
Alberts et al[26], 2019	3	2	1	6
Amin et al[27], 2019	3	1	1	5
Wanat et al[40], 2019	4	2	1	7
Coleman et al[28], 2020	3	2	1	6
Coleman et al[29], 2019	3	1	1	5
Deitelzweig et al[30], 2020	4	1	1	6
Graham et al[31], 2019	3	2	1	6
Gupta et al[32], 2019	4	2	1	7
Kido et al[34], 2019	4	1	1	6
Kjerpeseth et al[35], 2019	3	1	1	5
Lee et al[36], 2019	4	2	1	7
Lin et al[37], 2019	4	2	1	7
Martinez et al[38], 2019	4	1	1	6
Peterson et al[39], 2019	3	1	1	5
Jung et al[33], 2019	4	2	1	7

test showed significant heterogeneity among the studies ($I^2 = 100\%$, $p < 0.0001$), and a random-effects (RE) model was used. This evidence suggests that DOACs may be effective drugs for preventing bleeding symptoms in patients with NVAF after stroke (RR = 1.50, 95% CI: 1.47, 1.54), as shown in Figure 3.

Coronary Artery Disease

Thirteen distinct articles showed the meticulous examination of symptoms related to coronary artery disease, revealing a landscape characterized by noticeable heterogeneity across each subgroup ($I^2 = 100\%$, $p < 0.0001$), necessitating the utilization of the RE model. The synthesis of this diverse body of evidence yielded a compelling revelation - DOAC emerges as an effective intervention in the alleviation of coronary artery disease in NVAF (RR = 2.45, 95% CI: 2.42, 2.48), as unveiled by the metanalysis depicted in Figure 4.

Mortality

Three[24,26,30] distinct articles undertook a meticulous examination of mortality, revealing a landscape marked by noticeable heterogeneity across each subgroup ($I^2 = 38\%$, $p = 0.2$), warranting the use of the RE model. Synthesizing this disparate body of evidence yielded a compelling revelation - DOAC emerges as an effective intervention in the alleviation of mortality in NVAF (RR = 0.49, 95% CI: 0.43, 0.56), as unveiled by the metanalysis depicted in Figure 5.

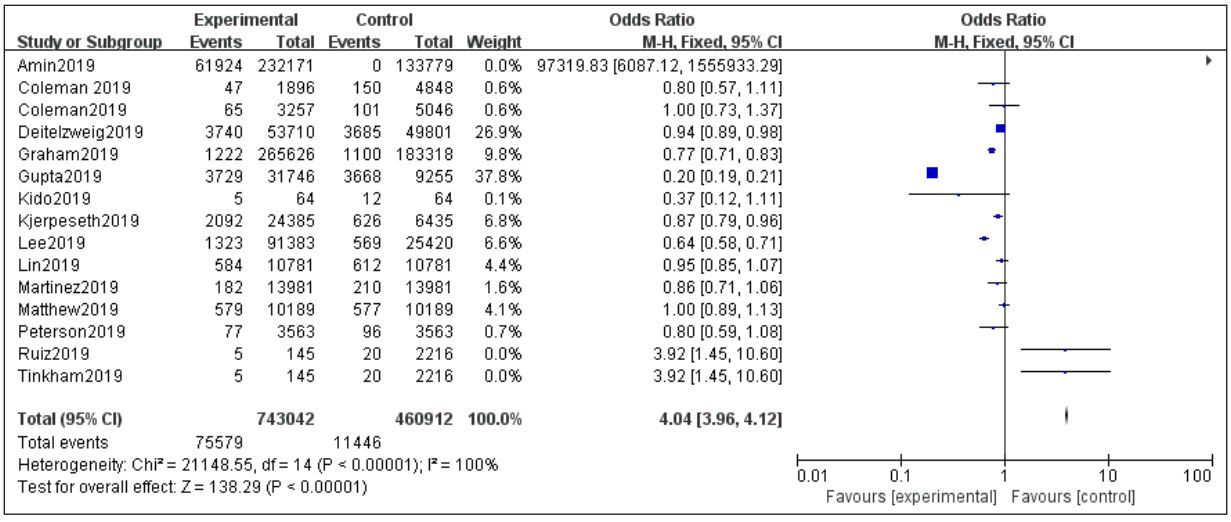

Figure 3. Forest plot of bleeding.

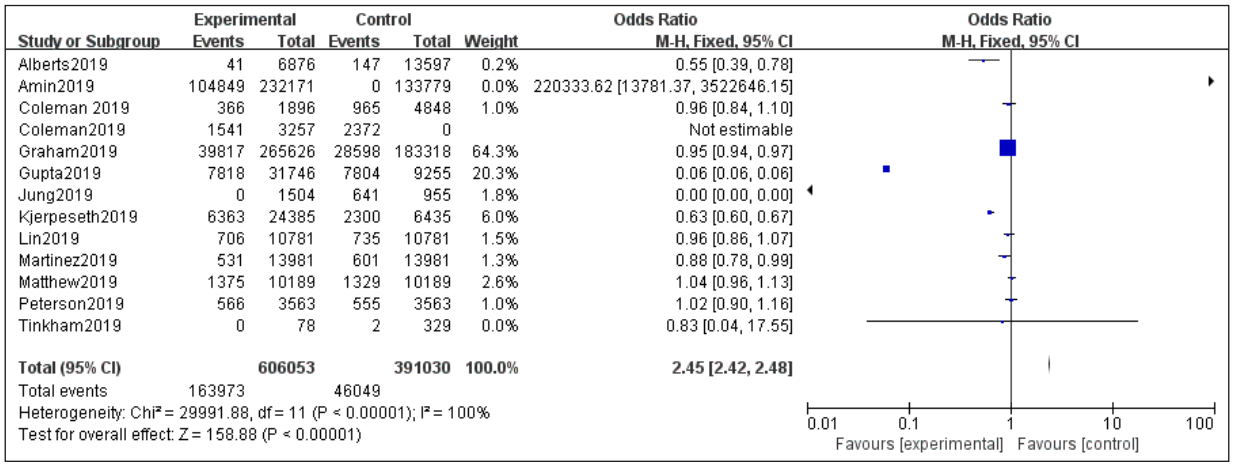

Figure 4. Forest plot of coronary artery disease.

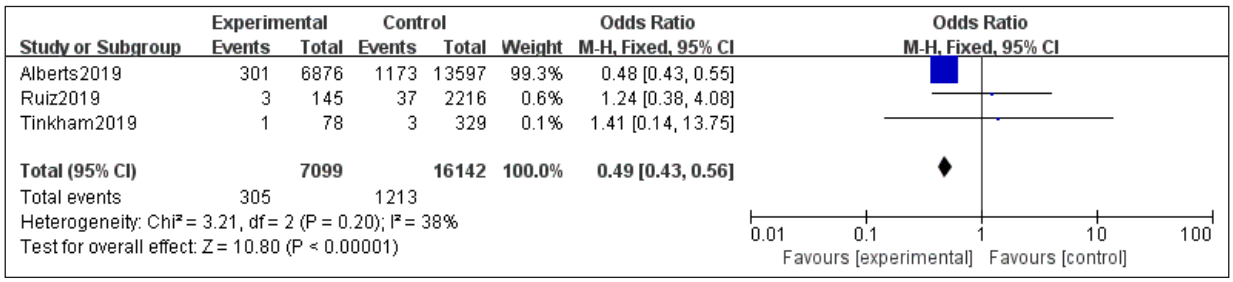

Figure 5. Forest plot of mortality.

Myocardial Infarction

12 distinct articles examined myocardial infarction symptoms, revealing a landscape characterized by noticeable heterogeneity across each subgroup ($I^2 = 100\%$, $p < 0.0001$), necessitating the adoption of the RE model. The synthesis of this diverse body of evidence yielded a compelling revelation - DOAC emerges as an effective intervention in the alleviation of myocardial infarction in NVAF (RR = 1.85, 95% CI: 1.81, 1.88), as unveiled by the metanalysis depicted in Figure 6.

Stroke

16[25-40] distinct studies performed a scrupulous examination of stroke symptoms, uncovering a landscape rife with evident heterogeneity across

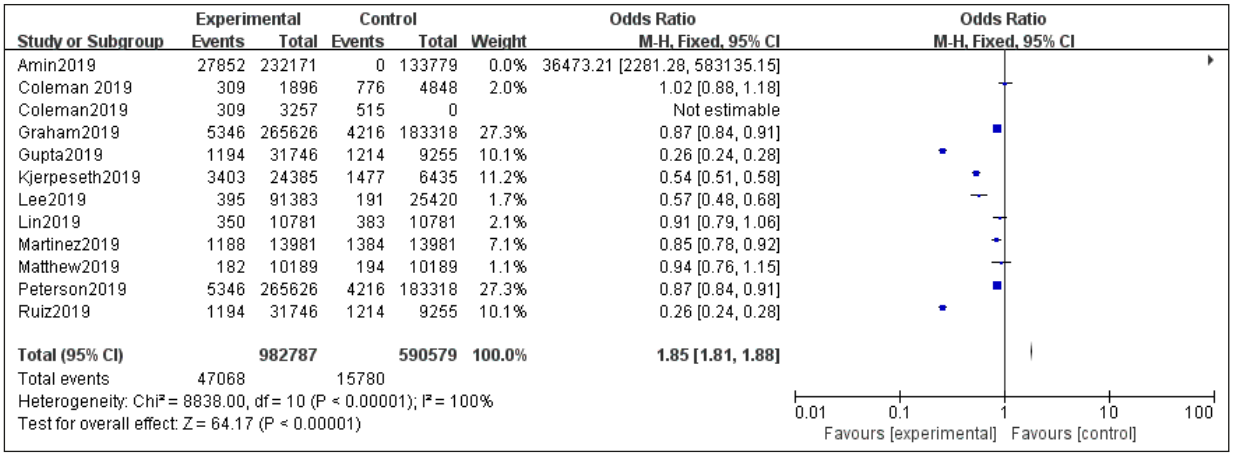

Figure 6. Forest plot of myocardial infarction.

each subgroup (I^2 = 100%, p < 0.0001), leading to the adoption of the RE model. Synthesizing this disparate body of evidence yielded a significant finding - DOACs emerge as a noteworthy intervention in the alleviation of stroke in NVAF (RR = 1.50, 95% CI: 1.47, 1.54), as unveiled by the metanalysis depicted in Figure 7.

Scrutiny of Publication Bias

As shown in Figure 8, the meta-analysis funnel plot displayed the varying expression levels of five indicators, which were significantly asymmetric. This asymmetry suggested a potential publication bias in this study.

Discussion

Anticoagulation therapy stands as a pivotal defense against the ominous specter of stroke in individuals with AF, a cardiac arrhythmia characterized by irregular and quivering heartbeats. This condition bears the potential for a cascade of detrimental outcomes, spanning from blood clots to heart failure[41]. The use of long-term oral warfarin is consistently championed in clinical wisdom for combating VAF[42]. However, the scenario changes when considering NVAF, revealing complex patterns influenced by the diverse range of blood clots and stroke risks. This leads us to a pivotal question: can DOACs effectively take the place of warfarin, providing a viable alternative for NVAF management?

As evidence continues to mount, shedding light on the effectiveness of anticoagulant therapy in guarding against thromboembolic events in individuals with NVAF, the landscape of prevention strategies becomes increasingly complex[43]. Among the contenders, DOACs have risen to prominence, offering a range of advantages: predictable pharmacokinetics, heightened efficacy, quick cessation of effect upon discontinuation due to their short half-lives, fewer restrictions on diet and drug interactions, and a reduced risk of intracranial hemorrhage, reducing the demand for frequent monitoring[44]. This collection of options holds the potential to improve patient adherence to the requirements of long-term anticoagulant therapy, thus enhancing the overall effectiveness of AF treatment[45]. Consequently, it is essential to explore whether the distinction between warfarin and DOACs results in a significant impact on the occurrence rate of stroke in NVAF patients.

In the context of empirical investigation, our analysis has unveiled a landscape of insights distinguished by methodological integrity and scientific precision. This study comprised 17 studies and a total of 1,224,932 patients. The meta-analysis assessed the effectiveness and safety of DOACs in anticoagulant therapy for NVAF patients and compared it with warfarin treatment. The results of this meta-analysis demonstrate that DOACs are associated with a lower risk of bleeding complications (both major and minor) compared to warfarin. Furthermore, DOACs appear to be superior to warfarin in preventing strokes and systemic embolism. Bleeding is a significant concern in anticoagulant therapy, as it is closely associated with morbidity and mortality. While warfarin can

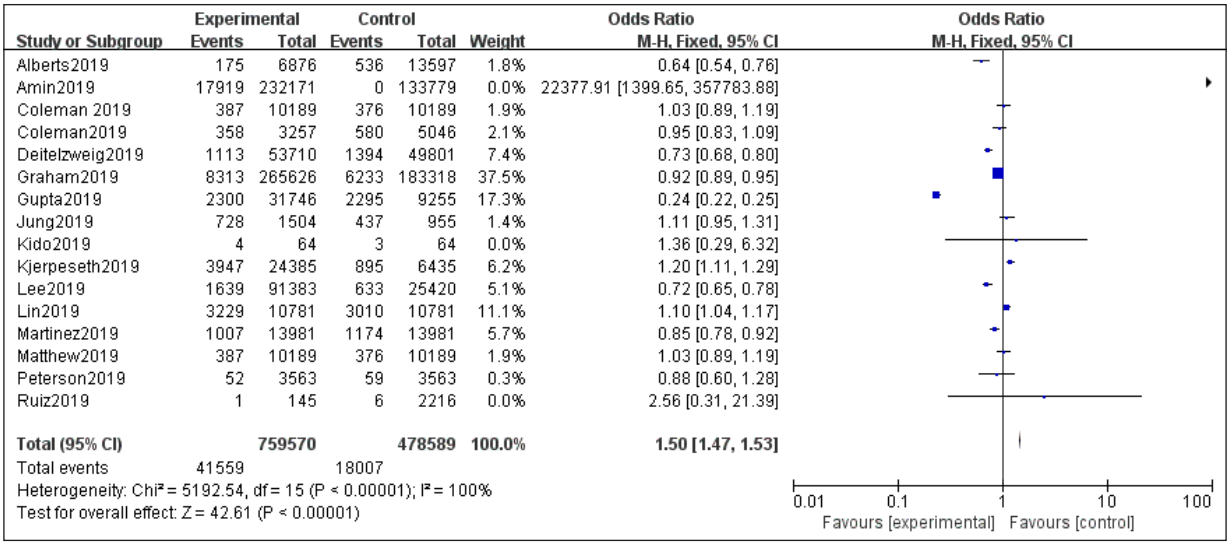

Figure 7. Forest plot of stroke.

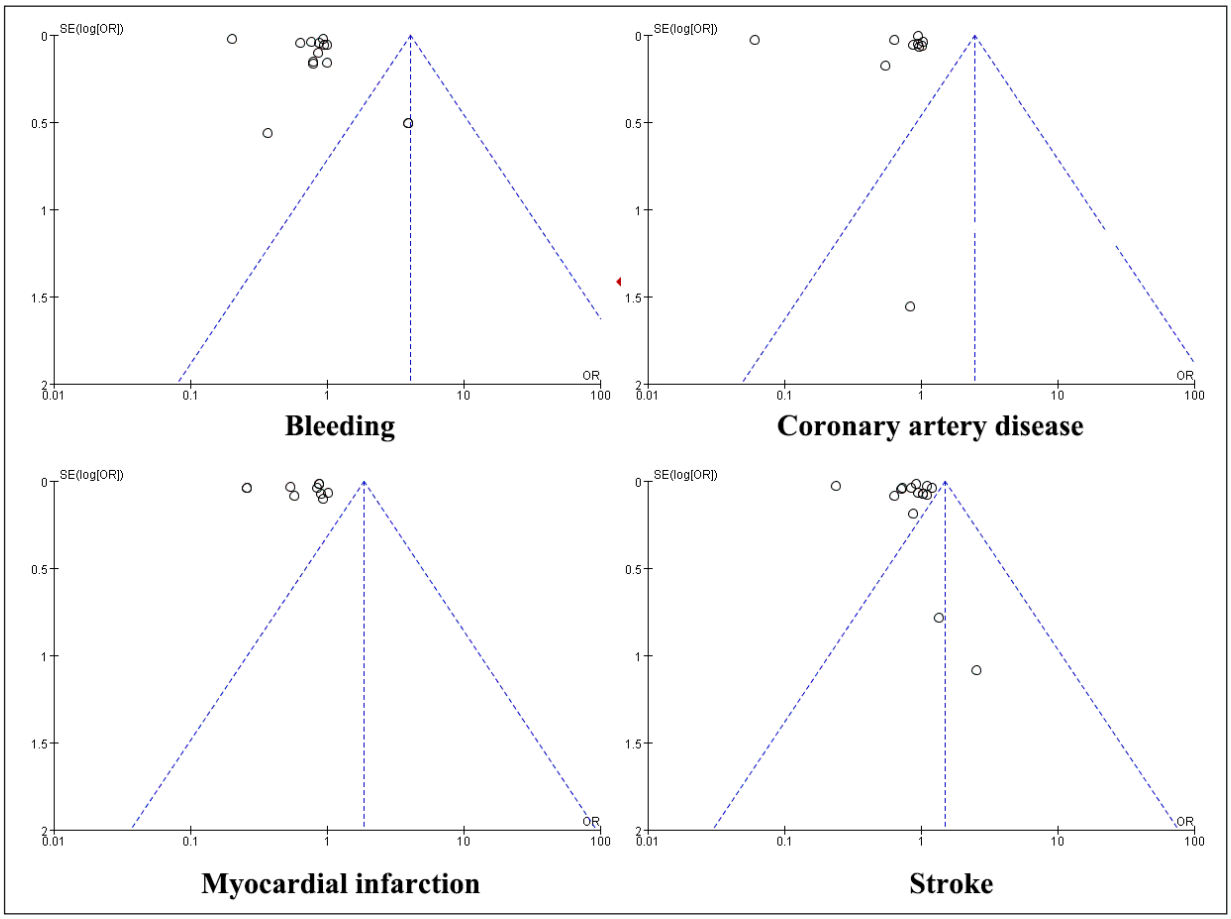

Figure 8. Funnel plot of publication bias.

reduce the risk of stroke and thromboembolism, it may increase the risk of bleeding. In a meta-analysis[46] examining hemorrhagic stroke and major bleeding rates, the incidence in the Asian population was twice that of non-Asian patients. This disparity might involve ethnic or genetic factors, but other considerations should also be considered. Cardoso et al[47] conducted a meta-analysis of nearly 5,000 patients from different countries, showing a bleeding event incidence of 0.9% for DOACs and 2.0% for warfarin. The incidence of thromboembolic events was 0.08% for the NOAC group and 0.16% for the warfarin group. Our meta-analysis results align with those of Cardoso et al[47], indicating a similar occurrence of major bleeding events. Overall, our findings suggest a lower incidence of bleeding events in the DOAC group compared to the warfarin group, with DOACs also performing better than warfarin in preventing thromboembolic complications.

Warfarin presents several drawbacks in these regards: it is susceptible to interactions with different foods and drugs, its optimal dosage varies between individuals, and regular monitoring of clotting function along with dose modifications guided by INR measurements is necessary. Therefore, actively seeking alternatives to warfarin for anticoagulation is essential. With the emergence of DOACs, warfarin is no longer the sole choice for oral anticoagulant therapy in treating NVAF. DOACs offer several advantages, including short half-lives, ease of management, fewer interactions, and no need for laboratory monitoring. Our results also corroborate this notion. It is worth noting that there is heterogeneity in the anticoagulation treatment regimens used in different observational studies. It is reasonable to speculate that differing proportions of continuous/interrupted warfarin regimens selected may induce different outcomes. DOACs, with their dose-response liberated from the need for frequent dose adjustments and hemostatic parameter evaluations, hold promise as a more patient-friendly alternative treatment approach. Our findings align with the results of a previous meta-analysis by Kumar et al[48].

Differing case sample sizes, evolving research contexts, regional disparities, and observational study designs can all have repercussions on the outcomes. Despite these variations, the core results remain unaffected, providing a foundation for our result analysis. This study not only comprehensively updates the existing knowledge about the risk of stroke in NVAF patients with DOACs but also represents an improvement in presenting previously unknown comprehensive evidence. In this analysis review, a promising prospect emerges - DOACs could potentially be demonstrated as a potent stroke prevention medication. However, our study is not without limitations. Firstly, critical data gaps impact the analysis of these results. Secondly, there is a notable lack of comprehensive reporting on DOACs for stroke prevention. Thirdly, the inherent nuances between prospective and retrospective studies must be acknowledged. In this study, heterogeneity arises from many aspects, stemming from variability in outcome measurements and differences in methodological rigor, particularly in RCTs, which could be a potential source of these differences. In upcoming research, researchers should aim for precision and substantial sample sizes. This steadfast and continual exploratory process, along with the culmination of experience, undoubtedly enhances researchers' understanding of the field, allowing more scholars to embark on future explorations in this intriguing domain with greater confidence.

Conclusions

This study is conducted through systematic review and meta-analysis, establishing that DOACs can significantly improve the risk of stroke in patients with NVAF. By comparing relevant literature and analyzing statistically significant results, this research identifies the potential effectiveness of DOACs as a fundamental component. However, the safety and occurrence of complications related to DOACs currently remain elusive, warranting further high-quality, multicenter, large-sample, randomized controlled trials to more accurately and comprehensively verify the effectiveness and safety of DOACs in the prevention of stroke in patients with NVAF.

Data Availability

The datasets generated and/or analyzed during the current study are available in the manuscript.

Ethics Approval and Informed Consent

Ethics approval and consent to participation are not applicable due to the design of the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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None.

Authors' Contributions

Zhi-Qiang Xu conceived the structure of the manuscript. Zhi-Hong Xu did the experiments and made the figures. Zhang Na reviewed and edited the manuscript. All authors read and approved the final manuscript.

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