Comparison of Ticagrelor and Clopidogrel Outcomes in Ischemic- and Hemorrhagic Stroke Patients after Percutaneous Coronary Intervention

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Abstract

Objective: Strokes related to contemporary percutaneous coronary intervention (PCI) are associated with substantially increased mortality and can result in life-altering disabilities. According to previous studies, most post-PCI strokes are ischemic and embolic, with a lower incidence of hemorrhagic strokes. Ticagrelor is a reversible and potent, oral antagonist that directly blocks platelet $P2Y_{12}$ receptors, potentially yielding more significant platelet aggregation inhibition than clopidogrel, but without the concerns surrounding genetic polymorphisms. However, it could carry a higher bleeding risk than clopidogrel. Previous studies have demonstrated that patients with minor stroke or transient ischemic attack treated with ticagrelor plus aspirin had a lower platelet reactivity than those treated with clopidogrel plus aspirin. Our systematic review analyzed the evidence from large clinical trials to assess and compare the efficacy and safety of ticagrelor versus clopidogrel as regards the incidence of stroke or bleeding events in patients receiving PCI for acute or chronic coronary syndrome.

Methods and Results: This meta-analysis comparing ticagrelor and clopidogrel involved 11 clinical trials with a total of 33,507 patients who received contemporary coronary intervention, including eight randomized controlled trials (RCTs) and three propensity score matched (PSM) cohort studies. There was no significant difference in any-type stroke (OR = 0.92, 95% CI: 0.73-1.16, and I^2 = 0%, p = 0.46) or major bleeding (OR = 1.10, 95% CI: 0.97-1.23, and I^2 = 59%, p = 0.13) between the ticagrelor group and the clopidogrel group. Similar outcomes were noted for ischemic stroke (95% CI: 0.75-1.34, I^2 = 0%, p = 0.97) and hemorrhagic stroke (95% CI: 0.65-2.30, I^2 = 0%, p = 0.53). Taking minor bleeding complications into consideration, ticagrelor showed a significant increase in any-type bleeding risk (OR = 1.18, 95% CI: 1.08-1.30, and I^2 = 75%, p < 0.001), compared with clopidogrel.

Conclusion: Based on this meta-analysis, among patients with ACS or CCS who underwent PCI in routine clinical practice, ticagrelor, compared with clopidogrel, was not associated with a significant difference in reduction of ischemic stroke or hemorrhagic stroke. The incidence of any-type bleeding, and especially minor bleeding, was higher for ticagrelor, compared with clopidogrel.

Keywords: Ticagrelor vs. clopidogrel

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Introduction

Stroke is a rare complication of percutaneous coronary intervention (PCI), but post-PCI stroke is strongly associated with higher in-hospital and long-term mortality and can result in life-altering disabilities.[1,2] Post-PCI strokes are primarily ischemic and embolic secondary to dislodgement of atherosclerotic plaque or embolization of coronary- or catheter-derived thrombus, with a lower incidence of hemorrhagic strokes.[3,4]

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is recommended for a minimum of 6 months in patients with chronic coronary syndrome (CCS) receiving a drug-eluting stent, and for 12 months in patients with acute coronary syndrome (ACS) who have undergone PCI with stenting.[5]

Ticagrelor is a reversible oral antagonist that directly blocks platelet $P2Y_{12}$ receptors and does not require metabolic activation for its antiplatelet effect. It may produce similar or greater levels of inhibition of platelet aggregation than clopidogrel.[6,7] Ticagrelor plus aspirin is superior to aspirin alone in reducing the risk of the composite of stroke or death within 30 days among patients with acute mild-to-moderate non-cardioembolic ischemic stroke (NIHSS score ≤ 5) or transient ischemic attack (TIA).[8] In the PRINCE (Platelet Reactivity in Acute Stroke or Transient Ischemic Attack) and CHANGE 2 (Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA) trials, patients with minor stroke or TIA treated with ticagrelor plus aspirin had a lower platelet reactivity and lower stroke recurrence than those treated with clopidogrel plus aspirin, particularly in CYP2C19 loss-of-function allele carriers.[9,10]

Clopidogrel is a commonly used $P2Y_{12}$ inhibitor recommended for the standard pharmaceutical treatment of patients who have undergone or are undergoing PCI. However, the incidence of bleeding and the degree of inhibition of platelet aggregation caused by $P2Y_{12}$ receptor inhibitors have been of great concern in recent years.[11,12] Issues with clopidogrel include lower bioavailability, slower platelet inhibition onset, uncertainty of patient response, and drug resistance.[12] These have led to the development of newer, highly potent $P2Y_{12}$ inhibitors such as ticagrelor. Recently, new drugs have been accepted for use in more and more patients who need antiplatelet therapy. Several meta-analyses have been conducted to explore the efficacy and safety of ticagrelor compared with clopidogrel in patients with ACS.[13,14] However, none of the meta-analyses involving the newer $P2Y_{12}$ inhibitors have comprehensively assessed any difference in ischemic- and hemorrhagic stroke risks compared to clopidogrel in patients after PCI for CCS or ACS. Therefore, in our study, we performed a systematic evaluation and meta-analysis to compare the efficacy and safety of ticagrelor relative to clopidogrel as regards the incidence of stroke and bleeding events, especially hemorrhagic stroke, in patients following PCI.

Methods

We conducted this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) and the Cochrane Collaboration guidelines. It was registered with the international prospective register of systematic reviews (PROSPERO) on July 04, 2021. (ID: 265104).

Data Sources and Search Strategy

The search strategy aimed to find both published and unpublished trials as far back as possible. Initially, we set intuitive index terms on the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases to find relative wording and Medical Subject Headings (MeSH) terms. We then used all identified keywords and index terms across all databases, including PubMed, MEDLINE, and Cochrane. Finally, the references listed in the selected articles were read and retained as gray articles if they met this reviewer's inclusion/exclusion criteria. From

our background knowledge, we knew that some global trials were already published and were still important in the field of cardiology. Hence, those trials were also selected if they met the inclusion criteria of this study. All potential literature was published between 2010 and 2021, and included the following major keywords: coronary intervention, percutaneous coronary intervention, clopidogrel and ticagrelor.

All retrieved studies were required to comprise two treatment arms, one with ticagrelor and one with clopidogrel. The databases were last searched on July 27, 2021 (Figure 1).

Selection criteria

Types of participants

The current review considered trials that included adult patients admitted with a diagnosis of ACS or CCS and scheduled to undergo PCI after coronary angiography.

Types of interventions

We defined the intervention as the prescription of ticagrelor at PCI and during the follow-up period. The control group consisted of patients who received clopidogrel at PCI and during the follow-up period.

Types of studies

Randomized controlled trials (RCTs) or propensity score matched (PSM) cohort studies that compared outcomes between ticagrelor and clopidogrel were selected for this review. In addition, articles published in Chinese or in English were also included.

Outcomes

The primary efficacy endpoint was the incidence of stroke, including ischemic and hemorrhagic stroke. The primary safety endpoint was the composite of major and minor bleeding events.

Study Selection

First, Endnote X9 was used to identify duplicate articles, retaining only one instance of each article. Then two reviewers examined the remaining articles by title and abstract to determine whether they were potentially relevant to the study purpose. Eligible literature was listed according to the inclusion criteria, and excluded articles were set aside with reasons. Finally, the two reviewers independently read the original articles and attempted to reach an agreement. Any disagreements between the reviewers were resolved by consulting a third reviewer.

Assessment of Study Quality

The quality of observational cohort studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.[15] In addition, RCTs were graded using the Cochrane Risk of Bias (RoB) tool.[16] This quality assessment was done by two reviewers independently, whereby any disagreement between them was resolved by discussion.

Data Extraction and Data Synthesis

Two investigators examined the retrieved articles and extracted data using a predetermined form. We recorded the trial name or the first author, year of publication, dose and method of drugs, number of patients, number of patients with cardiovascular events, follow-up time, and efficacy and safety of treatment. Discrepancies between reviewers were resolved through discussion under supervision of the corresponding author. To take into account the influence of study quality, sensitivity analyses were performed with- and without PSM cohort trials. The results of these were consistent with those of the primary analysis.

Meta-analyses were performed using Review Manager (RevMan) 5.4.1. Statistics were used to assess agreement between reviewers for study selection. The treatment effect was evaluated using the odds ratio (OR) and 95% confidence interval (CI). The studies' results were assessed using pooled ORs and 95% CIs by a fixed-effect model. The I^2 test was used to determine the heterogeneity of the results, with I^2 values greater than 75% indicating that the two groups

had a high heterogeneity, independence, and no significance of meta-analysis. The cut-off value for statistical significance for each test was set at $p = 0.05$.[16] Potential publication bias was evaluated using the funnel plots presented in supplements S1-S5.

Results

Literature Search

We retrieved 247 citations for a review of their titles and abstracts. A schematic of the study selection process is presented in Figure 1. After initial screening, 23 full-text articles were assessed. We excluded four studies due to data insufficiency, including having no definite stroke or bleeding events, three cohort studies without PSM data, two studies with cross-over design, two studies only focusing on platelet activity or gene polymorphism, and two studies only focusing on cost-effectiveness without considering clinical outcomes. Finally, 11 studies involving 33,507 patients were included in the systemic review.[17-27]

Methodological Quality of Studies Included

The detailed characteristics of the included 11 studies are shown in Tables 1 and 2. The methodological quality of the studies was determined by assessing the risk of bias (Figure 2), and three well-qualified PSM cohort studies were selected following the Newcastle-Ottawa Quality Assessment Scale. All disagreements concerning data evaluation were resolved by consensus. All enrolled studies were randomized controlled trials or PSM cohort studies.

Quantitative Data Synthesis

Primary Efficacy End Point of Stroke Events

The primary efficacy endpoint was post-PCI stroke, including transient ischemic attack (TIA) events. The rates of this primary efficacy endpoint were identified in the 11 studies. As shown in Figure 3, the trend was toward stroke reduction. (OR = 0.92, 95% CI: 0.73-1.16, $I^2 = 0\%$, $p = 0.46$). No obvious heterogeneity among the studies was observed.

Pooled Analysis of Ischemic Stroke

Of the 11 included studies, 6 analyzed ischemic stroke,[18,20,22,23,26,27] excluding TIA, in patients treated with ticagrelor or clopidogrel. There was no significant difference between the

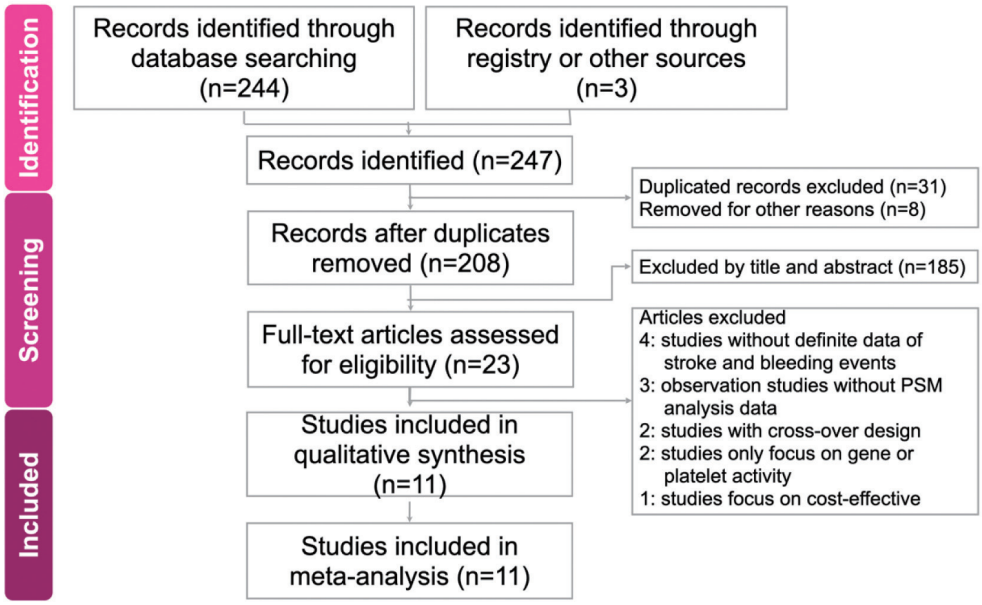

Figure 1. PRISMA flow diagram of study selection.

ticagrelor group and the clopidogrel group. Pooled data revealed that ticagrelor was not associated with a trend toward reduction of ischemic stroke, compared to clopidogrel, with the pooled OR being 1.01 (95% CI: 0.75-1.34, $I^2 = 0\%$, $p = 0.97$) (Figure 4).

Primary Safety End Point of Major Bleeding

The primary safety endpoint of major bleeding was a composite of TIMI major[28,29] and BARC 2,3,5[29] and PLATO-defined major bleeding criteria.[30] In 10 of the 11 articles, the authors identified the incidences of composite major bleeding events after PCI in patients receiving ticagrelor or clopidogrel. Ticagrelor showed a trend of increased risk of major bleeding compared with clopidogrel (OR = 1.10, 95% CI: 0.97-1.23, $I^2 = 59\%$, $p = 0.13$) (Figure 5).

Pooled Analysis of Hemorrhagic Stroke

The authors identified the rates of hemorrhagic stroke after PCI in patients receiving ticagrelor or clopidogrel in five of the 11 studies.[18,19,22,23,26] This was not statistically significant, but the pooled data revealed that ticagrelor was associated with a higher trend of hemorrhagic stroke than clopidogrel, with the pooled OR being 1.22 (95% CI: 0.65-2.30, $I^2 = 0\%$, $p = 0.53$) (Figure 6). The heterogeneity among the studies was low.

Pooled Analysis of Any-type Bleeding (Major and Minor)

The safety endpoint of any-type bleeding includes major and minor bleeding. As with major bleeding, minor bleeding was a composite of TIMI minor and BARC 0,1 and PLATO-defined minor bleeding criteria. The incidences of any-type bleeding events after PCI in patients receiving ticagrelor or clopidogrel were identified in all 11 articles. The risk of any bleeding was significantly higher in the ticagrelor group, compared with the clopidogrel group (OR = 1.18, 95% CI: 1.03-1.30, $I^2 = 75\%$, $p < 0.001$) (Figure 7). Although possible heterogeneity between the studies was found, no outliers were identified after sensitivity analysis.

Table 1. Main descriptions of the studies included

Trial Name or First Author	Type of Study	Type of Patients	Follow-up (month)	No. of Patients Randomized	
				Ticagrelor	Clopidogrel
PLATO	RCT	ACS	12	6732 (1)	6676
PHILO	RCT	ACS	12	401 (1)	400
ESTATE	Cohort (PSM+)	ACS	1-12	224 (3)	224
KAMIR-NIH	Cohort (PSM+)	ACS	6	1377 (3)	1377
Li, X.Y.	RCT	STEMI	12	161 (3)	281
TICAKOREA	RCT	ACS	12	400 (3)	400
ALPHEUS	RCT	CCS	1	941 (3)	942
POPular AGE	RCT	NSTE-ACS	12	502 (3)	500
TAILOR-PCI	RCT	ACS/CCS	12	903 (3)	946
Turgeon, R.D.	Cohort (PSM+)	ACS	12	3711 (3)	3711
TALOS-AMI	RCT	ACS	12	1348 (3)	1349

RCT: randomized clinical trial; Cohort(PSM+): propensity score matched, ACS: acute coronary syndrome; CCS: stable coronary syndrome.

Table 2. The original data of outcome indicators

Trial Name or First Author	Drug dose				Clinical outcome	
	Clopidogrel		Ticagrelor		Main Composite Efficacy Endpoints	Main Composite Safety Endpoints
	LD	MD	LD	MD		NON-CABG bleeding
PLATO	300/600 mg	75 mg	180 mg	90 mg bid	CV death, MI, Stroke	PLATO-defined major, minor bleeding
PHILO	300 mg	7 5mg	180 mg	90 mg bid	CV death, MI, Stroke	PLATO-defined major, minor bleeding
ESTATE	300/600 mg	75 mg	180 mg	90 mg bid	CV death, MI, Stroke, ST, all cause Death	PLATO-defined major, minor bleeding
KAMIR-NIH	300/600mg	7 5mg	180 mg	90 mg bid	CV death, non-fatal MI, Stoke, TVR	TIMI major or minor bleeding
Li, X.Y.	600 mg	75 mg	180 mg	90 mg bid	CV death, non-fatal MI, non-fatal stroke	BARC1: minor BARC 2,3: major
TICAKOREA	600 mg	75 mg	180 mg	90 mg bid	CV death, non-fatal MI, non-fatal Stroke	PLATO major, minor
ALPHEUS	300-600 mg	75 mg	180 mg	90 mg bid	PCI-MI (type 4a or 4b) or major myocardial injury; Death, MI (type 1, 4, and 5), or Stroke or TIA.	Major: BARC 3 or 5 Minor: BARC: 1 or 2 Any Bleeding: BARC 1-5
POPular AGE*	300-600 mg	75 mg	180 mg	90 mg bid	CV death, All-cause Death, MI, Stroke, ST	PLATO major or minor bleeding
TAILOR-PCI**	300-600 mg	75 mg	180 mg	90 mg bid	CV death, MI, Stroke, ST, SRI	TIMI major or minor bleeding
Turgeon, R.D.		75 mg		90 mg bid	All-cause death, ACS, ischemic Stroke, unplanned CR, ST	Major bleeding
TALOS-AMI***		75 mg		90 mg bid	CV death, MI, Stroke	BARC 2, 3, or 5 bleeding

*: Popular AGE trial: Ticagrelor group includes 95% ticagrelor and 5% prasugrel (60 mg LD, 10 mg MD).

** TAILOR-PCI trial: Focusing on LOF (Loss of function) allele (CYP2C19*2/*3) carriers: Ticagrelor group includes 85% ticagrelor, 15% clopidogrel; Clopidogrel group includes 99% clopidogrel and 1% ticagrelor.

***TALOS-AMI trial: all patients with AMI received standard ticagrelor treatment. 30 days after PCI, the clopidogrel group received 75mg clopidogrel, the ticagrelor group received 90mg ticagrelor bid.

Clinical outcomes: IDR: ischemia-driven revascularization, ST: stent thrombosis, TVR: Target vessel revascularization, TIA: transient ischemia attack, SRI: severe recurrent ischemia, CR: coronary revascularization.

LD, loading dose. MD: maintenance dose.

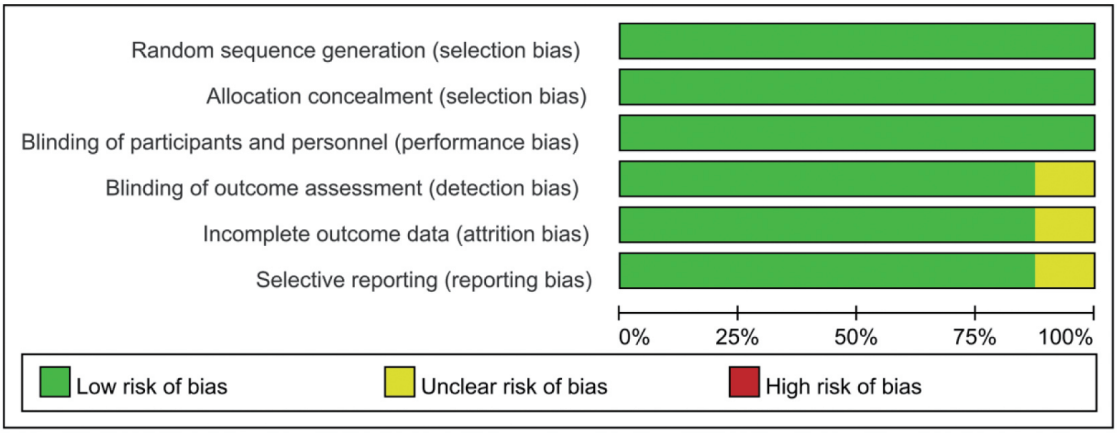

Figure 2. Risk of bias summary and risk of bias graph of included RCTs.

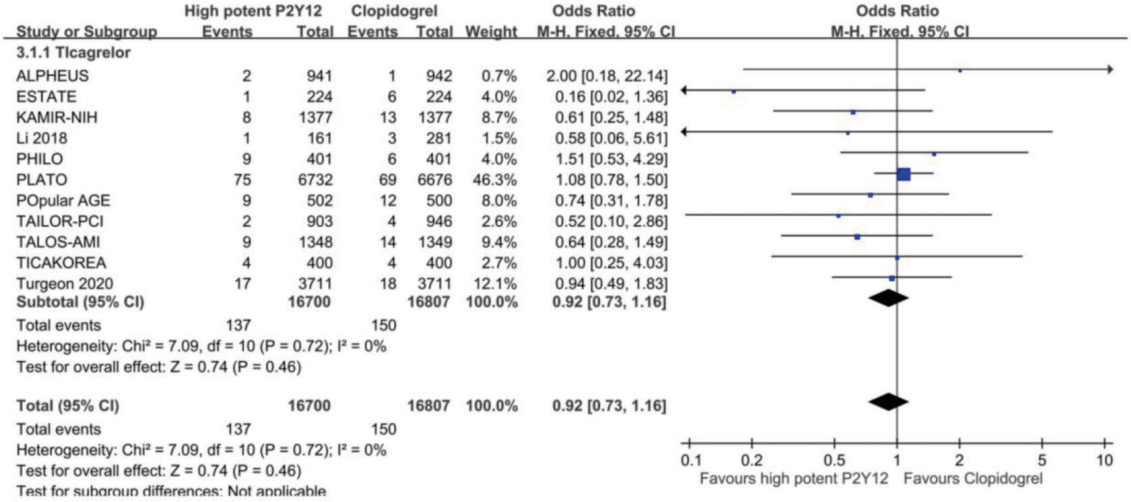

Figure 3. Meta-analysis of the primary efficacy endpoint of any stroke.

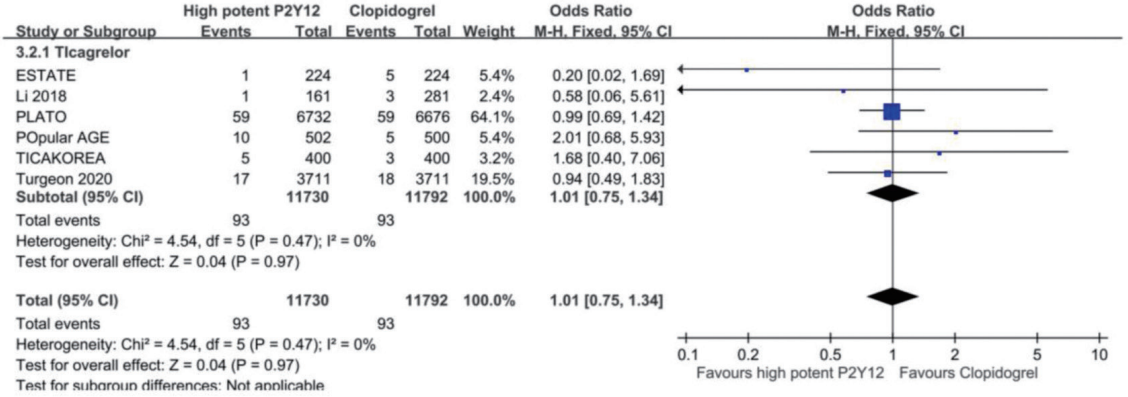

Figure 4. Meta-analysis of the primary efficacy endpoint of ischemic stroke.

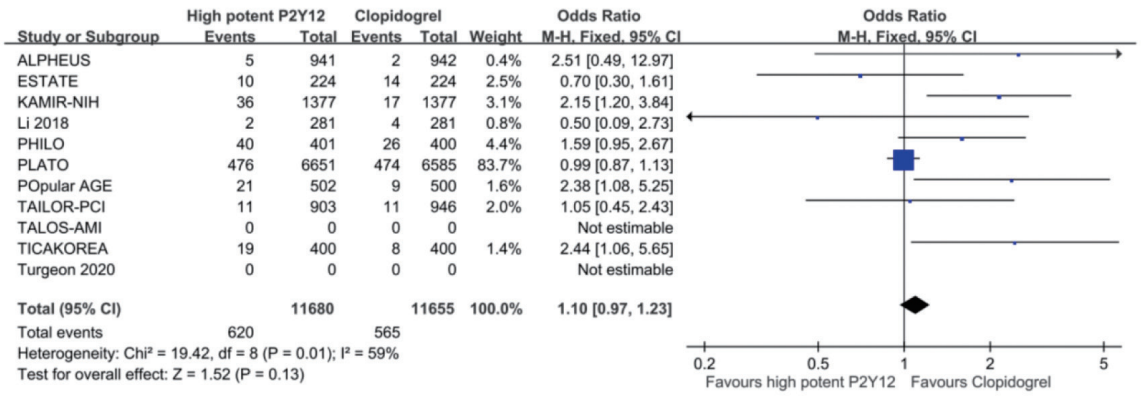

Figure 5. Meta-analysis of the primary safety endpoint of major bleeding.

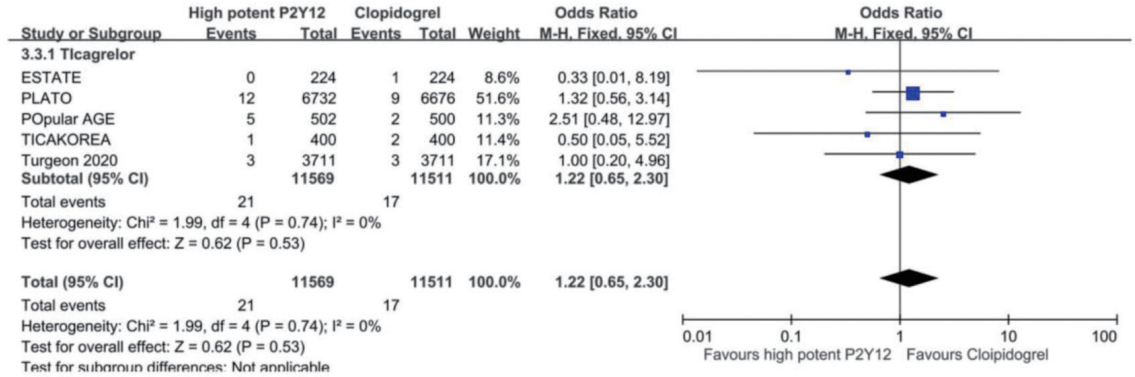

Figure 6. Meta-analysis of the primary efficacy endpoint of hemorrhagic stroke.

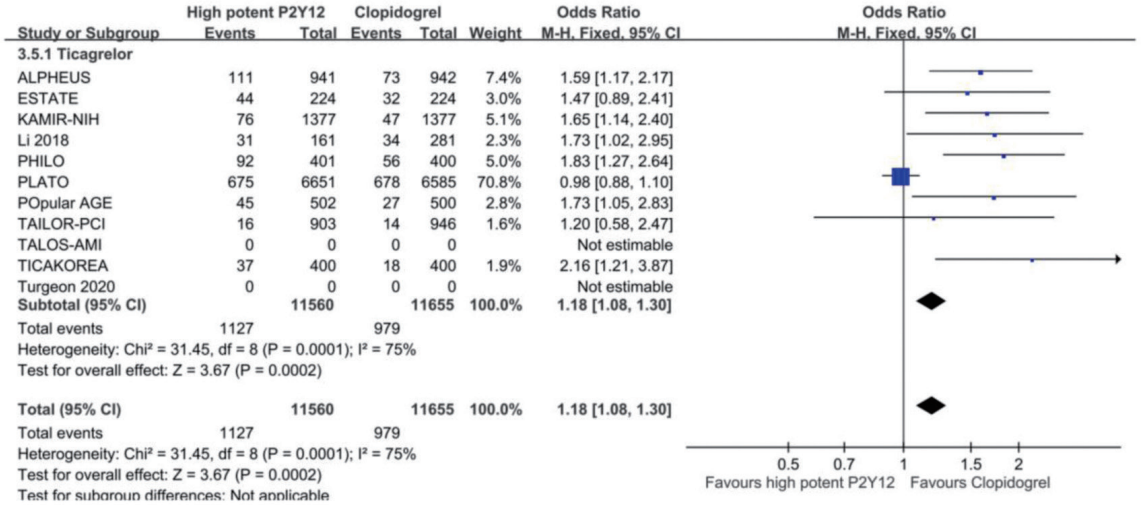

Figure 7. eta-analysis of the primary safety endpoint of any bleeding.

Discussion

Main Findings

This study represents a systematic analysis comparing the efficacy and safety of ticagrelor with that of clopidogrel in patients who have undergone or are undergoing coronary intervention due to ACS or CCS, focusing on post-PCI ischemic stroke, hemorrhagic stroke, major bleeding, and any-type bleeding. This meta-analysis does not provide evidence for the efficacy of ticagrelor, relative to clopidogrel in reducing the incidence of post-PCI stroke. A total of 11 studies with 33,507 patients were included in our analysis. There were 8 RCTs and 3 PSM cohort studies. The main findings can be summarized as follows:

1. With regard to effectiveness, the present analysis showed no statistically significant reduction in incidence of ischemic stroke in the ticagrelor group, compared with the clopidogrel group.
2. With regard to safety, the ticagrelor group was associated with a higher risk of any-type bleeding, especially minor bleeding, compared with the clopidogrel group. However, the incidence of major bleeding or hemorrhagic stroke was not statistically significantly increased in the ticagrelor group, compared with the clopidogrel group.

Clinical Significance

Dual antiplatelet therapy, usually accompanied with a $P2Y_{12}$ receptor antagonist and aspirin, is generally acknowledged as a vital approach in treating ACS, partly because of the increased risk of thrombogenesis during the period of ACS. Dual antiplatelet therapy has also been regarded as a standard therapy, especially after PCI, according to several clinical guidelines.[31,32]

Clopidogrel, a $P2Y_{12}$ receptor antagonist, has generally been used with aspirin as a prescribed antiplatelet agent in an attempt to decrease the risk of MI and stent thrombosis in patients with acute coronary syndrome, with or without ST elevation.[22] However, clopidogrel as an inactive pro-drug requires a 2-step hepatic activation metabolism that is strongly linked to delayed onset and various responses.[33,34]

Ticagrelor is a direct-acting, reversible, oral $P2Y_{12}$ receptor antagonist which does not require catabolite activation, which can produce a substantially faster and consistently greater platelet inhibition than clopidogrel.[6,35]

Clopidogrel resistance has been reported worldwide and varies from country to country and even between studies within countries. The resistance is reported to be high in Asians (> 55%), compared to Caucasians (30%) and those of African descent (40%).[36] Some large prospective randomized controlled trials have demonstrated greater reductions in periprocedural ischemic events after PCI for the newer, highly potent $P2Y_{12}$ inhibitor therapies, compared with clopidogrel. However, our meta-analysis documents that ticagrelor cannot significantly reduce post-PCI stroke events, compared with clopidogrel.

In summary, compared with clopidogrel, ticagrelor neither prevents post-PCI stroke nor does it increase the risk of hemorrhagic stroke or major bleeding; the only safety concern in the use of ticagrelor is a significant increase in minor bleeding events. Future large-scale and multi-center randomized controlled trials will draw more definite conclusions and provide a safe and effective antithrombotic strategy for the use of potent $P2Y_{12}$ inhibitors as an adjuvant treatment for patients undergoing PCI.

Limitations

There are several limitations to the present meta-analysis. First, this meta-analysis includes eight randomized controlled trials and three propensity score matched cohort studies. The 11 experiments differed in terms of their study design, including patient enrollment, timing of randomization and choice of antiplatelet therapies across treatment arms. However, general consistency in the results was seen across studies,

and study populations were broadly similar. Second, as with any meta-analyses, publication bias, also known as the 'file drawer problem,' could not be entirely avoided. Studies that showed no effect or were not statistically significant were not likely to be published and therefore did not appear in our meta-analyses. Third, the studies' definitions of clinical events, the disparities in treatment duration, use of adjuvant therapies including heparinization or glycoprotein IIb/IIIa inhibitors, the different types of coronary stents and the lack of description of details associated with patient characteristics, including baseline stroke or bleeding risk, were all likely important sources of heterogeneity related to our analysis. Random-effects pooling could attempt to mitigate these differences, but heterogeneity in our analysis appeared to be insignificant and did not affect the overall study conclusion. Of course, more large clinical trials are needed to achieve more accurate results.

Conclusion

Our meta-analysis of 11 trials with 33,507 patients provided a systematic analysis comparing the efficacy and safety of ticagrelor with clopidogrel in patients receiving PCI. This study demonstrated that ticagrelor neither decreases post-PCI stroke rates nor does it increase major bleeding rates, especially hemorrhagic stroke. However, ticagrelor could significantly increase minor bleeding, compared with clopidogrel. Therefore, the selection of the appropriate $P2Y_{12}$ inhibitor with the aim of minimizing the risk of adverse cardiovascular outcomes must be made in light of each patient's clinical ischemic or bleeding characteristics.

Conflicts of Interests Statement

There are no conflicts of interests including financial, consultant, institutional and other relationships that might lead to bias.

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