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SYSTEMATIC REVIEW

Direct Oral Anticoagulants Combined with Antiplatelet Therapy in the Treatment of Coronary Heart Disease: An Updated Meta-analysis

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Abstract

Background Direct oral anticoagulants (DOACs) 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 DOACs on stable coronary artery disease (CAD) needs to be elucidated. We conducted a meta-analysis to summarize the efficacy and safety of DOACs combined with antiplatelet therapy in the treatment of stable CAD and ACS.

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

Results For patients with stable CAD, DOACs combined with antiplatelet therapy significantly reduced the rate of major adverse cardiovascular events (MACE) (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 DOACs reduced the risk of MACE (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 reduced the incidence of MI in ACS patients, but the risk of bleeding from intracranial hemorrhaging outweighs the benefit of MACE driven by MI. That is due to combination therapy having no positive impact on mortality; thus, the benefit–risk balance may be more favorable in patients with stable CAD.

Key Points

Combination therapy reduced ischemic events in stable coronary artery disease (CAD) and acute coronary syndrome (ACS) patients.

The benefit–risk balance may be more favorable for patients with stable CAD.

The medication duration of < 1 year decreased the rate of fatal bleeding.

1 Introduction

Despite improvements in the administration of medications, the incidence of major adverse cardiovascular events (MACE) 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 underscores 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 (direct oral anticoagulants, DOACs) are as effective as vitamin K receptor antagonists in preventing ischemic stroke in patients with atrial fibrillation (AF) and have a lower risk of bleeding [5–8]. Direct factor Xa inhibitors, including apixaban, darexaban, rivaroxaban, etc., are DOACs 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 DOACs

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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 DOACs combined with standard antiplatelet therapy for the treatment of acute coronary syndrome (ACS). The results of these studies have suggested that the combination of DOACs with antiplatelet therapy increases the risk of different nonfatal bleeding events, but significantly reduces the occurrence of adverse cardiovascular events, emphasizing the significance of adding low-dose DOACs 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 AF [24]. To avoid systemic embolism, ischemic stroke, and recurrent coronary ischemic events, DOACs should be combined with antiplatelet therapy in the treatment of patients with a recent percutaneous transluminal coronary intervention (PCI), recent ACS, or high ischemic and low bleeding risk [25].

Therefore, this study includes the latest research to further clarify the safety and efficacy of combining DOACs with antiplatelet therapy for patients with CHD [22, 26–28]. Furthermore, to the best of our knowledge, this is the first and only meta-analysis that has focused on the efficacy and safety of DOACs combined with antiplatelet drugs in the treatment of stable CAD [29, 30]. The study aimed to determine the efficacy and safety of combining DOACs in the treatment of CHD, thereby better guiding secondary prevention for patients with CHD.

2 Methods

2.1 Literature Search

We performed a computerized literature search of PubMed, Web of Science, and Cochrane Central Register of Controlled Trials for articles published from inception until September 2021. The search was not restricted by region or document type. The search term was (apixaban OR edoxaban OR darexaban OR rivaroxaban OR otamixaban OR direct 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 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [31] and checklist [32] were applied to the methods for this present meta-analysis. Studies included were required to fulfill the following specifications: (a) randomized controlled trial (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 DOACs, control group including oral anticoagulation or placebo treatment; (d) efficacy and safety endpoints. Letters to the editor, reviews, and animal studies were excluded. The full text of articles deemed to meet inclusion criteria were retrieved and screened for their eligibility by two authors (Liu and Hu). Both authors agreed on the articles to be included in the systematic review and meta-analysis. In the event of any disagreements, these were resolved by a third author (Lei). The selection of studies was carried out with the software of Endnote X9.

2.3 Measurement of Results and Data Extraction

Two investigators (Liu and Hu) extracted data from the studies and tabulated them into a Microsoft Excel Spreadsheet. Two authors (Tang and Lei) conducted repeated verification of the data. The main efficacy outcome was the incidence of MACE, 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 revised Cochrane Risk of Bias (RoB 2.0) [33] including allocation concealment; evaluation of sequence generation; selective reporting of outcome data; blinding of participants, personnel, and outcome assessors; incomplete presentation 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 (95% CI) were reported in this study. Statistical heterogeneity between studies was assessed using the chi-square test with a 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. Subgroup analyses were performed to compare the differences in efficacy and safety

between stable CAD and ACS patients when additionally treated with DOACs. The test for subgroup differences was calculated by χ^2 statistics. A p value of < 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. Statistical analyses and graphs were carried out using Stata/SE (Version 12.0) and Review Manager (Version 5.2).

3 Results

3.1 Data Extraction and Quality Evaluation

A total of 1631 potential articles were identified. After removing duplicates and articles that did not meet the inclusion criteria, we screened 65 studies for full-text review. Of these, 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 (see electronic supplementary material [ESM]). A total of 82,080 patients with CHD were included, of which 26,650 had stable CAD and 55,430 were considered as having ACS. Additionally, of all patients, 46,569 were treated with rivaroxaban, 13,402 with apixaban, 1258 with darexaban, 13,813 with otamixaban, 1506 with edoxaban, 1709 with ximelagatran, and 3823 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 in the ESM).

3.2 Efficacy and Safety Endpoints of Direct Oral Anticoagulants (DOACs) Use in Patients with Coronary Heart Disease (CHD)

Collectively, the additional treatment of DOACs to the standard antiplatelet therapy significantly decreased the incidence of MACE (risk ratio [RR] 0.92; 95% CI 0.88–0.96), I^2 = 25.2%; cardiovascular death (RR 0.91; 95% CI 0.84–0.99), I^2 = 0%; MI (RR 0.90; 95% CI 0.84–0.97), I^2 = 6.3%; ischemic stroke (RR 0.69; 95% CI 0.59–0.81), I^2 = 8.6%; and stent thrombosis (RR 0.79; 95% CI 0.64–0.97), I^2 = 26.5%, in patients with CHD. Moreover, the combination of DOACs with antiplatelet therapy increased rate of ISTH major bleeding (RR 1.38; 95% CI 1.22–1.56), I^2 = 79.9%; TIMI major bleeding (RR 1.82; 95% CI 1.52–2.17), I^2 = 79.6%; TIMI minor bleeding (RR 1.39; 95% CI 1.17–1.66), I^2 = 71.1%; and intracranial hemorrhage (RR 1.37; 95% CI 1.01–1.84), I^2 = 50.1%. Besides, since there is adequate

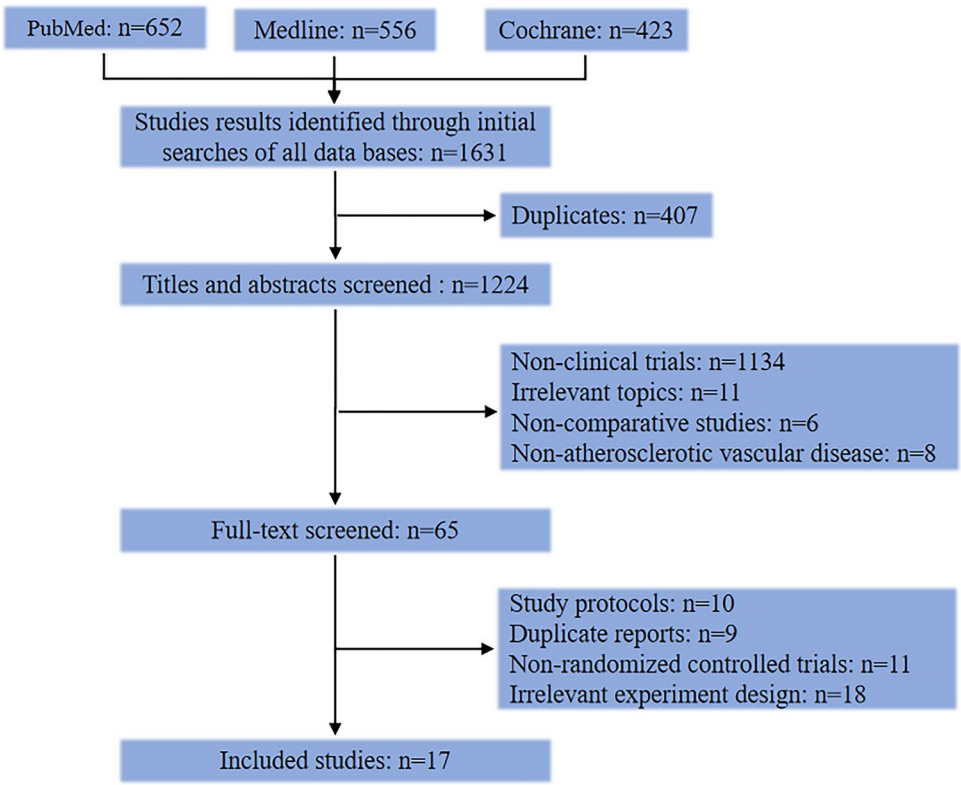

Fig. 1 Flow diagram of included studies

Table 1 Baseline characteristics of the included studies

Study	Year	Phase	Follow-up (mo)	Participants	Number of patients	Intervention	Total daily dose	Standard antiplatelet therapy	Total daily dose
COMPASS	2017	III	23	Stable atherosclerotic vascular disease including coronary artery disease, peripheral arterial disease, or both	27,395	Rivaroxaban	2.5 mg bid	Aspirin alone	Aspirin 100 mg od
COMMANDER HF	2018	III	21.1	Coronary artery disease with worsening chronic heart failure	5022	Rivaroxaban	2.5 mg bid	Aspirin alone or aspirin plus P2Y12-receptor antagonist	Aspirin100mg od
APPRAISE	2009	II	6	Acute coronary syndrome	1715	Apixaban	2.5 mg bid,10 mg od, 10 mg bid, 20 mg od	Aspirin alone or aspirin plus a clopidogrel	Aspirin ≤165 mg
APPRAISE-2	2011	III	8	Acute coronary syndrome	7392	Apixaban	5 mg bid	Aspirin alone or plus any P2Y12-receptor antagonist	Aspirin ≤165 mg
APPRAISE-J	2013	II	6	Acute coronary syndrome	151	Apixaban	2.5 mg bid or 5 mg bid	Aspirin alone or aspirin plus clopidogrel or ticlopidine	Aspirin ≤100 mg/day, clopidogrel 75 mg/day, ticlopidine 200 mg/day
ATLAS ACS-TIMI 46	2009	II	6	Acute coronary syndrome	3491	Rivaroxaban	Total daily dose 5, 10, 15, or 20 mg, od or bid	Aspirin alone or aspirin plus thienopyridine	75–100 mg daily
ATLAS ACS 2–TIMI 51	2012	III	13.1	Acute coronary syndrome	15,526	Rivaroxaban	2.5 mg bid or 5 mg bid	Aspirin alone or aspirin plus clopidogrel or ticlopidine	75–100 mg daily
GEMINI-ACS-1	2017	II	9.7	Acute coronary syndrome	3037	Rivaroxaban	2.5 mg bid	Clopidogrel or ticagrelor	Clopidogrel 75 mg od, ticagrelor 90 mg bid
RE-DEEM	2011	II	6	Acute coronary syndrome	1861	Dabigatran	50 mg, 75 mg, 110 mg, or 150 mg, bid	Aspirin alone or aspirin plus clopidogrel	Aspirin ≤100 mg, clopidogrel 75 mg daily
RUBY-1	2011	II	26	Acute coronary syndrome	1279	Darexaban	5 mg bid, 10 mg od,15 mg bid, 30 mg od, 30 mg bid, or 60 mg od	Aspirin alone or clopidogrel alone or a combination	Aspirin 75–325 mg clopidogrel 75 mg daily
SEPIA-ACS1 TIMI 42	2009	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/h	Aspirin plus clopidogrel	Not reported
TAO	2013	III	1	Acute coronary syndrome	10,572	Otamixaban	Intravenous bolus of 0.080 mg/kg followed by an infusion of 0.140 mg/kg/h	Aspirin plus clopidogrel, prasugrel or ticagrelor	Clopidogrel ≥600 mg

Table 1 (continued)

Study	Year	Phase	Follow-up (mo)	Participants	Number of patients	Intervention	Total daily dose	Standard antiplatelet therapy	Total daily dose
PIONEER AF-PCI	2016	III	12	Non-valvular atrial fibrillation and acute coronary syndrome	2124	Rivaroxaban	2.5 mg bid	Aspirin plus clopidogrel	Aspirin 75–100 mg daily, clopidogrel 75 mg daily
RE-DUAL PCI	2017	III	14	Nonvalvular atrial fibrillation and had acute coronary syndrome or stable coronary artery disease	2725	Dabigatran	110 mg or 150 mg bid	Clopidogrel or ticagrelor alone or plus aspirin	Aspirin ≤100 mg daily, clopidogrel 75 mg daily or ticagrelor 90 mg bid
ENTRUST-AF PCI	2019	III	12	Nonvalvular atrial fibrillation and had acute coronary syndrome or stable coronary artery disease	1506	Edoxaban	30 mg od	Aspirin alone or aspirin plus clopidogrel	Aspirin 100 mg od, clopidogrel 75 mg
AUGUSTUS	2019	III	6	Nonvalvular atrial fibrillation and had acute coronary syndrome or stable coronary artery disease	4614	Apixaban	5 mg bid or 2.5 mg bid	Clopidogrel or prasugrel or ticagrelor	Not reported
ESTEEM	2008	II	6	Acute coronary syndrome	1883	Ximelagatran	24, 36, 48, or 60 mg bid	Aspirin alone	160 mg od

bid twice daily, *od* once daily

power with several 10,000 patients, we also provided net clinical benefit calculations with numbers needed to treat (NNT) and numbers needed to harm (NNH). The NNT of MACE was the smallest among all the efficacy endpoints, while the NNH of intracranial hemorrhage was the largest among all the safety endpoints. These results suggested that the benefits of DOACS combined with antiplatelet therapy for MACE were considerable, and the risk of intracranial hemorrhage was small, which was consistent with our previous conclusions (Fig. 2).

4 Subgroup Analysis of Efficacy and Safety Endpoints

To investigate whether there is a difference in the safety and efficacy of DOACs combined with antiplatelet drugs in patients with stable CAD and ACS, we conducted a subgroup analysis. The studies 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 excluded the above three studies in the following subgroup analysis (see Supplementary Fig. 3A–J in the ESM). 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 MACE

Pooling the data from two studies that included a total of 23,300 patients with stable CAD [29, 30] showed that the addition of DOACs to the antiplatelet therapy significantly reduced the incidence of MACE (RR 0.88; 95% CI 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 also reduced the rate of MACE in patients with ACS (RR 0.91; 95% CI 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 DOACs to antiplatelet therapy did not reduce the incidence of cardiovascular death in patients with stable CAD (RR 0.91; 95% CI 0.82–1.01) [29, 30], $I^2 = 62.6\%$ and ACS (RR 0.89; 95% CI 0.77–1.03) [12–17, 22], $I^2 = 0\%$

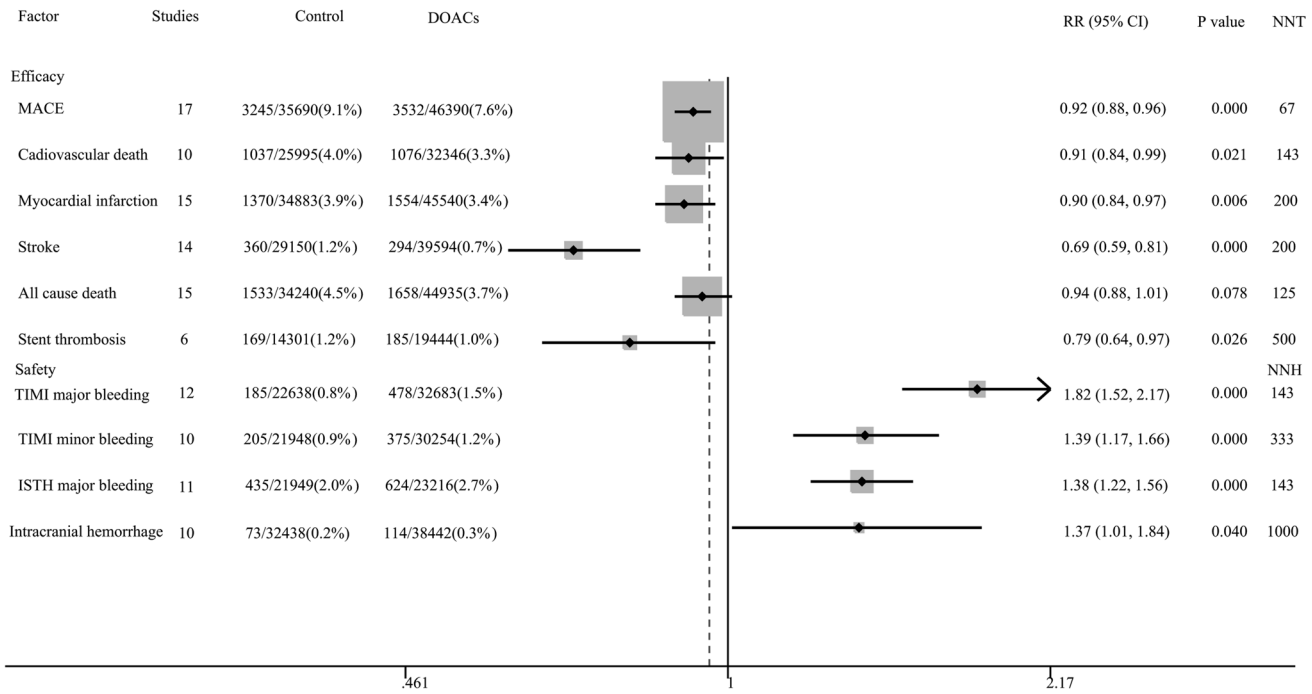

Fig. 2 Efficacy and safety endpoints of DOACs use in patients with CHD. *CHD* coronary heart disease, *RR* risk ratio, *CI* confidence interval, *DOACs* direct oral anticoagulants, *ISTH* International Society on Thrombosis and Hemostasis, *MACE* major adverse cardiovascular events, *NNT* numbers needed to treat, *NNH* numbers needed to harm, *TIMI* thrombolysis in myocardial infarction

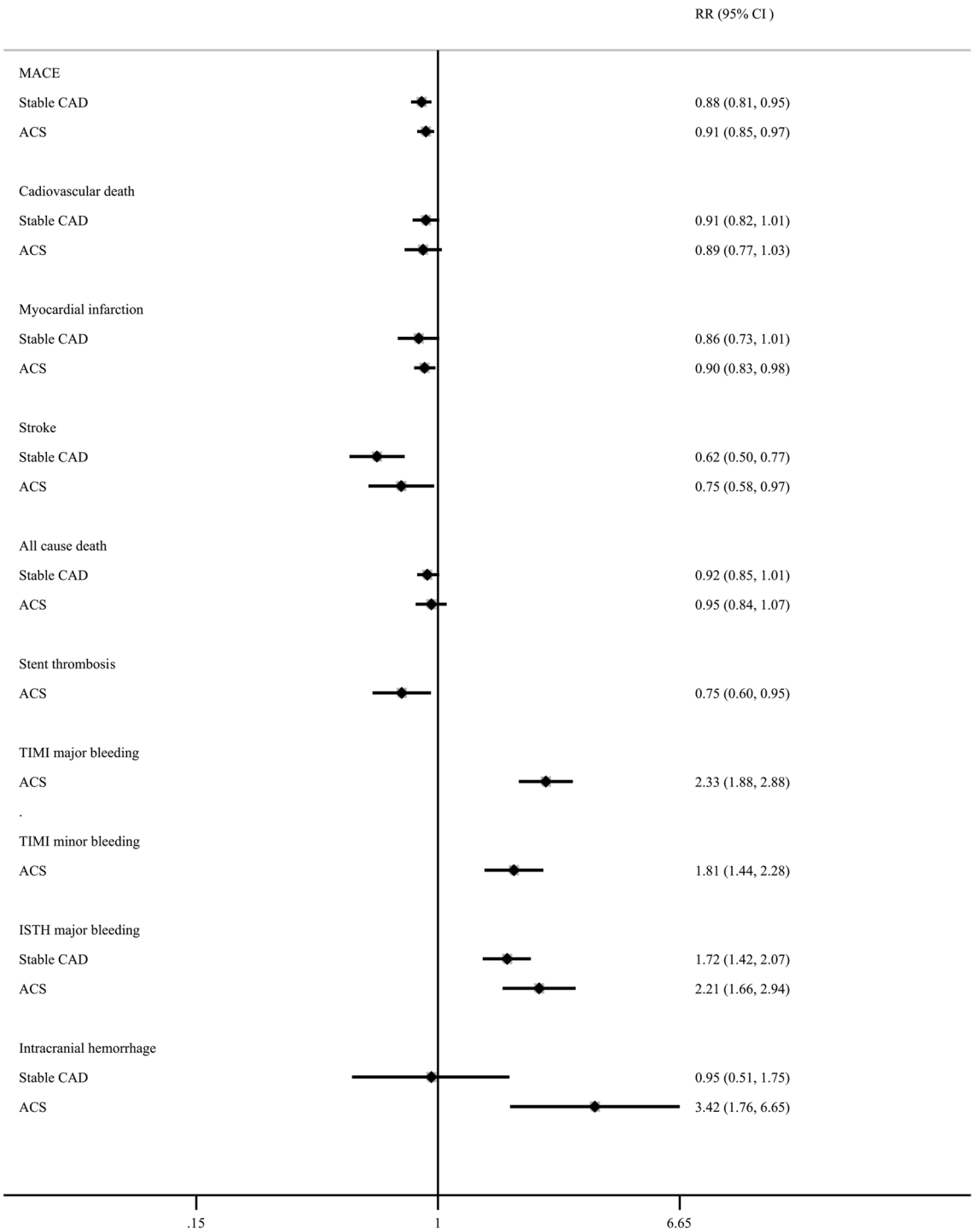

Fig. 3 Subgroup analysis of endpoints of DOACs use in patients with stable CAD and ACS. Effect of adding direct oral anticoagulants to single (aspirin or P2Y12 receptor antagonists) or dual (aspirin and P2Y12 receptor antagonists) antiplatelet therapy on efficacy and safety endpoints after stable CAD and ACS. *ACS* acute coronary syndrome, *CAD* coronary artery disease, *CI* confidence interval, *ISTH* International Society on Thrombosis and Hemostasis, *MACE* major adverse cardiovascular events, *RR* risk ratio, *TIMI* thrombolysis in myocardial infarction

(Fig. 3). There was no significant difference between groups ($p = 0.731$).

4.2.2 Myocardial Infarction

The combined DOACs with antiplatelet therapy did not reduce the occurrence of MI in patients with stable CAD (RR 0.86; 95% CI 0.73–1.01) [29, 30], $I^2 = 0\%$. However, the combined treatment reduced the incidence of MI in patients with ACS (RR 0.90; 95% CI 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 DOACs significantly reduced the incidence of ischemic stroke in patients with stable CAD (RR 0.62; 95% CI 0.50–0.77) [29, 30], $I^2 = 0\%$ and ACS (RR 0.75; 95% CI 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 DOACs to antiplatelet therapy did not decrease all-cause mortality in patients with stable CAD (RR 0.92; 95% CI 0.85–1.01) [29, 30], $I^2 = 71.2\%$ or ACS (RR 0.95; 95% CI 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, 34] showed that additional treatment with DOACs significantly reduced the risk of stent thrombosis in patients with ACS (RR 0.75; 95% CI 0.60–0.95), $I^2 = 0\%$ (Fig. 3).

4.3 Subgroup Analysis of Safety Endpoints

4.3.1 Thrombolysis in Myocardial Infarction (TIMI) Major Bleeding

Data from ten studies [12, 13, 15–22] showed that the DOACs together with antiplatelet therapy significantly increased the risk of TIMI major bleeding in ACS patients (RR 2.33; 95% CI 1.88–2.88), $I^2 = 64.4\%$ (Fig. 3).

4.3.2 TIMI Minor Bleeding

The results from eight studies [12, 13, 16–20, 22] showed that adding DOACs to antiplatelet therapy significantly increased the risk of TIMI minor bleeding in patients with ACS (RR 1.81; 95% CI 1.44–2.28), $I^2 = 46.7\%$ (Fig. 3).

4.3.3 International Society of Thrombosis and Hemostasis (ISTH) Major Bleeding

The addition of DOACs to antiplatelet therapy increased the rate of ISTH major bleeding in patients with stable CAD (RR 1.72; 95% CI 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 DOACs (RR 2.21; 95% CI 1.66–2.94) [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 DOACs did not increase the risk of intracranial hemorrhage in patients with stable CAD (RR 0.95; 95% CI 0.51–1.75) [29, 30], $I^2 = 53.6\%$. However, in patients with ACS, the combined regimen increased the rate of intracranial hemorrhage (RR 3.42; 95% CI 1.76–6.65) [12, 13, 16–18, 20], $I^2 = 0\%$ (Fig. 3). A 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 AF, we performed a subgroup analysis to determine if AF presence influenced the safety effect of the DOACs in patients with CHD. For patients with AF, combined use with DOACs did not increase the risk of TIMI major bleeding (RR 0.75; 95% CI 0.54–1.03), TIMI minor bleeding (RR 0.88; 95% CI 0.67–1.14), and intracranial hemorrhage (RR 0.87; 95% CI 0.41–1.82). However, for patients without AF, there were obvious increased risks of TIMI major bleeding (RR 2.64; 95% CI 2.10–3.31), TIMI minor bleeding (RR 1.98; 95% CI 1.55–2.52), ISTH major bleeding (RR 1.86; 95% CI 1.59–2.18), and intracranial hemorrhage (RR 1.49; 95% CI 1.07–2.07). More importantly, the degree of heterogeneity significantly decreased. Significant differences between subgroups were observed in endpoints of TIMI major bleeding ($p < 0.00001$), TIMI minor bleeding ($p < 0.00001$), and ISTH major bleeding ($p < 0.00001$). Despite the significant differences between the two

subgroups, the overall effect remained unchanged after excluding the results of patients with AF due to the relatively small sample size (see Supplementary Fig. 4A–D in the ESM). Moreover, since time is important for bleeding risk, we provided two different time strata studies with a follow-up of shorter and longer than 1 year. Compared with the results of shorter than 1 year, the medication duration of longer than 1 year reduced the incidence of MACE but significantly increased the incidence of fatal bleeding, such as intracranial hemorrhage (see Supplementary Fig. 5A–D in the ESM).

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 the COMMANDER HF study. Although the combination of rivaroxaban with antiplatelet therapy did not significantly reduce mortality in patients with stable CAD and heart failure, it significantly reduced their risk of ischemic stroke. More importantly, for patients with stable CAD maintaining normal cardiac function, adding rivaroxaban to the antiplatelet regimen also significantly decreased 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, we deleted all phase II studies. Compared with the data before the phase II trials were excluded, the risk of TIMI major bleeding (RR 2.39; 95% CI 1.88–3.02), TIMI minor bleeding (1.87; 95% CI 1.45–2.43), and intracranial hemorrhage (3.61; 95% CI 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 (RR 0.88; 95% CI 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 DOACs and antiplatelet therapy did not reduce the incidence of MACE in patients with stable CAD, all other efficacy outcomes were consistent with previous results (see Supplementary Fig. 6A–E in the ESM).

6 Publication Bias

The Egger's test of the studies included in this meta-analysis 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 [34]. 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 [35, 36] were performed to evaluate the efficacy and safety of DOACs 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 [34]. 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 DOACs significantly increased the risk of intracranial hemorrhage in patients with ACS compared with those with stable CAD. Similarly, our sensitivity analysis suggested that additional treatment of DOACs significantly increased the risk of TIMI major bleeding in patients with CHD after excluding RCT studies [26–28] that included the patients with CHD complicated with AF. The above results are likely to be explained by the fact that both patients with stable CAD and patients with CHD complicated with AF were treated with single antiplatelet therapy combined with DOACs. Thus, the use of a single antiplatelet agent with DOACs may be a more viable choice in patients with CHD, but more clinical trial data is needed to confirm individualized therapy regimens [37–40]. Moreover, Moscucci et al. [41] found that any type of invasive diagnostic or therapeutic procedure including PCI, coronary artery bypass surgery, and intra-aortic balloon pump placement was associated with an increased risk of bleeding in patients with ACS. The use of low-molecular-weight heparin within 48 hours pre-PCI, the longer PCI duration, higher rates of procedural complications including coronary artery dissection with reduced intraprocedural TIMI flow and thrombus formation were identified as significant predictors of bleeding risk in patients with ACS [42]. Thus, compared with patients with stable CAD, in addition to the difference in antiplatelet regimens, PCI-related preoperative anticoagulation, intraoperative operations, and

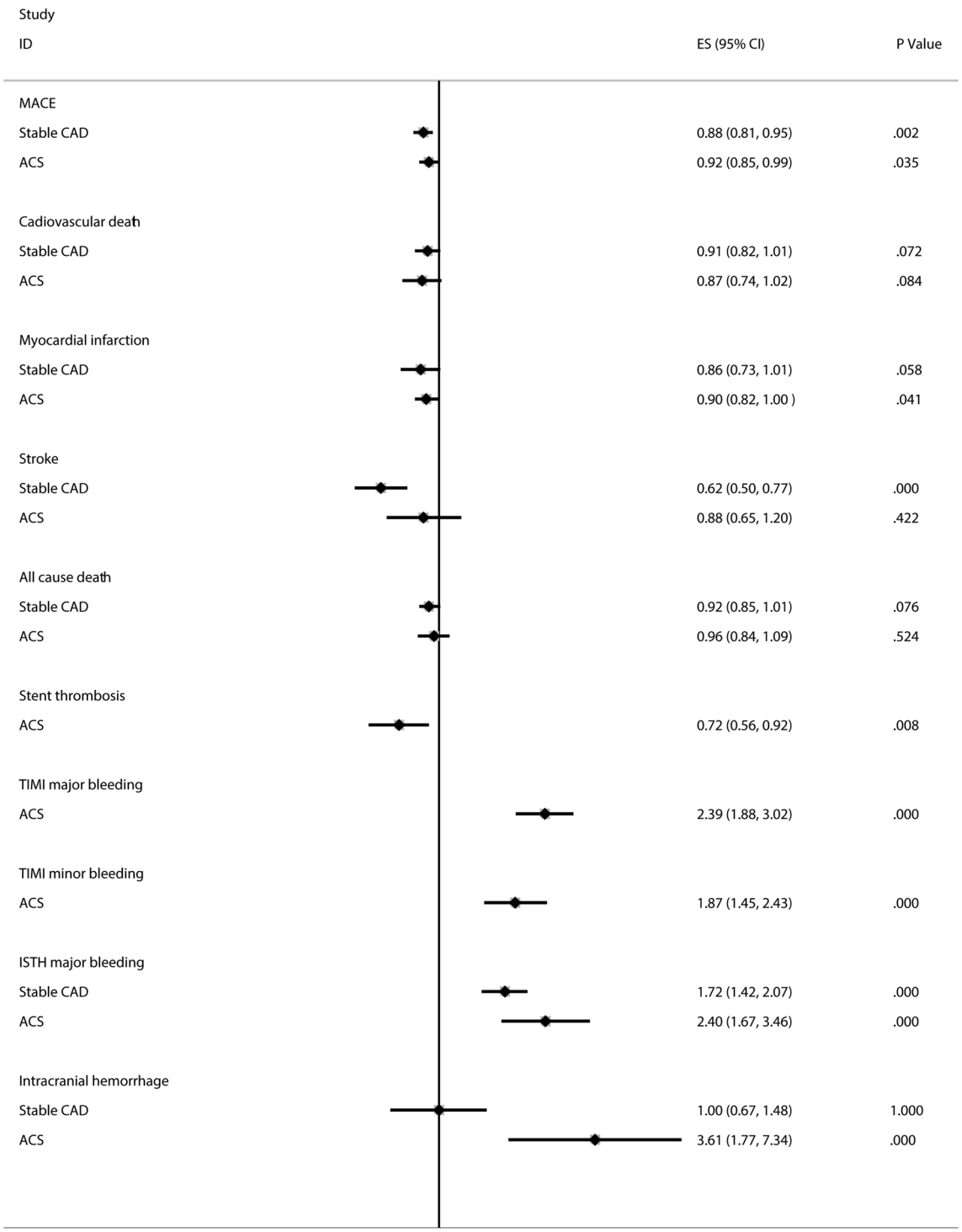

Fig. 4 Endpoints of DOACs use in patients with CHD in a subgroup of phase III studies. Subgroup analysis of efficacy and safety of adding direct oral anticoagulants to single (aspirin or P2Y12 receptor antagonists) or dual (aspirin and P2Y12 receptor antagonists) antiplatelet therapy after stable CAD or ACS in all phase III studies. *ACS* acute coronary syndrome, *CAD* coronary artery disease, *CHD* coronary heart disease, *CI* confidence interval, *ISTH* International Society on Thrombosis and Hemostasis, *MACE* major adverse cardiovascular events, *TIMI* thrombolysis in myocardial infarction

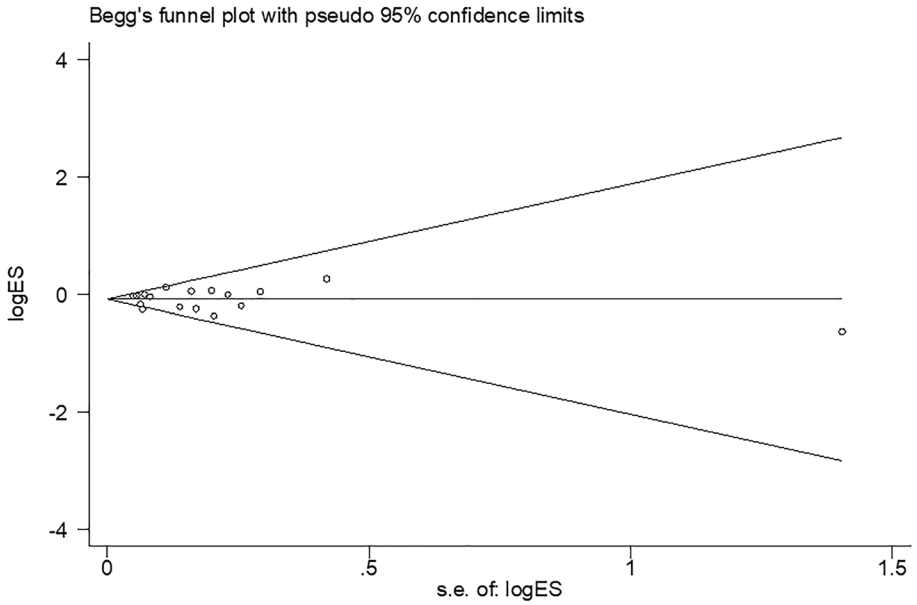

Fig. 5 Funnel plots illustrating meta-analysis of major adverse cardiovascular events

possible postoperative complications in ACS patients may all increase the risk of bleeding.

Additionally, when all the included studies were phase III trials, the combined use of DOACs significantly increased the risk of bleeding in patients with ACS, without improvements in efficacy endpoints, indicating that prolonging the duration of DOACs administration may not benefit patients with ACS but instead increase their risk of bleeding. The overall effects remained unchanged in all phase III 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 DOACs did not decrease the risk of ischemic stroke in patients with ACS after excluding all phase II trials; further studies are needed to determine whether combined DOACs with antiplatelet therapy can reduce the incidence of stroke in patients with ACS.

More importantly, Kupó et al. [43] performed a meta-analysis involving 28 RCTs and 196,761 patients that 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 DOACs when combined with antiplatelet therapy for patients with CHD. Nevertheless, we acknowledge the limitation of analyzing all DOACs together as if they represent a uniform therapeutic approach; thus, we compared the main safety and efficacy endpoints among different DOACs in patients with ACS. Although the results showed that there were no significant differences among the drugs, there should be a further evaluation between single and dual platelet therapy regimens (see Supplementary Fig. 7A–C in the ESM).

The different DOACs 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, 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, other studies have also 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, 44–46]. 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. However, other studies indicated that 2.5 mg twice daily was associated with a reduction in ischemic events, accompanied by increased major or clinically relevant nonmajor bleeding [14, 16, 26]. As for other DOACs, there were no significant differences in drug dosing among studies.

In general, in CHD patients with antiplatelet therapy, DOACs 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 DOAC use in CHD patients. To explore why the benefit observed on MACE by combination therapy was not translated into a benefit on all-cause mortality, we analyzed all included studies with dose comparisons to determine whether drug dose had a significant effect on all-cause mortality. Similar to the results of Cappato et al. [47], our study

showed that low-dose DOACs combined with antiplatelet therapy significantly improved all-cause mortality in CHD patients (RR 0.80; 95% CI 0.71–0.90). However, the combination of high-dose DOACs and antiplatelet drugs did not reduce all-cause mortality (RR 0.94; 95% CI 0.84–1.05) (see Supplementary Fig. 8A–B in the ESM). Since the COMPASS [30] and ATLAS ACS 2–TIMI 51 [12] studies have a relatively large weight, the overall effect mainly depends on the results of the above two studies. However, due to the large sample size, it still strongly suggested that the combination of low-dose DOACs and antiplatelet drugs may be more conducive to reducing all-cause death in patients with CHD.

8 Strengths and Limitations

This meta-analysis was the first to compare the safety and efficacy of DOACs combined with antiplatelet agents in patients with stable CAD and ACS. 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. We separately analyzed the MACE components, that is, cardiovascular death or all-cause mortality, MI, stroke, as well as stent thrombosis in this meta-analysis. Besides, we identified the main source of heterogeneity of some endpoints and significantly reduced the heterogeneity through sensitivity analysis. More importantly, we excluded all phase II studies to make our conclusion more reliable and provided two different time strata studies with a follow-up of shorter and longer than 1 year to explore the effects of drug duration on all endpoints. Finally, we also considered the effects of different drugs and different doses on all endpoints.

This meta-analysis has the following potential deficiencies. First, the main limitation of the meta-analysis is that patient-level data are not available. The lack of these data precludes the evaluation of baseline covariates on outcomes. Besides, the single and dual antiplatelet therapy 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. Moreover, a few studies used vitamin K antagonists [27, 28] as controls rather than a placebo. Although there were significant differences between the placebo-controlled subgroup and vitamin K antagonists-controlled subgroup in the main safety ($p < 0.00001$) and efficacy ($p = 0.02$) endpoints, the overall effect of DOACs combination therapy remained unchanged after excluding the RCTs in the vitamin K antagonists-controlled subgroup (see Supplementary Fig. 9A–B in the ESM). Besides, 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 sample size. Additionally, although we compared the main safety and efficacy endpoints among different DOACs in patients with ACS and the results showed that there were no significant differences among the drugs, published data shows heterogeneity among DOACs, which limits the generalizability of these types of analysis findings because different DOACs are not equal. Moreover, the numbers of patients receiving edoxaban (1506) and dabigatran (3823) were low. Ximelagatran was also not specified as a drug of clinical interest. However, all the results remained unchanged after removing a study (ESTEEM) investigating this agent (see Supplementary Fig. 10A–E in the ESM). Finally, there was no predefined protocol for this review.

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 DOACs to antiplatelet therapy significantly reduced ischemic events in patients with stable CAD and ACS, which may be beneficial for secondary prevention in patients with CHD. Moreover, although combination therapy reduced the incidence of MI in patients with ACS, the bleeding risk, especially intracranial hemorrhage, outweighs the benefit of MACE driven by MI. That is due to combination therapy having 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. DOACs combined with single antiplatelet therapy may be the best option since it considerably reduces the risk of bleeding. Reducing the duration and dose of medication may also be effective ways to reduce the occurrence of fatal 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 remains critical, which is beneficial for maximizing the balance between safety and efficacy for secondary prevention in patients with CHD.

Recent studies have shown that the clinical benefit of DOACs combined with antiplatelet drugs is not significantly related to the weight [47] and gender [48] of CHD patients. In addition, for CHD patients with moderate renal

dysfunction [46], diabetes mellitus [49], and ischemic stroke [50], combined therapy can still effectively improve the incidence of MACEs, especially reducing all-cause death in diabetic patients by more than three times. Moreover, the combination therapy was associated with a great reduction in MACEs, although it did not reduce the graft failure in patients with recent CABG surgery [45]. The above studies have further confirmed that the dual antithrombotic approach is critical to the prognosis of patients with CHD, especially when combined with other organ damage or high-risk diseases.

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Declarations

Authors' contributions All authors participating in this work are listed and we approve this version of the manuscript. L.L. and J.H. conceived the study and performed data extraction. Y.T. and H.L. repeatedly verified the data. L.L. critically revised the first draft. The supervision and editing were done by D.X.

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