MASTER IN BIOMEDICINE PROFESSIONAL FOCUS

Assessment of the risk of bleeding in patients with atrial fibrillation and acute coronary syndrome treated by a direct oral anticoagulant and anti-platelets therapy
A systematic review and meta-analysis of randomized controlled trials

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ASSESSMENT OF THE RISK OF BLEEDING IN PATIENTS WITH ATRIAL FIBRILLATION AND ACUTE CORONARY SYNDROME TREATED BY A DIRECT ORAL ANTICOAGULANT AND ANTI-PLATELETS THERAPY

A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Mémoire présenté pour l'obtention

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Assessment of the risk of bleeding in patients with atrial fibrillation and acute coronary syndrome treated by a direct oral anticoagulant and anti-platelets therapy: A systematic review and meta-analysis of randomized controlled trials

GAUTAM Vasudev

Abstract

Background: Atrial fibrillation (AF) is a common cardiac arrhythmia which confers a considerable risk of mortality and morbidity from thromboembolism and stroke. Patients exhibiting AF and coronary artery disease (CAD) with an acute coronary syndrome (ACS) or those who are undergoing Percutaneous Coronary Intervention (PCI) present an interesting challenge, especially since such patients are likely to develop cardiovascular-related mortality and morbidity. To prevent atherothrombotic events, oral anticoagulant therapy is provided with antiplatelet therapy as an auxiliary treatment in such patients. Recent studies have demonstrated that patients on triple therapy with a Vitamin K antagonist (VKA) regimen are at an increased risk of bleeding when compared to those on direct oral anticoagulant (DOAC) triple therapy.
Aim: We aim at performing a systematic review of the literature and a meta-analysis of s randomized controlled trials in patients treated with DOACs in addition to antiplatelet therapy to assess the benefit-risk profile of this strategy. The final objective is to provide a rationale for the restriction of this strategy only in those with a high risk of thrombosis.
Methods: A literature search of journal articles was conducted in 4 electronic databases. After the relevant study selections and extraction of the data, a random effects model was used and the summary statistics collected from each trial, structured around the type of treatment and the type of outcomes was calculated using the Mantel Haenszel Odds ratio (M-H OR). A one way sensitivity analysis assessed the robustness of the findings. Funnel plots were constructed to determine publication bias.
Analysis: In the setting of AF and ACS/PCI, 4 studies were selected and in the setting of DOAC plus antiplatelet therapy vs DOAC alone in AF patients, 4 post hoc studies were selected for the statistical analysis. Observational studies were part of the discussion.
Conclusion: Our meta-analysis shows that in the setting of AF patients with ACS/PCI**,** dual therapy of a DOAC plus an antiplatelet (P2Y12 inhibitor like clopidogrel) is preferable over a triple therapy containing aspirin. In the setting of AF with an indication for concomitant aspirin, it was shown that there was a statistically significant increase in both major bleeding and thromboembolic events. Due to the differences in the population of the recruited patients in terms of their comorbidities, the concomitant medications and the treatment regimens administered to them and the design of the clinical trials, it is advisable for a more calculated and personalised approach in treating higher risk AF patients with the added implementation of platelet function testing (PFT) as well.

Keywords: atrial fibrillation, acute coronary syndrome, percutaneous coronary intervention, direct oral anticoagulants, antiplatelet therapy

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Table of Contents

Abbreviations:

ACS	Acute coronary syndrome
AF	Atrial fibrillation
ASA	Acetylsalicylic acid (aspirin)
b.i.d.	Bis in die (twice a day)
BMS	Bare metal stent
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
COX	Cyclo-oxygenase
CrCl	Creatinine clearance
CYP	Cytochrome P450
DCC	Direct current cardioversion
DES	Drug eluting stent
DOAC	Direct oral anticoagulant
DTI	Direct thrombin inhibitor
ESC	European Society of Cardiology
ISTH	International Society of Thrombosis and Haemostasis
LAA	Left atrial appendage
LMWH	Low molecular weight heparin
MACE	Major adverse cardiovascular event
M-H OR	Mantel-Haenszel Odds ratio
MI	Myocardial Infarction
NA	Not available
NSTEMI	Non-ST elevation myocardial infarction
o.d.	onus in die (once a day)
PCI	Percutaneous coronary intervention
PFT	Platelet function testing
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROBE	Prospective randomized open, blinded end-point
SAN	Sinoatrial node
SD	Standard deviation
SE	Systemic embolism
STEMI	ST-elevation myocardial infarction
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TXA2	Thromboxane A_2
UFH	Unfractionated heparin
VKA	Vitamin K antagonist

Introduction

Atrial fibrillation and coronary heart disease

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias whereas coronary artery disease (CAD) is the most common cardiovascular disease which is characterised by the atherosclerosis in the coronary arteries **[1]**. In patients suffering from AF, the contraction of the atria of the heart is irregular which causes improper relaxation of the cardiac muscle. Consequently, there is a decrease in the heart's cardiac output. The abnormal firing of the electrical impulses in the atria causes the sinoatrial node (SAN) to lose control over the rhythm of the heart **[2].** It is believed that AF is precipitated by the interaction between the initiating triggers, namely the rapidly firing ectopic foci located inside one or more pulmonary veins, and an abnormal atrial tissue substrate which supports the arrhythmia **[3].** As a result, AF promotes the stasis of blood, paving the way for thrombus formation and subsequently causing emboli. This blood stagnation can be attributed to the reduced blood flow and diminished contractility of the left atrial appendage (LAA) **[4].** Due to the thromboembolism, there is a significant risk of mortality and morbidity in this population. This risk is found to be similar among patients with paroxysmal, persistent, or permanent AF **[5]**. In paroxysmal AF, the occurrence of AF is usually self-limiting (within 7 days). In persistent AF, it is present for longer than 7 days and which would require cardioversion for ceasing the arrhythmia, either with drugs or by direct current cardioversion (DCC). Permanent AF exists when the arrhythmia has been present for more than 1 year **[6]**. In some patients, both paroxysmal and permanent AF might progress to become a permanent AF. Preventing stroke is critical in the management of such patients. Ischemic stroke arising from AF was found to be more fatal than non AF stroke **[7].** CHA_2DS_2-VASc score is a clinical risk assessment tool recommended by the European Society of Cardiology (ESC) to be used to predict the risk of stroke and systemic embolism in AF patients. In this composite score, patients with congestive heart failure, hypertension, diabetes, vascular disease, age 65–74, and those belonging to the female sex are given a score of 1 for each corresponding risk factor whereas those with age ≥ 75 and a prior stroke or transient ischemic attack (TIA) or arterial thromboembolism, the score is doubled for the accompanying risk factor **[8].** Likewise, the HAS-BLED score is used to predict the risk of bleeding in these patients.

Acute coronary syndrome (ACS), a subcategory of CAD, is characterised by ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) or unstable angina. CAD is typically asymptomatic while ACS almost always presents with a symptom, such as unstable angina, and is often linked with myocardial infarction (MI) irrespective of the presence of CAD [**9, 10].** Many of the clinical manifestations of ACS are triggered by atherosclerotic plaque rupture of the affected coronary artery with the exposure of the thrombogenic lipid core to the blood flow causing luminal thrombosis **[11]**. The risk of ischemic events like MI and stroke is associated with major bleeding in these patients **[12].** Though the prevalence of CAD in AF patients is around 17% to 46.5%, the prevalence of AF in those with CAD is just around 0.2% to 5% **[1].** However, the incidence of new onset AF is increased in ACS patients especially in those presenting with severe complications **[13].**

More than 80% of AF patients with associated cardiovascular disease are advised for oral anticoagulation and around 20% of them requiring percutaneous coronary interventions (PCI) over time **[14].** Patients with AF are found to develop thrombi which are rich in fibrin when compared to patients with CAD who develop thrombi which are rich in platelets **[15]**. Almost all of these patients are indicated continuous oral anticoagulation and adjunct treatment with antiplatelet agents, either a single antiplatelet therapy or dual antiplatelet therapy **[16].** The type of antiplatelet could be either aspirin or a P2Y12 inhibitor like clopidogrel or the newer P2Y12 inhibitors like prasugrel or ticagrelor which primarily target at the stages of platelet activation and aggregation. As a matter of course, vitamin K antagonists (VKA) like warfarin had remained as the anticoagulant of choice for stroke prevention in AF patients. However, with the advent of the newer direct oral anticoagulants (DOACs), the role of warfarin especially in the context of non-valvular AF is being redefined.

As with the use of any antithrombotic drugs, clinicians need to consider the risks of ischemic stroke and thromboembolism, recurrent cardiac ischemia or myocardial infarction (MI) and/or stent thrombosis, with that of bleeding. Increase in the risk of bleeding in such patients increase the risk of mortality as well [**17]**. Among the OACs of choice in the setting of AF patients with ACS or those undergoing PCI, DOACs have shown to reduce mortality significantly by at least 11% to 12%, stroke and systemic embolism by 18% to 23%, and also intracranial haemorrhage by 21% to 54% compared to warfarin **[18]**. Also, since some DOACs have demonstrated their efficacy in the prevention of ischemic events in patients with only ACS [**19],** the question of whether additional antiplatelet therapy in AF patients with ACS or those undergoing PCI is required arose. Usually, during the first year after a cardiac ischemic event, dual antiplatelet therapy is used to prevent stent thrombosis **[20].**

VKA vs DOACs

VKAs like warfarin work by decreasing the K-dependent γ-carboxylation of clotting factors II, VII, IX, and X but also inhibit the synthesis of some endogenous anticoagulants, proteins C and S **[21].** The superiority of warfarin over antiplatelet therapies alone for AF was demonstrated in the ACTIVE W trial **[22].** Dual antiplatelet therapy, by itself, is not sufficient to provide adequate protection against stroke associated with AF **[23, 24].** However, the use of VKAs has many drawbacks, mainly involving the need to ensure good anticoagulation control and drug interactions **[25]**. As such, in a clinical environment, managing AF patients is difficult owing to the required drug dose adjustments wherein the suboptimal management of therapy with VKAs can lead to a lesser efficacy of the anticoagulant. The incidence of stroke can be reduced with an efficient oral anticoagulation **[26].** Also, for those who have undergone PCI, it is not known to prevent stent thrombosis **[22**, **27].** Additionally, there is a high risk of bleeding with the use of both VKA and dual antiplatelet therapy together **[28].** Increased bleeding events associated with the triple therapy of VKA can interrupt the treatment, thereby putting the patient at risk of ischemic complications **[29]**. Due to these disadvantages, the newer generation of anticoagulants, the

DOACs which do not require close monitoring and present a predictable dose response have found to be attractive alternatives in these scenarios.

Direct thrombin inhibitor

Dabigatran etexilate

Dabigatran is a synthetic reversible direct thrombin inhibitor (DTI). It reversibly binds to the active site on the thrombin molecule, preventing thrombin-mediated activation of coagulation factors **[30].** Since dabigatran, by itself is not lipophilic, its prodrug form (dabigatran etexilate) is provided for oral administration **[31].** For AF patients, two doses of dabigatran are available: dabigatran etexilate 110 mg and dabigatran etexilate 150 mg. It is not influenced by cytochrome P450 (CYP) metabolism. Concomitant administration of p-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin and ticagrelor) results in increased dabigatran plasma concentrations. It has a relatively longer half-life compared to the factor Xa inhibitors but has poor protein binding when compared with the same. The renal excretion is responsible for almost 80% of the total clearance of dabigatran . As such, dose adjustment is advised for those with an impaired renal clearance: 75 mg b.i.d for those with creatinine clearance (CrCl) 15 - 30mL/min **[32]**.

Direct factor Xa inhibitors

Unlike the indirect factor Xa inhibitors like unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux, which have to attach to antithrombin for the initiation of their anticoagulant activity, direct factor Xa inhibitors like rivaroxaban , apixaban and edoxaban do not have to interact with antithrombin but can bind to both soluble and clot bound factor Xa **[33].** The bioavailability of these types of DOACs is higher in comparison to dabigatran.

Rivaroxaban

The coagulation factor Xa promotes thrombin generation by catalysing the cleavage of prothrombin **[34].** Rivaroxaban inhibits factor Xa in a concentration-dependent manner and it is a competitive inhibitor of the amidolytic activity of factor Xa **[35].** It has a half-life of approximately 12 hours. Potent inhibitors of CYP3A4 and P-glycoprotein diminish the clearance of rivaroxaban. Drugs that could alter the gastric pH have no effect on the pharmacokinetics of rivaroxaban. It exhibits high protein binding and so, inversely has a low renal clearance (around 35%). Due to its high binding affinity, a dosing of once a day is sufficient. Normally, it is around 20 mg o.d. Those with a moderate renal impairment (CrCl of 15 - 50mL/min) are recommended a dosage of 15 mg o.d.

Apixaban

Apixaban is selective for factor Xa, with no impact on activated protein C, factor IXa, factor VIIa, or thrombin **[36].** It has a mean half-life of 12.7 hours [**32].** Apixaban is metabolized in the liver mainly by CYP3A4/5 with minor contributions from CYP1A2 and CYP2J2 **[37].** Just like rivaroxaban, CYP3A4 and P-glycoprotein inhibitors reduce its clearance, is highly protein bound (around 87%) and has low renal clearance. It is excreted majorly through the hepatobiliary route (around 50%). Dosing of apixaban for patients is 5 mg b.i.d and a lower dose of 2.5 mg is recommended for the elderly (age > 80 years), those with a decrease in body weight (<60 kg), serum creatinine concentrations ≥ 1.5 mg/dL, or users of strong CYP3A4 and P-gp inhibitors. Renal impairment has no effect on the maximum serum concentration of apixaban **[38]**.

Edoxaban

Edoxaban competitively inhibits factor Xa directly without needing antithrombin and factor Xa in the prothrombinase complex. It is administered as edoxaban tosylate. It has a half-life of around 9-10 hours. Less than 4% of the total edoxaban dose is metabolised by the CYP450 system, mainly CYP3A4**.** Similar to apixaban, it is eliminated mainly through the hepatobiliary route (60%) and to a lesser extent through urine (35%). It has a protein binding affinity of around 55%. Recommended dosing is 60 mg o.d. and the dose is reduced to 30 mg o.d. in patients with CrCl 15–50 mL/min, weight of <60 kg and those on potent p-gp inhibitors **[32].**

Antiplatelet agents

Aspirin (Acetylsalicylic acid)

Thromboxane A_2 (TXA2) is implicated in promoting platelet aggregation. Aspirin is an irreversible inhibitor of cyclo-oxygenase (COX) -1; therefore it contributes in suppressing the synthesis of TXA2 even at lower doses (around 75 mg/day) and at higher doses inhibits COX-2 **[39].** During the absorption phase, aspirin is partly hydrolysed to salicylic acid after oral administration. Salicylic acid is eliminated by renal excretion and by metabolic conversion to conjugates with glycine and glucuronic acid, respectively**.** The half-life of aspirin is dose dependent. Contrary to its anticoagulant counterparts, aspirin is inefficacious in the prevention of thromboembolism in patients with non-valvular AF. It has been shown that oral anticoagulants (both VKAs and DOACs) are superior to aspirin in preventing thromboembolic outcomes in patients who have a CHA_2DS_2-VASc scores ≥2 **[40].**

Clopidogrel

Clopidogrel is a second-generation thienopyridine. It is a prodrug which is converted into its active metabolite by the mediation of the cytochrome P450 (CYP) enzymes **[41].** It has a more rapid onset of action and a dosing regimen which requires the uptake of the drug once daily **[42].** The half-life of clopidogrel is approximately 6-7 hours. Studies have demonstrated that in AF patients, there was a significant reduction in the aggregation of platelets with the combined use of clopidogrel and aspirin when compared to the use of aspirin alone **[43, 44].** The irreversible binding of clopidogrel to $P2Y_{12}$, a subtype of the adenosine diphosphate (ADP) receptor, on the surface of platelets prevents their aggregation**.** It has been shown that there is increased bleeding and cardiovascular events in elderly patients and also those who also have associated comorbidities like diabetes mellitus with the use of clopidogrel and therefore, caution should be exercised in such patients while administering this medication **[45].** The activation of clopidogrel is mainly through cytochrome P450 enzymes, including CYP2C19. At present, clopidogrel is the standard P2Y12 inhibitor used in the setting of AF and ACS patients.

Ticagrelor

Ticagrelor is a reversible noncompetitive, direct-acting $P2Y_{12}$-receptor antagonist. The onset of action of ticagrelor is much faster and it is more potent than clopidogrel. Since it is not a prodrug, it does not require any metabolic activation for its antiplatelet effects to take place **[46].** Though the safety of the drug is not affected by renal impairment, patients with mild hepatic impairment do exhibit slightly elevated levels of both ticagrelor and its active metabolite but without any profound adverse effect on them. There is evidence which shows that it improves the clinical outcomes specifically in ACS patients when compared to clopidogrel **[47].**

Prasugrel

Like clopidogrel, prasugrel is a prodrug which is also an irreversible antagonist of $P2Y_{12}$ ADP receptors. But unlike clopidogrel, it perhaps has lower susceptibility to genetic variations and drug-drug interactions, namely with the inducers or inhibitors of cytochrome P450 enzymes **[78]**. It is metabolised by the carboxylesterase (CES) enzymes: CES1 in the liver and CES2 in the intestines **[65].**

It should be noted that in this review, we have discussed only those DOACs and antiplatelet agents which have been part of the treatment regimens of completed randomised controlled trials.

Methods

Specific Aims

The aims of this systematic review are to determine and review what will be the best strategy to apply for patients with AF suffering from ACS or those undergoing PCI: either the use of triple therapy or dual therapy. Second, we aim at assessing if add-on antiplatelet therapy on top of DOACs in AF patients is a requirement. Indeed, in order to prevent atherothrombotic events, anti-platelet therapy is often administered as an adjunct to anticoagulant therapy, thereby increasing the risk of bleeding in these patients. So, the question then arises to know if this additional anti-platelet therapy is required and if anticoagulant therapy may be sufficient. In this review, atrial fibrillation refers to non-valvular AF exclusively.

Eligibility criteria

Studies which were to be included in the review needed to have study arms where AF patients indicated for DOAC and concomitant antiplatelet therapy [single antiplatelet or dual antiplatelet] for ACS and/or undergoing PCI or for whom there is an indication for a combination therapy. Studies involving patients with central venous catheterization and/ or undergoing electrical cardioversion were excluded.

Literature search

We performed a systematic review and meta-analysis following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement. Figure 1 showcases the PRISMA flowchart. A literature search of journal articles was conducted in the following electronic databases - PubMed, Scopus and the Cochrane database and also in the trial register – clinicaltrials.gov. The search was carried out from 2009 through October 30, 2019. The following search and MeSH terms, but not limited to, were used in our search strategy ‘ atrial fibrillation ‘ OR ‘acute coronary syndrome’ OR ‘coronary heart disease’ OR ‘percutaneous coronary intervention’ AND ‘rivaroxaban’ OR ‘dabigatran etexilate’ OR ‘apixaban’ OR ‘edoxaban’ AND ‘platelet aggregation inhibitors’ OR ‘aspirin’ OR ‘clopidogrel’ OR ‘ticagrelor’ OR ‘prasugrel’. The complete search strategy for the systematic review can be found in the Supplementary appendix. Only English-language publications were considered. Cohort studies will not be included in the meta-analysis since the effect sizes in these studies are affected by confounders as they can vary from one study to the next.

Outcomes of interest

The primary safety outcomes are bleeding [major bleeding, minor bleeding, clinically relevant non-major bleeding, any bleed, and total bleed]. As some studies employ the use of Thrombolysis in Myocardial Infarction (TIMI) or the International Society of Thrombosis and Haemostasis (ISTH) criteria to classify the bleeding outcomes, these scores were considered as well. The secondary efficacy outcomes were the individual and the composite clinical endpoints of stroke and systemic embolism (SE), MI, stent thrombosis and death (MACE).

Data extraction

The title and abstract screening were performed by two reviewers (G.V And H.H). Full-text screening and data extraction were performed by one reviewer (G.V). Discrepancies arising in the review process were resolved by the third reviewer (J.D). A standardized data extraction form was used and the meta-analysis was executed using the software package Comprehensive Meta-Analysis V3. This software permits to compute the desired effect size data in different formats published in studies, thereby allowing multivariate analyses of effect sizes at different time points.

Quality assessment of the randomized trials

To confirm the validity of the included randomized trials, the reviewers will assess the quality of the individual studies using a validated scale (Jadad scale) based on the following criteria: the randomization sequence generation, the method of double blinding, and status of the patients in the trials (withdrawals and dropouts). One point is allocated for each criterion satisfied and one additional point for high quality of randomization and double blinding. The maximum points which can be obtained are 5 points. A study will be considered high quality if the score is > 2 and studies with a score ≤ 2 points will be considered low quality.

Statistical Analyses

The data will be obtained from the relevant studies using summary statistics collected from each trial, structured around the type of treatment and the type of outcomes. A random-effect model will be utilised since it would be improbable that all the studies were functionally identical. This model considers that the results could differ from one study to another. The approaches of these analyses are to breakdown the observed differences into the within-studies and the between-studies variance and then use both the components when assigning the weights. The summaries of treatment effects are provided by calculating the Mantel Haenszel Odds ratio (M-H OR) for each study. Forest plots will be constructed to view the treatment effects. To evaluate the stability of the results, a one-way sensitivity analyses will be performed by removing individual studies, one at a time. Any publication bias will be assessed by visual inspection of a funnel plot and Egger's test.

Results

Study selection

A total of 2227 studies were included for screening from the different databases [Pubmed: 773 articles**,** Scopus **:** 787 articles, Cochrane database : 405 articles, Clinicaltrials.gov: 141 studies], Eleven articles were included out of which 9 were randomised controlled trials, 1 sub-analysis of an randomised controlled trial and 1 cohort study (➤ **Figure 1**). Among the randomised controlled trials in the setting of AF and ACS or undergoing PCI, 4 studies were included namely:

- The Randomized Evaluation of Dual Antithrombotic Therapy with Non valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial **[48].** In addition, a separate meta-analysis is performed for a sub-analysis of the RE-DUAL PCI trial based on the antiplatelet agents used namely clopidogrel and ticagrelor **[49]**
- The Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) trial **[50]**
- The Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention (AUGUSTUS) trial **[51]**
- The Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI) trial **[52]**. However, for the meta-analysis, the data from the ENTRUST-AF PCI trial will not be considered as the patients were not assigned to a triple therapy arm of edoxaban.

In the setting of AF patients who were administered a DOAC with or without a concomitant antiplatelet, 4 randomised controlled trials were included namely:

- The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY trial) [**53]**
- The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial **[54]**
- The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial **[55]**
- The Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial **[56]**

Data were obtained from the sub-analysis of these 4 trials. An observational study using the data from the DIRECT registry in Japan, where AF patients on DOAC either with or without antiplatelets, was included as well **[57]**.

The AFIRE study (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) **[58]** will be discussed as well as it could not be included in our analysis based on our inclusion criteria. In this trial, AF patients were recruited if they underwent PCI or coronary artery bypass grafting (CABG) more than a year ago and where a reduced dose of rivaroxaban (15 mg or 10 mg) was preferred instead of the standard dose of 20 mg for AF and as such, it was not considered for both the settings.

Study and patient characteristics

➤ **Table 1** provides the design and the durations of the randomised controlled trials and the cohort study, the treatment arms considered for the analysis, the safety and the efficacy outcomes and the Jadad score the included studies.

➤ **Table 2** provides the baseline characteristics of patients in randomised controlled trials of AF with ACS/PCI. For the meta-analysis in this setting, a total of 5,468 patients were included from dabigatran etexilate, rivaroxaban and apixaban regimens with 751 patients of the edoxaban regimen from the ENTRUST-AF PCI trial analysed for discussion. 1862 patients were allocated in both the triple therapy and dual therapy arms of the PIONEER AF-PCI and AUGUSTUS trials. The REDUAL –PCI trial had 763 patients in the higher dose (i.e. dabigatran etexilate 150 b.i.d) and 981 patients in the lower dose (i.e. dabigatran etexilate 110 b.i.d) arms of dabigatran etexilate. In the REDUAL-PCI, patients were randomized in a 1:1:1 ratio to either dabigatran etexilate 110 dual therapy [dabigatran 110 mg twice daily (b.i.d) plus a P2Y12 inhibitor (either clopidogrel or ticagrelor)] ; dabigatran etexilate 150 dual therapy [dabigatran 150 mg b.i.d plus either clopidogrel or ticagrelor] ; or warfarin triple-therapy [warfarin plus either clopidogrel or ticagrelor, and aspirin (≤100 mg)]. However, prasugrel was not considered as an antiplatelet agent. In the PIONEER AF-PCI, patients were allocated in a 1:1:1 ratio as well. For group 1, low-dose rivaroxaban - 15 mg once daily (o.d.) plus a P2Y12 inhibitor for 12 months; for group 2, very-low-dose rivaroxaban - 2.5 mg b.i.d plus dual antiplatelet therapy for 1, 6, or 12 months. For group 3, standard therapy with a dose adjusted VKA (o.d.) plus dual antiplatelet therapy for 1, 6, or 12 months. In the AUGUSTUS trial, patients' stratification was based on a two-by-two factorial design where those planning to take a P2Y12 inhibitor were to receive apixaban (5 mg) or a VKA and to receive aspirin or matching placebo for 6 months. In the ENTRUST-AF PCI trial, patients were assigned to either edoxaban (60 mg o.d.) plus a P2Y12 inhibitor for a period of 12

months or a VKA with a P2Y12 inhibitor and aspirin (100 mg o.d. for 1–12 months). Patients in the edoxaban arm could transition to VKA at the end of the trial.

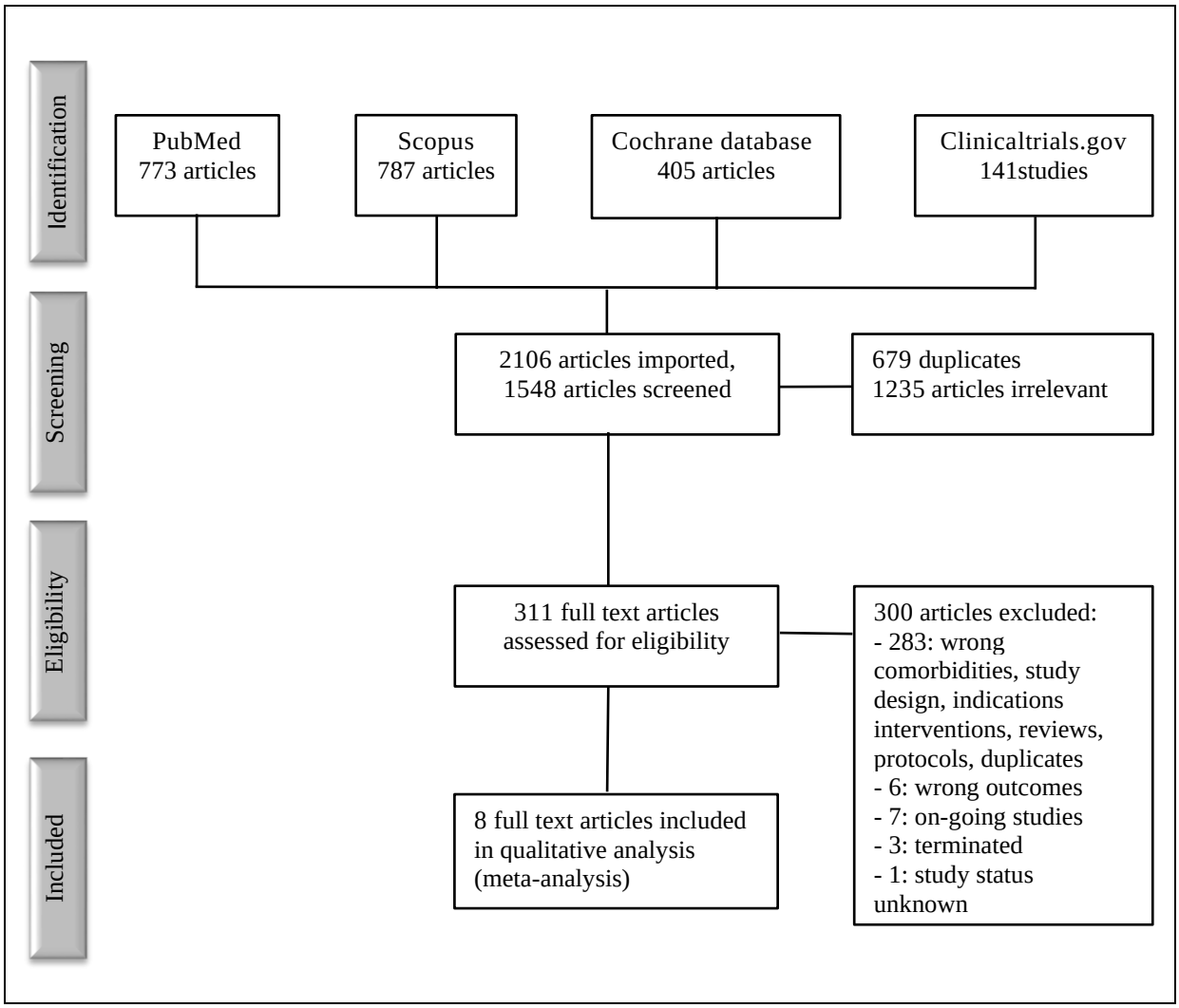

Figure 1: PRISMA flowchart

Altogether, the mean age of the recruited patients varied around 70 years of age. Females accounted for around 24% to 30 % of the total patients with the rest being males. Majority of these patients (both males and females included) were suffering from paroxysmal AF (around 45% to 54%).

➤ **Table 3** provides the baseline characteristics of AF patients in randomized controlled trials of DOACs with or without concomitant antiplatelet therapy. In this setting, a total of 48,216 patients were included for the meta-analysis. Among them, 14,357 patients were allocated in the DOAC plus adjunct antiplatelet therapy and 33,859 patients in DOAC alone. In the RE-LY trial, both dabigatran doses (dabigatran etexilate 110 mg and dabigatran

etexilate 150 mg were compared against warfarin. The trial demonstrated that dabigatran etexilate 150 mg b.i.d was superior and dabigatran etexilate 110 mg b.i.d was noninferior to warfarin in preventing stroke and SE in patients with AF **[59].** Additionally, a subset of patients was receiving antiplatelet drugs at some time during the trial. Out of the antiplatelet drugs provided, many of them were confined to median doses of aspirin with a few on aspirin ≥ 300 mg (1.6 %) , clopidogrel (1.9%) or both (i.e. dual antiplatelet therapy; 4.5%). Similarly**,** in the ROCKET-AF trial, rivaroxaban 20 mg o.d. was noninferior to warfarin **[60],** in the ARISTOTLE trial, apixaban 5 mg b.i.d was superior to warfarin **[61]**, and in the ENGAGE AF-TIMI 48 trial, edoxaban (both 30 and 60 mg o.d.) were non-inferior to warfarin with respect to the prevention of stroke or SE in AF patients **[62].** In these 3 trials, only single antiplatelet therapy was allowed. Aspirin was the only antiplatelet allowed in ROCKET-AF (< 100 mg) and ARISTOTLE (≤ 165 mg) trials. The ENGAGE AF-TIMI 48 trial, like the RE-LY trial, had a minority of patients indicated for clopidorel (7.9%). As opposed to the trials of AF and ACS / PCI, $P2Y_{12}$ inhibitors like prasugrel and ticagrelor were not used in these trials. Both the RE-LY and the ENGAGE AF TIMI 48 trials had a larger percentage of patients with paroxysmal AF, CAD and prior MI placed in the antiplatelet group whereas a similarly large percentage of permanent AF were placed in the group where concomitant antiplatelet therapy was omitted.

➤ **Table 4** provides the baseline characteristics of patients of an observational study from the DIRECT registry. Here, a total of 1739 patients were on any one of the DOAC regimen with 477 patients on DOAC and either a single antiplatelet therapy or dual antiplatelet therapy.

Table 1: Characteristics of the included studies.

Study	Design	Outcomes		Intervention	Comparator	Study duration	Jadad score
		Safety	Efficacy				
AF with ACS / PCI							
NCT02415400 (AUGUSTUS)	2 x 2 factorial design	Bleeding events	MACE	apixaban 5 mg / 2.5mg + P2Y12 inhibitor + ASA 81mg	apixaban 5 mg / 2.5 mg + P2Y12 inhibitor	6 months	5
NCT02164864 (REDUAL-PCI)	PROBE design	Bleeding events	MACE	dabigatran etexilate 150 mg + clopidogrel 75 mg o.d. / ticagrelor 90 mg b.i.d	dabigatran etexilate 110 mg + clopidogrel 75 mg o.d. / ticagrelor 90 mg b.i.d	14 months	3
NCT01830543 (PIONEER AF PCI)	Open label	Bleeding events	MACE	rivaroxaban 2.5 mg b.i.d (1 or 6 months), later rivaroxaban 15 mg o.d. + ASA 75 - 100 mg o.d. + clopidogrel 75 mg o.d. / prasugrel 10 mg o.d. / ticagrelor 90 mg b.i.d , later ASA 75 to 100 mg o.d.	rivaroxaban 15 mg o.d. + clopidogrel 75 mg o.d. / prasugrel 10 mg o.d. / ticagrelor 90 mg b.i.d	12 months	2
NCT02866175 (ENTRUST –AF PCI)	Open label	Bleeding events	MACE	edoxaban (60 mg o.d.) + clopidogrel 75 mg o.d. or prasugrel 5mg/10 mg o.d. or ticagrelor 90 mg b.i.d		12 months	3
DOAC with or without concomitant antiplatelets in AF							
NCT00262600 (RE-LY)	PROBE design	Bleeding events	MACE	dabigatran etexilate 110 mg (b.i.d) + ASA/clopidogrel	dabigatran etexilate 110 mg (b.i.d)	2 years	3
				dabigatran etexilate 150 mg (b.i.d) + ASA/clopidogrel	dabigatran etexilate 150 mg (b.i.d)		
NCT00412984 (ARISTOTLE)	Double blind	Bleeding events	MACE	apixaban 5 mg (b.i.d) + ASA (≤ 165 mg daily)	apixaban 5 mg	20 months	4
NCT00403767 (ROCKET AF)	Double blind	Bleeding events	MACE	rivaroxaban 20 mg o.d. + ASA (mean = 99.2 mg)	rivaroxaban 20 mg o.d	806 days	5
NCT00781391 (ENGAGE AF-TIMI48)	Double blind	Bleeding events	MACE	edoxaban 30 mg + ASA o.d. / clopidogrel 75 mg o.d.	edoxaban 30 mg	2.8 years	5
				edoxaban 60 mg + ASA o.d. / clopidogrel 75 mg o.d.	edoxaban 60 mg		
Observational study							
UMIN000033283 (DIRECT registry)	Prospective observational	Bleeding events	MACE	DOAC + Single antiplatelet / Dual antiplatelet	DOAC	407.2 ± 388.3 days	-

Abbreviations- *ACS: acute coronary syndrome; AF: atrial fibrillation; ASA: acetylsalicylic acid (aspirin); b.i.d: bis in die (twice a day); DOAC: direct oral anticoagulant; MACE: major adverse cardiovascular events; o.d: once a day; PCI: percutaneous coronary intervention; PROBE: prospective randomized open, blinded end-point*

Table 2: Baseline characteristics of patients in randomised controlled trials of AF with ACS/PCI.

Study			PIONEER AF-PCI (2016)		RE-DUAL PCI (2017)		AUGUSTUS (2019)		ENTRUST-AF PCI (2019)
DOAC			Rivaroxaban		Dabigatran etexilate		Apixaban		Edoxaban
Type of therapy			Triple therapy	Dual therapy	DE 150 (Dual therapy)	DE 110 (Dual therapy)	Triple therapy	Dual therapy	Edo (60&30) [Dual therapy]
Sample size- no./ total			709	709	763	981	1153 / 2306	1153 / 2306	751
Age - mean ± SD *Median (interquartile)			70.0 ± 9.1	70.4 ± 9.1	68.6 ± 7.7	71.5 ± 8.9	70.8 * (64.4 – 77.3)	70.4 * (64.1 – 77.2)	69 * (63 - 77)
Female - no. (%)			174 (24.5%)	181 (25.5%)	171 (22.4%)	253 (25.7%)	670 /2306 (29.1%)	696 /2306 (30.2%)	194 (26%)
Male - no. (%)			535 (75.5%)	525 (74%)	592 (77.6%)	728 (74.2%)	1636 / 2306 (70.9%)	1611 / 2306 (69.8%)	557(74%)
HAS-BLED score			NA	NA	2.6 ± 0.7	2.7 ± 0.7	2.9 ± 1.0	2.8 ± 0.9	3.0 (2.0-3.0)
CHA_2DS_2-VASc score			NA	NA	3.3 ± 1.5	3.7 ±1.6	3.9± 1.6	3.9 ± 1.6	4.0 (3.0-5.0)
CrCl (ml/min)			77.5 ± 31.8	78.3 ± 31.3	83.7 ± 31.0	76.3 ± 28.9	2101 / 2274 (< 1.5 mg/dl)		71.8 (53.7- 91.1)
Comorbidity	AF	Paroxysmal - no. (%)	325 (45.8%)	300 (42.4)	380 (49.8%)	487 (49.6%)	1145	1145	402 (54%)
		Persistent - no. (%)	146 (20.6%)	146(20.6%)	132(17.3%)	174(17.7%)			140(19%)
		Permanent - no. (%)	238 (33.6%)	262 (37.0%)	250 (32.8%)	320 (32.6%)			209 (28%)
	ACS - no. (%)		703	701	391 (51.2%)	509 (51.9%)	1420 / 2306 (61.8%)	1391 / 2306 (60.6%)	388 (52%)
	Prior MI- no. (%)		180 (25.4%)	140 (19.8%)	194 (25.4%)	237 (24.2%)	NA	NA	188 (25%)
	History of stroke- no. (%)		NA	NA	52 (6.8%)	74 (7.5%)	297 / 2289 (13.0%)	326 / 2289 (14.2%)	97 (13%)
Type of Antiplatelet used	Aspirin- no. (%)		702 (99.7%)	9 (1.3%)	NA	NA	NA	NA	NA
	P2Y12 inhibitor	Clopidogrel - no. (%)	664 (93.7%)	660 (93.1%)	659 (86.4%)	849 (86.5%)	2105 / 2253 (93.4%)	2105 / 2253 (93.4%)	696 (93%)
		Ticagrelor - no. (%)	34 (4.8%)	37 (5.2%)	104 (13.9%)	132 (13.5%)	121 / 2253 (5.4%)	121 / 2253 (5.4%)	49 (7%)
		Prasugrel - no. (%)	11 (1.6%)	12 (1.7%)	Nil	Nil	27 / 2253 (1.2%)	27 / 2253 (1.2%)	5
Stent	Drug eluting stents - no. (%)		471 / 705 (66.8%)	464 / 709 (65.4%)	621 / 762 (81.5%)	804 / 979 (82.1%)	877 / 2297 (38.2%)		NA
	Bare metal stents - no. (%)		220 / 705 (31.2%)	231 / 709 (32.6%)	123 / 762 (16.1%)	148 / 979 (15.1%)			NA
	Drug-eluting & bare-metal stents - no. (%)		14 / 705 (2.0%)	14 / 709 (2.0%)	10 / 762 (1.3%)	19 / 979 (1.9%)			NA

Abbreviations*- AF: atrial fibrillation; ACS: acute coronary syndrome; CrCl: creatinine clearance, DOAC: direct oral anticoagulant; DE: dabigatran etexilate; MI: myocardial infarction; NA: not available, SD: standard deviation.* ***Note****: As per the published data , the baseline characteristics from the apixaban regimen has been extracted based on the arm, not on the combination of antiplatelet therapy received (no – male, female, ACS, history of stroke, type of antiplatelet used.)*

Table 3 : Baseline characteristics of AF patients in randomised controlled trials of DOACs with or without concomitant antiplatelet therapy

Study		RE-LY				ARISTOTLE		ROCKET AF		ENGAGE AF TIMI 48	
DOAC		Dabigatran etexilate				Apixaban		Rivaroxaban		Edoxaban (E30 & E60)	
Type of therapy		DE110 +APT	DE110	DE150 +APT	DE150	ASA	No ASA	ASA	No ASA	SAPT	No SAPT
Sample size - no./ total		**2322**	**3693**	**2304**	**3772**	**2233** / 4434	**6852** / 13699	**2586** / 5205	**4545** / 9059	**4912**	**14997**
Age - Mean ± SD *Median (interquartile)		71.7 (8.5)	71.2 (8.8)	71.6 (8.6)	71.4 (9.0)	70 *(64, 76)	70* (62, 76)	72 (65, 78)*	73 (66, 78) *	72.0 (64.0-78.0)*	72.0 (64.0–77.0)*
Female— no(%)		763 (32.9%)	1387 (37.5%)	765 (33.2%)	1471 (39%)	1405 / 4434 (31.7%)	4990 /13699 (36.4%)	2011 / 5205 (38.64%)	3649 / 9059 (40.3%)	1566 (31.9%)	5958 (39.7%)
Male — no. (%)		1559 (67.1%)	2306 (62.4%)	1539 (66.8%)	2301 (61.0%)	3029 / 4434 (68.3%)	8709 /13699 (63.5 %)	3194 / 5205 (61.36%)	5410 / 9059 (59.72%)	3346 (68.1%)	9039 (60.3%)
AF	Paroxysmal- no.(%)	906 (39.0%)	1023 (27.7%)	915 (39.7%)	1063 (28.2%)	707 / 4434 (15.9%)	2066 / 13699 (15.1%)	1024 / 5205 (20%)	1490 / 9059 (16%)	1510 (30.8%)	3530 (23.5%)
	Persistent - no. (%)	763 (32.9%)	1187 (32.1%)	719 (31.2%)	1190 (31.5%)	3727 / 4434 (84.1%)	11630 /13699 (84.9%)	4090 / 5205 (79%)	7458 / 9059 (82%)	1211 (24.7%)	3376 (22.5%)
	Permanent- no. (%)	652 (28.1%)	1480 (40.1%)	669 (29.0%)	1519 (40.3%)					2189 (44.6%)	8089 (53.9%)
CAD- no. (%)		950 (40.9%)	711 (19.3%)	977 (42.4%)	733 (19.4%)	2264 / 4434 (51.1%)	4354 / 13699 (31.8 %)	1593/ 5205 (30.6%)	NA	2403 (48.9%)	4172 (27.8%)
Prior MI- no. (%)		572 (24.6%)	436 (11.8%)	581 (25.2%)	448 (11.9%)	1046 / 4434 (23.6%)	1529 / 13699 (11.2%)	1171 / 5205 (22%)	1297/ 9059 (14%)	869 (17.7%)	1395 (9.3%)
History of stroke- no. (%)		304 (13.1%)	457 (12.4%)	296 (12.8%)	460 (12.2%)	501/ 4434 (11.3%)	1624 / 13699 (11.9 %)	2889 / 5205 (55.5%)	4922 / 9059 (54.33%)	1387 (28.2%)	4216 (28.1%)

Abbreviations*- AF: atrial fibrillation; APT: antiplatelet therapy; CAD: coronary artery disease; CI: confidence interval; DE: dabigatran etexilate; MI: myocardial infarction; NA: not available, SAPT: single antiplatelet therapy, SD: standard deviation.*

Note*: As per the published data, the baseline characteristics from the apixaban and rivaroxaban regimens have been extracted based on the arms, not on the type of APT received (no – male, female, AF, CAD, prior MI, history of stroke.)*

Table 4 : Baseline characteristics of patients in the DIRECT registry.

DIRECT registry				
Baseline characteristics of patients treated by DOAC only				
DOAC	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Sample size- no. (%)	527/1739 (30.3%)	438/1739 (25.2%)	429/1739 (24.7%)	345/1739 (19.8%)
Age : mean ± SD	70.7 ± 11.2			
Female-no (%)	656/1739 (37.7%)			
Male - no. (%)	1083/1739(62.2%)			
HAS-BLED score	2.2 ± 1.1			
CHA2DS2-VASc score	3.0 ± 1.8			
CrCl (ml/min)	70.7 ± 31.4			
Baseline characteristics of patients treated by DOAC + single antiplatelet / dual antiplatelet				
Sample size- no. (%)	121/477 (25.3%)	161/477 (33.8%)	109/477 (22.9%)	86/477 (18%)
Age - mean ± SD	71.3±8.8	76.6±8.6	73.0±7.2	78.1±8.4
Female-no (%)	28/121 (23.1%)	65/161 (40.4%)	21/109 (19.3%)	36/86 (41.9%)
Male — no. (%)	93 (76.8%)	96 (59.6%)	88 (80.7%)	50 (58.1%)
HAS-BLED score	3.5±1.0	3.9±0.9	3.9±1.0	4.1±1.0
CHA2DS2-VASc score	3.9±1.5	5.0±1.6	4.6±1.5	5.1±1.6
CrCl (ml/min)	69.2±22.0	53.5±19.8	66.1±23.0	53.3±21.7
AF – no. (%)	121/477 (25.4%)	161/477 (33.8%)	109/477 (22.9%)	86/477 (18.0%)
CAD – no. (%)	46/121 (38.0%)	69/161 (42.9%)	44/108 (40.7%)	41/86 (47.7%)
Prior stroke – no. (%)	40/121 (33.1%)	55/161 (34.2%)	40/109 (36.7%)	29/86 (33.7%)

***Abbreviations**: AF: atrial fibrillation; CAD: coronary artery disease; CrCl: creatinine clearance; DOAC: direct oral anticoagulant; SD – standard deviation*

Analysis

Studies assessing patients with AF and ACS/PCI

Safety outcome

From the forest plot, we can see that the use of triple therapy of apixaban, P2Y12 and aspirin doubles the risk of bleeding compared to the dual therapy of apixaban and P2Y12 inhibitor, (M-H OR: 2.131, 95% CI: 1.287 – 3.527, *p= 0.003;* ➤ **Figure 2 and Table 5**). The summary effect shows a 40% increase in the risk of bleeding with the use of triple therapy regimen though this is found to be statistically non-significant (M-H OR: 1.404, 95% CI 0.609 – 3.233, *p=0.426*). Publication bias cannot be assessed with just two included studies.

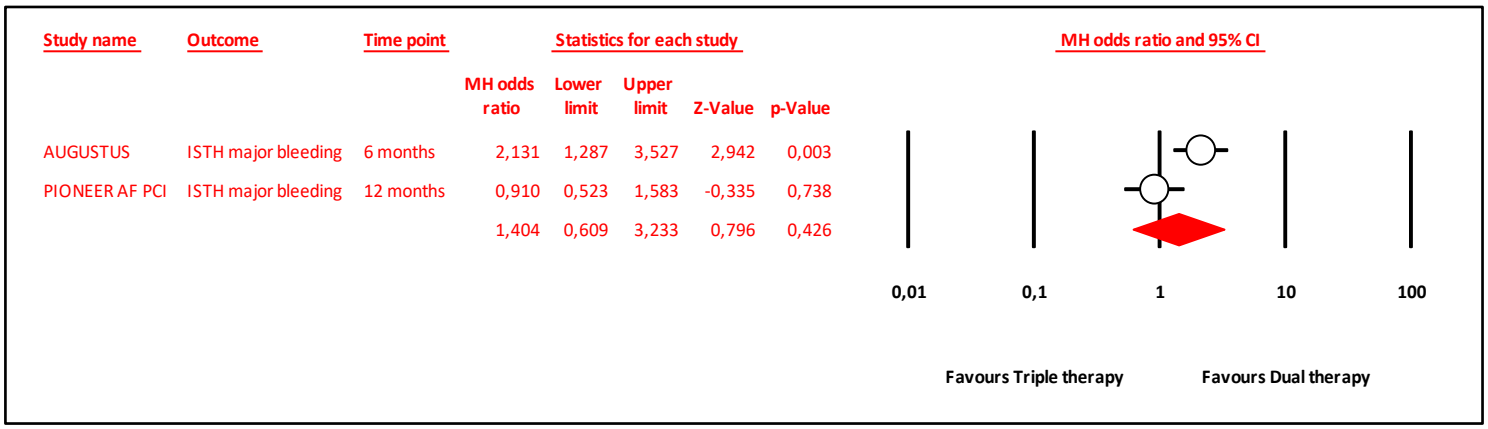

Figure 2 – Forest plot of the risk of major bleeding as defined by the ISTH in patients with AF and ACS/PCI

Study	Intervention	Comparator	MH Odds ratio (95% CI) (Random effects model)
	No of events / Total no (%)		
AUGUSTUS	48/1145	23/1143	2.131 (1.287 – 3.527)
PIONEER AF PCI	25/706	27/696	0.910 (0.523 – 1.583)
Overall			1.404 (0.609 – 3.233) *p = 0.426*

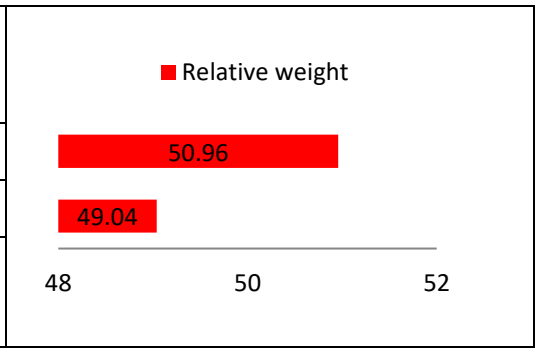

Table 5 – Risk of major bleeding as defined by the ISTH in patients with AF and ACS/PCI

It is also interesting to mention that when the different dose regimens from a subanalysis of the REDUAL PCI with two different P2Y12 inhibitors (ticagrelor and clopidogrel) were compared, the higher dose of dabigatran (dabigatran etexilate 150 mg) plus clopidogrel increased the risk of bleeding by 65% (M-H OR: 1.654, 95% CI 0.746 – 3.667, *p=0.216*) compared to use of a lower dose of dabigatran (dabigatran etexilate 110 mg) whereas ticagrelor plus dabigatran etexilate 150 mg decreased the risk of bleeding by around 15% (M-H OR: 0.843, 95% CI 0.138 – 5.141, *p=0.853*) over its lower dose counterpart [➤ **Figure 3 and Table 6**]. None of the treatment effects were of statistical significance.

The confidence intervals (CIs) were wider in the ticagrelor arm as there was a relatively small subgroup of patients receiving it compared to clopidogrel. The residual weight of a treatment effect is directly proportional to the surface area of the point estimate. This is represented in the forest plot by the area of the point estimates of the respective regimens. The higher the weight assigned, the larger will be the point estimate.

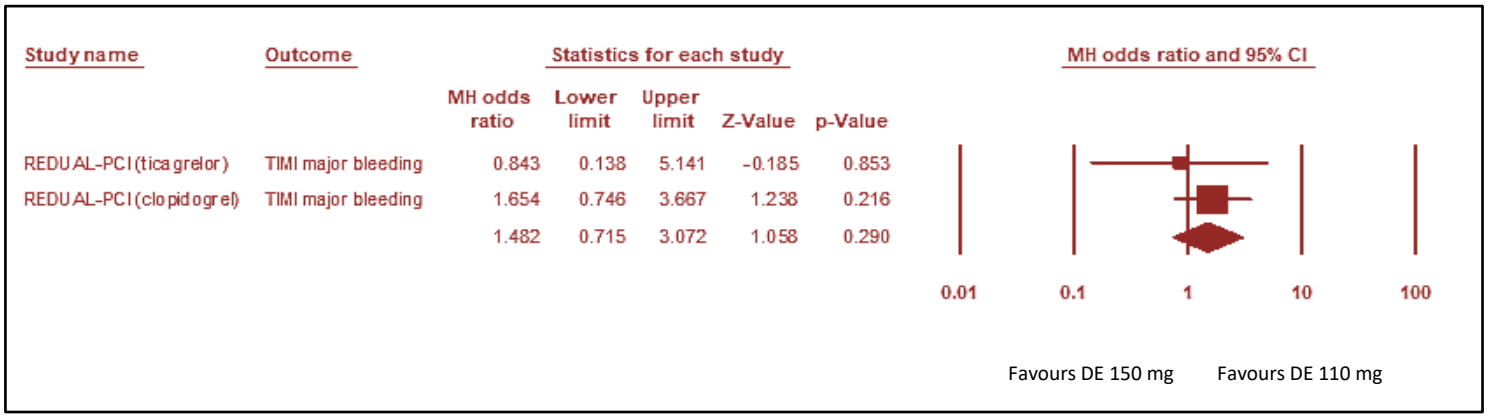

Figure 3 – Forest plot of the sub-analysis of the REDUAL PCI for the risk of TIMI major bleeding

Study	Intervention	Comparator	MH Odds ratio (95%CI) Random effects model
	No of events / Total no (%)		
REDUAL PCI (ticagrelor)	2/104	3/132	0.843 (0.138 – 5.141)
REDUAL PCI (clopidogrel)	14/659	11/849	1.654 (0.746 – 3.667)
Overall			1.482 (0.715 – 3.072) *p = 0.290*

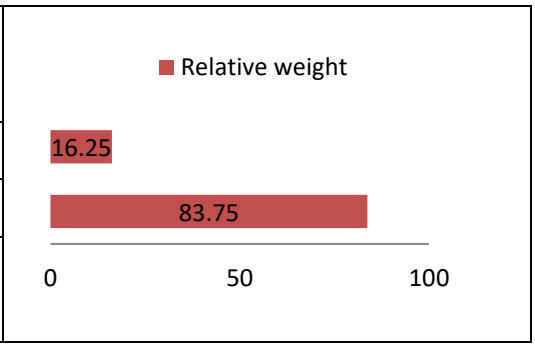

Table 6 - Risk of TIMI major bleeding in the REDUAL PCI

Efficacy outcome

➤ **Figure 4 and 5** provide the forest plots for the efficacy endpoints of the composite endpoint of thromboembolic events (MACE) and death. ➤ **Tables 7 and 8** provide the data for the MACE and death efficacy endpoints respectively. For the AUGUSTUS trial, the composite endpoint of MACE considered here refers to all cause death or ischemic events. For the PIONEER AF PCI, it was defined as the composite of death from cardiovascular causes, myocardial infarction, or stroke. So, 'death from cardiovascular causes' was the estimate for the endpoint of death.

On analysing the efficacy endpoints of both MACE and death of the included studies separately, there was a small non-significant reduction with the use of triple therapy over dual therapy (MACE – M-H OR: 0.939, 95% CI 0.715 – 1.233, *p= 0.649*; death - M-H OR: 0.958, 95% CI 0.651 – 1.410, *p= 0.828*). Publication bias cannot be assessed with just two included studies.

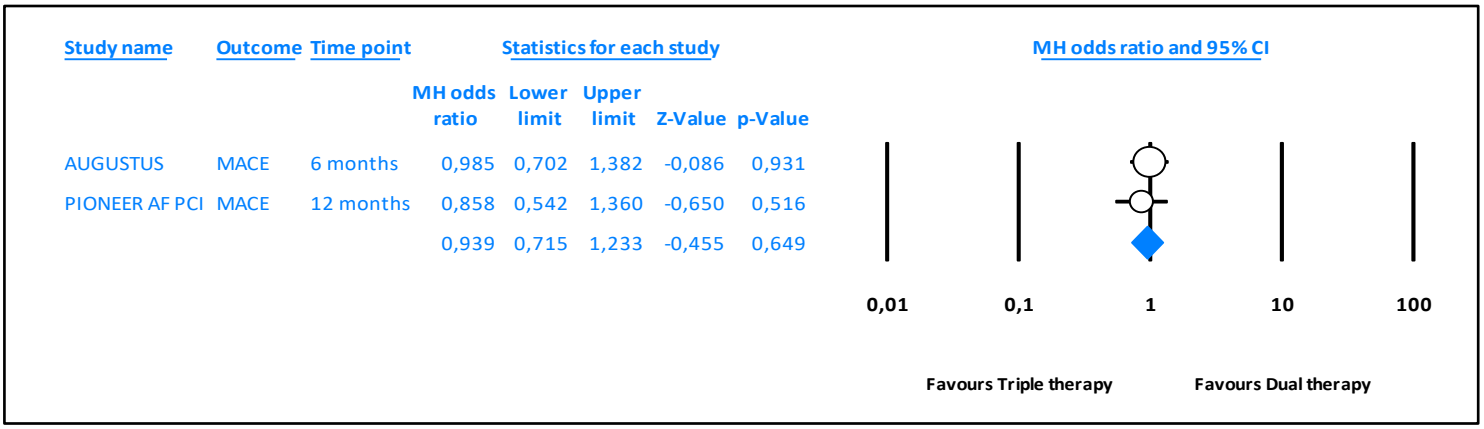

Figure 4 – Forest plot of the included studies for MACE in patients with AF and ACS/PCI

Study	Intervention	Comparator	MH Odds ratio (95% CI) Random effects model
	No of events / Total no (%)		
AUGUSTUS	71/1153	72/1153	0.985 (0.702 – 1.382)
PIONEER AF PCI	36/704	41/694	0.858 (0.542 – 1.360)
Overall			0.939 (0.715 – 1.233) *p = 0.649*

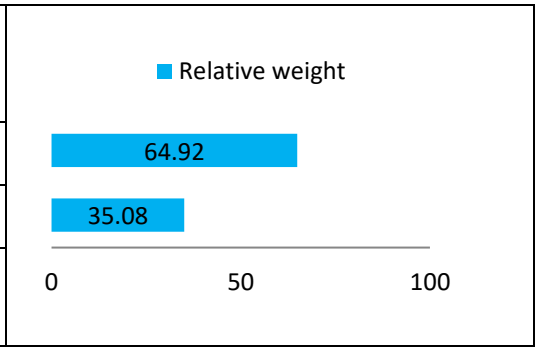

Table 7 – Risk of MACE in patients with AF and ACS/PCI

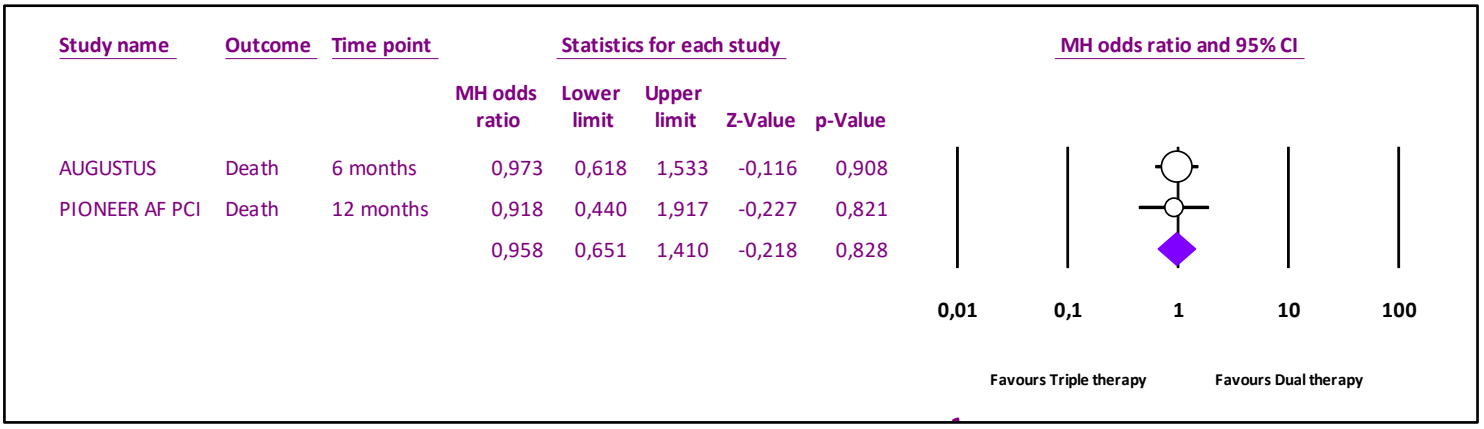

Figure 5 – Forest plot of the included studies for the risk of death in patients with AF and ACS/PCI. The AUGUSTUS trial reported the endpoint of all-cause death

Study	Intervention	Comparator	MH Odds ratio (95% CI) Random effect model
	No of events / Total no (%)		
AUGUSTUS	38/1153	39/1153	0.973 (0.618 – 1.533)
PIONEER AF PCI	14/704	15/694	0.918 (0.440 – 1.917)
Overall			0.958 (0.651 – 1.410) *p = 0.828*

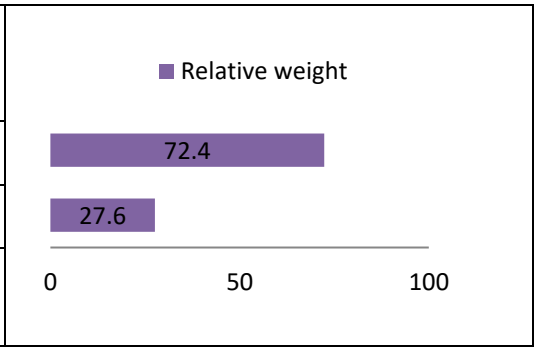

Table 8 – Risk of death in patients with AF and ACS/PCI

The same can be said when analysing the composite efficacy endpoint of MACE of the sub analysis of the REDUAL PCI which favours the use of the higher dosage of dabigatran irrespective of the type of antiplatelet used, but not statistically significant. (OR: 0.689, 95% CI: 0.342 – 1.387, *p= 0.297*) **[➤ Figure 6 and Table 9].** The CIs were wider in the arm where ticagrelor was administered as there was a relatively small subgroup of patients receiving it compared to clopidogrel.

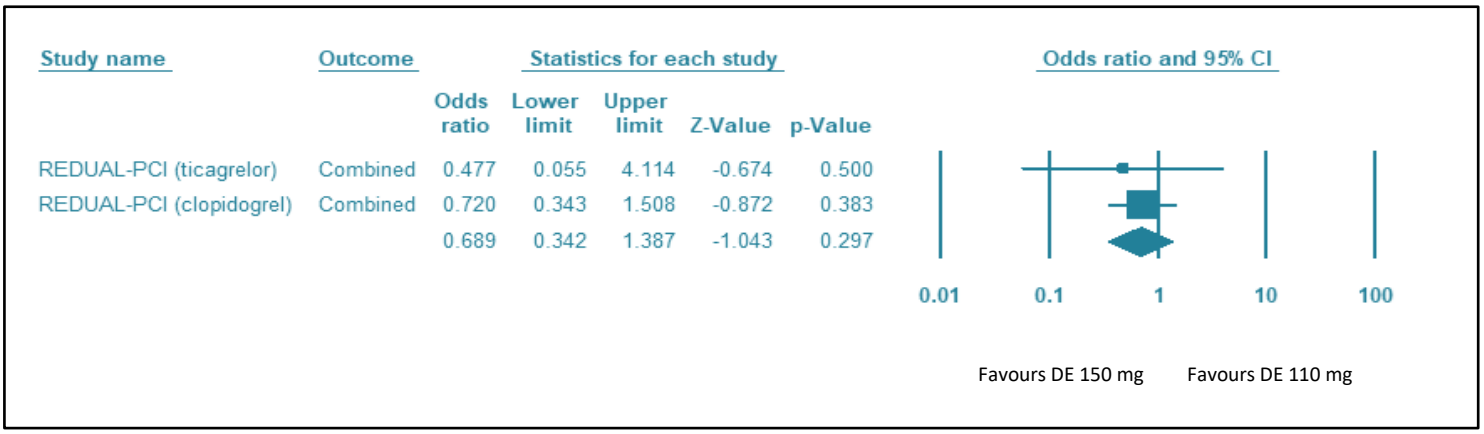

Figure 6 – Forest plot of the sub analysis of the REDUAL PCI for MACE

Study	Intervention	Comparator	Odds ratio (95% CI) Random effects model	
	No of events / Total no (%)			
REDUAL PCI (ticagrelor)	2/104	6/132	0.477 (0.055 – 4.114)	Relative weight
REDUAL PCI (clopidogrel)	16/659	27/849	0.720 (0.343 – 1.508)	10.55
Overall			1.404 (0.609 – 3.233) *p = 0.297*	89.45
				0 50 100

Table 9 - Risk of MACE in the REDUAL PCI

Studies assessing patients with AF and with or without concomitant antiplatelet therapy

Safety outcome

From our analysis, we have found that there is a significant increase in major bleeding with the use of DOAC plus antiplatelet therapy (60%) instead of DOAC alone across all the included studies (M-H OR: 1.598, 95% CI 1.430 – 1.785, *p=0.000*) compared to using DOAC plus antiplatelet therapy (➤ **Figure 7 and Table 10)**. All of the treatment effects of the respective regimens had statistical significance. Both the lower doses and the higher doses of dabigatran and edoxaban plus antiplatelet therapy produced significant major bleeding. Among the two doses of dabigatran, the combination therapies of dabigatran etexilate 110 mg with antiplatelet therapy saw an 81% increased risk of bleeding (M-H OR: 1.807, 95% CI 1.335 – 2.445, *p=0.000*) and dabigatran etexilate 150 mg with antiplatelet therapy saw a 70% increased risk of bleeding (M-H OR: 1.695, 95% CI 1.279 – 2.245, *p=0.000*) over their monotherapy counterparts. In case of edoxaban, the higher dose (60 mg) with antiplatelet therapy produced 76% increased risk of bleeding (M-H OR: 1.765, 95% CI 1.274 – 2.445, *p=0.001*) whereas the lower dose (30 mg) with antiplatelet therapy saw a 50% increased risk of bleeding with borderline significance (M-H OR: 1.500, 95% CI 0.999 – 2.253, *p=0.050*) over just edoxaban 60mg or 30 mg doses respectively. The combination therapy of apixaban 5 mg and rivaroxaban 20 mg saw an increase of 69% (M-H OR: 1.693, 95% CI 1.341 – 2.138, *p=0.000*) and 36 % increased risk of bleeding (M-H OR:1.366 , 95% CI:1.113 – 1.677, *p=0.003*) when compared to apixaban and rivaroxaban monotherapies.

The residual weights assigned to ROCKET AF and ARISTOTLE trials are higher than those assigned to the RE-LY and the ENGAGE AF TIMI 48 trials. This is represented in the forest plot by the area of the point estimates of the respective regimens. The higher the weight assigned, the larger will be the point estimate.

The robustness of the analysis was confirmed on performing a one way sensitivity analysis. It shows that similar results are obtained regardless of which study is excluded **(➤ Figure S1)**.

On visual inspection, an asymmetry of the funnel plot was observed **(➤ Figure S1p).** However, the Egger's regression test did not reveal any publication bias (y - intercept: 1.791, 95% CI: -2.641, 6.223, *p= 0.324*).

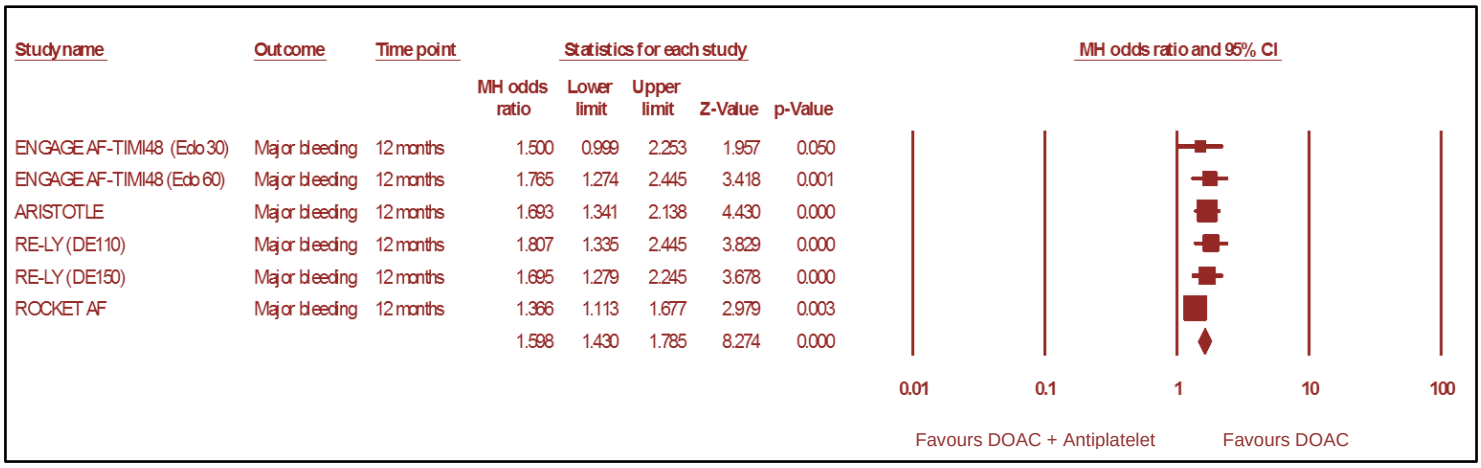

Figure 7 – Forest plot of the included studies for the risk of major bleeding

Study	DOAC + APT	DOAC	MH Odds ratio (95% CI) Random effect model
	No of events / Total no (%)		
ENGAGE AF TIMI48 (E 30)	35/1625	73/5046	1.500 (0.999 – 2.253)
ENGAGE AF TIMI48 (E 60)	59/1642	102/4953	1.765 (1.274 – 2.445)
ARISTOTLE	114/2233	211/6852	1.693 (1.341 – 2.138)
RE-LY (DE110)	91/2322	82/3693	1.807 (1.335 – 2.445)
RE-LY (DE150)	102/2304	100/3772	1.695 (1.279 – 2.245)
ROCKET AF	171/2586	224/4545	1.366 (1.113 – 1.677)
Overall			1.598 (1.430 – 1.785) *p = 0.000*

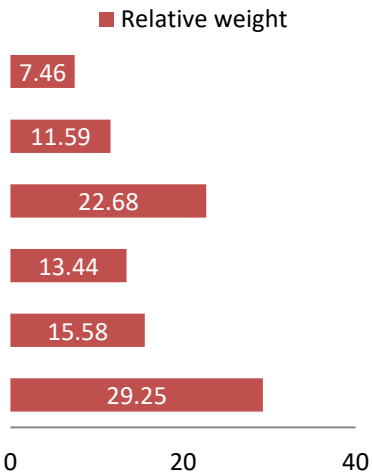

Table 10 – Risk of major bleeding in the included studies

Efficacy outcome

For computing the composite efficacy endpoint of MACE, we combined the individual efficacy endpoints. It should be noted that only the odds ratio is used here for the outcomes of MACE in the random effects model. This is due to the fact that the means of the individual outcomes cannot be used to compute the Mantel Haenszel Odds ratio.

The summary effect shows a 36% statistically significant increase in the risk of ischemic events (OR 1.362, 95% CI 1.174 – 1.580, *p = 0.000*) with the use of a DOAC with antiplatelet therapy rather than DOAC alone (➤ **Figure 8 and Table 11**). From the RE-LY trial, out of the two doses of dabigatran, we see that there is a 64% increase in the risk of ischemic events with the use of the combination of dabigatran etexilate 150mg with antiplatelet therapy (OR 1.640, 95% CI 1.086 – 2.478, *p = 0.019*) and a 43% increased risk of borderline significance with dabigatran etexilate 110mg (OR: 1.437, 95% CI 0.981 – 2.104, *p = 0.063*). From the ENGAGE AF TIMI48, there is a 25% increase in the MACE events (OR: 1.255, 95% CI 0.870 – 1.810, *p= 0.225*) on using 60 mg edoxaban and a 14% increase with the use of 30 mg edoxaban (OR: 1.139 95% CI: 0.712 – 1.821, *p= 0.587*). From the ARISTOTLE trial, there is a 37 % risk increase with the use of apixaban with antiplatelet therapy over the sole use of apixaban (OR: 1.368, 95% CI 0.947 – 1.975, *p= 0.095*). And the ROCKET AF, there was a 35 % increase with the use of rivaroxaban with antiplatelet therapy over using rivaroxaban alone (OR: 1.355, 95% CI:1.028 – 1.784, *p= 0.031*)

The residual weight assigned to ROCKET AF is higher relative to the other trials. This is represented in the forest plot by the area of the point estimates of the respective regimens. The higher the weight assigned, the larger will be the point estimate.

The robustness of the analysis was confirmed when a one way sensitivity analysis was performed. It shows that similar results are obtained regardless of which study is excluded **(➤Figure S2).**

On visual inspection, an asymmetry of the funnel plot was observed **(➤Figure S2p).** And the Egger's regression test did not reveal any publication bias (y - intercept: -0.246, 95% CI: -4.519, 4.025, *p= 0.880*).

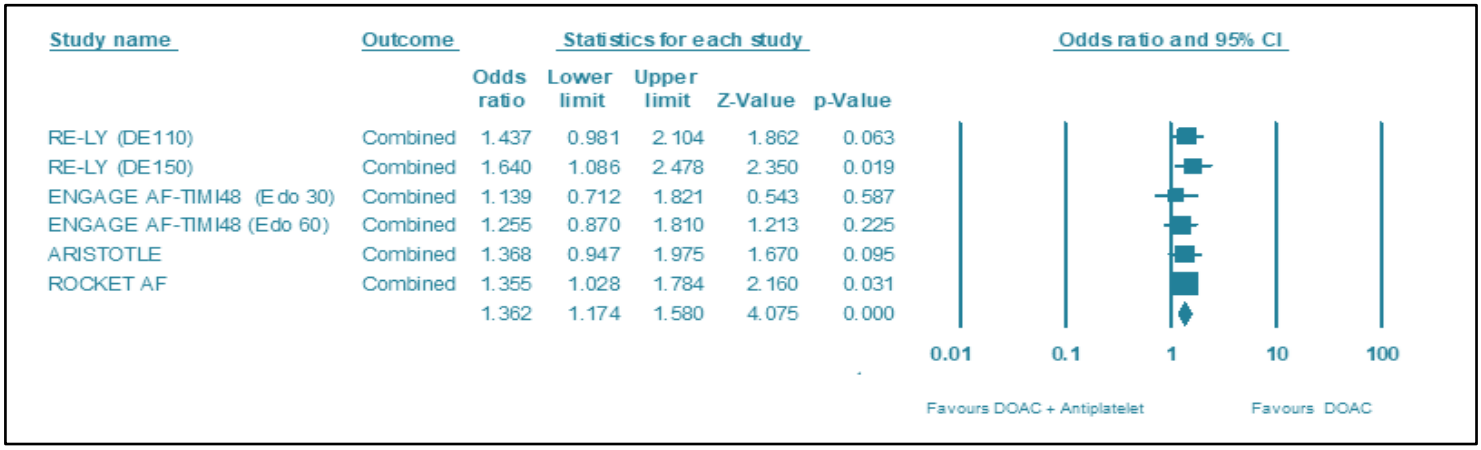

Figure 8 – Forest plot of the included studies for the risk of MACE

Study	DOAC + APT	DOAC	Odds ratio (95% CI) Random effect model
	No of events / Total no (%)		
RE-LY (DE110)	53/2343	59/3672	1.437 (0.981 – 2.104)
RE-LY (DE150)	49/2318	52/3758	1.640 (1.086 – 2.478)
ENGAGE AF TIMI48 (E 30)	30 / 1625	82 / 5046	1.139 (0.712 – 1.821)
ENGAGE AF TIMI48 (E 60)	67 / 1642	146 / 4953	1.255 (0.870 – 1.810)
ARISTOTLE	48 / 2233	120 / 6852	1.368 (0.947 – 1.975)
ROCKET AF	110 / 2586	148 / 4545	1.355 (1.028 – 1.784)
Overall			1.362 (1.174 – 1.580) *p = 0.000*

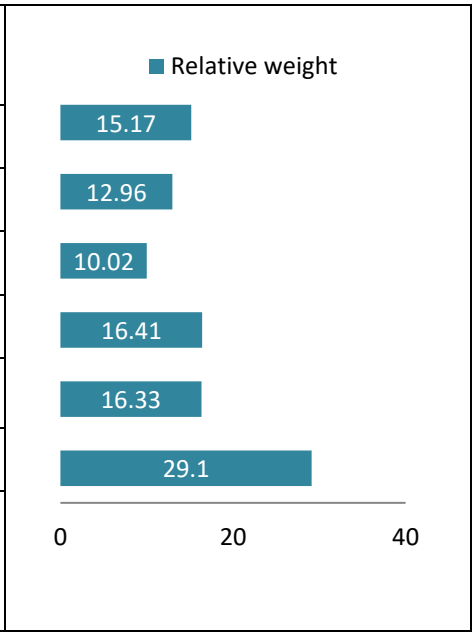

Table 11 – Risk of MACE in the included studies

The summary effect shows a 22 % borderline significance increase in the risk of stroke or SE (M-H OR 1.222, 95% CI 0.978 – 1.527, *p = 0.077*) with the use of a DOAC with antiplatelet therapy rather than DOAC alone (➤**Figure 9 and Table 12)**. From the RE-LY trial, out of the two doses of dabigatran, we see that there is a 2-fold increase in the risk of stroke or SE with the use of the combination of dabigatran etexilate 150mg with antiplatelet therapy (M-H OR 1.357, 95% CI 1.357 – 3.573, *p = 0.001*) and a 52% increased risk of statistical significance with dabigatran etexilate 110mg (M-H OR: 1.522, 95% CI 1.010 – 2.293, *p = 0.045*). From the ENGAGE AF TIMI48, there is a 9% increase in the risk of stroke or SE (M-H OR: 1.092, 95% CI 0.725 – 1.644, *p= 0.675*) on using 30 mg edoxaban but a slight decrease in the risk with the use of 60 mg edoxaban (M-H OR: 0.922, 95% CI: 0.567 – 1.498, *p= 0.742*). From the ARISTOTLE trial, there is almost no difference with the use of apixaban with antiplatelet therapy or just apixaban (M-H OR: 0.990, 95% CI 0.694 – 1.413, *p= 0.958*). In the ROCKET AF, there was a 13 % increase in the risk of stroke or SE with the use of rivaroxaban with antiplatelet therapy over using rivaroxaban alone (M-H OR: 1.131, 95% CI: 0.881 – 1.451, *p= 0.336*).

The residual weight assigned to ROCKET AF is higher relative to the other trials. This is represented in the forest plot by the area of the point estimates of the respective regimens. The higher the weight assigned, the larger will be the point estimate.

On performing the one way sensitivity analysis, a trend of a reduction in the risk of stroke or SE was maintained with the use of DOACs alone but they were no longer statistically significant for all of the treatment effects **(➤Figure S3).**

On visual inspection, no asymmetry of the funnel plot was observed **(➤Figure S3p).** And the Egger's regression test did not reveal any publication bias (y - intercept: 1.840, 95% CI: -5.055, 8.737, *p= 0.499*).

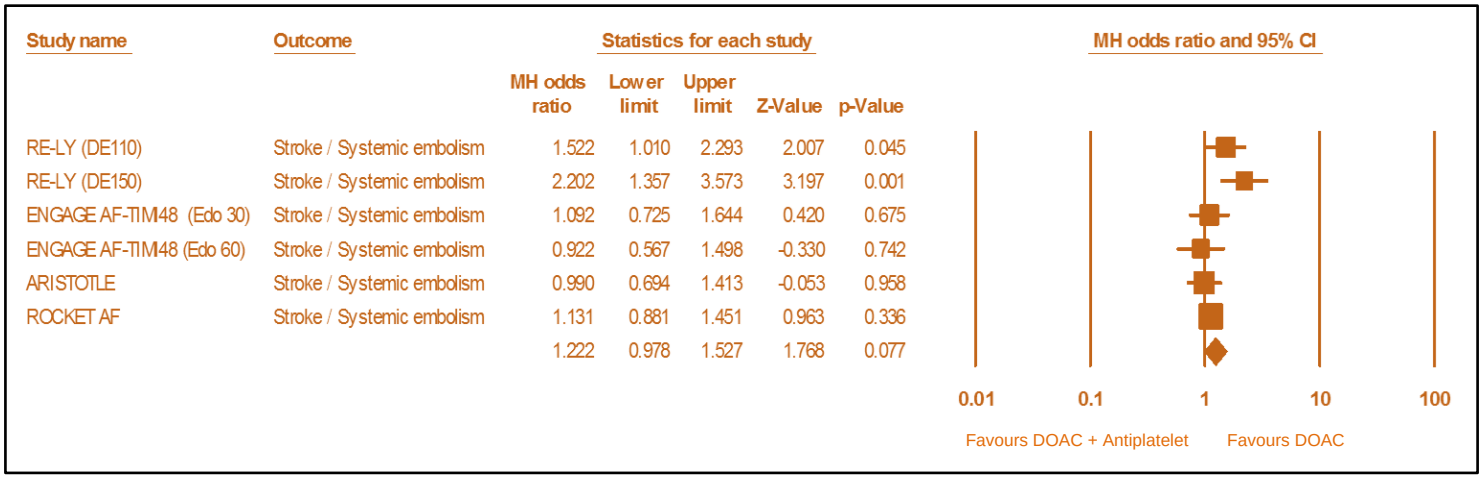

Figure 9 – Forest plot of the included studies for the risk of Stroke / SE

Study	DOAC + APT	DOAC	MH Odds ratio (95% CI) Random effect model
	No of events / Total no (%)		
RE-LY (DE110)	45 / 2322	48 / 3693	1.522 (1.010 – 2.293)
RE-LY (DE150)	39 / 2304	29 / 3772	2.202 (1.357 -3.573)
ENGAGE AF TIMI48 (E 30)	32 / 1625	90 / 5046	1.092 (0.725 – 1.644)
ENGAGE AF TIMI48 (E 60)	22 / 1642	70 / 4953	0.922 (0.567 – 1.498)
ARISTOTLE	41 / 2233	127 / 6852	0.990 (0.694 – 1.413)
ROCKET AF	105 / 2586	164 / 4545	1.131 (0.881 – 1.451)
Overall			1.222 (0.978 – 1.527) *p = 0.077*

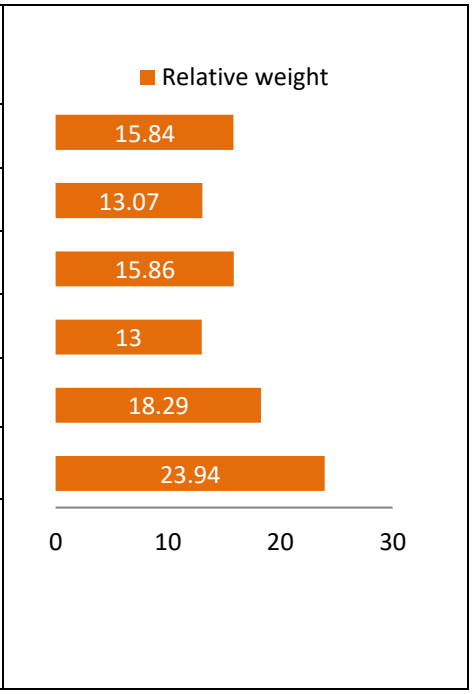

Table 12 – Risk of Stroke / Systemic embolism in the included studies

The summary effect shows a 57 % statistically significance increase in the risk of MI (M-H OR 1.569, 95% CI 1.361 – 1.809, *p = 0.000*) with the use of a DOAC with antiplatelet therapy rather than DOAC alone (➤**Figure 10 and Table 13)**. From the RE-LY trial, out of the two doses of dabigatran, we see that there is a 57% increase in the risk of MI with the use of the combination of dabigatran etexilate 150mg with antiplatelet therapy (M-H OR 1.568, 95% CI 1.050 – 2.343, *p = 0.028*) and a 41% increased risk with dabigatran etexilate 110mg (M-H OR: 1.410, 95% CI 0.945 – 2.102, *p = 0.092*). From the ENGAGE AF TIMI48, there is a 53% statistically significant increased risk of MI (M-H OR: 1.533, 95% CI 1.232 – 1.906, *p= 0.000*) on using 60 mg edoxaban and a 17% increase in the risk with the use of 30 mg edoxaban (M-H OR: 1.173, 95% CI: 0.639 – 2.152, *p= 0.607*). From the ARISTOTLE trial, there is almost a doubling of risk of MI with the use of combination therapy of apixaban with antiplatelet over apixaban monotherapy which is statistically significant (M-H OR: 2.219, 95% CI 1.416 – 3.480, *p= 0.001*). And finally in the ROCKET AF, there was a 62 % statistically significant increased risk of MI with the use of rivaroxaban with antiplatelet therapy over using rivaroxaban alone (M-H OR: 1.617, 95% CI: 1.142 – 2.290, *p= 0.007*).

Here, the residual weight assigned to the edoxaban 60 mg regimen (42.52%) of the ENGAGE trial is higher relative to the other trials whereas it is just 5.49% to the edoxaban 30 mg regimen. This is represented in the forest plot by the area of the point estimates of the respective regimens. The higher the weight assigned, the larger will be the point estimate.

The robustness of the analysis was confirmed when a one way sensitivity analysis was performed. It shows that similar results are obtained regardless of which study is excluded, even with the removal of the RE-LY trial **(➤Figure S4a& S4b).**

On visual inspection, no asymmetry of the funnel plot was observed **(➤Figure S4p).** The Egger's regression test did not reveal any publication bias (y - intercept: -0.00395, 95% CI: -3.34614, 3.33824, *p= 0.99754*). When the RE-LY trial was excluded (for both dabigatran etexilate 110 mg and dabigatran etexilate 150mg), the egger's test did not show any changes (y - intercept: 0.230, 95% CI: -7.241, 7.702, *p= 0.906*) **(➤Figure S4q).**

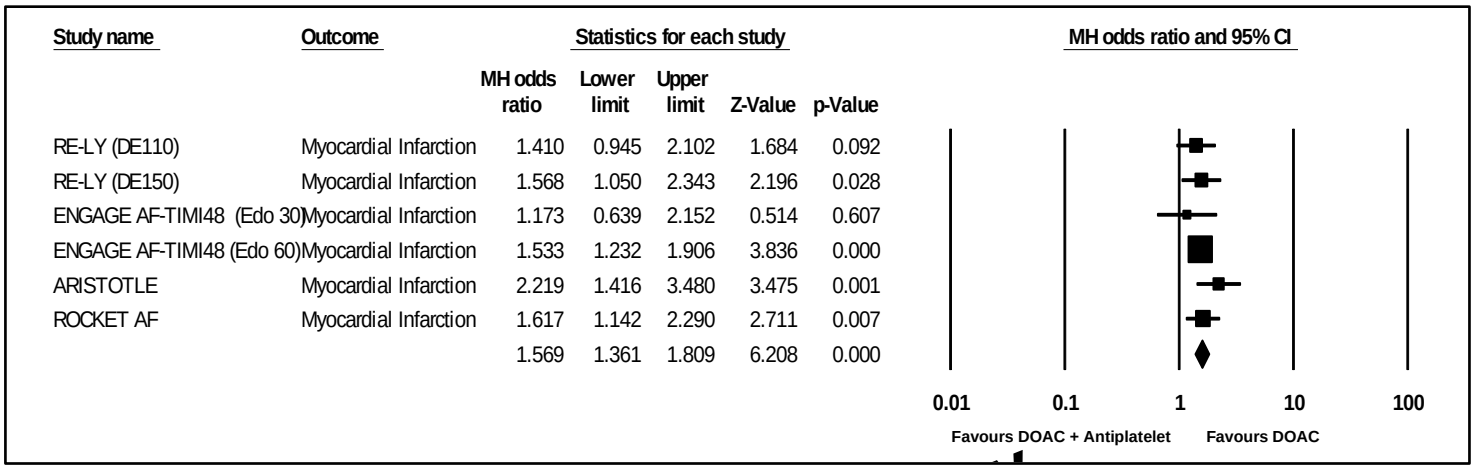

Figure 10 – Forest plot of the included studies for the risk of Myocardial Infarction

Study	DOAC + APT	DOAC	MH Odds ratio (95% CI) Random effect model
	No of events / Total no (%)		
RE-LY (DE110)	47 / 2386	51/ 3629	1.410 (0.945 – 2.102)
RE-LY (DE150)	48 / 2347	49 / 3729	1.568 (1.050 – 2.343)
ENGAGE AF TIMI48 (E 30)	14 / 1625	38 / 5046	1.173 (0.639 – 2.152)
ENGAGE AF TIMI48 (E 60)	130 / 1642	263 / 4953	1.533 (1.232 – 1.906)
ARISTOTLE	33 / 2233	46 / 6852	2.219 (1.416 – 3.480)
ROCKET AF	62 / 2586	68 / 4545	1.617 (1.142 – 2.290)
Overall			1.569 (1.361 – 1.809) *p = 0.000*

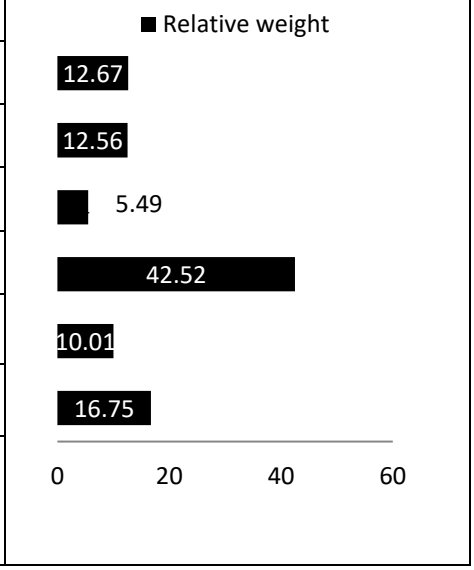

Table 13 – Risk of Myocardial Infarction in the included studies

The summary effect shows a 29 % statistical significance increase in the risk of vascular death (M-H OR 1.293, 95% CI 1.148 – 1.457, *p = 0.000*) with the use of a DOAC with antiplatelet therapy rather than DOAC alone (➤**Figure 11 and Table 12**). From the RE-LY trial, out of the two doses of dabigatran, we see that there is a 28% increase in the risk of vascular death with the use of the combination of dabigatran etexilate 150mg with antiplatelet therapy (M-H OR 1.278, 95% CI 0.910 – 1.795, *p = 0.157*) and a 38% increased risk of borderline significance with dabigatran etexilate 110mg (M-H OR: 1.382, 95% CI 0.995 – 1.921, *p = 0.054*). From the ENGAGE AF TIMI48, there is a 40% increase in the risk of vascular death of borderline significance (M-H OR: 1.399, 95% CI 0.990 – 1.976, *p= 0.057*) on using 60 mg edoxaban and a 15% increase in the risk with the use of 30 mg edoxaban (M-H OR: 1.154, 95% CI: 0.812 – 1.640, *p= 0.425*). Since in the ARISTOTLE trial, all cause death was the endpoint reported, there is a 16% increase in this risk with the use of apixaban with antiplatelet therapy over just apixaban (M-H OR: 1.164, 95% CI 0.882 – 1.536, *p= 0.283*). In the ROCKET AF, there was a 36 % statistically significant increase in the risk of vascular death with the use of rivaroxaban with antiplatelet therapy over using rivaroxaban alone (M-H OR: 1.359, 95% CI: 1.101 – 1.677, *p= 0.004*).

The residual weight assigned to ROCKET AF is higher relative to the other trials, followed by the ARISTOTLE trial. This is represented in the forest plot by the area of the point estimates of the respective regimens. The higher the weight assigned, the larger will be the point estimate.

The robustness of the analysis was confirmed when a one way sensitivity analysis was performed. It shows that similar results are obtained regardless of which study is excluded **(➤Figure S5).**

On visual inspection, no asymmetry of the funnel plot was observed **(➤Figure S5p).** But the Egger's regression test did not any reveal publication bias (y - intercept: -0.612, 95% CI: - 4.037, 2.812, *p= 0.645*).

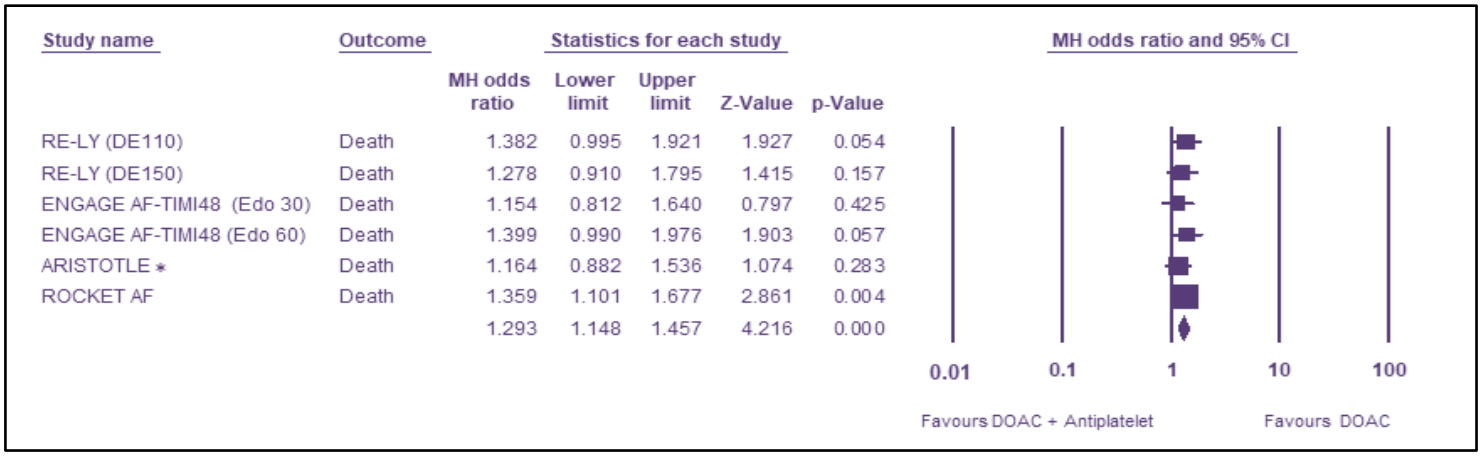

Figure 11 – Forest plot of the included studies for the risk of vascular death

(* refers to all-cause mortality)

Study	DOAC + APT	DOAC	MH Odds ratio (95% CI) Random effect model
	No of events / Total no (%)		
RE-LY (DE110)	68/2322	79 / 3693	1.382 (0.995 – 1.921)
RE-LY (DE150)	61 / 2304	78 / 3772	1.278 (0.910 – 1.795)
ENGAGE AF TIMI48 (E 30)	44 / 1625	118 / 5046	1.154 (0.812 – 1.640)
ENGAGE AF TIMI48 (E 60)	48 / 1642	105 / 4953	1.399 (0.990 – 1.976)
ARISTOTLE	71 / 2233	188 / 6852	1.164 (0.882 – 1.536)
ROCKET AF	162 / 2586	213 / 4545	1.359 (1.101 – 1.677)
Overall			1.293 (1.148 – 1.457) *p = 0.000*

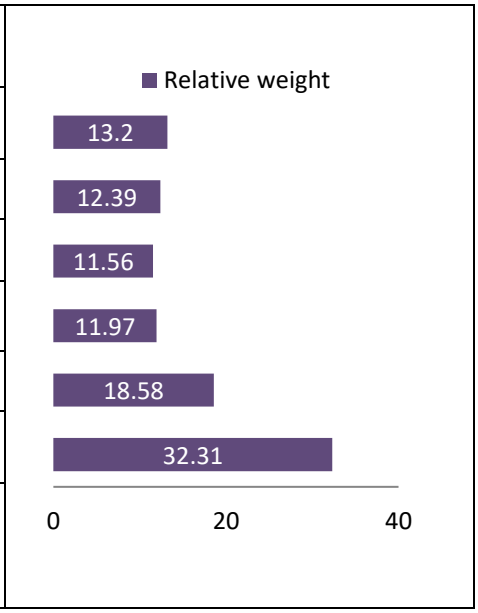

Table 14 – Risk of vascular death in the included studies

Discussion

Guidelines

The 2018 European Society of Cardiology (ESC) consensus document on the management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCIs **[63],** an update of the 2014 ESC consensus document on the same topic **[64]** and had put forth a series of consensus statements recommending the use of DOAC as part of triple or dual therapy are safer than VKA therapies like warfarin and that dual therapy with an oral anticoagulant plus one P2Y12 inhibitor (preferably clopidogrel) to be considered in patients who have a low thrombotic risk but have a high bleeding risk. Both the 2018 document, along with the 2016 ESC Guidelines for the management of atrial fibrillation mention that AF patients with a stable vascular disease in the previous 12 months should be managed by oral anticoagulation alone. The results from our meta-analysis further provide scientific evidence in support of the above-stated agreements.

AF patients with ACS / PCI

The results from our analysis are in line with the findings of similar meta-analyses performed in the context of AF patients with ACS or undergoing PCI **[66, 67][77]**. The publication of the results of the ENTRUST AF-PCI completes the quartet of DOACs (dabigatran etexilate, rivaroxaban, apixaban and edoxaban) in this backdrop, although the data from the aforementioned trial could not be explored in the meta-analysis owing to its design. Also, we must acknowledge the fact that there are significant differences between the trials in terms of the inclusion criteria, the number of patients enrolled and the dosages administered. Out of the 4 randomised controlled trials, we evaluated the safety and efficacy outcomes of the triple therapy and dual therapy of the PIONEER AF PCI and the AUGUSTUS trials. For the REDUAL PCI, we investigated the two doses of dabigatran with the P2Y12 inhibitors used. It should be noted that though both REDUAL PCI and PIONEER AF PCI had open-label designs, the blinding of the outcome adjudicators were appropriate. The same is applicable to the ENTRUST AF-PCI trial.

Major bleeding

Analysing the forest plot of the primary safety endpoint of ISTH major bleeding, we can observe that the point estimate is skewed in favour of dual therapy of DOACs. This is in large part attributed to the treatment effects of the apixaban regimen. There is a doubling of the risk of bleeding in the triple therapy arm of apixaban compared to its dual therapy counterpart (M-H OR: 2.131, 95% CI: 1.287 – 3.527, $p= 0.003$). Although the treatment effect of the rivaroxaban regimen shows an inclination towards triple therapy (M-H OR: 0.910, 95% CI:0.523 – 1.583, $p = 0.426$), the relative weights assigned by the random effects model shows that the AUGUSTUS trial holds more weight over the PIONEER AF PCI trial. As mentioned before, the reason for this boils down to the dosages administered, patients enrolled and the trial design. Firstly, in PIONEER AF PCI, the lower doses of rivaroxaban (2.5 mg b.i.d, later to 15 mg) was provided in the triple therapy arm, but not the approved dosage of rivaroxaban (20 mg) for AF patients as was the case in ROCKET AF trial. This

decision was taken into consideration based on the results of the ATLAS ACS–TIMI 46 trial where ACS patients given 15 -20 mg of rivaroxaban along with dual antiplatelet therapy experienced an increased risk in bleeding **[68].** Secondly, patients were not randomised to dual antiplatelet therapy but based on the clinicians' discretion which could have introduced bias. The low Jadad score of 2 is representative of the quality of this study. Unlike the PIONEER trial, the AUGUSTUS trial provided the recommended dose of apixaban for treating AF to the enrolled patients. The randomisation of patients was appropriate in terms of blinding of the patients. The two-by-two factorial design of the trial allowed stratifying the patients in both arms on either to aspirin or its equivalent placebo.

From the forest plot for the efficacy endpoints of MACE and death, we can see that the signal, though slightly non-significant, is in favour of triple therapy of both the factor Xa inhibitors as aspirin still plays a considerable role in preventing stent thrombosis. Around 65 -66% of the patients received a drug eluting stent (DES) and 31 – 32% received a bare metal stent (BMS) in the dabigatran arms of the PIONEER AF PCI trial. In the AUGUSTUS trial, out of a total of 2297 patients in both apixaban and VKA regimens, about 877 (38.2%) underwent elective PCI though there is no mention of the type of stent. As far as the secondary efficacy endpoints of thrombotic events are concerned, both the trials were underpowered to detect small relevant ischemic events. Moreover, due to the heterogeneity in the reporting of the individual efficacy endpoints between the trials, the interpretation of the results is varied.

REDUAL-PCI trial

In the RE-DUAL trial, as only the dual therapy of both the doses of dabigatan were compared with the triple therapy of VKA, we could not analyse the doses of dabigatran with that of rivaroxaban and apixaban due to the differences in the dosing regimens. However, a bivariate analysis of the PIONEER AF-PCI and RE-DUAL PCI trial has revealed that all combinations of rivaroxaban (rivaroxaban 15 mg o.d. and 2.5 mg b.i.d) and dabigatran (dabigatran etexilate 110 mg and dabigatran etexilate 150 mg) had a better net clinical benefit (NCB) when compared to the VKA regimen **[69].**

Looking at the type of antiplatelet users in the RE-DUAL trial, there were 659 (86.4%) clopidogrel users and 104 (13.9%) ticagrelor users in the dabigatran etexilate 150 arm and 849 (86.5%) clopidogrel users and 132 (13.5%) ticagrelor users in the dabigatran etexilate 110 arm. Since ticagrelor, a p-gp inhibitor was made available for a minority of AF patients as an adjunct therapy, like those with a higher risk for thromboembolic and bleeding events**,** it is interesting to see that the higher dose of dabigatran with ticagrelor was found to reduce the risk of major bleeding as defined by TIMI compared to the lower dose of dabigatran with ticagrelor. However, the overall effect of major bleeding was increased by 48% with the use of the higher dose of dabigatran with the corresponding antiplatelets (M-H OR: 1.482, 95% CI 0.715 – 3.072, *p=0.290*) compared to its lower dose. When it comes to the MACE composite efficacy endpoint, our analysis revealed that it was in favour of dabigatran etexilate 150 mg with either clopidogrel or ticagrelor which reduced the risk of thromboembolic events [OR 0.689, 95% CI 0.342 – 1.387, *p= 0.297*]. And in the main study as well, it was shown that the rates of MI and stent thrombosis were non-significantly higher among the patients

who were randomly assigned to receive dabigatran etexilate 110 mg. Notwithstanding, the subanalysis of the REDUAL PCI trial involved the non-randomized comparisons of P2Y12 inhibitors with a wide difference in the number of patients receiving them, therefore the elucidation of these results are limited in scope.

ENTRUST AF PCI trial

Like the previous 3 trials, the ENTRUST AF PCI trial demonstrated that the dual therapy of the approved dosage of the DOAC edoxaban was non inferior to the triple therapy of warfarin at least in terms of bleeding, although during the starting 2 week period, the patients in the VKA group did not achieve good-quality anticoagulation (INR < 2). 696 out of 751 patients (93%) were treated with clopidogrel in the edoxaban arm (60 mg) where 147 (20%) allotted to the edoxaban regimen were given the adjusted dose of 30 mg, based on renal impairment (moderate or severe), bodyweight (< 60 kg), or the use of specific strong P-glycoprotein inhibitors . Though the efficacy outcomes were similar between the two arms, the investigators noted that, as observed with the former trials, there was an increase in MACE events in patients who did not take aspirin (namely the dual therapy regimen). This phenomenon could be ascribed to the variability of clopidogrel response and residual platelet reactivity in patients due to the CYP2C19 loss-of-function alleles found in such patients especially in those with ACS on antiplatelet therapy which have an independent role in determining MACE events **[70][71].**

Viewpoint

When we analyse the results of our meta-analysis for these patients, we see that there is an overall increased risk of major bleeding observed with triple therapy but a decrease in the composite efficacy endpoints of MACE, though it is found to be statistically non-significant. Another subanalysis of the REDUAL PCI trial revealed how age influences bleeding rates. Japanese patients on dabigatran etexilate 110-mg dual therapy experienced higher bleeding rates (26%) compared to the overall cohort of the trial (15.4%) as the elderly in the Japanese subpopulation was around 72 %, whereas it was only 22.9% in the overall dabigatran etexilate 110-mg dual therapy group **[72]**. Also according to the patients' clinical presentation like ACS in the trials, it was found that there was no association noticed between the treatment effect and outcome which leads us to believe that the clinical benefit of DOACs may be safeguarded in patients with CAD **[73].** In view of the fact that the four trials were not adequately powered to assess the ischemic outcomes, the use of triple therapy should be limited to those only with high thromboembolic risk and low bleeding risk.

Many meta-analyses which were performed in the setting of AF patients with ACS/PCI have concluded that dual therapy takes precedence over triple therapy. However, it should be noted that almost all of these publications have actively made assessments of dual and triple therapy where at least one of the comparators had warfarin as the oral anticoagulant of choice **[74-77].** It is worthy to mention that there were a minority of patients in the ROCKET AF (1.1%) and the Aristotle trial (1.7%) who underwent PCI during the study period. Unfortunately, they

were not part of our analysis based on the sample size and since warfarin was the only other comparator used in these trials **[79, 80].**

DOAC with or without concomitant antiplatelets in AF

We had included 4 studies based on the randomised controlled trials on AF patients where a subanalysis was performed, namely the RE-LY trial, the ROCKET AF trial, the ARISTOTLE trial and the ENGAGE AF TIMI48 trial where patients were randomised to dabigatran, rivaroxaban, apixaban and edoxaban respectively. In all the 4 trials, aspirin was the concomitant antiplatelet of choice in such patients (except in the RE-LY and ENGAGE AF TIMI48 trials where clopidogrel was used as well). ROCKET AF had a large number of patients with a high CHADS2 score. In our analysis, we found that there is a significant increase in both major bleeding without any benefit in reducing thromboembolic events with the adjunct use of antiplatelet therapy along with any DOAC regardless of the dosage. Statistical significance was observed with the safety and efficacy endpoints. Our results corroborate with the results obtained by Kumar et al **[81]** in their meta-analysis, the difference being we also reported the efficacy endpoints of stroke or SE, MI AND death.

Major bleeding

Among the 4 combination therapies, our analysis revealed that the dabigatran etexilate 110 mg plus antiplatelet therapy escalated the risk of bleeding by 81%, followed by 70 % increase in the same risk by dabigatran etexilate 150 mg over the use of dabigatran doses alone. Edoxaban 60 mg and 30 mg with an antiplatelet therapy had a 76% and 50% increased risk of bleeding respectively. Both of these trials allowed either aspirin or clopidogrel to be used as a single antiplatelet therapy but the majority of them were on concomitant aspirin. Similar high rates of bleeding are observed with the other two trials where only aspirin was received by the patients with apixaban combination therapy having a 69 % increased risk of bleeding followed by rivaroxaban combination therapy having a 37% risk increase in bleeding events. As it has been shown that patients with paroxysmal AF are categorised as those with a low risk of bleeding **[82]**, the addition of an antiplatelet agent in such patients does not seem to have any added benefit but seems to aggravate the risk.

Thromboembolic events

One of the main reasons for the addition of antiplatelet therapy to anticoagulant therapy is to reduce the risk of thrombotic events in the patients with vascular disease. However, the data we obtained shows that when DOAC plus antiplatelet therapy instead of DOAC were used in these patients in the included trials, the risk of ischemic complications increased by 36%, risk of stroke or SE saw a 22% increase, efficacy endpoint of vascular death saw a 29% increase and a 57% increase in MI risk. Among the DOACs combination therapies, dabigatran etexilate 150 mg plus antiplatelet therapy seems to have a significant risk of causing MACE (64%). The same drug regimen is seen to double the risk of stroke / SE compared to the other DOAC combination therapies. And in the case for MI, apixaban plus the use of aspirin

doubles the risk in patients followed by rivaroxaban 20 mg combination therapy. It should be noted here that though both the add on therapies of dabigatran increases the risk of MI in patients, we obtained the data only for concomitant aspirin therapy. Nevertheless, on performing a sensitivity analysis by excluding the RE-LY trial, there was no change in the results. Previously, from the RE-LY trial, there were concerns of the risk of MI with the dabigatran doses when compared to warfarin although it was found to be a non-significant increase in the risk **[83, 84].** Also, a recently conducted Danish nationwide cohort study from their validated healthcare registries involving AF patients on oral anticoagulation for stroke prevention found that there were no significant risk differences among DOACs in their effects on MI or all-cause mortality and that dabigatran to be superior in terms of this outcome against both apixaban and rivaroxaban **[85, 86].** For the efficacy endpoint of vascular death, our results show edoxaban 60 mg causes a 40% increase in this risk followed by an almost equivalent 38% increase using dabigatran etexilate 110 mg and by rivaroxaban. It should be noted that the ROCKET AF recruited patients with the highest CHADS2 score.

Why the increase in the bleeding and thromboembolic events? Viewpoint

Several reasons can be provided for these occurrences. Firstly, we have to consider the baseline characteristics of the recruited in these trials. A lesser proportion of patients had arterial vascular diseases like CAD and stroke (< 38%)**.** The addition of the antiplatelet therapy was not randomised in these trials leading to selection bias where patients with less risk of developing the complications would have been selected for the concomitant therapy, mainly aspirin, with the use of clopidogrel or dual antiplatelet therapy being rare and prasugrel or ticagrelor not provided. Moreover, these subgroup analyses were performed sometime during the trial and not until the completion of the trials. Data published in these trials were those of the annualised events rates. Again, these could have exaggerated the results as well. Also, patients' adherence to the study drugs is questionable. In the ROCKET AF trial, temporary interruption in taking the oral anticoagulants led to an increase in the stroke and bleeding risks [**87].** In the RE-LY trial, it is believed that the dabigatan etexilate capsules composed of drug-coated tartaric acid which assists in creating an acidic microenvironment for gastrointestinal absorption of the drug was responsible for almost 12% of dyspepsia, promoting a higher rate of drug discontinuation **[32], [53].** A similar higher rate of non-adherence to dabigatran was reported among AF patients **[100],** though both rivaroxaban and dabigatran have better persistence compared to VKA **[101].** We will also have to consider the prior VKA antagonist exposure of these patients. Another observational study using the registry data of Danish cohort of patients showed that among patients with VKA naïve patients and VKA experienced patients, warfarin experienced patients who switched to dabigatran had an increased rate of MI, during an early treatment analysis **[88].** Since a stratification of patients with prior VKA use was not performed in our analysis, this should be done in a future study. In addition, the use of concomitant, contraindicated medications by these patients need to be considered. This could have an impact on the blood concentration of the anticoagulants, thereby affecting the bleeding risk **[89]**. A study reported potentially inappropriate dosing of drugs and switching between the anticoagulants in a proportion of AF patients aged over 65 years who were unsuitable for warfarin **[99].**

It should be noted that the reported events for the efficacy endpoint of MI from the RE-LY trial could not be obtained from the included study but from a similar meta-analysis which focused on the use of concomitant aspirin, but not clopidogrel **[90].**

AFIRE trial

The AFIRE trial was an open label , multicentre Phase 4 randomised controlled trial conducted in Japan where patients were randomised to either rrivaroxaban monotherapy (15 mg or 10 mg based on the creatinine clearance value) or rivaroxaban combination therapy with a single antiplatelet therapy (either aspirin or a P2Y12 inhibitor), to patients with AF who had undergone PCI or CABG performed more than a year before registration or those had angiographically confirmed CAD but not requiring revascularization. The trial demonstrated superiority of rivaroxaban monotherapy over the combination therapy in terms of bleeding events and non-inferiority in terms of the efficacy endpoints of stroke, SE, MI unstable angina requiring revascularization, or death. The trial had appropriate statistical power to detect the difference in the two regimens but because of an increased risk of death of any cause in the combination therapy and the high withdrawal rate, the trial had to be terminated early. Considering these facts, the results of the trial can be overestimated.

Observational study

DIRECT registry

The DIRECT registry was a single centre prospective, observational study based in Japan which analysed the data of patients with AF on both DOAC and concomitant antiplatelet therapy (➤**Table 4).** All the 4 DOACs were used for the analysis. The results of this study did show that patients on concurrent antiplatelet therapy did indeed have an increased bleeding risk. The study though had considerable limitations. It was a single centre observational study with relatively short follow-up duration. Confounding factors would have affected the analyses of the results. Nevertheless, the study does provide some information which can help in clinical practice specific to the geographical area.

There were a few other observational studies as well where a VKA was used as the comparator drug. A single centre observational study conducted in France observed that for dual therapy with clopidogrel, dabigatran lead to an increase in MACE events but with similar rates of major bleeding compared with VKA in AF patients with ACS/PCI **[91].** Here, the lower dose (dabigatran etexilate 110 mg) of dabigatran was administered to the treatment group while fluindione was the VKA for the control group patients and. It should be noted that there was no mention of prior VKA use by the treatment group.

Clinical implications

The implications of the results of our meta-analysis are manifold. Firstly, it adds to the established body of evidence, for at least the risk of major bleeding, that triple therapy is a bane rather than a boon for patients with AF especially those who with a comorbidity of coronary disease or those who are undergoing PCI, but has a slight benefit when it comes to preventing thromboembolic events in these patients. The type of stenting used to treat these patients also matter as it has been found out that the newer generation of drug-eluting stents (DES) in preventing stent thrombosis over their equivalent first-generation bare-metal stents **[92]**. Secondly, there is no benefit of an add-on antiplatelet therapy on top of a single administration of DOAC alone, regardless of the dosage in AF patients with stable vascular disease. Statistically speaking, our results have shown that the use of DOAC alone was superior to DOAC plus antiplatelet therapy in preventing both major bleeding and the ischemic and thromboembolic endpoints. The authors of the subgroup analysis of the RE-LY and ROCKET AF trial have concluded the same. Furthermore, it is in line with the current guidelines on high-risk AF patients with stable vascular disease. Our results seem to reinforce the notion.

Out with the old, in with the new?

A retrospective analysis of the Norway registries have found that at least in the context of AF patients with concomitant comorbidities like vascular disease, heart failure, and diabetes were associated with warfarin initiation, and previous stroke, age 65-74 and female sex with the initiation of DOACs **[8].** Moreover, VKAs remain the choice therapy for many diseases (e.g. valvular atrial fibrillation and mechanical prosthetic heart valves) **[21].** Gene polymorphisms of CYP2C9 (specially CYP2C9*2 and CYP2C9*3) have been implicated in the decrease in the metabolisation of warfarin and as such, prolonging the anticoagulant activity of warfarin **[93].** Based on these genetic variants, the dosing should be tailored accordingly.

Pharmacogenetic testing

The recent consensus statement on guiding P2Y12 Receptor Inhibitor Treatment in PCI **[71]** recommends the use of platelet function testing (PFT) in patients who had a recent stent thrombosis especially considering the high variability of clopidogrel response in such patients based on gene polymorphisms. The results of PFT and the presence of certain genetic markers will not only assist in anticipating the thrombotic events but bleeding events as well. Polymorphisms of CYP2C**9** and CYP2C**19** deem to have considerable effects on the metabolism of both warfarin and clopidogrel respectively. Consequently, genetic testing of such patients is warranted. Apart from CYP2C9, studies have also noted that in patients with ACS receiving clopidogrel treatment, the platelet reactivity in those carrying the CES1 143E-allele was lower than that in 143G-homozygotes. CES1 is a hepatic serine hydrolase that is also involved in the bioactivation of clopidogrel. The interracial differences of these polymorphisms have to be acknowledged as well as it was noted that the prevalence of clopidogrel resistance is expected to be higher in Asians compared to Caucasians **[45]**.

Strengths and Limitations

In this meta-analysis, we have directly assessed the bleeding risk in AF patients with associated coronary disease and/or PCIs where the primary oral anticoagulants used are DOACs. Also, this study has investigated the contrast between using a DOAC with an associated antiplatelet/s against a DOAC alone. The veracity of the results of our meta-analysis is further strengthened by the robustness of the sensitivity analysis. Also, we demonstrated that there was no evidence of publication bias through the use of funnel plots and egger's tests.

But this meta-analysis has its limitations as well. Firstly, the study design, the duration of therapies, the follow-ups and the reporting of the outcomes of the trials differed from each other. We acknowledge the fact that different bleeding definitions were reported in the different studies and as such, limited our ability to analyse the different safety outcomes from all the trials. Furthermore, in the setting of AF with ACS/PCI, the apparent heterogeneity in the composite efficacy endpoint of MACE defined in the different trials does alter the interpretation thereby leading to misleading conclusions **[94]**. Apart from the AUGUSTUS trial, the other three trials didn't assess the antiplatelet regimens separately. Importantly, since we have adopted a random effects model and the number of studies is less, the between studies variance is of poor precision, necessitating a Bayesian method **[95]**. As there was no triple therapy arm of the dabigatran doses in the REDUAL PCI and ENTRUST AF PCI, their exclusion from the meta-analysis does not provide a clear and complete picture.

In the setting of AF patients with an indication for concomitant antiplatelet therapy, there was no randomisation of antiplatelet therapy performed and only a minority of patients was using an antiplatelet agent continuously throughout the studies. The results published were that of a post-hoc analysis. They should always be interpreted cautiously as these subgroups will not be powered for a formal statistical testing of each individual subgroup.

Secondly, our meta-analysis, to provide an overall outlook, pooled the available data for the outcomes of interest irrespective of the bleeding and stroke risk of these patients. However, it should be noted that the included trials in the setting of AF with ACS/PCI was enriched by patients who had high HAS-BLED and CHA2DS2-VASc scores **(➤Table 2).** Due to the unavailability of specific datasets, a sub analysis of those aged 65-74 years and those over 75 years could not be performed. Furthermore, we had access to only study-level data instead of patient level data which would help in performing the time to event analysis. It would allow exploring and making refinements based on sex specific differences, ethnicities, clinical presentations of the patients.

Thirdly, since a meta-regression could not be performed, the implications of our study results when it comes to major bleeding in AF patients with an arterial vascular disease like CAD can be difficult to interpret given the fact that the included trials each had fewer patients with this comorbidity (38%) **[96].**

Ongoing trials

Some of the ongoing trials in the setting of AF with ACS/PCI include the Phase 4 Dabigatran Versus Warfarin With NVAF Who Undergo PCI (COACH AF PCI) trial [NCT03536611], CAPITAL PCI AF [NCT03331484] and the AVIATOR 2 observational study **[97].** The status of the RT-AF trial remains unknown **[98].**

Conclusion

In conclusion, our meta-analysis shows that in the setting of AF patients with ACS / PCI**,** dual therapy of a DOAC plus an antiplatelet (P2Y12 inhibitor like clopidogrel) is preferable over a triple therapy containing aspirin. In the setting of AF patients with an indication for concomitant antiplatelets, it was shown that there was a statistically significant increase in both major bleeding and thromboembolic events with the concomitant use of antiplatelet agents. Due to the differences in the population of the recruited patients in terms of their comorbidities, the concomitant medications and the treatment regimens administered to them and the design of the clinical trials, it is advisable for a more calculated and personalised approach in treating higher risk AF patients with the added implementation of PFTs as well.

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SUPPLEMENTARY MATERIAL

SEARCH STRATEGY

Databases:

1) PUBMED ADVANCED SEARCH STRATEGY

PLATELET AGGREGATION INHIBITORS

((((((((((((((((((((((((((((((((((((aspirin[MeSH Terms])) OR (2- AND (Acetyloxy) AND benzoic Acid)) OR (Acetylsalicylic Acid)) OR (Acetysal)) OR (Acylpyrin)) OR (Aloxiprimum)) OR (Colfarit)) OR (Dispril)) OR (Easprin)) OR (Ecotrin)) OR (Endosprin)) OR (Magnecyl)) OR (Micristin)) OR (Polopirin)) OR (Polopiryna)) OR (Solprin)) OR (Solupsan)) OR (Zorprin))) OR ((((((((((((dipyridamole[MeSH Terms])) OR (Antistenocardin)) OR (Apo-Dipyridamole)) OR (Cerebrovase)) OR (Cleridium)) OR (Curantil)) OR (Curantyl)) OR (Kurantil)) OR (Miosen)) OR (Novo-Dipiradol)) OR (Persantin)) OR (Persantine))) OR ((((triflusal)) OR (2-acetoxy-4-trifluoromethylbenzoic acid)) OR (Disgren))) OR ((((((((((((((((clopidogrel)) OR (clopidogrel napadisilate)) OR (clopidogrel, AND (S) AND -isomer)) OR (Iscover)) OR (PCR 4099)) OR (PCR-4099)) OR (clopidogrel-Mepha)) OR (SC 25989C)) OR (SC 25990C)) OR (SR 25989)) OR (clopidogrel besylate)) OR (clopidogrel besilate)) OR (clopidogrel hydrochloride)) OR (clopidogrel Sandoz)) OR (clopidogrel bisulfate)) OR (Plavix))) OR ((((((((((Prasugrel Hydrochloride[MeSH Terms])) OR (Prasugrel HCl)) OR (Prasugrel)) OR (CS 747)) OR (CS-747)) OR (LY 640315)) OR (LY-640315)) OR (LY640315)) OR (Effient)) OR (Efient))) OR (((((((Ticagrelor)) OR (3- AND (7- AND ((2- AND (3,4-difluorophenyl) AND cyclopropyl) AND amino) AND -5- AND (propylthio) AND -3H- AND (1-3) AND -triazolo AND (4,5-d) AND pyrimidin-3-yl) AND -5- AND (2-hydroxyethoxy) AND cyclopentane-1,2-diol)) OR (AZD 6140)) OR (AZD-6140)) OR (AZD6140)) OR (Brilinta)) OR (Brilique))) OR (((((((((Ticlopidine[MeSH Terms])) OR (Ticlopidine Hydrochloride)) OR (Ticlodix)) OR (Ticlodone)) OR (Ticlid)) OR (53-32C)) OR (53 32C)) OR (5332C))) OR (((((((cilostazol)) OR (2 AND (1H) AND -quinolinone, 6- AND (4- AND (1-cyclohexyl-1H-tetrazol-5-yl) AND butoxy) AND -3,4-dihydro-)) OR (6- AND (4- AND (1-cyclohexyl-1H-tetrazol-5-yl) AND butoxy) AND -3,4-dihydro-2 AND (1H) AND -quinolinone)) OR (OPC 13013)) OR (OPC-13013)) OR (Pletal))) OR ((((((vorapaxar)) OR (Zontivity)) OR (SCH 530348)) OR (SCH530348)) OR (SCH-530348))) OR (((((((abciximab)) OR (c7E3 Fab)) OR (chimeric 7E3 Fab)) OR (Clotinab)) OR (ReoPro)) OR (CentoRx))) OR ((((((eptifibatide)) OR (epifibatide)) OR (epifibratide)) OR (Integrilin)) OR (Integrelin))) OR ((((((((((((tirofiban)) OR (N-AND (butylsulfonyl) AND -O- AND (4- AND (4-piperidyl) AND butyl) AND -L-tyrosine)) OR (MK 383)) OR (MK-383)) OR (tirofiban hydrochloride)) OR (tirofiban hydrochloride monohydrate)) OR (Aggrastat)) OR (Agrastat)) OR (L 700462)) OR (L-700462)) OR (L-700,462))) OR (((((cangrelor)) OR (Kengreal)) OR (AR C69931MX)) OR (AR-C69931MX))) OR ((((((((((Platelet Aggregation Inhibitors[MeSH Terms])) OR (Platelet Antiaggregants)) OR (Antiplatelet Agents)) OR (Antiplatelet Drugs)) OR (Blood Platelet Aggregation Inhibitors)) OR (Blood Platelet Antagonists)) OR (Blood Platelet Antiaggregants)) OR (Platelet Antagonists)) OR (Platelet Inhibitors))) OR ((((((((((Purinergic P2Y Receptor Antagonists[MeSH Terms])) OR (ADP Receptor Antagonists)) OR (ADP Receptor Blockers)) OR (Adenosine Diphosphate Receptor Antagonists)) OR (P2Y Purinoceptor Antagonists)) OR (P2Y1 Purinoceptor Antagonists)) OR (P2Y12 Purinoceptor Antagonists)) OR (P2Y12 Receptor Antagonists)) OR (Purinergic P2Y12 Receptor Antagonists))))

DIRECT ORAL ANTICOAGULANTS

((((((((((Rivaroxaban[MeSH Terms])) OR (5-chloro-N- AND (((5S) AND -2-oxo-3- AND (4- AND (3-oxomorpholin-4-yl) AND phenyl) AND -1,3-oxazolidin-5-yl) AND methyl) AND thiophene-2-carboxamide)) OR (Xarelto)) OR (BAY 59-7939)) OR (BAY 59 7939)) OR (BAY 597939))) OR (((((((Dabigatran[MeSH Terms])) OR (BIBR 953)) OR (BIBR 1048)) OR (Dabigatran Etexilate)) OR (Dabigatran Etexilate Mesylate)) OR (Pradaxa))) OR (((((apixaban)) OR (BMS 562247)) OR (BMS562247)) OR (BMS-562247))) OR (((((edoxaban)) OR (DU-176b)) OR (DU-176)) OR (edoxaban tosylate))) OR (((((betrixaban)) OR (N- AND (5-chloropyridin-2-yl) AND -2- AND (4- AND (N, N-dimethylcarbamimidoyl) AND benzamido) AND -5-methoxybenzamide)) OR (BEVYXXA)) OR (PRT054021))

PATHOLOGIES AND INTERVENTIONS

((Atrial Fibrillation[MeSH Terms])) OR (Auricular Fibrillation)) OR (Familial Atrial Fibrillation)) OR (Paroxysmal Atrial Fibrillation)) OR (Persistent Atrial Fibrillation)) OR (myocardial ischemia[MeSH Terms])) OR (Ischemic Heart Disease)) OR (acute coronary syndrome[MeSH Terms])) OR (atrial flutter[MeSH Terms])) OR (Auricular Flutter)) OR (Angina Pectoris[MeSH Terms])) OR (Angor Pectoris)) OR (Stenocardia)) OR (coronary disease[MeSH Terms])) OR (Coronary Heart Disease)) OR (myocardial infarction[MeSH Terms])) OR (Cardiovascular Stroke)) OR (Heart Attack)) OR (Myocardial Infarct)) OR (Stroke[MeSH Terms])) OR (Apoplexy)) OR (CVA AND (Cerebrovascular Accident))) OR (Cerebral Stroke)) OR (Cerebrovascular Accident)) OR (Acute Cerebrovascular Accident)) OR (Cerebrovascular Apoplexy)) OR (Cerebrovascular Stroke)) OR (Acute Stroke)) OR (Brain Vascular Accident)) OR (Thrombosis[MeSH Terms])) OR (Blood Clot)) OR (Thrombus)) OR (Thromboembolism[MeSH Terms])) OR (Hemorrhage[MeSH Terms])) OR (Bleeding)) OR (Arteriosclerosis[MeSH Terms])) OR (Angioplasty[MeSH Terms])) OR (Transluminal Angioplasty)) OR (Endoluminal Repair)) OR (Percutaneous Transluminal Angioplasty)) OR (Percutaneous Coronary Intervention[MeSH Terms])) OR (Percutaneous Coronary Revascularization)) OR (Stents[MeSH Terms])

Complete search (Search results - **773** articles)

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Sandoz)) OR (clopidogrel bisulfate)) OR (Plavix))) OR (((((((((((Prasugrel Hydrochloride[MeSH Terms])) OR (Prasugrel HCl)) OR (Prasugrel)) OR (CS 747)) OR (CS-747)) OR (LY 640315)) OR (LY-640315)) OR (LY640315)) OR (Effient)) OR (Efient))) OR ((((((((Ticagrelor)) OR (3- AND (7- AND ((2- AND (3,4-difluorophenyl) AND cyclopropyl) AND amino) AND -5- AND (propylthio) AND -3H- AND (1-3) AND -triazolo AND (4,5-d) AND pyrimidin-3-yl) AND -5- AND (2-hydroxyethoxy) AND cyclopentane-1,2-diol)) OR (AZD 6140)) OR (AZD-6140)) OR (AZD6140)) OR (Brilinta)) OR (Brilique))) OR (((((((((Ticlopidine[MeSH Terms])) OR (Ticlopidine Hydrochloride)) OR (Ticlodix)) OR (Ticlodone)) OR (Ticlid)) OR (53-32C)) OR (53 32C)) OR (5332C))) OR (((((((cilostazol)) OR (2 AND (1H) AND -quinolinone, 6- AND (4- AND (1-cyclohexyl-1H-tetrazol-5-yl) AND butoxy) AND -3,4-dihydro-)) OR (6- AND (4- AND (1-cyclohexyl-1H-tetrazol-5-yl) AND butoxy) AND -3,4-dihydro-2 AND (1H) AND -quinolinone)) OR (OPC 13013)) OR (OPC-13013)) OR (Pletal))) OR ((((((vorapaxar)) OR (Zontivity)) OR (SCH 530348)) OR (SCH530348)) OR (SCH-530348))) OR (((((((abciximab)) OR (c7E3 Fab)) OR (chimeric 7E3 Fab)) OR (Clotinab)) OR (ReoPro)) OR (CentoRx))) OR ((((((eptifibatide)) OR (epifibatide)) OR (epifibratide)) OR (Integrilin)) OR (Integrelin))) OR ((((((((((((tirofiban)) OR (N- AND (butylsulfonyl) AND -O- AND (4- AND (4-piperidyl) AND butyl) AND -L-tyrosine)) OR (MK 383)) OR (MK-383)) OR (tirofiban hydrochloride)) OR (tirofiban hydrochloride monohydrate)) OR (Aggrastat)) OR (Agrastat)) OR (L 700462)) OR (L-700462)) OR (L-700,462))) OR (((((cangrelor)) OR (Kengreal)) OR (AR C69931MX)) OR (AR-C69931MX))) OR ((((((((((Platelet Aggregation Inhibitors[MeSH Terms])) OR (Platelet Antiaggregants)) OR (Antiplatelet Agents)) OR (Antiplatelet Drugs)) OR (Blood Platelet Aggregation Inhibitors)) OR (Blood Platelet Antagonists)) OR (Blood Platelet Antiaggregants)) OR (Platelet Antagonists)) OR (Platelet Inhibitors))) OR ((((((((((Purinergic P2Y Receptor Antagonists[MeSH Terms])) OR (ADP Receptor Antagonists)) OR (ADP Receptor Blockers)) OR (Adenosine Diphosphate Receptor Antagonists)) OR (P2Y Purinoceptor Antagonists)) OR (P2Y1 Purinoceptor Antagonists)) OR (P2Y12 Purinoceptor Antagonists)) OR (P2Y12 Receptor Antagonists)) OR (Purinergic P2Y12 Receptor Antagonists)))) AND ((((((((((((Rivaroxaban[MeSH Terms])) OR (5-chloro-N- AND (((5S) AND -2-oxo-3- AND (4- AND (3-oxomorpholin-4-yl) AND phenyl) AND -1,3-oxazolidin-5-yl) AND methyl) AND thiophene-2-carboxamide)) OR (Xarelto)) OR (BAY 59-7939)) OR (BAY 59 7939)) OR (BAY 597939))) OR (((((((Dabigatran[MeSH Terms])) OR (BIBR 953)) OR (BIBR 1048)) OR (Dabigatran Etexilate)) OR (Dabigatran Etexilate Mesylate)) OR (Pradaxa))) OR (((((apixaban)) OR (BMS 562247)) OR (BMS562247)) OR (BMS-562247))) OR (((((edoxaban)) OR (DU-176b)) OR (DU-176)) OR (edoxaban tosylate))) OR (((((betrixaban)) OR (N- AND (5-chloropyridin-2-yl) AND -2- AND (4- AND (N, N-dimethylcarbamimidoyl) AND benzamido) AND -5-methoxybenzamide)) OR (BEVYXXA)) OR (PRT054021)))) AND ((Atrial Fibrillation[MeSH Terms])) OR (Auricular Fibrillation)) OR (Familial Atrial Fibrillation)) OR (Paroxysmal Atrial Fibrillation)) OR (Persistent Atrial Fibrillation)) OR (myocardial ischemia[MeSH Terms])) OR (Ischemic Heart Disease)) OR (acute coronary syndrome[MeSH Terms])) OR (atrial flutter[MeSH Terms])) OR (Auricular Flutter)) OR (Angina Pectoris[MeSH Terms])) OR (Angor Pectoris)) OR (Stenocardia)) OR (coronary disease[MeSH Terms])) OR (Coronary Heart Disease)) OR (myocardial infarction[MeSH Terms])) OR (Cardiovascular Stroke)) OR (Heart Attack)) OR (Myocardial Infarct)) OR (Stroke[MeSH Terms])) OR (Apoplexy)) OR (CVA AND (Cerebrovascular Accident))) OR (Cerebral Stroke)) OR (Cerebrovascular Accident)) OR (Acute Cerebrovascular Accident)) OR (Cerebrovascular Apoplexy)) OR (Cerebrovascular Stroke)) OR (Acute Stroke)) OR (Brain Vascular Accident)) OR (Thrombosis[MeSH Terms])) OR (Blood Clot)) OR (Thrombus)) OR 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2) SCOPUS (Search results – 787 articles)

TITLE-ABS("aspirin") OR TITLE-ABS("Acetylsalicylic Acid") OR TITLE-ABS("Acetysal") OR TITLE-ABS("Acylpyrin") OR TITLE-ABS("Aloxiprimum") OR TITLE-ABS("Colfarit") OR TITLE-ABS("Dispril") OR TITLE-ABS("Easprin") OR TITLE-ABS("Ecotrin") OR TITLE-ABS("Endosprin") OR TITLE-ABS("Magnecyl") OR TITLE-ABS("Micristin") OR TITLE-ABS("Polopirin") OR TITLE-ABS("Polopiryna") OR TITLE-ABS("Solprin") OR TITLE-ABS("Solupsan") OR TITLE-ABS("Zorprin") OR TITLE-ABS("dipyridamole") OR TITLE-ABS("Antistenocardin") OR TITLE-ABS("Apo-Dipyridamole") OR TITLE-ABS("Cerebrovase") OR TITLE-ABS("Curantil") OR TITLE-ABS("Curantyl") OR TITLE-ABS("Kurantil") OR TITLE-ABS("Miosen") OR TITLE-ABS("Novo-Dipiradol") OR TITLE-ABS("Persantin") OR TITLE-ABS("Persantine") OR TITLE-ABS("triflusal") OR TITLE-ABS("Disgren") OR TITLE-ABS("clopidogrel") OR TITLE-ABS("clopidogrel napadisilate") OR TITLE-ABS("Iscover") OR TITLE-ABS("PCR 4099") OR TITLE-ABS("PCR-4099") OR TITLE-ABS("clopidogrel-Mepha") OR TITLE-ABS("SC 25989C") OR 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TITLE-ABS("vorapaxar") OR TITLE-ABS("Zontivity") OR TITLE-ABS("SCH 530348") OR TITLE-ABS("SCH530348") OR TITLE-ABS("SCH-530348") OR TITLE-ABS("abciximab") OR TITLE-ABS("c7E3 Fab") OR TITLE-ABS("chimeric 7E3 Fab") OR TITLE-ABS("Clotinab") OR TITLE-ABS("ReoPro") OR TITLE-ABS("CentoRx") OR TITLE-ABS("eptifibatide") OR TITLE-ABS("epifibatide") OR TITLE-ABS("epifibratide") OR TITLE-ABS("Integrilin") OR TITLE-ABS("Integrelin") OR TITLE-ABS("tirofiban") OR TITLE-ABS("MK 383") OR TITLE-ABS("MK-383") OR TITLE-ABS("tirofiban hydrochloride") OR TITLE-ABS("tirofiban hydrochloride monohydrate") OR TITLE-ABS("Aggrastat") OR TITLE-ABS("Agrastat") OR TITLE-ABS("L 700462") OR TITLE-ABS("L-700462") OR TITLE-ABS("L-700,462") OR TITLE-ABS("cangrelor") OR TITLE-ABS("Kengreal") OR TITLE-ABS("AR C69931MX") OR TITLE-ABS("AR-C69931MX") OR INDEXTERMS("Platelet Aggregation Inhibitors") OR ALL("Platelet Antiaggregants") OR ALL("Antiplatelet Agents") OR ALL("Antiplatelet Drugs") OR ALL("Blood Platelet Aggregation Inhibitors") OR ALL("Blood Platelet Antagonists") OR ALL("Blood Platelet Antiaggregants") OR ALL("Platelet Antagonists") OR ALL("Platelet Inhibitors") OR INDEXTERMS("Purinergic P2Y Receptor Antagonists") OR ALL("ADP Receptor Antagonists") OR ALL("ADP Receptor Blockers") OR ALL("Adenosine Diphosphate Receptor Antagonists") OR ALL("P2Y Purinoceptor Antagonists") OR ALL("P2Y1 Purinoceptor Antagonists") OR ALL("P2Y12 Purinoceptor Antagonists") OR ALL("P2Y12 Receptor Antagonists") OR ALL("Purinergic P2Y12 Receptor Antagonists") AND TITLE-ABS("Rivaroxaban") OR TITLE-ABS("Xarelto") OR TITLE-ABS("BAY 59-7939") OR TITLE-ABS("BAY 59 7939") OR TITLE-ABS("BAY 597939") OR TITLE-ABS("Dabigatran") OR TITLE-ABS("BIBR 953") OR TITLE-ABS("BIBR 1048") OR TITLE-ABS("Dabigatran Etexilate") OR TITLE-ABS("Dabigatran Etexilate Mesylate") OR TITLE-ABS("Pradaxa") OR TITLE-ABS("apixaban") OR TITLE-ABS("BMS 562247") OR TITLE-ABS("BMS562247") OR TITLE-ABS("BMS-562247") OR TITLE-ABS("edoxaban") OR TITLE-ABS("DU-176b") OR TITLE-ABS("DU-176") OR TITLE-ABS("edoxaban tosylate") OR TITLE-ABS("betrixaban") OR TITLE-ABS("BEVYXXA") OR TITLE-ABS("PRT054021") AND INDEXTERMS("Atrial Fibrillation") OR ALL("Auricular Fibrillation") OR ALL("Familial Atrial Fibrillation") OR ALL("Paroxysmal Atrial Fibrillation") OR ALL("Persistent Atrial Fibrillation") OR INDEXTERMS("myocardial ischemia") OR ALL("Ischemic Heart Disease") OR INDEXTERMS("acute coronary syndrome") OR INDEXTERMS("atrial flutter") OR ALL("Auricular Flutter") OR INDEXTERMS("Angina Pectoris") OR ALL("Angor Pectoris") OR ALL("Stenocardia") OR INDEXTERMS("coronary disease") OR ALL("Coronary Heart Disease") OR INDEXTERMS("myocardial infarction") OR ALL("Cardiovascular Stroke") OR ALL("Heart Attack") OR ALL("Myocardial Infarct") OR INDEXTERMS("Stroke") OR ALL("Apoplexy") OR ALL("Cerebral Stroke") OR ALL("Cerebrovascular Accident") OR ALL("Acute Cerebrovascular Accident") OR ALL("Cerebrovascular Apoplexy") OR ALL("Cerebrovascular Stroke") OR ALL("Acute Stroke") OR ALL("Brain Vascular Accident") OR INDEXTERMS("Thrombosis") OR ALL("Blood Clot") OR ALL("Thrombus") OR INDEXTERMS("Thromboembolism") OR INDEXTERMS("Hemorrhage") OR ALL("Bleeding") OR INDEXTERMS("Arteriosclerosis") OR INDEXTERMS("Angioplasty") OR ALL("Transluminal Angioplasty") OR ALL("Endoluminal Repair") OR INDEXTERMS("Percutaneous Transluminal Angioplasty") OR ALL("Percutaneous Coronary Intervention") OR ALL("Percutaneous Coronary Revascularization") OR INDEXTERMS("Stents")

3) COCHRANE LIBRARY (Search results – 405 articles)

ID Search Hits
#1) MeSH descriptor: [Aspirin] explode all trees (5635)
#2) 2- (Acetyloxy) benzoic Acid (5)
#3) Acetylsalicylic Acid (6609)
#4) Acetysal (4)
#5) Acylpyrin (4)
#6) Aloxiprimum (3)
#7) Colfarit (11)
#8) Dispril (13)
#9) Easprin (3)
#10) Ecotrin (10)
#11) Endosprin (4)
#12) Magnecyl (7)
#13) Micristin (11)
#14) Polopirin (4)
#15) Polopiryna (5)
#16) Solprin (4)
#17) Solupsan (6)
#18) Zorprin (4)
#19) #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 (11075)
#20) MeSH descriptor: [Dipyridamole] explode all trees (645)
#21) Antistenocardin (4)
#22) Apo-Dipyridamole (0)
#23) Cerebrovase (1)
#24) Cléridium (1)
#25) Curantil (4)
#26) Curantyl (8)
#27) Kurantil (5)
#28) Miosen (1)
#29) Novo-Dipiradol (1)
#30) Persantin (58)
#31) Persantine (43)
#32) #20 or #21 or 22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 (125136)
#33) triflusal (140)
#34) 2 acetoxy 4 trifluoromethylbenzoic acid (0)
#35) disgren (11)
#36) #33 or #34 or #35 (140)
#37) clopidogrel (4729)
#38) clopidogrel napadisilate (4)
#39) clopidogrel isomer (6)
#40) Iscover (6)
#41) PCR 4099 (2)
#42) PCR-4099 (1)
#43) clopidogrel-Mepha (1)
#44) SC 25989C (0)
#45) SC 25990C (0)
#46) SR 25989 (1)
#47) clopidogrel besylate (15)
#48) clopidogrel besilate (0)
#49) clopidogrel hydrochloride (243)
#50) clopidogrel Sandoz (4)
#51) clopidogrel bisulfate (42)
#52) Plavix (116)

#53) #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 (4739)
#54) MeSH descriptor: [Prasugrel Hydrochloride] explode all trees (312)
#55) Prasugrel HCl (0)
#56) Prasugrel (915)
#57) CS 747 (43)
#58) CS-747 (11)
#59) LY 640315 (0)
#60) LY-640315 (0)
#61) LY640315 (8)
#62) Effient (14)
#63) Efient (14)
#64) #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 (948)
#65) Ticagrelor (1122)
#66) 3- (7- ((2- (3,4-difluorophenyl) cyclopropyl) amino) -5- (propylthio) -3H- (1-3) -triazolo (4,5-d) pyrimidin-3-yl) -5- (2-hydroxyethoxy) cyclopentane-1,2-diol (0)
#67) AZD 6140 (2)
#68) AZD6140 (31)
#69) AZD-6140 (2)
#70) Brilinta (17)
#71) Brilique (6)
#72) #65 or #66 or #67 or #68 or #69 or #70 or #71 (1128)
#73) MeSH descriptor: [Ticlopidine] explode all trees (1916)
#74) Ticlopidine Hydrochloride (230)
#75) Ticlodix (2)
#76) Ticlodone (3)
#77) Ticlid (34)
#78) 53-32C (0)
#79) 53 32C (1)
#80) 5332C (0)
#81) #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 (1968)
#82) Cilostazol (719)
#83) 2 (1H) -quinolinone, 6- (4- (1-cyclohexyl-1H-tetrazol-5-yl) butoxy) -3,4-dihydro- (3)
#84) 6- (4- (1-cyclohexyl-1H-tetrazol-5-yl) butoxy) -3,4-dihydro-2 (1H) -quinolinone (3)
#85) OPC 13013 (15)
#86) OPC-13013 (15)
#87) Pletal (32)
#88) #82 or #83 or #84 or #85 or #86 or #87 (724)
#89) vorapaxar (128)
#90) Zontivity (2)
#91) SCH 530348 (34)
#92) SCH530348 (8)
#93) SCH-530348 (34)
#94) #89 or #90 or #91 or #92 or #93 (137)
#95) Abciximab (874)
#96) c7E3 Fab (47)
#97) chimeric 7E3 Fab (6)
#98) Clotinab (3)
#99) ReoPro (91)
#100) CentoRx (0)
#101) #95 or #96 or #97 or #98 or #99 or #100 (920)
#102)) Eptifibatide (410)
#103) Epifibatide (2)
#104) Epifibratide (0)
#105) Integrilin (108)
#106) Integrelin (12)
#107) #102 or #103 or #104 or #105 or #106 (432)
#108) Tirofiban (539)
#109) N- (butylsulfonyl) -O- (4- (4-piperidyl) butyl) -L-tyrosine (0)
#110) MK 383 (47)

#111) MK-383 (7)
#112) Tirofiban hydrochloride (9)
#113) Tirofiban hydrochloride monohydrate (0)
#114) Aggrastat (45)
#115) Agrastat (0)
#116) L 700462 (0)
#117) L-700462 (0)
#118) L-700,462 (2)
#119) #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 (595)
#120) Cangrelor (104)
#121) Kengreal (1)
#122) AR C69931MX (5)
#123) AR-C69931MX (5)
#124) #120 or #121 or #122 or #123 (107)
#125) MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees (3949)
#126) Platelet Antiaggregants (22)
#127) Antiplatelet Agents (1192)
#128) Antiplatelet drugs (900)
#129) Blood Platelet Aggregation Inhibitors (2009)
#130) Blood Platelet Antagonists (948)
#131) Blood Platelet Antiaggregants (10)
#132) Platelet Antagonists (1760)
#133) Platelet Inhibitors (5457)
#134) #125 or #126 or #127 or #128 or #129 or #130 or #131 or #132 or #133 (6739)
#135) MeSH descriptor: [Purinergic P2Y Receptor Antagonists] explode all trees (278)
#136) ADP Receptor Antagonists (108)
#137) Adenosine Diphosphate Receptor Antagonists (115)
#138) P2Y Purinoceptor Antagonists (0)
#139) P2Y1 Purinoceptor Antagonists (0)
#140) P2Y12 Purinoceptor Antagonists (0)
#141) P2Y12 Receptor Antagonists (207)
#142) Purinergic P2Y12 Receptor Antagonists (180)
#143) #135 or #136 or #137 or #138 or #139 or #140 or #141 or #142 (458)
#144) #19 or #32 or #36 or #53 or #64 or #72 or #81 or #88 or #94 or #101 or #107 or #119 or #124 or #134 or #143 (140264)
#145) MeSH descriptor: [Rivaroxaban] explode all trees (317)
#146) 5-chloro-N- (((5S) -2-oxo-3- (4- (3-oxomorpholin-4-yl) phenyl) -1,3-oxazolidin-5-yl) methyl) thiophene-2-carboxamide (0)
#147) Xarelto (34)
#148) BAY 59-7939 (35)
#149) BAY 59 7939 (35)
#150) BAY 597939 (8)
#151) #145 or #146 or #147 or #148 or #149 or #150 (356)
#152) MeSH descriptor: [Dabigatran] explode all trees (235)
#153) BIBR 953 (22)
#154) BIBR 1048 (35)
#155) Dabigatran Etexilate (255)
#156) Dabigatran Etexilate Mesylate (2)
#157) Pradaxa (31)
#158) #152 or #153 or #154 or #155 or #156 or #157 (408)
#159) apixaban (731)
#160) BMS 562247 (10)
#161) BMS562247 (0)
#162) BMS-562247 (10)
#163) #159 or #160 or #161 or #162 (731)
#164) edoxaban (396)
#165) DU-176b (40)
#166) DU-176 (3)
#167) edoxaban tosylate (5)
#168) #164 or #165 or #166 or #167 (412)

#169) betrixaban (100)
#170) N- (5-chloropyridin-2-yl) -2- (4- (N,N-dimethylcarbamimidoyl) benzamido) -5-methoxybenzamide (0)
#171) Bevyxxa (0)
#172) PRT054021 (9)
#173) #169 or #170 or #171 or #172 (102)
#174) #151 or #158 or #163 or #168 or #173 (1708)
#175) MeSH descriptor: [Atrial Fibrillation] explode all trees (4304)
#176) Auricular Fibrillation (72)
#177) Familial Atrial Fibrillation (34)
#178) Paroxysmal Atrial Fibrillation (1577)
#179) Persistent Atrial Fibrillation (1269)
#180) MeSH descriptor: [Myocardial Ischemia] explode all trees (27812)
#181) Ischemic Heart Disease (6426)
#182) MeSH descriptor: [Acute Coronary Syndrome] explode all trees (1712)
#183) MeSH descriptor: [Atrial Flutter] explode all trees (347)
#184) Auricular Flutter (14)
#185) MeSH descriptor: [Angina Pectoris] explode all trees (4571)
#186) Angor Pectoris (55)
#187) Stenocardia (59)
#188) MeSH descriptor: [Coronary Disease] explode all trees (13453)
#189) Coronary Heart Disease (18614)
#190) MeSH descriptor: [Myocardial Infarction] explode all trees (10984)
#191) Cardiovascular Stroke (9658)
#192) Heart Attack (2573)
#193) Myocardial Infarct (2952)
#194) MeSH descriptor: [Stroke] explode all trees (8879)
#195 Apoplexy (418)
#196) CVA (Cerebrovascular Accident) (322)
#197) Cerebral Stroke (10598)
#198) Cerebrovascular Accident (8350)
#199) Acute Cerebrovascular Accident (2528)
#200) Cerebrovascular Apoplexy (134)
#201) Cerebrovascular Stroke (12133)
#202) Acute Stroke (13691)
#203) Brain Vascular Accident (609)
#204) MeSH descriptor: [Thrombosis] explode all trees (4884)
#205) Blood Clot (2170)
#206) Thrombus (2017)
#207) MeSH descriptor: [Thromboembolism] explode all trees (2307)
#208) MeSH descriptor: [Hemorrhage] explode all trees (13859)
#209) Bleeding (32697)
#210) MeSH descriptor: [Arteriosclerosis] explode all trees (9322)
#211) MeSH descriptor: [Angioplasty] explode all trees (4891)
#212) Transluminal Angioplasty (2513)
#213) Endoluminal Repair (38)
#214) Percutaneous Transluminal Angioplasty (2291)
#215) MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees (5372)
#216) Percutaneous Coronary Revascularization (3025)
#217) MeSH descriptor: [Stents] explode all trees (4756)
#218) #175 or #176 or #177 or #178 or #179 or #180 or #181 or #182 or #183 or #184 or #185 or #186 or #187 or #188 or #189 or #190 or #191 or #192 or #193 or #194 or #195 or #196 or #197 or #198 or #199 or #200 or #201 or #202 or #203 or #204 or #205 or #206 or #207 or #208 or #209 or #210 or #211 or #212 or #213 or #214 or #215 or #216 or #217 (120155)
#219) #144 and #174 and #218 Publication Year from 2009 to 2018 (Word variations have been searched) (405)

4) Clinicaltrials.gov Expert search (Search results – 141 studies)

INFLECT EXACT NOT NOTEXT [RESULTS-FIRST-SUBMITTED] AND (atrial fibrillation OR acute coronary syndrome OR percutaneous coronary intervention OR atrial flutter OR myocardial ischemia OR angina pectoris OR coronary disease OR myocardial infarction OR angioplasty OR stents OR coronary artery disease) [DISEASE] AND (Antiplatelet Drug OR oral anticoagulant OR aspirin OR Acetylsalicylic Acid OR ASA OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR dipyridamole OR Antistenocardin OR Apo-Dipyridamole OR Cerebrovase OR Cleridium OR Curantil OR Curantyl OR Kurantil OR Miosen OR Novo-Dipiradol OR Persantin OR Persantine OR triflusal OR Disgren OR clopidogrel OR clopidogrel napadisilate OR clopidogrel OR Iscover OR PCR 4099 OR PCR-4099OR clopidogrel-Mepha OR SC 25989C OR SC 25990C OR SR 25989 OR clopidogrel besylate OR clopidogrel besilate OR clopidogrel hydrochloride OR clopidogrel Sandoz OR clopidogrel bisulfate OR Plavix OR Prasugrel Hydrochloride OR Prasugrel HCl OR Prasugrel OR CS 747 OR CS-747 OR LY 640315 OR LY-640315 OR LY640315 OR Effient OR Efient OR Ticagrelor OR AZD 6140 OR AZD-6140 OR AZD6140 OR Brilinta OR Brilique OR Ticlopidine OR Ticlopidine Hydrochloride OR Ticlodix OR Ticlodone OR Ticlid OR 53-32C OR 53 32C OR 5332C OR cilostazol OR OPC 13013 OR OPC-13013 OR Pletal OR vorapaxar OR Zontivity OR SCH 530348 OR SCH530348 OR SCH-530348 OR abciximab OR c7E3 Fab OR chimeric 7E3 Fab OR Clotinab OR ReoPro OR CentoRx OR eptifibatide OR epifibatide OR epifibratide OR Integrilin OR Integrelin OR tirofiban OR MK 383 OR MK-383 OR tirofiban hydrochloride OR tirofiban hydrochloride monohydrate OR Aggrastat OR Agrastat OR L 700462 OR L-700462 OR L-700,462 OR cangrelor OR Kengreal OR AR C69931MX OR AR-C69931MX OR Platelet Aggregation Inhibitors OR Platelet Antiaggregants OR Antiplatelet Agents OR Antiplatelet Drugs OR Blood Platelet Aggregation Inhibitors OR Blood Platelet Antagonists OR Blood Platelet Antiaggregants OR Platelet Antagonists OR Platelet Inhibitors OR Purinergic P2Y Receptor Antagonists OR ADP Receptor Antagonists OR ADP Receptor Blockers OR Adenosine Diphosphate Receptor Antagonists OR P2Y Purinoceptor Antagonists OR P2Y1 Purinoceptor Antagonists OR P2Y12 Purinoceptor Antagonists OR P2Y12 Receptor Antagonists OR Purinergic P2Y12 Receptor Antagonists OR Rivaroxaban OR Xarelto OR BAY 59-7939 OR BAY 59 7939 OR BAY 597939 OR Dabigatran OR BIBR 953 OR BIBR 1048 OR Dabigatran Etexilate OR Dabigatran Etexilate Mesylate OR Pradaxa OR apixaban OR BMS 562247 OR BMS562247 OR BMS-562247 OR edoxaban OR DU-176b OR DU-176 OR edoxaban tosylate OR betrixaban OR BEVYXXA OR PRT054021) [TREATMENT] AND (hemmorhage OR bleeding OR stroke OR thrombosis OR thromboembolism) [OUTCOME] AND INFLECT EXACT ("Adult" OR "Older Adult") [AGE-GROUP]

DATA EXTRACTION FORM

IDENTIFICATION

Title & study ID:

Ref number:

First author – year of publication:

Study location - Worldwide

		Intervention	Comparator
Baseline characteristics		**Anticoagulant –** **Antiplatelet –**	**Anticoagulant –** **Antiplatelet -**
Number of patients / sample size			
Age	Mean		
	65 - 74 years		
	≥ 75 years		
Female — no. (%)			
Male — no. (%)			
HAS-BLED score			
CHA2DS2-VASc score			
Creatinine clearance – ml/min			
Comorbidity (%):	**Atrial fibrillation**		
	Acute coronary syndrome		
	Coronary artery disease		
	Recent MI		
	History of stroke		
Concomitant medication (%):	**Aspirin**		
	P2Y12 inhibitor		
	Prior VKA use		
	NOAC		
	Proton pump inhibitor		
	NSAID		
Type of stent (%):	**Drug eluting stent**		
	Bare metal stent		
	Drug-eluting & bare-metal stents		
Risk of bias assessment: Jadad score			

Jadad Scale

Criteria	Score
Was the study described as randomized (this included such words as « randomly », « random » or « randomization »	/1
Was the method used to generate the sequence of randomization described and was it appropriate (e.g table of random numbers, computer-generated)	/1
Was the study described as double-blind?	/1
Was the method of double-blinding described and was it appropriate (e.g identical placebo, active placebo, dummy)?	/1
Was there a description of withdrawals and dropouts?	/1
Deduct 1 point if the method used to generate the sequence of randomization was described but was inappropriate (e.g. patient were allocated alternatively or according to date of birth of hospital number)	/-1
Deduct 1 point if the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. Injection with no double dummy)	/ -1

Primary safety endpoint :		Major bleeding							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Primary safety endpoint :		Minor bleeding							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Primary safety endpoint :		Clinically significant non major bleeding							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Primary safety endpoint :		Any bleed							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Primary safety endpoint :		Total bleed							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Secondary efficacy endpoint :				Systemic embolism					
Treatment		Intervention	Intervention	Comparator 1	6	12	Comparator 1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Secondary efficacy endpoint :				Stroke					
Treatment		Intervention	Intervention	Comparator 1	6	12	Comparator 1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☒ HR								
	IC 95% p-value								

Secondary efficacy endpoint :				Myocardial infarction					
Treatment		Intervention	Intervention	Comparator 1	6	12	Comparator 1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Secondary efficacy endpoint :		Stent thrombosis							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☐ HR								
	IC 95% p-value								

Secondary efficacy endpoint :		Death							
Treatment		Intervention	Intervention	Comparator			Comparator		
				1	6	12	1	6	12
Number of patients									
Number of events (or %)									
Statistic	☐ OR ☐ RR ☒ HR								
	IC 95% p-value								

Sensitivity analysis and Publication bias

Figure S1: One way sensitivity analysis for the safety outcome of major bleeding for DOAC with / without concomitant antiplatelet therapy in AF

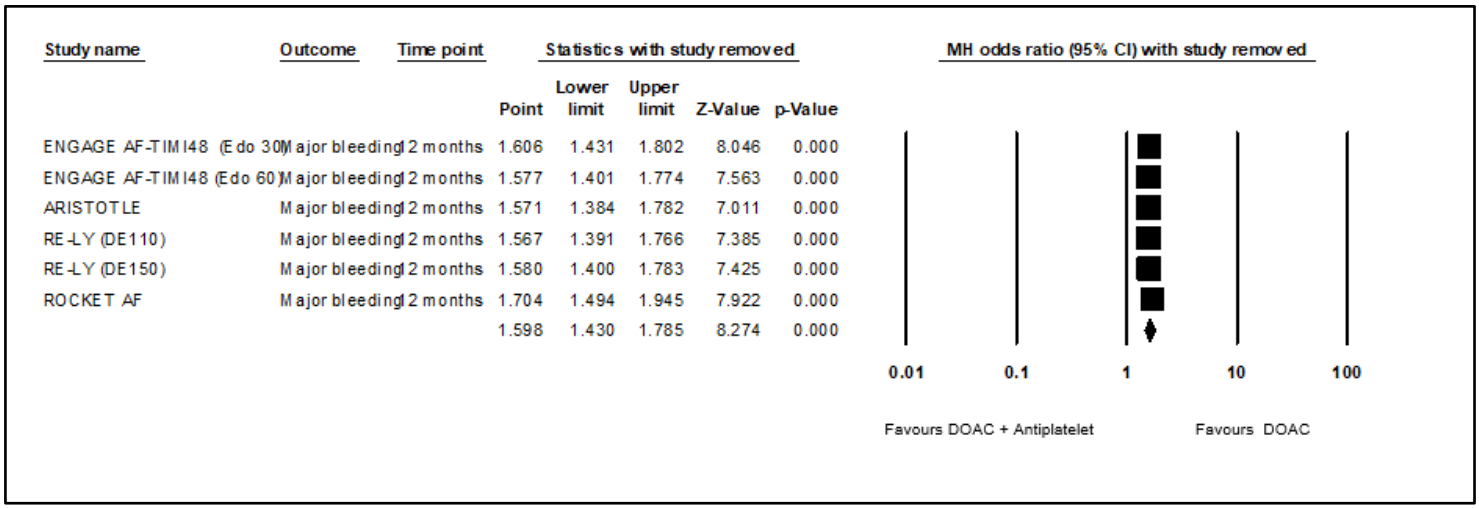

Figure S1p: Evaluation of publication bias using a funnel plot

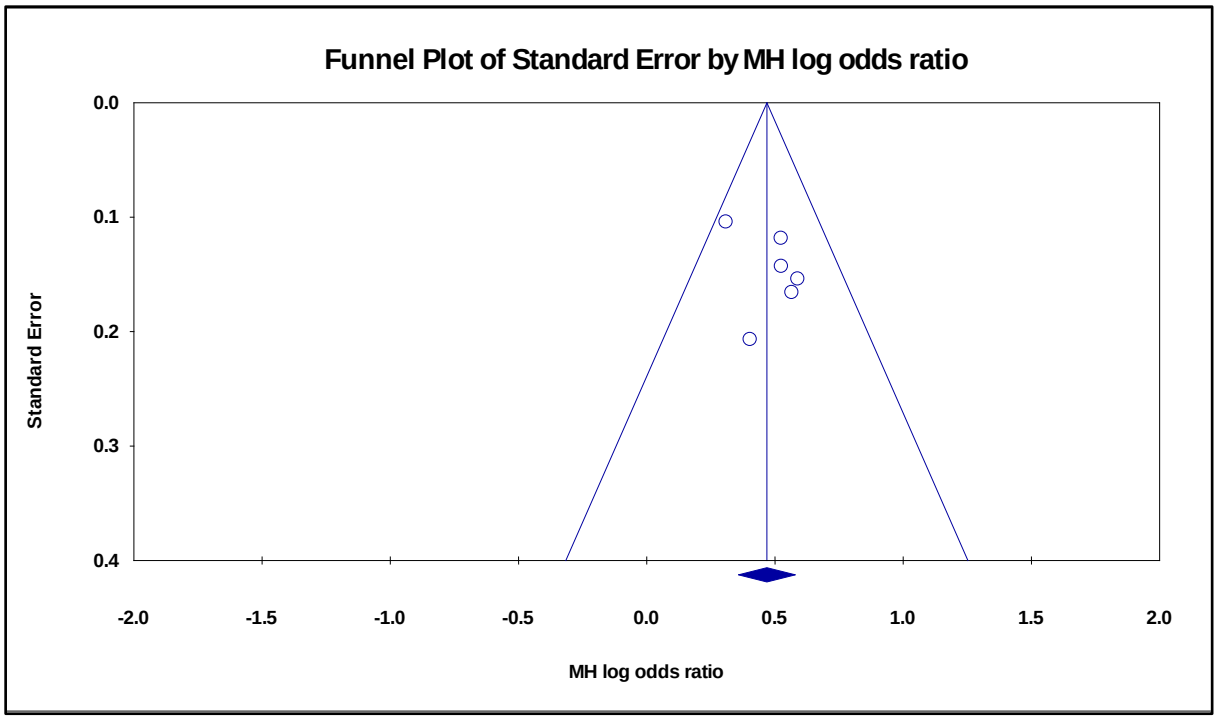

Figure S2: One way sensitivity analysis for the efficacy outcome of MACE for DOAC with / without concomitant antiplatelet therapy in AF

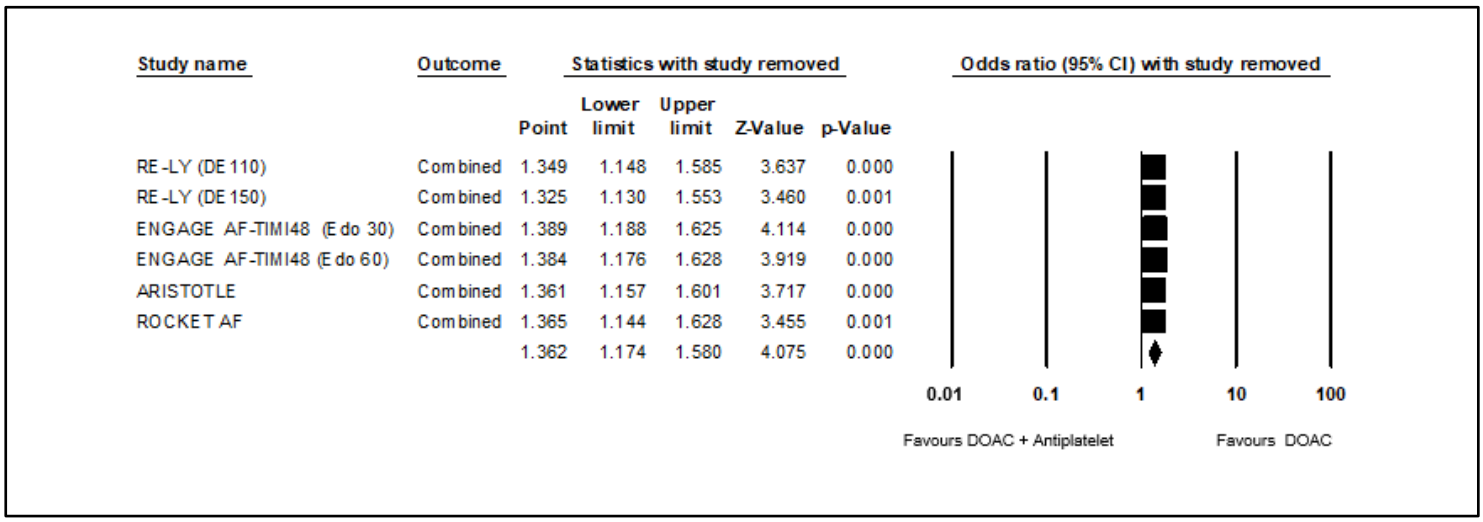

Figure S2p: Evaluation of publication bias using a funnel plot

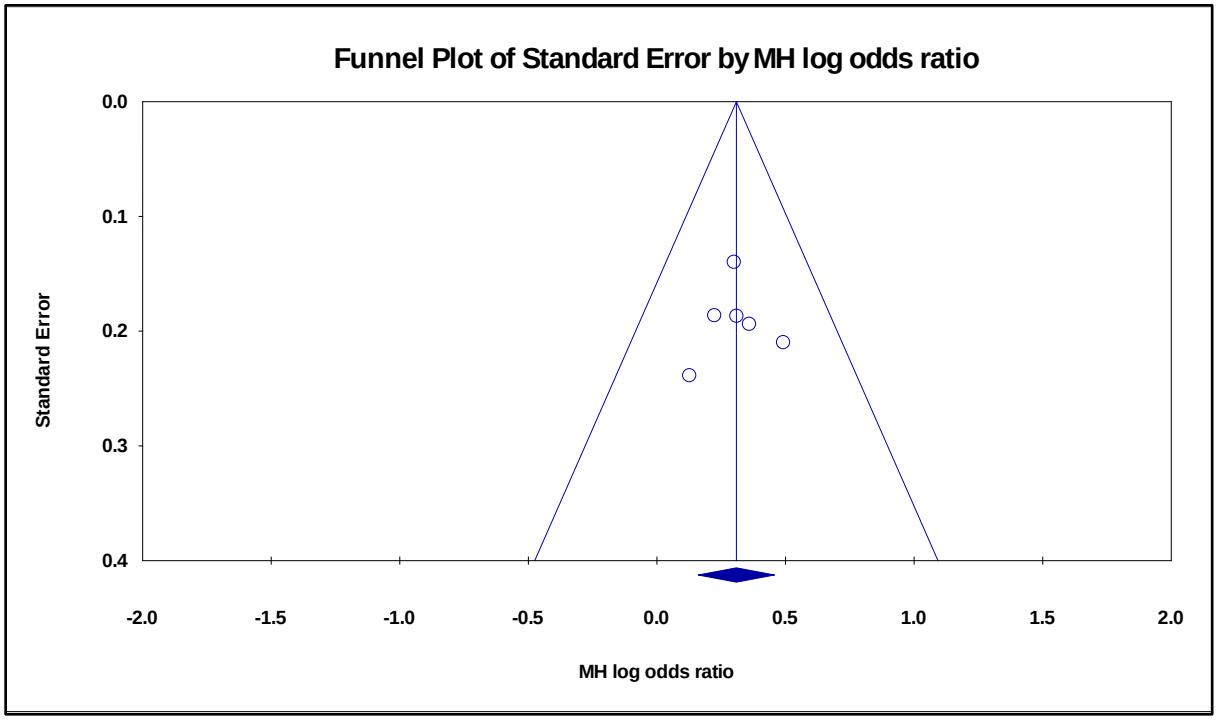

Figure S3: One way sensitivity analysis for the efficacy outcome of stroke or SE for DOAC with / without concomitant antiplatelet therapy in AF

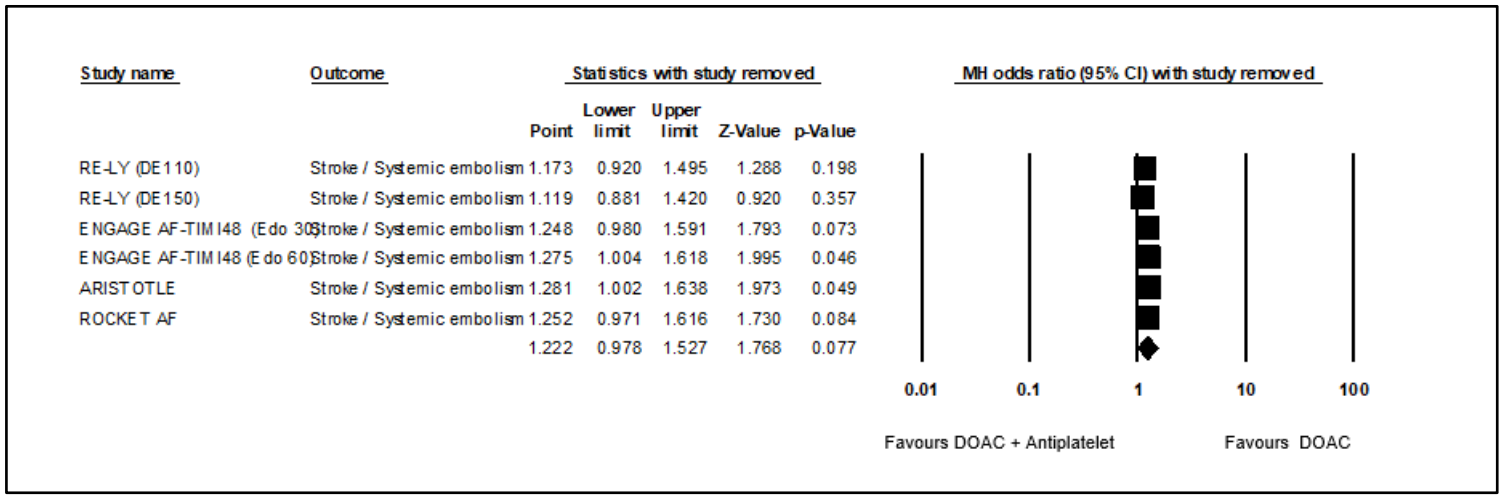

Figure S3p: Evaluation of publication bias using a funnel plot

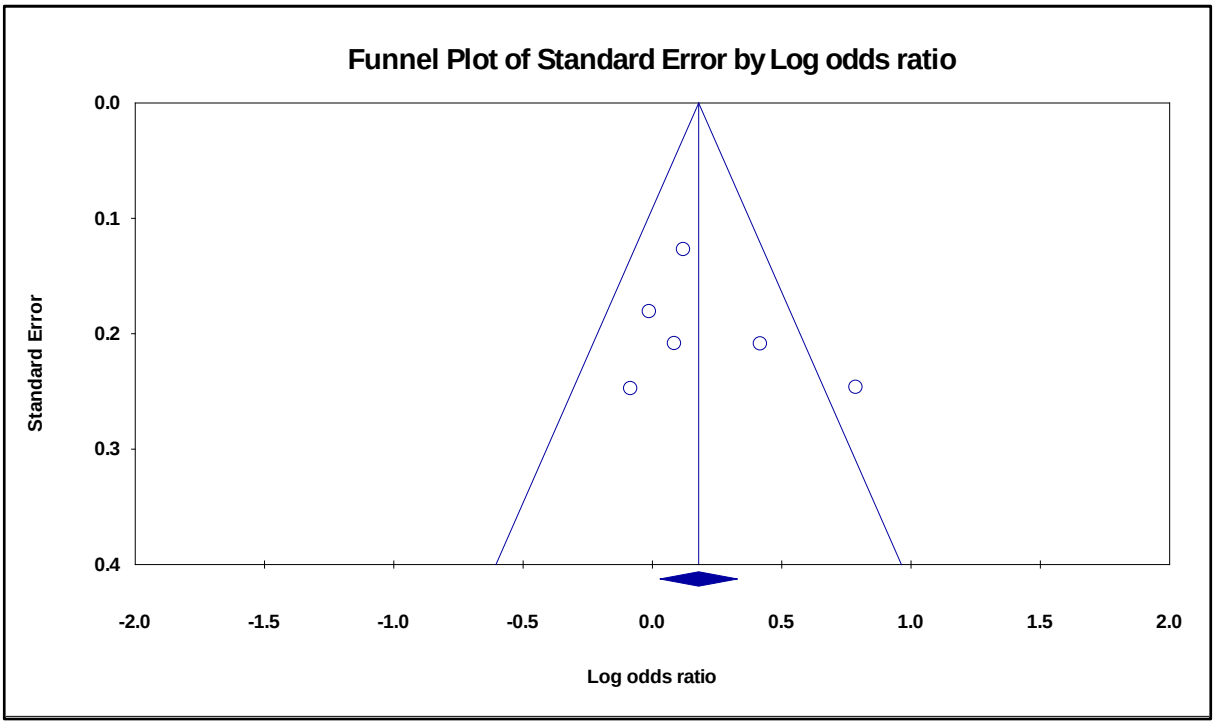

Figure S4a: One way sensitivity analysis for the efficacy outcome of MI for DOAC with / without concomitant antiplatelet therapy in AF

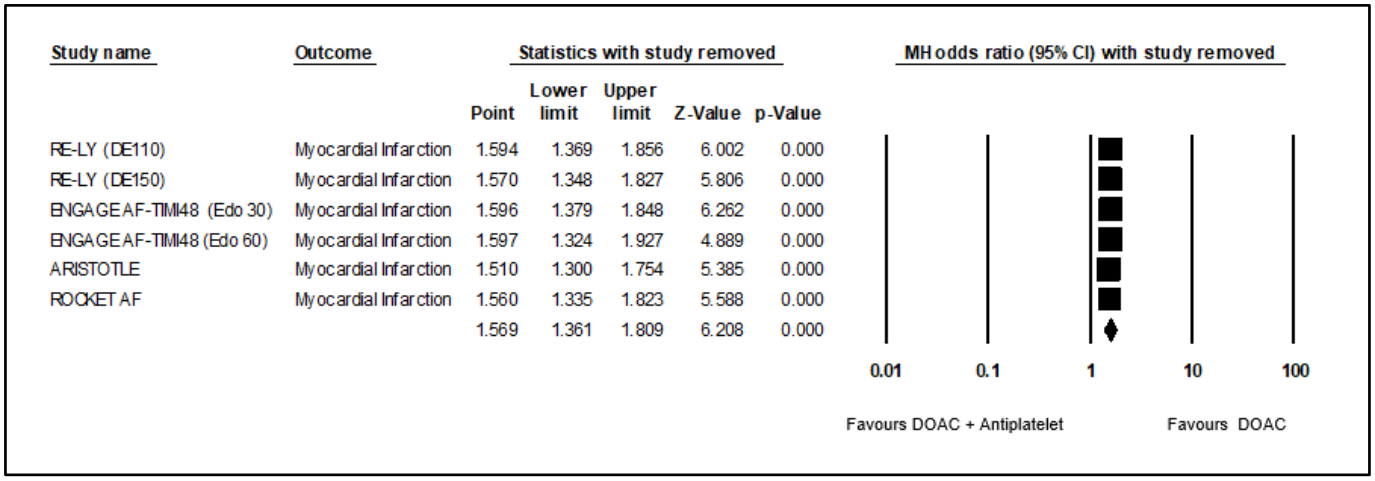

Figure S4p: Evaluation of publication bias using a funnel plot

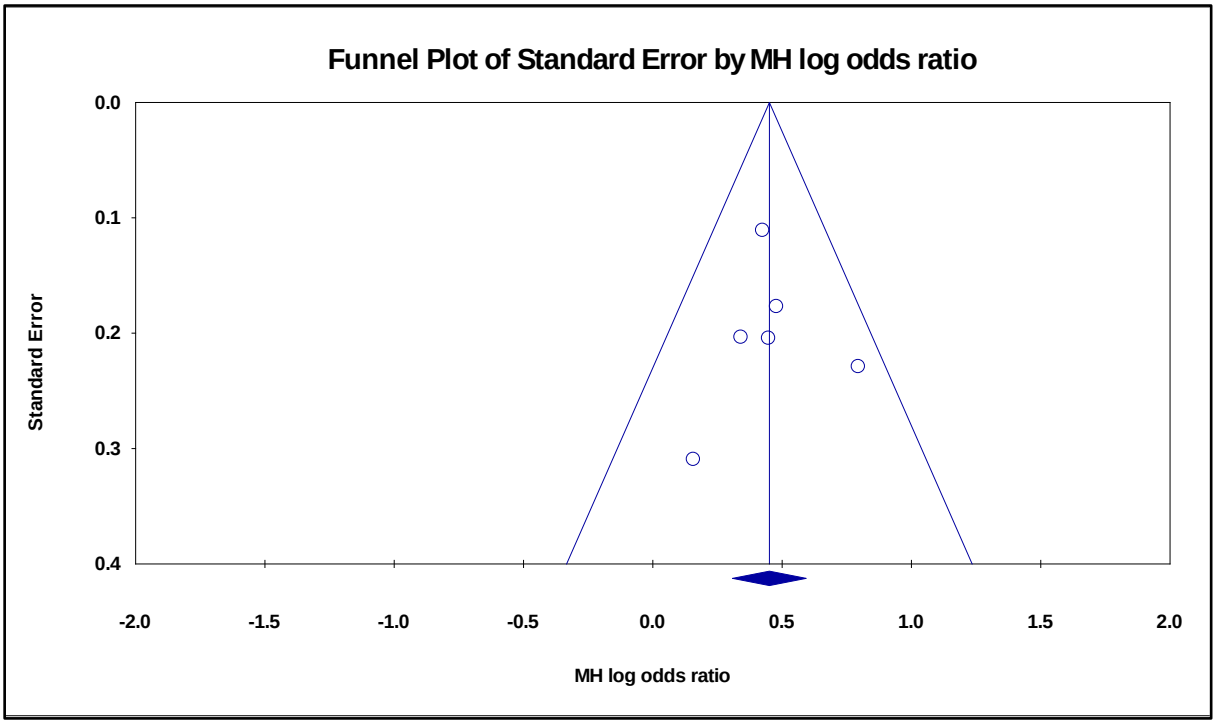

Figure S4b: One way sensitivity analysis for the efficacy outcome of MI for DOAC with / without concomitant antiplatelet therapy in AF (without RE-LY trial)

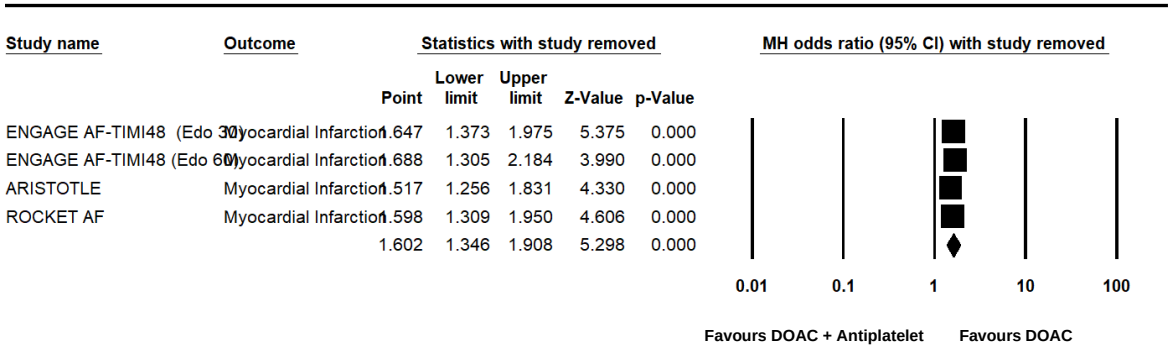

Figure S4q: Evaluation of publication bias using a funnel plot (without RE-LY trial)

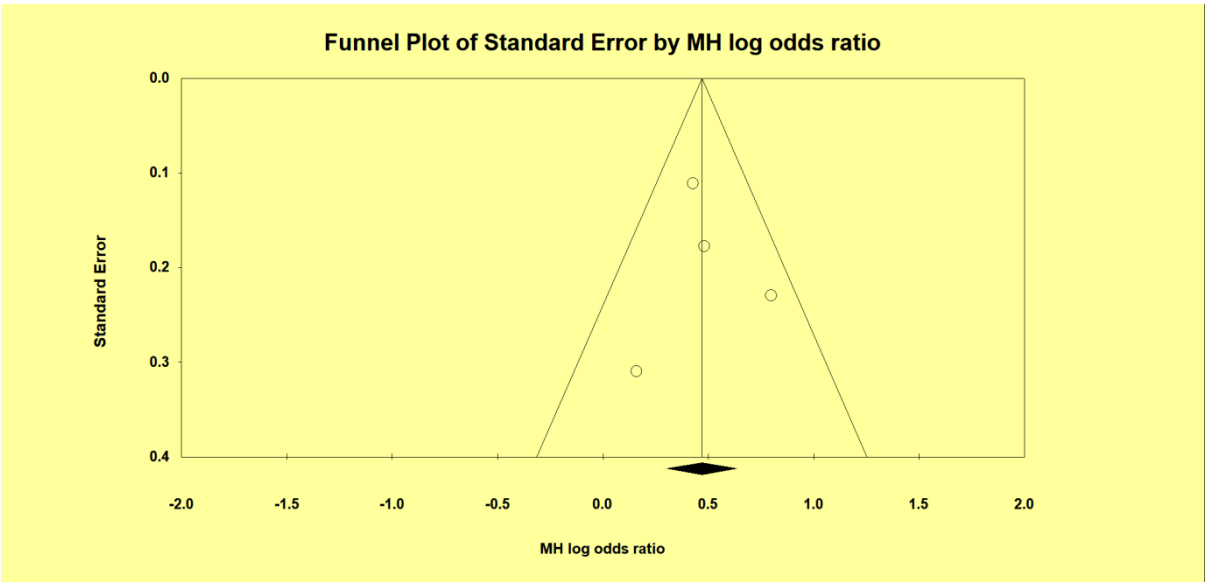

Figure S5: One way sensitivity analysis for the efficacy outcome of vascular death with / without concomitant antiplatelet therapy in AF

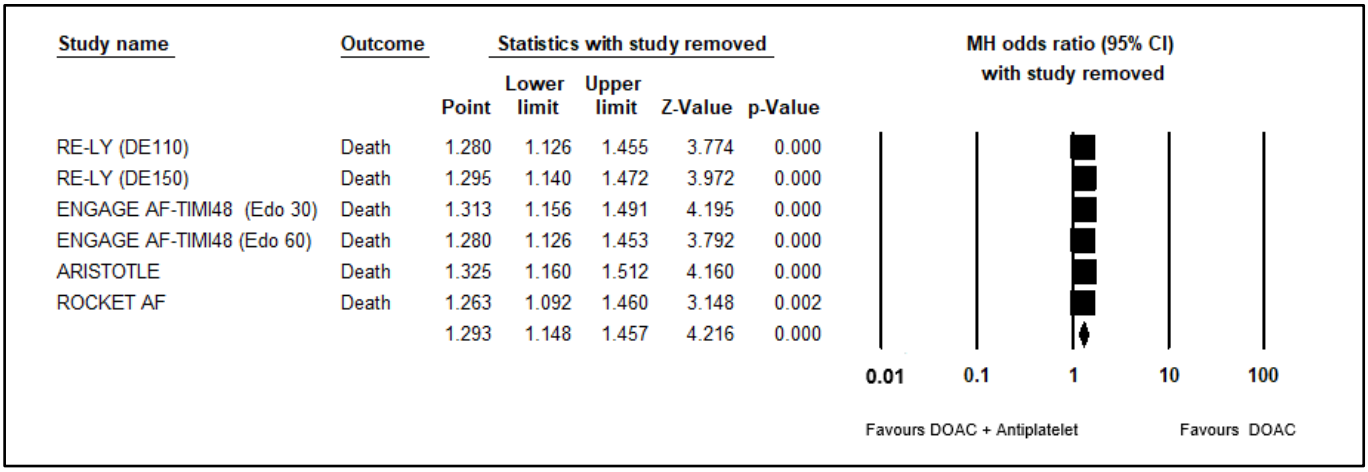

Figure S5p: Evaluation of publication bias using a funnel plot