El- Khidir IY, Elnour AA, Al Amoodi A, Alrashdi AA, Almansour HH, Almarwani TA, Alrowaili SF, Al Khudhairy SL, Alshammari AF, Sadeq A, Al Mazrouei N, Al-Kubaisi KA, EL Khidir HY, Alkaabi M, Ashoor A. Protocol for systematic review and meta-analysis on randomized clinical trials for direct oral anticoagulant in subjects with acute coronary syndrome. Pharmacy Practice 2023 Apr-Jun;21(2):2811.
https://doi.org/10.18549/PharmPract.2023.2.2811

Original Research

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

Israa Y El- Khidir [ID], Asim Ahmed Elnour [ID], Abdulla Al Amoodi [ID], Abrar Ayad Alrashdi [ID], Haifa Hamoud Almansour [ID], Teif Abdulkarim Almarwani [ID], Shahad Fayad Alrowaili [ID], Shouq Lutfi Al Khudhairy [ID], Asma Faisal Alshammari [ID], Adel Sadeq [ID], Nadia Al Mazrouei [ID], Khalid Awad Al-Kubaisi [ID], Hala Yousif EL Khidir [ID], Maisoun Alkaabi [ID], Afaf Ashoor [ID]

Received (first version): 31-Dec-2022   Accepted: 24-Jan-2023   Published online: 08-Jun-2023

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 antiplatelet 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 antiplatelet 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.

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)

Israa Yousif EL KHIDIR. Assistant Professor, Department of Clinical Pharmacy & Pharmacy Practice, (PhD, MSc, B Pharm), College of Pharmacy, Najran University, Kingdom Saudi Arabia. israamak81@gmail.com
Asim Ahmed ELNOUR*. PhD, MSc. Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Abu Dhabi campus, Abu Dhabi-United Arab Emirates. AAU Health and Biomedical Research Center, Al Ain University, Abu Dhabi, United Arab Emirates. asim.ahmed@aau.ac.ae
Abdalla ALAMOODI. Ambulatory Healthcare Services, Academic Affairs, Abu Dhabi Health Services (SEHA), UAE. alamoodi@seha.ae
Abrar Ayad ALRASHDI. Pharmacy student, College of Pharmacy, University of Hail (UOH), Hail - Saudi Arabia. ayaadabrar@gmail.com
Haifa Hamoud ALMANSOUR. Pharmacy student, College of Pharmacy, University of Hail (UOH), Hail - Saudi Arabia. haifa.alm6@gmail.com
Teif Abdulkarim ALMARWANI. Pharmacy student, College of Pharmacy, University of Hail (UOH), Hail - Saudi Arabia.

anan20100@gmail.com
Shahad Fayad ALROWAILI. Pharmacy student, College of Pharmacy, University of Hail (UOH), Hail - Saudi Arabia. shahad1421@outlook.sa
Shouq Lutfi Al KHUDHAIRY. Pharmacist (Pharm D), Umm Al Quraa University (UQU), Makkah- Saudi Arabia. Shouq.Alkhudhayri@gmail.com
Asma Faisal ALSHAMMARI, (Pharmacy student), College of Pharmacy, University of Hail (UOH), Hail - Saudi Arabia. asmafa4@yahoo.com
Adel SADEQ. PhD, MSc. Associate Professor, Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain-UAE. adel.sadeq@aau.ac.ae
Nadia Al MAZROUEI. Department of Pharmacy Practice and Pharmacotherapeutics, Faculty of Pharmacy, University of Sharjah, United Arab Emirates. nalmazrouei@sharjah.ac.ae
Khalid Awad AL-KUBAISI. Department of Pharmacy Practice and Pharmacotherapeutics, College of Pharmacy-University of Sharjah, United Arab Emirates. kalkubaissi@sharjah.ac.ae
Hala Yousif EL KHIDIR. Medical Doctor, King Abdul-Aziz

Article distributed under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International (CC BY-NC-ND 4.0) license

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)
© the Authors

Hospital, Makkah- Kingdom Saudi Arabia. d.hala5423140@gmail.com

Maisoun ALKAABI. General Manager, New Medical Center (NMC) Royal Women's Hospital, Abu Dhabi, UAE. maisounalkaabi@gmail.com; maisoun.alkaabi@nmc.ae

Afaf ASHOOR. Cardiologist, Alkuwaiti hospital-Dubai, UAE. dr_afaf18@hotmail.com

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 in subjects with coronary artery disease (CAD) undergoing PCI has been found to be associated with a lower incidence of clinically relevant bleeding events, but with similar risk of MACE, all-cause death, and cardiovascular death.[3]

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.[4-10] 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 (PICOs)

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 antiplatelet 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 antiplatelet 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 [NSTE-ACS])?

Objective of the review

We intend to assess the role of DOAC in addition to single or dual antiplatelet 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 [PICOs]) 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

angina). 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 CIANHL, EBESCO, EMBAE, NLM, PubMed, Scopus, and Web-of-Science. We will also retrieve the
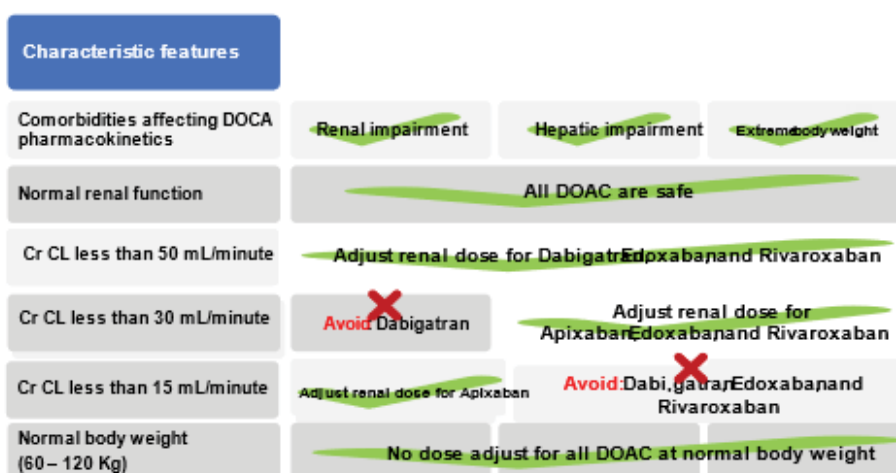

Figure 1. The characteristics features of DOAC

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 and assess quality and validity. Data extraction (selection and coding) will be performed on the relevant variables from the original RCT and supplementary materials. The data extraction will contain trial registration, study country, number of involved countries (trial centers), type of ACS, trial duration, follow-up duration, DOAC member, SAPT, DAPT, the efficacy data, primary endpoint (outcomes measures), the safety outcomes (adverse events) for the included trials. The above 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 RCT-s and assessment of risk of bias

In order to minimize and avoid bias in the selection of RCT-s for the current systematic review and meta-analysis, the quality of the RCT-s 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

hospitalization. **Stent thrombosis** is added by some authors to MACE.

MACCE: Major adverse cardiovascular and cerebrovascular events (stroke), including all-cause and cardiovascular mortality, ischemic stroke non-fatal MI, urgent revascularization, and transient ischemic attack (TIA).

Other terms which have been adapted were in Appendix 2 (illustration of bleeding criteria) as follows: -

Thrombolysis in myocardial infarction (TIMI) Major bleeding: Bleeding with a hemoglobin drop of ≥5 g/dL, intracranial hemorrhage or fatal bleeding regardless of whether or not a bleeding site had been identified, [19]; TIMI minor bleeding: bleeding with a hemoglobin drop of ≥3 to <5 g/dL with an identified bleeding site or if the patient had spontaneous gross hematuria, hemoptysis, or hematemesis, [19]); Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO, [20]); and Criteria of the International Society on Thrombosis and Hemostasis (ISTH, [21]).

DAPT: We have used the term dual antiplatelet therapy (DAPT) to indicate any antiplatelet (clopidogrel or prasugrel or ticagrelor) plus aspirin. While the terms dual antithrombotic therapy indicates the use of any antiplatelet or aspirin (SAPT) plus DOAC, the term triple antithrombotic therapy indicated the use of DOAC plus the DAPT.

RESULTS AND DISCUSSIONS

The Food and Drug Agency (FDA) compelling indication and off-label use of DOAC was exhibited in Table 1. The use of DOAC in valvular heart disease (VHD) was shown in Table 2. The characteristics features of DOAC were depicted on Figure 1.

Further in 2021 Yan Liang conducted This study was a multicenter, double-blind, randomized, placebo-controlled trial included 27395 of which subjects randomized 18278 two groups: Group one 9152 subjects receive rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily. Group two are 9126 subjects receive aspirin 100 mg once daily. Then follow up all subjects for f 23 month. The effects of the combination of rivaroxaban and aspirin compared with aspirin alone were similar in women and men for the primary outcome of cardiovascular (CV) death, stroke, or MI as well as for the expanded composite of CV death, ischemic stroke, MI, or vascular amputation. The effects of the rivaroxaban plus aspirin compared with aspirin alone were similar in women compared with men for modified ISTH major bleeding, and for net clinical benefit.[14] In 2020 Bainey conducted a double-blind, RCT (COMPASS trial), 27 395 subjects with chronic coronary syndromes or peripheral arterial disease (PAD). Subjects were receiving rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily with matching placebo twice daily, compared with aspirin 100 mg once daily with matching placebo for the prevention of the composite of CV death, MI, or stroke among those subjects with a history of stable CAD. There were 471 (4.8%) subjects who had the primary outcome event. In comparison with aspirin, the combination of rivaroxaban and aspirin was associated with fewer MACE regardless of previous PCI. As for CV mortality, the combination of rivaroxaban and aspirin was associated with lower mortality in comparison with aspirin alone with or without PCI.[15]

Table 1. FDA compelling indication and off-label use of DOAC					
	Apixaban	**Dabigatran**	**Edoxaban**	**Rivaroxaban**	**Betrixaban**
Target therapy	**FDA labelled indication**				
Stroke prevention in NVAF	Y	Y	Y	Y	-
Treatment of DVT and PE	Y	Y	Y	Y	-
Prevention of recurrent DVT and PE	Y	Y	-	-	-
Prevention of thromboembolism after total knee replacement and hip replacement	Y	-	-	Y	-
Prevention of thromboembolism after total hip replacement		Y	-		-
Prevention of thromboembolism in hospitalized acutely ill medical subjects	-	-	-	Y	-
Prevention of DVT and PE in adults hospitalized for acute medical illness	-	-	-	-	Y
Prevention of major cardiovascular events in subjects with chronic CAD and PAD	-	-	-	Y	-
Target therapy	**Off-label use**				
Prevention of thromboembolism after PCI with NVAF	Off	Off	-	Off	-
Prevention of thromboembolism after PCI with PAD	-	-	Off	-	-
Treatment of heparin induced thrombocytopenia	Off	-	-	-	-
Prevention and treatment of cancer associated DVT	Off	-	Off	-	-
Prevention of thromboembolism in hospitalized acutely ill medical subjects	Off	-	-	-	-
Prevention of thromboembolism after total knee replacement and hip replacement	-	-	Off	-	-
Prevention of thromboembolism after total knee replacement	-	Off	-	-	-

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.

Table 2. The compelling indication of DOAC in valvular heart disease (VHD)					
Use of DOAC in VHD	**Apixaban**	**Dabigatran**	**Edoxaban**	**Rivaroxaban**	**Betrixaban**
Mechanical prosthetic valve	X	X	X	X	Not indicated
Moderate to severe mitral stenosis	X	X	X	X	Not indicated
Bioprosthetic valve	OK	OK	OK	OK	Not indicated

Keys
VHD: valvular heart disease; X: contraindicated; OK: 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 nonmajor 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

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]

Hisao Ogawa (2013) held Phase II, RCT, double blind, placebo-controlled study in Japanese subjects with ACS either as MI UA. We enrolled 151 subjects. Median age of subjects was 64 years and 87.0% of the subjects were male. All the groups receive standard antiplatelet therapy for 24 hours. The first group were receiving apixaban 2.5 mg twice daily, while the second group receive apixaban 5mg twice a day. The third group were under placebo. 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]

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) for a mean of 13 months and up to 31 months. Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7%, with significant improvement for both the twice-daily 2.5-mg dose and the twice-daily 5-mg dose. The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% versus 4.1%, P= 0.002) and from any cause (2.9% versus. 4.5%, P= 0.002), 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]

Jonas Oldgren (2011) conducted a double blind, placebo-controlled, dose-escalation trial. Participant's enrollment included 1861 subjects randomly assigned hospitalized subjects with non-ST or ST-segment elevation myocardial infarction within the last 14 days.1861 subjects (99.2% on dual antiplatelet treatment) in 161 centers were enrolled at mean 7.5 days (SD 3.8) after STEMI (60%) or non-STEMI (40%) MI and randomized to twice daily treatment with dabigatran 50 mg, 75 mg, 110 mg, 150 mg for 6-month treatment period. Placebo (aspirin ≤100 mg; clopidogrel was 75 mg although loading doses of 300 – 600 mg) for 6-month treatment period.

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 regimens 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.

J L Mega (2009) conducted double-blind, dose-escalation, phase II study, with a total of 3491 subjects for a duration of 6 months. In this study, subjects were stratified on the basis of investigator decision to use aspirin only (stratum 1, n= 761) or aspirin plus a thienopyridine (stratum 2, n= 2730). 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 once daily or the same total daily dose given twice daily. Comparator Placebo Aspirin (75–81 mg daily) only or aspirin plus a thienopyridine for 6 months. The risk of clinically significant bleeding with rivaroxaban versus placebo increased in a dose-dependent manner (for 5, 10, 15, and for 20 mg doses; P<0.0001). Rates of the primary efficacy endpoint were 5.6% (126/2331) for rivaroxaban versus 7.0% (79/1160) for placebo (HR 0.79 [0.60–1.05], p=0.10). Rivaroxaban reduced the main secondary efficacy endpoint of death, MI, or stroke compared with placebo. The most common adverse event in both groups was chest pain (248/2309 [10.7%] versus 118/1153 [10.2%].[25]

Finally, in subjects with any type/stage of ACS, the use of DOAC such as apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban in addition to DAPT may prove non-inferiority or superiority over comparators in terms of reduction in ischemic events. In subjects with ACS with concurrent AF, DOAC may provide suitable addition to SAPT or DAPT as compared to

antiplatelet-warfarin regimen. The use of DOAC in addition to antiplatelet 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 NSTE-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, MIs, 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 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]

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.

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, cos-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

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
ODI   Oral direct inhibitor
P2Y12   Adenosine diphosphate receptor subtype
PAD   Peripheral arterial disease
PAOD   Peripheral arterial occlusive disease
PCI   Percutaneous coronary intervention
PE   Pulmonary embolism
PROSPERO   International Prospective Register of Ongoing Systematic Reviews
RCT   Randomized clinical trial
RCT-s   Randomized clinical trials
SAPT   Single antiplatelet therapy
SODA   Specific oral direct anticoagulant
START   Survey on anTicoagulated pAtients Regis-Ter
STEMI   ST-segment elevation myocardial infarction
TIA   Transient ischemic attack
TIMI   Thrombolysis in myocardial infarction
TSOAC   Target-specific oral anticoagulant
UA   unstable angina
VKA   Vitamin K antagonist
VTE   Venous thromboembolism

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.

Amendments: We plan to document important protocol amendments.

DECLARATIONS

Support sources: There is no any financial support or funding for this protocol of systematic review.

Sponsor: There is no any funder or sponsor for this protocol of systematic review.

Role of funder, sponsor and/or institution: There is no any funder, sponsor or institution for this systematic review.

Conflicts of interest/Competing interests: No conflicts of interest or competing interests

Ethics approval: Ethics approval not required for this type of protocol.

Prosperous registration: Registered.

Consent to participate: Not applicable.

Consent for publication: We declare our consent for the publication of our article.

Availability of data and material (data transparency): There was no any associated data.

Acknowledgements: No acknowledgement

References

1. Lip GYH, Laroche C, Dan G-A, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: Baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. EP Eur. 2014;16(6):308-319. https://doi.org/10.1093/europace/eut373

2. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: Primary results of the PREvention oF thromboemolic events—European Registry in Atrial Fibrillation (PREFER in AF) EP Eur. Europace. 2014;16(1):6-14. https://doi.org/10.1093/europace/eut263

3. Kheiri B, Simpson TF, Osman M, et al. Safety and efficacy of short-term (1 to 3 months) dual antiplatelet therapy in patients undergoing percutaneous coronary interventions: a meta-analysis of randomized controlled trials [published online ahead of print, 2020 Jun 30]. J Thromb Thrombolysis. 2020;50(4):867-873. https://doi.org/10.1007/s11239-020-02069-9

4. Ogawa H, Goto S, Matsuzaki M, et al. APPRAISE-J Investigators. Randomized, double-blind trial to evaluate the safety of apixaban with antiplatelet therapy after acute coronary syndrome in Japanese patients (APPRAISE-J). Circ J. 2013;77(9):2341-2348. https://doi.org/10.1253/circj.cj-13-0209

5. Alexander JH, Becker RC, Bhatt DL, et al. APPRAISE Steering Committee and Investigators. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009;119(22):2877-2885. https://doi.org/10.1161/circulationaha.108.832139

6. Alexander JH, Lopes RD, James S, et al. APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365(8):699-708.

7. Mega JL, Braunwald E, Mohanavelu S, et al. ATLAS ACS-TIMI 46 Study Group. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009;374(9683):29-38. https://doi.org/10.1016/s0140-6736(09)60738-8

8. Mega JL, Braunwald E, Wiviott SD, et al. ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary

syndrome. N Engl J Med. 2012;366(1):9-19. https://doi.org/10.1016/s0019-4832(12)60037-6

9. Steg PG, Mehta SR, Jukema JW, et al. RUBY-1 Investigators. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Eur Heart J. 2011;32(20):2541-2554. https://doi.org/10.1093/eurheartj/ehr334

10. Oldgren J, Budaj A, Granger CB, et al. RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011;32(22):2781-2789. https://doi.org/10.1093/eurheartj/ehr113

11. Leonardo Mees Knijnik, Marcelo Fernandes, Manuel Rivera Maza, et al. Direct oral anticoagulants strategies in acute coronary syndromes: systematic review and network meta-analysis. J Am Coll Crdiol. 2020;75 (11_ Supplement_1)55. https://doi.org/10.1016/S0735-1097(20)30682-3

12. Moher D, Larissa Shamseer, Mike Clarke, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1. https://doi.org/10.1186/2046-4053-4-1

13. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. https://doi.org/10.1016/0197-2456(95)00134-4

14. Yan Liang, Jun Zhu, Lisheng Liu, et al. Efficacy and safety of rivaroxaban plus aspirin in women and men with chronic coronary or peripheral artery disease. Cardiovascular Research. 2021;117(3):942-949. HTTPS://DOI.ORG/10.1093/CVR/CVAA100

15. Kevin R. Bainey, Robert C. Welsh, Stuart J. Connolly, et al. Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). Circulation. 2020;141(14):1141-1151. https://doi.org/10.1161/CIRCULATIONAHA.119.044598

16. Lopes RD, Heizer G, Aronson R, et al. AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Eng J Med. 2019;380(16):1509-1524. https://doi.org/10.1056/NEJMoa1817083

17. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet. 2019;394(10206):1335-1343. https://doi.org/10.1016/S0140-6736(19)31872-0

18. Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. Lancet. 2017;389(10081):1799-1808. https://doi.org/10.1016/S0140-6736(17)30751-1.

19. Connolly SJ, Eikelboom JW, Bosch J, et al. COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391(10117):205-218. https://doi.org/org/10.1016/S0140-6736(17)32458-3

20. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med. 2016;375(25):2423-2434. https://doi.org/10.1056/NEJMoa1611594

21. Ogawa H, Goto S, Matsuzaki M, et al. APPRAISE-J investigators. Randomized, double-blind trial to evaluate the safety of apixaban with antiplatelet therapy after acute coronary syndrome in Japanese patients (APPRAISE-J). Circ J. 2013;CJ-13-0209. https://doi.org/10.1253/circj.CJ-13-0209

22. Mega JL, Braunwald E, Wiviott SD, et al. ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Eng J Med. 2012;366(1):9-19. https://doi.org/10.1056/NEJMoa1112277

23. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Euro H J. 2011;32(22):2781-2789. https://doi.org/doi.org/10.1093/eurheartj/ehr113

24. Steg PG, Mehta SR, Jukema JW, et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Euro H J. 2011;32(20):2541-2554. https://doi.org/10.1093/eurheartj/ehr334

25. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009;374(9683):29-38. https://doi.org/10.1016/S0140-6736(09)60738-8