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ABSTRACT

BACKGROUND: Clopidogrel is routinely used to decrease ischemic complications during neurointerventional procedures. However, the efficacy may be limited by antiplatelet resistance.

PURPOSE: Our aim was to analyze the efficacy of prasugrel compared with clopidogrel in the cerebrovascular field.

DATA SOURCES: A systematic search of 2 large databases was performed for studies published from 2000 to 2018.

STUDY SELECTION: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we included studies reporting treatment-related outcomes of patients undergoing neurointerventional procedures under prasugrel, and studies comparing prasugrel and clopidogrel.

DATA ANALYSIS: Random-effects meta-analysis was used to pool the overall rate of complications, ischemic and hemorrhagic events, and influence of the dose of prasugrel.

DATA SYNTHESIS: In the 7 included studies, 682 and 672 unruptured intracranial aneurysms were treated under prasugrel (cases) and clopidogrel (controls), respectively. Low-dose (20 mg/5 mg; loading and maintenance doses) prasugrel compared with the standard dose of clopidogrel (300 mg/75 mg) showed a significant reduction in the complication rate (OR = 0.36; 95% CI, 0.17–74, P = .006; I^2 = 0%). Overall, the ischemic complication rate was significantly higher in the clopidogrel group (40/672 = 6%; 95% CI, 3%–13%; I^2 = 83% versus 16/682 = 2%; 95% CI, 1%–5%; I^2 = 73%; P = .03). Low and high loading doses of prasugrel were associated with 0.6% (5/535; 95% CI, 0.1%–1.6%; I^2 = 0%) and 9.3% (13/147; 95% CI, 0.2%–18%; I^2 = 60%) intraperiprocedural hemorrhages, respectively (P = .001), whereas low and high maintenance doses of prasugrel were associated with 0% (0/433) and 0.9% (2/249; 95% CI, 0.3%–2%; I^2 = 0%) delayed hemorrhagic events, respectively (P = .001).

LIMITATIONS: Retrospective series and heterogeneous endovascular treatments were limitations.

CONCLUSIONS: In our study, low-dose prasugrel compared with clopidogrel premedication was associated with an effective reduction of the ischemic events with an acceptable rate of hemorrhagic complications.

ABBREVIATIONS: ASA = acetylsalicylic acid; AT = antiplatelet therapy; CP = clopidogrel; PRU = P2Y12 reaction unit; PS = prasugrel

Prophylactic antiplatelet therapy (AT) is widely used to prevent thromboembolic complications in patients undergoing endovascular treatment of intracranial aneurysms, especially when stent-assisted techniques are adopted.[1] Clopidogrel (an inhibitor of the P2Y12 adenosine diphosphate receptors) is one of the most common ATs adopted to minimize the risk of thromboembolic events.[2] However, one of the limitations of this drug is the individual patient variability of its efficacy, with approximately 30% of patients showing clopidogrel (CP) resistance.[3] Given that patients who are resistant to CP have a higher risk of ischemic events, different types of AT have been proposed. Prasugrel (PS) (Effient) is a new antiplatelet agent that has been used extensively among patients undergoing cardiovascular treatment.[4] Like CP, this drug works through the inhibition of the P2Y12 adenosine diphos-

Indicates article with supplemental on-line tables.

Indicates article with supplemental on-line photos.

phate receptors. However, different from CP, PS requires a 1-step activation, allowing more effective platelet inhibition and a lower degree of resistance.[4] The experience with PS in the field of cerebrovascular diseases is still limited, and its safety and efficacy remain unclear. The aim of our meta-analysis was to investigate whether PS can be a conceivable alternative to CP during the endovascular treatment of unruptured intracranial aneurysms.

MATERIALS AND METHODS

Literature Search
A comprehensive literature search of PubMed and Ovid EMBASE was conducted for studies published from January 2000 to October 2018. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses[5] guidelines were followed. The key words and the detailed search strategy are reported in On-line Table 1, and the studies included in our review are reported in On-line Table 2. The inclusion criteria were the following: 1) studies reporting series of patients with unruptured intracranial aneurysms endovascularly treated in whom PS was administrated as an AT; 2) studies reporting outcome comparisons between PS (cases) and CP (control) used as an AT for the endovascular treatment of unruptured intracranial aneurysms. Exclusion criteria were the following: 1) case reports, 2) review articles, 3) studies published in languages other than English, and 4) in vitro/animal studies. In cases of overlapping patient populations, only the series with the largest number of patients or the most detailed data were included. Two independent readers screened articles in their entirety to determine eligibility for inclusion. A third author solved discrepancies.

Data Collection
We extracted the following: 1) treatment-related complications, 2) type of complications, 3) clinical outcome, 4) mean P2Y12 reaction unit (PRU) value, 5) mean percentage of platelet inhibition, and 6) angiographic outcome. The reported results were compared between the PS and CP groups of patients.

Treatment-related complications were divided into the following: 1) periprocedural/early events (within 30 days) and delayed events (after 30 days); 2) transient (asymptomatic events or complete neurologic recovery) and permanent complications (symptomatic events with permanent deficits); and 3) ischemic and hemorrhagic complications. Finally, good outcome was defined as a modified Rankin Scale score of 0–2 or a Glasgow Outcome Score of 4–5, or it was assumed if the study used terms such as "no morbidity," "good recovery," and "no symptoms."

Outcomes
The primary objectives of this study were to compare treatment-related complication rates between the PS and CP groups. The secondary objectives were to define the type of complications and the influence of the loading and maintenance doses of PS on the periprocedural and delayed hemorrhagic events, respectively.

Quality Scoring
The Newcastle-Ottawa Scale[6] was used for the quality assessment of the included studies (details in On-line Tables 3 and 4). The

quality assessment was performed by 2 authors independently, and a third author solved discrepancies.

Statistical Analysis
We estimated, from each cohort, the cumulative prevalence (percentage) and 95% confidence interval for each outcome. Heterogeneity of the data were assessed by the Higgins index (I^2), and subsequently, the DerSimonian and Laird random-effects model was applied. The graphic representation is shown by a forest plot. To evaluate the heterogeneity and bias, we analyzed the metaregression and the funnel plot that was followed by the Egger linear regression test, respectively. To verify the consistency of outcome meta-analysis results, we assessed the influence of each individual study on the summary effect estimate by the sensitivity analysis (leave-one-out approach) and the subgroups analysis. To compare the percentages of each group and to calculate the P values, we used the 1-way analysis of variance and the Z-test when appropriate. Differences were considered significant at $P <$ .05. Meta-analysis was performed with ProMeta-2 (Internovi, Cesena, Italy) and OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta/download.html).

RESULTS

Literature Review
Studies included in our meta-analysis are summarized in On-line Table 2. The search flow diagram is shown in On-line Fig 1.

Seven studies and 1354 aneurysms/procedures (1232 patients) were included in our review. Overall, 682 unruptured aneurysms were treated endovascularly using PS (cases), whereas 672 unruptured aneurysms were treated endovascularly using CP (controls). Five studies compared treatment-related outcomes between the PS and the CP groups,[7-10,14] whereas 2 studies reported series of patients exclusively treated with PS.[12,13]

Quality of Studies
Six studies were retrospective series,[7,8,10,12,13] whereas 1 study presented a prospective design.[9] Overall, 5 articles were rated as "high-quality" studies. Details of the ratings of the included studies are reported in the On-line Tables 3 and 4.

Patient Population and Aneurysm Characteristics
Detailed characteristics of the patient population are reported in On-line Table 5. The mean age of patients was comparable between the 2 groups. The proportion of male patients was higher among the PS group (56%; 95% CI, 51%–59% versus 45.6%; 95% CI, 41%–49%; P = .001), as well as the proportion of aneurysms in the anterior circulation (87%; 95% CI, 84%–89% versus 82%; 95% CI, 78%–85%) (P = .01). Posterior circulation aneurysms were more common among the CP group (18%; 95% CI, 14%–21% versus 13%; 95% CI, 10%–15%) (P = .01). Mean aneurysm size was comparable between the 2 groups. The proportion of aneurysms treated with stent-assisted coiling or flow diversion was higher among the PS group (63.6%; 95% CI, 58%–67% versus 54.7%; 95% CI, 50%–58%) (P = .001).

In 4 studies,[8,13,14] the loading dose of PS was 20 mg 1 day before treatment; in one study[9] it was 30 mg 1 day before treatment; in 2 studies,[10,12] the loading dose was between 40 and 60 mg

1 day before treatment; and in 1 study,[7] 60 mg of PS was associated with 325 mg of acetylsalicylic acid (ASA). In 3 studies, CP, 75 mg, was combined with ASA, 100 mg[7,9] or ASA, 325 mg[10], 5 days before treatment, whereas CP, 300 mg, was used alone in 2 studies[8,14] 5 days before the procedure. The maintenance dose of PS was 5 mg/day in 3 studies,[8,13,14] 5–10 mg/day in 2 studies,[9,12] and 10 mg/day in 2 studies.[7,10] The maintenance dose of AT in the CP group was CP, 75 mg/day, + ASA, 75–100 mg/day, in 4 studies,[8-10,14] whereas in 1 study CP, 75 mg/day, was associated with ASA, 325 mg/day.[7]

The VerifyNow P2Y12 assay (Accumetrics, San Diego, California) was used to test the platelet activity in all the reported studies (in 1 series, there were no data about the platelet function testing[10]).

The mean radiologic follow-up was 14 months (range, 12–24 months; median, 12 months; interquartile range = 12–24 months) and 13 months (range, 12–22 months; median, 12 months; interquartile range = 12–22 months) among the PS and CP groups, respectively. The mean clinical follow-up was 15 months for both groups.

Treatment-Related Outcomes among PS and CP Groups

Treatment-related complications were analyzed with random-effect meta-analysis because this model incorporates heterogeneity among studies. When we included all series comparing PS and CP (5 studies[7-14]), AT with PS was not significantly associated with a reduction of the overall rate of treatment-related complications (OR = 0.76; 95% CI, 0.27–2.14; P = .603; I^2 = 70.31%) (Fig 1). The funnel plot followed by the Egger linear regression test excluded publication bias (P = .798). Meta-regression showed a significant variation of the effect size (P = .001) during the investigated period (from 2013 to 2018) (On-line Fig 2). The sensitivity analysis (Fig 2 and On-line Fig 3), removing 1 study at a time, showed that the removal of the study of Akbari et al,[7] was associated with a significant reduction of the overall complication rates with the use of PS (OR = 0.51; 95% CI, 0.26–0.99; P = .047; I^2 = 32.5%). This study reported the highest dose of AT: loading-dose of 60 mg of PS + 325 mg of ASA and maintenance dose of 10 mg of PS + 325 mg of ASA.

The aneurysm occlusion rate was comparable between the 2 groups (OR = 1.21; 95% CI, 0.43–3.39; P = .723; I^2 = 60.2%) (Table).
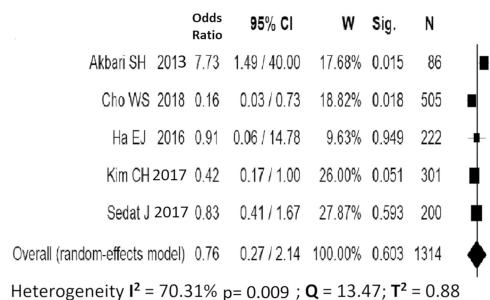
FIG 1. Forest plot with the random-effects model demonstrating the overall effect (odds ratio) of prasugrel versus clopidogrel on the treatment-related complication rate.
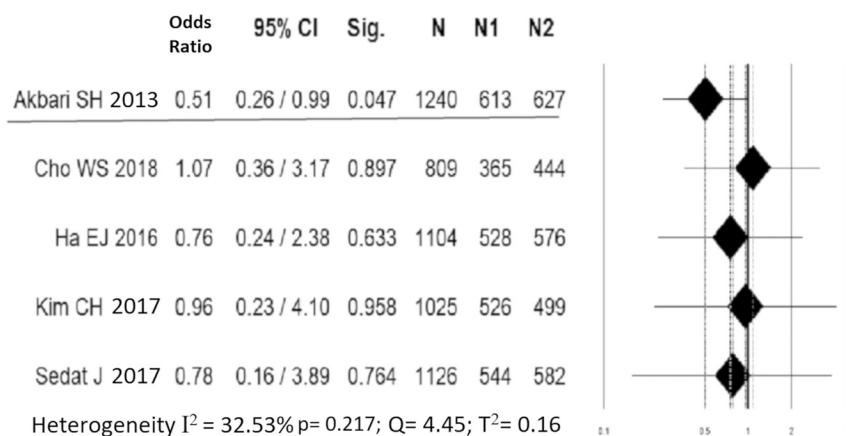
FIG 2. Sensitivity analysis (leave-one-out meta-analysis) with the random-effects model showing a significant reduction (odds ratio) of the treatment-related complications with the use of PS compared with CP after the removal of the study of Akbari et al.[7]

Treatment-related complication rates and mean values of PRU and platelet inhibition among PS and CP groups of patients

Type of Complications[a]	PS Group (95% CI)	No. of Articles	CP Group (95% CI)	No. of Articles	P Value
Permanent complications	6/651 = 1% (1–4) (I^2 = 19%)	6	11/617 = 2% (1–4) (I^2 = 81%)	12	.6
Ischemic/thromboembolic	16/682 = 2% (1–5) (I^2 = 73%)	7	40/672 = 6% (3–13) (I^2 = 83%)	5	.003[b]
Hemorrhagic	17/682 = 3% (1–9) (I^2 = 73%)	7	16/672 = 3% (1–5) (I^2 = 19%)	5	.7
Periprocedural complications	23/682 = 4% (1–11) (I^2 = 80%)	7	35/672 = 5% (2–11) (I^2 = 82%)	5	.7
Delayed complications	12/682 = 3% (1–6) (I^2 = 41%)	7	23/672 = 3% (1–8) (I^2 = 71%)	5	.8
Treatment-related mortality	0/682	7	1/617 = 0.4% (0.1–2) (I^2 = 0%)	4	.09
Good neurologic outcome	631/635 = 98% (96–99) (I^2 = 5%)	6	606/617 = 97% (97–99) (I^2 = 20%)	4	.2
Platelet inhibition values[c]					
Mean resistance rate	9/433 = 1.8% (0.5–3) (I^2 = 0%)	4	99/344 = 30% (23–33) (I^2 = 0%)	2	.001[b]
Mean PRU	125.2 (118–132) (I^2 = 0%)	3	247.8 (239–256) (I^2 = 18%)	2	.00[b]
Aneurysm occlusion rate (PS vs CP)	Odds Ratio = 1.21 (95% CI, 0.43–3.39, I^2 = 60.2%)			3	.723

[a] Complications rates were pooled using proportional meta-analysis.
[b] Significant.
[c] Platelet inhibition values were pooled using proportional meta-analysis.

		Odds Ratio	95% CI	W	Sig.	N	N1	N2
Cho WS	2018	0.16	0.03 / 0.73	23.01%	0.018	505	277	228
Ha EJ	2016	1.10	0.07 / 17.73	6.94%	0.949	222	106	116
Kim CH	2017	0.42	0.17 / 1.00	70.05%	0.051	301	118	183
PS-LD=20mg+PS-MD=5mg		0.36	0.17 / 0.74	100.00%	0.006	1028	501	527
Heterogeneity I^2= 0% p=0.41; Q= 1.83; T^2= 0								
Akbari SH	2013	7.73	1.49 / 40.00	44.25%	0.015	86	31	55
Sedat J	2017	0.83	0.41 / 1.67	55.75%	0.593	200	100	100
PS-LD=60mg+PS-MD=10mg		2.22	0.25 / 19.59	100.00%	0.472	286	131	155
Heterogeneity I^2 = 83.38 p=0.014; Q = 6.02; T^2 = 2.09								

PS-LD= prasugrel loading-dose; PS-MD= prasugrel maintenance dose

FIG 3. Subgroup analysis of the low and high doses of PS versus a standard dose of CP. Low-dose PS was associated with a significant reduction (odds ratio) of the treatment-related complication rate compared with CP.

Subgroup Analysis: Relationship between the Dose of PS and Treatment-Related Complications

Studies comparing PS and CP were dichotomized into 2 groups (low-dose versus high-dose) based on the PS loading (20 versus 60 mg) and maintenance doses (5 versus 10 mg) (Fig 3). Subgroup analysis of studies reporting a low dose (20 mg/5 mg) of PS[8,9,14] (the series of Kim et al[9] was the only study reporting 30 mg of PS as loading dose) showed a significant reduction in the complication rate (OR = 0.36; 95% CI, 0.17–74; P = .006; I^2 = 0%). On the contrary, meta-analysis of studies reporting a high dose (60 mg/10 mg) of PS[7,10] showed higher odds of complications among the PS group, though this result was not statistically significant (OR = 2.22; 95% CI, 0.25–19.59; P = .472; I^2 = 83.38%).

Low and high loading doses of PS were associated with 0.6% (5/535; 95% CI, 0.1%–1.6%; I^2 = 0%) and 9.3% (13/147; 95% CI, 0.2%–18%; I^2 = 60%) intraprocedural/very early (within 24 hours) hemorrhagic events, respectively (P = .001). Low and high maintenance doses of PS were associated with 0% (0/433) and 0.9% (2/249; 95% CI, 0.3%–2%; I^2 = 0%) hemorrhagic events during follow-up, respectively (P = .001) (On-line Table 6).

Subgroups of Treatment-Related Complications

When we investigating data about the type of complications retrieved from all the included series (7 studies), the rates of periprocedural complications, delayed complications, hemorrhagic events, treatment-related morbidity/mortality, and good neurologic outcome were comparable between the 2 groups (P > .05) (Table). On the contrary, the ischemic complication rate was significantly higher among the CP group (40/672 = 6%; 95% CI, 3%–13%; I^2 = 83% versus 16/682 = 2%; 95% CI, 1%–5%; I^2 = 73%; P = .003). When we compared the PS and CP groups, the PRU values were 125.2 (95% CI, 118–132; I^2 = 0%) and 247.8 (95% CI, 239–256; I^2 = 18%; P = .001) and the mean platelet resistance rates were 1.8% (9/433; 95% CI, 0.5%–3%; I^2 = 0%) and 30% (99/344; 95% CI, 23%–33%; I^2 = 0%) (P = .001), respectively. Meta-regression (On-line Fig 4) showed a trend toward a significant association between the ischemic complication rate and the PRU value (P = .06).

In both the prasugrel and clopidogrel groups, treatment-related complications were higher among patients treated with flow diverters or stent-assisted coiling, compared with those treated with coiling or balloon-assisted coiling. Among the prasugrel group, the overall complication rates were 7% (22/254; 95% CI, 2%–13%; I^2 = 70%) and 1.1% (3/281; 95% CI, 0.5%–13%; I^2 = 0%) after treatment with stents/flow diverters and coiling, respectively. Among the clopidogrel group, the overall complication rates were 10% (28/265; 95% CI, 3%–20%; I^2 = 90%) and 2% (5/247; 95% CI, 0.1%–4%; I^2 = 0%) after treatment with stents/flow diverters and coiling, respectively (On-line Table 7).

Study Heterogeneity

Substantial heterogeneity (>50%) was noted for the overall effect size of treatment-related complications (Fig 1) and the complication rate among the subgroup of high-dose PS (Fig 3). Among the subtypes of complications, substantial heterogeneity was reported for ischemic and periprocedural complications, permanent and delayed complications (CP group), and hemorrhagic complications (PS group) (Table). Heterogeneity was also reported for the analysis of the aneurysm occlusion rate.

DISCUSSION

Our meta-analysis of 1354 unruptured intracranial aneurysms highlighted several important findings comparing PS with CP used as an AT for endovascular treatment. Both sensitivity and subgroup analysis demonstrated that low-dose PS (loading and maintenance doses with 20 and 5 mg, respectively) was associated with a reduction of the overall rate of treatment-related complications. In addition, intra-, periprocedural, and delayed hemorrhagic events were significantly lower when the low-dose PS was used instead of the high-dose. Overall, the ischemic complication rate was significantly lower among the PS group (2% versus 6%, P = .003), and it is likely related to the lower PRU value after treatment with PS. Because clinical data of PS are limited in the field of cerebrovascular pathology, these findings are important, suggesting that low-dose PS can be safe and effective compared with CP premedication in patients undergoing endovascular treatment of intracranial aneurysms.

Previous series have demonstrated that premedication with CP (irreversible P2Y12 inhibitor) was associated with a reduction of the treatment-related ischemic events during cerebrovascular intervention.[2] While approximately 85% of CP is hydrolyzed to an inactive metabolite, about 15% of the drug is converted in the liver into the active form through the activity of the cytochrome P450 enzymes.[3] One of the main shortcomings of this drug is the variable responsiveness of individuals, related to a genetic polymorphism of cytochrome P450 2C19, one of the hepatic cytochrome P450 enzymes.[15] Accordingly, almost 30% of patients are biochemically CP-resistant, partially due to enzyme or P2Y12 receptor polymorphisms.[3] Higher PRU values have been associated with increased thromboembolic complications both after percutaneous coronary intervention[16] and in the neurointerventional field.[17]

PS is a third-generation thienopyridine (P2Y12 receptor an-

tagonist) largely used for coronary heart disease because it is associated with high efficacy and a notable decrease of ischemic events.[4] Indeed, PS is rapidly converted into the active metabolite in 1 step, without dead-end inactive pathways, with a faster onset of action and less variability in response.[4] However, data about the use of PS for the treatment of cerebrovascular disease are scanty and heterogeneous. One of the first series was described in 2013 by Akbari et al.[7] The author reported 22% and 4% of treatment-related complications in the PS and CP groups, respectively. Most complications (85%) in the PS group were hemorrhagic events. In this study, PS, 60 mg, + ASA, 325 mg, were used 1 day before the treatment, whereas PS, 20 mg, was used as a maintenance dose. However, more recent series reporting lower doses of PS showed different results. Comparing low-dose PS and a standard dose of CP in a large series of 277 (PS group) and 228 (CP group) intracranial aneurysms treated endovascularly, Cho et al[8] reported approximately 1% and 4% treatment-related complications, respectively. Similar results were achieved by other authors reporting low-dose PS with 20 and 5 mg used as loading and maintenance doses, respectively.[9,13,14]

To our knowledge, our meta-analysis is the largest study comparing the outcomes of low-dose and high-dose PS versus standard-dose CP. First, the leave-one-out sensitivity meta-analysis (it was performed by iteratively removing 1 study at a time) showed that the exclusion of the series of Akbari et al[7] resulted in a significant reduction in the overall complication rate with the use of PS (OR = 0.51; 95% CI, 0.26–0.99; P = .047) with low heterogeneity among studies (I^2 = 32.5%). As described above, this study on the series of Akbari et al[7] reported the highest dose of AT with a not negligible rate of hemorrhagic events. These findings are in accordance with the concern that larger doses of PS can be associated with higher cerebrovascular hemorrhagic risk. Accordingly, because this was one of the main concerns with the use of PS in the cerebrovascular field, we performed a subgroups analysis investigating the influence of the drug doses on the hemorrhagic intra-, periprocedural, and delayed events, based on the loading and maintenance doses of PS, respectively. Most interesting, we found that 20 mg/5 mg (low dose) of PS was associated with <1% hemorrhagic events, compared with 40–60 mg/10 mg (high dose), which was related to higher rates of bleeding events, especially in the perioperative period (9%) (On-line Table 6).

In addition, the subgroup analysis confirmed a significant reduction of the overall rate of complications exclusively in the group of patients treated with low-dose PS (OR = 0.36; 95% CI, 0.17–74; P = .006, I^2 = 0%) (Fig 3).

Finally, in our meta-analysis, both the PRU value (125 versus 247) and the mean platelet resistance rates (1.8% versus 30%) were significantly lower in the PS group. In recent studies, low-dose PS with 20 mg/5 mg (loading and maintenance doses) achieved stronger inhibition of platelet activity and a lower rate of resistance than the standard dose of CP (300 mg/75 mg).[8,18] In accordance with studies reporting a direct correlation between PRU values and ischemic complications,[2,16,17] meta-regression of all the included studies (On-line Fig 4) found a trend toward a significant association between the ischemic complication rate

and the PRU value (P = .06): The lower the PRU value, the better were outcomes in terms of ischemic complications. Accordingly, one of the main results highlighted by our meta-analysis was the effective reduction of the thromboembolic events with the use of PS: The overall rate of ischemic events was 2% and 6% in the PS and CP groups, respectively (P = .003).

Strengths and Limitations

Our study has limitations. Most series had a retrospective design. Although the heterogeneity among studies has been, in part, explained with the sensitivity and subgroup analyses, there was heterogeneity within studies related to different endovascular techniques adopted. The influence of the intraprocedural heparin administration was not evaluated. In addition, the duration and dose of ASA in conjunction with prasugrel or clopidogrel and the length of the antiplatelet therapy were not evaluated, and they can have a significant impact on the bleeding risk. The overall effect size (reduction of the treatment-related complication rate among the prasugrel group) could be overestimated due to the search strategy and terminology. However, publication bias was reasonably excluded, and our study is the largest to date comparing PS and CP for the endovascular treatment of intracranial aneurysms.

CONCLUSIONS

Compared with clopidogrel premedication, low-dose prasugrel is associated with an effective reduction of ischemic events with an acceptable rate of hemorrhagic complications. Our results support prasugrel as an alternative to clopidogrel in patients undergoing endovascular treatment of unruptured intracranial aneurysms.

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