Ticagrelor versus Clopidogrel in Stent-assisted Coil Embolization of Unruptured Intracranial Aneurysms

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Research Article

Keywords: Ticagrelor, stent-assisted coiling, intracranial aneurysm, endovascular embolization, dual antiplatelets.

Posted Date: March 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-288126/v1

Version of Record: A version of this preprint was published at Interventional Neuroradiology on November 18th, 2021. See the published version at https://doi.org/10.1177/15910199211054959.

Abstract

Background: In order to prevent thromboembolic events, dual antiplatelet therapy (DAPT) is widely used in stent-assisted coil embolization (SACE) for unruptured intracranial aneurysms (UIAs). Compared to clopidogrel associated with aspirin, knowledge of the safety and efficacy of ticagrelor are lacking in large studies to this date.

Methods: A retrospective cohort study from January 2016 to December 2018 with at least one year follow in a single institution and systemic review.

Results: Altogether 153 patients with UIA receiving SACE were separated into two groups: 113 patients receiving clopidogrel plus aspirin and 40 patients receiving ticagrelor plus aspirin. Acute in-stent thrombosis events were noted in 2 patients in the clopidogrel group (1.77%) and none in the ticagrelor group (0%). Another 1 patient (0.88%) in the clopidogrel group had an early ischemic stroke (<3 months). Delayed ischemic stroke was noted in 6 patients (5.31%) in the clopidogrel group and 3 patients (7.50%) in the ticagrelor group. There was no major hemorrhagic event in either group. The two groups had no significant differences with regard to ischemic stroke or hemorrhagic stroke.

Conclusion: Compared to the clopidogrel based regimen, ticagrelor can reduce thromboembolic events without increasing bleeding tendency for stent-assisted coil embolization of unruptured intracranial aneurysms. Ticagrelor plus aspirin is a safe and effective alternative option for SACE.

Introduction

Endovascular techniques, especially stent-assisted coil embolization (SACE), has been widely applied for the treatment of unruptured intracranial aneurysms (UIAs) [1–3]. Coil embolization under stent protection can not only increase the occlusion rate but also reduce the recurrence of the aneurysm [2, 4–9]. However, thromboembolic events (TE) remain major complications after stent implantation [10–14]. Clopidogrel associated with aspirin as the dual antiplatelet therapy (DAPT) was the most common regimen and routinely used for prevention [15–17]. Clopidogrel resistance is known to occur in up to 30%-44% of the population, which depends on genetic predispositions, comorbidities, concomitant drug administration, age, race, etc.[15–17] Because patients who are resistant to clopidogrel have a higher risk of TE [4, 8, 9], different types of antiplatelet agents are substituted. DAPT as aspirin plus ADP P2Y12 inhibitor ticagrelor have been proven safe, efficacious, and reduce the incidence of ischemic events compared with clopidogrel in acute coronary syndromes [18–20]. The use of ticagrelor remains limited in the field of cerebrovascular diseases because of the lack of large clinical data for DAPT in SACE of UIA. Only a few studies have reported the results of ticagrelor in flow diverter stents [21]. Herein, we performed a comparative study to demonstrate the safety and efficacy against TE between clopidogrel and ticagrelor for aneurysms undergoing SACE.

Methods

Study design

This was a retrospective cohort study from January 2016 to December 2018. We compared two consecutive groups of patients who had unruptured intracranial aneurysms (UIAs) treated by SACE with at least one year of follow-up. Ruptured aneurysms and aneurysms treated by surgical clipping, endovascular intervention without stents (simple coiling or balloon-assisted coiling), and flow diverters were excluded from this study. Patients who did not complete the full course of DAPT or lost to follow-up were also excluded. Informed consent was obtained from all patients after a detailed consultation that delineated the risks, benefits, and alternatives of the procedures as part of multidisciplinary neurosurgical and neurointerventional decision-making. The database of all patients and endovascular procedures were retrospectively reviewed to identify the patients. All methods were pledged to perform in accordance with the ethical regulations. The study was granted by our institution (no. CMRPG3H0741) and approved institutional review board (IRB no. 201800342B0).

DAPT protocol and clinical follow up

In total, 153 patients with 168 UIAs received SACE. We divided them into two groups, with 113 patients receiving clopidogrel plus aspirin (clopidogrel group) and 40 patients receiving ticagrelor plus aspirin (ticagrelor group). All stent-assisted coil embolization (SACE) procedures were performed by 4 experienced neurointerventionalists.

DAPT was administered 1 week before embolization. In the clopidogrel group, patients received daily dose of 75 mg of aspirin and 75 mg clopidogrel, administered orally. In the ticagrelor group, patients received a daily dose of 75 mg of aspirin and 180mg of ticagrelor. All patients in both groups were admitted for preoperative surveys, including hemogram, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet function test (closure time: Col/EPI & Col/ADP), CXR, and EKG. SACE was performed in the same angiography room. After the procedure, DAPT was continued for 3 months and then shifted to a single antiplatelet agent (aspirin) for at least 12 months. The patients were closely followed up at the outpatient department. Follow-up imaging studies included digital subtraction angiography (DSA) or magnetic resonance angiography (MRA), carried out after 1 year.

Outcome measurements

1. Baseline characteristics: We reviewed medical records and compared two groups with regard to age, gender, personal history, past history, aneurysm numbers, sizes, types, locations, laboratory data (including hemogram, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet function test (closure time: Col/EPI & Col/ADP).
2. Thromboembolic events: We measured the occurrence of TE and divided the events into acute in stent thrombosis and early and delayed ischemic strokes. Early ischemic stroke includes all ischemic events, such as acute in stent thrombosis, transient ischemic attack (TIA), and infarction, occurring

within 3 months (covered by DAPT); delayed stroke occurred 3 months after embolization (covered by aspirin only).

3. Bleeding events: We measured the occurrence of bleeding events that were divided into major events and minor events. Major bleeding events include intracranial hemorrhage or gastrointestinal bleeding, which require invasive treatment. On the other hand, minor events include spontaneous skin ecchymosis, epistaxis, and hemorrhoid bleeding during DAPT.

Statistical analyses

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as values and percentages, and continuous variables are summarized as the means and standard deviation groups. Baseline characteristics of all patients were assessed and compared between the two groups using the chi-square test or Fisher's exact test for categorical variables and independent sample t-test for parametric variables. To assess and compare thromboembolic events or hemorrhagic complications between the two groups, we used a subgroup analysis and percentage analysis with binomial distribution. In all analyses, p values ≤ 0.05 were defined as statistically significant. Angiographic and clinical data were reviewed by noninterventionist authors, and the collected data were analyzed by a statistician.

Results

Baseline characteristics

Finally, we enrolled 153 patients who received SACE for grouping and retrospective analysis. Among these patients, were 113 receiving clopidogrel plus aspirin (clopidogrel group) and 40 receiving ticagrelor plus aspirin (ticagrelor group). The baseline characteristics and past history are listed in Table 1. In the clopidogrel group, there were 49 men and 64 women; in the ticagrelor group, there were 12 men and 28 women. The average age was 54.45 versus 56.39-years-old. There was no significant difference between the two groups. As for laboratory data, platelet count and platelet function test were also no significant difference between two groups. Table 1 also demonstrates the location of the 168 aneurysms within 153 patients. There was also no significant difference between the clopidogrel and ticagrelor groups.

Safety

In total, there were 12 TE (7.84%) noted in our study, including 9 patients in the clopidogrel group and 3 patients in the ticagrelor group (Table 2). Two patients in the clopidogrel group had acute stent thrombosis (1.77%). No acute stent thrombosis occurred in the ticagrelor group. Only one other patient (0.88%) had an early ischemic stroke that occurred within 3 months in the clopidogrel group (a total of 3 patients, 2.65%, having an early stroke); none occurred in the ticagrelor group. Delayed ischemic stroke occurred in 9 patients (5.88%), including 6 patients (5.31%) in the clopidogrel group and 3 patients (7.50%) in the ticagrelor group. There was one patient noted to have infarction and hemorrhagic transformation in the ticagrelor group. Major hemorrhagic events did not occur in either group (Table 3).

Minor bleeding, such as skin ecchymosis, epistaxis, and hemorrhoid bleeding, occurred in 13 patients (8.50%), including 9 patients (7.96%) in the clopidogrel group and 4 patients (10%) in the Ticagrelor group. The two groups had no significant difference with regard to TE (early: $p = 0.236$; total: $p = 0.215$) or hemorrhagic events ($p = 0.744$).

Discussion

Over time, dealing with thromboembolic complications related to neuroendovascular procedures, since the first detachable stent was introduced in 1991, has remained a challenge [22]. Finding more potent antiplatelet medications could make these procedures much safer and allow neurointerventionalists to use longer stents with confidence. Routinely, aspirin plus clopidogrel as DAPT has been used for prevention. However, a previous study indicated that antiplatelet resistance of clopidogrel might be related to TE [14-16]. The effectiveness of ticagrelor in preventing thromboembolic complications of endovascular procedures has been proven in coronary disease patients [18-20]. Therefore, ticagrelor might be an alternative prophylactic medication and we hope it can replace clopidogrel. To the best of our knowledge, the use of ticagrelor in neurovascular procedures was first published in 2014. Hanel et al. prescribed ticagrelor for 18 patients who were non-responders to clopidogrel and underwent neurointervention. All patients showed immediate platelet inhibition after a loading dose of 180 mg of ticagrelor, with no adverse effects. Ticagrelor offers an effective alternative to clopidogrel non-responders [23]. Narata et al. published a retrospective single-center study of 154 consecutive patients with unruptured aneurysms in 2019. This study compared aspirin plus ticagrelor between flow diverter and stent-assisted coiling. In total, 41 patients underwent stent-assisted coiling. Nine patients (5.8%) presented with symptomatic neurological complications post-stenting (3 ischemic, 6 hemorrhagic) [21]. According to these two studies, ticagrelor has adequate potency to prevent TE in SACE and is not inferior to clopidogrel. It may be a safer alternative option if the patient has a poor response to clopidogrel, but the number of cases remains small.

In the current study, platelet function test is no statistical differences between two groups according to preoperative laboratory data. On the other hands, the P2Y12 reaction unit value and Ticagrelor prescription were not routinely checked covered in guideline and also not covered by national health insurance which cause socioeconomic burden. Therefore, it’s difficult to set the randomize control grouping to choose patients who have received Ticagrelor protocol. However, Ticagrelor was prescribed in the patients who have risk factors of TE in the current study. Risk factors of TE after neuro-intervention of UIA were proposed and well explained in the several studies. In patient’s demography and past history, TE occurred more frequently in patients with vascular status associated with old age, diabetes, dyslipidemia and previous stroke. In characteristics of aneurysms, increased TE were noted when manage wide-neck and/or large aneurysms may be due to complex techniques and longer procedure time. Based on aforementioned evidence-based factors, we made the decision to have chosen patients who have received ticagrelor protocol in current study. Besides, the patients with previous allergy history of Clopidogrel were prescribed Ticagrelor.

As for the results of hemorrhagic events and adverse events, we used minor bleeding events to describe ecchymosis, epistaxis, or hemorrhoids. However, some patients complained of gastralgia, constipation, nausea/vomiting, or dizziness. In our opinion, those seen as adverse events were related to antiplatelet usage and affected patient compliance. For a further evaluation of the TE associated with dual antiplatelet therapy in SACE, we conducted a literature review. We searched PubMed using the terms “stent-assisted coil embolization and intracranial aneurysm”. We limited our search to articles published from January 1, 2013 to December 31, 2019. In total, 21 studies (shown in Table 4) were selected for the analysis [7-9, 12, 21, 23-37]. Studies with ruptured aneurysms or endovascular procedures without stenting were excluded. Aspirin plus clopidogrel was used in most of the studies (20 studies, 95.2%). Two studies used ticagrelor and three studies used prasugrel. In total, TE rates ranged from 0 to 22.22% in SACE, with an average of approximately 9.94%. Compared to our results, early thromboembolic event rates were 2.65%. Our findings revealed good results, but still fell within the average range of previously published papers. In the limited literature, the rate of ischemic stroke after ticagrelor therapy was only 0–1.9% (excluding the flow diverter). Although there is no statistical significance between clopidogrel and ticagrelor, ticagrelor may tend to have stronger potency in terms of reducing acute TE when compared with clopidogrel. This trend was also observed in other studies. On the other hand, there are some disadvantages regarding the clinical use of ticagrelor, including the cost of medication and patient compliance (for twice a day doses) [38].

Limitations

This study has some limitations. First, there are relatively fewer cases in the cohort study, since the effect of other variables may have been underestimated. In the comparison of these two groups, there are much fewer cases in the ticagrelor group. Otherwise because of the clinically lower thromboembolic risk, the P2Y12 reaction unit value was not routinely checked and covered by national health insurance. Therefore, the true percentage of clopidogrel resistance was unknown. In order to create clinical guidelines, a prospective randomized controlled study is warranted to prove the effectiveness and safety of clopidogrel and ticagrelor.

Conclusion

According to our study, ticagrelor plus aspirin is a safe and effective dual antiplatelet therapy. Compared to a clopidogrel-based regimen, ticagrelor can also reduce thromboembolic events without increasing bleeding tendency in the stent-assisted coil embolization of unruptured intracranial aneurysms. Ticagrelor plus aspirin is an alternative option. Further large studies are still warranted to validate the results and render stent-assisted coil embolization much safer.

List Of Abbreviations

SACE: stent-assisted coil embolization; UIA: unruptured intracranial aneurysm; DAPT: dual antiplatelet therapy.

Declarations

Ethics approval and consent to participate: The study was a retrospective review. Informed consent was obtained from all patients after a detailed consultation that delineated the risks, benefits, and alternatives of the procedures, as part of multidisciplinary neurosurgical and neurointerventional decision-making. All methods were pledged to perform in accordance with the ethical regulations. The study was approved by the institutional review board (201800342B0) by Chang Gung Memorial Hospital, Linkou Medical Center.

Consent for publication: All images or clinical details in the study are presented anonymously.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: All authors certify that there are no actual or potential competing interests in relation to this article, and there are no financial interests to disclose.

Funding: This work was supported by a grant from Chang Gung Memorial Hospital, Taiwan CMRPG3H0741 (CCC).

Acknowledgments

The authors thank Chen-Ying Liu for assisting in the endovascular procedures. We also acknowledge Editage Academic Editing Services Co. for editing the manuscript.

Authors contribution statement

S.C. performed the conception of the study, analysis and interpretation of the data, and drafting the original article. C.C. contributed to the design of the study, acquisition of data, analysis and Interpretation of data, critically revising the article, approved the final version of the manuscript, statistical analysis, and study supervision. C.T. contributed to review and editing of various drafts and enrolment of patients. A.Y.C had technical support, design of the study and enrolment of patients. C.H. reviewed and edited of various drafts and material support. C.Y. had technical and material support of this study. H.L. had material support of this study. C.W. had material support of this study. T.L. had material support of this study. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics in patients and aneurysms location undergo stent-assisted coiling

	Clopidogrel	Ticagrelor	Total	P value
Patients no.	113	40	153	NA
Aneurysms no.	124	44	168	NA
Procedure no.	113	40	153	NA
Male	49	12	61	0.188
Female	64	28	92	0.188
Age	54.45±13.64	56.39±10.272		0.351
Underlying diseases				
Hypertension	36	17	53	0.249
DM	7	2	9	1.000
Dyslipidemia	8	2	10	1.000
CVA	9	3	12	1.000
CAD	1	0	1	1.000
ESRD	1	0	1	1.000
Aneurysm location				
ICA	46	20	66	0.355
ACA	11	4	15	1.000
MCA	13	3	16	0.564
P-com A	13	7	20	0.413
A-com A	21	4	25	0.319
Posterior circulation	20	6	26	0.810
Platelet function: Col/EPI (82~150) Col/ADP (62~100)	 184.9 270.0	 177.5 277.9	 183.0 272.1	 1.000 1.000

No.: number; DM: diabetes mellitus; CVA: cerebrovascular accident; CAD: coronary artery disease; ESRD: end stage renal disease

ICA: internal carotid artery; ACA: anterior cerebral artery; MCA: middle cerebral artery; P-com A: posterior communicating artery; A-com A: anterior communicating artery

Table 2. Thromboembolic events after embolization

	Clopidogrel	Ticagrelor	Total	P value
Procedure no.	113	40	153	
Acute in stent thrombosis	2 (1.77%)	0	2 (1.31%)	0.729
Early ischemic stroke (< 3 months) *	3 (2.65%)	0	3 (2.65%)	0.236
Delay ischemic stroke (>3 months)	6 (5.31%)	3 (7.50%)	9 (5.88%)	0.698
Total ischemic stroke	9 (7.96%)	3 (7.50%)	12 (7.84%)	0.215

* Include the acute in stent thrombosis

Table 3. Bleeding complications in stent-assisted coiling embolizations

	Clopidogrel	Ticagrelor	Total	P value
Patients no.	113	40	153	NA
Major bleeding	0	0	0	NA
Minor bleeding	9	4	13	0.744
Spontaneous skin ecchymosis	9	4	13	0.744
Epistaxis	1	1	2	0.456
Hemorrhoids bleeding	0	1	1	0.261
Total bleeding events	9 (7.96%)	4 (10.00%)	13 (8.50%)	0.744

Table 4. Systemic review of antiplatelets regiment for stent in treatment of intracerebral aneurysms

Study	Case No.	Antiplatelets	Procedures	In stent thrombosis	Early TE[1]
Hwang 2013[7]	116	Aspirin + Clopidogrel	SACE	1.72%	5.17%
Kono 2013[24]	36	Aspirin + Clopidogrel	SACE	0%	0%
	4	Aspirin + Clopidogrel + Cilostazol	Y-stent coiling	0%	50%
Hwang 2014[25]	395	Aspirin + Clopidogrel	SACE	4.05%	7.59%
Starke 2014[26]	120	Aspirin + Clopidogrel	SACE	4.17%	7.50%
Matsumoto 2014[27]	18	Aspirin + Clopidogrel	SACE	N/A	22.22%
	25	Aspirin + Cilostazol	SACE	N/A	20.00%
Takigawa 2014[12]	43	Aspirin + Clopidogrel	SACE	6.98%	6.98%
Hong 2014[8]	753	Aspirin + Clopidogrel	SACE	N/A	17.6%
Song 2015[28]	125	Aspirin + Clopidogrel	SACE	0%	1.6%
Matsumoto 2015[29]	51	Aspirin + Clopidogrel	SACE	0%	13.73%
	28	Aspirin + Clopidogrel + Cilostazol	SACE	0%	0%
Ha 2016[30]	96	Clopidogrel	Endovascular procedure [2]	0%	0%
	98	Prasugrel	Endovascular procedure [2]	0%	0%
Kim 2016[37]	246	Aspirin + Clopidogrel	SACE	N/A	10.16%
	124	DRT [3]	SACE		2.46%
Bechan 2016[9]	46	Aspirin + Clopidogrel	SACE	N/A	4.35%
Park 2016[31]	105	Aspirin + Clopidogrel	SACE	0%	0.95%
	229	Aspirin + Clopidogrel [4]	SACE	4.8%	15.81%
	102	Aspirin + Clopidogrel + cilostazol or ticlopidine	SACE	3.9%	6.86%
Song 2017[32]	99	Aspirin + Clopidogrel	SACE	4.04%	14.14%
Choi 2017[34]	90	Aspirin + Clopidogrel	SACE	3.33%	6.67%
	207	Prasugrel	SACE	0.48%	0.97%
Sedat 2017[33]	100	Aspirin + Clopidogrel	SACE	3%	20%
	100	Aspirin + Prasugrel	SACE	0%	12%
Kim 2018[35]	507	Aspirin + Clopidogrel	SACE	0.19%	1.38%
Soize 2019[36]	40	Aspirin + Clopidogrel	Flow diverter	12.5%	20%
	40	Aspirin + Ticagrelor	Flow diverter	5%	7.5%
Hanel 2014[23]	18	Ticagrelor	All stent procedure [5]	0%	0%
Narata 2019[21]	154	Aspirin + Ticagrelor	Flow diverter and SACE	N/A	1.9%
Current study	**113**	**Aspirin + Clopidogrel**	**Stent-assisted coiling**	**1.77%**	**2.65%**
	40	**Aspirin + Ticagrelor**	**Stent-assisted coiling**	**0%**	**0%**

SACE: stent assisted coiling embolization; N/A: no mention in the article

:ly TE: thromboembolic events < 3 months or under dual antiplatelets (include in stent ombosis)

lude SACE, flow diverter, double catheters, etc.

T: drug resistant therapy, no detail in the article

ɔup for Clopidogrel resistance

lude carotid stent, intra-, extra-cranial stents, and flow diverter

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table120210301.docx
- Table220210301.docx
- Table320210301.docx
- Table4systemicreview20210301.docx