Comparison between prasugrel and clopidogrel used as antiplatelet medication for endovascular treatment of unruptured intracranial aneurysms.

A meta-analysis.

Abstract

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

Purpose: To analyze the efficacy of prasugrel (PS) compared to clopidogrel (CP) in the cerebrovascular field.

Data Sources: A systematic search of two large databases was performed for studies published from 2000 to 2018.

Study Selection: According to PRISMA guidelines, we included studies reporting treatment-related outcomes of patients undergoing neurointerventional procedures under PS, and studies comparing PS and CP.

Data Analysis: Random-effects meta-analysis was used to pool the following: overall rate of complications, ischemic and hemorrhagic events, influence of the dose of PS.

Data Synthesis: Including 7 studies, 682 and 672 unruptured intracranial aneurysms were treated under PS (cases) and CP (controls), respectively. Low-dose (20mg/5mg) (loading and maintenance doses) of PS compared with the standard dose of CP (300mg/75mg) showed a significant reduction of the complication rate (OR=0.36,95%CI=0.17-74,p=0.006, I^2=0%). Overall, ischemic complication rate was significantly higher among the CP group (40/672=6%,95%CI=3%-13%, I^2=83% vs 16/682=2%, 95%CI=1%-5%, I^2=73%,p=0.03). 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%) of intra-periprocedural hemorrhages, respectively (p=.001), whereas 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%) of delayed hemorrhagic events, respectively (p=.001)

Limitations: Retrospective series and heterogeneous endovascular treatments.

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

Abbreviations: PS=prasugrel; CP=clopidogrel

Introduction

Prophylactic antiplatelet therapy (AT) is widely used to prevent thromboembolic complications in patients undergoing endovascular treatments 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 AT 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 CP resistance[3]. Giving that patients who are resistant to CP present higher risk of ischemic events, different types of AT have been proposed. Prasugrel (PS) (brand name Efient, Eli Lilly and Company, Indianapolis, IN, USA) is a new antiplatelet agent that has been extensively used among patients undergoing cardiovascular treatments[4]. Like CP, this drug works through the inhibition of the P2Y12 adenosine diphosphate receptors. However, differently to CP, PS requires a one step activation, allowing more effective platelet inhibition and lower degree of resistance[4]. The experience of 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 whatever 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. PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses[5]) 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 the On-line Table 2. The inclusion criteria were the following: 1) studies reporting series of patients with unruptured intracranial aneurysms endovascularly treated for whom PS was administrated as AT; 2)

studies reporting outcome comparison between PS (cases) and CP (control) used as 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 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 $P2Y_{12}$ reaction unit (PRU) value; 5) mean percentage of platelet inhibition; and 6) angiographic outcome. The reported results were compared between PS group and CP group of patients.

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

Outcomes

The primary objectives of this study were to compare treatment-related complication rate betwwen the PS group and the CP group. The secondary objectives were to define: 1) type of complications; and 2) the influence of the loading dose and maintenance dose 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 the On-line Table 3). The quality assessment was performed by two 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 was assessed by the Higgins index (I^2) and, subsequently, the DerSimonian and Laird random-effects model was applied. The graphical representation was performed by forest plot. To evaluate the heterogeneity and bias, the meta-regression and funnel plot followed by Egger's linear regression test were analyzed, respectively. To verify the consistency of outcome meta-analysis results, the influence of each individual study on the summary effect estimate was assessed by the sensitivity analysis ("leave-one-out" approach) and the sub-groups analysis. To compare the percentages of each groups and to calculate the *p-values*, the one-way analysis of variance (ANOVA) and the z-test were used when appropriate. Differences were considered significant at $p<0.05$. Meta-analysis was performed with ProMeta-2 (Internovi-Cesena-Italy) and OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta/).

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 Figure 1.

A total of 7 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 group and the CP group[7-10], whereas two studies reported series of patients exclusively treated with PS[11, 12].

Quality of Studies

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

Patient Population and Aneurysm Characteristics

Detailed characteristics of the patient population are reported in the On-line Table 4. The mean age of patients was comparable between the two groups. The proportion of male patients was higher among the PS group (56%, 95%CI=51%-59% vs 45.6%, 95%CI=41%-49%, p=.001), as well as the proportion of aneurysms in the anterior circulation (87%, 95%CI=84-89% vs 82%, 95%CI=78%-85%). Posterior circulation aneurysms were more common among the CP group (18%, 95%CI=14-21% vs 13%, 95%CI=10%-15%) (p=.01). Mean aneurysm size was comparable among the two 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% vs 54.7%, 95%CI=50%-58%) (p=.01).

In 4 studies[8, 9, 13, 14], the loading dose of PS was 20mg one day before treatment, in 2 studies[10, 12] the loading dose was between 40mg and 60mg 1 day before treatment, and in one study[7] 60mg of PS were associated with 325 mg of ASA (acetyl salicylic acid). In 3 studies[7, 9, 10], CP75mg was associated with ASA100mg or ASA325mg five days before treatment, whereas CP300mg was used alone in two studies[8, 14] five days before the procedure. The maintenance dose of PS was 5mg/day among 3 studies[8, 13, 14], 5mg-10mg/day among 2 studies[9, 12], and 10mg/day among 2 studies[7, 10]. The maintenance dose of AT in the CP group was CP75mg/day + ASA75mg-100mg/day among 4 studies[8-10, 13, 14], whereas in one study CP75mg/day was associated with ASA325mg/day[7].

Verify Now has been used to test the platelet activity in all the reported studies (in one series, there was no data about the platelet function testing[10])

The mean radiological follow-up was 14 months (range 12-24, median12, IQR=12-24) and 13 months (range 12-22, median 12, IQR=12-22) among the PS and CP group, respectively. The mean clinical follow-up was 14 months for both groups.

Treatment-related Outcomes among PS group and CP group

Treatment-related complications were analyzed with both fixed-effect and random-effect models, however the results were presented with the random-effect meta-analysis because this model incorporates heterogeneity among studies. Including all series comparing PS and CP (5 studies[7-10]), 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%) (Figure 1). The funnel-plot, followed by Egger's linear regression test, excluded publication bias (p=.798). Meta-regression showed a significant variation of the effect size (p=.001) over the investigated period (from 2013 to 2018). The sensitivity analysis (Figure 2), removing one study at the time, showed that the removal of the study of Akbari SH 2013 et al[7] determined a significant reduction of the overall complication rate 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 with 60mg of PS + 325mg of ASA, and maintenance dose with 20mg of PS + 325mg of ASA.

The aneurysm occlusion rate was comparable between the two groups (OR=0.1.21, 95%CI=0.43-3.39, p=.723, I^2 = 60.2%) (Table 1).

Sub-groups analysis: relationship between the dose of PS and treatment-related complications

Studies comparing PS and CP were dichotomized into two groups (low-dose vs high-dose) based on the PS loading (20mg vs 60mg) and maintenance doses (5mg vs 10mg) (Figure 3). Sub-group analysis of studies reporting low-dose (20mg/5mg) of PS[8, 9, 14] showed a significant reduction of the complication rate (OR=0.36, 95%CI=0.17-74, p=.006, I^2 = 0%). Contrariwise, meta-analysis of studies reporting high-dose (60mg/10mg) of PS[7, 10] showed a higher odds of complications among the PS group, although this result was not statistical 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%) of 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%) of hemorrhagic events during follow-up, respectively (p=.001) (On-line Table 5).

Sub-groups of treatment-related complications

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 neurological outcome were comparable between the two groups (p>0.05) (Table 1). Contrariwise, ischemic complication rate was significantly higher among the CP group (40/672=6%, 95%CI=3%-13%, I^2=83% vs 16/682=2%, 95%CI=1%-5%, I^2=73%, p=0.03). Comparing PS group and CP group, the PRU (platelet reactivity units) value was 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 rate was 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 Figure 2) showed a trend toward a significant association between the ischemic complication rate and the PRU value (p=.06).

Study Heterogeneity

Substantial heterogeneity (>50%) was noted for the: overall effect size of treatment-related complications (Figure 1) and the complication rate among the sub-group of high-dose of PS (Figure 3). Among the sub-types of complications, substantial heterogeneity was reported for the: ischemic and periprocedural complications, permanent and delayed complications (CP group), and hemorrhagic complications (PS group) (Table 1). 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 AT for the endovascular treatments. Both sensitivity and sub-groups analysis demonstrated that low-dose of PS (loading and maintenance doses with 20mg and 5mg, 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 of PS was used instead of the high-dose. Overall, ischemic complication rate was significantly lower among the PS group (2% vs 6%, p=0.03), and it is likely related to the lower PRU value after treatment with PS. Because clinical data of PS is limited in the field of cerebrovascular pathology, these findings are important suggesting that low-dose of PS can be safe and effective

compared to CP premedication in patients undergoing endovascular treatment of intracranial aneurysms.

Previous series demonstrated that premedication with CP (irreversible $P2Y_{12}$ inhibitor) was associated with a reduction of the treatment-related ischemic events during cerebrovascular intervention[2]. While approximately 85% of CP is hydrolyzed to 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 CYP2C19, one of the hepatic cytochrome P450 enzymes[15]. Accordingly, almost 30% of patients are biochemically CP-resistant, partially due to enzymes or $P2Y_{12}$ receptors 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 ($P2Y_{12}$ receptor antagonist) largely used for coronary heart disease because associated with high efficacy and a significant decrease of ischemic events[4]. Indeed, PS is rapidly converted into the active metabolite in one step, without dead-end inactive pathways, displaying a faster onset of action and less variability in response[4]. However, data about the use of PS for the treatment of cerebrovascular disease is 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 among the PS and CP group, respectively. Most of the complications (85%) among the PS group were hemorrhagic events: in this study, PS60mg + ASA325mg were used one day before the treatment, whereas PS20mg was used as maintenance dose. However, more recent series reporting lower dose of PS, showed different results. Comparing low-dose of PS and 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% of treatment-related complications, respectively. Similar results were achieved by other authors reporting low-dose of PS with 20mg and 5mg used as loading and maintenance doses, respectively[9, 13, 14].

To our knowledge, our meta-analysis is the first largest study comparing the outcomes of low-dose and high-dose of PS vs standard dose of CP. First of all, the "leave-one-out" sensitivity meta-analysis (it was performed by iteratively removing one study at a time) showed that the exclusion of the series of Akbari SH et al[7] determined a significant reduction of the overall complication rate with the use of PS (OR=0.51, 95% CI=0.26-0.99, p=.047) with low heterogeneity between studies (I^2=32.5%). As described above, this study reported the highest dose of AT with a not negligible rate of hemorrhagic events. Moreover, patients included in this study were quite heterogeneous, with approximately 10% of them underwent other endovascular treatments (dural arteriovenous fistula or extra-intracranial carotid angioplasty and stenting). These findings are in accordance with the concern that greater doses of PS can be associated with higher cerebrovascular hemorrhagic risk. Accordingly, because this was one of main concern of the use of PS in the cerebrovascular field, we performed a sub-groups 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. Interestingly, we found that 20mg/5mg (low-dose) of PS were associated with less than 1% of hemorrhagic events, comparing to 40-60mg/10mg (high-dose) that was related with higher rates of bleedings events, especially in the perioperative period (9%) (On-line Table 5).

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

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

ischemic complication rate and the PRU value (p=.06): the lower PRU value, the better 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).

Strength and Limitations

Our study has limitations. Most of series present a retrospective design. Although the heterogeneity between studies has been in part explained with the sensitivity and sub-group analysis, it is important to point out that there was heterogeneity within studies related to different endovascular techniques adopted. The influence of the intraprocedural heparin administration was not evaluated. However, publication bias was reasonably excluded, and our study is the largest today comparing PS and CP for the endovascular treatment of intracranial aneurysms.

Conclusions

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

References

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Figure Legend

Figure 1. (A, B, C, D). Forest plot with fixed-effect (A) and random-effect (B) models demonstrating the overall effect of prasugrel vs clopidogrel on the treatment-related complication rate. The funnel plot followed by Egger's linear regression test excludes publication bias (C). Meta-regression showed a significant variation of the effect size (D) over the investigated years.

Figure 2. (A, B, C, D). Sensitivity analysis (leave-one-out meta-analysis) with fixed (A) and random-effect models (B) showing a significant reduction of the treatment-related complications with the use of PS compared to CP after the removal of the study of Akbari SH et al. Excluding the study of Akbari SH et al, the funnel plot followed by Egger's linear regression test excludes publication bias (C), and the meta-regression showed a non-significant variation of the effect size (D).

Figure 3. Sub-groups analysis of the low and high doses of PS vs standard dose of CP. Low-dose of PS was associated with a significant reduction of the treatment-related complication rate when compared with CP.

On-line Figure 1. PRISMA diagram detailing the specifics of the systematic literature review

On-line Figure 2. Meta-regression showing a significant decrease of the ischemic complications rate in relation to the mean PRU value.

Figure 1

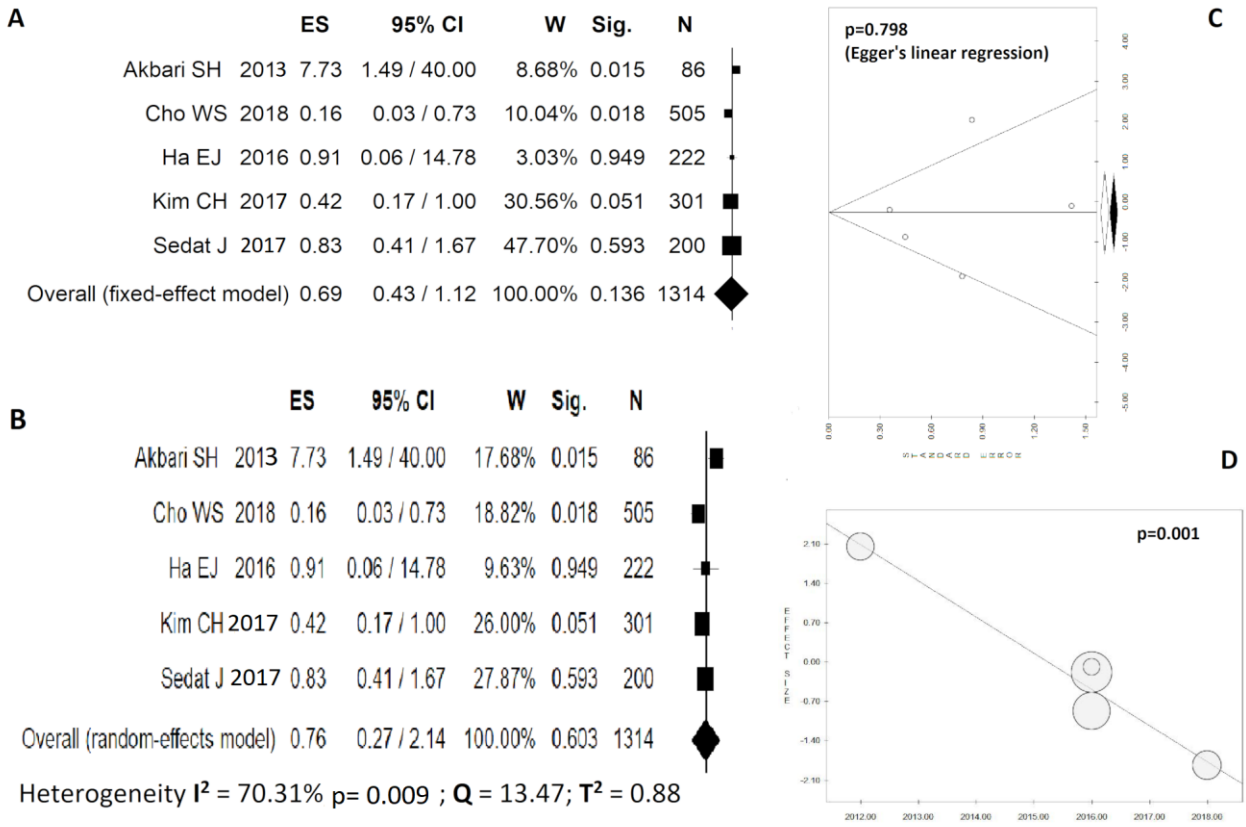

A
ES 95% CI W Sig. N
Akbari SH 2013 7.73 1.49 / 40.00 8.68% 0.015 86
Cho WS 2018 0.16 0.03 / 0.73 10.04% 0.018 505
Ha EJ 2016 0.91 0.06 / 14.78 3.03% 0.949 222
Kim CH 2017 0.42 0.17 / 1.00 30.56% 0.051 301
Sedat J 2017 0.83 0.41 / 1.67 47.70% 0.593 200
Overall (fixed-effect model) 0.69 0.43 / 1.12 100.00% 0.136 1314
B
ES 95% CI W Sig. N
Akbari SH 2013 7.73 1.49 / 40.00 17.68% 0.015 86
Cho WS 2018 0.16 0.03 / 0.73 18.82% 0.018 505
Ha EJ 2016 0.91 0.06 / 14.78 9.63% 0.949 222
Kim CH 2017 0.42 0.17 / 1.00 26.00% 0.051 301
Sedat J 2017 0.83 0.41 / 1.67 27.87% 0.593 200
Overall (random-effects model) 0.76 0.27 / 2.14 100.00% 0.603 1314
Heterogeneity I² = 70.31% p= 0.009 ; Q = 13.47; T² = 0.88
C
p=0.798
(Egger's linear regression)
D
p=0.001

Figure 2

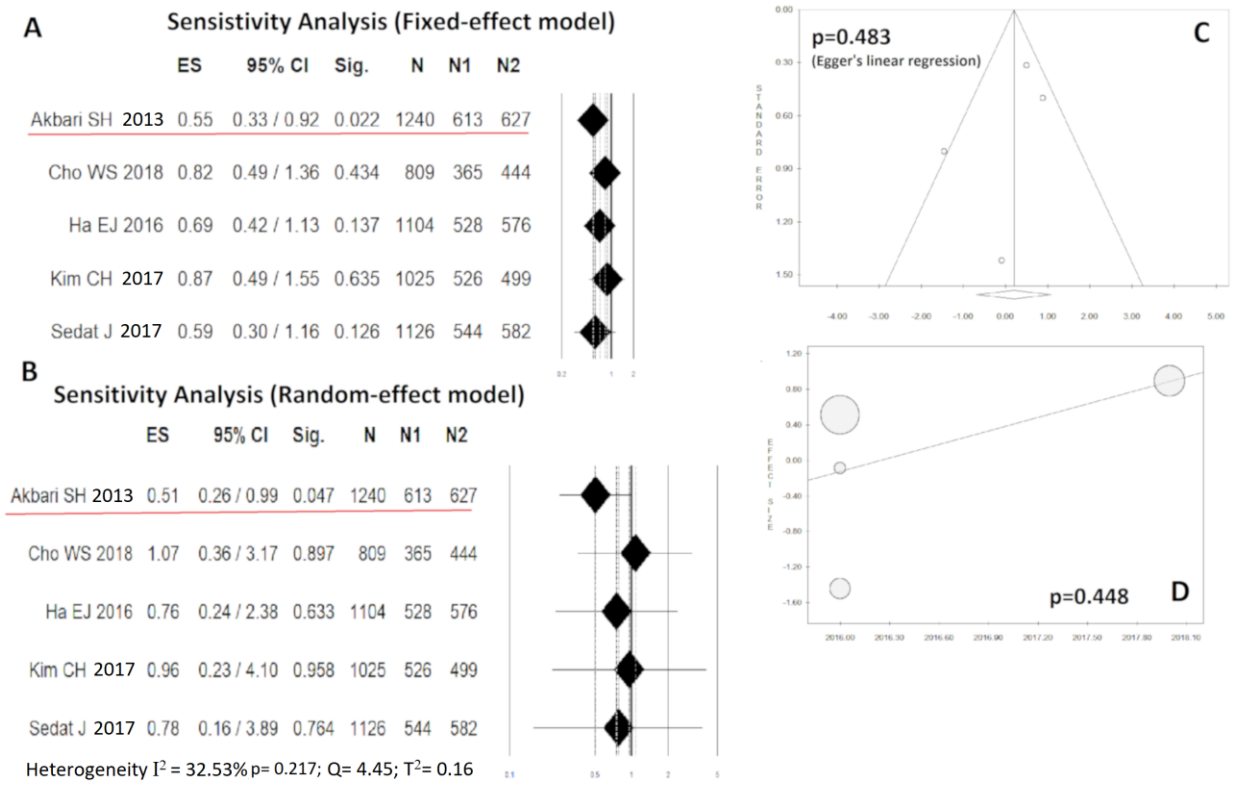
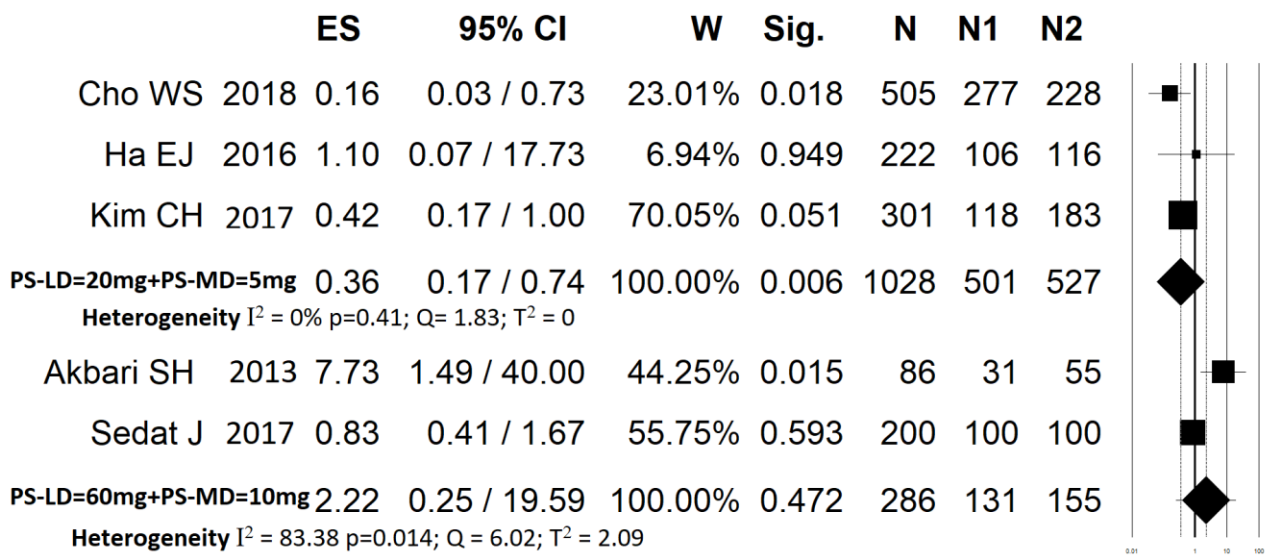

A
Sensistivity Analysis (Fixed-effect model)
ES 95% CI Sig. N N1 N2
Akbari SH 2013 0.55 0.33 / 0.92 0.022 1240 613 627
Cho WS 2018 0.82 0.49 / 1.36 0.434 809 365 444
Ha EJ 2016 0.69 0.42 / 1.13 0.137 1104 528 576
Kim CH 2017 0.87 0.49 / 1.55 0.635 1025 526 499
Sedat J 2017 0.59 0.30 / 1.16 0.126 1126 544 582
B
Sensitivity Analysis (Random-effect model)
ES 95% CI Sig. N N1 N2
Akbari SH 2013 0.51 0.26 / 0.99 0.047 1240 613 627
Cho WS 2018 1.07 0.36 / 3.17 0.897 809 365 444
Ha EJ 2016 0.76 0.24 / 2.38 0.633 1104 528 576
Kim CH 2017 0.96 0.23 / 4.10 0.958 1025 526 499
Sedat J 2017 0.78 0.16 / 3.89 0.764 1126 544 582
Heterogeneity I² = 32.53% p= 0.217; Q= 4.45; T²= 0.16
p=0.483
(Egger's linear regression)
C
STANDARD ERROR
p=0.448
D
EFFECT SIZE

Figure 3



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

On-line Table 1. Search syntax

PubMed search accessed on 20 October 2018 (24 studies)	**Embase search accessed on 20 October 2018 (37 studies)**
((Prasugrel[Title/Abstract] AND intracranial aneurysms[Title/Abstract]) OR (Prasugrel[Title/Abstract] AND endovascular[Title/Abstract])) OR ((prasugrel[Title/Abstract] AND clopidogrel[Title/Abstract]) AND aneurysms[Title/Abstract])	'prasugrel':ti,ab,kw AND 'intracranial aneurysm':ti,ab,kw OR ('prasugrel':ti,ab,kw AND 'endovascular':ti,ab,kw) OR ('prasugrel':ti,ab,kw AND 'clopidogrel':ti,ab,kw AND 'aneurysms':ti,ab,kw)

On-line Table 2. Summary of studies included in meta-analysis

Study Name	Design	N pts/N of aneurysms (PS group)	N pts/N of aneurysms (CP group)	PS loading dose	CP loading dose	PS Maintenance dose	CP Maintenance dose	Overall Complications (PS group)	Overall Complications (CP group)	Quality of Studies (NOS)
Akbari SH, 2013[7]	R	31/31	55/55	PS 60 mg 1 day before + ASA 325 mg	CP 75 mg + ASA 325 mg 7 days before	PS 10 mg /day	CP 75 mg/day + ASA 325 mg/day	7/31 (6ICH+1thromboembolism)	2/55 (2ICH)	6
Stetler WR, 2013[12]	R	16/16	NA	PS 40 mg 1 day before	NA	PS 5-10 mg /day	NA	1/16 (retroperitoneal hematoma)	NA	3
Ha EJ, 2016[14]	R	98/116	96/106	PS 20 mg 1 day before + PS 5 mg int the morning of the procedure	CP 300 mg 1 day before + CP 75 mg in the morning of the procedure	PS 5 mg/ day for 3 months, after ASA lifelong	CP 75 mg/day + ASA 100 mg/day for at least 3 months	1/116 (aneurysm perforation)	1/106 (aneurysm perforation)	6
Kim CH, 2017[9]	P	118/118	183/183	PS 30 mg 1 day before	CP 75 mg CP + ASA 100 mg 5 days before	PS 5-10 mg /day	CP 75 mg/day + ASA 100 mg/day for at least 3 months	7/118 (2thromboembolisms+5ICH)	24/183 (16thromboembolisms+ 8ICH)	8
Sedat J, 2017[10]	R	100/100	100/100	PS 60 mg 1 day before	CP 75 mg + ASA 75 mg 7 days before	PS 10 mg /day for 6 months	CP 75 mg/day + ASA 75 mg/day for at least 6 months	18/100 (1aneurysm perforation+3ICH+2groin hematoma+12thromboembolisms)	21/100 (1aneurym perforation+1ICH+2groin hematoma+17thromboembolisms)	6
Lee D, 2018[13]	R	24/24	NA	PS 20 mg 1 day before	NA	PS 5 mg /day	NA	0/24	NA	3
Cho WS, 2018[8]	R	225/277	186/228	PS 20 mg 1 day before	CP 300 mg 1 day before	PS 5 mg / day for 3 months, after ASA lifelong	CP 75 mg/day + ASA 100 mg/ day (or triple AT) for at least 3 months, after ASA lifelong	2/277 (1thromboembolism+1ICH)	10/228 (7thromboembolisms+3 ICH)	6

R=retrospective study; P=prospective study; Pts=patients; CP=clopidogrel; ASA= Acetylsalicylic acid; AT=antiplatelet therapy; PS= Prasugrel

On-line Table 3. Quality measure of included studies by the Newcastle-Ottawa quality assessment scale

Study Name	Selection				Comparability		Exposure			Total
	1)	2)	3)	4)	a)	b)	1)	2)	3)	
RETROSPECTIVE DESIGN (score 0 to 9; "high-quality"=studies with 6 or more stars)										
Akbari SH, 2013[7]	*	*		*	*		*	*		6
Stetler WR, 2013[12]	*	*					*			3
Ha EJ, 2016[14]	*	*		*	*		*	*		6
Sedat J, 2017[10]	*	*		*	*		*	*		6
Lee D, 2018[13]	*	*					*			3
Cho WS, 2018[8]	*	*		*	*		*	*		6
Study Name	**Selection**				**Comparability**		**Outcome**			**Total**
	1)	**2)**	**3)**	**4)**	a)	b)	**1)**	**2)**	**3)**	
PROSPECTIVE DESIGN/COHORT (score 0 to 9; "high-quality"=studies with 6 or more stars)										
Kim CH, 2017[9]	*	*	*	*	*		*	*	*	8

Each star (*) indicates one point of the scale

Note= a) Comparability (point A) was tested comparing treatment-related outcomes among the Prasugrel group and the Clopidogrel group.
b) Comparability (point B) was tested comparing the secondary outcomes (type of complications, aneurysm occlusion, platelet inhibition value) among patients treated with Prasugrel vs patients treated with Clopidogrel.

On-line Table 4. Characteristics of patients with intracranial aneurysms treated endovascularly: comparison between antiplatelet therapy with prasugrel and clopidogrel.

Variables	*Patients under Prasugrel (95% CI)*	*Patients under Clopidogrel (95% CI)*	*p-value*
Total of studies	***7***	***5***	
N of Patients	**612**	**620**	
N of aneurysms/procedures	**682**	**672**	
Mean Age (years)	**57**, range 20-70	**56**, range 19-73	0.3
Male/Overall population	342/612**=56%** (51-59)	283/620**=45.6%** (41-49)	**0.001**
Aneurysm Location **Anterior Circulation** **Posterior Circulation**	 557/641= **87%** (84-89) 84/641= **13%** (10-15)	 456/571= **82%** (78-85) 99/571= **18%** (14-21)	 **0.01** **0.01**
Mean aneurysm size	7mm (3-21)	8mm (3-23)	0.2
Type of Treatment **Coiling/BAC** **SAC/FD**	 245/672=**36.4%** (32-40) 427/672=**63.6%** (58-67)	 259/571=**45.3%** (41-49) 312/571=**54.7%** (50-58)	 **0.002** **0.001**
Mean radiological follow-up (months)	Median 12 IQR (12-24) Mean 14	Median 12 IQR (12-22) Mean 13	
Mean clinical follow-up (months)	Median 14 IQR (11-23) Mean 15	Median 14 IQR (13-24) Mean 14	

BAC= balloon-assisted coiling; SAC=stent-assisted coiling; FD=flow-diverter

On-line Table 5. Hemorrhagic complication rate after low-dose and high-dose of prasugrel.

Periprocedural outcomes related to the dose of PS	**PS 20mg one day before treatment (LOW-DOSE)**	**PS 40mg-60mg one day before treatment * (HIGH-DOSE)**	**P value**
Intraprocedural/very early hemorrhagic complications (CI) [I^2]	5/535=**0.6%** (0.1-1.6) [I^2 =0%] (4 articles)	13/147=**9.3%** (0.2-18) [I^2 =60%] (3 articles)	**0.001**
Delayed outcomes related to the dose of PS	**PS 5mg / day after treatment (LOW-DOSE)**	**PS 10 mg / day after treatment (HIGH-DOSE)**	
Delayed hemorrhagic complications (CI) [I^2]	0/433=0**%** (4 articles)	2/249=**0.9%**** (0.3-2) [I^2 =0%] (3 articles)	**0.001**

PS= Prasugrel,

*In one study, patients were treated with ASA 325 mg + PS 60 mg 1 day before treatment

**Two cases of groin hematoma

CI= confidence interval ; $I^{2=}$ heterogeneity , ASA= acetylsalicylic acid: PS= prasugrel

Table 1. Treatment-related complication rate, mean value of PRU and mean value platelet inhibition among PS group and CP group of patients

TYPE OF COMPLICATIONS	PS group (95% CI)	*N* of Articles	CP group (95% CI)	N of Articles	P value
Permanent complications	6/651=**1%** (1-4) [I^2=19%]	6	11/617= **2%** (1-4) [I^2=81%]	12	0.6
Ischemic/Thromboembolic	16/682=**2%** (1-5) [I^2=73%]	7	40/672=**6%** (3-13) [I^2=83%]	5	**0.003**
Hemorrhagic	17/682=**3%** (1-9) [I^2=73%]	7	16/672=**3%** (1-5) [I^2=19%]	5	0.7
Periprocedural complications	23/682=**4%** (1-11) [I^2=80%]	7	35/672=**5%** (2-11) [I^2=82%]	5	0.7
Delayed complications	12/682=**3%** (1-6) [I^2=41%]	7	23/672=**3%** (1-8) [I^2=71%]	5	0.8
Treatment-related mortality	0/682	7	1/617=**0.4%** (0.1-2) [I^2=0%]	4	0.09
Good Neurological Outcome	631/635= **98%** (96-99) [I^2=5%]	6	606/617= **97%** (97-99) [I^2=20%]	4	0.2
PLATELET INHIBITION VALUES	**PS group (95% CI)**	***N* of Articles**	**CP group (95% CI)**	**N of Articles**	**P value**
Mean Resistance Rate	9/433= **1.8%** (0.5-3) [I^2=0%]	4	99/344= **30%** (23-33) [I^2=0%]	2	**0.001**
Mean PRU	**125.2** (118-132) [I^2=0%]	3	**247.8** (239-256) [I^2=18%]	2	**0.001**
ANEURYSM OCCLUSION RATE (PS vs CP)	**1.21** (95%CI=0.43-3.39, I^2=60.2%)			3	0.723

PS= prasugrel; CP= clopidogrel, PRU= platelet reactivity unit