Protocol for systematic review and meta-analysis on randomized clinical trials for direct oral anticoagulant in subjects with acute coronary syndrome


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

Abstract

Background: Recently, direct oral anticoagulant (DOAC) has been projected for secondary prevention of recurrent ischemic events post-acute coronary syndrome (ACS). The addition of a DOAC to the antplatelet regimen of subjects with the ACS is clinically practiced in candidates where compelling anticoagulation is indicated by high thromboembolic risk. The current evidence provides approved compelling indication for the DOAC, particularly for rivaroxaban which bears the strongest existing evidence. Objective: We intend to assess the role of DOAC in addition to single or dual antplatelet therapy in subjects with ACS. We will compare the clinical characteristics and explore the efficacy and safety of the DOAC class members (apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban) in terms of reduction in ischemic events in subjects with ACS (ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation (NSTEMI)) or subjects who underwent percutaneous coronary intervention (PCI) and or ACS and coexisting atrial fibrillation (AF). Methods: Relevant data will be searched on known data-bases such as Embase, Google Scholar, the Cochrane Central, and PubMed. The trials included will be randomized controlled trials from 2009 to 2022. Subjects will be receiving DOAC for ACS were evaluated for inclusion. The extraction, synthesis, quality, and validity of data will follow the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The risk of bias tool, version 2.0 (Cochrane) will be used for risk of bias assessment. Data will be pooled using random-effects models. The primary outcome measure will be efficacy end point (composite of cardiovascular death, myocardial infarction, and stroke), while the safety outcome will be minor/major bleeding. Results: We will report the primary efficacy end point risk in the various regimens (DOAC plus SAPT or DAPT) with odds ratio (confidence interval) and both statistical and clinical significance. Further results of risk of bleeding will be compared between the regimens in the subsets of subjects with ACS (e.g. STEMI or NSTEMI) or with comorbid AF or heart failure (HF). Conclusion: We will critically appraise the evidence to support the effects of DOAC plus SAPT or DAPT based on the clinical presentation of subjects. The risk-benefit profile of DOAC will be presented in the two regimens of dual antithrombotic or triple antithrombotic therapy.

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BACKGROUND

The spectrum of acute coronary syndrome (ACS), included unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Antithrombotic therapy is indicated in all types of ACS where no contraindication is established such as in subjects with mechanical heart valve, moderate-to-severe mitral stenosis, and severe renal insufficiency. The use of oral dual antiplatelet therapy (DAPT) containing aspirin plus adenosine diphosphate receptor subtype (P2Y12) inhibitors (clopidogrel or prasugrel or ticagrelor) has been proved to diminish major cardiovascular adverse events (MACE) in subjects with ACS or in those undergoing procedures such as percutaneous coronary intervention (PCI). Some subset of subjects might have ACS with coexisting atrial fibrillation (AF) and vice versa.1,2 Recently, in a meta-analysis (7 RCTs, comprising 35,857 subjects and 53,321 patient-years of follow-up) the use of short-term DAPT (1-3 months) followed with single antiplatelet therapy (SAPT) versus standard DAPT; or low-dose DOAC plus SAPT (average stenting rates comprising 35,857 subjects and 53,321 patient-years of follow-up) the use of short-term DAPT (1-3 months) followed with single antiplatelet therapy (SAPT) versus standard DAPT. 

The controversies concerning the duration of DAPT (ultrashort [1 to 3 month such as in PCI], shorter [3 to 6 months] versus longer 12 to 24 months) and the associated risk of major bleeding impose more challenges to the dual regimen. In the last few years, direct-acting oral anticoagulant (DOAC) such as apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban, have been evaluated for secondary prevention of ischemic events in subjects with ACS given their efficacy, safety and ease of use in comparison to warfarin.6-10 A systematic review and network meta-analysis evaluated six RCTs on 32261 subjects, receiving DAPT or DOAC plus DAPT; or low-dose DOAC plus DAPT; or low-dose DOAC plus SAPT (average stenting rates were 62% of the trial population). Low-dose DOAC plus DAPT has shown the best option in MACE including MI.11

Rationale

In the current protocol of systematic review and meta-analysis we will report both the efficacy and safety profiles of the DOAC plus antiplatelet (SAPT or DAPT) in subjects with ACS exhibiting ischemic events. The efficacy and safety of either regimen will be critically appraised with the minimization of MACE, revascularization, hospitalization, readmission, bleeding, and stent thrombosis. The rationale for combining DOAC and antiplatelet therapy for subjects with ACS is well-known. However, variability exists in the type of DOAC, and the consequent adverse effects of each member of the DOAC. Moreover, the strategy for subjects with ACS and co-existing AF undergoing PCI, regarding dual antithrombotic therapy with DOAC plus SAPT, with a periprocedural period of aspirin, need further investigation.

OBJECTIVES

Research questions (PICO$s$)

In subjects (participants/population) with any type/stage of ACS:- Does the use of DOAC (intervention) such as apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban in addition to antplatelet therapy (DAPT/warfarin/comparators) prove non-inferiority or superiority over comparators in terms of reduction in ischemic events (outcome), in RCT (study design).

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

Is there any differences aligned between the members (apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban) based on of efficacy, precautions and safety profile and/or ACS type (i.e., ST-segment elevation myocardial infarction [STEMI] vs non–ST-segment elevation myocardial infarction [NSTEMI])?

Objective of the review

We intend to assess the role of DOAC in addition to single or dual antplatelet therapy in subjects with ACS and/or ACS and coexisting AF. We will compare the clinical characteristics and explore the efficacy and safety of the DOACs class members (apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban) in terms of reduction in ischemic events in subjects with ACS ([NSTE-ACS] or [STEMI]) or subjects who underwent PCI.

Ethics approval

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

METHODS

We have developed a protocol for the current systematic review and meta-analysis by using the PRISMA-P checklist http://www.prisma statement.org/Extensions/Protocols.aspx. The developed protocol has been registered on the PROSPERO website, [https://www.crd.york.ac.uk/prospero/#myprospero] ICD number CRD42020201605.

Eligibility criteria

We have developed a systematic review and meta-analysis (participants, interventions, comparisons, outcomes, and study design [PICO$s$]) on (phase II and phase III RCT-s) for subjects with ACS who have received DOAC as supplementation to SAPT and/or to DAPT.

Types of participants/population, interventions, comparisons and outcomes

Subjects diagnosed with ACS any type (STEMI/NSTEI/unstable...
Subjects receiving one of the following interventions: apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban. The primary efficacy endpoint will be the major cardiovascular events (MACE), cardiovascular death, myocardial infarction (fatal/nonfatal), and stroke (fatal/nonfatal) and/or their composite. While the secondary safety endpoint will be the major bleeding (fatal or nonfatal). The measure of effect will be expressed as relative risks, odds ratios, risk difference, and/or 'number needed to treat.'

The inclusion criteria will be the following: subjects diagnosed with ACS (all types), adult ≥18 years, both genders, hospitalized and non-hospitalized, RCT design (phase II RCT or Phase III RCT), with placebo/comparator, subjects receiving intervention drug DOAC (apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban); trials published in English language, full-text articles, primary outcomes reported status of MACE, conducted on humans within the last years (2011 - 2022). We will exclude non RCT and trials with primary outcome other than the efficacy of DOAC in ACS. We will exclude the following: non-RCT, retrospective trials, trial on pediatric population, trials which have evaluated other primary outcomes. Furthermore, we will exclude trials that have been conducted on: pregnant subjects and transplant subjects.

Types of studies
The current protocol is intended for systematic review in (RCT-s phase II and phase III) for subjects with ACS receiving DOAC and SAPT or DAPT. We will conduct the search on the known data-bases for relevant studies published on English language reporting the efficacy of DOAC in ACS. We have developed a protocol for the current systematic review and meta-analysis on the efficacy and safety profiles of DOAC (apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban) in subjects with ACS with the primary end-point of improvement in MACE. The setting will be out/in subjects (hospitalized or not hospitalized). Trials should be conducted during the period from the year 2011 to the year 2022, and published in English language in full text.

The search of trials retrieved will be conducted for studies involving subjects with ACS who have had received DOAC as supplementation to SAPT and/or DAPT versus placebo, or comparators (warfarin, aspirin, SAPT and/or DAPT). The database will be retrieved between the years 2011 to 2022 with the Medical Subject Headings (MeSH) search terms: acute coronary syndrome (ACS); “direct oral anticoagulant (DOAC)”; “apixaban”; “betrixaban”; “dabigatran”; “edoxaban”; “rivaroxaban”; “randomized clinical trials (RCTs- phase II and phase III)”, “placebo”; “comparator”; “safety”; “efficacy”, which was shown as images in the supplementary material, [Search prove image]. The selected trials citations will be imported into systematic review managers/software (COVIDENCE https://www.covidence.org/ or RAYYAN https://rayyan.qcri.org/welcome). In addition, we will use the manual searched citations with the same MeSH terms and conditions.

Search method for identification
The search method for identification for all intended information sources will be via (CINAHL, EMBASE, Google Scholar, Medline via EBSCO-host, PubMed, Web-of-Science) in addition to trial registers, and other grey literature sources. We will contact the study authors for any further information. We will use the predefined Cochrane library approved structured modified forms to report the trials. The search strategy included in the current systematic review was exemplified in Figure 1 diagram flow. We will access full articles, screened and reviewed content with predefined checklist (Cochrane templates) developed and modified specifically to ensure the strict inclusion criteria. We will follow the checklist that has been adapted for use with protocol submissions to Systematic Reviews from Table 3 in Moher study.12

The methods will be used for identifying published trials will be the common data-bases such as CINAHL, EBESCO, EMBAE, NLM, PubMed, Scopus, and Web-of-Science. We will also retrieve the

**DOAC characteristic features**

<table>
<thead>
<tr>
<th>Characteristic features</th>
<th>Apixaban</th>
<th>Betrixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidities affecting DCCO pharmacokinetics</td>
<td>Normal renal function</td>
<td>Cr Cl less than 50 mL/minute</td>
<td>Cr Cl less than 30 mL/minute</td>
<td>Cr Cl less than 15 mL/minute</td>
<td>Cr Cl less than 30 mL/minute</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>All DOAC are safe</td>
<td>Adjust renal dose for Dabigatran, Edoxaban and Rivaroxaban</td>
<td>Adjust renal dose for Apixaban, Edoxaban and Rivaroxaban</td>
<td>Adjust renal dose for Apixaban, Edoxaban and Rivaroxaban</td>
<td>Avoid Dabigatran</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>All DOAC are safe</td>
<td>Avoid Dabigatran</td>
<td>Avoid Dabigatran</td>
<td>Avoid Dabigatran</td>
<td>Avoid Dabigatran</td>
</tr>
<tr>
<td>Extensive body weight</td>
<td>All DOAC are safe</td>
<td>Avoid Dabigatran</td>
<td>Avoid Dabigatran</td>
<td>Avoid Dabigatran</td>
<td>Avoid Dabigatran</td>
</tr>
</tbody>
</table>

*Figure 1. The characteristics features of DOAC.*
clinicaltrials.gov trials registers searching for unpublished trials. We will use a structured, predefined and specific MeSH terms for identifying eligible trials for inclusion in the current systematic review and meta-analysis. We will follow a strict checklist with pre-specified inclusion and exclusion criteria to ensure that the identified trials are as per the current systematic review methodology of the protocol. The authors will double check the process and repeat the search terms individually and will compare between the two attempts, whereby, discrepancies will be resolved with discussions in reporting.

The trials will be selected by all the authors based on the inclusion criteria. The selected trials were reviewed by 4 authors, were double checked by another three authors and will be verified by repeating the process mentioned-above. The type of ACS, trial duration, follow-up duration and primary end point (outcomes measures) will be shown in the supplementary material, [Appendix I]. The trials registration, DOI, author details, and grade of the respective included RCT will be presented in the appendices. The safety outcomes (AEs) for the ten trials included in the current systematic review will be presented too.

We will use the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to abstract data, primary endpoint (outcomes measures), the safety outcomes (AEs) for the included trials. The above data, and coding) will be performed on the relevant variables from the original RCT and supplementary materials. The data will be collated with structured forms, verified, reviewed, double-checked, and recorded in the final format in excel sheets and conveyed to the RivMan databases.

Outcomes and prioritization

The primary outcome measure will be the clinical improvement and prognosis at the end of treatment in the ITT population. The differences in treatment between the intervention drug (NOAC) with antiplatelets, and placebo/comparators (other anticoagulants) as non-inferiority or superiority will be reported.

Quality of RCTs and assessment of risk of bias

In order to minimize and avoid bias in the selection of RCTs for the current systematic review and meta-analysis, the quality of the RCTs will be evaluated based on the five-point scale outlined by Jadad.13 We will assess the risk of bias in trials by confirming the following points: the randomization technique (with proper concealment of the allocation sequence), blinding (subjects and investigator to treatment allocation) with a description of the blinding method for maintaining prognostic groups balance, completeness of follow up, reporting discontinuation, loss to follow-up, and failure to adhere to the intent to treat (ITT) principle; performing analyses considering all subjects for whom outcome data were clinically evaluable; there is no selective outcome reporting and finally no use of any invalidated outcome measures. The risk of bias tool, version 2.0 (Cochrane) will be used for the risk of bias assessment.

Data synthesis

The purpose of the current protocol of systematic review and meta-analysis is to assess the role of DOAC in ACS, compare and explore the efficacy and safety of the DOAC class members (apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban) with antiplatelets (single or dual) in terms of reduction in ischemic events as well as to guide protocol design for future randomized trials. The data synthesis will be qualitative and descriptive data will be presented, and inferential statistics and meta-analysis will be performed.

Exploration of variation in effects

The variations of effects (heterogeneity) in the RCTs included in the current systematic review and meta-analysis comprised a set of clinical covariates (clinical heterogeneity) from the relevant population level (matched groups of ACS, such as STEMI versus NSTEMI versus unstable angina), the intervention level (intervention vs. comparator), outcomes level (ITT: clinical success, reduction in MACE, hospitalization, and mortality. We will conduct meta-analysis in the current systematic review as well as reporting the sensitivity analysis. However, we also plan structured synthesis of data and comparison between the inferences in the respective trials. Data will be pooled using random-effects models. Data analysis and strategy for data synthesis: The data synthesis (quantitative, qualitative, descriptive, inferential statistics and meta-analysis) will be carried out. The quantitative synthesis for the variation in effects (clinical heterogeneity) in the trials included will be at all levels of trials. Inferential statistics will be conducted for each type of intervention. We will present measures of statistical uncertainty, sensitivity analysis, changes in the protocol, assumptions, and subgroup analysis. The strength of the body of evidence will be assessed (e.g., GRADE). The studies type of randomization technique (methodological heterogeneity), will be retrieved and reported.

The operational definitions

The operational definitions used to define ACS types will be shown in appendices. The excluded trials, and the reasons for exclusion will be presented too. The full electronic search strategy in database, limits of search used, check of duplication as per the PRISMA guidelines, will be shown in; [Figure-diagram 1]. The PRISMA chart and the complete PRISMA form will be provided in the supplementary material. The below-mentioned definitions will be used in the current systematic review and meta-analysis.

Secondary prevention: This is the long-term treatment to prevent recurrent cardiac morbidity and mortality, and to improve quality of life in people who had either MI or ACS, or who are at high risk of ischemic cardiac events for other reasons, such as severe coronary artery stenosis or prior coronary surgical procedures.

MACE: Major adverse cardiovascular events (cardiac death, non-fatal and fatal MI and stroke) sometimes termed major adverse clinical events (MACCE), which is a composite of total death, MI, coronary revascularization, stroke, and
Table 1. FDA compelling indication and off-label use of DOAC

<table>
<thead>
<tr>
<th>Target therapy</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
<th>Betrixaban</th>
<th>FDA labelled indication</th>
<th>Off-label use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke prevention in NVAF</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Treatment of DVT and PE</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of recurrent DVT and PE</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of thromboembolism after total knee replacement and hip replacement</td>
<td>Y</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of thromboembolism after hip replacement</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of thromboembolism in hospitalized acutely ill medical subjects</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of DVT and PE in adults hospitalized for acute medical illness</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of major cardiovascular events in subjects with chronic CAD and PAD</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of thromboembolism after PCI with NVAF</td>
<td>Off</td>
<td>Off</td>
<td>-</td>
<td>Off</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of thromboembolism after PCI with PAD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Off</td>
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<tr>
<td>Treatment of heparin induced thrombocytopenia</td>
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<td>-</td>
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<td>-</td>
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<tr>
<td>Prevention and treatment of cancer associated DVT</td>
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<tr>
<td>Prevention of thromboembolism in hospitalized acutely ill medical subjects</td>
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<tr>
<td>Prevention of thromboembolism after PCI with PAD</td>
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<td>Off</td>
<td>-</td>
</tr>
<tr>
<td>Prevention of thromboembolism after PCI with NVAF</td>
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<td>-</td>
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<td>Off</td>
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</table>

Keys
- CAD: coronary artery disease; DVT: deep vein thrombosis; FDA: Food Drug Agency; NVAF: Non valvular atrial fibrillation; Off: Off-label use; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; PE: pulmonary embolism, Y: Yes, compelling indication.
Renato (2019) conducted an international, multi center, randomized clinical trial, with two-by-two factorial designed subjects with AF who had ACS or had undergone PIC and planning to take P2Y12 inhibitor to receive apixaban or a vitamin K antagonist (VKA) and to receive aspirin or matching placebo for 6 months (4614 subjects from 33 countries). Among the subjects who underwent randomization, 1714 of 4595 (37.3%) had ACS and underwent PCI, 1097 (23.9%) had medically managed ACS, and 1784 (38.8%) underwent elective PCI. 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 patient receiving aspirin as compared with 9.0% of those receiving placebo. 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 ischemic event that was similar to that in the placebo.16

Pascal Vranckx (2019) conducted RCT, multicenter, open-label, non-inferiority phase 3b trial (ENTRUST-AF PCI) with 1506 subjects who were diagnosed with PCI with AF were randomly assigned to receive an open-label edoxaban-based regimen (751) or a VKA-based regimen (755). 746 (99%) subjects assigned to the edoxaban-based regimen and 740 (98%) assigned to the VKA regimen received at least one dose of their assigned drug. The median CHA2DS2-VASc score was 4-0, and the median HAS-BLED score was 3-0. 456 (30%) subjects had previously used VKAs and 365 (24%) had used DOAC. After random group assignment, 1391 (92%) of 1506 subjects were treated with clopidogrel. 147 (20%) of 746 subjects assigned to the edoxaban regimen started with an adjusted dose of 30 mg. Among subjects assigned to the VKA regimen, triple antithrombotic therapy was taken for a median of 66 days. The median follow-up time in the trial was 364 days. At 12 months, the main efficacy outcome (the composite of CV death, stroke, MI, and definite stent thrombosis) occurred in 49 (7%) of 751 subjects (annualized event rate 7.3%) receiving the edoxaban compared with 46 (6%) of 755 (annualized event rate 6.9%) subjects receiving the VKA. The trial showed that, among subjects with AF who had successful PCI, a full-dose anticoagulation therapy with edoxaban 60 mg once daily plus a P2Y12 inhibitor is non-inferior to a triple therapy with VKA (aspirin given for 1–12 months) regarding the risks of major or clinically relevant non-major (CRNM) bleeding events at 12 months.17

E Magnus Ohman (2017) conducted a multicenter, double-blind, randomized trial (GEMINI-ACS-1) at 371 clinical centers in 21 countries, eligible subjects > 18 years with unstable angina (UA), NSTEMI, or STEMI. Subjects received low-dose rivaroxaban (2.5 mg twice daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) or aspirin (100 mg daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor). The primary endpoint was TIMI clinically significant bleeding not related to coronary artery bypass grafting (CABG); (major, minor, or requiring medical attention) up to day 390. The frequency of TIMI non-CABG clinically significant bleeding for rivaroxaban versus aspirin was similar in the ticagrelor stratum compared with the clopidogrel stratum with no significant treatment interactions noted. For the exploratory ischemic endpoint, the frequency of the composite ischemic endpoint of cardiovascular death, myocardial infarction, stroke, or definite stent thrombosis was 76 participants (5%) in the rivaroxaban group versus 72 (5%) with aspirin. Although there was a numerically lower rate of the composite ischemic endpoint with ticagrelor than clopidogrel, this was not statistically significant.18

Stuart J Connolly (2017) conducted multicenter, double-blind, RCT, placebo-controlled, outpatient trial, with a total of 27395 subjects with CAD had to have had a MI in the past 20 years for a duration of 6 months. Eligible and consenting subjects entered a 30-day run-in period during which time they received low-dose rivaroxaban plus aspirin, rivaroxaban alone (with aspirin placebo), or aspirin alone (with rivaroxaban placebo) in a 1:1:1 ratio. Intervention group received low-dose rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day). Comparator group received rivaroxaban alone (5 mg twice a day plus aspirin placebo once a day), or aspirin alone (100 mg once a day plus rivaroxaban placebo twice a day). Subjects in the rivaroxaban alone group had increased major bleeding compared with subjects in the aspirin alone group (95% CI 1.23–1.84, p<0·0001). Intracranial and fatal bleeding were not significantly different between the rivaroxaban plus aspirin group and the aspirin alone group. The low-dose rivaroxaban to aspirin resulted in an improvement in the primary efficacy outcome both in subjects with a previous myocardial infarction (HR 0.74, 95% CI 0.63–0.88) and those without previous myocardial infarction. There were significant reductions in all three secondary outcomes in the low-dose rivaroxaban plus aspirin group compared with aspirin with regard MI, ischemic stroke, coronary heart disease (CHD) death, or acute limb ischemia.19

C. Michael Gibson (2016) conducted international, multicenter, RCT open-label trial., with a total of 2124 subjects with coronary artery for a duration of 12 months. In this study, intervention group received low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2). Comparator group received standard therapy with dose-adjusted (VKA) (once daily) plus DAPT
Hisao Ogawa (2013) held Phase II, RCT, double blind, placebo-controlled trial, were randomly assigned 15,526 subjects with Jessica L. Mega guarantee of any conclusions regarding efficacy.20 although the observed broad confidence intervals diminish the causes, myocardial infarction, or stroke were similar in the standard therapy. The rates of death from cardiovascular 3). The rates of clinically significant bleeding were lower in the apixaban 2.5mg. One patient who was on apixaban 5 mg BID treatment experience cardiac arrest and it any subjects in the apixaban 2.5mg. One patient who was on apixaban 5 mg BID treatment experience cardiac arrest and it considered to be related to the study treatment.21

Jessica L. Mega (2012) conducted double blind, RCT, placebo-controlled trial, were randomly assigned 15,526 subjects with a recent ACS and in whom STEMI, NSTEMI, or UA. Subjects were assigned to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months following double-blind, placebo-controlled trial. Placebo (aspirin; clopidogrel or ticlopidine) aspirin; 100 mg orally once a day). Clopidogrel was 75 mg although loading doses of 300 – 600 mg). The incidence of all bleeding events was significantly higher in the apixaban groups than in the placebo group. The incidence of all bleeding events was greater 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. One patient who was on apixaban 5 mg BID treatment experience cardiac arrest and it considered to be related to the study treatment.21

The primary outcome was the composite of major or clinically relevant minor bleeding during the 6-month treatment period. There were 96 primary outcome events and, compared with placebo, a dose-dependent increase with dabigatran, for 50, 110 mg, 150 mg consecutively. Fourteen (3.8%) subjects died, had a MI or stroke in the placebo group compared with 17 (4.6%) in 50 mg, 18 (4.9%) in 75 mg, 12 (3.0%) in 110 mg, and 12 (3.5%) in the 150 mg dabigatran groups. 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.23

Gabriel Steg (2011) conducted a multi-center, double blind, RCT, parallel group study, with a total of 1279 subjects for a duration of six months. In this study, subjects were assigned to received one of six darexaban regimen for six months (5 mg b.i.d., 10 mg o.d., 15 mg b.i.d., 30 mg o.d., 30 mg b.i.d., or 60 mg o.d). Placebo (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 for six months. Bleeding rates were numerically higher in all darexaban arms versus placebo. Using placebo as reference (bleeding rate 3.1%), there was a dose—response relationship for increased bleeding with increasing darexaban dose (6.2, 6.5, and 9.3% for 10, 30, and 60 mg daily, respectively), which was statistically significant for 30 mg BID. Darexaban when added to dual antiplatelet therapy 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.

Debilitating in nature or not tolerated, or Combination of ASA 75–325 mg and clopidogrel 75 mg daily for six months. The primary outcome was the composite of major or clinically relevant minor bleeding during the 6-month treatment period. There were 96 primary outcome events and, compared with placebo, a dose-dependent increase with dabigatran, for 50, 110 mg, 150 mg consecutively. Fourteen (3.8%) subjects died, had a MI or stroke in the placebo group compared with 17 (4.6%) in 50 mg, 18 (4.9%) in 75 mg, 12 (3.0%) in 110 mg, and 12 (3.5%) in the 150 mg dabigatran groups. 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.23


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aspirin (75 to 100 mg per day) for 1, 6, or 12 months (group 3). The rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy. The rates of death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups. The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the guarantee of any conclusions regarding efficacy.20
antiplaetelet-warfarin regimen. The use of DOAC in addition to antiplaetelet therapy may prove better safety profile over comparators in subjects with any type/stage of ACS. There are differences aligned between the DOAC members based on of efficacy, precautions, and safety profile and/or ACS type (i.e., STEMI versus NSTEME-ACS).

**SUMMARY**

The effects of the combination of rivaroxaban and aspirin compared with aspirin alone were similar in women compared with men for modified ISTH major bleeding as well as for net clinical benefit.14 In cardiovascular, combination of rivaroxaban and aspirin was associated with lower mortality in comparison with aspirin alone with or without PCI.15 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.16 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 once daily plus a P2Y12 inhibitor is non-inferior to a triple therapy with VKA regarding the risks of major or CRNM bleeding events.17 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 clopidogrel, this was not statistically significant.18 The low-dose rivaroxaban to aspirin resulted in an improvement in the primary efficacy outcome both 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 group compared with aspirin with regard myocardial infarction, ischemic stroke, coronary heart disease death, or acute limb ischemia.19

The international multicenter study, of three groups (low-dose rivaroxaban 15 mg once daily plus a P2Y12 inhibitor for 12 months - group 1), very-low-dose rivaroxaban 2.5 mg twice daily plus DAPT for 1, 6, or 12 months - group 2), Compared to group received (standard therapy with dose-adjusted VKA once daily plus DAPT aspirin 75 to 100 mg per day for 1, 6, or 12 months - group 3) had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy.20

In the study by Hisao Ogawa the incidence of all bleeding events was greater 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, Mls, or cases of UA during the study were observed for any subjects in the apixaban 2.5mg.21

Jessica L. Mega stated that rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo. The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular, a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting.22

The study by Jonas Oldgren reported that, dabigatran, in addition to dual antiplaetelet therapy, was associated with a dose-dependent increase in bleeding events and significantly reduced coagulation activity in subjects with a recent myocardial infarction.23

Darexaban when added to dual antiplaetelet therapy 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.

Rivaroxaban reduced the main secondary efficacy endpoint of death, myocardial infarction, or stroke compared with placebo.25

**CONCLUSION**

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

**LIST OF ABBREVIATIONS**

ACS Acute coronary syndrome
AF Atrial fibrillation
CABG Coronary artery bypass graft
CAD coronary artery disease
CHD coronary heart disease
CI confidence interval
CRNM clinically relevant non-major
CV cardiovascular
DAPT Dual antiplatelet therapy
DOAC Direct oral anticoagulant
DVT Deep venous thrombosis
FDA Food Drug Administration
HAS-BLED Hypertension, Abnormal Renal function,
Liver Function, Stroke, Bleeding History or Predisposition,
Labile INR, Elderly, Drugs/Alcohol Concomitantly
HR hazard ratio
IHD ischemic heart disease
ISTH International Society on Thrombosis and Hemostasis
MACCE Major adverse cardiovascular and cerebrovascular
AUTHORS’ CONTRIBUTIONS

We declare that all authors, have made substantial contributions to the conception, design of the work; the acquisition, analysis, interpretation of data, drafted the work, revised it critically 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.

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