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META-ANALYSIS

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Efficacy and Safety of Antiplatelet Therapy Plus Xa Factor Inhibitors in Patients with Coronary Heart Disease: A Meta-Analysis

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Background: The aim of this study was to systematically evaluate the effect of oral Xa inhibitors plus antiplatelet therapy in the treatment of coronary artery disease.

Material/Methods: All randomized controlled trials (RCTs) about antiplatelet therapy plus Xa factor inhibitors for coronary artery disease from database inception to January 2019 were searched for and collected from PubMed, Embase, and the Cochrane Library. Two reviewers extracted and analyzed the data independently. Additionally, RevMan 5.0 software was applied for meta-analysis.

Results: Seven RCTs with 50 044 patients were included. The meta-analysis results showed that treatment with antiplatelet therapy plus Xa factor inhibitors in patients with coronary artery disease could significantly reduce the risk of ischemic events ($P<0.00001$). Besides, risk of all-cause mortality ($P=0.003$), myocardial infarction ($P=0.02$) and ischemic stroke ($P<0.0001$) were also significantly reduced. However, risk of massive hemorrhage after TIMI ($P<0.00001$), minor hemorrhage after TIMI ($P<0.00001$), and intracranial hemorrhage ($P=0.006$) were significantly increased, respectively. Xa inhibition drugs also intended to increase risk of fatal bleeding, but there was no significant difference ($P=0.08$).

Conclusions: Antiplatelet therapy plus Xa factor inhibitors in patients with coronary artery disease was effective, which could reduce the risk of ischemic composite endpoints, all-cause mortality, myocardial infarction, and ischemic stroke. However, it could significantly increase risk of bleeding in terms of safety.

MeSH Keywords: Coronary Disease • Meta-Analysis • Platelet Aggregation Inhibitors

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Background

Coronary heart disease (CHD) is mainly caused by the formation of atherosclerotic plaques, which narrow the lumen and reduce the blood and oxygen supplied to the myocardium. Unstable plaques are prone to rupture, causing platelet aggregation, the activation of clotting pathway and thrombosis. Acute thrombosis blocks the coronary lumen, leading to myocardial cell ischemia and necrosis [1]. Current guidelines recommend antiplatelet therapy to patients with coronary heart disease, especially patients with acute coronary syndrome (ACS) or after percutaneous coronary intervention (PCI) who may even need dual antiplatelet therapy (DAPT) [2]. Nevertheless, about 10% of CHD patients have major adverse cardiovascular events (MACE) [3]. Therefore, whether to add anticoagulant therapy on the basis of antiplatelet therapy is controversial. Heparin and warfarin are currently the main anticoagulants, but these drugs have many shortcomings [4]. For example, heparin therapy leads to heparin-induced thrombocytopenia in 2% to 3% of patients. Warfarin, however, has a narrow anticoagulant window, is susceptible to drug and food effects and requires blood monitoring.

Xa factor is in the intersection of the exogenous coagulation cascade and plays a central role in blood clotting response [5]. Xa factor inhibitors can selectively inhibit blood coagulation factor Xa, reduce the generation of thrombin and thus play an antithrombotic role [6]. In addition, the Xa factor inhibitors are not affected by food and drugs. No dose adjustment and blood monitoring are needed [7]. Current clinical oral Xa factor inhibitors mainly include rivaroxaban, apixaban, edoxaban, darexaban, and betrixaban [8]. In patients with non-valvular atrial fibrillation, rivaroxaban has been shown to be superior to traditional warfarin in reducing stroke and systemic embolism and reducing bleeding risk [9]. In ACS patients, the addition of apixaban on the basis of DAPT could further reduce the risk of ischemic events, but the risk of bleeding is significantly increased [10].

At present, the efficacy and safety of Xa factor inhibitors are still unknown. So, we searched the current existing studies about antiplatelet therapy plus Xa factor inhibitors for patients with CHD and analyzed these studies by meta-analysis to determine the efficacy and safety of antiplatelet therapy plus Xa factor inhibitors on CHD. By this research, we hoped to provide clinical doctors with reliable evidence-based medicine for the treatment of CHD.

Material and Methods

Search strategy

Two reviewers searched PubMed, Embase, and the Cochrane Library databases independently to collect randomized controlled trials (RCTs) of CHD patients with oral Xa factor inhibitor drugs. The retrieval time was from inception to January 2019. The search term was: "Xa factor inhibitor, rivaroxaban, apixaban, darexaban, coronary artery disease, acute coronary syndrome, percutaneous coronary intervention".

Inclusion and exclusion criteria

Inclusion criteria was as follows: 1) research types was all designed randomized controlled trials of antiplatelet therapy plus Xa factor inhibitors for CHD patients and follow-up time was unlimited; 2) study participants were aged >18 years old with CHD including stable angina pectoris, unstable angina pectoris, ST-elevation myocardial infarction and non-ST-elevation myocardial infarction; 3) interventions included experimental group to give oral Xa factor inhibition drugs and control group without using Xa factor inhibition drugs and both groups were on the basis of other antiplatelet drugs; 4) the outcome indicators of the study included at least 1 that we included in our study.

Exclusion criteria was as follows: 1) other types of studies other than RCTs (observational studies, repeated studies, reviews, meta-analysis, case reports); 2) the study used II factor inhibition drugs, heparin, warfarin anticoagulation drugs; 3) there was no record of endpoint events in the study; 4) the population studied was combined with other diseases; 5) the study included too few people (<100); 6) the study was republished; 7) non-English literatures.

Data extraction and quality assessment

Two reviewers independently extracted and assessed the included studies. Data were extracted and bias risk was evaluated. Differences were discussed or determined by a third reviewer. Data included: study and year, population, sample size, interventions, mean age, and outcome indicators.

We used the modified Jadad scale [11] to evaluate the quality of the included RCTs. Blinding, randomization, concealment allocation and withdrawal in the study were analyzed respectively. Studies with scores greater than or equal to 4 were considered high quality, while studies with scores less than 4 were considered low quality. In addition, we would exclude studies with too low quality.

Outcome indicators

All the outcome indicators are as follows: 1) total incidence of ischemic events; 2) all-cause mortality; 3) incidence of myocardial infarction; 4) incidence of ischemic stroke; 5) massive hemorrhage after thrombolysis in myocardial infarction (TIMI) – the bleeding was classified as massive hemorrhage if was intracranial or associated with a decrease in hemoglobin

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>5 g/dL (of 15% in hematocrit); 6) small hemorrhage after TIMI – the bleeding was considered small hemorrhage if it was spontaneous and observed as gross hematuria of hematemesis, or if blood loss was observed (for example, heme-positive coffee ground emesis, heme-positive melena, hematoma of retroperitoneal bleeding); 7) intracranial hemorrhage; 8) fatal hemorrhage.

Statistical analysis

We used RevMan 5.0 software (London, UK) for statistical analysis. Q test combined with I^2 was used to analyze the heterogeneity between studies (α=0.05). If statistical heterogeneity existed among the results of each study, the source of heterogeneity would be further analyzed. After excluding the influence of obvious clinical heterogeneity, the random effect model would be adopted for analysis. Odds ratio (OR) was used as the pooled statistic and 95% confidence interval (CI) was calculated. Funnel plots were used to analyze publication bias. If the funnel plots showed good symmetry, the publication bias of the included studies was negligible. If the symmetry of funnel plots was poor, it indicated that the included study had obvious publication bias.

Results

Study selection and study characteristics

A total of 7 RCTs [12–18] were included in this study. The literature screening process and results were shown in Figure 1. The intervention measures in the experimental group of 2 studies [12,13] were apixaban, the intervention measures in the experimental group of 4 studies [14–17] were rivaroxaban and the intervention measures in the experimental group of 1 study [18] were darexaban. The participants of 6 studies [12,13,15–18] were ACS patients and the participants of 1 study [14] were stable angina pectoris patients. There was a total of 50 044 patients were included, including 28 510 patients with oral Xa factor inhibitors. The basic data of included studies were shown in Table 1.

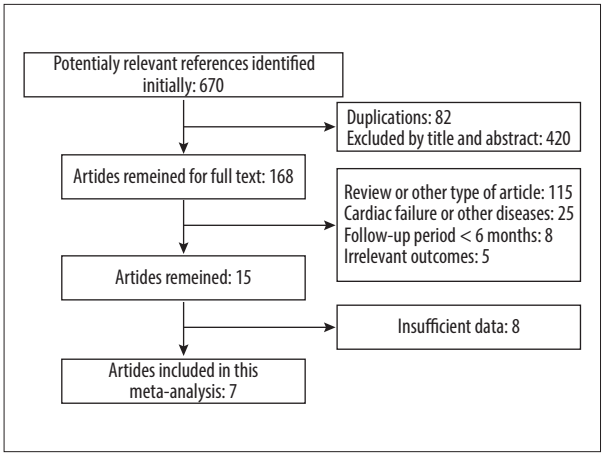

Figure 1. Study flow and selection diagram.

Results of meta-analysis

Total incidence of ischemic events

A total of 7 studies [12–18] analyzed total incidence of ischemic events. There was no significant heterogeneity (I^2=35%) among the studies, so the fixed-effect model was used for analysis. Results show that compared with only using antiplatelet

Table 1. Baseline characteristics of included studies.

Studies	Region	NO. of patients (T/C)	Mean age (T/C, years)	Intervention measures		Outcomes
				T	C	
Alexander 2009	Multicenter	635/611	61/60	Apixaban+DAPT	Placebo	abcdefg
Alexander 2011	Multicenter	3705/3687	67/67	Apixaban+DAPT	Placebo	abcdefgh
Connolly 2017	Multicenter	8313/8261	69/69	Rivaroxaban+Aspirin	Aspirin	abcdgh
Mega 2009	Multicenter	2331/1160	57.2/57.8	Rivaroxaban+DAPT	Placebo	aef
Mega 2012	Multicenter	10229/5113	61.8/61.5	Rivaroxaban+DAPT	Placebo	abcdefgh
Ohman 2017	Multicenter	1519/1518	62/63	Rivaroxaban+P2Y12 inhibitor	Aspirin+P2Y12 inhibitor	abcdefgh
Steg 2011	Multicenter	939/319	–	Darexaban+DAPT	Placebo	abcdef

T – treatment group; C – control group; DAPT – dual antiplatelet therapy; a – total incidence of ischemic events; b – all-cause mortality; c – incidence of myocardial infarction; d – incidence of ischemic stroke; e – massive hemorrhage after thrombolysis in myocardial infarction; f – small hemorrhage after thrombolysis in myocardial infarction; g – intracranial hemorrhage; h – fatal hemorrhage.

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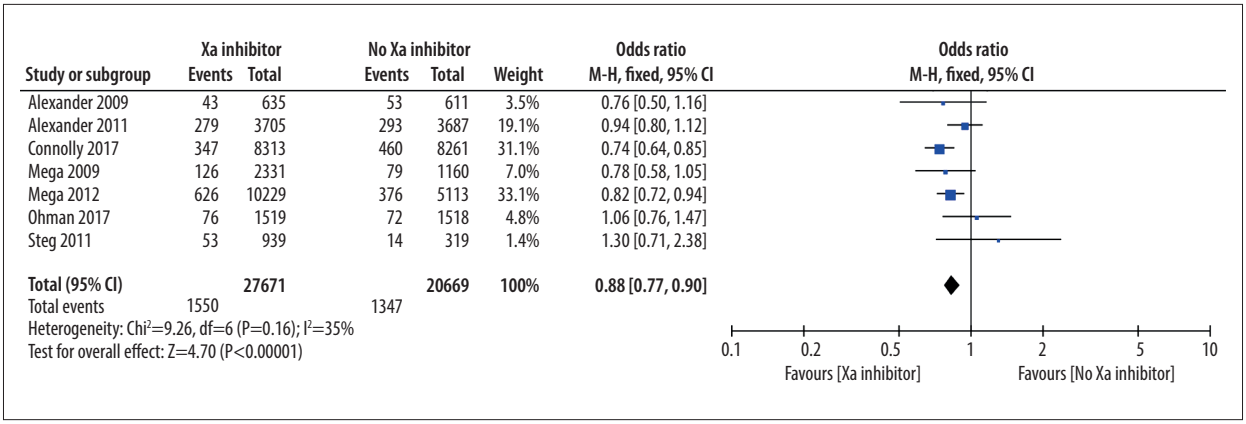

Figure 2. Forest plot for comparison of total incidence of ischemic events between 2 groups.

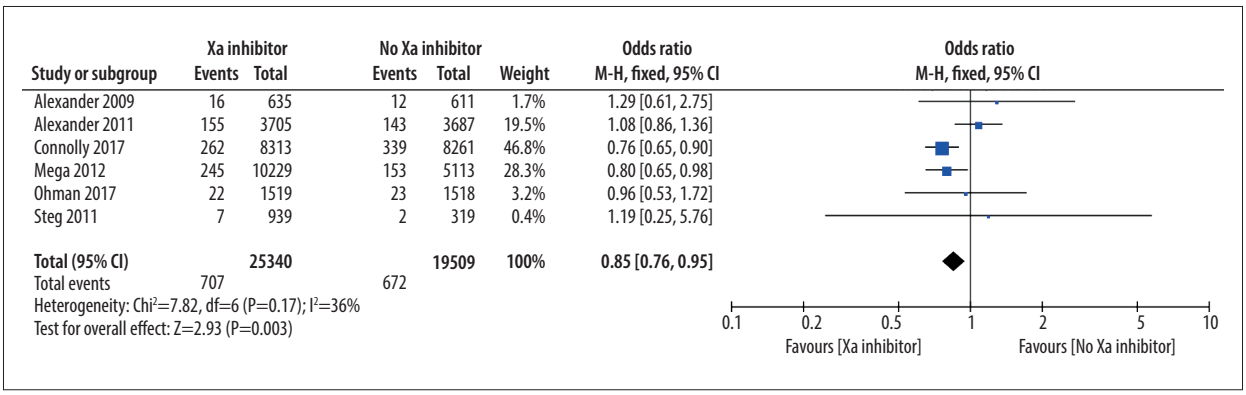

Figure 3. Forest plot for comparison of all-cause mortality between 2 groups.

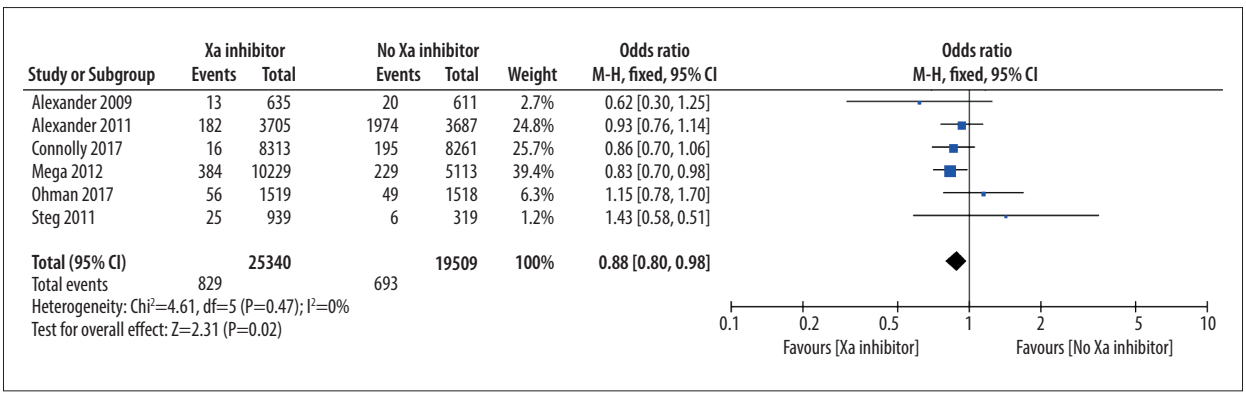

Figure 4. Forest plot for comparison of incidence of myocardial infarction between 2 groups.

therapy, antiplatelet therapy plus oral Xa factor inhibitors could reduce the incidence of total incidence of ischemic events (OR=0. 83, 95% confidence interval [CI]=0.77~0.90, *P*<0.00001) (Figure 2).

All-cause mortality

A total of 6 studies [12–14,16–18] analyzed all-cause mortality. There was no significant heterogeneity (I^2=36%) among the studies, so the fixed-effect model was used for analysis. Results show that compared with only using antiplatelet therapy, the addition of oral Xa factor inhibitors could reduce all-cause mortality (OR=0.85, 95% CI=0.76~0.95, *P*=0.003) (Figure 3).

Incidence of myocardial infarction

A total of 6 studies [12–14,16–18] analyzed the incidence of myocardial infarction. There was no significant heterogeneity (I^2=0%) among the studies, so the fixed-effect model was used for analysis. Results showed that in terms of decreasing

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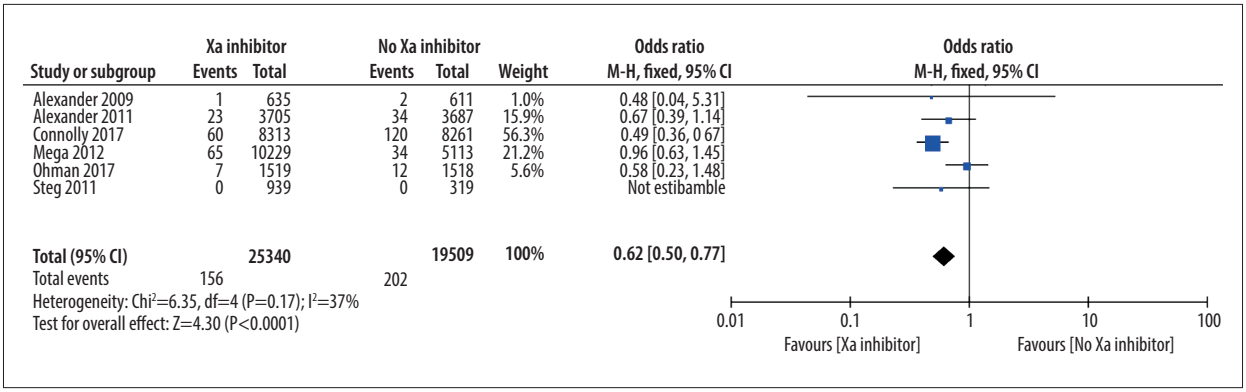

Figure 5. Forest plot for comparison of incidence of ischemic stroke between 2 groups.

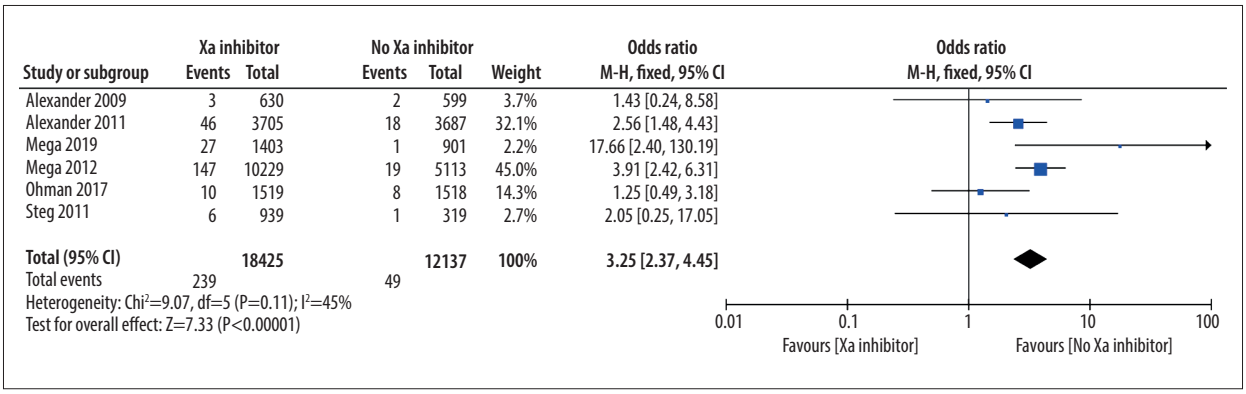

Figure 6. Forest plot for comparison of massive hemorrhage after TIMI between 2 groups.

the rate of myocardial infarction, the curative effect of antiplatelet therapy plus Xa factor inhibitors was better than that of antiplatelet therapy (OR=0.88, 95% CI=0.80~0.98, *P*=0.02) (Figure 4).

Incidence of ischemic stroke

A total of 6 studies [12–14,16–18] analyzed incidence of ischemic stroke. There was no significant heterogeneity (I^2=37%) among the studies, so the fixed-effect model was used for analysis. Results showed that after using Xa factor inhibitors, the incidence of ischemic stroke was reduced significantly (OR=0.62, 95% CI=0.50~0.77, *P*<0.0001) (Figure 5).

Massive hemorrhage after TIMI

A total of 6 studies [12,13,15–18] analyzed massive hemorrhage after TIMI. There was no significant heterogeneity (I^2=45%) among the studies, so the fixed-effect model was used for analysis. Results show that, compared with only using antiplatelet therapy, antiplatelet therapy plus oral Xa factor inhibitors could increase the incidence of massive hemorrhage after TIMI (OR=3.25, 95% CI=2.37~4.45, *P*<0.00001) (Figure 6).

Minor hemorrhage after TIMI

A total of 6 studies [12,13,15–18] analyzed minor hemorrhage after TIMI. There was no significant heterogeneity (I^2=0%) among the studies, so the fixed-effect model was used for analysis. Results showed that in terms of the increase in minor hemorrhage after TIMI, the efficacy of antiplatelet therapy plus factor oral Xa factor inhibitors was superior to that of antiplatelet therapy (OR=2.42, 95% CI=1.70~3.44, *P*<0.00001) (Figure 7).

Intracranial hemorrhage

A total of 5 studies [12–14,16,17] analyzed intracranial hemorrhage. There was no significant heterogeneity (I^2=48%) among the studies, so the fixed-effect model was used for analysis. Results showed that compared with only using antiplatelet therapy, antiplatelet therapy plus Xa factor inhibitors could increase the incidence of intracranial hemorrhage (OR=1.83, 95% CI=1.19~2.81, *P*=0.006) (Figure 8).

Fatal hemorrhage

A total of 4 studies [13,14,16,17] analyzed fatal hemorrhage. There was no significant heterogeneity (I^2=0%) among the studies, so the fixed-effect model was applied for analysis.

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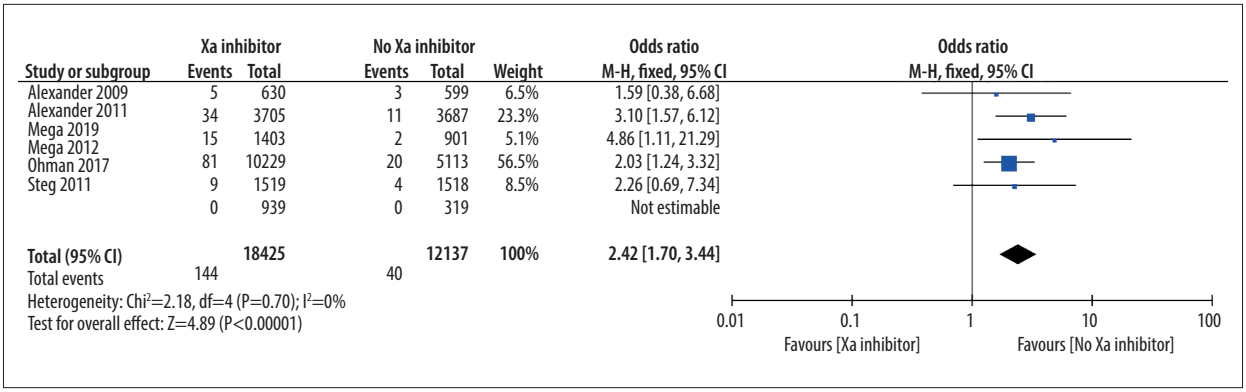

Figure 7. Forest plot for comparison of minor hemorrhage after TIMI between 2 groups.

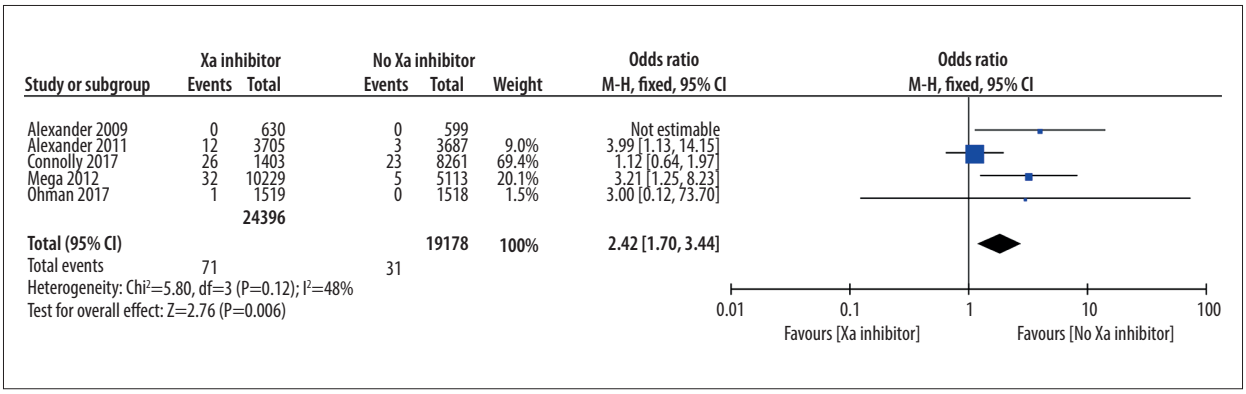

Figure 8. Forest plot for comparison of intracranial hemorrhage between 2 groups.

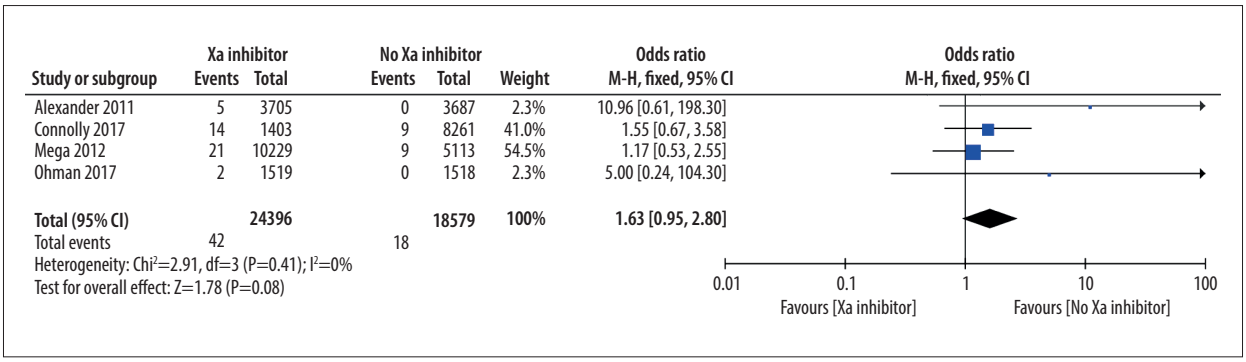

Figure 9. Forest plot for comparison of fatal hemorrhage between 2 groups.

No statistically significant difference was found in the risk of fatal hemorrhage between the 2 groups (OR=1.63, 95% CI=0.95~2.80, *P*=0.08) (Figure 9).

Publication bias and quality assessment

We analyzed publication bias of the included studies by making funnel plots. As shown in Figure 10, the asymmetry of the funnel diagrams of all-cause mortality and intracranial hemorrhage was significant, indicating the existence of publication bias. The other funnel plots were basically symmetrical. The quality assessment of the included studies was shown in Table 2. The Jadad score of each study was greater than 4, indicating that the included studies are of high quality.

Discussion

A total of 50 044 patients with CHD from 7 studies were collected in our study. Experimental design and methodology were described in detail in 7 studies. Risk of publication bias was assessed for studies according to the modified Jadad scale. Overall, the quality of the included studies was high. Results showed that antiplatelet therapy plus Xa factor

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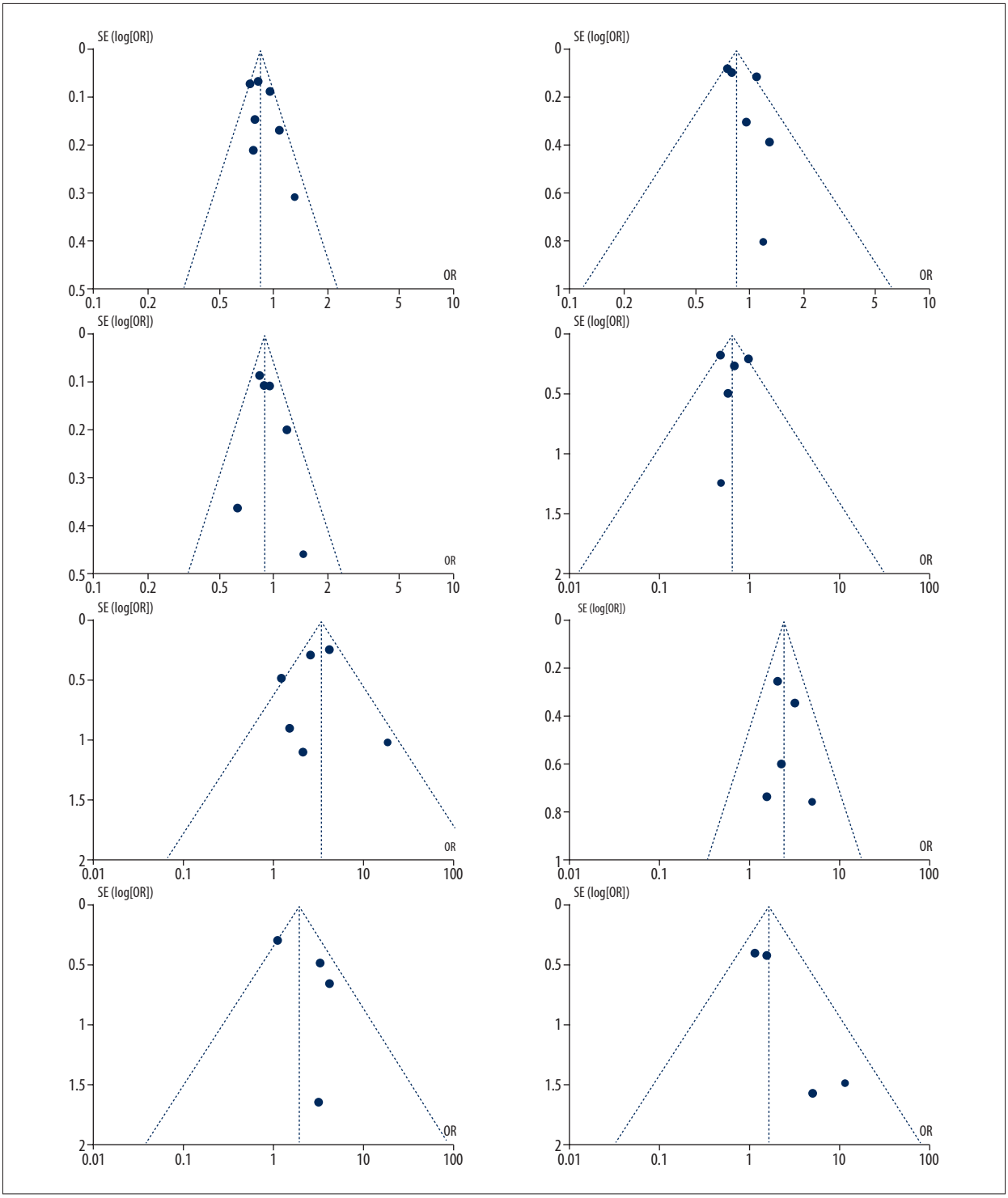

Figure 10. Funnel plots for publication bias assessment.

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Table 2. Modified Jadad scale.

Studies	Blinding	Randomization	Concealment allocation	Withdrawal	Total scores
Alexander 2009	2	2	1	1	6
Alexander 2011	2	2	1	1	6
Connolly 2017	2	2	1	1	6
Mega 2009	1	2	1	1	5
Mega 2012	1	2	2	1	6
Ohman 2017	2	2	1	1	6
Steg 2011	1	2	2	1	6

inhibitors in CHD patients could effectively reduce ischemic events, reduce the risk for all-cause mortality and myocardial infarction, especially the risk of ischemic stroke. In terms of safety, adding with oral Xa factor inhibitors could increase the risk of hemorrhage, especially intracranial hemorrhage risk.

A previous study showed that Xa factor inhibitors could help patients with non-valvular atrial fibrillation reduce the risk of stroke and systemic embolism, while bleeding risk in the 2 groups were similar [19]. However, Alexander et al. study [12] included 1715 ACS patients and compared the effects of apixaban at different doses. The results showed that apixaban could reduce ischemic events in ACS patients, but the risk of bleeding was increased and showed a dose-related effect. This study concluded that the use of apixaban in ACS patients should depend on the background of antiplatelet therapy. Mega series of studies [15,16] showed that the addition of rivaroxaban on the basis of the acceptance of DAPT in ACS patients could reduce the risk of cardiovascular events of ACS patients. The Connolly et al. study [14] showed that the combined use of rivaroxaban and aspirin was significantly superior to aspirin in the prevention of cardiovascular events in patients with stable CHD who did not require DAPT therapy. The X-PLORER study [20] showed that the selective interventional therapy for stable CHD and the perioperative use of rivaroxaban could improve the short-term prognosis. The present study results show that for patients with ACS or stable CHD, the addition of Xa factor inhibitors on the basis of antiplatelet therapy can further reduce the high risk of cardiovascular event and increased bleeding risk, especially intracranial hemorrhage. Therefore, antiplatelet therapy plus Xa factor inhibitors of CHD patients should give full consideration to its benefit and risk of bleeding.

This meta-analysis was different from Khan et al. meta-analysis [21]. The latter included dabigatran etexilate into research, while our meta-analysis simply chose studies about oral Xa factor inhibitors. Because the Gibson et al. study [22] selected patients of non-valvular atrial fibrillation with PCI therapy, it didn't accord with the inclusion criteria of this meta-analysis and was excluded. Results also differ between the 2 meta-analysis. The results of the Khan et al. study showed that DAPT plus new oral anticoagulants could reduce the incidence of MACE, but increase the risk of bleeding, while monotherapy with antiplatelet plus new oral anticoagulants were similar in MACE and bleeding events between the 2 groups and no significant difference was found. However. our meta-analysis showed that antiplatelet therapy plus oral Xa factor inhibitors could significantly reduce the incidence of cardiovascular events for patients with CHD but increase the incidence of bleeding, including intracranial hemorrhage.

CHD patients have a high risk of blood clotting and are prone to thrombosis and cause acute lesions. Therefore, the rational use of antithrombotic drugs is the key to preventing acute lesions in patients with CHD. The results of this study give clinicians a strong basis for clinical medication. For patients with a risk of head bleeding or cranial lesions, the use of Xa factor inhibitors requires caution. For patients with good physical condition and no brain-based lesions, the use of Xa factor inhibitors may lead to a better prognosis.

Due to the small amount of literature searched, sub-group analysis is inconvenient. Therefore, there were some limitations in this study. 1) Few studies were selected, which may have an impact on the results of the study. 2) Antiplatelet treatment strategies were different in different studies and we didn't further analysis the difference between single-agent antiplatelet therapy and DAPT in the treatment plus oral Xa factor inhibitors. 3) In different studies, Xa factor inhibitors were different and the dose were not uniform. 4) We did not further use other definitions of bleeding events to analyze the efficacy of drugs.

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Conclusions

In general, the addition of Xa factor inhibitors on the basis of antiplatelet therapy in patients with CHD are effective and could reduce the risk of ischemia events, all-cause mortality, myocardial infarction and ischemic stroke. However, on the safety side, oral Xa factor inhibitors could increase the risk of bleeding.

Conflict of interest

None.

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