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Original Research

A Systematic review on randomized clinical trials for direct oral anticoagulant in subjects with acute coronary syndrome: primary and secondary outcomes

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Abstract

Background: In recent years, direct oral anticoagulant (DOAC) has been projected for secondary prevention of recurrent ischemic events post-acute coronary syndrome (ACS). However, there is still uncertainty about the efficacy/safety of DOACs in sub-populations. We hypothesized that for those with ACS, the use of DOAC in addition to antiplatelet therapy proves non-inferiority/superiority/or safety in terms of reduction in ischemic events or bleeding. This review aimed to evaluate the efficacy and safety of DOAC in addition to single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT) as antithrombotic therapy in subjects with ACS. **Methods:** We have followed the methods of the PRISMA guideline to report the systematic review findings of included randomized controlled trials (RCTs), including adult patients with ACS. The intention to treat analysis was evaluated in all included trials, and the adverse events were reported. **Findings:** A total of 13 trials (105322 subjects) were included in this systematic review. In subjects (both genders) with STEMI, the combination of rivaroxaban and aspirin (DATT) was associated with lower mortality in comparison with aspirin alone with or without PCI. Adding low-dose rivaroxaban to aspirin improved the primary efficacy outcome in subjects with a previous MI and those without. In subjects with STEMI or NSTEMI with or without PCI, the effects of DATT (rivaroxaban plus aspirin) were inferior to SAPT (aspirin therapy) for the primary safety endpoint and superior for primary efficacy outcome (MACE, CV death, MI, stroke). The twice-daily 2.5 mg dose of rivaroxaban reduced cardiovascular death rates but increased major bleeding rates. In subjects with AF who had successful PCI, a full-dose anticoagulation therapy with edoxaban 60 mg OD plus a P2Y12 inhibitor is non-inferior to triple antithrombotic therapy (TATT) with VKA about the risks of major or non-major bleeding events. **Implications:** Compared with TATT, DATT is associated with lower bleeding risks and mortality in subjects with ACS. While for subjects with ACS (STEMI/NSTEMI) with/without PCI, DATT (rivaroxaban plus aspirin) was superior to SAPT for primary efficacy outcome (MACE, CV death, MI, stroke). Nevertheless, based on current guidelines for subjects with ACS and co-existing AF, DOAC should be preferred over VKA supported by a favorable risk/benefit profile. The newer and more potent P2Y12 inhibitors (ticagrelor and prasugrel) are recommended over the former clopidogrel. Further, research needs to address the evidence-based indications of the DOAC members in subjects with specific comorbidities (e.g., AF, HF) and the transitioning between antithrombotic regimens.

Keywords: acute coronary syndrome (ACS); atrial fibrillation; direct oral anticoagulant (DOAC); dual antiplatelet therapy (DAPT); meta-analysis; non–ST-segment elevation myocardial infarction (NSTEMI), percutaneous coronary intervention (PCI); ST-segment elevation myocardial infarction (STEMI), secondary prevention; single antiplatelet therapy (SAPT)

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BACKGROUND

The standard antithrombotic therapy for post-acute coronary syndromes (ACS) is dual antiplatelet therapy (DAPT). However, preventing recurrent ischemic events is still challenging. Despite the evidence for the benefits of direct-acting oral anticoagulant (DOAC) in managing ACS, there are challenges in selecting the appropriate DOAC, the optimal duration, and the subgroup of patients that will benefit the most in a clinical setting. This is particularly evident in specific subpopulations with a compelling indication for DOAC in ACS, such as subjects with stable atherosclerotic cardiovascular disease (ASCVD), co-existing atrial fibrillation (AF), recurrent ischemic events, with/without percutaneous coronary intervention (PCI), cancer, and heart failure (HF).

The APPRAISE-J trial in the Japanese population did not provide any superiority in terms of bleeding and was terminated, as were the prior APPRAISE-1 and APPRAISE-2 trials.[1,2,3] A small dose of rivaroxaban 2.5 mg BID in addition to SAPT or DAPT represents the most successful option of appropriate DOCA in ACS. The dual or triple combined antithrombotic regimen (DATT, TATT) has provided a significant reduction in major adverse cardiovascular events (MACE) composite of cardiovascular death, myocardial infarction (MI), or stroke (9.1 versus 10.7%, hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.72–0.97, P = 0.02) with no increase in fatal bleeding.[4,5,6]

An earlier study (2011), with four doses (50, 75, 110, and 150 mg) of the DOAC dabigatran among1861 ACS subjects on DAPT, concluded that the triple regimen (DAPT plus DOAC) was associated with a dose-dependent increase in bleeding events (major and minor). The results showed HR 1.77 [95% CI 0.70-4.50] for 50 mg, HR 2.17 [0.88-5.31] for 75 mg, HR 3.92 [95% CI 1.72-8.95] for 110 mg, and HR 4.27 [1.86-9.81] for 150 mg respectively. Further, significantly reduced coagulation activity in subjects with a recent MI was reported for the triple regimen.[7]

A network systematic meta-analysis (2020) was conducted on six RCTs, including DOAC for ACS with major MACE and bleeding outcomes. It comprised 32,261 subjects (mean follow-up was 8.5 months) receiving either one of four regimens (DAPT; DOAC plus DAPT [TATT]; low-dose DOAC plus DAPT [TATT]; and low-dose DOAC plus SAPT [DATT]). The regimen of low-dose DOAC plus DAPT (TATT) had the highest probability of being the best. In contrast, the regimen of DAPT had the highest likelihood of being the best regarding significant bleeding.[8] Of the newer drugs studied, the antiplatelet agents, cangrelor and vorapaxar, and DOAC rivaroxaban (at a low dose) have shown promise for the reduction of ischemic events when administered during and in the acute phase following ACS in addition to standard treatment. However, a significantly increased bleeding risk was noted.[9]

The WOEST-3 trial is set to study the optimal antithrombotic strategy in subjects with AF undergoing PCI (NCT04436978). WOEST-3 is a multicenter, open-label, phase 4 RCT that will enroll 2000 subjects undergoing PCI who have previously or newly diagnosed AF and indication for DOAC within 72 hours after PCI and are randomly assigned to receive edoxaban plus P2Y12 inhibitor, aspirin limited to in-hospital use or up to 30 days in selected high-risk patients. The primary efficacy endpoint is a composite of all-cause death, MI, stroke, systemic embolism, or stent thrombosis at six weeks after PCI. Another primary safety endpoint is major or clinically relevant non-major (CRNM) bleeding, as defined by the International Society on Thrombosis and Hemostasis (ISTH) at six weeks after PCI.[10] Optimal antithrombotic therapy for subjects with ACS concomitant with AF and implanted with new-generation drug-eluting stent (DES). The (OPTIMA-3, 4) sub-study is a multi-center RCT that enrolls 3746 patients with ACS concomitant non-valvular atrial fibrillation (NVAF) and undergoing DES implantation at 70 centers nationwide in China and contains two sub-studies.[11] The study will be completed in 2024.

In the OPTIMA-3 sub-study, 2274 subjects who choose warfarin as an anticoagulant will randomly receive triple antithrombotic therapy (warfarin with targeted target international normalized ratio-INR 2.0-3.0, clopidogrel 75 mg OD and aspirin 100 mg OD [DAPT]) for one month or six months in a 1:1 ratio then quit aspirin till 12 months after PCI. The primary endpoint of the OPTIMA-3 is a composite of cardiovascular death, MI, ischemic stroke, systemic thromboembolism, and unplanned revascularization up to 12 months; the major secondary endpoint is the ISTH major bleeding or CRNM bleeding. In the OPTIMA-4 sub-study, 1472 subjects who prefer dabigatran will be randomly assigned in a 1:1 ratio to dual antithrombotic therapy (DATT) of dabigatran 110 mg BID with ticagrelor 90 mg BID daily or with clopidogrel 75 mg OD for 12 months after PCI. The primary safety endpoint of the OPTIMA-4 is ISTH major bleeding or CRNM bleeding at 12 months; the primary efficacy endpoint is a composite of cardiovascular death, MI, ischemic stroke, systemic thromboembolism, and unplanned revascularization.[11]

Rationale

In recent years, DOAC has been used increasingly in the secondary prevention of recurrent ischemic events post-ACS. However, there is still uncertainty in the efficacy/safety of DOAC in sub-populations such as subjects with stable ASCVD, AF, with/without recent PCI, AF with concomitant artificial heart valves, and cancer-associated thromboembolism. There is growing evidence for the use of DOAC in ACS; however, a more robust systematic review can provide more insights into the benefits of the emerging DOAC use in ACS.

The aim and specific objectives of the current systematic review questions

The current systematic review evaluated the evidence for the effective and safe use of DOAC for subjects with ACS who

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received single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT) compared to those who received SPAT and DAPT alone. Strategies, including DOACs post-ACS, have been studied in recent randomized clinical trials (RCTs) to decrease thrombotic events further.

Specific review questions

1. In subjects with any type/stage of ACS: - Does the use of DOAC (intervention) such as apixaban, betrixaban, dabigatran, darexaban, edoxaban, and rivaroxaban in addition to antiplatelet therapy (comparators) prove non-inferiority or superiority over comparators in terms of reduction in ischemic events or bleeding (outcome)?

2. Does the use of DOAC (apixaban, betrixaban, dabigatran, darexaban, edoxaban, and rivaroxaban) in addition to antiplatelet therapy prove better efficacy/safety profile over comparators in subjects with any type/stage of ACS?

3. Are there any differences aligned between the members (apixaban, betrixaban, dabigatran, darexaban, edoxaban, and rivaroxaban) based on efficacy, precautions, and safety profile and ACS type (i.e., ST-segment elevation myocardial infarction [STEMI-ACS] versus non–ST-segment elevation myocardial infarction [NSTEMI-ACS]), with/without PCI?

Operational definition of terms used in the review

We have critically appraised the role of DOAC in addition to SAPT or DAPT as antithrombotic therapy. The combined DOAC plus SAPT will be denoted as dual antithrombotic therapy [DATT], and the combined DOAC plus DAPT will be marked as triple antithrombotic therapy [TATT]) in subjects with ACS, with and- without coexisting AF or HF, with and without prior PCI.

Ethics approval

Ethics approval was not required for this type of systematic review.

METHODS

The current systematic review strictly follows the PRISMA checklist at [add reference]. The previously developed protocol registered on the PROSPERO website, [https://www.crd.york.ac.uk/prospero/#myprospero] ICD number CRD42020201605, and published elsewhere.

Data source and search strategy

We searched EMBASE, Google Scholar, and Medline to identify relevant literature via EBSCO-host, PubMed, and Web-Of-Science databases [Figure 1 diagram flow]. We have used the following medical subject headings (MeSH) based on PICOs to identify relevant trials:

“acute coronary syndrome (ACS); STEMI”; NSTEMI”; “heart failure (HF)”; “atrial fibrillation (AF)”; “(percutaneous coronary intervention (PCI)”; “direct oral anticoagulant (DOAC)”; “apixaban”; “betrixaban” “dabigatran”; “darexaban”; “edoxaban”; “rivaroxaban”; “dual antiplatelet therapy (DAPT)”; “single antiplatelet therapy (SAPT)”; “vitamin K-antagonist (VKA)”; “placebo”; “comparator”; “combined DOAC plus SAPT=dual antithrombotic therapy (DATT)”; combined DOAC plus DAPT =triple antithrombotic therapy (TATT)”; “ major adverse cardiovascular events (MACE)”; “cardiovascular death,” “myocardial infarction (fatal/nonfatal)”; “stroke (fatal/nonfatal)”; “primary percutaneous coronary intervention (pPCI)”; “hospitalization”; “readmission”; “efficacy”; “safety”; “(major bleeding)”; Randomized controlled trials (RCTs); Systematic review; and Safety (2009 -2020). The included RCT-s supplementary material, citations, author’s emails, and any relevant associated documents utilized as appropriate.

Study selection

The **eligibility criteria** followed the pneumonic PICOs (participants, interventions, comparisons, outcomes, and study design). The **types of participants/population (**subjects diagnosed with ACS any type STEMI/NSTEI/unstable angina [UA]**)** who have received DOAC (apixaban, dabigatran, darexaban, edoxaban, and rivaroxaban) plus SAPT and DAPT (**interventions),** as compared to SAPT/DAPT alone, **(comparators)**. The primary/secondary outcome was the efficacy endpoint of minimization of death, MI (fatal/nonfatal), stroke (fatal/nonfatal), and their composite (**outcome**). The primary/secondary safety endpoint was major bleeding (fatal or nonfatal) and NCRM bleeding.

The trials were published in English, full-text articles, and primary/secondary outcomes reported the status of MACE/bleeding conducted on humans during the last 11 years (2009-2020). We have excluded all other study design types, trials that evaluated other primary/secondary outcomes, and trials on pediatrics, pregnant women, and transplant subjects. The search was performed on the known databases, out/inpatient subjects (hospitalized or not hospitalized).

Data extraction and quality assessment

Data were extracted in duplicate, and the Quality of RCTs was assessed using the five-point scale outlined by Jaded.[12,13] The quality evidence is determined using the GRADE of the respective RCT depicted in [Appendix 1]. The PRISMA flow diagram for systematic review included database searches, as reported in [Appendix 2]. The reporting of trials is exhibited in [Appendix 3]. The registration status of the included trials (registration of the RCT in NRC) is depicted in [Appendix 4].

Data analysis and synthesis

A total of 13 RCTs were included in this systematic review. The PICOS were extracted for each trial. The superiority, non-inferiority, and bleeding events (a **measure of effect)** are reported as relative risks, odds ratios, risk differences, and HR for the number needed to treat the population. The results were summarized thematically as ACS with STEMI, ACS with STEMI/NSTEMI underwent PCI, and ACS with AF.

Operational definitions

CAD is characterized by atherosclerosis in the coronary arteries (can be asymptomatic). In contrast, ACS always presents with a symptom, such as unstable angina (UA), and is frequently

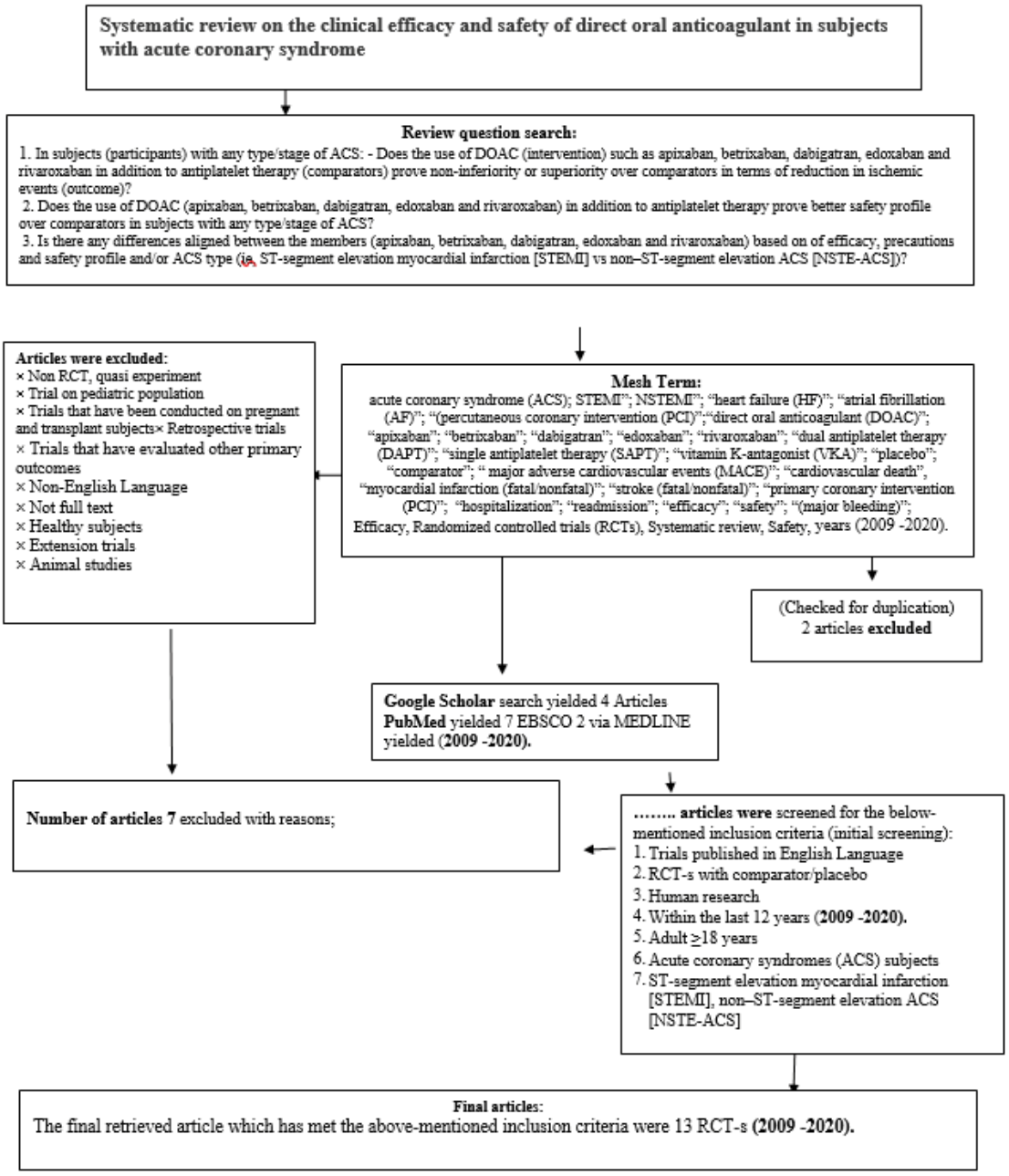

Figure 1. Flow diagram of included and excluded articles in the current systematic review

associated with myocardial infarction (MI) regardless of the presence of CAD.

CAD: coronary artery disease defined as patients who have either myocardial infarction within 20 years, multi-vessel coronary artery disease (CAD), history of stable or unstable Angina (UA), previous multi-vessel percutaneous coronary Intervention (PCI), or previous multi-vessel coronary artery bypass graft surgery (CABG).[14-16]

CRNM: clinically relevant non-major bleeding,[1,18,20] as defined by the International Society on Thrombosis and Hemostasis (ISTH).

DAPT: dual antiplatelet therapy (aspirin plus $P2Y_{12}$ inhibitor).[7,15-18,20,22]

DATT: The combined DOAC plus SAPT will be denoted as dual antithrombotic therapy (DATT).[14-18,20-22]

ISTH: International Society on Thrombosis and Hemostasis.[1,7,14-21]

SAPT: Single antiplatelet therapy.[7,15-18,20,21]

TATT: The combined DOAC plus DAPT is denoted as triple antithrombotic therapy (TATT).[21]

TIMI: thrombolysis in myocardial infarction.[4,5,17]

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RESULTS

We have reported and interpreted 13 RCTs in the current systematic review.[1,4,5,7,14-21] based on the different types of ACS. Our reporting involved three thematic categorizations of the included RCTs based on the type of ACS: subjects mainly with STEMI or with either STEMI/NSTEMI/UA who have undergone PCI and subjects with STEMI or NSTEMI with AF. For the population (P), we have retrieved thirteen trials based on the PICO approach in terms of the characteristics of the population (P). The total population of the RCTs included in the current systemic review was 99735 subjects. There were some minor discrepancies between the recruited subjects. The population ranges from 18 to 65 years.[1,7,14-18,21] and a maximum of 75 years.[4,5,19,20,22] Duration of ACS ranges between 6 months.[4,7,16-18] and one year in most trials. Some subjects diagnosed with ACS (STEMI or NSTEMI) had undergone PCI.[1,4,5,7,16-18] At the same time, some trials included subjects diagnosed with ACS or peripheral artery disease (PAD).[15-16] and mainly with STEMI.[14,15] Other included subjects were diagnosed with ACS (STEMI or NSTEMI) with AF.[19-22] The minimum and maximum sample sizes in the trials were 90 and 24824 subjects, respectively.[1,15] Some international trials were conducted in 602 centers in 33 countries,[15] and others in 321 clinical centers in 21 countries.[21]

The intervention and comparators (I and C) Regarding the intervention in subjects mainly with STEMI, it was administered as a combination (DOAC plus SAPT) of rivaroxaban 2.5 mg BID plus aspirin 100 mg OD versus aspirin 75-100 mg OD.[14,15] The intervention for subjects with ACS with either STEMI or NSTEMI and who underwent PCI was a combination (DOAC plus SAPT) of rivaroxaban 2.5 mg BID plus aspirin 100 mg OD.[16] Monotherapy with rivaroxaban 2.5 mg or 5 mg, BID[5] or rivaroxaban 2.5 mg BID,[17]or rivaroxaban 5 mg or 20 mg OD.[4] Other DOAC included apixaban 2.5 mg or 5 mg BID[1] dabigatran 50, 75, 110, and 150 mg BID[7] or darexaban 5 mg BID, 10 mg OD,15 mg BID, 30 mg OD, 30 mg BID; and 60 mg OD).[18] The comparators were either aspirin 75 -100 mg OD.[4,16-18] or placebo (aspirin 100 mg, clopidogrel 75 mg OD).[1,5,7] For the subjects with STEMI or NSTEMI with AF, the intervention was a combination (DOAC plus SAPT) of rivaroxaban 2.5 mg BID plus aspirin 100 mg OD.[21] Monotherapy with rivaroxaban 10 mg or 15 mg OD,[22] apixaban 2.5 mg BID or (VKA),[19] and edoxaban 60 mg OD plus P2Y 12 inhibitor.[20] The comparators were either aspirin 75 -100 mg OD [19, 20] or SAPT (aspirin 81, 100 mg, clopidogrel 75/50 mg or prasugrel 3.7/2.5 mg OD)[22] or TATT as VKA OD (doses adjusted to INR) plus DAPT (aspirin 75 to 100 mg OD and P2Y 12 inhibitor).[21] The entire details of the included thirteen trails are depicted in [Tables 1a, 1b, and 1c].

The other results (primary/secondary) of trials were categorized based on subjects with STEMI or STEMI/NSTEMI who underwent PCI and STEMI/NSTEMI with atrial fibrillation. The primary efficacy outcomes were reported in the trials for subjects with STEMI.[14,15] For subjects with STEMI/NSTEMI and who underwent PCI, the primary efficacy outcomes were reported in the trials.[5,16,17] Finally, the primary efficacy outcomes were reported in the trials for subjects with STEMI/NSTEMI/AF.[22] In the trials for subjects with STEMI, the primary safety outcomes were reported in two trials.[14,15] In the trials for subjects with STEMI/NSTEMI who underwent PCI, the primary safety outcomes were reported trials.[1,4,5,7,16-18] Finally, in the trials for subjects with STEMI/NSTEMI/AF, the primary safety outcomes were reported trials.[19-22] There are no trials for subjects with STEMI with secondary efficacy outcomes reported. In the trials for subjects with STEMI/NSTEMI and who underwent PCI, the secondary efficacy outcomes were reported in four trials.[1,4,7,18] Finally, in the trials for subjects with STEMI/NSTEMI/AF, the secondary efficacy outcomes were reported in three trials.[19-21] No trials for subjects with STEMI and secondary safety outcomes were reported. There are no trials for subjects with STEMI/NSTEMI who underwent PCI with secondary safety outcomes.

The findings of the efficacy and safety of the 13 trials

Subjects mainly with STEMI

Yan Liang (2020) (COMPASS) conducted a multicenter, double-blind, placebo-controlled RCT in 18278 subjects randomized to two groups: group one, 9152 subjects received (Rivaroxaban 2.5 mg BID plus aspirin 100 mg OD. In group two, 9126 subjects received 100 mg of aspirin OD. The combination DATT (DOAC plus SAPT) was superior to the SAPT for the primary efficacy outcome of CV events such as death, stroke, and MACE (women: 3.8% versus 5.2%, HR 0.72, [95% CI 0.54–0.97]; men: 4.2% versus 5.5%, HR 0.76, [95% CI 0.66–0.89]; P interaction 0.75). For the primary safety outcome, major bleeding (women: 3.1% versus 1.4%, HR 2.22, [95% CI 1.42– 3.46]; men: 3.2% versus 2.0%, HR 1.60, [95% CI 1.29–1.97]; P interaction 0.19).[14]

Stuart J Connolly (2017) (COMPASS-PCI) performed a multicenter, double-blind, placebo-controlled RCT in 24824 subjects who have had CAD (ACS or PAD) with a previous MI in the past 20 years. Subjects were randomly assigned (1:1:1) to receive rivaroxaban (2.5 mg orally BID) plus aspirin (100 mg OD) DAPT, compared with rivaroxaban alone (5 mg orally BID) DOAC, or aspirin alone (100 mg orally OD) SAPT. The DAPT reduced the primary efficacy outcome more than SAPT (347 [4%] of 8313 versus 460 [6%] of 8261; hazard ratio [HR] 0·74, 95% CI 0·65–0·86, P< 0·0001). DAPT resulted in the primary safety outcome more major bleeds than SAPT (263 [3%] of 8313 versus 158 [2%] of 8261. The HR 1·66, 95% CI 1·37–2·03, P <0·0001), and similarly, more bleeds were seen in the DOAC group than in the SAPT (236, [3%] of 8250 versus 158 [2%] of 8261; HR 1·51, 95% CI 1·23–1·84, P<0·0001. There was a significant net benefit in favor of DATT (SAPT plus DOAC) when compared with SAPT (aspirin alone) for reduced mortality (262 [3%] of 8313 versus 339 [4%] of 8261; HR 0·77, 95% CI 0·65–0·90, P=0·0012).[15] The results of outcomes are shown in [Table 2].

Subjects with STEMI or NSTEMI and underwent PCI

Bainey (2020) conducted a double-blind RCT (COMPASS-PCI) in 27395 subjects with CAD. Subjects received DATT (Rivaroxaban 2.5 mg or 5 mg BID plus aspirin 100 mg OD), compared with aspirin 100 mg OD with a matching placebo. For the primary safety outcome, in comparison with aspirin, the DATT resulted in more significant bleeds irrespective of previous PCI (PCI:

Table 1a. The characteristics [**PICOs**]* of the RCT included in the current systematic review for DOAC plus SAPT or DAPT in subjects with mainly STEMI [14,15]

Author [Reference]	**Article title**	**Study design**	**Target population (P)**	**Investigated drug (Intervention) (I)**	**Comparator (C)**	**Trial stated outcome measure (O)**
Yan Liang, et al. 202[014]	Efficacy and safety of Rivaroxaban plus Aspirin in women and men with chronic coronary or peripheral artery disease.	Multicenter, double-blind, randomized, placebo-controlled.	- 18278 patients - 4048 were women and 14230 were men. - Compared with men, women were older (69.0 ± 8.0 years vs. 68.0 ± 7.9 years). - Women likely to be white, had a higher prevalence of hypertension, baseline total cholesterol level, diabetes, PAD, prevalence of moderate or severe renal dysfunction and lower prevalence of CAD history. - Women were more likely never to have used tobacco.	- Rivaroxaban2.5mg BID daily plus aspirin 100mg OD daily.	-Aspirin 100 mg OD.	**Primary safety outcome:** The modification of the ISTH major bleeding. **Primary efficacy outcome** The prevention of CV death, stroke, or MI, ischemia.
Stuart J Connolly; et al. 2017[15]	Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial	- Male and female. - Patients aged at least 65 years - Diagnosed patients with CAD had to have had a MI in the past 20 years, or (NSTE)-ACS or (STE)-ACS - Number in ITT 23824 - Rivaroxaban (2·5 mg) plus aspirin (100 mg)8313 - Rivaroxaban alone (5 mg)8250 - aspirin alone (100 mg).8261	- Rivaroxaban (2·5 mg orally BID) plus aspirin (100 mg OD)	- Rivaroxaban alone (5 mg BID plus aspirin placebo OD), or aspirin alone (100 mg OD plus rivaroxaban placebo BID)	**Primary safety outcome:** Incidence of fatal bleeding, symptomatic bleeding into a critical organ or area. **Primary safety outcome:** The composite of all-cause mortality, stroke, CV death, CHD, MI, UA and acute limb ischemia.

Table 1b. The characteristics [**PICOs**]* of the RCT included in the current systematic review for DOAC plus SAPT or DAPT in subjects with STEMI or NSTEMI and underwent PCI with ACS [1,4,5,7, 16-18]

Author [Reference]	**Article title**	**Study design**	**Target population (P)**	**Investigated drug (Intervention) (I)**	**Comparator (C)**	**Trial stated outcome measure (O)**
Hisao Ogawa; et al. 2013,[1]	Randomized, Double-Blind Trial to Evaluate the Safety of Apixaban with Antiplatelet Therapy After Acute Coronary Syndrome in Japanese Patients (APPRAISE-J).	Phase II, randomized, double-blind, placebo-controlled study.	- Male and female. - Patients aged ≥20 years - Diagnosed (STE)-ACS within 7 days with symptoms of MI lasting ≥10min and one of troponin T or I, or creatinine kinase-MB above the upper limit of normal or ST deviation >0.1mV (1.0mm) - Number in ITT 90 (Rivaroxaban 2.5 mg) mg 19 (Rivaroxaban 5.0 mg): 50 Number in ITT (Placebo): 21	- Apixaban 2.5 mg BID. - Apixaban 5mg BID.	- Placebo (aspirin; clopidogrel or ticlopidine) aspirin; 100 mg orally OD). clopidogrel was 75 mg (loading doses of 300 – 600 mg).	**Primary safety outcome:** Incidence of major or clinically relevant non-major (CRNM) bleeding within 12 months, TIMI, ISTH. **Secondary efficacy outcome** The composite of all-cause mortality, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.

J L Mega, et al. 2009[4]	Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial.	Randomized, double-blind, placebo-controlled, phase II, dose-escalation study	- Adults aged 18–75 years and older than 75 years. - Diagnosed with STEMI or non-STEMI or UA. - Number in ITT 3491 -761 in stratum 1 (aspirin only) (508 randomized to rivaroxaban and 253 randomized to placebo). -2730 in stratum 2 aspirin + thienopyridine (1823 randomized to rivaroxaban and 907 randomized to placebo).	Rivaroxaban (at doses 5–20 mg) given OD or the same total daily dose given BID daily.	- Aspirin (75–81 mg daily) only or aspirin plus a thienopyridine	**Primary safety outcome:** Clinically significant bleeding (TIMI major, TIMI minor). **Secondary efficacy outcome:** The time to death, MI, stork and severe recurrent ischemia

Table 1c**.** The characteristics [**PICOs**]* of the RCT included in the current systematic review for DOAC plus SAPT or DAPT in subjects with STEMI or NSTEMI and underwent PCI with ACS [1,4,5,7,16-18]

Author [Reference]	**Article title**	**Study design**	**Target population (P)**	**Investigated drug (Intervention) (I)**	**Comparator (C)**	**Trial stated outcome measure (O)**
Jessica L. Mega; et al. 2012, [5]	Rivaroxaban in Patients with a Recent Acute Coronary Syndrome	Randomized, double-blind, placebo-controlled, event-driven trial	- Male and female. - Ages (≥18 years of age) - Diagnosed with (NSTE)-ACS or (STE)-ACS within the last 14 days, or UA. - Follow-up duration was13 months and up to 31 months - Number in ITT 10350 (Rivaroxaban 2.5 mg) mg 5176 (Rivaroxaban 5.0 mg): 5174 Number in ITT (Placebo): 5176	- Rivaroxaban 2.5 mg or 5.0 mg, BID.	- Placebo (aspirin; clopidogrel or ticlopidine) aspirin; 100 mg orally OD). clopidogrel was 75 mg although loading doses of 300 – 600 mg)	**Primary safety outcome:** Incidence of TIMI major bleeding **Primary efficacy outcome:** The composite of all-cause mortality, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.
Jonas Oldgren; et al. 2011, [7]	Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial	Multi-center, prospective, randomized, double-blind, placebo-controlled, dose-escalation trial	- Male and female - Aged 18 or older years - Diagnosed with (NSTE)-ACS or (STE)-ACS, MI within the last 14 days - Number in ITT 1878 (Intervention): 1505 Number in ITT (Placebo): 373	- Dabigatran 50 mg, 75 mg, 110 mg, 150 mg BID	- Placebo (aspirin ≤100 mg; clopidogrel was 75 mg although loading doses of 300 – 600 mg)	**Primary safety outcome:** Incidence of TIMI major bleeding, ISTH. **Secondary efficacy outcome:** The composite of all-cause mortality, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.
Kevin R; et al. 2020 [16]	Rivaroxaban Plus Aspirin Versus Aspirin Alone in Patients with Prior Percutaneous Coronary Intervention (COMPASS-PCI)	Randomized trial with a 3 x 2 partial factorial design, double- blind.	- Male and female. - Number in ITT 27395 - Patients aged 65 years or older - Diagnosed with stable CAD or PAD	- Rivaroxaban 2.5 mg BID daily plus aspirin 100 mg OD.	- Aspirin 100 mg OD.	**Primary safety outcome:** Incidence of TIMI major bleeding. **Primary efficacy outcome:** Composite consisting of the first occurrence of CV death, MI, or stroke (ischemic or hemorrhagic). **Secondary efficacy outcome:** All-cause mortality

Table 1d. The characteristics [**PICOs**]* of the RCT included in the current systematic review for DOAC plus SAPT or DAPT in subjects with STEMI or NSTEMI and underwent PCI with ACS [1,4,5,7,16-18]

Author [Reference]	**Article title**	**Study design**	**Target population (P)**	**Investigated drug (Intervention) (I)**	**Comparator (C)**	**Trial stated outcome measure (O)**
E Magnus Ohman, et al. 2017[17]	Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double- blind, multicenter RCT	A double-blind, multicenter, randomized trial.	- Male and female. - Patients aged ≥65 year. - Diagnosed with UA–NSTEMI – STEMI. Median duration of treatment with blinded study drug was 291 days (IQR 239–354) and median duration of follow-up was 326 days (284–383). Number in ITT 3037 . (Rivaroxaban2.5 mg): 1519 . (Aspirin100 mg): 1518	- Rivaroxaban 2·5 mg BID.	- Aspirin 100 mg OD.	**Primary safety outcome:** Incidence surgery clinically significant bleeding (non-CABG major, minor). **Primary efficacy outcome:** The composite of all-cause mortality, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.
Ph. Gabriel Steg; et al. 2011[18]	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	Prospective, randomized, double-blind, multi-center, multiple-dose, placebo-controlled, parallel-group trial	- Male or female - Diagnosed with (NSTE)-ACS or (STE)-ACS within the last 14 days -Number in ITT 1258 (Darexaban): 939 Number in ITT (Placebo): 319	Darexaban 5 mg BID, 10 mg OD, 15 mg BID., 30 mg OD 30 mg BID, or 60 mg OD.	- Acetylsalicylic acid 75–325 mg daily - lower dose range of ASA (75–81 mg daily) Or - Clopidogrel 75 mg daily if ASA was contraindicated or not tolerated, or Combination of ASA 75–325 mg and clopidogrel 75 mg daily	**Primary safety outcome:** Incidence of major or clinically relevant non-major (CRNM) bleeding events, TIMI, ISTH. **Secondary efficacy outcome:** The composite of all-cause mortality, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.

Table 1e. The characteristics [**PICOs**]* of the RCT included in the current systematic review for DOAC plus SAPT or DAPT in subjects with STEMI or NSTEMI with atrial fibrillation [19, 20, 21,2]

Author [Reference]	**Article title**	**Study design**	**Target population (P)**	**Investigated drug (Intervention) (I)**	**Comparator (C)**	**Trial stated outcome measure (O)**
Renato D. Lopes, et al. 2019,[19]	Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation	International, multi center, randomized, open-label trial.	- Males and females. - Patients median aged 70 years. - Diagnosed with AF who had an ACS or had undergone PCI a NSTE-ACS - Follow-up duration was 12 months - Number in ITT 4614. - Clopidogrel was the P2Y12 inhibitor used in 92.6% of the patients. - A total of 229 of 2290 patients (10.0%) who had been randomly assigned to receive apixaban received the dose of 2.5 mg twice daily - 59% among patients assigned to receive a VKA	- Apixaban received the dose of 2.5 mg BID or (VKA).	- Aspirin 85 mg OD.	**Primary safety outcome:** Incidence of major or clinically relevant non-major (CRNM) bleeding within 12 months, TIMI, ISTH. **Secondary efficacy outcome:** The composite of all-cause mortality, SEE, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.

Pascal Vranckx; et al. 2019,[20]	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	A randomized, multicenter, open-label, non-inferiority phase 3b trial	- Male and female - Patients aged ≥18 years - Patients had AF requiring NOAC, were and had a successful PCI with (STE)-ACS - Follow-up duration was 12 months - Number in ITT 1196 . (Edoxaban 60 mg): 616 . (VKA): 580	- Edoxaban (60 mg OD plus a P2Y12 inhibitor for 12 months - (VKA) in combination with a P2Y12 inhibitor and	- Aspirin (100 mg OD, for 1–12 months)	**Primary safety outcome:** Incidence of major or clinically relevant non-major (CRNM) bleeding within 12 months, TIMI, ISTH. **Secondary efficacy outcome:** The composite of all-cause mortality, SEE, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.

Table 1f. The characteristics [**PICOs**]* of the RCT included in the current systematic review for DOAC plus SAPT or DAPT in subjects with STEMI or NSTEMI with atrial fibrillation[19-22]

Author [Reference]	**Article title**	**Study design**	**Target population (P)**	**Investigated drug (Intervention) (I)**	**Comparator (C)**	**Trial stated outcome measure (O)**
C. Michael Gibson, et al. 2016 [21]	Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI	An open-label, randomized, controlled, multicenter	- Male and female - at least 18 years of age - Diagnosed patients paroxysmal, persistent, or permanent non-valvular AF. - Number in ITT 2124 - 338 Were in 1-mo DAPT stratum 737 Were in 6-mo DAPT stratum 1049 Were in 12-mo DAPT stratum	- Low-dose rivaroxaban (15 mg OD) plus a P2Y12 inhibitor 75 mg OD for 12 months (group 1). - Very-low-dose rivaroxaban (2.5 mg BID) plus DAPT aspirin (75 to 100 mg per day) for 1, 6, or 12 months (group 2)	- Standard therapy with dose-adjusted (VKA) OD plus DAPT aspirin (75 to 100 mg OD) for 1, 6, or 12 months (group 3).	**Primary safety outcome:** Incidence surgery clinically significant bleeding (non-CABG major, minor). **Secondary efficacy outcome:** The composite of all-cause mortality, stroke, MI, UA, systemic thromboembolism, and severe recurrent ischemia.
Satoshi Yasuda; et al. 2019[22]	Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease	Multicenter, a randomized, open label, parallel-group trial.	- Males and females. - Age ≥20 years. - Diagnosed with AF and stable CAD. - Follow-up duration was 12 months. - Number in ITT 2200. - 1005 were assigned to the rivaroxaban monotherapy group. - 968 were assigned to the Combination-therapy group.	- Monotherapy with rivaroxaban (10 mg OD daily for patients with a creatinine clearance of 15 to 49 ml per minute or 15 mg OD daily for patients with a creatinine clearance of ≥50 ml per minute)	- Combination rivaroxaban and single antiplatelet drug (aspirin 81, 100 mg, clopidogrel 75mg or prasugrel 3.7mg OD)	**Primary safety outcome:** Incidence of TIMI major bleeding. **Primary efficacy outcome:** A composite of stroke, systemic embolism, MI, UA requiring revascularization, or death from any cause.

Keys:
ACS: Acute Coronary Syndrome; BID: twice daily; CAD: Coronary Artery Disease; CHD: Coronary Heart Disease; CV: Cardiovascular event; DAPT: Dual Antiplatelet Therapy; DOAC: Direct-Acting Oral Anticoagulants; ISTH; International Society on Thrombosis and Hemostasis; ITT: Intent-To-Treat; MI; Myocardial Infarction; NSTE; Non-ST-Segment Elevation, OD: Once Daily; PAD: Peripheral Arterial Disease; PICOs: Population; Intervention, Comparison, Outcome, and study design [population: target population (P); intervention: investigated drug (I); comparison: comparator (C); outcome: Outcome measure (O)]; study design: study design (s); RCT: Randomized Clinical Trial; SAPT: Single Antiplatelet Therapy; STE; ST-Segment Elevation; STEMI: ST-Elevation Myocardial Infarction; UA: Unstable Angina; VKA: vitamin K antagonist

Table 2a. The primary efficacy and primary safety outcomes of RCT for the intervention and comparator arms [5,14-17,22]

RCT Author Reference	Intervention arm	Comparator arm	primary safety outcome	Difference	primary efficacy outcome	Difference
Kevin R; et al. 2020[16]	combination of Low-dose rivaroxaban plus Aspirin (DATT)	Aspirin Alone	DATT resulted in more major bleeds irrespective of previous PCI (PCI: 3.3% vs 2.0%; HR 1.72 [95% CI, 1.34–2.21]; no PCI: 2.9% vs 1.8%; HR 1.58 [95% CI, 1.15–2.17]; P-interaction=0.68; in comparison with aspirin.	The intervention arm (DATT) is **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (Aspirin Alone).	DATT compared with (Aspirin Alone) was associated with fewer MACE regardless of previous PCI (PCI: 4.0% vs 5.5%; [HR], 0.74 [95% (CI) 0.61–0.88]; no PCI: 4.4% vs 5.7%; HR, 0.76 [95% CI 0.61–0.94]; P= 0.85.	The intervention arm (DATT) was **superior** for primary efficacy outcome (MACE, CV death, MI, stork) compared with the comparator arm (aspirin alone)
Yan Liang, et al. 2020[14]	DPI (Rivaroxaban plus aspirin) (DATT)	Aspirin	DPI (DATT) compared with (aspirin Alone) was associated with more major bleeds (women: 3.1% vs. 1.4%, HR 2.22, [95% CI 1.42– 3.46]; men: 3.2% vs. 2.0%, HR 1.60, [95% CI 1.29–1.97]; P interaction 0.19).	The intervention arm (DPI) was **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (Aspirin Alone).	DPI compared with (Aspirin Alone) was associated with was reduce MACE (women: 3.8% vs. 5.2%, HR 0.72, [95% CI 0.54–0.97]; men: 4.2% vs. 5.5%, HR 0.76, [95% CI 0.66–0.89]; P interaction 0.75).	The intervention arm (DPI) was **superior** for the primary efficacy outcome of CV events such as (death, stroke, and MACE) compared with the comparator arm (aspirin Alone).
E Magnus Ohman, et al. 2017[17]	Rivaroxaban	Aspirin	TIMI non-CABG clinically significant bleeding was similar with rivaroxaban versus aspirin therapy [5%] vs [5%]; (HR 1·09 [95% CI 0·80–1·50]; p=0·5840).	The intervention arm (rivaroxaban) was non-**inferiority and similar** to combination therapy (aspirin) for the primary safety endpoint (major bleeding)	Combination of (Rivaroxaban) 5% was associated with a similar ischemic endpoint with aspirin 5% (HR 1·06 [95% CI 0·77–1·46]; P= 0·7316).	The intervention arm (rivaroxaban) was **non-inferiority and similar** to combination therapy (aspirin) for the primary efficacy endpoint CV event (death, MI, stroke).

Table 2b**.** The primary efficacy and primary safety outcomes of RCT for the intervention and comparator arms [5,14-22]

RCT Author Reference	Intervention arm	Comparator arm	primary safety outcome	Difference	primary efficacy outcome	Difference
Stuart J Connolly; et al. 2017[15]	DPI (Rivaroxaban plus aspirin) (DATT)	Aspirin or placebo	DPI resulted in more major bleeding than treatment with (aspirin alone) (3% vs 2%; HR 1·66, 95% CI 1·37–2·03, p<0·0001)	The intervention arm (DPI) was **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (Aspirin Alone).	DPI reduced the primary outcome more than aspirin alone (4% vs 6%; [HR] 0·74, 95% CI 0·65–0·86, p<0·0001)	The intervention arm (DPI) was **superior** for the primary efficacy outcome of CV events such as (death, stroke, and MACE) compared with the comparator arm (aspirin Alone).
Jessica L. Mega; et al. 2012[5]	Rivaroxaban	Placebo (aspirin, clopidogrel or ticlopidine)	Rivaroxaban increased the rate of TIMI major bleeding that was not related to CABG, as compared with placebo, with rates of 2.1% and 0.6%, respectively (HR, 3.96; [95% CI, 2.46–6.38]; P<0.001).	The intervention arm (rivaroxaban Plus Aspirin) was **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (placebo).	Rivaroxaban reduced the rates of CV event (MI or stroke, death) compared with placebo, with rates of 8.9% and 10.7%, respectively (HR, 0.84; [95%; CI, 0.74–0.96]; P=0.008).	The intervention arm (rivaroxaban) was **superior** to combination therapy (VKA plus aspirin) for the primary efficacy endpoint CV event (stroke, MI, death).

Satoshi Yasuda; et al. 2019[22]	Rivaroxaban	SAPT (Rivaroxaban and single antiplatelet drug [DATT])	Rivaroxaban monotherapy was superior to SAPT therapy for the primary safety endpoint (major bleeding), with event rates of 1.62% and 2.76% per patient-year, respectively (HR, 0.59; 95% CI, 0.39 to 0.89; P=0.01 for superiority)	The intervention arm (rivaroxaban) was **superior** to SAPT therapy for the primary safety endpoint (major bleeding).	(Rivaroxaban) monotherapy was non-inferior to SAPT therapy for the primary efficacy endpoint, with event rates of 4.14% and 5.75% per patient-year respectively (HR, 0.72; [95% CI: 0.55–0.95]; P <0.001 for non-inferiority).	The intervention arm (Rivaroxaban) was **superior** to SAPT therapy for the primary efficacy endpoint CV event (stroke, systemic embolism, MI, death).

Table 2c. The primary safety and secondary efficacy outcomes of RCT for the treatment and comparator ar[m4,7,18-21]

RCT Author Reference	Intervention arm	Comparator arm	primary safety outcome	Difference	Secondary efficacy outcome	Difference
Renato D. Lopes, et al. 201[91]9	(Apixaban) or (VKA)	Aspirin or placebo	Major or clinically relevant no major bleeding was noted in 10.5% of the patients receiving (Apixaban), as compared with 14.7% of those receiving a (VKA) (HR, 0.69; 95% [CI], 0.58 to 0.81; P<0.00. and in 16.1% of the patients receiving (aspirin), as compared with 9.0% of those receiving (placebo) (HR, 1.89; 95% CI,1.59 to 2.24; P<0.001).	The intervention arm (Apixaban or VKA) was **superior** for primary safety outcome (major or clinically relevant no major bleeding) compared with the comparator arm (aspirin alone or placebo).	Subjects in the apixaban group had a lower incidence of death or hospitalization than those in the VKA group (23.5% vs 27.4%; HR, 0.83; [95% CI, 0.74–0.93]; P= 0.002). Subjects in the aspirin group had an incidence of death or hospitalization and ischemic event that was similar to that in the placebo	The intervention arm (Apixaban or VKA) was superior for primary efficacy outcome (death or hospitalization) compared with the comparator arm (aspirin alone or placebo).
Pascal Vranckx; et al. 2019[20]	Edoxaban	(VKA)	The primary outcome of ISTH-defined major or CRNM bleeding events occurred in 17% of patients with the edoxaban regimen and 20% of patients with the VKA regimen (HR for edoxaban 0·83 [95% CI 0·65–1·05], p=0·0010 for non-inferiority, margin HR 1·20, p =0·1154 for superiority.	The intervention arm (edoxaban) was **superior** to combination therapy (rivaroxaban and single antiplatelet drug) for the primary safety endpoint (major bleeding).	The main efficacy outcome of the composite of CV event occurred in 7% of patients receiving the edoxaban regimen compared with 6% of patients receiving the VKA regimen (HR for edoxaban 1·06 [95% CI 0·71–1·69].	The intervention arm (Edoxaban) was inferior to combination therapy (VKA) for the primary efficacy endpoint CV event (death, stroke, SEE, MI, stent thrombosis).
C. Michael Gibson, et al. 2016[21]	(Group1), rivaroxaban plus a P2Y12 inhibitor (Group2) rivaroxaban plus DAPT.	VKA plus aspirin	The rates of bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; HR for group 1 vs group 3, 0.59; [95% CI 0.47–0.76]; P< 0.001; HR for group 2 vs. group 3, 0.63; [95% CI 0.50–0.80]; P<0.001)	The intervention arm (rivaroxaban) was **superior** to combination therapy (VKA plus aspirin) primary safety endpoint (major bleeding).	The rates of CV event (MI or stroke, death) were similar in the three groups (group 1, 5.6% in group 2, and 6.0% in group 3; P values for all comparisons were non-significant), (P>0.050 for both comparisons.	The intervention arm (rivaroxaban) was superior to combination therapy (VKA plus aspirin) for the primary efficacy endpoint CV event (stroke, MI, death).
Hisao Ogawa; et al. 2013[1]	Apixaban	Placebo (aspirin; clopidogrel or ticlopidine)	All bleeding events were greater in the apixaban groups than in the placebo group, the major or clinically relevant non-major CRNM bleeding occurred in 1 patient (2.0%) in the placebo group and 2 patients (4.1%) in each of the apixaban treatment groups.	The intervention arm (Apixaban) was **superior** for primary safety outcome (major or clinically relevant non-major bleeding) compared with the comparator arm (aspirin alone or placebo).	No deaths, non-hemorrhagic strokes, MIs, or cases of UA during the study were observed for any subjects in the apixaban 2.5 mg	The intervention arm (Apixaban) was superior for primary safety outcomes (stroke, MI, UA, death) compared with the comparator arm (aspirin alone or placebo).

Table 2d. The primary safety and secondary efficacy outcomes of RCT for the treatment and comparator arm [4,7,18-21]

RCT Author Reference	Intervention arm	Comparator arm	Primary safety outcome	Difference	Secondary efficacy outcome	Difference
Jonas Oldgren; et al. 2011[7]	Dabigatran	Placebo (aspirin or clopidogrel)	The risk of incidence of major clinical bleeding events was increased in the dabigatran groups compared with placebo, with a HR; 1.77 (95% CI; 0.70, 4.50) for 50 mg; HR; 2.17 (0.88, 5.31) for 75 mg; HR 3.92 (1.72, 8.95) for 110 mg; and HR 4.27 (1.86, 9.81) for 150 mg. P<0.001	The intervention arm (Dabigatran) was **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (placebo).	The safety endpoint was that dabigatran significantly reduced coagulation activity and may have the potential to reduce cardiovascular events when added to dual antiplatelet treatment in doses of 110 –150 mg twice daily	The intervention arm (Dabigatran) was superior for primary safety outcomes (stroke, MI, UA, death) compared with the comparator arm (placebo).
Ph. Gabriel Steg; et al. 2011[18]	Darexaban	Placebo (aspirin or clopidogrel).	The bleeding rate was numerically higher in all darexaban treatments than in the placebo (HR: 2.275; CI: 1.13–4.60; P= 0.022)	The intervention arm (Darexaban) was **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (placebo).	The main efficacy outcome the composite of CV event occurred in 1.1% of patients receiving the darexaban compared with 0.4% of patients receiving placebo.	The intervention arm (darexaban) was superior for primary safety outcomes (stroke, MI, UA, death) compared with the comparator arm (placebo).
J L Mega, et al. 2009[4]	Rivaroxaban	Placebo (Aspirin).	The risk of clinically significant bleeding with rivaroxaban vs placebo increased in a dose-dependent manner (HR; 2·21 [95% CI 1·25–3·91] for 5 mg, 3·35 [2·31–4·87] for 10 mg, 3·60 [2·32–5·58] for 15 mg, and 5·06 [3·45–7·42] for 20 mg doses; p<0·0001).	The intervention arm (Rivaroxaban) was **inferior** for primary safety outcome (major bleeding) compared with the comparator arm (placebo).	Rivaroxaban reduced the of CV events (stroke, MI, UA, death) compared with placebo (3·9% vs. 5·5%; HR 0·69, [95% CI 0·50–0·96], p= 0·0270	The intervention arm (Rivaroxaban) was superior for primary safety outcomes (stroke, MI, UA, death) compared with the comparator arm (placebo).

Keys: CABG: non-coronary artery bypass graft; CI: confidence interval; CV: Cardiovascular event; DATT: dual antithrombotic therapy; DPI: Rivaroxaban plus aspirin (DATT); MACE: Major adverse cardiovascular events; MI: Myocardial infarction; HR: hazard ratio; PCI: percutaneous coronary intervention; SAPT: Rivaroxaban and single antiplatelet plus Rivaroxaban; TIMI: Thrombolysis in myocardial infarction; CI: Confidence interval; CRNM: Clinically relevant non-major; CV: Cardiovascular event; DAPT: Dual antiplatelet therapy; HR: Hazard ratio; ISTH: International Society on Thrombosis and Hemostasis; MI: Myocardial infarction; UA: Unstable angina; VKA: Vitamin K antagonist

3.3% versus 2.0%; HR 1.72 [95% CI, 1.34–2.21]; no PCI: 2.9% versus 1.8%; HR 1.58 [95% CI, 1.15–2.17]; P-interaction=0.6. For the primary efficacy outcome, in comparison with aspirin, the DAPT was associated with fewer MACE regardless of previous PCI or not (PCI: 4.0% versus 5.5%; HR 0.74 [95% CI 0.61–0.88]; no PCI: 4.4% versus 5.7%; HR 0.76 [95% CI 0.61–0.94]; P = 0.85). However, for secondary efficacy outcomes (CV mortality), the DATT was associated with lower mortality in comparison with aspirin alone with or without PCI (PCI: 1.3% versus 1.9%; HR 0.72 [95% CI 0.53–0.99]; no PCI: 2.2% versus 2.8%; HR 0.78 [95% CI 0.57–1.05]; P = 0.76).[16]

Magnus Ohman (2017) completed multicenter, phase 2, and double-blind RCT (GEMINI-ACS-1) with 3037 subjects with ACS (UA, NSTEMI, or STEMI). They were randomly assigned 1519 to receive low-dose rivaroxaban (2.5 mg BID) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) DATT and 1518 to receive aspirin (100 mg OD) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) DAPT, followed-up for one year. The DATT combination (DOAC plus SAPT) was not associated with the bleeding endpoint (P =0.6152) for the primary safety outcome. The frequency of TIMI non-CABG clinically significant bleeding was similar with rivaroxaban versus aspirin therapy [5%] vs [5%]; (HR 1·09 [95% CI 0·80–1·50]; p= 0.5840). For the primary efficacy outcome, the frequency of the composite ischemic endpoint of CV death, MI, stroke, or definite stent thrombosis was 76 participants (5%) in the rivaroxaban group versus 72 (5%) with aspirin (HR 1.06 [95% CI 0.77–1.46]; P interaction= 0.7316).[17]

APPRAISE-J, a small multicenter, phase 2, double-blinded, placebo-controlled RCT (APPRAISE-J), included 151 Japanese subjects with ACS who were randomized to receive apixaban 2.5 mg or apixaban5 mg BID in the first group, or placebo (aspirin) in addition to standard antiplatelet therapy (clopidogrel or ticlopidine) SAPT in the second group for 24 weeks. For the primary safety outcome, the incidence of all bleeding events was more significant in the apixaban groups than in the placebo group. The major or CRNM bleeding occurred in one patient

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(2.0%) in the placebo group and two subjects (4.1%) in each of the apixaban treatment groups. For the secondary efficacy outcome, there were no deaths, non-hemorrhagic stroke, MI, or cases of UA reported for any subjects in the apixaban 2.5 mg.[1]

Jessica L. Mega (2012) conducted a double-blind, placebo-controlled RCT in 15526 subjects with a recent ACS and STEMI, NSTEMI, or UA. Subjects were randomly assigned in a 1:1:1 fashion to the administration of either 2.5 mg or 5.0 mg of rivaroxaban (BID) or placebo (aspirin; 100 mg orally OD, clopidogrel 75 mg [loading doses of 300 – 600 mg]), with a maximum follow-up of 31 months. Rivaroxaban significantly reduced the primary efficacy outcome of death from CV causes, MI, or stroke, as compared with placebo, with rates of 8.9% and 10.7%, respectively (HR 0.84; [95% CI 0.74–0.96]; P =0.008). For primary safety outcome, rivaroxaban significantly increased the rate of TIMI major bleeding that was not related to CABG, as compared with placebo, with rates of 2.1% and 0.6%, respectively (HR 3.96; [95% CI 2.46–6.38]; P<0.001).[5]

Jonas Oldgren (2011) conducted a double-blind, placebo-controlled, dose-escalation RCT in 1861 subjects with ACS diagnosis of STEMI or NSTEMI within the last 14 days. Subjects were randomized to receive treatment with BID dabigatran 50 mg, 75 mg, 110 mg, and 150 mg for a 6-month treatment period in the first group, and placebo plus aspirin ≤100 mg and clopidogrel75 mg) for a 6-month treatment period in the second group. The risk of incidence of major clinical bleeding events was increased in the group receiving dabigatran groups compared with the second group, with HR 1.77 (95% CI 0.70 - 4.50) for 50 mg; HR; 2.17 (95% CI 0.88 - 5.31) for 75 mg; HR 3.92 (1.72 - 8.95) for 110 mg; and HR 4.27 (1.86 - 9.81) for 150 mg. The secondary efficacy outcome was that dabigatran significantly reduced CV events when added to DAPT in doses of 110 –150 mg BID.[7]

Gabriel Steg (2011) (YM150) conducted a multi-center, double-blind, parallel-group RCT in 1,279 subjects diagnosed with STEMI or NSTEMI. Subjects were assigned to receive one of six darexaban regimens for six months (5 mg BID, 10 mg OD, 15 mg BID, 30 mg OD, 30 mg BID, or 60 mg OD). Placebo (75–325 mg OD or Clopidogrel 75 mg OD) for six months. The primary safety outcome of the bleeding rate was numerically higher in all Darexaban treatments than in the placebo (HR 2.275; 95% CI 1.13–4.60; P= 0.022). Nevertheless, the drug darexaban was discontinued. The main secondary efficacy outcome of the composite CV event occurred in 1.1% of patients receiving darexaban compared with 0.4% of patients receiving a placebo.[18]

ATLAS ACS-TIMI 46, a randomized, double-blind, placebo-controlled phase II dose-escalation RCT, included 3491 subjects with ACS diagnosis of STEMI, NSTEMI, or UA. Subjects were stratified based on the investigator's decision to use aspirin only (stratum1) or aspirin plus a thienopyridine (stratum 2). Participants were randomized within each stratum and dose tier with a block randomization method at 1:1:1 to receive either placebo or rivaroxaban at doses (5–20 mg) given OD or the same total daily dose given BID. Comparator placebo with aspirin (75–81 mg) daily or aspirin plus thienopyridine for six months. For the primary safety outcome, the risk of clinically significant bleeding with rivaroxaban was increased in a dose-dependent manner as compared to the placebo group (HR 2.21 [95% CI 1.25–3.91] for 5 mg, 3.35 [2.31–4.87] for 10 mg, 3.60 [2.32–5.58] for 15 mg, and 5.06 [3.45–7.42] for 20 mg doses; P<0.0001). Rivaroxaban reduced the primary secondary efficacy outcome of death, MI, or stroke compared with placebo (87/2331 [3.9%] versus 62/1160 [5.5%]; HR 0.69, [95% CI 0.50–0.96], P= 0.0270).[4] The results of outcomes are shown in **[Table 2].**

Subjects with STEMI or NSTEMI with atrial fibrillation

Renato (2019) conducted multicenter, international RCT in 4614 subjects with AF who have had ACS or have had PCI and are planning to take a P2Y12 inhibitor (clopidogrel) to receive apixaban or VKA and to receive aspirin or a matching placebo for six months. There was no significant interaction between the two randomization factors about the primary safety outcome (P =0.64 for interaction). The major or clinically relevant non-major bleeding was noted in 10.5% of the subjects receiving apixaban, as compared with 14.7% of those receiving a VKA, and in 16.1% of patients receiving aspirin, as compared with 9.0% of those receiving a placebo. For the secondary efficacy outcome, subjects in the apixaban group had a lower incidence of death or hospitalization than those in the VKA group (23.5% versus 27.4%; HR 0.83; [95% CI 0.74–0.93]; P =0.002). Subjects in the aspirin group had an incidence of death or hospitalization and an ischemic event that was similar to that in the placebo.[19]

Pascal Vranckx (2019) (ENTRUST-AF PCI) conducted a multicenter, open-label, non-inferiority phase 3b RCT (ENTRUST-AF PCI) in 1506 subjects who underwent PCI and were diagnosed with AF. Subjects were randomly assigned to receive an open-label edoxaban-based regimen of 60 mg OD or 30 mg OD and clopidogrel (75 mg OD) or prasugrel (5 mg or 10 mg OD) or ticagrelor (90 mg BID) in the first group. Active comparators were randomly assigned to receive VKA in combination with clopidogrel 75 mg OD (DATT) or prasugrel 5 mg or 10 mg OD or ticagrelor 90 mg BID and aspirin 100 mg OD (DAPT) for a minimum of 1 month and up to 12 months duration. The primary outcome of ISTH-defined major or CRNM bleeding events occurred in 17% of patients with the edoxaban regimen and 20% of patients with the VKA regimen (HR for edoxaban 0·83 [95% CI 0·65–1·05], p=0·0010 for non-inferiority, margin HR 1·20, p =0·1154 for superiority. The primary efficacy outcome of the composite of CV event (death, stroke, Systemic embolic events [SEE], MI, and definite stent thrombosis) occurred in 7% of patients receiving the edoxaban regimen compared with 6% of patients receiving the VKA regimen (HR for edoxaban 1·06 [95% CI 0·71–1·69].[20]

Michael Gibson (2016) (PIONEER AF-PCI) conducted an international, multicenter, open-label RCT in 2124 subjects with ACS for 12 months. The intervention group received low-dose rivaroxaban 15 mg OD plus a P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel) for 12 months (DATT, group 1), very-low-dose rivaroxaban (2.5 mg BID) plus DAPT for 1, 6, or 12 months (group 2). The comparator group received standard therapy

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with dose-adjusted VKA OD plus DAPT aspirin (75 to 100 mg daily) for 1, 6, or 12 months (group 3). For the primary safety outcome, the rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3. The HR for group 1 versus group 3, 0.59; [95% CI 0.47–0.76]; P< 0.001; HR for group 2 versus group 3, 0.63; [95% CI 0.50–0.80]; P <0.001). For the secondary efficacy outcome, the rates of death from CV event causes, MI, or stroke were similar in the three groups (Kaplan– Meier estimates, 6.5% in group 1, 5.6% in group 2, and 6.0% in group 3; P values for all comparisons were non-significant).[21]

Satoshi Yasuda (2019) (AFIRE) conducted a multicenter, open-label, parallel-group RCT in 2236 subjects with AF who had undergone PCI or CABG for over one year. Subjects were assigned to receive monotherapy with rivaroxaban 10 mg or 15 mg OD in the first group and DATT (a combination of rivaroxaban and SAPT drug (aspirin, clopidogrel, or prasugrel) in the second group. Rivaroxaban monotherapy was non-inferior to DATT for the primary efficacy outcome, with event rates of 4.14% and 5.75% per patient-year, respectively (HR 0.72; [95% CI: 0.55–0.95]; P <0.001 for non-inferiority). For the primary safety outcome, rivaroxaban monotherapy was superior to DATT for the lower incidence of non-major bleeding events, with event rates of 1.62% and 2.76% per patient-year, respectively (HR 0.59; [95% CI: 0.39–0.89]; P =0.01 for superiority).[22]

The guidelines for acute myocardial infarction (AMI)

The European Society of Cardiology (ESC) published guidelines in 2017 and 2020.[23,24] for the management of acute myocardial infarction (AMI) for NSTEMI. Where in patients with AF, post a short period of TATT (up to 1 week from the acute event), DATT (e.g., DOAC SAPT agent, preferably clopidogrel) is recommended, with cessation of the antiplatelet after 6 to 12 months.[24] DOAC to be continued as monotherapy.[25] The guidelines recommended DOAC with potent P2Y12 inhibitor (prasugrel Europe dose: 60 mg loading dose and 10 mg maintenance dose OD; Japan: 20 mg loading dose and 3.75 mg maintenance dose OD), or ticagrelor loading dose 180 mg and 90 mg maintenance dose twice daily, or clopidogrel.[25,26]

The MASTER DAPT trial compared short and prolonged DAPT following stent implantation in high-bleeding risk subjects, indicating that the short regimen resulted in a lower incidence of major or clinically relevant non-major bleeding.[28] However, a sub-study of MASTER DAPT showed safety and effectiveness (clopidogrel and DOAC) and enabled discontinuation of DAPT at one month in high-bleeding risk subjects with or without an indication for DOAC. While the short DAPT strategy significantly reduced clinically relevant bleeding risk in high-bleeding subjects without DOAC, the reduction in bleeding risk was not significant compared to the DOAC population.[29] Many studies supported the clinical utility of DOAC in ACS (with/without AF or PCI) [30-34] in addition to support from meta-analysis.[35]

Summary of findings

Subjects mainly with STEMI.[14,15]

In cardiovascular events, a combination of rivaroxaban and aspirin (DATT) was associated with lower mortality than aspirin alone with or without PCI.[14]

The Low-dose rivaroxaban to aspirin improved the primary efficacy outcome in subjects with a previous myocardial infarction and those without. There were significant reductions in all three secondary outcomes in the low-dose rivaroxaban plus aspirin (DATT) group compared with aspirin about myocardial infarction, ischemic stroke, coronary heart disease death, or acute limb ischemia.[15]

Subjects with STEMI or NSTEMI or UA underwent PCI.[1,4,5,7,16-18]

The effects of the DATT (rivaroxaban plus aspirin) were inferior to SAPT (aspirin therapy) for the primary safety endpoint (bleeding event) with or without previous PCI and superior for primary efficacy outcome (MACE, CV death, MI, stork) compared with SAPT.[16]

For the exploratory ischemic endpoint, the frequency of the composite ischemic endpoint of cardiovascular death, myocardial infarction, stroke, or definite stent thrombosis was similar in the rivaroxaban group versus aspirin. Although there was a numerically lower rate of the composite ischemic endpoint with ticagrelor than with clopidogrel, this was not statistically significant.[17]

In the study by **Hisao Ogawa,** the incidence of all bleeding events was more significant in the apixaban groups than in the placebo group, with a trend towards a dose-dependent increase in all bleeding events observed with apixaban in APPRAISE-J, as was seen in the APPRAISE-1 Phase II study. No deaths, non-hemorrhagic strokes, MIs, or cases of UA during the study were observed for any subjects in the apixaban 2.5mg.[1]

Jessica L. Mega stated that rivaroxaban significantly reduced the primary efficacy endpoint compared to placebo. The twice-daily 2.5-mg dose of rivaroxaban decreased cardiovascular death rates, a survival benefit not seen with the twice-daily 5-mg dose. As compared with the placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting.[4]

The study by Jonas Oldgren reported that dabigatran, in addition to dual antiplatelet therapy, was associated with a dose-dependent increase in bleeding events and significantly reduced coagulation activity in subjects with a recent myocardial infarction.[7]

Darexaban, when added to DAPT after ACS, produces an expected dose-related two- to four-fold increase in bleeding, with no other safety concerns but no signal of efficacy. Establishing the potential of low-dose darexaban in preventing major cardiac events after ACS requires a large phase III trial.[24] However, the development of darexaban was discontinued in September 2011.[18]

Rivaroxaban reduced the main secondary efficacy endpoint of death, myocardial infarction, or stroke compared with placebo.[18]

Subjects with STEMI or NSTEMI with atrial fibrillation.[19-22]

IN four large trials (WOEST, PIONEER AF, RE-DUAL PCI, and

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AUGUSTUS), DOAC and P2Y12 inhibitors reduced bleeding risk (no increased risk of ischemic events up to 1-year post-PCI), compared to VKA plus DAPT (i.e., TATT).

Subjects in the apixaban group had a lower incidence of death or hospitalization than those in the VKA group. Subjects in the aspirin group had an incidence of death or hospitalization and ischemic event that was similar to that in the placebo.[19]

Rivaroxaban monotherapy was non-inferior to combination therapy for efficacy and superior safety in subjects with AF and stable CAD.[22]

The ENTRUST-AF PCI trial showed that among subjects with atrial fibrillation who had successful PCI, a full-dose anticoagulation therapy with edoxaban 60 mg OD and a P2Y12 inhibitor is non-inferior to triple therapy with VKA regarding the risks of major or CRNM bleeding events.[20]

The international multicenter study of rivaroxaban plus SAPT/DAPT, compared to the group that received standard therapy with dose-adjusted VKA OD plus DAPT, had similar efficacy rates. However, the observed broad confidence intervals undermine the conclusive evidence.[21]

Key messages

DATT, compared with TATT, is related to lower bleeding risks (intra-cranial hemorrhage and a slight, non-significant excess of cardiac ischaemic events) in subjects with ACS.

For subjects with mainly STEMI with or without PCI or with/without prior MI, DATT was associated with lower mortality

For subjects with ACS (STEMI/NSTEMI) with/without PCI, DATT (rivaroxaban plus aspirin) was superior to SAPT for primary efficacy outcome (MACE, CV death, MI, stork).

For subjects with ACS and co-existing AF, based on current guidelines, DOAC should be preferred over VKA supported by a favorable risk/benefit profile.

The newer and more potent P2Y12 inhibitors (ticagrelor and prasugrel) are recommended over former clopidogrel.

CONCLUSION

The risk rate of recurrent ischemic events is high in subjects with ACS. DOAC indicated secondary prevention post-ACS. The cardiologist may need to stratify subjects with ACS to select the most effective, economical, and safe DOAC in dual and triple antithrombotic regimens (DATT/TATT). Further, research needs to address the evidence-based indications of the DOAC members in subjects with specific comorbidities (e.g., AF, HF), transitioning between antithrombotic regimens, and cost considerations (pharmacoeconomic evaluation such as cost-utility, cost-effectiveness, and cost-benefit).

LIST OF ABBREVIATIONS

ACS: Acute coronary syndrome

AF: Atrial fibrillation

AFIRE: Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery.

APPRAISE-J: A Study to Evaluate the Safety of Apixaban in Acute Coronary Syndrome (ACS) Japanese Patients.

ASCVD: atherosclerotic cardiovascular disease.

ATLAS ACS-TIMI 46: Rivaroxaban in Combination with Aspirin Alone or With Aspirin and a Thienopyridine in Patients with Acute Coronary Syndromes (The ATLAS ACS TIMI 46 Trial.

BID: Twice daily

CABG: Coronary artery bypass graft

CAD: Coronary artery disease

CHD: Coronary heart disease

CI: Confidence interval

COMPASS: Cardiovascular OutcoMes for People using Anticoagulation StrategieS.

COMPASS-PCI: Cardiovascular OutcoMes for People using Anticoagulation StrategieS - Percutaneous coronary intervention.

CRNM: Clinically relevant non-major bleeding

CV: Cardiovascular

DAPT: Dual antiplatelet therapy

DATT: dual antithrombotic therapy (DOAC plus SAPT)

DES: Drug-eluting stent.

DOAC: Direct oral anticoagulant.

DOI: Digital Object Identifier.

DVT: Deep venous thrombosis.

EMBASE: Excerpta Medica database.

ENTRUST-AF PCI: Edoxaban Treatment versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

EBSCO: Elton B. Stephens CO.

FDA: Food Drug Administration.

GEMINI-ACS-1: A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome.

HAS-BLED: Hypertension, Abnormal Renal Function, Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

HF: Heart failure.

HR: Hazard ratio.

IHD: Ischemic heart disease.

INR: International normalized ratio.

ISTH: International Society on Thrombosis and Hemostasis.

MACCE: Major adverse cardiovascular and cerebrovascular events.

MACE: Major adverse cardiac events.

MeSH: Medical Subject Headings.

MI: Myocardial infarction.

NOAC: Novel oral anticoagulant/new oral anticoagulant.

NSTEMI: Non-ST segment elevation myocardial infarction.

NVAF: Non-valvular atrial fibrillation.

NVKA: Non-vitamin K anticoagulant.

OD: Once Daily.

ODI: Oral direct inhibitor.

OPTIMA-3, 4: Optimal Antithrombotic Therapy for ACS Patients Concomitant With AF and Implanted With New-generation DES (OPTIMA-3, 4)

P2Y12: Adenosine diphosphate receptor subtype.

PAD: Peripheral arterial disease.

PAOD: Peripheral arterial occlusive disease.

PCI: Percutaneous coronary intervention.

PE: Pulmonary embolism.

PICOs: Population; Intervention, Comparison, Outcome.

PIONEER AF-PCI: A Study Exploring Two Strategies of Rivaroxaban (JNJ39039039; BAY-59-7939) and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention**.**

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

PROSPERO: International Prospective Register of Ongoing Systematic Reviews.

$P2Y_{12}$ inhibitor: purinergic-signaling receptor Y12.

RCT: Randomized clinical trial.

RCT-s: Randomized clinical trials.

SAPT: Single antiplatelet therapy.

SEE: Systemic embolic events.

SODA: Specific oral direct anticoagulant.

START: Survey on anTicoagulated subjects Regis-Ter.

STEMI: ST-segment elevation myocardial infarction.

TATT: Triple antithrombotic therapy (DOAC plus DAPT).

TIA: Transient ischemic attack.

TIMI: Thrombolysis in myocardial infarction.

TSOAC: Target-specific oral anticoagulant.

UA: Unstable angina.

VKA: Vitamin K antagonist.

VTE: Venous thromboembolism.

WOEST-3: What is the Optimal Antithrombotic Strategy in Patients with Atrial Fibrillation Undergoing PCI?

YM150: Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects with Acute Coronary Syndromes.

AUTHORS' CONTRIBUTIONS

We declare that the following individual authors (Asim Ahmed Elnour[*1] [A A Elnour], Israa Y Al- Khidir;[1] Fai Mutaz Alharbi;[3] Hajer Shaty Alshammari;[4] and Shroog Farhan Altwalah[5]) have made substantial contributions to the conception and design of the work. The following individual authors (Aliyah Hamdan Alshammari;[6] Talal Ahmed Alshammari;[7] Ibrahim Khalid Alhajaji;[8] Majd Habib Alshammari;[9] and Norah Aljohani[10]) have made substantial contributions to the data acquisition, analysis, and interpretation. The following individual authors completed revising the results and tables (Yasmin Khaled;[11] Shahd Alanazi;[12] Semira Abdi Beshir;[13] Vineetha Menon[14]). All authors have made substantial contributions to the manuscript writing, critically evaluated for important intellectual content, approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICTS OF INTEREST

No conflicts of interest or competing interests

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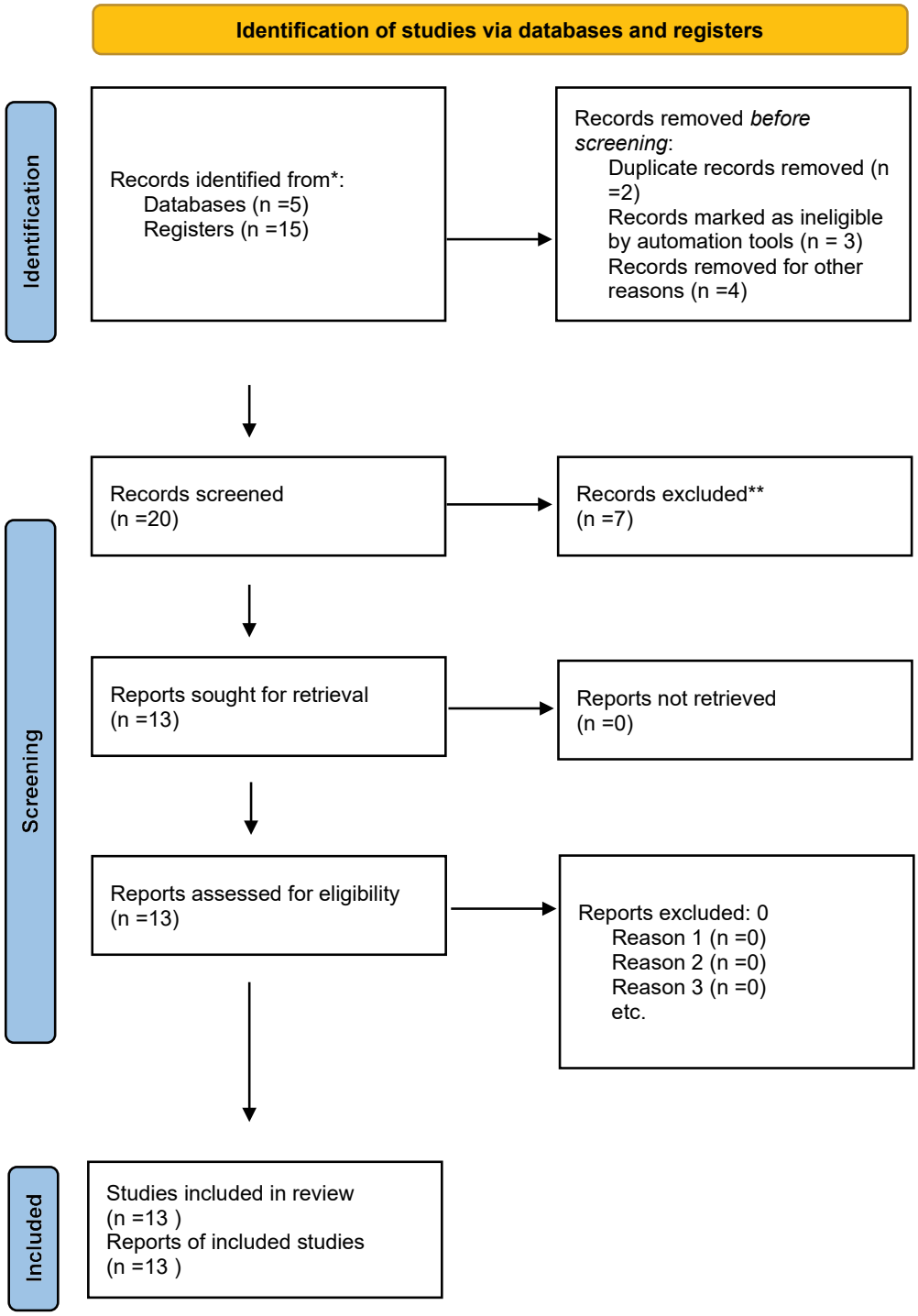
Appendix 1 supplementary. The quality of the trials based on modified Jadad scale scoring system.[1,4,5,7,14-22]

Criteria → / **Author [Reference] ↓**	**1. Was the study described as randomized? (Yes +1) **(NO 0)**	**2. Was the method of randomization appropriate? (Yes +1 *(No -1) (Not described 0)**	**3. Was the research described as blinding? (Yes +1) **(NO 0)**	**4. Was the approach of blinding appropriate? (Yes +1 *(No -1) (Not described 0)**	**5. Was there a presentation of withdrawal and dropouts? (Yes +1) **(NO 0)**	**6. Was there a presentation of the inclusion/ exclusion criteria? (Yes +1) **(NO 0)**	**7. Was the approach used to assess adverse effects described? (Yes +1) **(NO 0)**	**8. Was the approach of statistical analysis described? (Yes +1) **(NO 0)**	**Total**
Kevin R,et al ,2020 [16]	1	1	0	**0**	1	1	1	1	6
[Yan Liang, et al. 2020 [14]	1	1	1	1	0	1	1	1	7
Renato D. Lopes, et al. 2019 [219]	1	1	1	0	1	1	1	1	7
Satoshi Yasuda; et al. 2019 [22]	1	1	0	0	1	1	1	1	6
Pascal Vranckx; et al. 2019 [20]	1	1	0	0	1	1	1	1	6
E Magnus Ohman, et al. 2017 [17]	1	1	1	1	1	1	1	1	8
Stuart J Connolly; et al. 2017 [15]	1	1	1	1	1	1	1	1	8
C. Michael Gibson, et al. 2016 [21]	1	0	0	0	1	1	1	1	5
Hisao Ogawa; et al. 2013 [1]	1	1	1	1	1	1	1	1	8
Jessica L. Mega; et al. 2012 [5]	1	0	1	1	1	1	1	1	7
Jonas Oldgren; et al. 2011 [7]	1	1	1	1	1	1	1	1	8
Ph. Gabriel Steg; et al. 2011 [18]	1	1	1	1	0	1	1	1	7
J L Mega, et al. 2009 [4]	1	1	1	1	1	1	1	1	8

Keys: +1 =Yes; *-1 =No; **0 =NO; 0=Not described



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2020 Checklist

Section andTopic	Item#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1, 2 and 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6 and 7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8 and 9 Appendix 2
Informationsources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify thedate when each source was last searched or consulted.	8 and 9 Appendix 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	8 and 9 Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each recordand each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8 and 9 Appendix 2
Data collectionprocess	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in theprocess.	8 and 9 Appendix 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	12
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6 and 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7-9
Synthesismethods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics andcomparing against the planned groups for each synthesis (item #5)).	8-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or dataconversions.	7-10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe themodel(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8 -11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8 -11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not found

PRISMA 2020 Checklist

Section andTopic	Item#	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8 and 9 Appendix 2
Study characteristics	17	Cite each included study and present its characteristics.	10 and 11
Risk of bias instudies	18	Present assessments of risk of bias for each included study.	9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision(e.g. confidence/credible interval), ideally using structured tables or plots.	12, 13, 14, 15, 16, 17 and 18
Results ofsyntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g.confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12, 13, 14, 15, 16, 17 and 18
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	12, 13, 14, 15, 16, 17 and 18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	12, 13, 14, 15, 16, 17 and 18
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty ofevidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	19 and 20
	23b	Discuss any limitations of the evidence included in the review.	19and20
	23c	Discuss any limitations of the review processes used.	19 and 20
	23d	Discuss implications of the results for practice, policy, and future research.	19 and 20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7 and Appendix 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competinginterests	26	Declare any competing interests of review authors.	Title page
Availability of data, code andother materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from includedstudies; data used for all analyses; analytic code; any other materials used in the review.	Appendix 2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 4. The registration status of the included RCT trials [1, 4, 5, 7, 14-22]

S.N.	References	Registration of the RCT
1	Kevin R, et al. 2020 [16]	Registration with https://www.clinicaltrials.gov; [NCT01776424].
2	Yan Liang, et al. 2020 [14]	Registration with https://www.clinicaltrials.gov; [NCT01776424].
3	Renato D. Lopes, et al. 2019 [19]	Registration with https://www.clinicaltrials.gov; [NCT02415400].
4	Satoshi Yasuda, et al. 2019 [22]	Registration with https://www.clinicaltrials.gov; NCT02642419].
5	Pascal Vranckx, et al. 2019 [20]	Registration with https://www.clinicaltrials.gov; [NCT02866175].
6	E Magnus Ohman, et al. 2017 [17]	Registration with https://www.clinicaltrials.gov; [NCT02293395].
7	Stuart J Connolly, et al. 2017 [15]	Registration with https://www.clinicaltrials.gov; [NCT01776424].
8	C. Michael Gibson, et al. 2016 [21]	Registration with https://www.clinicaltrials.gov; [NCT01830543].
9	Hisao Ogawa, et al. 2013 [1]	Registration with https://www.clinicaltrials.gov; [NCT00852397].
10	Jessica L. Mega, et al. 2012 [5]	Registration with https://www.clinicaltrials.gov; [NCT00809965].
11	Oldgren, et al. 2011 [7]	Registration with https://www.clinicaltrials.gov; [NCT00621855].
12	Ph. Gabriel Steg, et al. 2011 [18]	Registration with https://www.clinicaltrials.gov; [NCT00994292].
13	J L Mega, et al. 2009 [4]	Registration with https://www.clinicaltrials.gov; [NCT00402597].

Keys: NCT: National Controlled Trial; **S.N**: serial number; **RCT**: randomized clinical trial

Appendix 5. The analysis used in the included RCT trials (Just tick (✓)[1,4,5,7,14-22]

S.N.	References	Per protocol analysis	ITT analysis	Sensitivity analysis	Subgroup analysis	Uncertainty analysis	Other type of analysis (define)
1	Kevin R, et al. 2020 [16]						
2	Yan Liang, et al. 2020 [14]						
3	Renato D. Lopes, et al. 2019 [19]						
4	Satoshi Yasuda, et al. 2019 [22]						
5	Pascal Vranckx, et al. 2019 [20]						
6	E Magnus Ohman, et al. 2017 [17]						
7	Stuart J Connolly, et al. 2017 [15]						
8	C. Michael Gibson, et al. 2016 [21]						
9	Hisao Ogawa, et al. 2013 [1]						
10	Jessica L. Mega, et al. 2012 [5]						
11	Oldgren, et al. 2011 [7]						
12	Ph. Gabriel Steg, et al. 2011 [18]						
13	J L Mega, et al. 2009 [4]						

Keys: ITT analysis: ; **RCT**: randomized clinical trial; **S.N**: serial number;