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Efficacy and Safety of Direct Oral Anticoagulants in Stable Coronary Artery Disease and Atrial Fibrillation: A Systematic Review and Network Meta-Analysis

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Abstract

Direct Oral Anticoagulants (DOACs) , which partially replace warfarin, have been developed as a safe and effective therapy for patients with stable coronary artery disease (SCAD) and atrial fibrillation (AF). However, the choice of DOACs and warfarin remains controversial. We conducted a network meta-analysis (NMA) using randomized controlled trials (RCTs) through a systematic literature review to evaluate the the efficacy and safety of DOACs in SCAD and AF patients. Five RCTs with 6524 patients were included. The results showed that patients taking DOACs had a lower risk of stroke/systemic embolism (OR, 0.64; 95% CI, 0.54-0.76, $P < .00001$, $I^2 = 89\%$), intracranial bleeding (OR, 0.41; 95% CI, 0.26-0.64, $P = .0001$, $I^2 = 0\%$), major bleeding (OR, 0.98; 95% CI, 0.81-1.148, $P = .80$, $I^2 = 88\%$), and all-cause mortality (OR, 1.04; 95% CI, 0.88-1.22, $P = .66$, $I^2 = 51\%$) than those taking warfarin. Compared to warfarin, rivaroxaban (20 mg, once/day) was more advantageous in preventing stroke/systemic embolism, as was apixaban (5 mg or 2.5 mg, twice/day) in reducing major bleeding (OR, 0.79; 95% CI, 0.48-1.3) and all-cause mortality (OR, 0.97; 95% CI, 0.69-1.4). Different doses of DOACs showed obvious advantages against intracranial hemorrhage, without significant differences. Thus, DOACs have more effective than warfarin in clinical efficacy and safety.

Keywords

stable coronary artery disease, atrial fibrillation, direct oral anticoagulants, network meta-analysis

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Introduction

Stable coronary artery disease (SCAD) is a common coronary heart disease that can lead to myocardial ischaemia and hypoxia.[1] According to the 2016 data from the American Heart Association, SCAD is approximatelyt twice as common as myocardial infarction. It is expected to affect approximately 18% of adults by 2030, making it one of the most important public health problems endangering human life.[2] In addition, atrial fibrillation (AF) is one of the most frequently observed persistent arrhythmias as well as a complication of SCAD.[3] The prevalence of AF is approximately 0.5% globally and 0.77% in Asia; the incidence rate of AF progresses rapidly with age.[4] It has been reported that SCAD and AF have similar risk factors, such as age, hypertension, and diabetes, and these factors influence each other.[5] Anticoagulation therapy is an important strategy for the treatment of SCAD and AF. The traditional anticoagulant drug is the vitamin K antagonist warfarin; however, its predisposition for drug and food interactions, risk of bleeding, and need for close monitoring of the intensity of the anticoagulation effect using the

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international normalized ratio (INR) limit its application in clinical use.[5,6] Therefore, it is urgent to develop new anticoagulants for SCAD and AF.

Direct Oral Anticoagulants (DOACs), such as rivaroxaban, apixaban, edoxaban and dabigatran, have been approved to replace warfarin for thromboembolic prophylaxis in patients with AF.[7] The 2019 European Society of Cardiology guidelines for the diagnosis and treatment of chronic coronary syndrome indicated that DOACs are preferred over vitamin K antagonists in patients with SCAD and AF.[8] Numerous studies have demonstrated that compared to vitamin K antagonists, DOACs have higher efficacy, more stable anticoagulation, and less risk of bleeding, and they do not require anticoagulation monitoring.[9,10] However, there is a lack of clinical research investigating the efficacy and safety of DOACs in patients with SCAD and AF.

This study conducted a systematic evaluation and network meta-analysis (NMA) to compare the efficacy and safety of DOACs and warfarin in the treatment of patients with SCAD and AF, providing a reliable basis for clinical treatment.

Materials and Methods

Literature Search

The literature databases, such as PubMed, Web of knowledge, Chinese National Knowledge Infrastructure Database, VIP Database, Chinese Biomedical Database, and Wan Fang Database,were searched from 1 January 2010 to 31 December 2021. A combination of keywords and free words was used to retrieve the relevant research articles. The following key words were used: ("Direct Oral Anticoagulants" or "DOACs" or "rivaroxaban" or "apixaban" or "edoxaban" or "dabigatran") in combination with ("warfarin") and ("stable coronary artery disease" or "SCAD") and ("atrial fibrillation" or "AF").

Selection Criteria

The inclusion criteria for article selection based on different parameters were as follow: (1) study method: randomized clinical trials (RCTs), limited to English and Chinese languages, and single-blind, double-blind or non-blind trials; (2) study participants: patients fulfilling the diagnostic criteria for SCAD in the 2013 European Guidelines for Stable Coronary Artery Disease[11] and those for AF in the in the 2013 US Guidelines for the Management of Atrial Fibrillation;[12] (3) interventions: control group was administered warfarin or aspirin therapy and international normalized ration (INR) was tested after 2-3 days for the adjustment of the dose, while the treatment group was administered DOACs (rivaroxaban or apixaban or edoxaban or dabigatran) or aspirin therapy; and (4) outcome indicators: stroke/systemic embolism, major bleeding, intracranial hemorrhage, and all-cause mortality.

The exclusion criteria (1) non-RCTs; (2) non-compliance with the diagnosis of SCAD and AF; (3) animal experimental literature, reviews, empirical summaries, case reports, and repeated publications; (4) DOACs (rivaroxaban, apixaban, edoxaban, or dabigatran) not used in the treatment group; (5) warfarin not used in the control group; and (6) endpoint events not specified.

Data Extraction and Quality Assessment

Data were extracted from all included studies, and they comprised basic information and main outcomes. The basic information included the author's name, age of the patients, intervention methods of the treatment group and control group, sample size of aspirin administration, $CHADS_2$ score, and follow-up time. The clinical outcomes included stroke/systemic embolism, intracranial hemorrhage, major bleeding, and all-cause mortality (Table 1).

The RCT assessment was performed based on the Cochrane risk-assessment tool[18], which includes 6 domains: random allocation, allocation concealment, blind method, loss of outcome data, selection of outcome reporting and other bias parameters. The assessment included assigning "yes", "no", or "unclear" to each domain to designate a low, high, or unclear risk of bias, respectively. Publication bias was evaluated using the Review Manager, version 5.4. All studies were independently screened by two investigators to determine whether they met the selection criteria, and disagreements were resolved through discussion or by a third reviewer.

Statistical Analysis

The outcome measures of stroke/systemic embolism, intracranial bleeding, major bleeding, and all-cause mortality were assessed for heterogeneity. Review Manager (version 5.4) and R software were used, and the odds ratio (OR) was calculated for dichotomous results with 95% confidence intervals (CI). Chi-square and I^2 tests were used to assess the heterogeneity of the clinical trial data and to determine the appropriate analysis model (fixed-effects model or random effects model). When the chi-square test P value was .05 and I^2 tests value was > 50%, the heterogeneity was defined as acceptable, and the data were assessed using the random-effects model. Conversely, if the chi-square test P value was >.05 and I^2 tests value was 50%, the data were defined as homogeneous and was assessed using the fixed-effects model.[19] The efficacy and safety of DOACs in patients with SCAD with AF were further evaluated using network evidence relationships, forest maps, rank probability maps, funnel plots, and corresponding statistics.

Results

Characteristics of the Literature Search and Study

According to the search strategy and inclusion criteria, 114 articles were identified in the initial search. The meta-analysis included five RCTs[13–17] comprising 6524 patients, of which 3207 participants administered rivaroxaban or apixaban therapy (eligible articles receiving dabigatran or edoxaban

Table 1. Basic Information of Included Studies.

Study	T/C(age)		T/C (samplesize)		Intervention		Aspirin (samplesize)		$CHADS_2$ score (SD)	Follow-up time	Outcome
					T	C	T	C			
Maria 2013[13]	63-76	63-76	1916	1922	Apixaban 5mg bid Scr > 133μmol/L 2.5mg bid	Warfarin INR 2-3	/	/	2.3	1.8 Y	①②③④
Kenneth 2014[14]	66-79	67-79	1182	1286	Rivaroxaban 20mg qd Clcr 30-49mL/min 15mg qd	Warfarin INR 2-3	569	602	3	3 M	①②③④
Wu 2018[15]	57-76	56-77	25	25	Rivaroxaban 20mg qd Clcr /	Warfarin 2.5mg qd INR /	/	/	2	N	①②
Zhang 2019[16]	47-75	46-76	30	30	Rivaroxaban 20mg qd Clcr /	Warfarin 2.5mg qd INR /	/	/	2	N	①②
Qu 2020[17]	51-86	50-85	54	54	Rivaroxaban 10mg qd Clcr /	Warfarin 1.5mg qd INR 1.5-2.5	/	/	2	4w	①②

Note: T: the treatment group; C: the control group; outcome index: ① stroke and systemic circulation embolism ② intracranial hemorrhage ③ massive hemorrhage ④ all-cause mortality.

were not found), and 3317 participants administered only warfarin therapy. The Cochrane Collaboration tool was used to evaluate the quality of eligible studies. Finally, five studies were included that reported the efficacy and safety of DOACs in the treatment of SCAD and AF. The details of the search strategy are shown in Figure 1.

Quality Assessment

Based on the risk of bias assessment strategy provided by the Cochrane Collaboration, the quality of the included articles was systematically evaluated. The included studies were RCTs, and the specific methods of random sequence generation, allocation schemes, and concealment methods were specifically described. The methodological quality of the included studies was evaluated (Figure 2). One study[14] had a high methodological quality grade of A, while the remaining four[13,15,16] showed a moderate quality of grade B.

Outcomes of the Meta-Analysis

Stroke/Systemic Embolism. The random-effects model was used to analyze major bleeding in five studies because of the high data heterogeneity (I^2 > 75%). The results showed that DOACs was significantly more effective than warfarin in reducing the incidence of stroke/systemic embolism in patients with SCAD and AF (OR, 0.64; 95% CI, 0.54-0.76, $P < .00001$, $I^2 = 89\%$; Figure 3A). Rivaroxaban (20mg, once/day, OR, 0.19; 95% CI, 0.033-0.91; Figure 3B) was more advantageous than warfarin in preventing stroke/systemic embolism.

Intracranial Hemorrhage. The incidence of intracranial bleeding was reported in all 5 included studies. Considering that the P value of the chi-square test was > .05 ($P = .94$) and the I^2 test value was < 50% ($I^2 = 0\%$), the fixed-effect model was used to analyze the clinical efficacy of DOACs. The result indicated that the risk of intracranial bleeding was lower with DOACs than with warfarin (OR, 0.41; 95% CI, 0.26-0.64, $P = .0001$, $I^2 = 0\%$; Figure 4A). However, compared to warfarin, the different doses of DOACs showed obvious advantages against intracranial hemorrhage, but without significant differences (Figure 4B).

Major Bleeding. The random-effects model was used to analyze major bleeding because of the high-data heterogeneity (I^2 > 75%). The incidence of major bleeding was reported in two studies.[13,14] The results showed that DOACs were better than warfarin in reducing the incidence of major bleeding in patients with SCAD and AF (OR, 0.98; 95% CI, 0.81-1.148, $P = .80$, $I^2 = 88\%$; Figure 5A), but there was no statistical difference between the two groups. Moreover, apixaban (5mg or 2.5 mg twice/day; OR, 0.79; 95% CI, 0.48-1.3; Figure 5B) was associated with a lower risk of bleeding than warfarin.

All-Cause Mortality. The two studies[13,14] reported all-cause mortality. The results indicated that there were no statistical

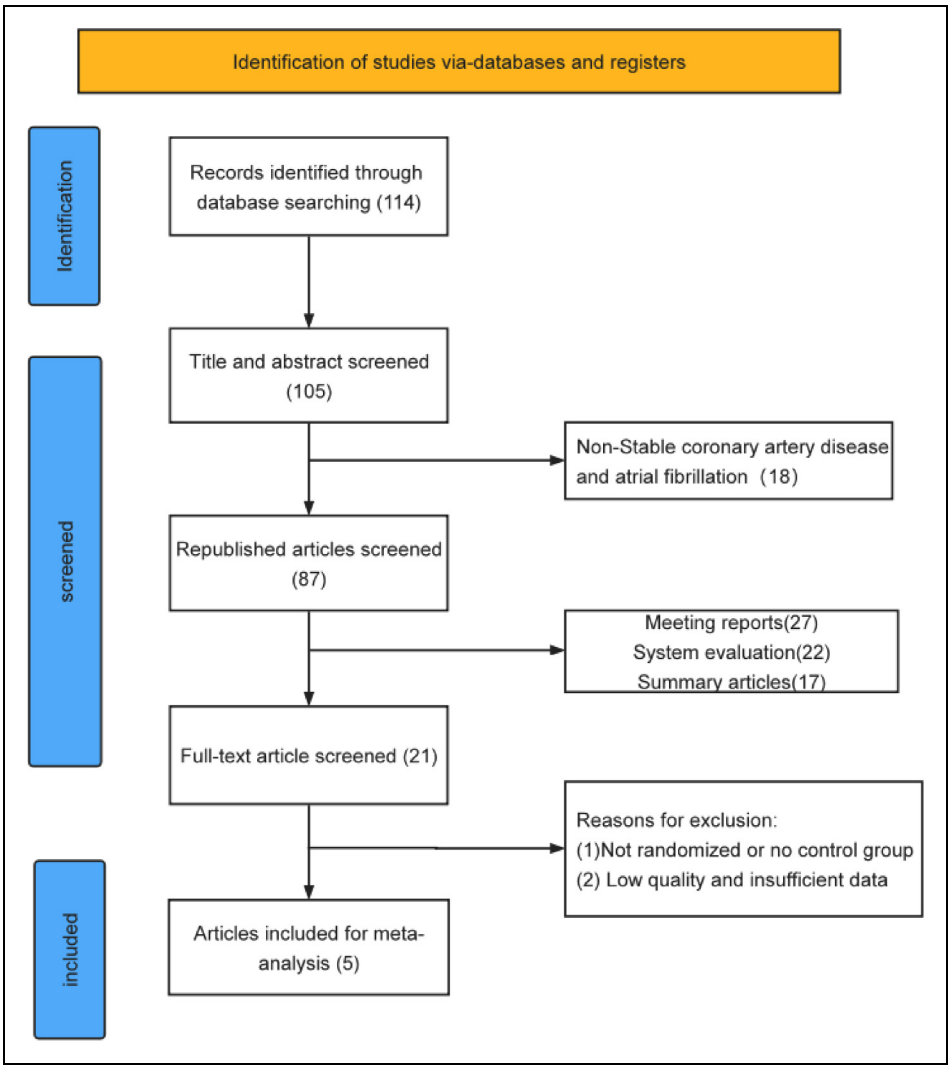

Figure 1. Flow diagram of the literature search and selection process.

differences in all-cause mortality (OR, 1.04; 95% CI, 0.88-1.22, $P = .66$, $I^2 = 51\%$; Figure 6A). Furthermore, compared to warfarin, apixaban (5mg or 2.5 mg twice/day, OR, 0.97; 95% CI, 0.69-1.4; Figure 6B) was associated with lower all-cause mortality than warfarin.

Diagram of Intervention Measures. Five studies reported stroke/systemic embolism and intracranial bleeding, involving five methods (Figure 7A); while two studies reported major bleeding and all-cause mortality, including three methods (Figure 7B). The network relationship was centered on the traditional anticoagulant warfarin, with a star-shaped structure of intervention nodes and no closed loop.

Classification of Treatment Options. The five RCTs included stroke/systemic embolism and intracranial bleeding, and the results of the various treatment regimens according to the rank value showed that DOACs were significantly better than warfarin in preventing stroke/systemic embolism and intracranial hemorrhage. Among them, rivaroxaban 20 mg once/day was the most effective for stroke/systemic embolism, followed by rivaroxaban 10 mg once/day, rivaroxaban 20 mg or 15 mg once/day and apixaban 5 mg or 2.5 mg twice/day (Figure 7C). Furthermore, 10 mg rivaroxaban once/day was the most advantageous against intracranial hemorrhage, followed by 20 mg rivaroxaban once/day, 5 mg or 2.5 mg apixaban twice/day, and 20 mg or 15 mg rivaroxaban once/day (Figure 7D).

Evaluation of Small-Sample Effects. The effects of small samples of stroke/systemic embolism and intracranial hemorrhage were assessed using funnel plots. Since only two studies reported major bleeding and all-cause mortality, funnel plots were not used for these outcomes. The results showed that the funnel diagram of stroke/systemic embolism was asymmetrically distributed, suggesting a high probability of a small sample size (Figure 7E). The intracranial hemorrhage samples were roughly symmetrically distributed on both sides of the vertical

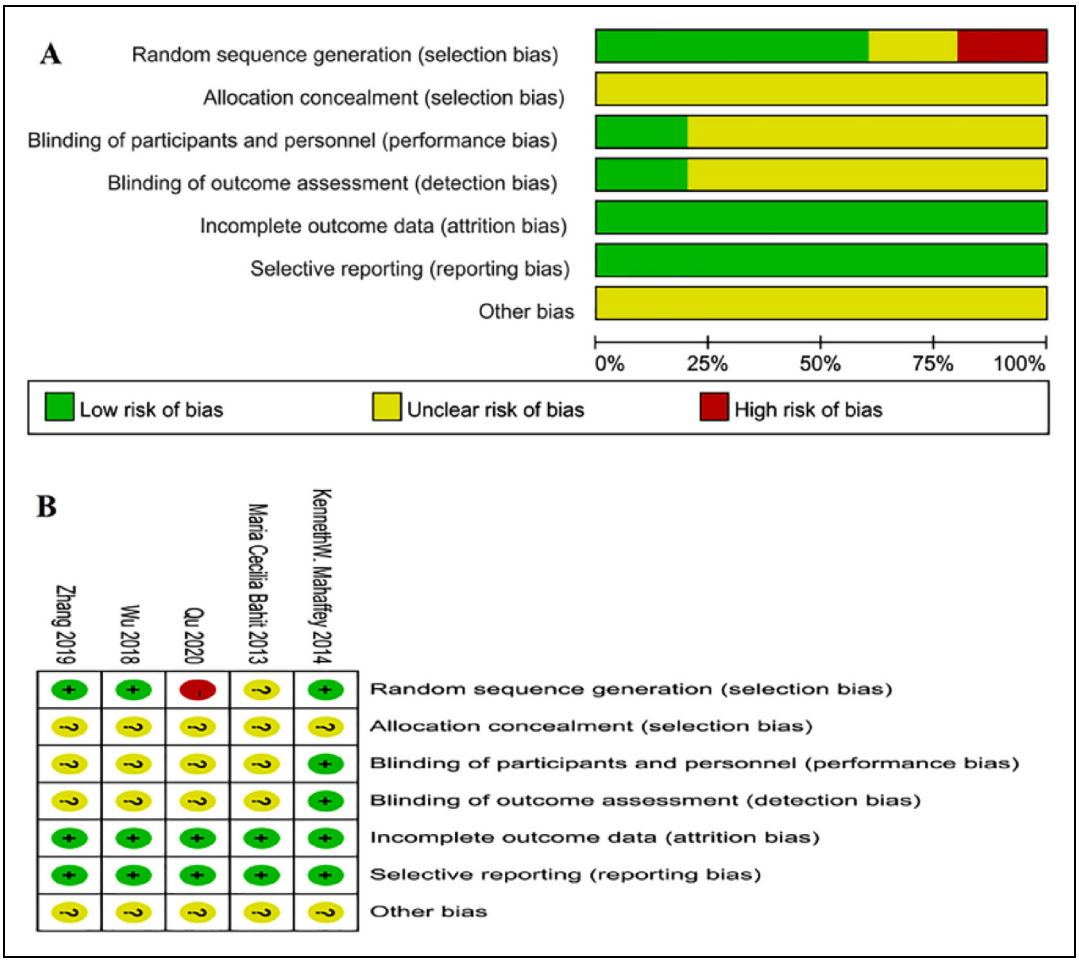

Figure 2. Overall risk (A) and detailed risk (B) of bias in include studies.

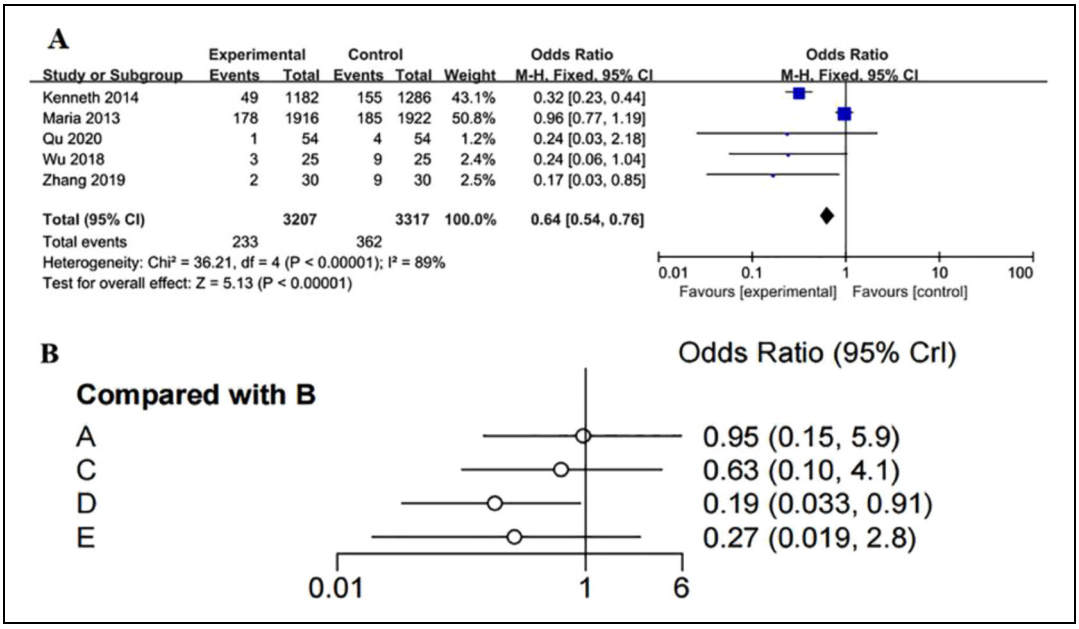

Figure 3. Comparison of the forest plot of stroke and systemic circulatory embolization in patients with new oral anticoagulants (NOACs) and warfarin treatment for stable coronary heart disease combined with atrial fibrillation.
(A: apixaban 5mg or 2.5 mg twice/day; B: warfarin 2.5mg once/day; C: Rivaroxaban20mg twice/day; D: Rivaroxaban20mg once/day; E: Rivaroxaban10mg once/day).

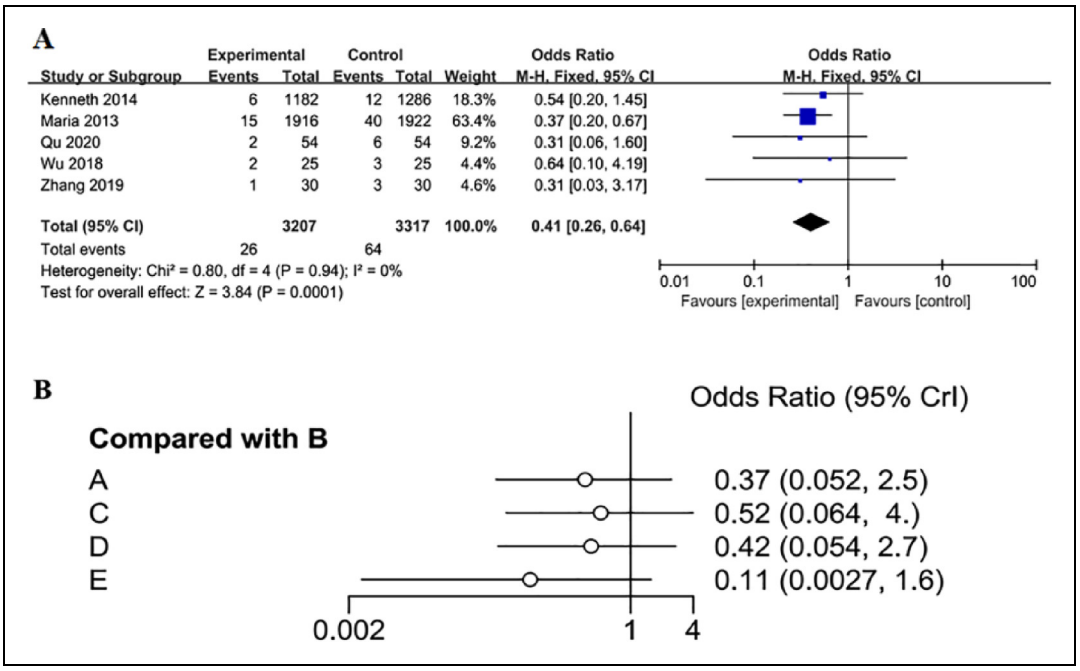

Figure 4. Forest comparison of intracranial hemorrhage in patients with NOACs with atrial fibrillation.
(A: apixaban 5mg / 2.5 mg twice/day; B: warfarin 2.5mg once/day; C:Rivaroxaban20mg twice/day; D: Rivaroxaban20mg once/day; E: Rivaroxaban10mg once/day).

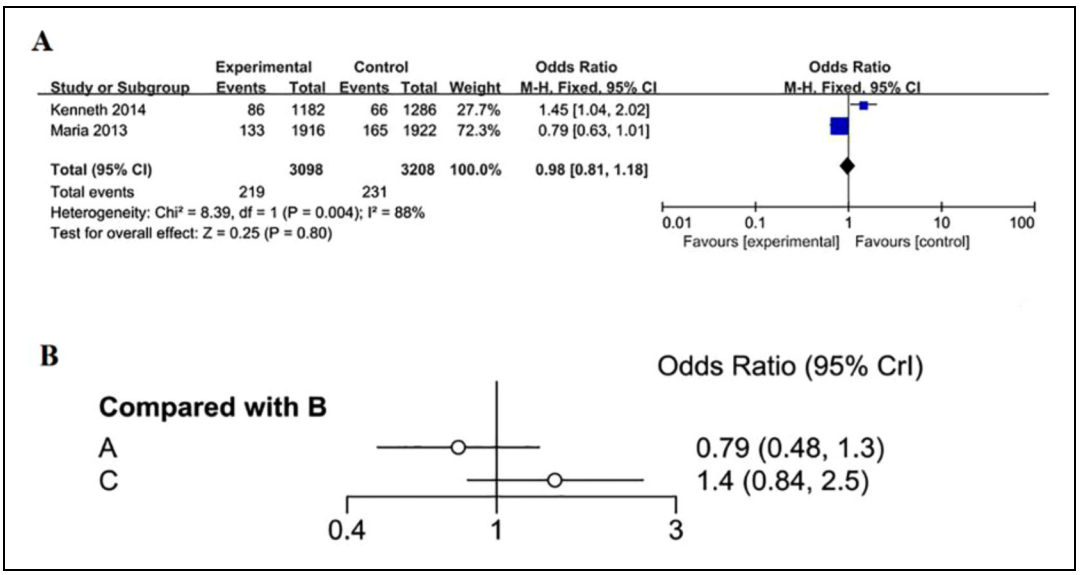

Figure 5. Forest comparison of major bleeding in patients with NOACs with atrial fibrillation.
(A: apixaban 5mg / 2.5 mg twice/day; B: warfarin 2.5mg once/day; C: Rivaroxaban 20mg twice/day).

line (X = 0), suggesting a low probability of a small samplesize (Figure 7F).

Discussion

The pathogenesis of SCAD with AF is very complex, and it is a common cardiovascular disease in the elderly population.[20] Although SCAD and AF have been effectively controlled with the gradual improvement in medical technology, the hospitalization rate of this condition is far higher than that of heart failure and myocardial infarction. This not only wastes medical resources but also places a heavy burden on the patients' families.[21] Thrombi formation is a universal complication of SCAD and AF, which can increase the risk of disability and death in patients.[22] Therefore, it is necessary to perform anticoagulant therapy actively and effectively to reduce platelet-related coronary artery thrombosis.

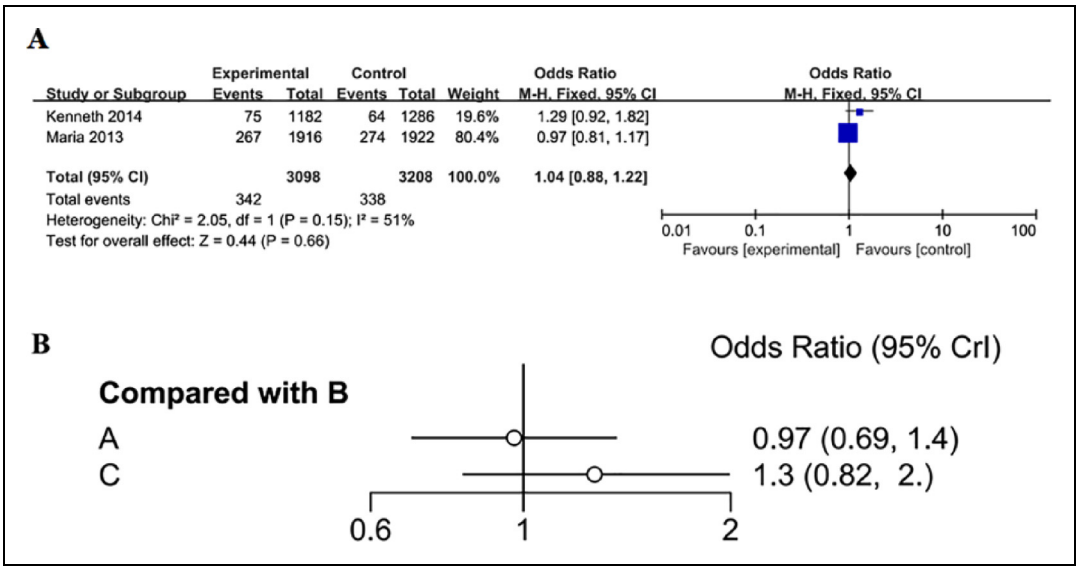

Figure 6. Forest comparison of all-cause mortality in patients with NOACs with atrial fibrillation.
(A: apixaban 5mg / 2.5 mg twice/day; B: warfarin 2.5mg once/day; C: Rivaroxaban 20mg twice/day).

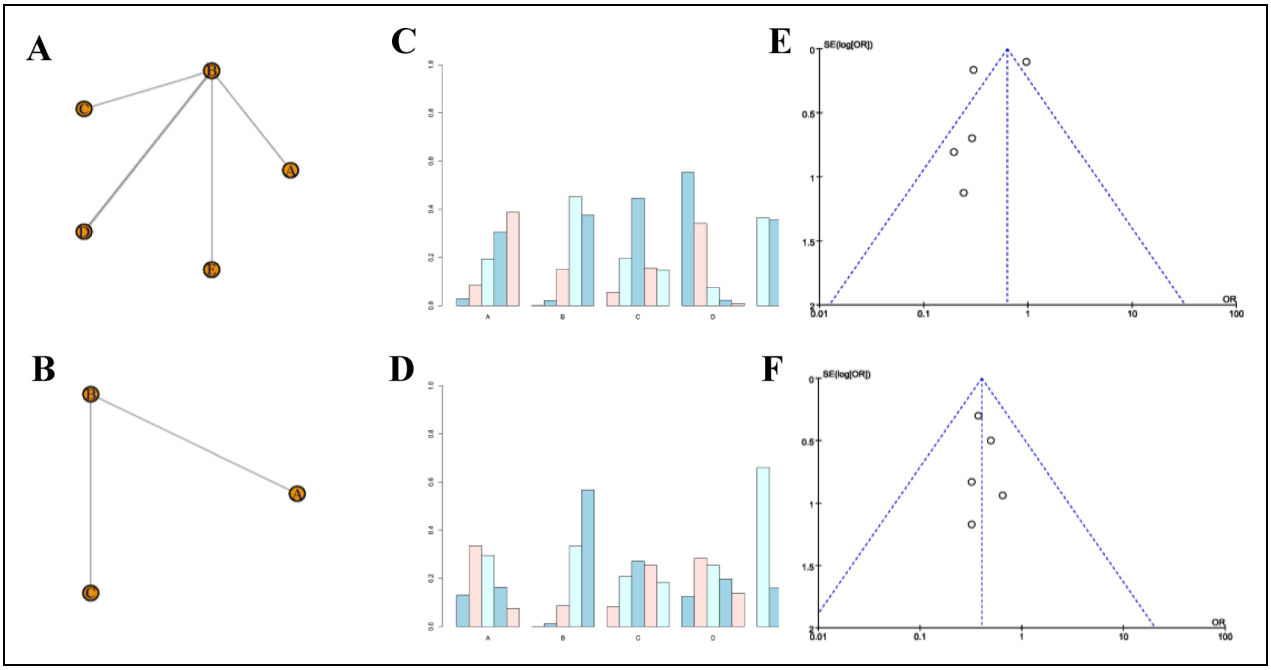

Figure 7. Evidence network relationship, ranking map, and index funnel map among interventions.
(A: apixaban 5mg / 2.5 mg twice/day; B: warfarin 2.5mg once/day; C: Rivaroxaban20mg twice/day; D: Rivaroxaban20mg once/day; E: Rivaroxaban10mg once/day).

Anticoagulant therapy is one of the key factors in controlling disease development, avoiding adverse events, and reducing the readmission and mortality rate. Warfarin, a bicoumarin derivative, has been widely used as a classical anticoagulant in thromboembolic diseases since the 1950s. It acts by inhibiting the mutual conversion of vitamin K and its epoxide or by inhibiting anticoagulant action.[23,24] It could effectively decrease the risk of thromboembolism in patients with AF, with an optimal anticoagulation parameter of INR of 2.0-3.0, which could reduce the risk of bleeding.[25] However, it has various limitations, such as a narrow therapeutic window and the need for strict anticoagulation monitoring among others.[26,27] DOACs mainly comprise factor Xa (FXa) inhibitors and factor IIa inhibitors; the former includes rivaroxaban, apixaban, and edoxaban, while the latter includes dabigatran. However, according to statistics, the most commonly used DOACs are rivaroxaban and

apixaban, which effectively induce anticoagulation by mainly inhibiting FXa.[28,29] Several studies have confirmed the efficacy and safety of DOACs over warfarin in anticoagulation therapy.[30,31] However, previous studies have not investigated the clinical efficacy and safety of both drugs sufficiently.

In this study, five RCTs involving 6524 patients were included to assess the risk of stroke/systemic embolism, intracranial hemorrhage, major bleeding, and all-cause mortality in patients with SCAD and AF who underwent DOACs treatment. The systematic review revealed that DOACs had obvious advantages over warfarin in reducing the incidence of stroke/systemic embolism, intracranial hemorrhage, major bleeding, and all-cause mortality, without a statistical difference in major bleeding and all-cause mortality between the two groups ($P > .05$), and the values remained within the reference range. A meta-analysis by Miller et al[32] included three clinical studies totaling 44 563 patients and found that DOACs obviously reduced the incidence of stroke/systemic embolism in patients with AF. The study by Sarder et al[33] indicated that the risk of DOACs was significantly lower than that of warfarin, as seen in the results of the systematic evaluation in this study. Furthermore, the NMA results indicated that DOACs of different doses (rivaroxaban or apixaban) were safer than warfarin, rivaroxaban (20mg, once/day) were more advantages in preventing stroke/systemic embolism, as was apixaban (5mg or 2.5 mg, twice/day) in reducing major bleeding and all-cause mortality. However, there were no significant differences between the different doses of DOACs with aspect to intracranial hemorrhage. Rivaroxaban, one of the most widely used anticoagulants, has the highest bioavailability (> 80%) and limited effect on the platelet count.[34] Animal models have shown that rivaroxaban could safely and effectively reduce the rate of thrombosis and bleeding event.[35] Both the ROCKET-AF trial[36] and the REVISIT-US study[37] confirmed that rivaroxaban 20 mg/day was effective in reducing the risk of stroke in patients with nonvalvular AF. Ai Yang et al[38] confirmed that 10mg/day rivaroxaban showed similar efficacy as that of warfarin. Apixaban achieved anticoagulant effects through inhibition of activated FXa, with a bioavailability of 50% at a usual dose of 5mg twice daily.[39] Meanwhile, the ARISTOTLE trial indicated that apixaban not only reduced the risk of all major bleeding events better than warfarin but also outperformed rivaroxaban in terms of safety.[40] Moreover, it presented a statistically significant risk of apixaban reducing all major bleeding events compared to warfarin and rivaroxaban.[41] A randomized study of healthy participants found that apixaban (5mg, twice/day) had more stable anti-factor activity compared to rivaroxaban (20mg, once/day).[42] Furthermore, in order to prevent in-stent thrombosis or cardiovascular events in patients with AF, therapy is usually combined with antiplatelet drugs and anticoagulants.[8] Only one study[14] in this review included aspirin in the treatment of SCAD and AF patients. The results showed that DOACs with aspirin was associated with the highest risk of intracranial bleeding, and there was no significant difference in the incidence of stroke and all-cause mortality when compared with the other doses of DOACs. Several studies have shown that DOACs and warfarin combined with aspirin increased the risk of bleeding, with no significant effect on stroke and all-cause mortality,[43] which is consistent with the results of this review.

This study has some limitations. First, the included studies were heterogeneous in many aspects, such as population, age, and follow-up time. Second, the population included in the clinical institute was younger than the actual population, and some studies did not recorded the INR, Ccr, or Scr in detail. This may have affected the reliability of the results in the actual clinical work. Third, we did not retrieve data on edoxaban and dabigatran due to data unavailability. Moreover, some complications, such as hemorrhagic stroke and gastrointestinal bleeding, were not included in this analysis.

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Authors Note

Chu Chen, Xinli Wen and Fang Ma participated in data curation; Chu Chen, Fang Ma and Li Yuan participated in formal analysis; Yangyang Wang, Qiaofei Li, and Fang Ma performed the investigation; Li Yuan and Chu Chen performed the methodology; Fang Ma performed software and contributed to the writing of the original draft; Chu Chen, Fang Ma, Yangyang Wang, Qiaofei Li, and Li Yuan participated in the writing of the review and editing. All authors proofread and approved the final manuscript.

Declaration of Conflicting Interests

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