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Efficacy and safety of new oral anticoagulants combined with antiplatelet drugs in the treatment of coronary heart disease: Systematic evaluation and meta-analysis

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Abstract

Objective: To analyze the efficacy and safety of antiplatelet drugs combined with new oral anticoagulants (noac) in the treatment of coronary atherosclerotic heart disease (CAD).

Methods: The randomized controlled trials of noac combined with antiplatelet therapy in Cochrane, CNKI, PubMed, EMBASE, Wanfang, Google Scholar, and Baidu library were searched using the literature database. Two researchers independently searched and screened to ensure the consistency of the results, and the literature was summarized and analyzed by Revman 5.3 software.

Results: Five research results were included. The results showed that the incidence of mace [95% CI 0.75–0.95, or = 0.84,p = .04], the incidence of major and minor bleeding [95% CI 1.25–5.16, or = 2.54,p = .01], the mortality of cardiovascular disease [95% CI 0.78–0.96, or = 0.86, p = .05], the total mortality [95% CI 0.79–0.95, or = 0.87, p = .003], and the incidence of myocardial infarction in patients with CAD treated with noac and antiplatelet drugs [95% CI 0.77–0.95, or = 0.85, p = .004] was lower than that treated with antiplatelet drugs alone, and the difference was statistically significant (p < .05); the incidence of fatal bleeding [95% CI 0.81–2.08, or = 1.30, p = .28], the incidence of stroke [95% CI 0.50–1.03, or = 0.71, p = .07], and the incidence of intracranial hemorrhage [95% CI 1.02–2.56, or = 1.61, p = .06]. There was no significant difference with antiplatelet drugs alone (p > .05).

Conclusion: Noac combined with antiplatelet drugs can reduce mace, total mortality, the incidence of myocardial infarction, and cardiovascular mortality in patients with CAD, but may increase the risk of bleeding.

KEYWORDS
antiplatelet drugs, coronary atherosclerotic heart disease, meta-analysis, new oral anticoagulants, stroke

Alimila·Saiyitijiang and Mayila·Aizezi are the first authors and contribute equally.

1 | INTRODUCTION

Coronary atherosclerotic heart disease (CAD) has become a global health problem. It is one of the most important diseases leading to residents' disease death, accounting for about 40% of the total disease deaths (Wen et al. 2020). Antiplatelet therapy and interventional surgery are the two main methods for clinical treatment of CAD, but the incidence of coronary events in patients with CAD is still high after treatment. Therefore, it is widely believed that antiplatelet therapy alone for CAD still has some limitations (Zhu et al. 2019). In the long-term treatment of chronic vascular diseases, the antiplatelet effect is only implemented, the antithrombotic effect is slow, and there is still a high incidence of thrombosis events. Therefore, the clinical recommendation of a combined drug strategy (Gurbel et al. 2019). Oral anticoagulants can inhibit the formation of coronary atherosclerotic plaque in patients with CAD and play a positive role in improving the condition and prognosis of patients. However, the traditional oral anticoagulant warfarin needs long-term and frequent blood sampling to monitor the international standardized ratio, and the treatment effect is easily affected by the type of diet of patients (Wu and Liao 2020). To make up for the deficiency of traditional oral anticoagulants in the treatment of CAD, researchers have developed new oral anticoagulants (noac), including direct coagulation factor Xa inhibitors (apixaban, betalisaban, edoxaban, rivaroxaban, etc.) and direct thrombin inhibitors (dabigatran, etc.), which can effectively reduce the interaction between drugs and food and improve the quality of prognosis of patients (Valencia et al. 2019). The specific mechanism of action of the new oral anticoagulant is mainly to inhibit the two most important targets Xa and IIa in the coagulation waterfall. It has a quick effect after oral administration. Compared with traditional therapies, it has a shorter half-life and a good dose–effect relationship, and there is no need to monitor conventional coagulation. Indicators that can reduce or reduce the risk of adverse drug efficacy or bleeding events (Koutsoumpelis et al. 2018). However, studies have pointed out that the main indications for oral anticoagulation therapy are atrial fibrillation, venous thromboembolism, and conditions after heart valve replacement. It is contraindicated in patients with mechanical heart valves. The scope of application of this medication needs to be further expanded in the future (Altiok and Marx 2018). However, there is still a lack of evidence-based research on the effectiveness and safety of noac in the secondary prevention of CAD. Therefore, this study collects previous relevant research results to evaluate the effectiveness and safety of noac combined with antiplatelet drugs in the treatment of CAD.

2 | DATA AND METHODS

2.1 | Inclusion and exclusion criteria of literature

2.1.1 | Study type

Randomized controlled trial study, whether the blind method is used or not, and the literature language is Chinese or English.

2.1.2 | Inclusion criteria

(1) Patients in the literature were definitely diagnosed with CAD, regardless of race and nationality. (2) Noac and antiplatelet drugs were clearly used in the literature to treat patients with CAD. (3) The treatment plan of the experimental group contained noac drugs. (4) Both the experimental group and the control group contained antiplatelet drugs. 5. Follow up time ≥6 months. (6) According to the research data involved in the literature, the calculated outcome indicators are ≥5.

2.1.3 | Exclusion criteria

(1) Patients selected in the literature include non CAD patients; (2) CAD patients selected in the literature are complicated with diseases that seriously affect the prognosis outcome (such as congenital coagulation dysfunction, acute infection, primary renal dysfunction, etc.); (3) the research types are literature review, conference summary, retrospective, or cross-sectional research and meta-analysis research; and (4) the original data are lacking or incomplete

2.1.4 | Treatment scheme

The treatment group was given noac drugs (apixaban, rivaroxaban, edoxaban, dabigatran, and betalixaban) and antiplatelet drugs; the control group was only given antiplatelet drugs

2.1.5 | Outcome measures outcome after treatment

(1) major adverse cardiovascular events (MACE); (2) total mortality; (3) cardiovascular mortality; (4) incidence of myocardial infarction; (5) incidence of stroke; (6) incidence of major bleeding or minor bleeding. Grade according to thrombolysis in myocardial infarction (TIMI) (Sabatine and Braunwald 2021); (7) the incidence of fatal bleeding; and (8) incidence of intracranial hemorrhage.

2.1.6 | Literature retrieval strategy

The combination of subject words and free text words is mainly used to search PubMed, EMBASE The Cochrane Library (10th issue of 2020), web of science website and other databases, search for coronary artery disease, acute coronary syndrome, stable coronary artery disease, New oral anticoagulants, apixaban, betarexaban, edoxaban, rivaroxaban, dabigatran, and randomized controlled trials.

2.1.7 | Literature screening and data extraction

Two researchers independently search and screen the literature. If there is any difference, the third researcher shall arbitrate or the

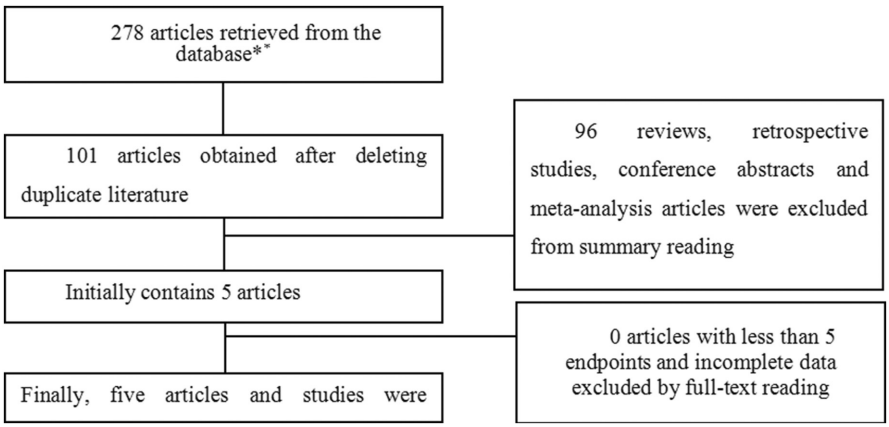

FIGURE 1 Document selection process. *Literature search results: PubMed (129), EMBASE (88), ScienceNet (56), Cochran Library (5), CNKI (0), and Wanfang Data (0)

research group shall jointly discuss to extract the information such as literature author, research type, publication time, grouping method, research object, sample number, use tools, intervention measures, outcome indicators, and so on.

2.1.8 | Literature quality evaluation adopts

Cochrane Collaboration bias risk evaluation 6.0 to evaluate the quality of literature methodology. The evaluation process is compared after being completed independently by two researchers. If there are differences, consensus conclusions are drawn after negotiation. The evaluation items include random sequence generation, selective report of results, blinding of research object/implementer, the integrity of result data, blinding of result evaluator, allocation concealment, and other sources of bias. The literature quality is divided into three grades, and the grading standard (Glass et al. 2017): the original research fully meets the above quality standards, which is class A. The original research part meets the above quality standards and is grade B. Highly biased and seriously divorced from the above criteria, it is grade C. This study is not included in Grade C literature.

2.1.9 | For statistical analysis

Revman 5.3 software (Review Manager Version 5.3) is used for literature summary and analysis; for secondary metadata, odds ratio (or) is used for analysis, and mean difference (MD) is used for continuous data as the effect size and the confidence interval of each result (confidence interval, CI) is 95%; I2 index is used to judge the heterogeneity and analyze the heterogeneity of effect values. The fixed effect model is used to analyze the low heterogeneity of $p > .10$ and $I2 < 50\%$, the random effect model is used to evaluate the source of heterogeneity for high heterogeneity of $p \leq .10$ and $I2 \geq 50\%$, and the fixed effect model is used to analyze after excluding the studies with obvious heterogeneity through analysis Each funnel was visually examined to assess small study effects and publication bias. Subgroup analysis is explored on MACE and bleeding outcomes in patients stratified by MI classification and percutaneous coronary intervention (PCI) treatment. Statistical significance level setting $\alpha = .05$.

3 | RESULTS

3.1 | Literature search results

A total of 101 kinds of literature were obtained through the preliminary examination, of which 96 citations were excluded after layer by layer screening, and finally included in 5 randomized controlled trials. The selection process of literature retrieval is shown in Figure 1.

3.2 | Basic characteristics of the included study

The five randomized controlled studies (Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018) included 43,650 patients with CAD, 25,020 in the treatment group (57.32%), and 18,630 in the control group (42.68%), of which the treatment group received noac drug rivaroxaban (2.5 mg/time, 2 times/day) and antiplatelet drugs, while the control group only received antiplatelet drugs. The basic characteristics are shown in Table 1. The type of disease and the number of myocardial infarctions (MI) and PCI-related subgroup populations are shown in Table 2.

3.3 | The five studies included

In publication bias have high evidence quality and low bias risk. The summary of bias risk is shown in Figure 2 and the bias risk diagram is shown in Figure 3. The funnel plot does not show asymmetry, indicating that there is no publication bias in the efficacy of the five randomized controlled trials, as shown in Figure 4.

3.4 | Summary and analysis results of literature

3.4.1 | Mace was reported

In 5 studies (Mega et al. 2009; Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018) included in 1

mace incidence. The results of heterogeneity analysis showed that the level of heterogeneity was high (p = .08, I2 = 52%). Further analysis by the random effect model showed that or = 0.84, 95% CI (0.75,0.95), p = .004; analysis results: the incidence of mace in CAD treated with noac combined with antiplatelet drugs was lower than that treated with antiplatelet drugs alone, and the difference was statistically significant (p < .05). In subgroup analysis, whether previous MI or not, NOAC reduced the incidence of MACE. Other results are less robust due to the small number of included studies (Figure 5).

3.4.2 | Total mortality

Five studies included (Mega et al. 2009; Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018) reported total mortality. The results of heterogeneity analysis showed that the level of heterogeneity was low (p = .16, I2 = 39%). Further analysis by the fixed effect model showed that or = 0.87, 95% CI (0.79,0.95), p = .003; analysis results: the total mortality of CAD treated with noac combined with antiplatelet drugs was lower than that treated with antiplatelet drugs alone, and the difference was statistically significant (p < .05).

3.4.3 | Cardiovascular mortality

Four studies included (Sabatine and Braunwald 2021; Glass et al. 2017; Mega et al. 2009; Mega et al. 2012) reported cardiovascular mortality. The results of heterogeneity analysis showed that the level of heterogeneity was low (p = .21, I2 = 34%). Further analysis by the fixed effect model showed that or = 0.86, 95% CI (0.78,0.96), p = .005; analysis results: the cardiovascular mortality of CAD treated with noac combined with antiplatelet drugs was lower than that treated with antiplatelet drugs alone, and the difference was statistically significant (p < .05).

3.4.4 | Incidence of myocardial

Infarction 5 included studies (Mega et al. 2009; Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018)

TABLE 1 Basic characteristics of the included study

Inclusion study	time	Number of cases (*n*)		Gender male/female (*n*)		Age (years)		Follow up time (months)	Outcome indicators
		Treatment group	control group	Treatment group	control group	Treatment group	Control group		
Mega[7]	2009	2331	1160	1810/521	885/275	57.2 ± 9.5	57.8 ± 9.6	6	ABDEFGH
Mega[8]	2012	10,350	5176	7718/2632	3882/1294	61.8 ± 9.2	61.5 ± 9.4	13	ABCDEFGH
Ohman[9]	2017	1519	1518	1134/385	1141/377	63(57–69)	62(57–69)	12	ABCDEFGH
Connolly[10]	2017	8313	8261	1736/6577	1646/6615	69(65–67)	69(65–67)	23	ABCDEFGH
Zannad[11]	2018	2507	2515	1956/551	1916/599	66.5 ± 10.1	66.3 ± 10.3	21	ABCDEG

Abbreviations: A, MACE; B, total mortality; C, cardiovascular mortality; D, incidence of myocardial infarction; E, incidence of stroke; F, the incidence of major or minor bleeding; G, the incidence of fatal bleeding; H, incidence of intracranial hemorrhage.

TABLE 2 Type of disease and number of MI and PCI-related subgroup populations in each included study

Study	time	Type of disease	Whether included AF patients	STEMI		NSTEMI		Unstable angina	
				treatment	control	treatment	control	treatment	control
Mega[7]	2009	Acute coronary syndrome	NA	1218	603	687	355	426	202
Mega[8]	2012	Acute coronary syndrome	NA	5185	2632	2656	1323	2509	1221
Ohman[9]	2017	ACute coronary syndrome	NA	743	741	611	612	165	165
Connolly[10]	2017	STable coronary artery disease	No	NA	NA	NA	NA	NA	NA
Zannad[11]	2018	Heart failure, Sinus rhythm, and Coronary disease	No	NA	NA	NA	NA	NA	NA

Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; NA, not available; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

reported the incidence of myocardial infarction. The results of heterogeneity analysis showed that the level of heterogeneity was low (p = .60, I2 = 0%). Further analysis by the fixed effect model showed that or = 0.85, 95% CI (0.77,0.95), p = .004; analysis results: the incidence of myocardial infarction in CAD treated with noac combined with antiplatelet drugs was lower than that treated with antiplatelet drugs alone, the difference was statistically significant ($p < .05$).

3.4.5 | Stroke incidence

Five studies included (Mega et al. 2009; Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018) reported stroke incidence. The results of heterogeneity analysis showed that the level of heterogeneity was high (p = .02, I2 = 66%). Further analysis by the random effect model showed that or = 0.71, 95% CI (0.50,1.03), p = .07; analysis results: there was no significant difference in the incidence of stroke between noac combined with antiplatelet drugs and antiplatelet drugs alone ($p > .05$).

3.4.6 | Incidence of major or minor bleeding

The incidence of major or minor bleeding was reported in 4 included studies [10–14]. The results of heterogeneity analysis showed that the level of heterogeneity was high (p = .01, I2 = 81%). Further analysis by the random effect model showed that or = 2.54, 95% CI (1.25,5.16), p = .01; analysis results: the incidence of major and minor bleeding in CAD treated with noac combined with antiplatelet drugs was higher than that treated with pure antiplatelet drugs, and the difference was statistically significant ($p < .05$). In subgroup analysis, for ST-segment elevation myocardial infarction (STEMI), unstable angina, and no previous MI population, NOAC increase the bleeding risk. However, due to the small number of included studies, results needed to be further confirmed (Figure 6).

3.4.7 | Incidence of fatal bleeding

Five studies included (Mega et al. 2009; Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018) reported the incidence of fatal bleeding. The results of heterogeneity analysis showed that the level of heterogeneity was low (p = .86, I2 = 0%). Further analysis by the fixed effect model showed that or = 1.30, 95% CI (0.81,2.08), p = .28; analysis results: there was no significant difference in the incidence of fatal bleeding between noac combined with antiplatelet drugs and antiplatelet drugs alone ($p > .05$).

3.4.8 | Incidence of intracranial hemorrhage

The incidence of intracranial hemorrhage was reported in 3 included studies (Mega et al. 2009; Mega et al. 2012; Ohman et al. 2017; Connolly et al. 2018; Zannad et al. 2018), The results of heterogeneity analysis showed that the level of heterogeneity was low (p = .15, I2 = 47%). Further analysis by the fixed effect model showed that or = 1.61, 95% CI (1.02,2.56), p = .06; analysis results: there was no significant difference in the incidence of intracranial hemorrhage between noac combined with antiplatelet drugs and antiplatelet drugs alone ($p > .05$).

4 | DISCUSSION

Antiplatelet drugs are commonly used in the clinical treatment of CAD. In 2016, the professional committee of cardiovascular and

PCI (for index event)		No PCI (for index event)		Previous MI		No previous MI		Previous PCI		No previous PCI	
treatment	control	treatment	control	treatment	control	treatment	control	treatment	control	treatment	control
1475	745	856	415	486	250	1845	910	NA	NA	NA	NA
6261	3126	4089	2050	2766	1415	7584	3761	NA	NA	NA	NA
1325	1320	194	198	314	345	1205	1173	286	315	1233	1203
4095	4971	3356	3342	5654	5721	2659	2540	NA	NA	NA	NA
NA	NA	NA	NA	1911	1892	596	623	NA	NA	NA	NA

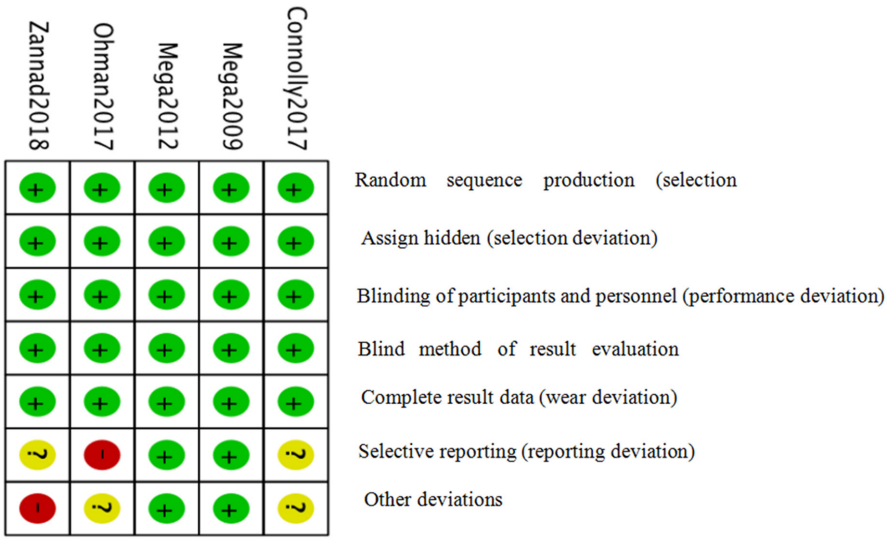

FIGURE 2 Summary of bias risk of 5 randomized controlled trials

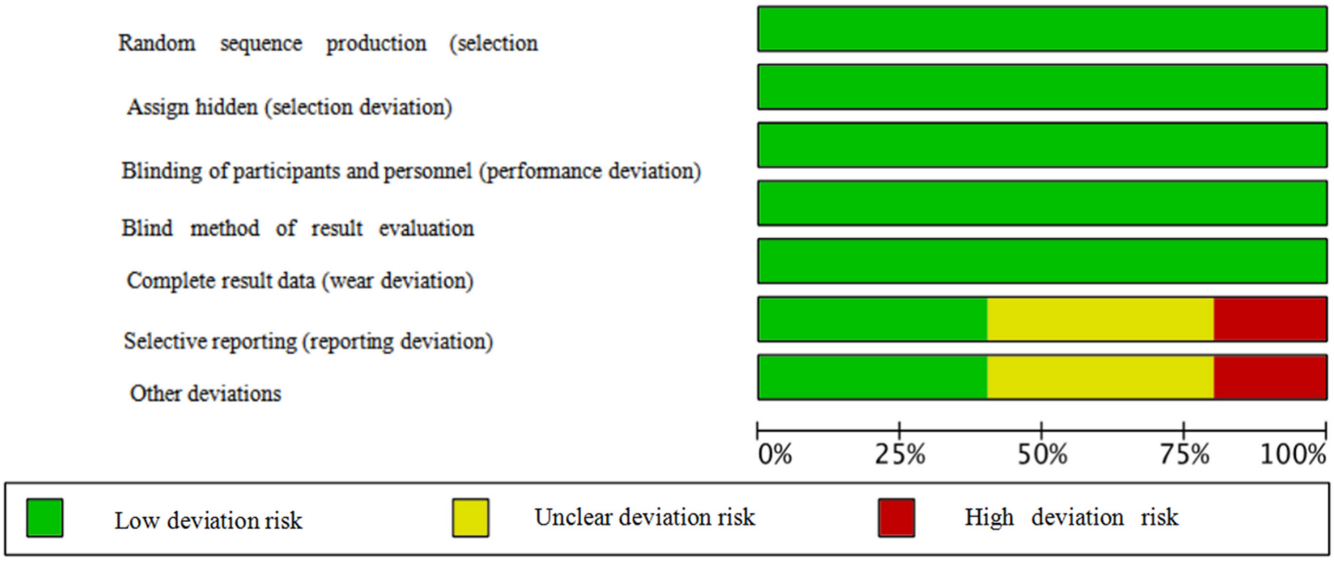

FIGURE 3 Deviation risk diagram of 5 randomized controlled trials

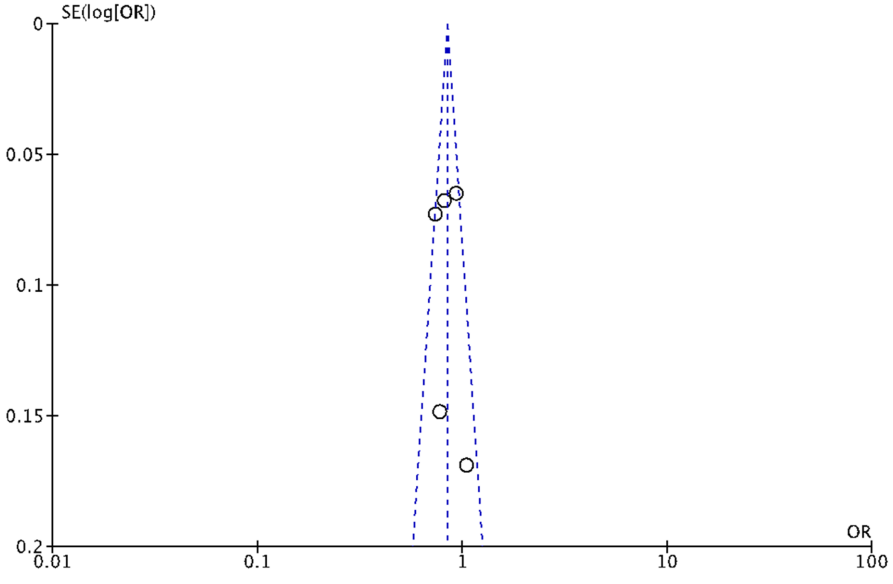

FIGURE 4 Efficacy funnel of 5 randomized controlled trials

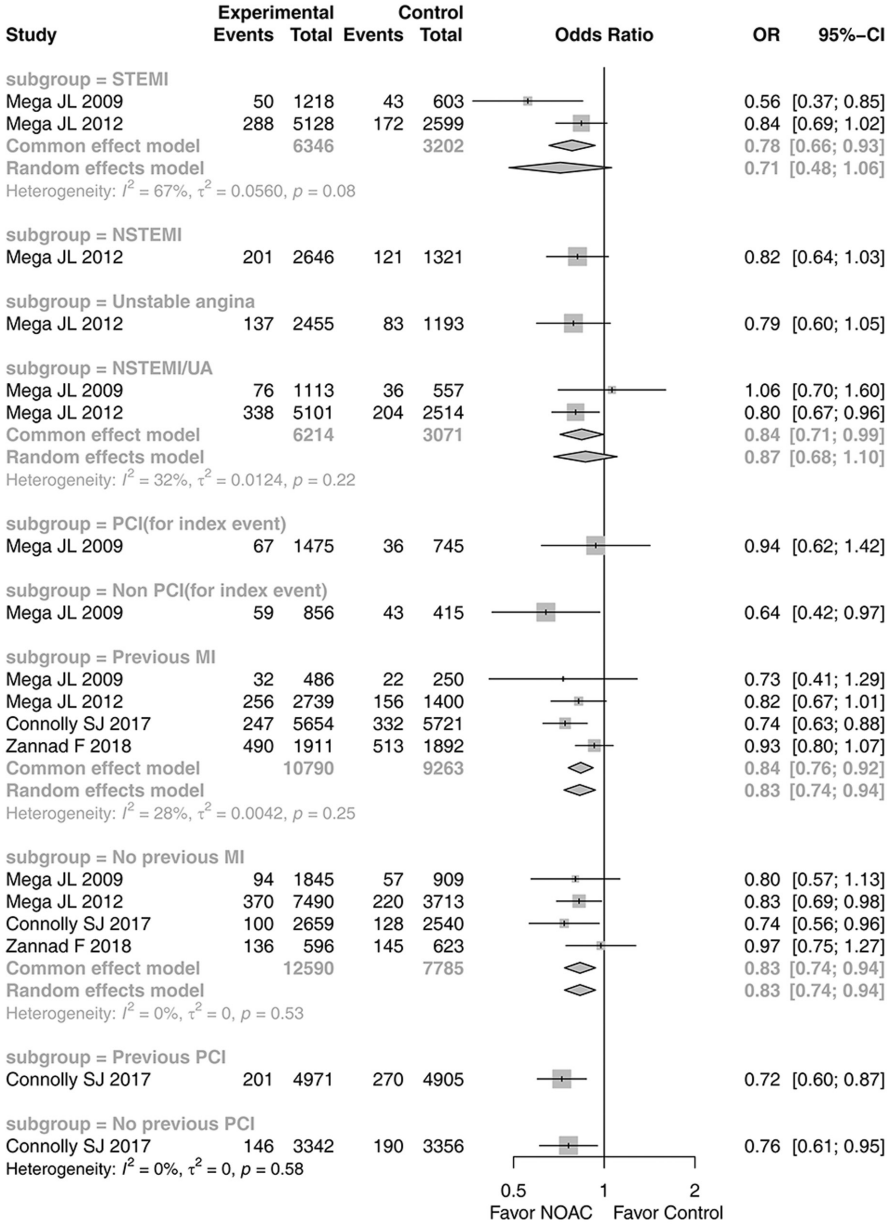

FIGURE 5 Forest plot of subgroup analysis of MACE stratified by MI classification and PCI treatment. MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

cerebrovascular diseases of the Chinese gerontology Society issued the Chinese expert consensus on oral antiplatelet drugs for stable coronary heart disease (Chinese Journal of cardiovascular disease 2016), which recommended that stable CAD patients with low thrombotic risk should adopt aspirin or clopidogrel for secondary prevention. Patients with high thrombotic risk were treated with aspirin combined with clopidogrel. At the same time, it was also pointed out that dual antiplatelet combined with noac may prolong the bleeding time. For example, Alexander et al. (2011) aimed to analyze the efficacy and safety of apixaban combined with standard antiplatelet therapy in patients with at least two ischemic events and recent ACS, but the study was finally terminated due to the increase of bleeding events in the 5 mg apixaban combined with an antiplatelet therapy group. Therefore, the effectiveness and safety of noac combined with antiplatelet therapy are still controversial. At this stage, a large number of clinical studies have discussed the clinical value of noac in the treatment of CAD (de Souza Lima Bitar et al. 2019). As another example, the remence phase II trial (Oldgren et al. 2011) evaluated the efficacy and safety of dabigatran combined with dual antiplatelet therapy for CAD. According to different doses of dabigatran and placebo groups, the patients were randomly divided into four experimental groups. After 6 months of follow-up, it was found that except for the reduction of D-dimer, dabigatran did not significantly reduce cardiovascular adverse events. Both major and minor bleeding events increased significantly, so the study was terminated before the phase III clinical trial. The purpose of this study was to evaluate the efficacy and safety of noac combined with antiplatelet drugs in the treatment of CAD.

In this study, the main noac used in the five randomized trials was rivaroxaban. Rivaroxaban is a direct factor Xa inhibitor. The recommended dose is 2.5 or 5 mg, twice a day. The five studies

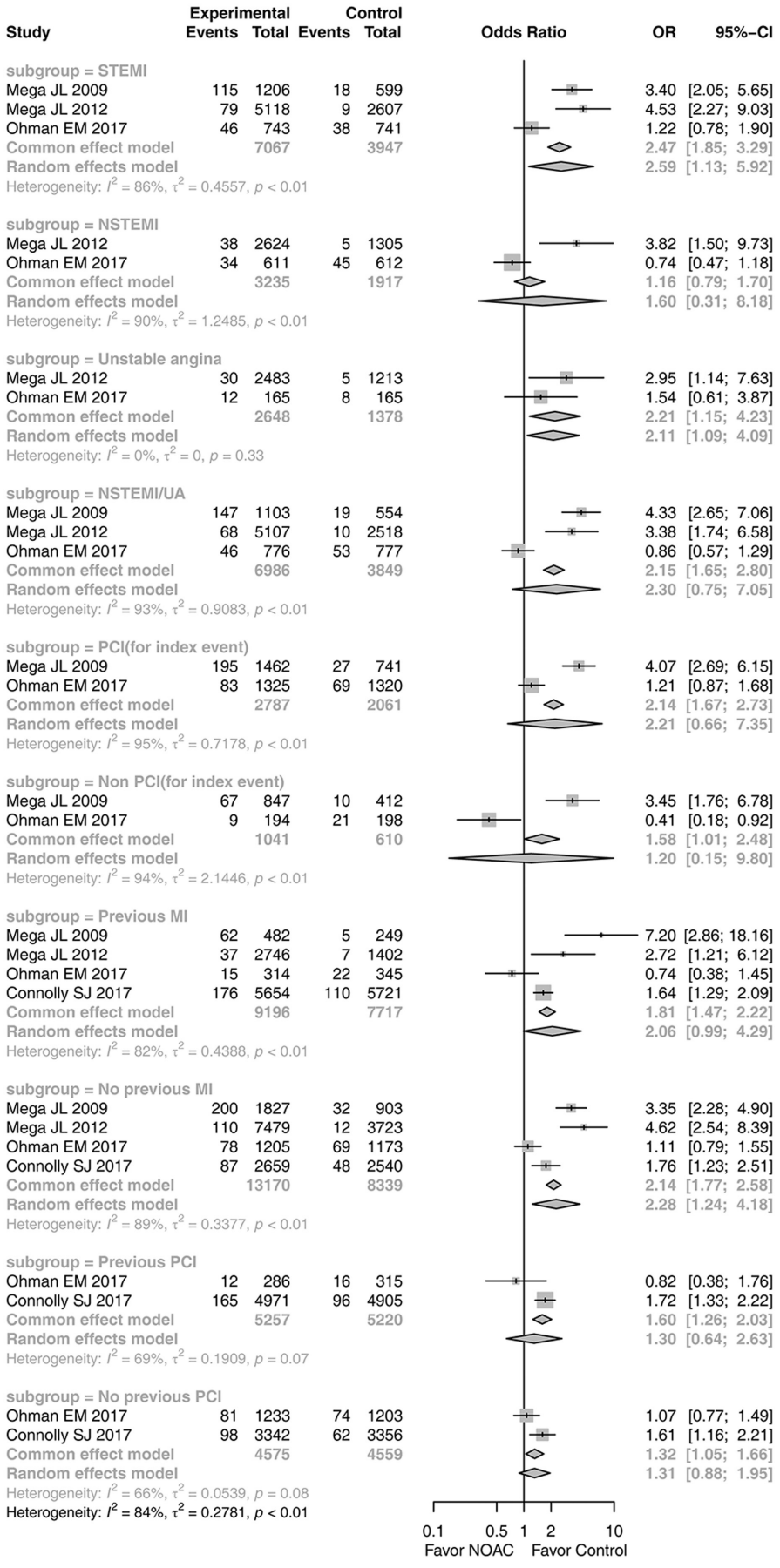

FIGURE 6 Forest plot of subgroup analysis of major/minor bleeding stratified by MI classification and PCI treatment. MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

included in rivaroxaban are within the recommended dose range. Its oral absorption bioavailability is about 80% of that of food, and its half-life is 6–9 h. It is mainly excreted through kidneys, feces, or bile. Its blood concentration is closely related to the change in prothrombin time (Liang et al. 2021; Bai et al. 2021; Eikelboom et al. 2019). This study conducted a meta-analysis of five randomized trials. The results showed that the mace, total mortality, incidence of myocardial infarction, and cardiovascular mortality of CAD patients treated with noac combined with antiplatelet drugs were lower than those treated with antiplatelet drugs alone. This result showed that noac combined with antiplatelet drugs could effectively reduce the risk of cardiovascular events and mortality of CAD patients. The clinical efficacy is better than that of antiplatelet drugs alone, which corresponds to previous clinical studies (Cen et al. 2020; Zhao et al. 2019). The results also showed that the incidence of major and minor bleeding in CAD treated with noac combined with antiplatelet drugs was higher than that treated with antiplatelet drugs alone, indicating that noac combined with antiplatelet drugs can increase the risk of bleeding in patients with CAD. It basically corresponds to the contents pointed out in the Chinese expert consensus on oral antiplatelet drug treatment (Ohman et al. 2017) issued by the professional committee of cardio-cerebrovascular diseases of Chinese gerontology society in 2016.

In conclusion, noac combined with antiplatelet drugs is effective and safe in the treatment of CAD. It can further reduce mace, total mortality, the incidence of myocardial infarction, and cardiovascular mortality in patients with CAD on the basis of antiplatelet drugs alone, but it may increase the risk of bleeding. It is necessary to choose an appropriate treatment scheme according to the actual situation of the patients.

AUTHOR CONTRIBUTIONS

Alimila·Saiyitijiang is responsible for the guarantor of integrity of the entire study, study concepts and design, definition of intellectual content, statistical analysis, and manuscript preparation and editing; Mayila·Aizezi is responsible for the study design, literature research, data analysis, and manuscript preparation; Ying Zhao is responsible for the literature research, experimental studies, and data acquisition; Ying Gao is responsible for the study concepts, clinical studies, and manuscript review. All authors read and approved the final manuscript.

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Not applicable.

CONFLICT OF INTEREST

There are no potential conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this. Further enquiries can be directed to the corresponding author.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

CONSENT FOR PUBLICATION

Not applicable.

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