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Meta-analysis study on direct oral anticoagulants vs warfarin therapy in atrial fibrillation and PCI: Dual or triple approach?

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ABSTRACT

Background: Dual antiplatelet therapy and anticoagulants may be required in the case of coexistence of coronary artery disease and atrial fibrillation (AF) undergoing (PCI), with associated increased bleeding rates. The introduction of direct oral anticoagulants (DOACs), however, significantly reduced the incidence of bleeding complications in this clinical setting of patients. We therefore sought to assess whether the recent publication of the AUGUSTUS and ENTRUST-AF PCI studies significantly impacted current evidence on the use of DOACs in AF patients treated with PCI.

Methods: We performed a meta-analysis of randomized controlled studies enrolling patients with non-valvular AF undergoing PCI. We assessed pooled estimates of risk ratios (RRs) and 95%CIs for any bleeding (AB), cardiovascular events (CVE), and death at follow-up: 12,542 patients have been included in the analysis. We particularly analyzed data comparing dual anti-thrombotic therapy (DOAC plus single anti-platelet therapy) with triple (DOAC plus dual anti-platelet therapy).

Results: When compared with patients receiving standard triple therapy with warfarin, patients receiving DOACs had a significantly lower risk of AB (RR 0.65; 95% CI, 0.61–0.70, $p < 0.00001$) and of MB (RR 0.63; 95% CI, 0.53–0.73, $p < 0.00001$). The risk of cardiovascular events and mortality were comparable between DOAC and VKA groups (RR 1.05, 95% CI 0.93–1.18, RR 1.14, 95% CI 0.94–1.37, respectively, p n.s.). Similar results were observed comparing triple therapy vs dual therapy.

Conclusions: DOACs are safer than and as effective as warfarin when used in patients with AF undergoing PCI; dual therapy with DOACs is comparable to triple therapy in terms of safety and efficacy.

Contents

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1. Introduction

Atrial fibrillation (AF) affects approximately 33 million of patients worldwide; about 30% of such patients may have coronary artery disease (CAD) and 5–10% will undergo percutaneous coronary intervention (PCI) during their lifetimes [1–3]. The therapy cornerstone for CAD has been antiplatelet and anticoagulant therapy, with an adjunctive invasive approach in patients with moderate-to-high risk clinical features. Anticoagulation, however, is required for the prevention of thrombo-embolic complications related to AF. This combination of treatment strategies, antiplatelet therapy required both for CAD and revascularization with coronary angioplasty (PCI) and anticoagulant therapy for AF, must carefully balance the reduction in ischemic and thrombotic events achievable with antithrombotic therapy with the consequent increased risk of bleeding.

In the recent past, the advent of direct oral anticoagulants (DOACs) has significantly changed the prevention of thrombo-embolic complications in patients with AF. DOACs may represent a safe and effective alternative to warfarin, as shown in four great registration trials on AF [4–7], and even more than warfarin according to some meta-analyses [8].

In a prior meta-analysis study we showed that DOACs are safer than and as effective as warfarin when used in patients with AF undergoing PCI; dual therapy with DOACs is comparable to triple therapy in terms of safety and efficacy [9].

After the recent publication of the AUGUSTUS trial [10], which explored the events related to apixaban and one $P2Y_{12}$ antagonist (mostly clopidogrel 75 mg daily) [11], either in dual and in triple therapy with or without aspirin, and the ENTRUST-PCI trial [12], which assessed a dual edoxaban plus $P2Y_{12}$ antagonist against triple anti-thrombotic therapy (dual anti-platelet therapy plus vitamin-K antagonist), we aimed to perform a novel meta-analysis study to assess, with this new set of data, the safety and efficacy of DOACs in patients with non-valvular AF undergoing PCI. We also sought to compare safety and efficacy of either triple or dual anti-thrombotic therapy (ADP antagonist plus anticoagulant plus/minus aspirin).

2. Methods

The present meta-analysis has been planned, conducted, and reported in accordance with currently available statements for the design, analysis, and reporting of meta-analyses of randomized and observational studies. We have performed researches in PubMed, the Clinical Trials Registry (www.clinicaltrials.gov), the Cochrane Library, and Web of Science. Search terms used were "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban" AND "atrial fibrillation" AND "PCI" OR "angioplasty". Web sites, including acc.org, escardio.org, were also assessed for relevant materials. References of the articles identified in this manner were also searched through to locate additional references that—not identified by the search strategy—might be useful for the purpose.

The research was limited to the English-language publications. We included study-level data derived from randomized, controlled trials comparing DOACs with warfarin in patients with AF undergoing PCI (Fig. 1).

2.1. Study selection

After study selection, four randomized controlled trials reporting early outcome data of AF patients randomized to DOACs or vitamin-K antagonists (VKAs) and treated with antiplatelets after PCI were selected and included in the analysis: PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS and ENTRUST-AF PCI [10,12–14] (Table 1).

The co-primary endpoints were divided into safety endpoints and efficacy ones. Any bleeding (AB), ranging from severe to minor, and major bleeding (MB) represented the former end points, according to the International Society on Thrombosis and Hemos-

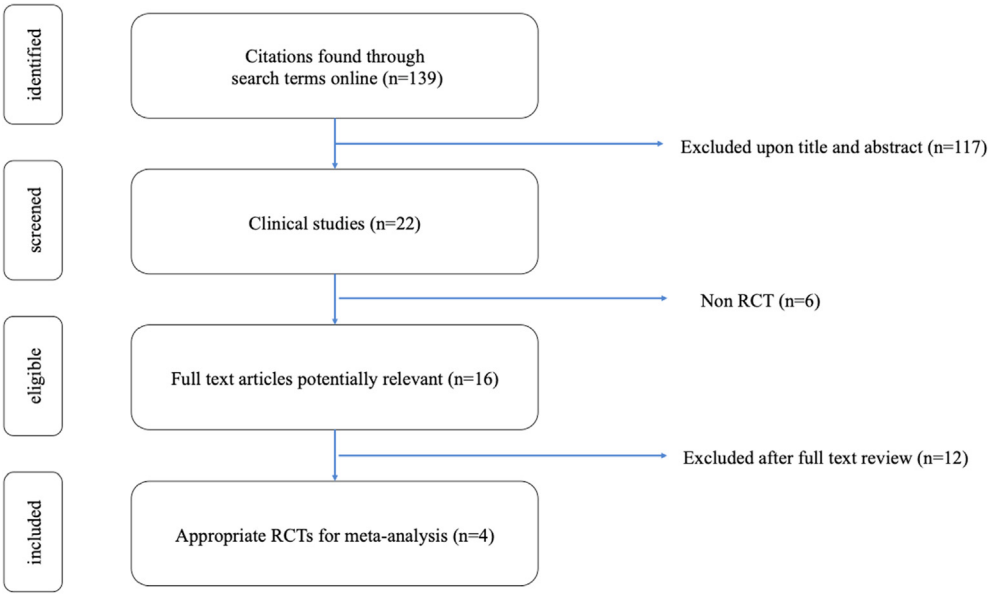

Fig. 1. Prisma flow chart with studies' selection.

Table 1
Characteristics of the trials included in the meta-analysis.

Study	PIONEER AF-PCI			RE-DUAL PCI			AUGUSTUS			ENTRUST-AF PCI	
Population	2124			2725			4614			1506	
ACS	52%			50%			61%			52%	
Follow up	12 months			14 months			6 months			12 months	
Subgroup	Rivaroxaban 15 mg + $P2Y_{12}$	Standard triple therapy	Rivaroxaban 2.5 mg + DAPT	Dabigatran 150 mg + $P2Y_{12}$	Standard triple therapy	Dabigatran 110 mg + $P2Y_{12}$	Apixaban + DAPT	Standard triple therapy	Apixaban + $P2Y_{12}$	Edoxaban + $P2Y_{12}$	Standard triple therapy
N total bleeding (%)	16.8	26.7	18	33.3	42.9/41.4	27.1	13.8	18.7	7.3	17	20
N MACE (%)	6.5	5.6	6	11.8	13.4/12.8	15.2	6.2	5.7	6.2	7	6
Total bleeding HR	0.59 (0.47–0.76)		0.63 (0.50–0.80)	0.72 (0.61–0.84)		0.54 (0.46–0.63)	0.72 (0.62–0.83)		0.39 (0.31–0.50)	0.83 (0.65–1.05)	
P value	<0.001		<0.001	<0.001		<0.001	<0.01		<0.001	0.11	
MACE HR	1.08 (0.69–1.68)		0.93 (0.59–1.48)	0.89 (0.67–1.14)		1.13 (0.90–1.43)	0.93 (0.75–1.16)		1.09 (0.79–1.51)	1.06 (0.71–1.69)	
P value	0.75		0.76	0.44		0.30	0.45		0.53	0.73	
Ticagrelor prasugrel	5.6%			12%			7.2%			7.4%	

tastis (ISTH) and Thrombolysis in Myocardial Infarction (TIMI) criteria, while cardiovascular events (CVE) and mortality constituted the efficacy aims according to study definition. Cardiovascular events were considered as a composite of death from cardiovascular causes, myocardial infarction, or stroke in the PIONEER-AF PCI study, thromboembolic events, death, or unplanned revascularization for the RE-DUAL PCI, all-cause death or ischemic events for the AUGUSTUS, cardiovascular death, stroke, systemic embolic event, myocardial infarction, or definite stent thrombosis for the ENTRUST-AF PCI. Mortality data were obtained mixing cardiovascular mortality from PIONEER AF-PCI with total mortality from the RE-DUAL PCI, AUGUSTUS and ENTRUST-AF PCI study.

2.2. Statistical analysis

From abstracted data, we calculated the risk ratio (RR) using the Mantel-Haenszel method for each study outcome to allow for pooling of similar outcomes. We obtained the average effects for the outcomes and 95% of confidence interval (CI) using a random-effects model. Heterogeneity of the effect across studies was evaluated by means of the Cochrane Q χ^2 and I^2 statistics. Lack of homogeneity was assessed for Cochrane Q χ^2 test P 0.10 and/or for an I^2 statistic 50%.We computed the z statistic for each clinical outcome and considered results statistically significant at a $p < 0.05$.

An additional partition of populations enrolled in the study was done, according to dual or triple antithrombotic therapy used; RR calculated in two groups were compared with Breslow-Day test in a per strata analysis.

We also assessed the likelihood of publication bias using funnel plots by displaying individual study RR with 95% CIs for the endpoints of interest, and evaluated it by the Egger regression asymmetry test ($p < 0.05$ was here considered as indicative of statistically significant publication bias).

3. Results

A population of 12,542 patients was finally included in the meta-analysis. When compared with patients receiving standard triple therapy with warfarin, patients receiving DOACs had a significantly lower risk of AB (RR 0.65; 95% CI, 0.61–0.70, $p < 0.00001$) and of MB (RR 0.63; 95% CI, 0.53–0.73, $p < 0.00001$), with significant statistical heterogeneity for AB (Cochrane Q $p < 0.0001$; $I^2 = 80\%$) (Figs. 2 and 3).

The risk of cardiovascular events and mortality rates were comparable between DOAC and VKA groups (RR 1.05, 95% CI 0.93–1.18, p n.s., I^2 0%, RR 1.14, 95% CI 0.94–1.37, p n.s., I^2 0%, respectively, Figs. 4 and 5).

3.1. Triple vs dual therapy subgroup analysis of safety and efficacy endpoints

We observed similar results analyzing the two antithrombotic regimens used in the three studies, triple therapy (used in the PIONEER and AUGUSTUS study) vs dual therapy, used in all 4 studies (p for interaction n.s. in all cases). Egger's test did not find any significant publication bias when performed for MB (p n.s.); funnel plot was reported in Fig. 6.

4. Discussion

To the best of our knowledge this is the one of the first meta-analysis study comparing both dual and triple therapy with DOACs vs triple therapy with VKA only with data from RCTs with DOACs. Several prior meta-analysis dealt with one aspect (dual with

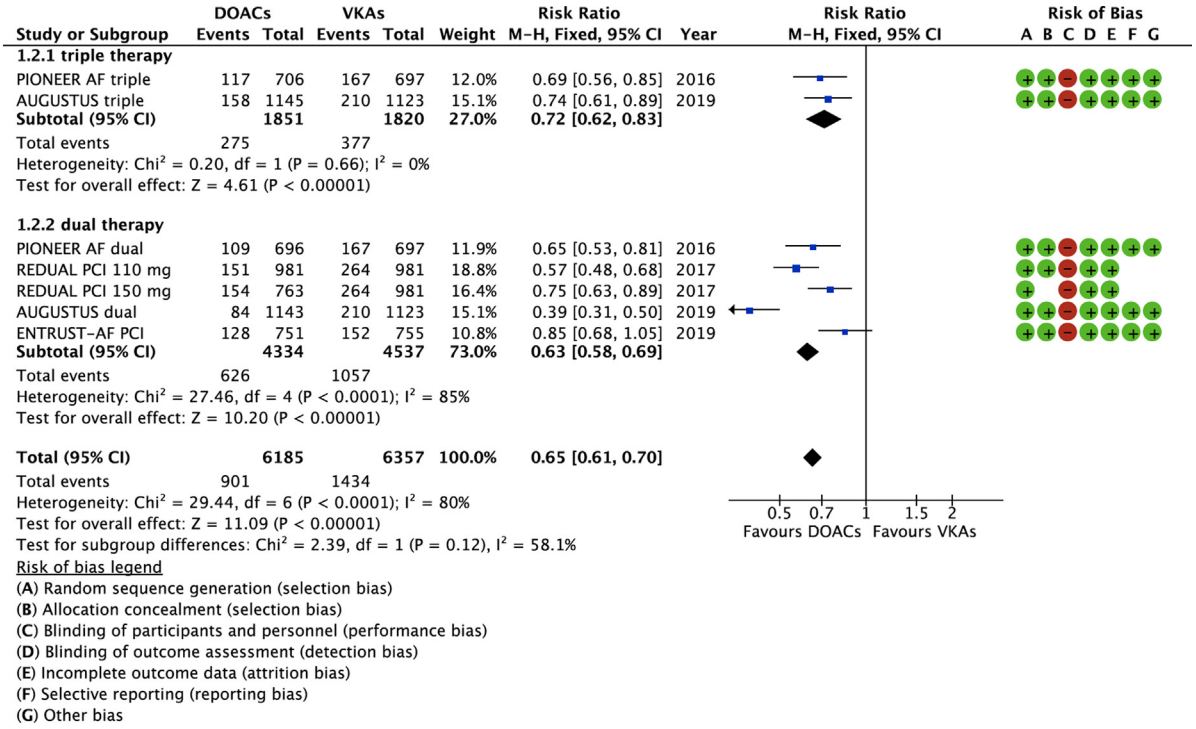

Fig. 2. Forest plot illustrating the risk ratio of any bleeding and GRADE assessment.

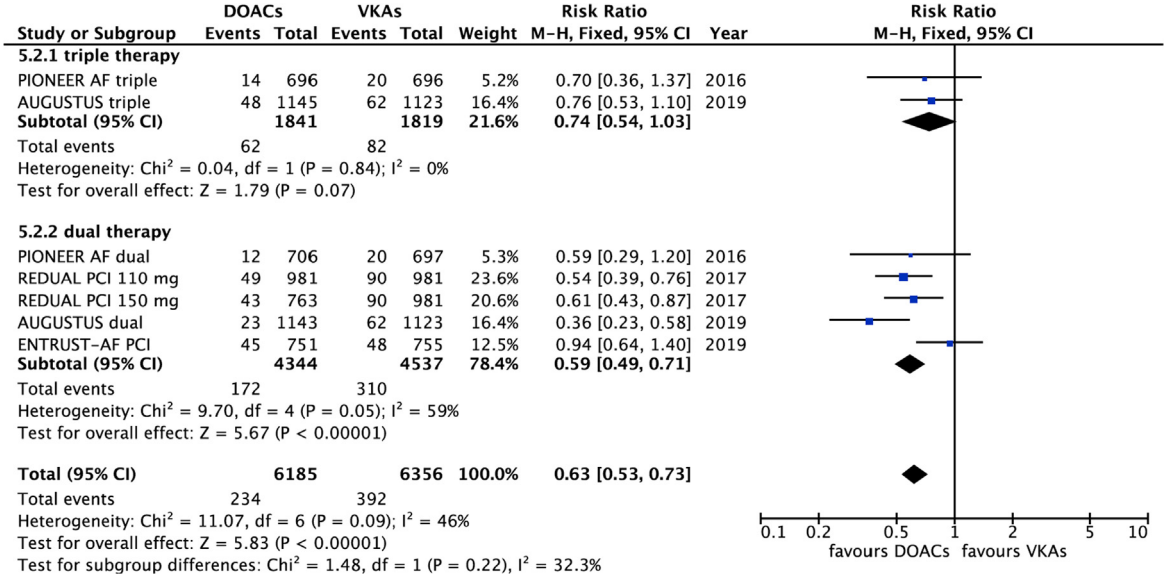

Fig. 3. Forest plot illustrating the risk ratio of major bleeding.

DOACs vs triple with VKA [12]) or included also study without DOACs.

Patients with indications for anticoagulation and antiplatelet therapy pose a clinical dilemma because of the fine balance that exists between minimizing the risk of bleeding and preventing thrombotic complications. In this meta-analysis study we compared the use of DOACs with VKAs in patients with nonvalvular AF following PCI, after the publication of the AUGUSTUS and ENTRUST-AF PCI trial. Our results, in line with our prior meta-analysis, confirm a significant superiority of DOACs vs VKA in terms of safety with comparable efficacy profile; moreover and originally, dual therapy with DOACs appears even safer than and as effective as triple therapy in this clinical set of patients, although non significantly.

The PIONEER-AF PCI study investigators compared low-dose rivaroxaban 15 mg once a day plus P2Y12 inhibitor regimen and very-low dose rivaroxaban 2.5 mg BID triple therapy to the triple therapy with warfarin after PCI [13]. The RE-DUAL PCI study, instead, compared low-dose dabigatran 110 mg BID plus P2Y12 inhibitor regimen and usual dose dabigatran 150 mg BID plus P2Y12 inhibitor regimen to the triple therapy with warfarin [14]. The studies found that both DOAC regimens were associated with less bleeding and similar rates of cardiovascular events compared with the warfarin triple therapy regimen.

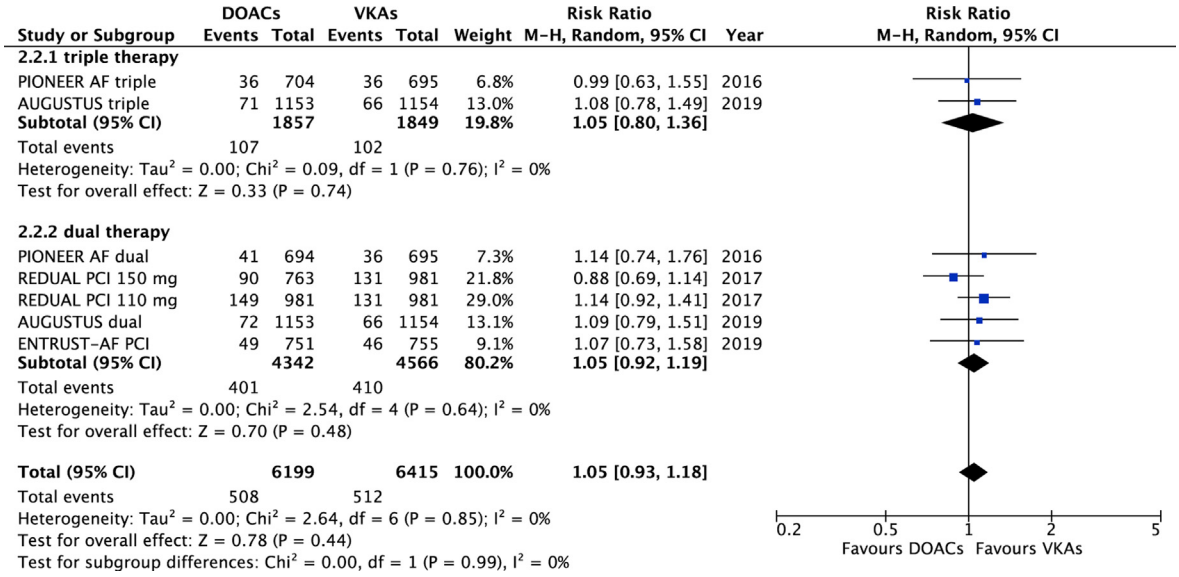

Fig. 4. Forest plot illustrating the risk ratio of cardiovascular events.

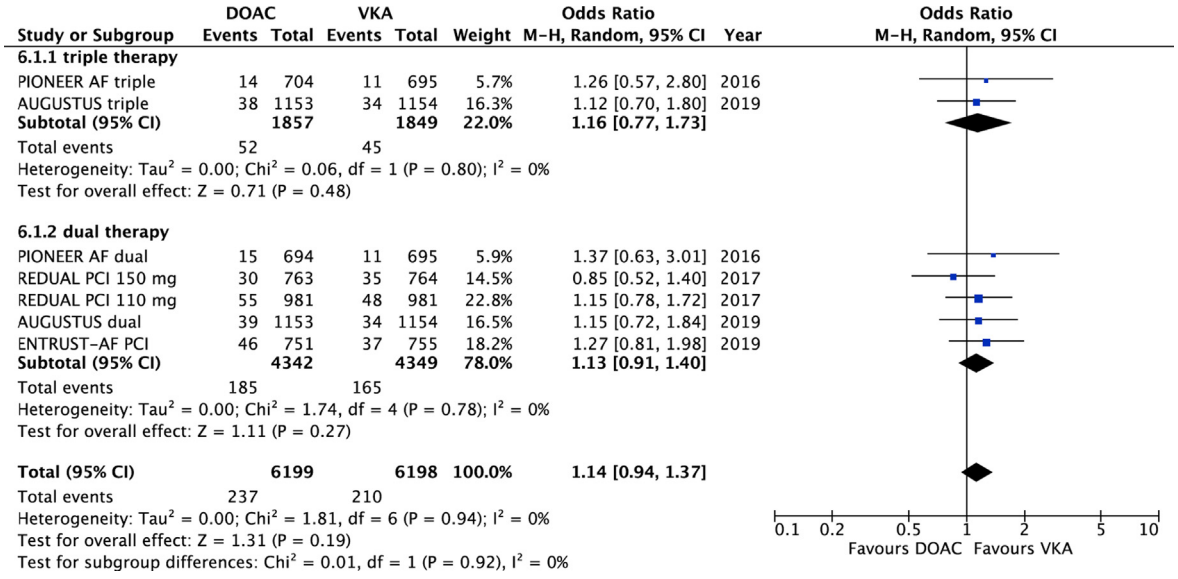

Fig. 5. Forest plot illustrating the risk ratio of death.

The recently published AUGUSTUS trial compared, in patients with AF and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin to a regimen that included a VKA, or aspirin, or both. The apixaban plus P2Y12 inhibitor resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events [10]. Even more recently, the ENTRUST-AF PCI compared edoxaban in dual anti-thrombotic therapy against traditional triple VKA based approach [12].

Another meta-analysis that included the WOEST, ISAR-TRIPLE, PIONEER-AF PCI, and RE-DUAL PCI trials found that patients with AF undergoing PCI who received dual antithrombotic therapy had 47% less TIMI major or minor bleeding than patients receiving triple therapy [15]. This pooled analysis also did not detect any differences in trial-defined MACE events or individual outcomes of death, cardiovascular death myocardial infarction, stent thrombosis, or stroke among patients taking oral anticoagulants plus single antiplatelet therapy vs dual therapy.

In another meta-analysis from Chiarito et al. on 6 studies that compared DOAC plus DAPT with DAPT alone in patients with acute coronary syndrome (ACS), a differential in outcome based on type of ACS was found [16]. The primary efficacy endpoint was significantly lower in patients treated with DOAC in addition to DAPT compared with those treated with DAPT alone (OR 0.85; 95% CI, 0.77–0.93; $p < 0.01$); however, the DOAC plus DAPT group also had a higher risk of MB (OR 3.17; 95% CI, 2.27–4.42; $p < 0.01$). When stratified by type of ACS, there was a difference in results; in patients with STEMI, DOAC plus DAPT significantly lowered the risk of primary efficacy endpoint as compared with DAPT alone (OR 0.76; 95% CI 0.66–0.88; $p < 0.01$), whereas there was no significant difference in the NSTE-ACS group (OR 0.92; 95% CI 0.78–1.09; p 0.361). Triple therapy groups had higher rates of bleeding regardless of ACS type. One suggested explanation for this difference in outcome between STEMI and NSTEMI is the presence of higher thrombotic burden and increased coagulation cascade activation after STEMI.

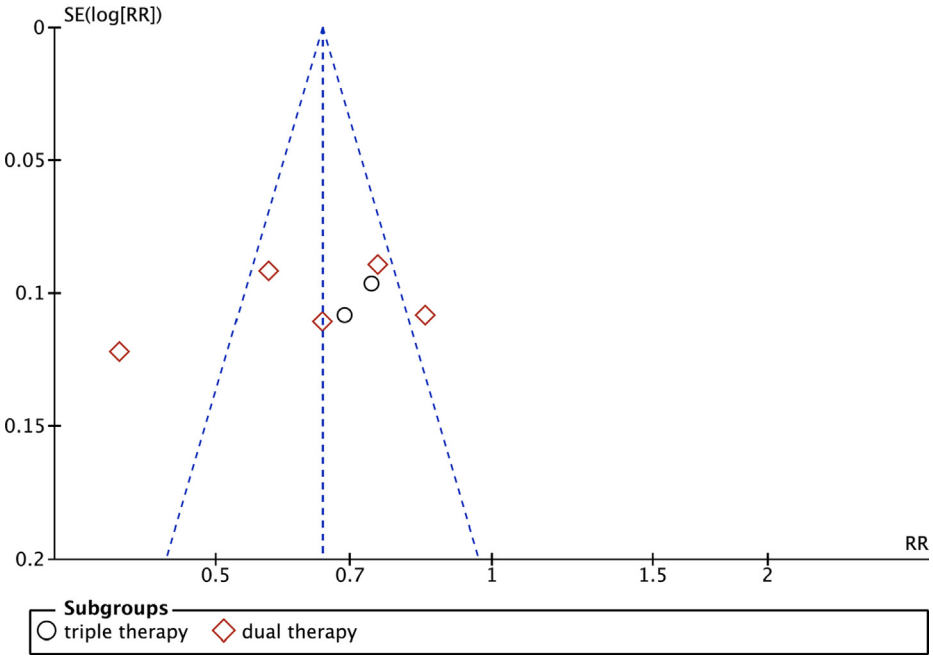

Fig. 6. Forrest plot showing risk of bias (major bleeding).

Even more recently, in a network meta-analysis, a regimen of DOACs plus P2Y12 inhibitor was associated with less bleeding compared with VKAs plus DAPT [17]. Strategies omitting aspirin caused less bleeding, including intracranial bleeding, without significant difference in MACE, compared with strategies including aspirin. According to authors' conclusions, the use of DOAC plus P2Y12 inhibitor should be considered as the preferred regimen post-PCI while a regimen of VKA plus DAPT should generally be avoided. This meta-analysis, however, does not include data on edoxaban and includes also WOEST data, which is not a DOAC based RCT.

In a more recent meta-analysis, the same authors suggest that an antithrombotic regimen of VKA plus DAPT should generally be avoided, because regimens in which aspirin is discontinued may lead to lower bleeding risk and no difference in antithrombotic effectiveness; the use of a NOAC plus a P2Y12 inhibitor without aspirin may be the most favorable treatment option and the preferred antithrombotic regimen for most patients with AF undergoing PCI [18].

On the base of such data, expert begin questioning the claimed lack of alternatives to the "anticoagulant always and immediately" approach in most such patients, and propose that skipping anticoagulation in the presence of modern DAPT for one month after an ACS in the context of a high bleeding risk and a high coronary risk is a valuable, currently unlisted option, and raise the need of a proper trial on this controversial issue [19].

However, according to other recent meta-analyses, dual antithrombotic therapy, compared to triple, conferred a significantly reduced risk of overall bleeding but with a significant increase of stent thrombosis risk in the overall population and a significant 43% increase of MI in the ACS/PCI subgroup [20].

Our data, however, are exclusively focused on DOAC RCTs and on the analysis dual vs triple DOAC based strategy after PCI. Interestingly, total bleeding rates occurring with dual therapy and apixaban were the lowest achieved with any anti-thrombotic approach. Whether such results are related to drug characteristics, study design, patients' selection, bleeding definition, or anti-platelet approach still remains uncertain.

An appendix meta-analysis from the ENTRUST-AF PCI also provided meta-analysis from the same four studies included in ours. However, the analysis was exclusively focused on dual DOAC based therapy vs triple VKA based, ignoring triple DOAC based. Our data are therefore more complete, enrolling a larger population and providing a direct comparison triple vs dual DOAC based therapy.

5. Limitations

DOAC doses and regimen of antithrombotic therapy used in the studies included in the meta-analysis are different: in the PIONEER AF-PCI study a triple therapy with reduced dose of rivaroxaban and a dual therapy with standard low dose were used, in the REDUAL PCI study standard dose of dabigatran in dual antithrombotic therapy, in the AUGUSTUS study standard dose of apixaban in dual or triple therapy. Not all subjects were treated with PCI in the AUGUSTUS study,

Follow-up periods were different, 12 months for the PIONEER AF-PCI and the ENTRUST-AF PCI studies, 14 months for the REDUAL PCI study, 6 months for the AUGUSTUS. The number of patients who withdrew the consent or discontinued the treatment was around 20% in the PIONEER-AF PCI and the AUGUSTUS, 17% in the ENTRUST-AF PCI, 13% in the REDUAL PCI.

Ticagrelor was used in 6% of patients enrolled in the AUGUSTUS trial, 7–8% in the ENTRUST-AF PCI, 12% of the REDUAL PCI.

Little is known about compliance, drug interaction and bridging with heparin in patients treated with warfarin.

Mortality data were obtained mixing cardiovascular mortality from PIONEER AF-PCI with total mortality from the REDUAL-PCI, AUGUSTUS and ENTRUST-AF PCI studies.

Cardiovascular events were differently defined in different studies. No data are available from the AUGUSTUS study on acute myocardial infarction and stent thrombosis incidence and therefore no adjunctive comparison is possible.

The control group was duplicated for the PIONEER-AF PCI study and the REDUAL PCI study with the aim to analyze subgroups of both studies.

6. Conclusions

DOACs are safer than and as effective as warfarin when used in patients with AF undergoing PCI; dual therapy with DOACs is comparable to triple therapy in terms of safety and efficacy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100569.

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