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

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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).
| 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               | aspirin100mg, 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 P2Y12–receptor antagonist | aspirin100mg, 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 P2Y12–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., 60 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 | 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. |

### 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 SafetyEndpoints

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
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.

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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...

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Figure 1

Flow diagram of included studies.
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.
### Efficacy

| Factor                  | Studies | Control                  | NOACs                  | ES (95% CI) | P Value |
|-------------------------|---------|--------------------------|------------------------|-------------|---------|
| MACE                    | 17      | 3245/35690(9.1%)         | 3532/46390(7.6%)       | 0.92 (0.88, 0.96) | .000    |
| Cardiovascular death    | 10      | 1037/25995(4.0%)         | 1076/32346(3.3%)       | 0.91 (0.84, 0.99) | .021    |
| Myocardial infarction   | 15      | 1370/34883(3.9%)         | 1554/45540(3.4%)       | 0.90 (0.84, 0.97) | .006    |
| Stroke                  | 14      | 360/29150(1.2%)          | 294/39594(0.7%)        | 0.69 (0.59, 0.81) | .000    |
| All cause death         | 15      | 1533/34240(4.5%)         | 1658/44935(3.7%)       | 0.94 (0.88, 1.01) | .078    |
| Stent thrombosis        | 6       | 169/14301(1.2%)          | 185/19444(1.0%)        | 0.79 (0.64, 0.97) | .026    |

### Safety

| Factor                  | Studies | Control                  | NOACs                  | ES (95% CI) | P Value |
|-------------------------|---------|--------------------------|------------------------|-------------|---------|
| TIMI major bleeding     | 12      | 185/22638(0.8%)          | 478/32683(1.5%)        | 1.58 (0.98, 2.55) | .059    |
| TIMI minor bleeding     | 10      | 205/21948(0.9%)          | 375/30254(1.2%)        | 1.38 (0.94, 2.03) | .097    |
| ISTH major bleeding     | 11      | 435/21949(2.0%)          | 624/23216(2.7%)        | 1.39 (1.00, 1.94) | .049    |
| Intracranial hemorrhage | 10      | 73/32438(0.2%)           | 114/38442(0.3%)        | 1.49 (0.86, 2.58) | .154    |

*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 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.

| Factor                  | Control                  | NOACs                  | ES (95%CI)   | P Value |
|-------------------------|--------------------------|------------------------|--------------|---------|
| Stable CAD              | 1154/1164 (9.9%)         | 1005/1165 (8.6%)       | 0.88 (0.81, 0.95) | .002    |
| ACS                     | 1374/2000 (6.7%)         | 1811/3069 (9.3%)       | 0.91 (0.85, 0.97) | .005    |
| Coronary death          |                          |                        |              |         |
| Stable CAD              | 679/1164 (5.8%)          | 613/1165 (5.3%)        | 0.91 (0.82, 1.01) | .072    |
| ACS                     | 300/1204 (2.5%)          | 406/1838 (2.2%)        | 0.89 (0.77, 1.03) | .124    |
| Myocardial infarction   |                          |                        |              |         |
| Stable CAD              | 323/1164 (2.8%)          | 276/1165 (2.4%)        | 0.86 (0.73, 1.01) | .058    |
| ACS                     | 934/1995 (4.7%)          | 1162/3094 (3.8%)       | 0.90 (0.83, 0.98) | .021    |
| Stroke                  |                          |                        |              |         |
| Stable CAD              | 218/1164 (1.9%)          | 134/1165 (1.1%)        | 0.62 (0.50, 0.77) | .000    |
| ACS                     | 110/1422 (0.8%)          | 130/2464 (0.5%)        | 0.75 (0.58, 0.97) | .028    |
| All cause death         |                          |                        |              |         |
| Stable CAD              | 934/1164 (8.0%)          | 859/1165 (7.4%)        | 0.92 (0.85, 1.01) | .076    |
| ACS                     | 472/1931 (2.4%)          | 466/2998 (2.3%)        | 0.95 (0.84, 1.07) | .376    |
| Stent thrombosis        |                          |                        |              |         |
| ACS                     | 140/1103 (1.3%)          | 156/1615 (0.97%)       | 0.75 (0.60, 0.95) | .015    |
| TIMI major bleeding     |                          |                        |              |         |
| ACS                     | 119/1973 (0.6%)          | 426/2942 (1.4%)        | 1.96 (1.27, 3.03) | .003    |
| TIMI minor bleeding     |                          |                        |              |         |
| ACS                     | 103/1868 (0.5%)          | 280/2698 (1.0%)        | 1.72 (1.19, 2.48) | .004    |
| ISTH major bleeding     |                          |                        |              |         |
| Stable CAD              | 166/1163 (1.4%)          | 288/1165 (2.3%)        | 1.72 (1.42, 2.07) | .000    |
| ACS                     | 66/6299 (1.0%)           | 173/7543 (2.3%)        | 2.21 (1.66, 2.94) | .000    |
| Intracranial hemorrhage |                          |                        |              |         |
| Stable CAD              | 49/1163 (0.4%)           | 49/1165 (0.4%)         | 0.95 (0.51, 1.75) | .086    |
| ACS                     | 9/1754 (0.1%)            | 52/2352 (0.2%)         | 3.42 (1.76, 6.65) | .000    |
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.

| Study ID | ES (95% CI) | P Value |
|----------|-------------|---------|
| MACE     |             |         |
| Stable CAD | 0.88 (0.81, 0.95) | .002 |
| ACS      | 0.92 (0.85, 0.99) | .015 |
| Cardiac death |               |         |
| Stable CAD | 0.91 (0.82, 1.01) | .072 |
| ACS      | 0.87 (0.74, 1.02) | .064 |
| Myocardial infarction |               |         |
| Stable CAD | 0.86 (0.73, 1.01) | .058 |
| ACS      | 0.90 (0.82, 1.00) | .041 |
| Stroke   |             |         |
| Stable CAD | 0.62 (0.50, 0.77) | .000 |
| ACS      | 0.88 (0.65, 1.20) | .422 |
| All-cause death |           |         |
| Stable CAD | 0.92 (0.85, 1.01) | .076 |
| ACS      | 0.96 (0.84, 1.09) | .324 |
| Stent thrombosis |           |         |
| ACS      | 0.72 (0.56, 0.92) | .008 |
| TIMI major bleeding |        |         |
| ACS      | 2.39 (1.88, 3.02) | .000 |
| TIMI minor bleeding |          |         |
| ACS      | 1.87 (1.45, 2.43) | .000 |
| ISTH major bleeding |           |         |
| Stable CAD | 1.72 (1.42, 2.07) | .000 |
| ACS      | 2.40 (1.87, 3.04) | .000 |
| Intracranial hemorrhage |               |         |
| Stable CAD | 1.00 (0.67, 1.48) | 1.000 |
| ACS      | 3.61 (1.77, 7.34) | .000 |
| Study ID | ES (95% CI) | P Value |
|---------|-------------|---------|
| MACE    |             |         |
| Stable CAD | 0.88 (0.81, 0.95) | .002 |
| ACS     | 0.92 (0.85, 0.99) | .015 |
| CAD death |             |         |
| Stable CAD | 0.91 (0.82, 1.01) | .072 |
| ACS     | 0.87 (0.74, 1.02) | .064 |
| Myocardial infarction | | |
| Stable CAD | 0.86 (0.73, 1.01) | .058 |
| ACS     | 0.90 (0.62, 1.00) | .041 |
| Stroke   |             |         |
| Stable CAD | 0.62 (0.50, 0.77) | .000 |
| ACS     | 0.68 (0.56, 1.20) | .422 |
| All-cause death | | |
| Stable CAD | 0.92 (0.85, 1.01) | .076 |
| ACS     | 0.96 (0.84, 1.09) | .324 |
| Stent thrombosis | | |
| ACS     | 0.72 (0.56, 0.92) | .008 |
| TIMI major bleeding | | |
| ACS     | 2.39 (1.88, 3.02) | .000 |
| TIMI minor bleeding | | |
| ACS     | 1.87 (1.45, 2.43) | .000 |
| ISTH major bleeding | | |
| Stable CAD | 1.72 (1.42, 2.07) | .000 |
| ACS     | 2.40 (1.67, 3.40) | .000 |
| Intracranial hemorrhage | | |
| Stable CAD | 1.00 (0.67, 1.48) | 1.000 |
| ACS     | 3.61 (1.77, 7.34) | .000 |

**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.
Figure 5

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

Supplementary Files

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