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ORIGINAL RESEARCH

Safety and Efficacy Comparison of Ticagrelor versus Other P2Y12 Inhibitors in Combination with Oral Anticoagulants as a Part of DAPT/SAPT in Patients with Concomitant Atrial Fibrillation and Coronary Artery Disease: A Meta-Analysis

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Objective: We performed a meta-analysis of randomized controlled trials to assess the safety and efficacy of ticagrelor or other P2Y12 inhibitors in combination with oral anticoagulants as a part of DAPT/SAPT for the patients with atrial fibrillation (AF) and acute coronary disease (ACS) or undergoing percutaneous coronary intervention (PCI).

Methods: We searched PubMed, Web of Science and ClinicalTrials.gov for randomized controlled trials (published from January 1, 1998, up to June 6, 2023; no language restrictions) comparing safety and efficacy of ticagrelor and DOACs or VKAs combination treatment arm with or without aspirin to other P2Y12 inhibitors treatment strategies. Main endpoints were clinically relevant bleeding as safety outcomes, all-cause mortality, and major adverse cardiovascular events (MACE) as efficacy outcomes.

Results: Of 248 identified studies, 3 were eligible and were included in our analysis (N= 9463 participants). Ticagrelor and DOAC or VKA combination treatment with or without aspirin strategy was associated with an increased rate of bleeding compared with clopidogrel (odds ratio [OR] 1.39, 95% CI 1.15 to 1.67, I^2=0%). MACE was similar between ticagrelor versus clopidogrel (OR 1.00, 95% CI 0.54 to 1.86, I^2=68.1%) and between ticagrelor versus prasugrel (OR 0.86, 95% CI 0.28 to 2.65, I^2=0%).

Conclusion: The use of ticagrelor is associated with significantly higher rates of bleeding when compared with clopidogrel in patients with concomitant atrial fibrillation and coronary artery disease.

Keywords: atrial fibrillation, percutaneous coronary intervention, ticagrelor, other P2Y12 inhibitors, anticoagulation

Introduction

Patients with atrial fibrillation (AF) and CHA2DS2-VASc risk score of 2 or higher require oral anticoagulation (OAC) to decrease the risk of stroke or systemic embolism.[1] However, the best choice of antithrombotic strategies in patients with AF and acute coronary disease (ACS) or undergoing percutaneous coronary intervention (PCI) is still being explored, because the events between bleeding and anti-platelets should be balanced.[2–5] Meta-analysis results have revealed that dual antithrombotic therapy (Direct oral anticoagulant [DOAC]+ $P2Y_{12}$ inhibitor [$P2Y_{12}$i]) could significantly reduce bleeding events, and there is no significant difference in efficacy compared with triple therapy (OAC+$P2Y_{12}$i+aspirin).[6–9] Guidelines recommend double antithrombotic therapy with an OAC (DOAC preferred unless contraindicated) or vitamin K antagonist (VKAs) and a $P2Y_{12}$i is preferred to triple antithrombotic therapy.[10–12]

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) recommend clopidogrel as the preferable P2Y12i for

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patients with AF undergoing PCI,[13] however, ticagrelor may be an alternative in patients with high thrombotic burden and acceptable bleeding risk.[11,12] Some experimental and clinical studies showed that ticagrelor could also reduce infarct size,[14–17] which indicates a valuable option of using ticagrelor in ischemic patients with dual effects. Studies also demonstrated that the antiplatelet effects of ticagrelor and prasugrel were stronger than clopidogrel,[18,19] thus might be more effective as other P2Y12 inhibitors. So far, there is still a lack of research on how to choose a $P2Y_{12}$i in AF patients with ACS or PCI as a part of antithrombotic therapy, and few randomized clinical trials (RCT) compared the efficacy and safety of ticagrelor, prasugrel and clopidogrel. This article aims to summarize and analyze published RCTs in this field and highlights the effectiveness and safety and efficacy of ticagrelor in comparison with other P2Y12 inhibitors including prasugrel or clopidogrel in patients with AF and ACS or PCI.

Methods

Search Strategy and Selection Criteria

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[20] We selected relevant studies published up to June 6, 2023, by searching PubMed, Web of Science and the Cochrane Central Register of Clinical Trials. We applied no language restrictions. The following terms were used: atrial fibrillation AND (acute coronary syndrome OR ACS OR percutaneous coronary intervention OR PCI) AND (oral anticoagulation OR novel oral anticoagulant OR NOAC OR direct oral anticoagulation OR DOAC OR vitamin K antagonist OR VKA OR warfarin) AND (P2Y12 inhibitor clopidogrel OR prasugrel OR Ticagrelor). All potentially eligible studies were considered for review, irrespective of the primary outcome or language. We also performed a manual search, using the reference lists of key articles published in English.

Study Selection and Data Extraction

Studies were regarded as eligible for inclusion if they were randomized clinical trials enrolling patients with AF and ACS or undergoing PCI, compared ticagrelor and DOACs or VKAs combination with or without aspirin to other treatment strategies, and reported clinically relevant bleeding as safety outcomes, all-cause mortality, major adverse cardiovascular events (MACE) as efficacy outcomes. Exclusion criteria were as follows: observational and retrospective studies; studies without ticagrelor, and studies that did not assess ticagrelor and DOACs or VKAs combination treatment; small sample studies ($n<200$ in each treatment arm). We compared combination treatment consisting of ticagrelor and OAC (DOAC or VKA) to any other anticoagulation treatment strategies, with no restriction on treatment history. The outcomes assessed were as follows: the safety endpoint was trial defined clinically relevant bleeding, the efficacy endpoint was trial defined MACE and all-cause mortality. Two independent investigators reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text assessment. Disagreements were resolved via consensus and by a third investigator.

We extracted the following data from each selected study: publication year, total number of participants, age (mean), anticoagulation treatments, patient population, CHA_2DS_2-VASc score (mean), HAS-BLED score (mean), $P2Y_{12}$i, safety endpoint, efficacy endpoint. Assessment for risk of bias was evaluated by two authors. Assessment for risk of bias in RCTs was assessed using the Cochrane Collaboration risk of bias tool.[21]

Statistical Analysis

All statistical analyses were performed using Stata, V15.0. A P-value <0.05 was considered statistically significant. Outcomes were pooled using crude number of events retrieved from each study and compared using a fixed-effect or random-effect model according to the heterogeneity among the included studies. Treatment effect was reported as odds ratio (OR) using the Mantel–Haenszel method with 95% CI. We used the Cochran Q test to assess heterogeneity between studies. I^2 testing was used to assess the magnitude of the heterogeneity between studies. For analyses with low heterogeneity (defined as I^2 <25%), fixed effect models were used, otherwise random effects models were used.

The sensitivity analyses excluded the rivaroxaban 2.5 mg bid combining P_2Y_{12}i and aspirin regimen, since 2.5 mg rivaroxaban dose has not been tested for stroke prevention in AF patients. The analysis of different $P2Y_{12}$i in VKA-based

triple therapy and DOAC-based dual therapy and DOAC-based triple therapy was conducted for all outcomes. A separate sensitivity analysis of safety and efficacy outcomes were performed by comparing clopidogrel with prasugrel.

Results

We identified 248 studies, of which 3 (with data for 9463 participants) were included in our analysis (Figure 1). Randomized controlled trials included: Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (PIONEER-AF), Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation (RE-DUAL PCI) and Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation (AUGUSTUS).[22–24] Study characteristics were described in Table 1. The 3 trials were all published between 2016 and 2019. Except patients in AUGUSTUS enrolled atrial fibrillation with ACS or undergoing PCI, other two studies consisting of patients undergoing

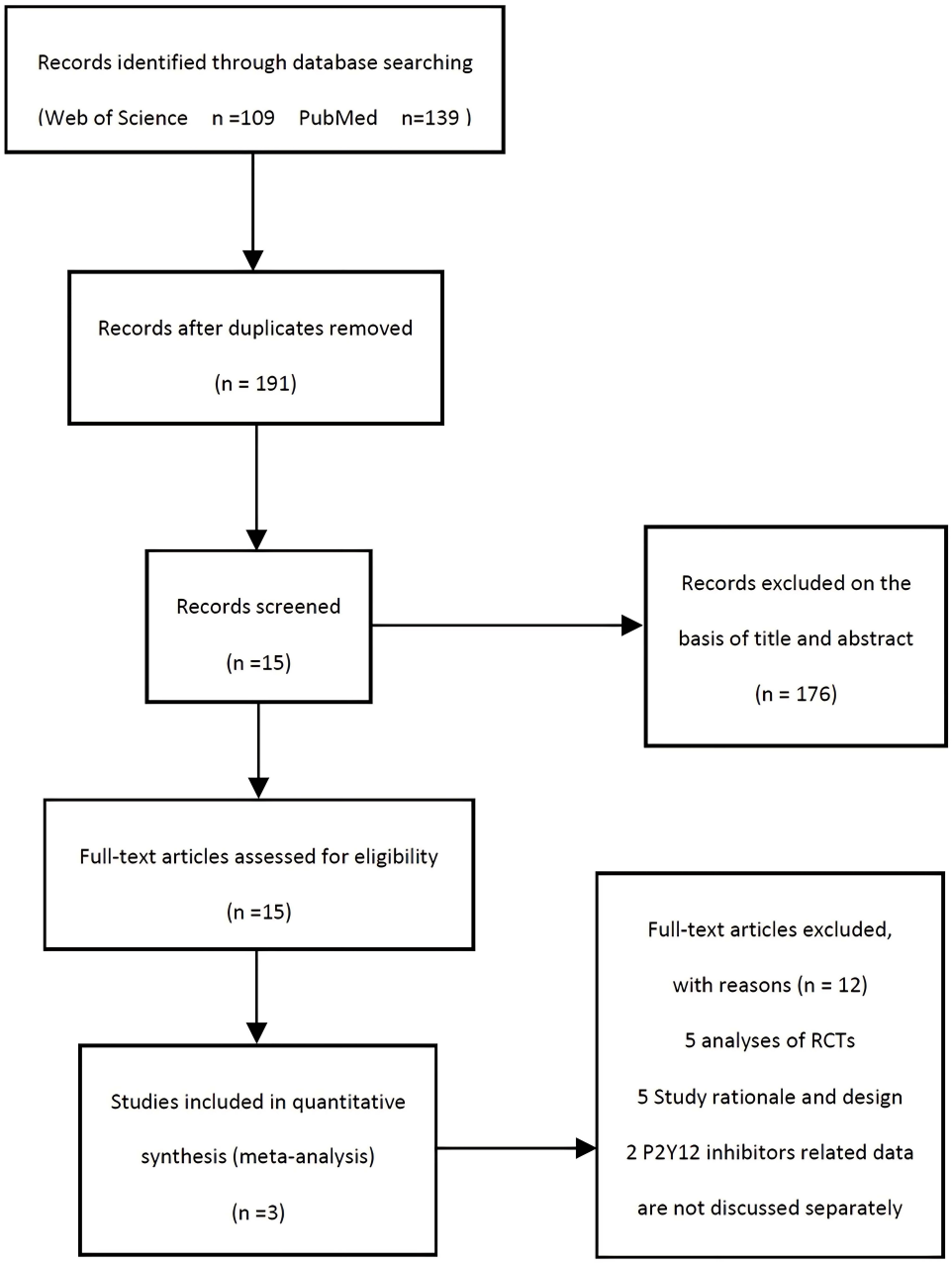

Figure 1 Study selection process.

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Table 1 Characteristics of Included Studies

	PIONEER AF-PCI	RE-DUAl PCI	AUGUSTUS
Year	2016	2017	2019
N	2124	2725	4614
Mean age	70.1	70.8	70.7
Patient population	Nonvalvular atrial fibrillation + PCI	Nonvalvular atrial fibrillation + PCI	Atrial fibrillation +ACS or PCI
Therapy group	Low-dose rivaroxaban (15 mg once daily) + $P2Y_{12}i$ very-low-dose rivaroxaban (2.5 mg twice daily) + $P2Y_{12}i$ +ASA VKA + $P2Y_{12}i$ + ASA	Dabigatran (110 mg or 150 mg twice daily) + $P2Y_{12}i$ VKA + $P2Y_{12}i$ + ASA	2 × 2 Factorial Apixaban (5 mg twice daily) vs VKA And aspirin vs placebo + P_2Y_{12} inhibitor
Mean follow-up	12 months	14 months	6 months
CHA2DS2-VASc score (mean)	3.8±1.6	3.6±1.5	3.9±1.6
HAS-BLED score (mean)	3.0±0.9	2.7±0.7	2.9±0.9
P_2Y_{12} inhibitor	Clopidogrel (94.4%) Ticagrelor (4.3%) Prasugrel (1.3%)	Clopidogrel (88.0%) Ticagrelor (12.0%)	Clopidogrel (92.6%) Ticagrelor (6.2%) Prasugrel (1.1%)
Safety endpoint	Clinically significant bleeding (a composite of major or minor bleeding according to TIMI criteria or bleeding requiring medical attention)	Major or clinically relevant nonmajor bleeding event (defined by ISTH)	ISTH major or clinically relevant nonmajor bleeding event or CRNMB
Efficacy endpoint	Major adverse cardiovascular event (a Composite of cardiovascular death, MI, or stroke)	Thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularisation	Composite of death or hospitalization Composite of death or ischaemic events (stroke, MI, stent thrombosis, or urgent revascularization)

Notes: Apixaban take 2.5 mg twice daily if patients met two or more of the following dose-reduction criteria: were at least 80 years of age, had a weight of no more than 60 kg, or had a creatinine level of at least 1.5 mg per deciliter (133 μmol per liter). Missing data: n = 118 (AUGUSTUS).
Abbreviations: ACS, acute coronary syndrome; $P2Y_{12}i$, P2Y12 inhibitor; CRNMB, clinically relevant non-major bleeding; ISTH, International Society on Thrombosis and Haemostasis bleeding categorization; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction bleeding categorization.

PCI. The choice of $P2Y_{12}i$ was at the discretion of the investigator. In these studies, patients all accepted antithrombotic treatment of DOACs or VKAs plus a $P2Y_{12}i$ with or without aspirin. Of the 9463 patients, 7.4% received ticagrelor treatment, 90.5% received clopidogrel treatment, and 0.1% received prasugrel treatment. These facts showed that compared with ticagrelor or prasugrel, investigators preferred to choose clopidogrel as the $P2Y_{12}i$, which may be attributed to the current guideline recommendations. The three randomized trials used different DOACs (rivaroxaban, dabigatran, apixaban). The average CHA_2DS_2-VASc score (mean) greater than 3 was recommended to be treated with oral anticoagulants. The average HAS-BLED score not greater than or equal to 3 was defined as non-high-risk bleeding, but there was still a risk of bleeding, and medication should be used with caution. Outcomes were described in Table 2 according to the antithrombotic treatment regimen.

Safety Outcomes

Overall, the clinically relevant bleeding events risk was greater in patients received anticoagulant therapy and ticagrelor than patients received anticoagulant and clopidogrel (OR 1.39, 95% CI 1.15 to 1.67, I^2 = 0%) (Figure 2A). Patients receiving prasugrel and ticagrelor had similar bleeding risk (OR 0.84, 95% CI 0.48 to 1.47, I^2 0%) (Figure 2B).

Table 2 Outcomes According to the Antithrombotic Treatment Regimen Respectively by P2Y12is

		Ticagrelor	Clopidogrel	Prasugrel
		Events Number/Total Number (%)		
Safety outcomes				
PIONEER	R15+ $P2Y_{12}i$	5/36(14%)	99/648(15%)	5/12(42%)
	R2.5+ $P2Y_{12}i$ +ASA	9/33(27%)	104/662(16%)	4/11(36%)
	VKA+ $P2Y_{12}i$ +ASA	8/21(38%)	157/671(23%)	2/5(40%)
RE-DUAL	D110+ $P2Y_{12}i$	28/132(21%)	123/849(14%)	-
	VKA+ $P2Y_{12}i$ +ASA	34/91(37%)	230/890(26%)	-
	D150+ $P2Y_{12}i$	24/104(23%)	130/659(20%)	-
AUGUSTUS	A5/VKA+ $P2Y_{12}i$±ASA)	52/277(19%)	499/4106(12%)	9/51(18%)
Efficacy outcomes				
PIONEER	R15+ $P2Y_{12}i$	1/36(3%)	40/646(6%)	0/12(0%)
	R2.5+ $P2Y_{12}i$ +ASA	0/33(0%)	35/660(5%)	1/11(9%)
	VKA+ $P2Y_{12}i$ +ASA	0/21(0%)	36/669(5%)	0/5(0%)
RE-DUAL	D110+ $P2Y_{12}i$	25/132(19%)	124/849(15%)	-
	VKA+ $P2Y_{12}i$ +ASA	20/91(22%)	111/890(12%)	-
	D150+ $P2Y_{12}i$	16/104(15%)	74/659(11%)	-
AUGUSTUS	A5/VKA+ $P2Y_{12}i$ (±ASA)	17/280(6%)	286/4165(7%)	3/51(6%)

Abbreviations: ASA, aspirin; A5, treatment with apixaban 5 mg twice daily; D110, treatment with Dabigatran 110 mg twice daily; D150, treatment with Dabigatran 150 mg twice daily; $P2Y_{12}i$, platelet P2Y12 receptor inhibitor; R15, treatment with Rivaroxaban 15 mg once daily; R2.5 treatment with Rivaroxaban 2.5 mg twice daily; VKA, vitamin K antagonist.

A sensitivity analysis was performed by excluding patients receiving R2.5+$P2Y_{12}i$ +ASA treatment (in PIONEER-AF PCI), and results remained the same as with these patients (Table S1).

Efficacy Outcomes

Overall, the risk of MACE for patients treated with ticagrelor was similar to clopidogrel (OR 1.00, 95% CI 0.54 to 1.86, I^2 = 68.1%) (Figure 3A). Efficacy outcome was also similar between ticagrelor and prasugrel (risk of MACE: OR 0.86, 95% CI 0.28 to 2.65, I^2 = 0%) (Figure 3B). In the sensitivity analysis, after excluding patients with R2.5+ $P2Y_{12}i$ +ASA treatment, results were similar with these patients, in that OR 1.07, 95% CI 0.63 to 1.82, I^2 = 58% between ticagrelor and clopidogrel group; OR 1.02, 95% CI 0.31 to 3.30, I^2 = 0% for ticagrelor and prasugrel group (Table S1).

Bias Assessment

The assessment of risk of bias was shown in the trial (Figure S1). All three randomized controlled trials reported adequate randomization, none was stopped early, but they were all open label trials, so performance bias risk should be considered as high. In AUGUSTUS trial, aspirin versus placebo was double blind, so its performance bias was unclear. The publication bias was not evaluated because of the small number of included studies.

Sensitivity Analysis

We also compared the therapeutic effects of prasugrel and clopidogrel (Figure S2), and the results showed that bleeding risk was higher in prasugrel-based regimen than clopidogrel-based regimen (OR 1.76, 95% CI 1.07 to 2.90, I^2 = 0%). In addition, we compared the safety outcomes between ticagrelor and two other $P2Y_{12}i$ through different antithrombotic strategies (Table S2). In VKA-based antithrombotic therapy, the risk of bleeding of ticagrelor regimen was higher than that of clopidogrel (OR 1.48, 95% CI 1.02 to 2.15, I^2 =0%), bleeding risk was similar between ticagrelor and prasugrel regimens. In DOAC-based antithrombotic therapy, ticagrelor, prasugrel and clopidogrel presented similar bleeding risk.

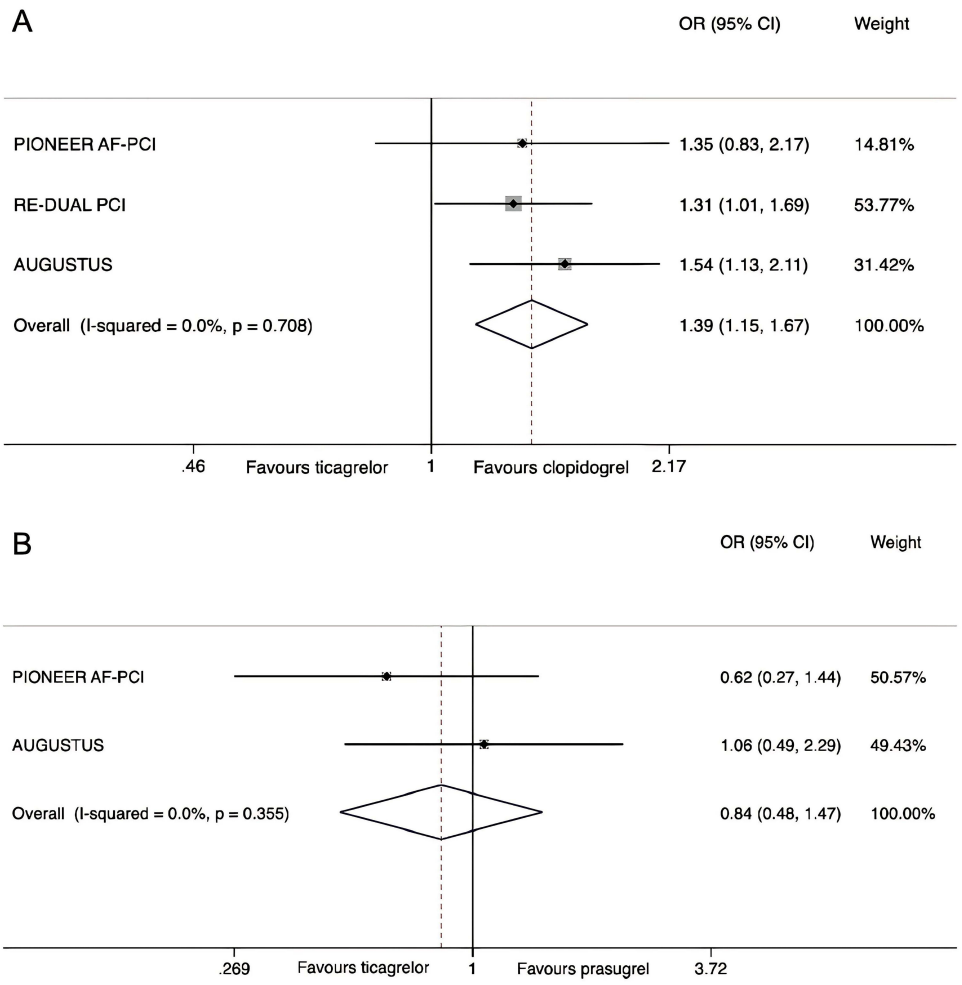

Figure 2 Forest plot for the comparative safety outcomes with ticagrelor versus clopidogrel (**A**) and ticagrelor versus prasugrel (**B**) in combination with oral anticoagulation.

In triple antithrombotic therapy, bleeding risk was higher in ticagrelor regimen as compared with clopidogrel regimen (OR 1.50, 95% CI 1.07 to 2.10, I^2 =0%), and the bleeding risk of ticagrelor was similar to the other two $P2Y_{12}$i in the double antithrombotic therapy treatment group. No matter which antithrombotic strategy was applied, based on VKA or DOAC, double or triple therapy, there was no significant difference in MACE between ticagrelor and other two $P2Y_{12}$i.

Discussion

Our results showed that, in patients with AF associated with ACS or PCI, choosing ticagrelor as part of dual or triple antithrombotic treatment strategy would increase the risk of bleeding, triple antithrombotic treatment with ticagrelor is linked with higher bleeding risk as compared to clopidogrel, safety profile is similar between ticagrelor and prasugrel. Efficacy outcome in terms of MACE is similar among patients treated with ticagrelor, clopidogrel or prasugrel. Our research provides a reference for the selection of antithrombotic strategies for patients with AF and ACS or undergoing PCI. A newly published meta-analysis compared the safety and efficacy of ticagrelor and prasugrel with clopidogrel in combination with OAC for patients undergoing PCI and requiring OAC treatment with data from both RCTs and non-RCTs. They also found that bleeding rate was higher in the ticagrelor or prasugrel group compared to clopidogrel group, and MACE was similar among the 3 groups.[25] Our analysis revealed similar results based on findings derived from RCTs.

Since patients with ACS and AF have an increased risk of systemic thromboembolism (based on the CHA_2DS_2-VASc risk score), anticoagulant therapy should be used unless the bleeding risk exceeds the expected benefit. For patients

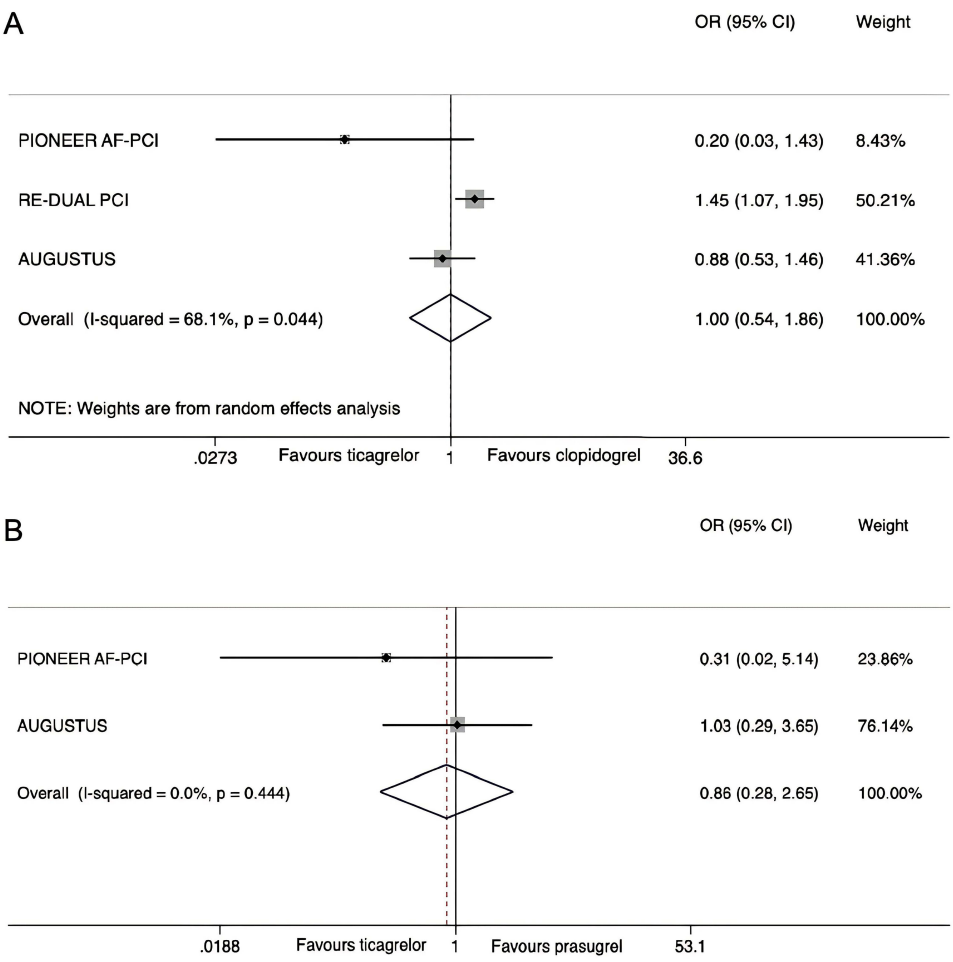

Figure 3 Forest plot for the comparative efficacy outcomes with ticagrelor versus clopidogrel (**A**) and ticagrelor versus prasugrel (**B**) in combination with oral anticoagulation.

undergoing PCI complicated with AF, the guidelines recommend triple antithrombotic therapy for at least 1 month after PCI. For patients with a higher risk of bleeding, this strategy should be limited to dual antithrombotic therapy (one antiplatelet drug plus one anticoagulant).[26] All guidelines recommend clopidogrel as part of dual or triple antithrombotic therapy, and prasugrel or ticagrelor are not recommended due to the lack of clinical data.[11,12,26]

Previous studies have shown that a considerable number of patients, especially those at high risk (such as ACS, diabetes, or chronic kidney disease) respond poorly to clopidogrel, which might potentially increase the risk of thrombotic complications in these patients.[27] These observations have aroused interest in the sue of novel $P2Y_{12}$ i. (ticagrelor and prasugrel) as part of dual or triple antithrombotic therapy in patients receiving OAC.[5]

At present, there is no clear recommendation for the use of ticagrelor in patients requiring OAC. Our meta-analysis provided reliable data and more insights in the context of ticagrelor. The results showed that compared with clopidogrel plus OAC regimen, the ticagrelor plus OAC regimen is associated with significantly higher bleeding risk with similar efficacy outcome between the two regimens. We also demonstrated that the bleeding and MACE events were similar with prasugrel or ticagrelor regimen. Among patients receiving VKA-based triple antithrombotic therapy, the use of ticagrelor was also associated with a higher risk of bleeding based on analysis of data from the PIONEER AF-PCI and RE-DUAL PCI studies. There were four types of DOAC available now (apixaban, dabigatran, rivaroxaban, edoxaban), but due to the limitations of experimental data, only one set of data was collected in this study. It is to note that the treatment with ticagrelor, clopidogrel or prasugrel was not randomized, which may lead to bias, it is possible the investigator might have chosen to administer ticagrelor only in patients with a higher risk of ischemia or a lower risk of bleeding. In conclusion,

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in the patient group requiring antiplatelet and anticoagulant therapy, it is difficult to determine the preference between ticagrelor, prasugrel and clopidogrel which is due to many uncontrollable factors. When used together with anticoagulants, it is difficult to differentiate the contribution on bleeding risk by different antiplatelet drugs or different $P2Y_{12}i$.

In the case of ticagrelor, the previous comparative study of clopidogrel and ticagrelor had shown that ticagrelor was more effective and better than clopidogrel in preventing thrombosis. Therefore, ticagrelor is more likely to improve antithrombosis theoretically, but present analysis showed that MACE was similar among groups. Future RCTs are warranted to explore this issue.

Limitations

This meta-analysis has several important limitations that should attract attention. First, the research included in this article selected different DOACs, which may have potential heterogeneity. Between studies, the definitions of safety and efficacy outcomes were slightly different. Second, most patients in the trial received clopidogrel as part of the anticoagulation regimen, of the population treated with prasugrel and ticagrelor was small in the trial population, so their efficacy may be underestimated. The lower number of retrievable studies together with the small sample size may also limited the statistical power of subgroup analysis. In addition, the choice of P2Y12 inhibitors was determined by doctors involved in the studies and which could have resulted in selection bias.

Conclusions

In patients with AF combined with ACS or PCI, choosing ticagrelor as a part of dual or triple antithrombotic treatment is linked with higher risk of bleeding, especially in triple antithrombotic treatment compared with clopidogrel. The bleeding risk is compared between ticagrelor and prasugrel. Efficacy outcome expressed by MACE is similar among ticagrelor, clopidogrel and prasugrel based regimen. Therefore, until more data accrue, ticagrelor should be used cautiously in AF patients combined with ACS or PCI. Future studies are needed to support the results from this meta-analysis.

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Disclosure

The authors report no conflicts of interest in this work.

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