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Review Article

Efficacy and safety of prasugrel therapy for intracranial aneurysms with endovascular treatment: A meta-analysis

Pengfei Xia[a], Chang He[b], Lanlan Chen[c], Liang Zou[a], Shihao Sun[d], Pengyu Cui[d], Wei Wang[a,*]

[a] Department of Neurosurgery, The Second Clinical Medical School of Inner Mongolia University for the Nationalities, Hulun Buir, China
[b] College of Basic Medical Sciences of Jilin University, Changchun, China
[c] Clinical Medicine of Jilin University, Changchun, China
[d] Inner Mongolia University for the Nationalities, Tongliao, China

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ABSTRACT

Background: Prasugrel as a second generation P2Y12 adenosine diphosphate receptor antagonist which in the cerebral aneurysms with Endovascular treatment have become more emphasized.
Objective: To compare the efficacy and safety of prasugrel therapy for intracranial aneurysms with endovascular treatment.
Methods: The databases of PubMed, Embase, Cochrane Library databases and China Biology Medicine disc were retrieved with computers for collecting controlled trials about the comparison in the efficacy and safety of prasugrel and clopidogrel published from inception to September 2018. At the same time, the reference materials of included literature were retrieved manually. After rigorous evaluation on literature quality, the eligible data of the trials was extracted and given a Meta-analysis by applying RevMan5.3 software.
Results: Of the 96 studies identified, 7 trials were included. Results of meta-analysis showed that compared with patients receiving clopidogrel treatment, novel platelet $P2Y_{12}$ receptor inhibitor prasugrel were effective in reducing the incidence of thromboembolic events (OR = 0.19, 95%CI: 0.08–0.45, P = .0001), but did not increase the risk of hemorrhagic complication (OR = 1.00, 95%CI: 0.53–1.89, P = 1.00), and the PRU (OR = 0.19, 95%CI: 0.08–0.45, P = .0001) and Percentage inhibition of platelet (MN = 37.05, 95%CI: 33.37–40.73, P < .00001) were controlled in a better range.
Conclusion: In antiplatelet therapy after aneurysmal interventional therapy, the second generation of $P2Y_{12}$ adenosine receptor antagonist prasugrel can significantly reduce the risk of thrombosis without increasing the risk of bleeding.

1. Introduction

Endovascular treatment is accepted as an effective therapy to decrease the disability and mortality of patients with intracranial aneurysms. However, the thromboembolism and cerebral ischemia during the regular coiling procedures of aneurysms is a common and serious complication [1]. A growing body of evidence suggests that preoperative and postoperative prophylactic antiplatelet therapy is effective in reducing thrombotic events in the treatment of intracranial aneurysms with or without stent-assisted during intravascular coils [2–4]. During the perioperative period, in order to reduce the incidence of ischemic complications, two antiplatelet drugs, aspirin and clopidogrel, are generally used clinically. It is worth noting that for these patients with poor response to clopidogrel, the risk of cerebral ischemia or stent thrombosis is significantly higher [5,6].

Recently, prasugrel as a second generation $P2Y_{12}$ adenosine diphosphate receptor antagonist which has a higher conversion rate of precursors to active metabolites and higher bioavailability compared with clopidogrel [7]. Therefore, some medical centers have begun to use prasugrel as prophylactic antiplatelet therapy for endovascular treatment of intracranial aneurysms [8]. Despite the theoretical benefits of prasugrel, only a few studies have reported attempted to used prasugrel regimen in interventional therapy of intracranial aneurysms. This article provides a systematic review and meta-analysis of available data from published literature to determine the feasibility, efficacy and safety of prasugrel in the treatment of intracranial aneurysms.

Abbreviations: PRU, $P2Y_{12}$ reaction unit; OD, Odds Ratio; CI, confidence interval; I^2, inconsistency index statistic

* Corresponding author.
E-mail address: X15750554485@outlook.com (W. Wang).

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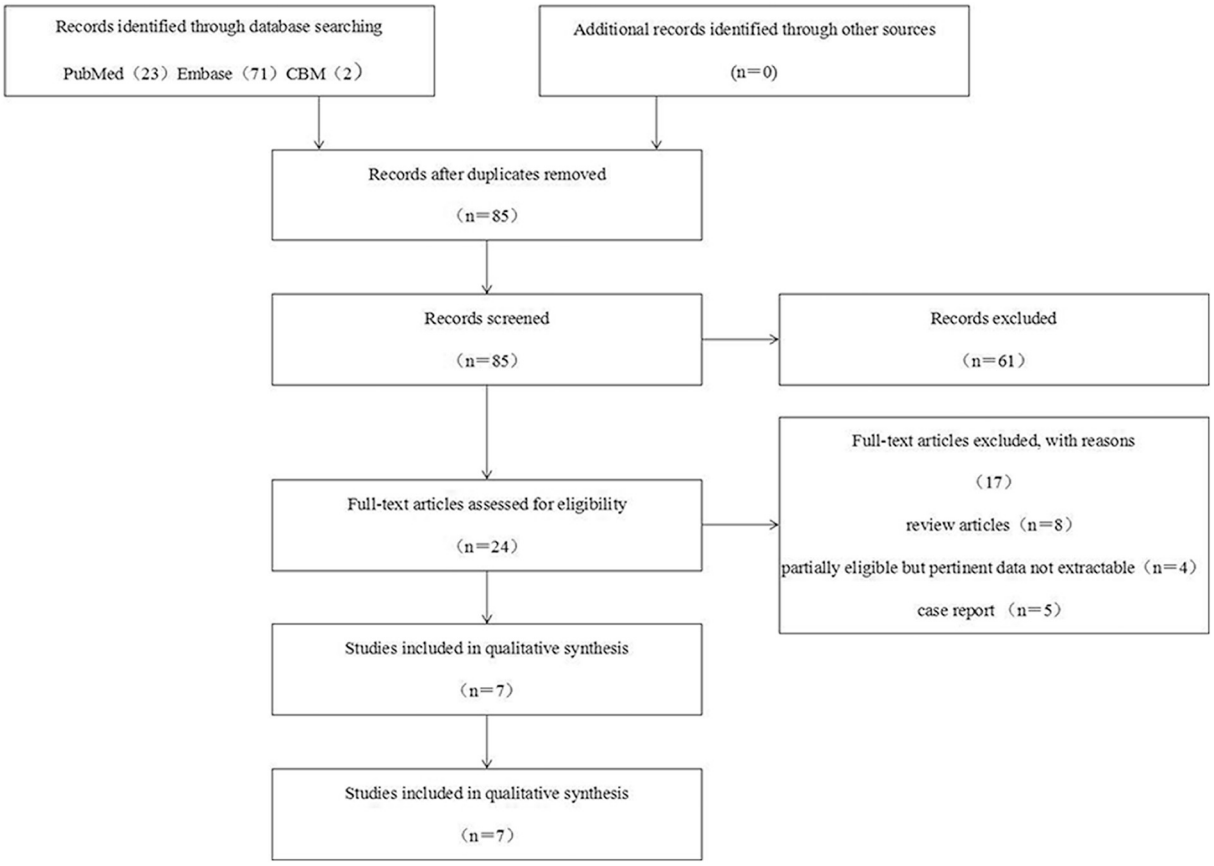

Fig. 1. Flow diagram of the study selection process.

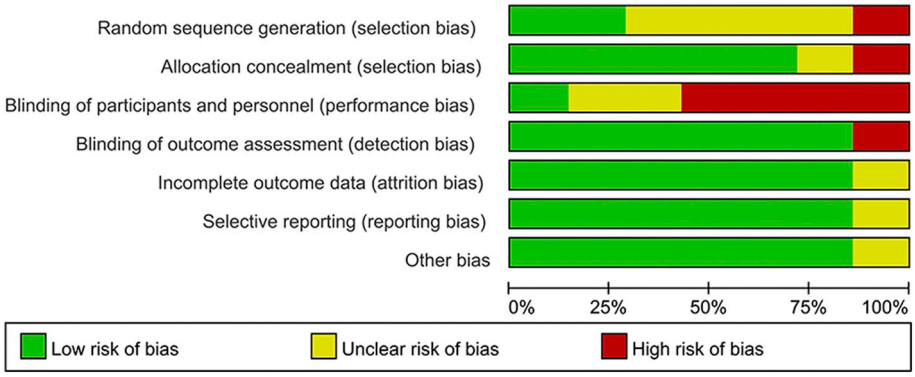

Fig. 2. Risk of bias percentile chart.

2. Methods

2.1. Search strategy

The search protocol is pre-defined based on the preferred reporting items in the System Review and Meta-analysis (PRISMA) guide [9]. A systematic search was conducted by two of the authors in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials identified 23, 71 and 2 citations, 1 additional studies were available from the China Biology Medicine disc. The databases were from inception to September 2018, with no language restrictions. The following search terms were used the combination of Mesh and free-text words: (prasugrel/Efient/CS747) AND (Intracranial Aneurysms/ Brain Aneurysms/ Cerebral Aneurysm). The PRISMA flow diagram of the study selection process is displayed in Fig. 1.

2.2. Inclusion and exclusion criteria

Only randomized controlled trials and observational prospective or retrospective trials were included. At least one group patients were received prasugrel for intracranial aneurysms with endovascular treatment, the data onto overall hemorrhagic complication and thromboembolism can be extracted from each of the included studies. The antiplatelet therapy duration of < 4 weeks or the total sample size is less than ten were excluded.

2.3. Date extraction and quality assessment

Two investigators selected and summarized the following related date from all eligible studies independently: authors, years, study design, type of aneurysm, types and doses of antiplatelet drug, follow-up time, incidence of hemorrhagic complication and thromboembolism,

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

Study	Year	Cases	Type of aneurysm	Antiplatelet drug	Follow-up time	Hemorrhagic complication	Thromboemb-olism
Akbari	2013	74	Unruptured + ruptured	Prasugrel 10 mg/d (25)	20 month	4	1
				Clopidogrel 75 mg/d (49)		2	0
Cho	2018	411	Unruptured	Prasugrel 5 mg/d (225)	17 month	1	1
				Clopidogrel 75 mg/d (186)		3	7
Choi	2017	297	Unruptured	Prasugrel 20–30 mg/d (207)	2 month	1	2
				Clopidogrel 75 mg/d (90)		2	6
Delgado	2014	44	Unruptured + ruptured	Prasugrel 10 mg/d (12)	6 month	2	0
				Clopidogrel 75 mg/d (31)		2	1
Ha	2016	194	Unruptured	Prasugrel 20–30 mg/d (98)	2 month	1	0
				Clopidogrel 75 mg/d (96)		1	0
Kim	2017	175	Unruptured	Prasugrel 30 mg/d (118)	1 month	5	1
				Clopidogrel 75 mg/d (57)		4	7
Sedat	2017	200	Unruptured	Prasugrel 10 mg/d (100)	1 month	6	0
				Clopidogrel 75 mg/d (100)		5	3

$P2Y_{12}$ reaction unit (PRU) and Percentage inhibition of platelet. The risk of bias was assessed with the domain-based Cochrane Collaboration's tool (Fig. 2). Any discrepancies were resolved and arbitration by a third investigators. The characteristics of studies included in the meta-analysis display in Table 1.

2.4. Statistical methods

The meta-analysis was performed using the Review Manager 5.3 Version software (The Cochrane Collaboration, Oxford, UK). For each outcome, the efficacy and safety were assessed by a random-effects model using pooled Odds Ratio (OD), along with 95% confidence interval (CI) for dichotomous variables for the incidence of hemorrhagic complication and thromboembolism, differences with $P < .05$ indicates statistically significant. The heterogeneity from each study was assessed by inconsistency index statistic (I^2). Heterogeneity was considered substantial if $I^2 > 50\%$.

3. Results

3.1. System literature review

Overall, the literature searches identified 96 clinical trials were retrieved, after 11 duplication were excluded, 85 eligible literature for screen by title and abstract, of which 24 met our inclusion criteria. Then, after the full-text screening and quality evaluation, 17 reviews, 14 case reports and 4 literature pertinent data note extractable were further excluded. Finally 7 trials were include in this review.

3.2. Study characteristics

Of the 7 studies, 1 [10] were randomized controlled trial, and the remaining 6 [8,11–15] were retrospective trials which were considered to be low risk, 1 [12] of the article was Epub ahead of print, the main patients characteristics showed no significant diffidence. The total number of 1394 patients met our criteria were analyzed in this study, and the sample sizes ranged from 44 to 411, including 785 in the prasugrel group and 605 in the clopidogrel group. All 7 studies were reported the rate of hemorrhagic complication and thromboembolism, and 3 of these studies were carried out to detected PRU and Percentage inhibition of platelet.

3.3. Efficacy and safety

There are 7 studies were enrolled in the hemorrhagic complication rate analyses (Fig. 3). NO heterogeneity ($x^2 = 7.27$, $P = .30$, $I^2 = 17\%$) was observed in these studies. A fixed-effects meta-analysis showed that the risk of hemorrhagic complication was not statistically significant in the prasugrel and clopidogrel group (OR = 1.00, 95%CI: 0.53–1.89, P = 1.00).

6 studies were enrolled in the thromboembolism rate analyses. NO heterogeneity ($x^2 = 6.68$, $P = .25$, $I^2 = 25\%$) was observed in these 6 studies. The risk of thromboembolism was lower in the prasugrel group than in the clopidogrel group, and the fixed-effects meta-analysis showed that difference was statistically significant. (OR = 0.20, 95%CI: 0.06–0.61, P = .005).

3 studies were enrolled in the PRU analyses. NO heterogeneity ($x^2 = 3.20$, $P = .20$, $I^2 = 38\%$) was observed in these 3 studies. The PRU of prasugrel lower than that of clopidogrel group, and the results of Meta analysis of the random effects model showed that the difference was statistically significant (MN = −117.46, 95%CI: −129.48 to −105.44, $P < .00001$).

3 studies were enrolled in the Percentage inhibition of platelet analyses. NO heterogeneity ($x^2 = 3.37$, $P = .19$, $I^2 = 41\%$) was observed in these 3 studies. The Percentage inhibition of prasugrel higher than that of clopidogrel group, and the results of Meta analysis of the random effects model showed that the difference was statistically significant (MN = 37.05, 95%CI: 33.37–40.73, $P < .00001$).

3.4. Publication bias evaluation and sensitivity analysis

Due to the small number of references, this study adopts the Egger test to analyze the publication bias [16], hemorrhagic complication (P = .729), thromboembolism (P = .144), PRU (P = .507), percentage inhibition (P = .697), the value of $P < .05$ indicates significant asymmetry. Sensitivity analysis was carried out for each result, and all the studies in each index were deleted one by one to recombine the data. The results were still statistically significant, and the random effect model was used for reanalysis.

4. Discussion

In recent years, a number of large-scale clinical trials have demonstrated that platelet $P2Y_{12}$ receptor inhibitors combined with aspirin can effectively reduce the incidence of thrombotic events after endovascular intervention in patients with aneurysms [17–19]. However, there are also many limitations in this drug strategy. First, clopidogrel is an inactive drug precursor, which needs to be used after metabolism in the body. Due to the differences in individual enzyme catalysis and metabolic activity, the drug has relatively large individual differences. Secondly, the incidence of drug resistance of clopidogrel is as high as 15%–30% in the process of clinical medication [20]. Patients often have to increase the dosage due to drug tolerance, so the incidence of hemorrhagic complications related to clopidogrel is also increased accordingly [21,22]. Thirdly, the inhibitory effect of clopidogrel on platelets is irreversible. If the patient shows any symptoms

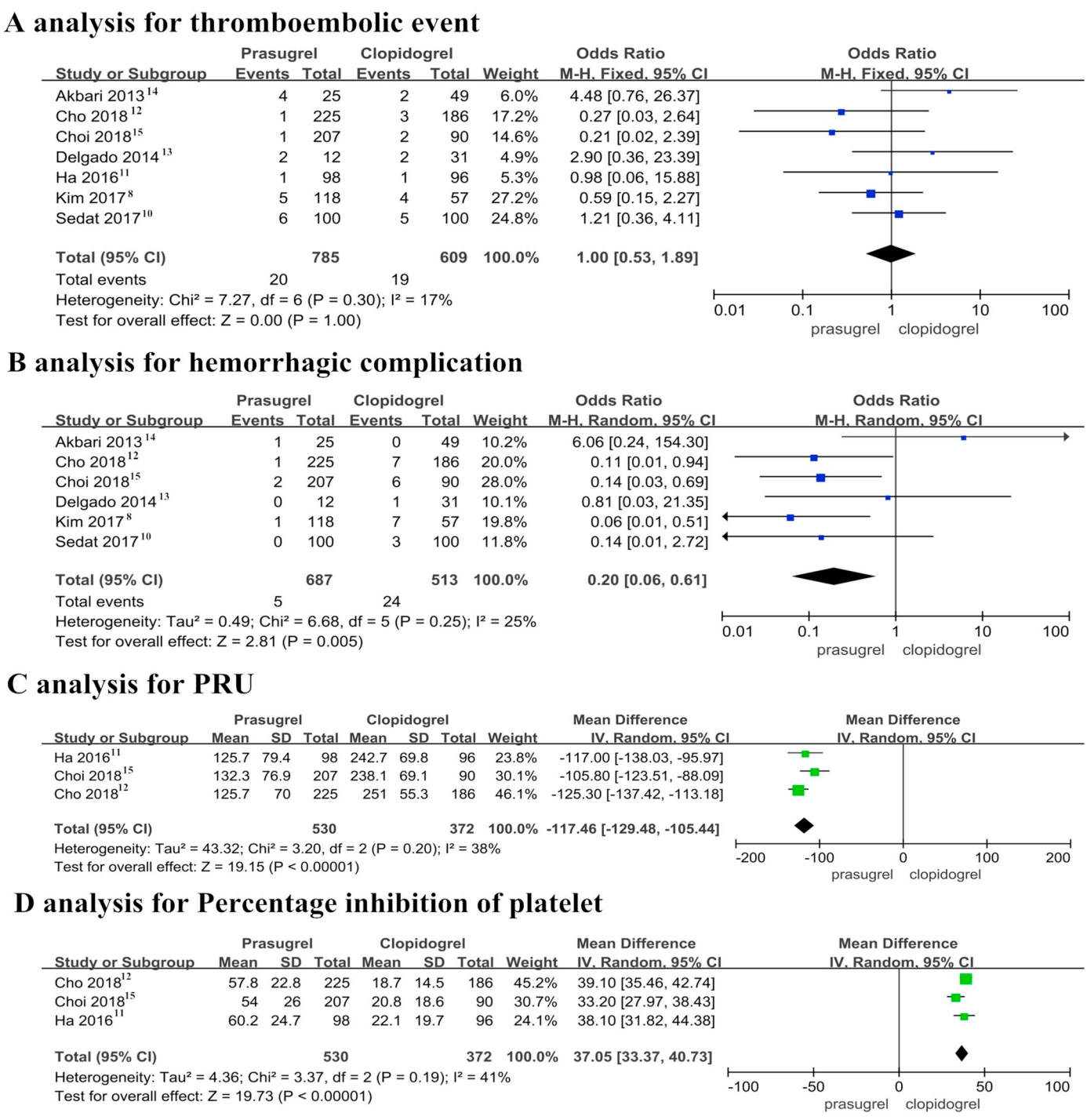

Fig. 3. Forest plot of comparison: prasugrel group versus prasugrel group. (A) the analysis for thromboembolic events; (B) the analysis for hemorrhagic complication; (C) the analysis for PRU; (D) the analysis for Percentage inhibition of platelet (%).

after taking the drug and needs emergency surgery, the risk of perioperative bleeding will be greatly increased.

The newly developed third-generation thiophenopyridine platelet $P2Y_{12}$ receptor inhibitor, prasugrel compared with clopidogrel, the precursor drug to active metabolite has a higher rate and higher bioavailability, and can be reversible inhibition of platelet aggregation, so it works faster and can reduce the effect of differences between individuals, a greater degree to reduce the incidence of major ischemic events. This meta-analysis has enrolled 7 studies comprising 1394 patients in the pooled analysis. All the 7 included studies collected the incidence of risk of hemorrhagic complication, but only 6 included the incidence of thromboembolism because no thromboembolism event was sent in the prasugrel group and the clopidogrel group. In the included studies, though, prasugrel's use measures ranged from 5 mg to 30 mg, the results of quantitative synthesis indicated that compared with clopidogrel, prasugrel was able to reduce the risk of thromboembolization (OR = 0.19, 95%CI: 0.08–0.45, P = .0001) after intravascular interventional therapy for aneurysms without increasing the bleeding rate (OR = 1.00, 95%CI: 0.53–1.89, P = 1.00) among which the hemorrhage was intracranial hemorrhage proved by CT or MRI scanning, and the thromboembolization event was confirmed by cerebral angiography. Mete analysis, which measured the PRU and the

percentage inhibition of platelet collected in the 3 studies, showed that although the average PRU and the percentage inhibition of the two groups (On the basis of VerifyNow test results) were within the normal range, the prasugrel group was able to reduce PRU to a lower incidence of thromboembolization events (MN = −117.46, 95%CI: −129.48 to −105.44, P < .00001), as well as a stronger inhibition of platelets (MN = 37.05, 95%CI: 33.37–40.73, P < .00001).

In addition to the 7 trials enrolled, several single-arm trials have also reported an efficacy of prasugrel therapy for intracranial aneurysms with endovascular treatment [23,24]. A cohort study of patients that had no response to clopidogrel to $P2Y_{12}$ receptor found that prasugrel could effectively control the patient's PRU in a better range and the incidence of thrombotic events was reduced by 10% in Interventional therapy for patients with aneurysm, demonstrating that prasugrel had a positive effect on patients with clopidogrel resistance [8]. Both clopidogrel and prasugrel are precursors for biotransformation of active metabolites by cytochrome P450 enzyme. Although the active metabolites of the two drugs have similar affinity for $P2Y_{12}$ receptors in vitro, the difference in the in vivo response seems to be mediated by the difference in metabolic pathways leading to the formation of active metabolites [25]. Hepatic esterase transduces most (about 85%) of the clopidogrel into a single pathway, and the remaining prodrugs require two separate cytochrome P450-dependent oxidation steps [26]. On the contrary, esterase is part of the activation pathway of prasugrel, which is oxidized into its active metabolite in a single cytochrome P450-dependent step, without obvious dead-end pathway. This suggests that prasugrel is of greater value in patients with $P2Y_{12}$ receptor resistance.

5. Limitations

This study has various limitations. Only 7 studies have been included, and there are fewer randomized controlled trials, and some trials have a shorter follow-up period, which may lead to incomplete statistics of complications. At the same time, because only published literature has been retrieved, the inclusion of literature is incomplete, so the clinical significance of meta-analysis results is still open to question. More randomized controlled trials, higher quality studies, further increased follow-up time, more comprehensive and unified patient enrollment criteria, and outcome indicators need to be collected to confirm the study.

6. Conclusion

This meta-analysis demonstrated that prasugrel was more effective than clopidogrel in preventing thromboembolization event after interventional therapy for aneurysms, and prasugrel did not increase the additional risk of bleeding. Therefore, prasugrel is safe and effective in preventing thrombosis after interventional therapy for aneurysms.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Xia. Acquisition of data: Xia, He. Analysis and interpretation of data: Zou, Sun. Drafting the article: Xia, Cui. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Xia. Study supervision: Wang.

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