A Meta-Analysis on the Efficacy and Safety of New Oral Anticoagulants (NOACs) in the Management of Acute Myocardial Infarction (AMI)

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Introduction. In order to cope with the limitations of warfarin, a variety of new oral anticoagulants (NOACs) are being developed and approved for clinical use. As the aging population increases and cardiovascular disease becomes younger, the use of NOACs as an alternative of traditional anticoagulant in patients with acute myocardial infarction (AMI) need to be discussed. A systematic review and meta-analysis of controlled trials and high-quality cohort studies were used to compare the efficacy and safety of new oral anticoagulants with warfarin and placebo trials in patients with AMI and related disease. Through a systematic search, 11 studies were included that compared the effectiveness of NOACs with warfarin by complete resolution of thrombus (OR, 1.58 95% CI 1.00, 2.50). In order to reflect the safety of NOACs, major bleeding (OR, 0.50 95% CI 0.16, 1.61) (OR, 3.20 95% CI 2.14, 4.81), stroke (OR, 0.77 95% CI 0.32, 1.90) (OR, 0.87 95% CI 0.63, 1.20), cardiovascular events (OR, 1.37 95% CI 0.73, 2.57) (OR, 0.94 95% CI 0.84, 1.07), and all-cause death (OR, 1.09 95% CI 0.42, 2.85) (OR, 0.90 95% CI 0.79, 1.02) are compared by subgroup analysis (NOACs VS. Warfarin / Placebo). The results showed that NOACs had a higher risk of bleeding compared with placebo. At the same time, no major statistical differences in efficacy and risk of negative outcomes were found when comparing with warfarin. In conclusion, new oral anticoagulants are more suitable than traditional oral anticoagulants for AMI patients which need to take long-term anticoagulant drugs because they do not require frequent blood monitoring. But at the same time, specific reversal agent for NOACs also need to be further discussed.

1. INTRODUCTION

In today 's society where aging and obese population continue to increase, the incidence of cardiovascular disease is also rising, and shows a trend of getting younger[1,2,3].Among different types of heart related problems, acute myocardial infarction (AMI) is currently the leading cause of heart-related morbidity and death worldwide[4] . Myocardial infarction (MI) is sometimes also called a heart attack[5] . Its common manifestation is myocardial ischemia,which leads to myocardial necrosis because the myocardium does not receive enough blood[5]. There are many reasons may cause MI, the most common of which is the occurrence of epicardial artery thrombosis, which blocks the blood vessel and reduces blood flow to the myocardium[5] . But it 's not just blood clots that can cause AMI[5]. There are many causes of myocardial ischemia. For example, some

coronary artery diseases can cause a large amount of atherosclerosis in the heart blood vessels, which can also cause the stenosis of the heart blood vessels and lead to insufficient blood supply to the heart muscles[6] . According to the actual situation of different patient, the current treatment methods for AMI mainly include percutaneous coronary intervention, thrombus removal, coronary stent surgery, and the use of thrombolytic drugs to dissolve thrombus[7] . Anticoagulation therapy is indispensable in the treatment of myocardial infarction[8]. Patients who have experienced myocardial ischemic events require anticoagulant drugs to reduce the recurrence of thrombosis[9] . Before the emergence of new non-vitamin K antagonist oral anticoagulants, the most commonly used oral anticoagulant was warfarin[8]. However, there are some disadvantages that come with the use of warfarin. For example, the use of warfarin is associated with a higher risk of bleeding, and the dosage varies widely among individuals[8,9,10] . Requires close monitoring by a medical provider, this may reduce patient medication compliance[11]. With the emergence and continued research of New Oral Anticoagulants (NOACs), New Oral Anticoagulants are gradually replacing the use of warfarin in many cases, thus serving as the main oral anticoagulant treatment after vascular disease[12]. The main new oral anticoagulants at this stage are: rivaroxaban, apixaban, edoxaban and dabigatran[12]. Among them, rivaroxaban, edoxaban and apixaban are factor Xa inhibitors, while dabigatran is a thrombin inhibitor[13,14,15]. Compared with warfarin, new oral anticoagulants do not require routine coagulation monitoring and are administered in fixed doses, which can increase patient compliance and reduce medication errors[12]. Many current studies have shown that compared with warfarin and placebo, new oral anticoagulants do not show significant differences in safety and effectiveness. In this study, we conducted a meta-analysis on the NACs use in MI-related patients, and discussed its effectiveness and safety.

2. METHODS

2.1. Data Sources and Search Strategy

In this meta-analysis study, a literature search was first conducted. elevant literature searches were conducted using PubMed, Embase and Web of Science[16,17,18] . Search keywords used include: “New Oral Anticoagulants” , “NOACs” , “Rivaroxaban” Dabigatran” , “Apixaban” , “Acute Myocardial Infarction” , “AMI” , “ MI” , “ Factor Xa Inhibitor” , “ Inferior Wall Myocardial Infarction” , “Anterior Wall Myocardial Infarction” , “ BAY 59-7939” , “ BIBR

1048" , "BMS 562247" . First, a PubMed search was conducted, and all entry terms related to the subject headings were identified and retrieved. The relevant specific search strategies are shown in section S1 of the Supplementary.

2.1. Selection Criteria

No language restriction was set when going to the initial search. At this stage, a preliminary review of titles and abstracts was conducted on these studies. Studies were excluded if (1) writing and data recording were in a language other than English. In order to better read and understand the content of the included studies, 6 non-English documents were excluded. (2) Documents in the form of letters, comments and replies. (3) Research on meta-analysis. (4) Literature analysis in the form of Review. (5) The content is irrelevant, such as research on the pharmacology of NOACs or the treatment of diseases unrelated to AMI. And (6) Excluded 87 studies with missing research data. After initially excluding 402 studies, the remaining studies were reviewed in full text. Studies without a control group or with a control group other than Placebo or warfarin were further excluded. Studies with incomplete data records and inconsistent experimental designs were also excluded. Studies were included if (1) the experimental design conformed to random control trials or cohort studies (because too few qualified RCT studies included high-quality cohort experiments). (2) The experimental group is NOACs, while the control group is warfarin or placebo (warfarin can help compare the effectiveness of NOACs compared with existing commonly used vitamin-K antagonists, and the placebo experiment can compare the safety of NOACs). (3) Patients included in the study were diagnosed with AMI-related diseases. Because acute coronary syndrome and AMI are often closely related, and it is also defined as a series of conditions from unstable angina (UA) to myocardial infarction (MI), and patients with acute myocardial infarction (AMI) often present with ST-segment elevation[19,20]. Therefore, this study also included studies related to acute coronary syndrome and patients with ST-segment elevation. (4) The research results include complete resolution of thrombus, major bleeding, stroke or embolism, cardiovascular event and all-cause mortality. Because in many cases of MI patients will develop thrombus[21]. So this primary outcome can help compare the effectiveness of NOACs versus warfarin as anticoagulant therapy. Patients were also tracked for major bleeding, stroke, and death as secondary safety outcomes[22,23]. After two rounds of screening, 11 studies were included.

2.3 Data Extraction

The authors of this article independently extracted data from 11 articles. When there are experimental groups with different NOAC dosages in the study, only one set of data is selected for analysis. To ensure the accuracy of data extraction, data were reviewed by a third party. The data extracted from the study include: the name of the first author, study period, study design, patient age, number of male participants, sample size of the

experimental group and control group, treatment, control, intervention and control group drug dosage, and follow-up time. At the same time, complete resolution of thrombus, major bleeding, stroke or embolism, cardiovascular event and all-cause mortality were extracted as effectiveness and safety outcomes.

2.4 Quality Assessment

Because the studies included included RCTs and cohort studies, Subgroup assessments were conducted during the quality evaluation[24]. RCT studies were assessed using the Cochrane risk of bias assessment[25]. The evaluation items included are: whether the randomization method of the RCT is correct, the allocation plan is correct, the blinding method, the completeness of the result data, whether there is selective reporting of research results, and whether there are other sources of bias[25,26]. And use Review manager as an statistic tool to make an RCT quality evaluation chart[27] . The Newcastle Ottawa Scale (NOS) was used to assess the included cohort studies. The evaluation criteria include: Selection, Comparability and Outcome, a total of nine items, so the total score is nine points[28,29].

2.5 Statistical Analysis

This study mainly used Stata 16.0 and RevMan 5.4 as biostatistical tools to conduct a meta- analysis[30,31] . Overall and subgroup analyzes were performed on the extracted data for each outcome. The extracted outcome data were analyzed using a fixed effects meta-analysis model using the Mantel-Haenszel method[32,33]. If the heterogeneity results (I^2) obtained are high (> 50%), Random effects Mantel-Haenszel can be used instead[34,35]. Because when I^2 is larger, it means that the results of the included studies are more heterogeneous[35]. The random effects model assumes that "different studies estimate different but related intervention effects " using the inverse variance method[34] . Therefore, when using the random effects model, the confidence interval will be wider than the fixed effects model, and the statistical significance requirements will be more conservative[34] . During the meta-analysis, the Odds Ratio (OR) of the experimental group and the control group data was calculated, as well as the corresponding 95% confidence interval (CI), statistic ($p < 0.05$ was considered significant), and a forest plot was drawn. Sensitivity analyzes were performed on

subgroups with higher heterogeneity (I^2) to examine possible sources of heterogeneity. Finally, publication bias analysis and testing were conducted using funnel plot and Egger and Begg tests[36,37]. When the P value of the Egger and Begg test result is less than 0.05, it indicates that the study has obvious publication bias[36,37]. If the results of Egger test and Begg test are different, the result of Egger test should take precedence[38].

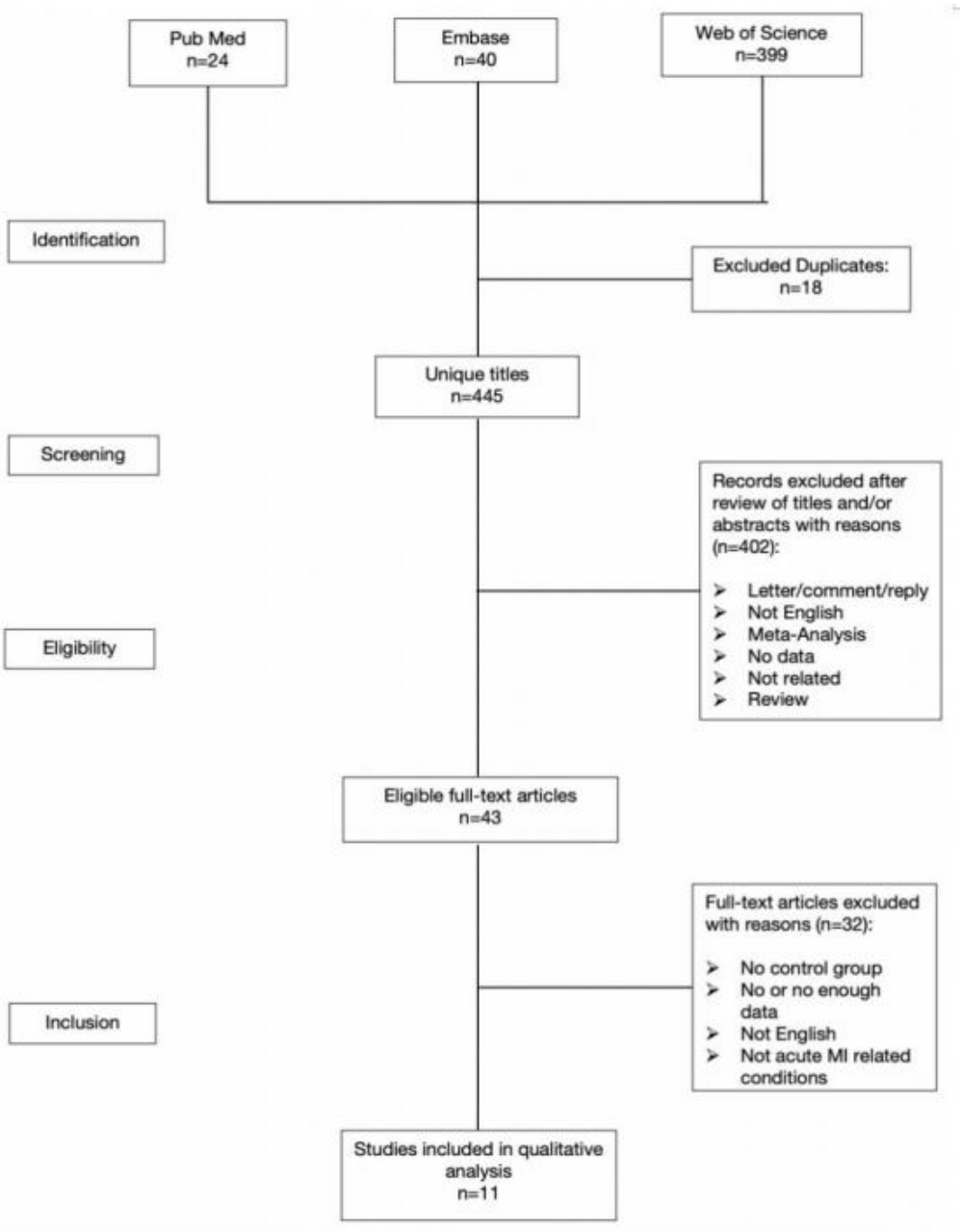


Figure 1. Flow chart describing systematic research search and study selection process.

Characteristic	Trial																					
	R. Alcalai et al.		J . H. Alexander et al.		J . H. Alexander et al.		J . Dahe et al.		H. Iqbal et al.		D. A. Jones, et al.		J . Liang, et al.		J . L. Mega, et al.		J . Oldgren, et al.		T. Seiler, et al.		A. A. Youssef, et al.	
	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs	Control	NOACs
study period	2018-2020		2006-2008		2010-2011		2010-2019		2012-2018		2015-2018		015-2019		2008-2011		2008-2009		2015-2021		2018	
study design	RCT		RCT		RCT		retrospective cohort		retrospective cohort		retrospective cohort		retrospective cohort		RCT		RCT		retrospective cohort		RCT	
Medication	Warfarin	Apixaban	Placebo	Apixaban	Placebo	Apixaban	Warfarin	Rivaroxaban, Apixaban, Dabigatran	Warfarin	Rivaroxaban, Apixaban, Dabigatran	Warfarin	apixaban, edoxaban, rivaroxaban	Warfarin	rivaroxab, dabigatran, ticagrelor	Placebo	Rivaroxaban	Placebo	Dabigatran	Warfarin	rivaroxaban, apixaban	Warfarin	Apixaban
No. of participants	15	17	599	315	3687	3705	42	17	62	22	60	41	72	56	5176	5174	371	369	53	48	25	25
Median length of follow-up	89 days		26 weeks		15 month		3 month		3.0 years		2.2 years		12 month		13 month		28 weeks		839 days		6 month	
Age (years), mean SD or median (IQR)	58.8 ± 10.2	55.5 ± 12.9	60 (52, 69)	62 (53, 69)	67 (58–74)	67 (59–73)	61±13	57±14	62 ± 14	62 ± 13	60.81 ± 14.3	58.73 ± 14.2	55.1±11.2	55.0±11.6	61.5±9.4	61.8±9.2	61.5 ±11.3	61.9±12.3	62.2±14.2	64.3±12.1	53 ± 7.9	52 ±8.2
Male	15	13	74.30%	76.30%	2518 (68.3%)	2496 (67.4%)	35 (83.3%)	14 (82.4%)	55 (89%)	20 (91%)	51 (85%)	33 (80.4%)	62 (86.1%)	51 (91.1%)	3882 (75.0%)	3875 (74.9%)	291(78.45%)	285 (77.2%)	41 (77.4%)	42 (87.5%)	/	/
Dose (mg)	target international normalized ratio (INR) of 2.0–3.0	5 mg twice a day	same amount placebo	2.5 mg twice daily	same amount placebo	5 mg twice daily	target international normalized ratio (INR) of 2.0–3.0	Apixaban was prescribed at doses of 2.5/5 mg twice a day, dabigatran at 110/150 mg twice a day, and rivaroxaban at 15–20 mg	target international normalized ratio (INR) of 2.0–3.0	13 were prescribed rivaroxaban (20 mg once daily), eight prescribed apixaban (5 mg twice daily), and one dabigatran (150 mg twice daily).	target international normalized ratio (INR) of 2.0–3.0	Rivaroxaban (46.2% at 15 mg, 12.3% at 20 mg), apixaban (17% at 2.5 mg daily), edoxaban (2.5% at 30 mg daily, 2.5% at 60 mg daily)	target international normalized ratio (INR) of 2.0–3.0	rivaroxaban (26 on 20 mg and 22 on 15 mg once daily), dabigatran (6 on 150 mg and 2 on 110 mg twice daily), ticagrelor (3 on 90 mg twice daily).	same amount placebo	2.5 mg twice dailyof rivaroxaban	same amount placebo	50 mg b.d.	target international normalized ratio (INR) of 2.0–3.0	/	target international normalized ratio (INR) of 2.0–3.0	apixaban 5 mg twice daily
Complete resolution of thrombus	14 (93.3%)	16 (94.1%)	/	/	/	/	71.4% (30/42)	70.6% (12/17)	42 (76%)	13 (65%)	29 (48.3%)	29 (70.1%)	69(95.8 %)	55(98.2%)	/	/	/	/	36 (75.5%)	41 (76.7%)	24 (96%)	23 (92%)
major bleeding (TIMI or ISTH)	2	0	0.80%	5.70%	40 (1.1%)	98 (2.7%)	/	/	3 (5%)	0	4 (6.7%)	0	2(2.8%)	0	19 (0.6%)	65 (1.8%)	1 (0.3%)	2 (0.5%)	2 (4.3%)	3 (5.9%)	0	0
stroke / embolism	1	0	0.30%	0	34 (0.9%)	23 (0.6%)	4 (9.5%)	2 (11.8%)	1 (2%)	0	3 (5%)	1 (2.4%)	2(2.8%)	1(1.8%)	41 (1.2%)	46 (1.4%)	3 (0.8%)	0	4 (8.7%)	4 (7.8%)	0	0
Cardiovascular event	2	3	8.70%	7.60%	299 (8.1%)	295 (8.0%)	/	/	9 (15%)	7 (32%)	/	/	1(1.4%)	0	229 (6.6%)	205 (6.1%)	4 (1.1%)	9 (2.4%)	16 (34.8%)	15 (29.4%)	0	0
all-cause mortality	0	1	2.00%	3.50%	143 (3.9%)	155 (4.2%)	/	/	6 (10%)	3 (14%)	/	/	0	0	376 (10.7%)	313 (9.1%)	14 (3.8%)	8 (2.2%)	6 (13%)	4 (7.8%)	0	0

Table 1. Patient- and study-level characteristics of RCT and cohort comparing new oral anticoagulants to warfarin/placebo in patients with AMI related disease

3. RESULTS

After the first round of searching, we found a total of 463 related studies. Among them, 24 articles are from PubMed, 40 articles are from Embase, and 399 articles are from Web of Science. First, 18 duplicate studies were excluded. Those information are illustrated in Figure 1. After screening the article titles and abstracts, 402 studies were excluded based on the exclusion criteria. The remaining 43 studies were further went through the full-text screening. Finally, 11 studies were included in this meta-analysis. Six of the articles were randomized controlled trials related to AMI and NOACs, and five of the articles were related retrospective cohort studies (Table 1).

Different NOACs were used as experimental groups in the 11 included studies, 7 studies used warfarin as the control group, and 4 RCT studies used the same dose of placebo as the control group[41-49] . The basic information of the included studies, the included indicators and essential baseline characteristics are shown in Table 1. Studies with placebo as the control group mainly evaluate the safety of NOACs and whether there are significant differences in negative outcomes such as major bleeding, stroke, and cardiovascular events compared with placebo[40,41,46,47]. Studies compared with warfarin show the safety and effectiveness of newer non-vitamin K antagonist oral anticoagulants compared with commonly used oral anticoagulants[39,42,43,44,45,48,49]. The effectiveness of the drug is mainly compared by the number of Complete resolution of thrombus. At the same time, drug safety was compared by the negative results mentioned above.

Because the studies included in this article include both RCTs and cohort studies, suitable quality assessment tools are used for different study types when conducting quality analysis. The Cochrane risk of bias assessment tools was used for RCT studies, and the Newcastle– Ottawa Scale (NOS) was used to assess the quality of included cohort studies. For the six included RCT studies, Youssef, et al. (2023) showed that correct and clear blinding methods were not clearly indicated[49] . Patients were not blinded to the medication they were taking. Therefore, there may be have risk of bias. The other five studies did not show a high risk of bias. However, the blinding of the study results assessment was not clear, which may lead to unclear risk of bias. The detailed RCT quality assessment table and diagram are shown in Supplementary S2A . Five cohort studies were evaluated for quality using the NOS tool. Their average score is 7.6 out of 9 (Table 2). This shows that the five included cohort studies have relatively high quality. Through quality assessment, it was found that the main disadvantage of the included studies was that they did not include comparability on other risk factors (Supplementary S2B).

Authors	Study period	Country	Study design	Patients (n) off-control/NOAcs	Median follow-up (months)	Level of evidence	Quality score (NOS)
Daher et al.(2020)	2010-2019	France	retrospective	42/17	3		7
Iqbal et al.2020()	2012-2018	UK	retrospective	62/22	36		8
Jones, et al.(2021)	2015-2018	UK	retrospective	60/41	26.4		8
Liang, et al.(2022)	2015-2019	China	retrospective	72/56	12		7
Seiler, et al.(2023)	2015-2021	Switzerland	retrospective	53/48	28		8

Table 2 Quality assessment by Newcastle–Ottawa Scale (NOS) for cohort studies

In order to study the effectiveness and safety of NOACs, subgroup analyzes were conducted on each of the five outcomes included in this analysis, which including complete resolution of thrombus, major bleeding, stroke/embolism, cardiovascular event and all-cause mortality. The 11 studies were distinguished according to different control groups. The data of the warfarin group and the placebo group were compared and analyzed separately by subgroups. Efficacy is assessed by the outcome complete resolution of thrombus. In studies comparing NOACs with warfarin, found that NOACs were superior to warfarin in the complete resolution of thrombus (OR, 1.58 95% CI 1.00, 2.50) (Figure 2). However, this result was not statistically significant based on the 95% CI. At the same time (I2 = 12.8%, p = 0.332) showed no major heterogeneity between studies. In addition to analyzes of drug effectiveness, safety outcome analyzes were conducted using major bleeding, stroke, cardiac events, and all-cause death. NOACs were associated with a lower risk of major bleeding outcomes compared with warfarin (OR, 0.50 95% CI 0.16, 1.61) (Figure 3). NOACs were also associated with a higher risk of major bleeding outcomes compared with placebo (OR, 3.20 95 % CI 2.14, 4.81) (Figure 3). The 95% CI including 1 indicates that this result are statistically significant. The results of major bleeding was significantly different between the placebo subgroup and the warfarin subgroup, so overall it showed relatively large heterogeneity (I2= 49.9%, p = 0.043). A sensitivity analysis was performed on this result.

Which show that Alexander et al. (2011) and Mega, et al. (2012) may be the main sources of heterogeneity (Supplementary S3A). NOACs were inferior to warfarin and placebo in the incidence of stroke and embolism after taking the treatment (OR, 0.77 95% CI 0.32, 1.90) (OR, 0.87 95% CI 0.63, 1.20) (Figure 4). But these results are also not statistically significant. There was no statistically significant difference in the incidence of cardiovascular events between the NOACs and warfarin or placebo (OR, 1.37 95% CI 0.73, 2.57) (OR, 0.94 95% CI 0.84, 1.07) (Figure 5). Both results of cardiovascular events and stroke are not shown large heterogeneity. The analysis of the data on all-cause mortality also showed no significant statistical difference (OR, 1.09 95% CI 0.42, 2.85) (OR, 0.90 95% CI 0.79, 1.02) (Figure 6). However, in the placebo subgroup found high heterogeneity (I2= 59.2%, p = 0.061). A sensitivity analysis was performed on this subgroup showing that Alexander et al.(2011) are possible sources of heterogeneity (Supplementary S3B). In order to better understand the source of heterogeneity, besides sensitivity test a meta- regression analysis was performed on data with high heterogeneity. The analysis showed that different experimental designs and control

groups were not the source of heterogeneity (Supplementary S4A&B). To test whether the eleven included studies have major publication bias, Egger 's test (Supplementary S5A) and Begg 's test (Supplementary S5B) were performed on all data in this study and a funnel plot (Supplementary S5C) was drawn. The P value of each result through Egger 's test and Begg 's test are greater than 0.05 showed that there was no obvious publication bias (Supplementary S5).

4. DISCUSSION

This meta-analysis study aimed to compare the efficacy and safety of new oral anticoagulants in patients with acute myocardial infarction-related diseases. In this study, in order to better understand the efficacy and safety of NOACs, comparison and subgroup analysis were conducted with placebo and warfarin. In this meta-analysis, three databases were systematically searched and a total of 11 studies were included[39-49]. The results of this meta-analysis found that overall there was no significant difference in efficacy between warfarin and new non-vitamin K oral anticoagulants. Therefore, from this set of data analysis we can assume that warfarin can be replaced by other new oral anticoagulants in terms of drug efficacy. New oral anticoagulants were also found to be associated with lower risks of key secondary outcomes, including major bleeding and stroke, when compared with warfarin. However, these advantages are not statistically significant, so overall through this meta- analysis, NOACs have no significant differences in efficacy and safety compared with warfarin[39,42,43,44,45,48,49] . However, during subgroup analysis, it was found that NOACs had a relatively high risk of bleeding in the safety RCT study comparing new oral anticoagulants with placebo[40,41,46,47]. However, there were no significant differences from the placebo group for other secondary negative outcomes[40,41,46,47]. Overall, the results of this meta-analysis did not find that new oral anticoagulants have higher negative risks than warfarin, including major bleeding, stroke, cardiac events, and all-cause mortality[39,42,43,44,45,48,49] . And in the context of thrombus resolution, no significant statistical difference in effectiveness was found between warfarin and NOACs. Although an increased risk of bleeding was found when compared with placebo, in general new oral anticoagulants commonly used on the market can still be used as alternative treatments to warfarin for long-term anticoagulation therapy after primary or surgical treatment of AMI patients. Patients with AMI require anticoagulation therapy during medical treatment and after some procedures, such as percutaneous intervention (PCI) or occasionally coronary artery bypass graft surgery[50]. Warfarin is a commonly used oral drug for anticoagulant treatment[51]. However, warfarin requires frequent monitoring because of different reactions due to drug- drug, drug-food interactions, and genetic polymorphisms[51]. At the same time, because patients may require long-term anticoagulant oral medication, these limitations of warfarin may lead to complex patient management and reduced medication compliance[51]. Data indicate that approximately 6%-8% of patients undergoing percutaneous intervention for acute myocardial infarction require oral anticoagulant therapy[52] . And related atrial fibrillation (AF) and acute coronary syndrome (ACS) are likely to occur in patients with AMI[52]. To reduce the occurrence of these events, the use of anticoagulant therapy is necessary[52]. Besides, AMI patients not only need anticoagulant drugs for some thrombolytic treatment[53]. Studies have

shown that thrombin may elevate after patients experience an acute cardiac event, and thrombin may continue to contribute to adverse cardiac events in a period of time[53]. Therefore, patients may need long-term use of oral anticoagulants to prevent cardiac ischemic events[53]. So given the shortcomings of warfarin, we need to provide evidence comparing warfarin with novel treatment alternatives to find suitable alternatives and to provide evidence-based information to clinical decision-makers.

Compared with warfarin, NOACs are more convenient[54]. NOACs can be safely taken in fixed doses and do not require frequent blood monitoring[54] . But while finding better alternatives to warfarin is now a research priority, widespread use of non-vitamin K-antagonist oral anticoagulants (NOACs) has been slow[54] . This may be because research on reversal drugs for NOACs still requires further research and development[54] . Unlike warfarin, which can be easily reversed by vitamin K and other drugs called clotting factors, NOACs require specific reversal agents to reverse the drug 's effects[55,56]. This can be very fatal if the patient have bleeding after the medication use[56] . NOACs were also found to have a risk of major bleeding in the placebo RCT studies of this meta-analysis. And statistics show that about 30% to 50% of bleeding events occur in the gastrointestinal tract[57]. A study of annual standardized risk rates of major bleeding in the United Kingdom found 21. 8 cases per 1, 000 people for dabigatran, 15.4 for apixaban, and 26.5 for rivaroxaban[58] . These bleeding events require the use of reversal agents but currently only two NOACs have approved reversal agents[57] . One is that dabigatran has a reversal agent called idarucizumab[57]. And the FXa inhibitors apixaban and rivaroxaban can be reversed by andexanet alfa[57] . Other NOACs such as edoxaban currently do not have approved reversal agents[54] . This may be the main reason for the slow progress in the promotion of clinical application of NOACs.

Idalizumab is a kind of humanized monoclonal antigen-binding fragment (Fab) antibody and has been approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) as an antidote for dabigatran[57] . Reversal medications to control bleeding[57] . It binds to dabigatran and rapidly reverses the anticoagulant effects of dabigatran[57]. Can immediately, completely and sustainably reverses the effects of dabigatran without causing intrinsic activity in the coagulation system[57] . The specific reversal agent for the FXa inhibitors apixaban and rivaroxaban is Andexanet alfa, a recombinant protein lacking a membrane-bound gamma-carboxyglutamic acid (GLA) domain[57] . Andexanet alfa can act as a decoy to neutralize the anticoagulant effects of FXa inhibitors so is able to preventing the inhibitor from binding to endogenous FXa[57] .

Combined with the research results of this meta-analysis, to a certain extent, NOACs are supported as a replacement drug for warfarin. Given the development and approval of specific reversal antidotes, dabigatran, apixaban and rivaroxaban have a better safety profile than other NOACs in resolving bleeding problems[57] . Therefore, dabigatran, apixaban and rivaroxaban may be widely used in clinical practice as the main replacement drugs for warfarin in the future for anticoagulant treatment of AMI patients.

There may be some limitations in this meta-analytic study. First, there were relatively few RCT trials comparing warfarin included in this study. In order to make the results more accurate, some high-quality cohort studies were added during the inclusion process. In subsequent studies, further systematic investigation and search need to be

conducted, and more relevant RCT trials can be included for data analysis. Second, high heterogeneity was found in the data analysis for the major bleeding and all-cause mortality groups. This may be due to differences in physical conditions and region among the people participating in the study. Therefore, a random effects model was used for analysis of groups with high heterogeneity. And sensitivity analysis and meta-regression were used to analyze possible sources of heterogeneity. Moreover, the results of egger test and Begg test showed no obvious publication bias, so the analysis results are still relatively reliable. Third, there were not enough studies included in this study to support subgroup analysis of different NOACs, so it was difficult to compare the effectiveness and safety of different NOACs types. More relevant studies will be included in future studies to help compare the safety and effectiveness of different types of NOACs. This can help medical decision-makers decide on specific drug use options.

5. CONCLUSION

This meta-analysis found that although NOACs have a certain risk of bleeding, compared with warfarin, no higher risk of secondary negative outcomes was found. And there was no significant difference in drug efficacy. Three NOAC drugs with approved reversal agents, dabigatran, apixaban and rivaroxaban, can be widely used as replacement drugs for warfarin in the anticoagulation treatment of AMI patients.

Acknowledgement:
This work was sponsored in part by National Natural Science Foundation of China (2345678)

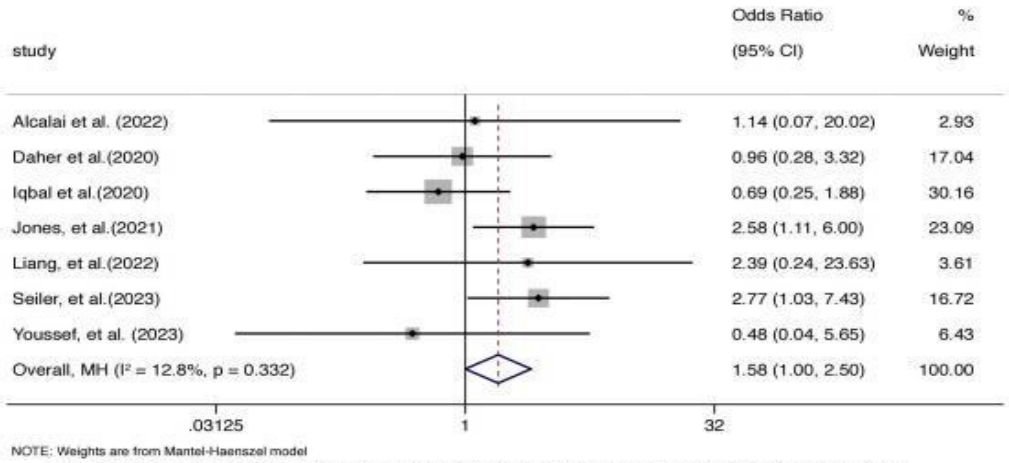


Figure 2. Forest plot for complete resolution of thrombus, new oral anticoagulants (NOA) versus warfarin in patients with AMI relative diseases.

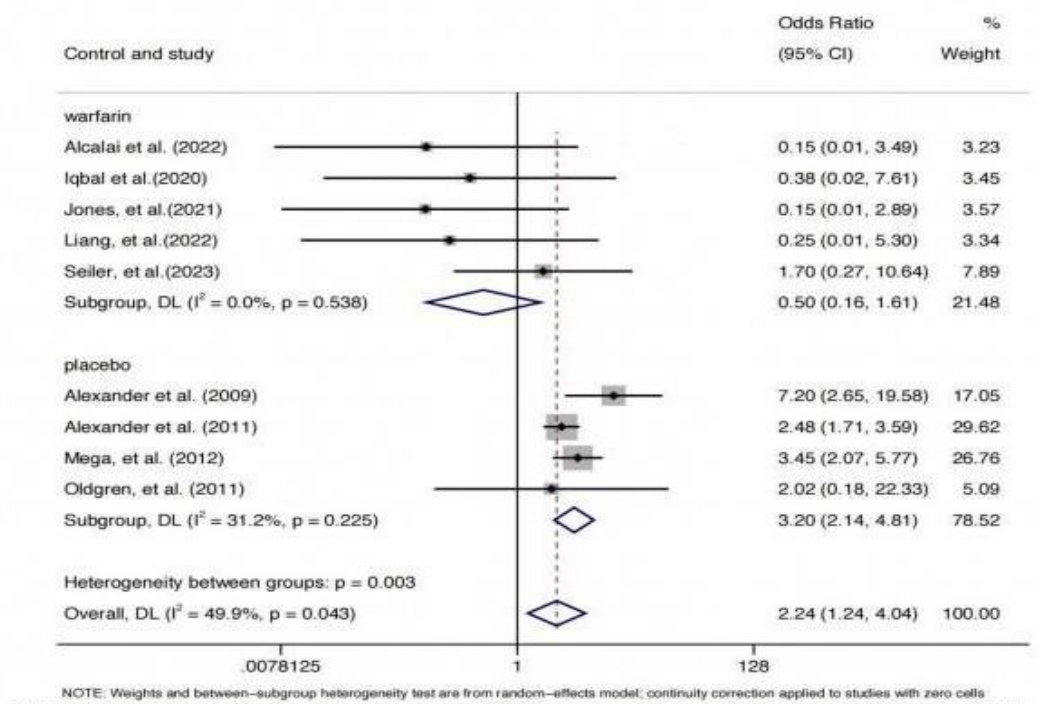
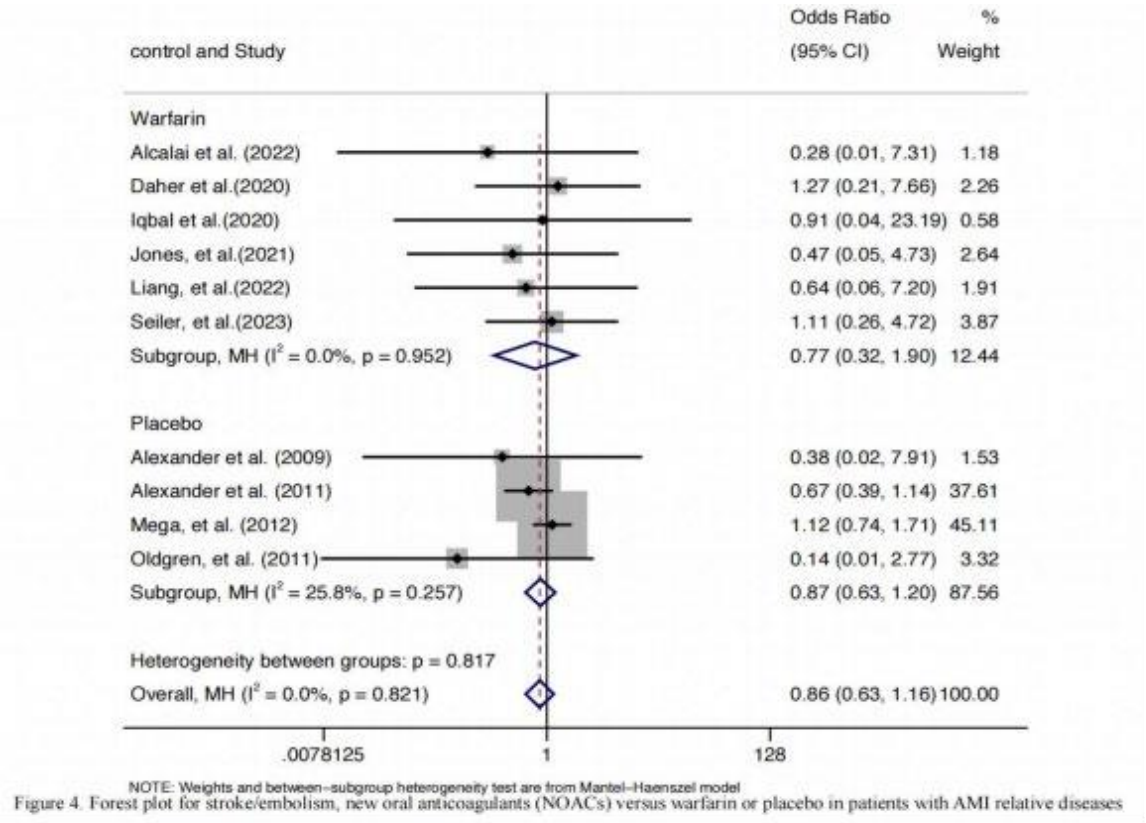
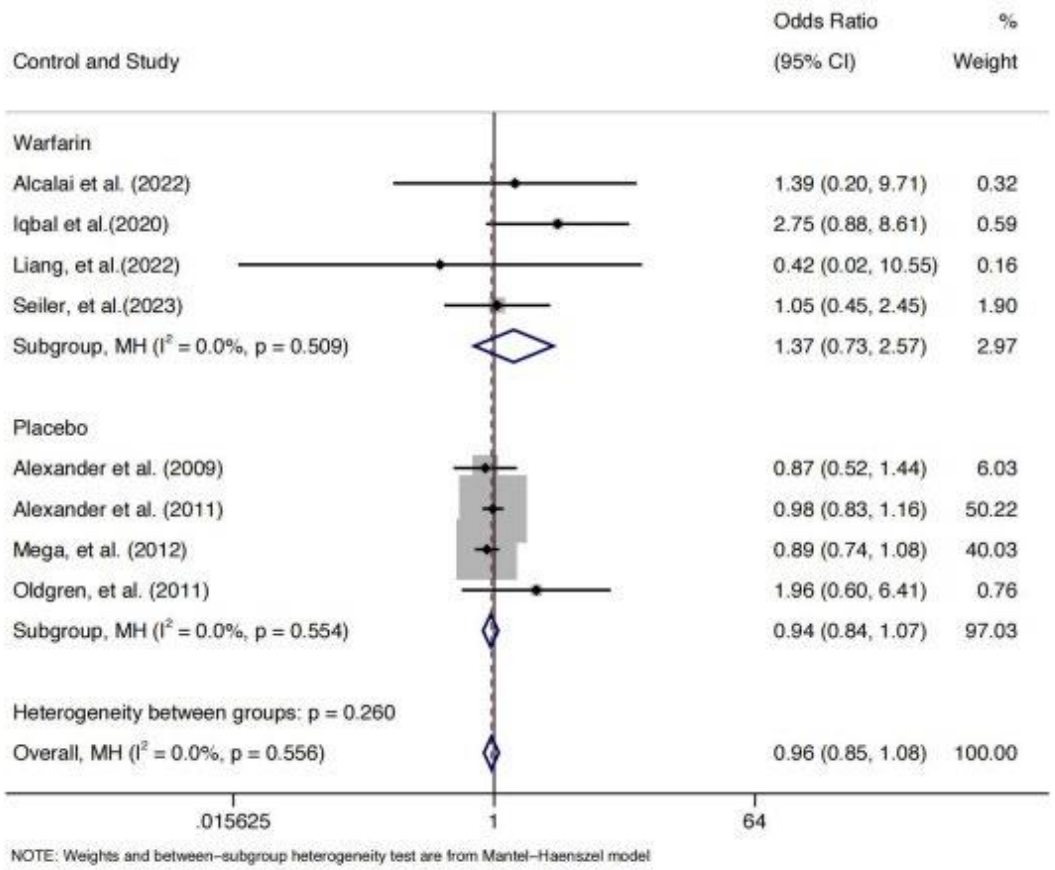


Figure 3. Forest plot for major bleeding, new oral anticoagulants (NOACs) versus warfarin or placebo in patients with AMI relative diseases



NOTE: Weights and between-subgroup heterogeneity test are from Mantel-Haenszel model

Figure 4. Forest plot for stroke/embolism, new oral anticoagulants (NOACs) versus warfarin or placebo in patients with AMI relative diseases



NOTE: Weights and between-subgroup heterogeneity test are from Mantel-Haenszel model

Figure 5. Forest plot for cardiovascular events, new oral anticoagulants (NOACs) versus warfarin or placebo in patients with AMI relative diseases

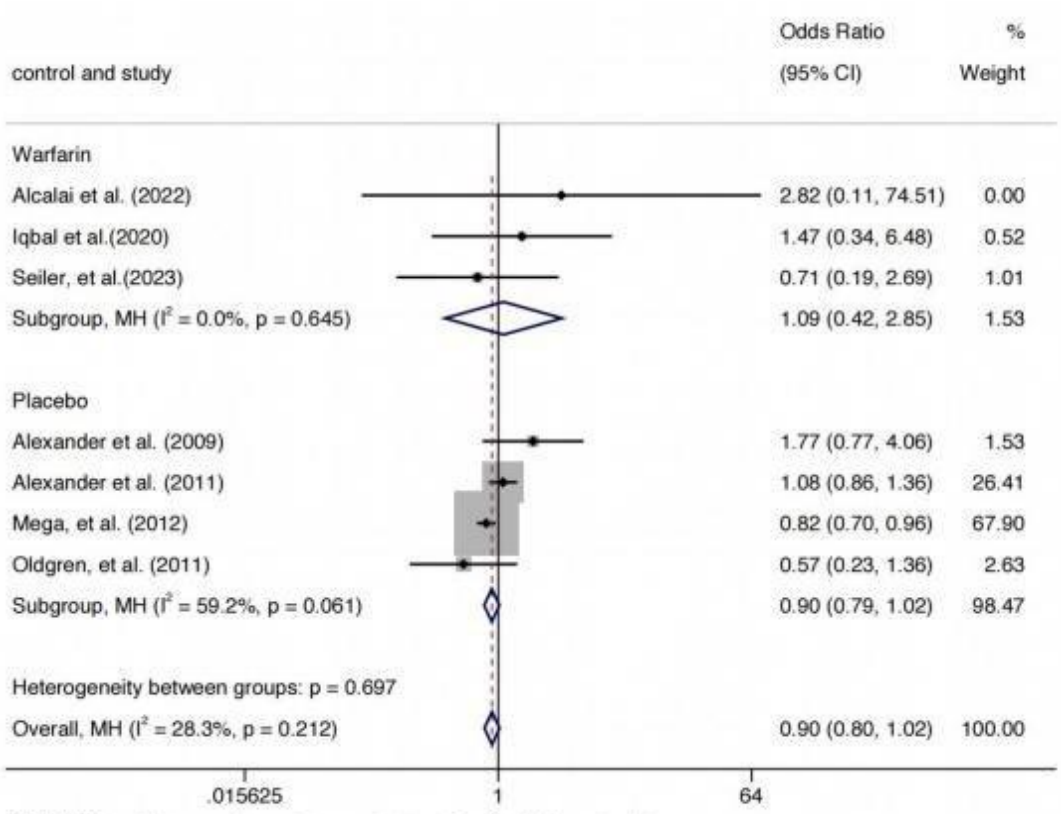


Figure 6. Forest plot for all-cause mortality, new oral anticoagulants (NOACs) versus warfarin or placebo in patients with AMI relative diseases

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