New oral anticoagulants combined with antiplatelet therapy in the treatment of coronary heart disease: an updated meta-analysis

Leiling Liu

Second Xiangya Hospital

Jiahui Hu

Second Xiangya Hospital

Yating Wang

Second Xiangya Hospital

Hao Lei

Second Xiangya Hospital

Danyan Xu (✉ xudanyan02@csu.edu.cn)

Second Xiangya Hospital <https://orcid.org/0000-0003-2113-0800>

Research

Keywords: stable coronary artery disease, acute coronary syndrome, new oral anticoagulants, antiplatelet therapy, meta-analysis

Posted Date: August 26th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-64078/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective New oral anticoagulants (NOACs) combined with antiplatelet therapy for acute coronary syndrome (ACS) may reduce ischemic events, but there is no consensus on bleeding risk. Moreover, the effect of NOACs on stable coronary artery disease (CAD) needs to be elucidated. We conducted a meta-analysis, to summarize the efficacy and safety of NOACs combined with antiplatelet therapy in the treatment of stable CAD and ACS.

Methods We searched PubMed, Web of Science, and the Cochrane Library, then performed a systematic review of all 17 randomized controlled trials.

Results For patients with stable CAD, rivaroxaban combined with antiplatelet therapy significantly reduced the rate of major adverse cardiovascular events (MACEs) (risk ratio; 95% confidence interval: 0.88; 0.81–0.95) and ischemic stroke (0.62; 0.50–0.77), with a relatively low risk of major bleeding (1.72; 1.42–2.07). For patients with ACS, the combination of NOACs could reduce the risk of MACEs (0.91; 0.85–0.97), myocardial infarction (MI) (0.90; 0.83–0.98) and ischemic stroke (0.75; 0.58–0.97), accompanied by increased non-fatal bleeding events and intracranial hemorrhage (3.42; 1.76–6.65). Results were similar when restricting the analysis to phase III studies except for the rate of stroke in patients with ACS.

Conclusions Combination therapy can reduce the incidence of MI in ACS patients, but the risk of bleeding from intracranial hemorrhaging outweighs the benefit of MACEs driven by MI. That is due to combination therapy having no positive impact on mortality, thus the benefit-risk balance may be more favorable with patients with stable CAD.

1. Introduction

Despite improvements in the administration of medications, the incidence of major adverse cardiovascular events (MACEs) such as cardiovascular death, myocardial infarction (MI), and ischemic stroke in patients with coronary heart disease (CHD) remains high [1–3]. Besides, the activation of prothrombin after acute MI as well as the correlation between the severity of multi-branch coronary artery disease and thrombogenesis underscore the necessity of treatments with a combination of anticoagulant drugs and standard antiplatelet therapy for CHD [4]. Studies have shown that non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) are as effective as vitamin K receptor antagonists in preventing ischemic stroke in patients with atrial fibrillation and have a lower risk of bleeding [5–8]. Direct factor Xa inhibitors, including apixaban, darexaban, rivaroxaban, etc., are NOACs that have a more steady bioavailability through oral delivery compared with vitamin K antagonists [9]. Moreover, direct thrombin inhibitors, including ximelagatran and dabigatran, are also NOACs that overcome the downsides of the conventional anticoagulants-unfractionated and low molecular weight heparins and vitamin K antagonists [10, 11]. Thus, an increasing number of studies have begun to explore the safety and efficacy of NOACs combined with standard antiplatelet therapy for the treatment of acute coronary syndrome (ACS). The results of these studies have suggested that the combination of NOACs with antiplatelet therapy increases the risk of different non-fatal bleeding events, but significantly reduces the occurrence of adverse cardiovascular events, emphasizing the significance of adding low-dose NOACs to antiplatelet therapy for secondary prevention of ACS [12–23]. Nevertheless, patients with stable coronary artery disease (CAD) are at higher risk for ischemic events and up to 15% of patients have atrial fibrillation [24]. To avoid systemic embolism, ischemic stroke, and recurrent coronary ischemic events, NOACs should be combined with antiplatelet therapy in the treatment of those patients with the recent percutaneous transluminal coronary intervention (PCI), recent ACS, or high ischemic and low bleeding risk [25].

Therefore, this study included the latest research to further clarify the safety and efficacy of combining NOACs with antiplatelet therapy for patients with CHD [22, 26–28]. Furthermore, this meta-analysis is the first to summarize the efficacy and safety of NOACs combined with antiplatelet drugs in the treatment of stable CAD [29, 30]. The study aimed to determine the efficacy and safety of combining NOACs in the treatment of CHD, thus providing a more comprehensive treatment to guide the administration of clinical medication for secondary prevention for patients with CHD.

2. Methods

2.1 Literature search

We performed a computerized literature search of PubMed, Web of Science, and The Cochrane Library for articles published from January 1990 to October 2019. The search was not restricted by region or document type. The search term was (Apixaban OR Edoxaban OR Darexaban OR Rivaroxaban OR Otamixaban OR New oral anticoagulants) AND (Myocardial Ischemia OR Acute Coronary Syndrome OR PCI OR Coronary Disease OR MI) AND (aspirin OR P2Y12 receptor antagonists OR antiplatelet). The related articles function of the search engines was also used to broaden the search. We also manually reviewed the reference lists of all retrieved articles to avoid missing any relevant publications.

2.2 Inclusion and exclusion criteria

The PRISMA statement for reporting systematic reviews and meta-analyses was applied to the methods for this study. Studies included were required to fulfill the following specifications: (a) randomized controlled trials (RCT) design; (b) target population meeting diagnostic criteria for stable CAD or ACS; (c) standard antiplatelet therapy treatment (using aspirin and/or P2Y12 receptor antagonists) with NOACs, control group including oral anticoagulation or antiplatelet or placebo treatment; (d) efficacy and safety endpoints. Letters to the editor, reviews, and animal studies were excluded.

2.3 Measurement of results and data extraction

Two authors (Liu and Sun) independently performed data extraction on the baseline characteristics and endpoints of the included studies. Two authors (Hu and Wang) conducted repeated verification of the data. All included and excluded articles were agreed upon by all authors. The main efficacy outcome was the incidence of MACEs, which is defined as a composite of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization. Secondary efficacy indicators included cardiovascular death, MI, ischemic stroke, all-cause death, and stent thrombosis. Safety indicators included Thrombolysis in MI (TIMI) major bleeding, TIMI minor bleeding, International Society of Thrombosis and Hemostasis (ISTH) major bleeding, and intracranial hemorrhage.

2.4 Quality evaluation

The methodological quality was assessed by the Cochrane risk-of-bias tool including evaluation of sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete presentation of outcome data, selective reporting of outcome data, and other sources of bias.

2.5 Statistical analysis

Data were summarized using the Mantel–Hansel risk ratio (RR) fixed-effects model, and the RR value and 95% confidence interval were reported in this study. Statistical heterogeneity between studies was assessed using the chi-square test with significance set at $p < 0.10$. Heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. The random-effects model was used if there was significant heterogeneity among studies. Subgroup analyses were performed to compare the differences in efficacy and safety between stable CAD and ACS patients when additionally treated with NOACs. The test for subgroup differences was calculated by χ^2 statistics. $P < 0.05$ for the interaction suggested that the effect of treatment differed between the tested subgroups. Funnel plots and Egger's test were used to screen for potential publication bias.

3. Results

3.1 Data extraction and quality evaluation

A total of 1,223 potential articles were identified. After removing duplicates and articles that did not meet the inclusion criteria, we screened 40 studies for full-text review. 17 RCTs fulfilled the inclusion criteria, thus were the focus of this study (Fig. 1). The basic characteristics of the included studies are shown in Table 1, and the clinical characteristics and the efficacy and safety endpoints of included studies are shown in supplemental Tables 1 and 2. A total of 82,080 patients with CHD were included, of which 26,650 were with stable CAD and 55,430 were considered ACS. Additionally, of all patients, 46,569 were treated with rivaroxaban, 13,402 with apixaban, 1,258 with darexaban, 13,813 with otamixaban, 1,506 with edoxaban, 1,709 with ximelagatran, and 3,823 with dabigatran. Participants in the above studies were all treated with standard antiplatelet therapy (aspirin and/or P2Y12 receptor antagonist). All studies were randomized, double-blind, and none of the publications reported data selectively. Generally, a low risk of bias was identified in the included studies (see Supplementary Fig. 1 and Fig. 2).

Table 1
Baseline Characteristics of the Included Studies

Study	Year	Phase	Follow-up (month)	Participants	Number	Intervention	Total daily dose	Standard antiplatelet therapy	Total daily dose
COMPASS	2017	phase III	23	stable atherosclerotic vascular disease including coronary artery disease, peripheral arterial disease, or both	27395	Rivaroxaban	2.5 mg, twice	aspirin alone	aspirin 100mg, once
COMMANDER HF	2018	phase III	21.1	Coronary artery disease with worsening chronic heart failure	5022	Rivaroxaban	2.5 mg, twice	aspirin alone or aspirin plus P2Y ₁₂ -receptor antagonist	aspirin 100mg, once
APPRAISE	2009	phase II	6	Acute coronary syndrome	1715	Apixaban	2.5 mg twice, 10 mg once, 10 mg twice, 20 mg once daily	aspirin alone or aspirin plus a clopidogrel	aspirin ≤ 165 mg
APPRAISE-2	2011	phase III	8	Acute coronary syndrome	7392	Apixaban	5 mg twice	aspirin alone or plus any P2Y ₁₂ -receptor antagonist	aspirin ≤ 165 mg
APPRAISE-J	2013	phase II	6	Acute coronary syndrome	151	Apixaban	2.5 mg bid or 5 mg bid	aspirin alone or aspirin plus a clopidogrel or ticlopidine	aspirin ≤ 100 mg/day clopidogrel 75 mg/day ticlopidine 200 mg/day
ATLAS ACS-TIMI 46	2009	phase II	6	Acute coronary syndrome	3491	Rivaroxaban	once or twice a day (total daily dose 5,10,15, or 20 mg)	aspirin alone or aspirin plus a thienopyridine	75–100 mg daily
ATLAS ACS 2–TIMI 51	2012	phase III	13.1	Acute coronary syndrome	15526	Rivaroxaban	2.5 mg, twice or 5 mg twice	aspirin alone or aspirin plus clopidogrel or ticlopidine	75–100 mg daily
GEMINI-ACS-1	2017	phase II	9.7	Acute coronary syndrome	3037	Rivaroxaban	2.5 mg, twice	Clopidogrel or ticagrelor	clopidogrel 75 mg daily ticagrelor 90 mg twice daily
RE-DEEM	2011	phase II	6	Acute coronary syndrome	1861	Dabigatran	50 mg, 75 mg, 110 mg, or 150 mg, twice daily	aspirin alone or aspirin plus a clopidogrel	Aspirin ≤ 100 mg, clopidogrel 75 mg daily
RUBY-1	2011	phase II	26	Acute coronary syndrome	1279	Darexaban	5 mg b.i.d., 10 mg o.d., 15 mg b.i.d., 30 mg o.d., 30 mg b.i.d., or 60 mg o.d.	Acetylsalicylic acid alone or clopidogrel alone or a combination	ASA 75–325 mg clopidogrel 75 mg daily
SEPIA-ACS1 TIMI 42	2009	phase II	6	Acute coronary syndrome	3241	Otamixaban	0.08 mg/kg intravenous bolus followed by an infusion of 0.035, 0.070, 0.105, 0.140, or 0.175 mg/kg/hour	aspirin plus a clopidogrel	Not reported

b.i.d., twice daily; o.d., once daily;

Study	Year	Phase	Follow-up (month)	Participants	Number	Intervention	Total daily dose	Standard antiplatelet therapy	Total daily dose
TAO	2013	phase III	1	Acute coronary syndrome	10572	Otamixaban	intravenous bolus of 0.080 mg/kg followed by an infusion of 0.140 mg/kg/hour	aspirin plus clopidogrel, prasugrel or ticagrelor	clopidogrel ≥ 600 mg
PIONEER AF-PCI	2016	phase III	12	Non-valvular atrial fibrillation and acute coronary syndrome	2124	Rivaroxaban	2.5 mg twice daily	aspirin plus clopidogrel	aspirin 75 to 100 mg daily clopidogrel 75 mg daily
RE-DUAL PCI	2017	phase III	14	Nonvalvular atrial fibrillation and had acute coronary syndrome or stable coronary artery disease	2725	Dabigatran	110 mg or 150 mg twice daily	aspirin alone or aspirin plus a clopidogrel	aspirin ≤ 100 mg daily clopidogrel 75 mg daily
ENTRUST-AF PCI	2019	phase III	12	Nonvalvular atrial fibrillation and had acute coronary syndrome or stable coronary artery disease	1506	Edoxaban	30 mg once daily	aspirin alone or aspirin plus a clopidogrel	aspirin 100 mg once daily clopidogrel 75 mg
AUGUSTUS	2019	phase III	6	Nonvalvular atrial fibrillation and had acute coronary syndrome or stable coronary artery disease	4614	Apixaban	5 mg twice daily or to 2.5 mg twice daily	clopidogrel or prasugrel or ticagrelor	Not reported
ESTEEM	2008	phase II	6	Acute coronary syndrome	1883	Ximelagatran	24, 36, 48, or 60 mg bid	aspirin alone	160 mg o.d.
b.i.d., twice daily; o.d., once daily;									

3.2 Efficacy and safety endpoints of NOACs use in patients with CHD

Collectively, despite the rate of all cause death (0.94; 0.88–1.01), $I^2 = 0\%$, the additional treatment of NOACs to the standard antiplatelet therapy significantly decrease the incidence of MACEs (0.92; 0.88–0.96), $I^2 = 25.2\%$, cardiovascular death (0.91; 0.84–0.99), $I^2 = 0\%$, MI (0.90; 0.84–0.97), $I^2 = 6.3\%$, ischemia stroke (0.69; 0.59–0.81), $I^2 = 8.6\%$ and stent thrombosis (0.79; 0.64–0.97), $I^2 = 26.5\%$ in patients with CHD. Moreover, though complicated with increased rate of ISTH major bleeding (1.39; 1.00–1.94), $I^2 = 79.9\%$, the combination of NOACs with antiplatelet therapy could not increase the

incidence of TIMI major bleeding (1.58; 0.98–2.55), $I^2 = 79.6\%$, TIMI minor bleeding (1.38; 0.94–2.03), $I^2 = 71.1\%$ and intracranial hemorrhage (1.49; 0.86–2.58), $I^2 = 50.1\%$ (Fig. 2). We used the random-effects models to analyze all safety endpoints since there were significant heterogeneity among studies in these outcomes.

4. Subgroup Analysis Of Efficacy And Safety Endpoints

To investigate whether there is a difference in the safety and efficacy of NOACs combined with antiplatelet drugs in patients with stable CAD and ACS, we conducted a subgroup analysis. RE-DUAL PCI [28], ENTRUST-AF PCI [27], and AUGUSTUS [26] included all patients with stable CAD and ACS, but the data of all endpoints in individual populations were not available, we subsequently exclude the above three studies in the following subgroup analysis (see Supplementary Fig. 3A-J). Thus, some of the safety and efficacy results may differ from those when the studies were not excluded. Since most of the excluded RCT trials are for single antiplatelet therapy, the exclusion may have a greater impact on safety outcomes. However, the ensuing results still have to be interpreted with appropriate caution.

4.1 MACEs

Pooling the data from two studies that included a total of 23,300 patients with stable CAD [29, 30] showed that the addition of NOACs to the antiplatelet therapy could significantly reduce the incidence of MACEs (0.88; 0.81–0.95), $I^2 = 86.1\%$. The results of 50,699 patients with ACS from a total of twelve studies [12–23] showed that the combination therapy could also reduce the rate of MACEs in patients with ACS (0.91; 0.85–0.97), $I^2 = 0\%$ (Fig. 3). No significant difference was found between groups ($P = 0.768$).

4.2 Subgroup analysis of secondary efficacy outcomes

4.2.1 Cardiovascular death

The addition of NOACs to antiplatelet therapy did not reduce the incidence of cardiovascular death in patients with stable CAD (0.91; 0.82–1.01) [29, 30], $I^2 = 62.6\%$ and ACS (0.89; 0.77–1.03) [12–17, 22], $I^2 = 0\%$ (Fig. 3). There was no significant difference between groups ($P = 0.731$).

4.2.2 MI

The combined NOACs with antiplatelet therapy did not reduce the occurrence of MI in patients with stable CAD (0.86; 0.73–1.01) [29, 30], $I^2 = 0\%$. However, the combined treatment could reduce the incidence of MI in patients with ACS (0.90; 0.83–0.98) [12, 13, 15–23], $I^2 = 0\%$ (Fig. 3). No significant difference was found between groups ($P = 0.599$).

4.2.3 Ischemic stroke

The combination of NOACs could significantly reduce the incidence of ischemic stroke in patients with stable CAD (0.62; 0.50–0.77) [29, 30], $I^2 = 0\%$ and ACS (0.75; 0.58–0.97) [12–19, 22, 23], $I^2 = 4.3\%$ (Fig. 3). There was no significant difference between groups ($P = 0.265$).

4.2.4 All-cause death

The addition of NOACs to antiplatelet therapy did not decrease all-cause mortality in patients with stable CAD (0.92; 0.85–1.01) [29, 30], $I^2 = 71.2\%$ or ACS (0.95; 0.84–1.07) [12–23], $I^2 = 0\%$ (Fig. 3). No significant difference was found between groups ($P = 0.853$).

4.2.5 Stent thrombosis

The results of four studies with a combined total of 27,170 patients with ACS [12, 22, 31] showed that additional treatment with NOACs could significantly reduce the risk of stent thrombosis in patients with ACS (0.75; 0.60–0.95), $I^2 = 0\%$ (Fig. 3).

4.3 Subgroup analysis of safety endpoints

4.3.1 TIMI major bleeding

Data from ten studies [12, 13, 15–22] showed that the NOACs together with antiplatelet therapy could significantly increase the risk of TIMI major bleeding in ACS patients (1.96; 1.27–3.03), $I^2 = 64.4\%$ (Fig. 3). The random-effects model was used since there was heterogeneity among studies ($p = 0.003$).

4.3.2 TIMI minor bleeding

The results from eight studies [12, 13, 16–20, 22] showed that adding NOACs to antiplatelet therapy could significantly increase the risk of TIMI minor bleeding in patients with ACS (1.72; 1.19–2.48), $I^2 = 46.7\%$ (Fig. 3). Since there was heterogeneity among studies, we used the random-effects model ($p = 0.069$).

4.3.3 ISTH major bleeding

The addition of NOACs to antiplatelet therapy increased the rate of ISTH major bleeding in patients with stable CAD (1.72; 1.42–2.07) [29, 30], $I^2 = 0\%$. In patients with ACS, the risk of ISTH major bleeding was higher with the combined treatment of new oral anticoagulants (2.21; 1.68–2.94) [13–17, 23], $I^2 = 0\%$ (Fig. 3). The result showed that there was no significant difference between groups ($P = 0.154$).

4.3.4 Intracranial hemorrhage

Additional treatment with NOACs did not increase the risk of intracranial hemorrhage in patients with stable CAD (0.95; 0.51–1.75) [29, 30], $I^2 = 53.6\%$. However, in patients with ACS, the combined regimen increased the rate of intracranial hemorrhage (3.42; 1.76–6.65) [12, 13, 16–18, 20], $I^2 = 0\%$ (Fig. 3). Significant difference between groups was observed ($P = 0.005$).

5. Sensitivity Analysis

Due to the significant heterogeneity among the results of TIMI major bleeding, TIMI minor bleeding, ISTH major bleeding, and intracranial hemorrhage in patients with CHD, we used a random-effects model to analyze the results. Moreover, to identify the source of heterogeneity, we performed a sensitivity analysis. Since the PIONEER AF–PCI [22], RE–DUAL PCI [28], ENTRUST–AF PCI [27] and AUGUSTUS [26] studies included patients with ACS complicated with atrial fibrillation, the above four studies were excluded in the sensitivity analysis of the above safety outcomes. There were obvious changes in the significance of TIMI major bleeding (2.64; 2.10–3.31), TIMI minor bleeding (1.98; 1.55–2.52) and intracranial hemorrhage (1.49; 1.07–2.07), which indicated an increased risk of bleeding events for additional treatment of NOACs to antiplatelet therapy in patients with CHD. More importantly, the degree of heterogeneity significantly decreased for the above four endpoints (see Supplementary Fig. 4A–D).

Besides, there was heterogeneity between the two studies [29, 30] in the subgroup of stable CAD for some efficacy endpoints. This heterogeneity may be explained by the inclusion of the patients with stable CAD complicated with heart failure in COMMANDER HF study. Although the combination of rivaroxaban with antiplatelet therapy could not significantly reduce mortality in patients with stable CAD and heart failure, it did significantly reduce their risk of ischemic stroke. More importantly, for patients with stable CAD maintaining normal cardiac function, adding rivaroxaban to antiplatelet regimen could also significantly decrease their risk of cardiovascular death and even all-cause mortality, which highlighted the necessity of additional treatment with rivaroxaban in patients with simple, stable CAD.

Moreover, to exclude the impact of the experimental phase on the endpoints, we deleted all Phase II studies. Compared with the previous data before the phase II trials were excluded, the risk of TIMI major bleeding (2.81; 2.18–3.64), TIMI minor bleeding (1.87; 1.45–2.43), and Intracranial hemorrhage (3.61; 1.77–7.34) were all increased in patients with ACS. Additionally, the combination therapy did not reduce the occurrence of ischemic stroke in patients with ACS in all phase III studies (0.88; 0.65–1.20). The overall effects of other efficacy outcomes in the phase III trials were not significantly altered (Fig. 4).

Additionally, since the benefit confidence interval in most instances is barely crossing the unity line, we used the random-effects model to analyze all the efficacy outcomes of the subgroups as well. Except that the combination of NOACs and antiplatelet therapy did not reduce the incidence of MACEs in patients with stable CAD, all other efficacy outcomes were consistent with previous results (see supplementary Fig. 5A–E).

6. Publication Bias

The Egger's test of the studies included in this meta-analysis that reported MACEs rate showed that no evidence of publication bias was observed ($P = 0.977$). Moreover, the funnel plot indicated that all studies lie inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias (Fig. 5).

7. Discussion

CHD patients exhibit a high risk of ischemic events despite antiplatelet therapy [31]. Thus, anticoagulation and dual antiplatelet therapy (triple therapy) in patients who are undergoing PCI with stent implantation may be critical for the prevention of cardiovascular events, including stent thrombosis. Two meta-analyses [32, 33] were performed to evaluate the efficacy and safety of NOACs in ACS patients. However, these analyses did not include the results of some pivotal recent trials including the COMPASS [30], COMMANDER HF [29], ENTRUST–AF PCI [27], and AUGUSTUS [26]. Moreover, patients with stable CAD were not included in the two previous meta-analyses. Although one meta-analysis included the COMPASS study, the number of studies included in the analysis is limited [31]. In contrast, we included the latest studies and performed a subgroup analysis for ACS and stable CAD patients. There was a statistical difference between the two subgroups in the intracranial hemorrhage of safety endpoints. The results showed that combined use of NOACs significantly increased the risk of intracranial hemorrhage in patients with ACS compared to those with stable CAD. This may be due to the possibility that ACS patients are often treated with dual antiplatelet therapy, which increases the risk of bleeding. Our sensitivity analysis also suggested that additional treatment of NOACs significantly increased the risk of TIMI major bleeding in patients with CHD after excluding RCT studies [26–28] which included the patients with CHD complicated with atrial fibrillation. This result is also likely to be explained by the fact that most of those patients were treated with single antiplatelet therapy combined with NOACs. Thus, the use of a single antiplatelet agent with NOACs may be a more viable choice in patients with CHD, but more clinical trial data is needed to confirm individualized therapy regimens [34–37].

Additionally, when all the included studies were phase III trials, the combined use of NOACs significantly increased the risk of bleeding in patients with ACS, without improvements in efficacy endpoints, indicating that prolonging the duration of NOACs administration may not benefit patients with ACS but instead increase their risk of bleeding. Most of the results were similar in the phase II trials, which indicated the reliable conclusion of the safety and efficacy endpoints. However, the result of the sensitivity analysis showed that the combination therapy of NOACs did not decrease the risk of ischemic stroke in patients with ACS after excluding all phase II trials, further studies are needed to determine why the longer follow-up time led to poorer prevention of the occurrence of ischemic stroke or further confirm whether combined NOACs with antiplatelet therapy can reduce the incidence of

stroke in patients with ACS. Moreover, more RCTs are needed to explore the most optimal duration for combination therapy to ensure a reduced incidence of adverse cardiovascular events with minimal bleeding costs.

More importantly, Kupó et al. [38] performed a meta-analysis involving 28 RCTs and 196,761 patients have identified significant differences in cardiovascular safety among oral anticoagulants. The risk of MI is lowest with rivaroxaban, followed by apixaban and edoxaban, while it is the highest for vitamin K antagonists and dabigatran. Differences in risk of MI may influence the choice of NOACs when combined with antiplatelet therapy for patients with CHD. Nevertheless, future literature show focus on comparing the differences in MACEs and major bleeding among DOAC agents, which is of great importance for guiding the development of personalized antithrombotic regimens for patients with CHD.

The different NOACs dosing in analyzed RCTs could impact the results, especially the safety endpoints. The ATLAS ACS 2–TIMI 51 study [12] suggested that the twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes and any cause, but a survival benefit that was not seen with the twice-daily 5-mg dose. Moreover, the twice-daily 2.5-mg dose also resulted in fewer fatal bleeding events than the twice-daily 5-mg dose. Further, most of the studies have suggested that 2.5 mg of rivaroxaban taken twice daily can exert protective effects on patients with CHD without the risk of major bleeding or fatal bleeding events [13, 22, 39–41]. The latest guidelines indicated that triple medications treatment that lasts one month can be used as a basic administration regimen for patients after PCI, and the use of rivaroxaban can be extended appropriately for those at high risk of ischemic events (one month to six months) [1]. For Apixaban, the APPRAISE–2 study [17] suggested that a dose of 5 mg twice daily was associated with a significant increase in the risk of bleeding, without a significant effect on the incidence of recurrent ischemic events. Further, most of the studies indicated that 2.5 mg twice daily increased major or clinically relevant nonmajor bleeding and a trend toward a reduction in ischemic events [14, 16, 26]. The APPRAISE study [16] also suggested that apixaban at a total daily dose of 10 mg appears attractive for patients at high risk of ischemic events. As for other NOACs, there were no significant differences in drug dosing among studies. For example, Dabigatran significantly reduced coagulation activity and has the potential to reduce cardiovascular events when added to dual antiplatelet treatment in doses 110–150 mg twice daily [15, 28].

In general, in CHD patients with antiplatelet therapy, NOACs exhibited cardiovascular benefits for reducing MACE, cardiovascular death, MI, stroke, and stent thrombosis at the cost of an increased risk of major bleeding events. The large sample size from phase III studies and high–quality design provided solid conclusions for the efficacy and safety of NOAC use in CHD patients.

8. Strengths And Limitations

The strength of this meta-analysis is the inclusion of all the latest randomized, controlled, and double-blind trials, and the quality of each study was assessed to be high without significant risk of publication bias. Besides, this meta-analysis was the first to compare the safety and efficacy of NOACs combined with antiplatelet agents in patients with stable CAD and ACS. More importantly, we performed sensitivity analyses for all phase III studies to explore the impact of the trial phase on outcomes, especially the safety endpoints. We also separately analyzed the MACE components, i.e. cardiovascular death or all-cause mortality, MI, stroke as well as stent thrombosis in this meta-analysis. Finally, we identified the main source of heterogeneity of some endpoints and significantly reduced the heterogeneity through sensitivity analysis.

This meta-analysis has the following potential deficiencies. First, the main limitation of the meta-analysis is that patient-level data are not available. Lack of these data precludes the evaluation of baseline covariates on outcomes. Besides, the single and dual antiplatelet therapy as well as the duration of drug administration may have different effects on endpoints, especially on safety outcomes. However, since a large amount of the data was not accessible, we were unable to perform subgroup analysis on these factors. Finally, there were only two RCT studies concerning patients with stable CAD. However, the two studies were critically important for guiding the clinical drug administration of secondary prevention in patients with stable CAD due to the relatively large number of included patients. Despite these limitations, our conclusions were strongly supported because of the consistent overall effect after the sensitivity analysis, the extremely low heterogeneity, and no publication bias. More importantly, we have unprecedentedly compared the benefit-risk difference between patients with stable CAD and ACS, providing a new direction for the clinical treatment of CHD.

9. Conclusion

Although accompanied by an increased risk of bleeding events, the addition of low dose NOACs to antiplatelet therapy can significantly reduce ischemic events in patients with stable CAD and ACS, which may be beneficial for secondary prevention in patients with CHD. Moreover, although combination therapy can reduce the incidence of MI in patients with ACS, the bleeding risk, especially intracranial hemorrhage outweighs the benefit of MACEs. This is driven by the benefit of MI because the combination therapy has no beneficial impact on mortality and even the incidence of stroke in phase III trials. Thus, combination therapy may be more favorable for patients with stable CAD. NOACs combined with single antiplatelet therapy may be the best option since it considerably reduces the risk of bleeding. However, to achieve a balance between benefits and safety, a thorough assessment of risk factors for ischemic events and bleeding complications in individual patients remain critical. Future research should be conducted to explore the optimal duration of NOACs treatment as a combination drug to maximize the balance between safety and efficacy for the secondary prevention of patients with CHD.

List Of Abbreviations

NOACs, New oral anticoagulants; ACS, acute coronary syndrome; CAD, coronary artery disease; MACEs, major adverse cardiovascular events; MI, myocardial infarction; CHD, coronary heart disease; TIMI, Thrombolysis in MI; ISTH, International Society of Thrombosis and Hemostasis; RR, risk ratio; PCI, percutaneous transluminal coronary intervention;

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This work was supported by the National Natural Science Foundation of China (81672264, 81871858).

Authors' contributions:

All authors participating in this work are listed and we approve this version of the manuscript. L.L. and H.L. conceived the study and performed data extraction. J.H. and Y.W. repeatedly verified the data. L.L. critically revised the first draft. The supervision and editing were done by D.X...

Acknowledgments:

This work was supported by the National Natural Science Foundation of China (81672264, 81871858).

References

1. Rapsomaniki, Thuresson, Yang et al. Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. *Eur Heart J Qual Care Clin Outcomes*. 2016;2:172-83.
2. Collet, Roffi, Byrne, Costa, Valgimigli. Case-based implementation of the 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease. *Eur Heart J*. 2018;39:e1-e33.
3. Gurbel, Fox, Tantry, Ten Cate, Weitz. Combination Antiplatelet and Oral Anticoagulant Therapy in Patients With Coronary and Peripheral Artery Disease. *Circulation*. 2019;139:2170-85.
4. Verheugt, Ten Berg, Storey, Cuisset, Granger. Antithrombotics: From Aspirin to DOACs in Coronary Artery Disease and Atrial Fibrillation (Part 3/5). *J Am Coll Cardiol*. 2019;74:699-711.
5. Nazha, Pandya, Cohen et al. Periprocedural Outcomes of Direct Oral Anticoagulants Versus Warfarin in Nonvalvular Atrial Fibrillation. *Circulation*. 2018;138:1402-11.
6. Halperin, Hankey, Wojdyla et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation*. 2014;130:138-46.
7. O'Donoghue, Ruff, Giugliano et al. Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation. *Eur Heart J*. 2015;36:1470-7.
8. Nielsen, Skjoth, Sogaard et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *Bmj*. 2017;356:j510.
9. Lauer, Pfeilschifter, Schaffer, Lo, Foerch. Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies. *Lancet Neurol*. 2013;12:394-405.
10. Harenberg, Marx, Krejczyk, Wehling. New anticoagulants - promising and failed developments. *Br J Pharmacol*. 2012;165:363-72.
11. Andersson, Bergstrom, Branalt et al. Macrocyclic Prodrugs of a Selective Nonpeptidic Direct Thrombin Inhibitor Display High Permeability, Efficient Bioconversion but Low Bioavailability. *J Med Chem*. 2016;59:6658-70.
12. Mega, Braunwald, Wiviott et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9-19.

13. Ohman, Roe, Steg et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet*. 2017;389:1799-808.
14. Ogawa, Goto, Matsuzaki, Hiro, Shima. Randomized, double-blind trial to evaluate the safety of apixaban with antiplatelet therapy after acute coronary syndrome in Japanese patients (APPRAISE-J). *Circ J*. 2013;77:2341-8.
15. Oldgren, Budaj, Granger et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J*. 2011;32:2781-9.
16. Alexander, Becker, Bhatt et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation*. 2009;119:2877-85.
17. Alexander, Lopes, James et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365:699-708.
18. Mega, Braunwald, Mohanavelu et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet*. 2009;374:29-38.
19. Sabatine, Antman, Widimsky et al. Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial. *Lancet*. 2009;374:787-95.
20. Steg, Mehta, Pollack et al. Anticoagulation with otamixaban and ischemic events in non-ST-segment elevation acute coronary syndromes: the TAO randomized clinical trial. *Jama*. 2013;310:1145-55.
21. Steg, Mehta, Jukema et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. *Eur Heart J*. 2011;32:2541-54.
22. Gibson, Mehran, Bode et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med*. 2016;375:2423-34.
23. Tanguer, Frison, Weaver et al. Effect of ximelagatran on ischemic events and death in patients with atrial fibrillation after acute myocardial infarction in the efficacy and safety of the oral direct thrombin inhibitor ximelagatran in patients with recent myocardial damage (ESTEEM) trial. *Am Heart J*. 2008;155:382-7.
24. Lemesle. Aspirin on Top of Anticoagulation in Patients With Concomitant Stable Coronary Artery Disease and Atrial Fibrillation. *Circulation*. 2019;139:617-9.
25. Verheugt. Return of Oral Anticoagulation in Chronic Stable Coronary Disease. *Circulation*. 2018;137:1655-7.
26. Lopes, Heizer, Aronson et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med*. 2019;380:1509-24.
27. Vranckx, Valgimigli, Eckardt et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394:1335-43.
28. Cannon, Bhatt, Oldgren et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017;377:1513-24.
29. Zannad, Anker, Byra et al. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med*. 2018;379:1332-42.
30. Eikelboom, Connolly, Bosch et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med*. 2017;377:1319-30.
31. Fu, Zhu, Huang et al. Efficacy and Safety of the Use of Non-vitamin K Antagonist Oral Anticoagulants in Patients with Ischemic Heart Disease: A Meta-Analysis of Phase III Randomized Trials. *Am J Cardiovasc Drugs*. 2019;19:37-47.
32. Villablanca, Holmes, Mohananey et al. Direct Xa inhibitors in addition to antiplatelet therapy in acute coronary syndrome: meta-analysis of randomized trials. *Coron Artery Dis*. 2017;28:395-405.
33. Oldgren, Wallentin, Alexander et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J*. 2013;34:1670-80.
34. Guedeney, Vogel, Mehran. Non-vitamin K Antagonist Oral Anticoagulant After Acute Coronary Syndrome: Is There a Role? *Interv Cardiol*. 2018;13:93-8.
35. Pop, Matei, Petris. Anticoagulation in Acute Coronary Syndrome: Review of Major Therapeutic Advances. *Am J Ther*. 2019;26:e184-e97.
36. Lam, Bell, Hira. Concomitant Use of Antiplatelets and Anticoagulants in Patients with Coronary Heart Disease and Atrial Fibrillation: What Do Recent Clinical Trials Teach Us? *Curr Atheroscler Rep*. 2018;20:4.
37. Jacobs, Tieleman. Optimal antithrombotic treatment of patients with atrial fibrillation undergoing percutaneous coronary intervention: triple therapy is too much! *Neth Heart J*. 2018;26:334-40.
38. Kupo, Szakacs, Solymar et al. Direct Anticoagulants and Risk of Myocardial Infarction, a Multiple Treatment Network Meta-Analysis. *Angiology*. 2020;71:27-37.
39. Mehra, Vaduganathan, Fu et al. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J*. 2019;40:3593-602.
40. Lamy, Eikelboom, Sheth et al. Rivaroxaban, Aspirin, or Both to Prevent Early Coronary Bypass Graft Occlusion: The COMPASS-CABG Study. *J Am Coll Cardiol*. 2019;73:121-30.
41. Fox, Eikelboom, Shestakovska et al. Rivaroxaban Plus Aspirin in Patients With Vascular Disease and Renal Dysfunction: From the COMPASS Trial. *J Am Coll Cardiol*. 2019;73:2243-50.

Figure 1

Flow diagram of included studies.

Figure 2

Efficacy and safety endpoints of NOACs use in patients with CHD. CHD: coronary heart disease; RR: risk ratio; CI: confidence interval; ISTH: International Society on Thrombosis and Hemostasis; TIMI: Thrombolysis in Myocardial Infarction.

Figure 3

Subgroup analysis of endpoints of NOACs use in patients with stable CAD and ACS. CAD: coronary artery disease; ACS: acute coronary syndrome; Effect of adding new oral anticoagulants to single (aspirin or P2Y12 receptor antagonists) or dual (aspirin and P2Y12 receptor antagonists) antiplatelet therapy on efficacy and safety endpoints after a stable CAD and an ACS. RR: risk ratio; CI: confidence interval; ISTH: International Society on Thrombosis and Hemostasis; TIMI: Thrombolysis in Myocardial Infarction.

Figure 4

Endpoints of NOACs use in patients with CHD in a subgroup of phase III studies. CHD: coronary heart disease; Subgroup analysis of efficacy and safety of adding new oral anticoagulants to single (aspirin or P2Y12 receptor antagonists) or dual (aspirin and P2Y12 receptor antagonists) antiplatelet therapy after a stable CAD or an ACS in all phase III studies. RR: risk ratio; CI: confidence interval; ISTH: International Society on Thrombosis and Hemostasis; TIMI: Thrombolysis in Myocardial Infarction.

Figure 5

Funnel plots illustrating meta-analysis of major adverse cardiovascular events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalMaterials.docx](#)
- [SupplementalMaterials.docx](#)