Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms

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Abstract

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

Methods: A retrospective cohort study was conducted from January 2016 to December 2018 with at least one year of follow-up 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 thrombotic events were noted in two patients in the clopidogrel group (1.77%) and none in the ticagrelor group (0%). Additionally, one 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 were no major hemorrhagic events in either group. The two groups showed no significant differences with regard to ischemic stroke or hemorrhagic stroke.

Conclusion: Compared to the clopidogrel based regimen, ticagrelor can also reduce TEs without increasing bleeding tendency for SACE of UIAs. Ticagrelor combined with low-dose aspirin is a safe and effective alternative option for SACE.

Keywords

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

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Introduction

Endovascular techniques, especially stent-assisted coil embolization (SACE), have been widely applied in the treatment of unruptured intracranial aneurysms (UIAs).1–3 Coil embolization under stent protection not only increases the occlusion rate but also reduces aneurysm recurrence.2,4–9 However, thromboembolic events (TEs) remain the major complications after stent implantation.10–14 Clopidogrel associated with aspirin as the dual antiplatelet therapy (DAPT) has been the most common regimen and routinely used for prevention of TEs.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, and others.15–17 Because patients who are resistant to clopidogrel have a higher risk of TE,4,8,9 different antiplatelet agents have been proposed and substituted. DAPT with aspirin plus a P2Y12 receptor antagonist ticagrelor has been proven safe and efficacious and reduces the incidence of ischemic events compared to 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 use with flow diverter stents and neurologic procedures.21,22 Herein, we performed a comparative study to demonstrate the safety and efficacy of clopidogrel and ticagrelor against TE in aneurysms undergoing SACE.

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Methods

Study design

This retrospective cohort study was conducted between January 2016 and December 2018. We compared two consecutive groups of patients with 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 were lost to follow-up were also excluded. Enterprise stents (Codman, Raynham, MA, USA) were used in all patients who underwent SACE. 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 databases of all patients and endovascular procedures were retrospectively reviewed to identify the patients. All methods were performed in accordance with the ethical regulations. The study was approved by our institution (No. CMRPG3H0741) and by the Institutional Review Board (IRB no. 201800342B0).

DAPT protocol and clinical follow-up

In total, 153 patients with 168 UIAs underwent SACE. We divided the patients into two groups: 113 patients receiving clopidogrel plus aspirin (clopidogrel group) and 40 patients receiving ticagrelor plus aspirin (ticagrelor group). All SACE procedures were performed by four experienced neurointerventionalists.

DAPT was administered 7 days before embolization. In the clopidogrel group, patients received a daily dose of 100 mg of aspirin and 75 mg of clopidogrel, administered orally. In the ticagrelor group, patients received a daily dose of 100 mg aspirin and ticagrelor 90 mg twice daily. 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 and Col/ADP), chest X-ray, and electrocardiogram. SACE was performed in the 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 in the outpatient department. Follow-up imaging studies included digital subtraction angiography or magnetic resonance angiography performed after 1 year.

Outcome measurements

1. Baseline characteristics: We reviewed medical records and compared two groups with regard to age, sex, personal history, past history, aneurysm numbers, sizes, types, locations, laboratory data (including hemogram, PT, PTT, INR, and platelet function test [closure time: Col/EPI and Col/ADP]), chest X-ray, and electrocardiogram. SACE was performed in the 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 in the outpatient department. Follow-up imaging studies included digital subtraction angiography or magnetic resonance angiography performed after 1 year.

2. TEs: We measured the occurrence of TE and divided the events into acute stent thrombosis and early and delayed ischemic strokes. Early ischemic stroke includes all ischemic events, such as acute 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 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 means and standard deviations. 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 TEs or hemorrhagic complications between the two groups, we performed a subgroup analysis and percentage analysis with a 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 underwent SACE for grouping and retrospective analyses. Among these patients, 113 received clopidogrel plus aspirin (clopidogrel group) and 40 received 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 vs. 56.39-years-old, respectively. There were no significant differences between the two groups. As for laboratory data, platelet count and platelet function tests were not significantly different between the two groups. Table 1 also shows the location of the 168 aneurysms in 153 patients. There was also no significant difference between the clopidogrel and ticagrelor groups.

Safety
In total, there were 12 TEs (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 in-stent thrombosis (1.77%). No acute in-stent thrombosis occurred in the ticagrelor group. Only one patient (0.88%) had an early ischemic stroke that occurred within 3 months in the clopidogrel group (a total of 3 patients, 2.65%, with an early stroke); none occurred in the ticagrelor group. The locations of the stent deployment in the three patients who had early ischemic stroke were all in the internal carotid artery. Delayed ischemic stroke occurred in nine patients (5.88%), including six patients (5.31%) in the clopidogrel group and three patients (7.50%) in the ticagrelor group. In the Plavix group, five of six ischemic events were mild (TIA or self-expressed short-term weakness). Only one patient had image-proven cerebral infarction and occurred 2 days after abdominal hernia surgery. One patient was noted to have delayed 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 nine patients (7.96%) in the clopidogrel group and four patients (10%) in the ticagrelor group. There were no significant differences between the two groups 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 coil was introduced in 1991, has remained a challenge. Finding better antiplatelet medications could make these procedures safer and allow

| Table 2. Thromboembolic events after embolization. |
|--------------------------------------------------|
|                     | Clopidogrel | Ticagrelor | Total | P value |
|-------------------------------------------------|-------------|------------|-------|---------|
| Procedure no.                                             | 113         | 40         | 153   | 0.729   |
| Acute in stent thrombosis                                | 2 (1.77%)   | 0          | 2     | 1.13%   |
| Early ischemic stroke (<3 months)*                      | 3 (2.65%)   | 0          | 3     | 0.236   |
| Delay ischemic stroke (>3 months)                       | 6 (5.31%)   | 3 (7.50%)  | 9     | 0.698   |
| Total ischemic stroke                                   | 9 (7.96%)   | 3 (7.50%)  | 12    | 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    | 0.744   |

(8.50%)
neurointerventionalists to use longer coiling and stents with confidence. Routinely, aspirin plus clopidogrel as DAPT has been used for the prevention of TEs. However, a previous study indicated that antiplatelet resistance to clopidogrel might be related to a high incidence of TE.\textsuperscript{14–16} The effectiveness of ticagrelor in preventing thromboembolic complications for endovascular procedures has been proven in patients with coronary disease patients.\textsuperscript{18–20} Therefore, ticagrelor might be an alternative prophylactic medication, and we hope that 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 the use of ticagrelor in 18 patients who were non-responders to clopidogrel and underwent neurointerventional procedures. All patients showed immediate platelet inhibition after a loading dose of 180 mg ticagrelor administered orally, with no adverse effects. Ticagrelor offers an effective alternative to clopidogrel non-responders.\textsuperscript{22,24} 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 diverters and stent-assisted coiling. In total, 41 patients underwent stent-assisted coiling. Nine patients (5.8%) presented with symptomatic neurological complications post-stenting (three ischemic and six hemorrhagic).\textsuperscript{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 literature, ticagrelor was prescribed to patients who presented with TE risk factors. Risk factors for TE after neuro-intervention of UIA were proposed and explained in all studies. In terms of patient demographics and past history, TE occurred more frequently in patients with vascular status associated with old age, diabetes, dyslipidemia, and previous stroke. In aneurysm characteristics, increased TE was noted in the treatment of wide-neck and/or large aneurysms, which may be due to more complex techniques and longer procedure times. In our current study, platelet function testing was not statistically different between the two groups according to preoperative laboratory data. On the other hand, the P2Y12 reaction unit value and ticagrelor prescription were neither routinely checked nor covered by national health insurance, which causes socioeconomic burden. Therefore, it is difficult to set a randomized control group to select patients who have received the protocol. But we tried to equally choose patients who had received the ticagrelor protocol in the current study. Otherwise, patients with a history of allergy to clopidogrel were also 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, these are adverse events that are related to antiplatelet usage and affect patient compliance. For 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 between January 1, 2013 and December 31, 2019. In total, 21 studies (shown in Table 4) were selected for analysis.\textsuperscript{7–9,12,21,24–38} 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, the early thromboembolic event rate was 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 was no statistically significant difference between clopidogrel and ticagrelor, ticagrelor may tend to have stronger potency in terms of reducing acute TE when compared with clopidogrel. This trend has also been observed in other studies. However, there are some disadvantages regarding the clinical use of ticagrelor, including the cost of medication and patient compliance (for twice a day doses).\textsuperscript{39}

**Limitations**

This study has some limitations. First, there were relatively fewer cases in the cohort study, and the effects of other variables may have been underestimated. First, the location and vessel size of stent deployment may affect the incidence of thrombus formation. In all three patients who had an early ischemic stroke, stent delivery occurred in the internal carotid artery. Otherwise, the therapeutic vessels between the two groups showed no obvious difference in distribution. By comparing these two groups, there were fewer cases of adverse events in the ticagrelor group. In addition, because of the clinically lower thromboembolic risk, the P2Y12 reaction unit value was not routinely evaluated and not covered by national health insurance. Therefore, the true percentage of clopidogrel resistance remains unknown. However, in the two groups, because there were no differences between pre-stenting platelet function and random selection of the two groups, the bias might have been reduced. In order to create clinical guidelines, a prospective randomized controlled study is warranted to validate the effectiveness and safety of clopidogrel and ticagrelor for the treatment of intracranial aneurysms.

**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 TEs without increasing the bleeding rate for stent-assisted coiling embolization of UIAs. Ticagrelor plus aspirin is an
alternative treatment option. Further large studies are warranted to validate the results and render SACE much safer.

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.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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| Table 4. Systemic review of antiplatelets regiment for stent in treatment of intracerebral aneurysms. |
|-------------------------------------------------------------|
| Study            | Case No. | Antiplatelets               | Procedures               | In stent thrombosis | Early TE¹ |
|------------------|----------|-----------------------------|--------------------------|---------------------|-----------|
| Hwang et al. 2013⁷ | 116      | Aspirin + Clopidogrel       | SACE                     | 1.72%               | 5.17%     |
| Kono et al. 2013²⁵| 36       | Aspirin + Clopidogrel       | SACE                     | 0%                  | 0%        |
|                  | 4        | Aspirin + Clopidogrel + Cilostazol | Y-stent coiling        | 0%                  | 50%       |
| Hwang et al. 2014⁶⁶| 395      | Aspirin + Clopidogrel       | SACE                     | 4.05%               | 7.59%     |
| Matsumoto et al. 2016⁵⁸| 18     | Aspirin + Clopidogrel       | SACE                     | N/A                 | 22.22%    |
|                  | 25       | Aspirin + Cilostazol        | SACE                     | N/A                 | 20.00%    |
| Takigawa et al. 2014⁶⁷| 63      | Aspirin + Clopidogrel       | SACE                     | 6.98%               | 6.98%     |
| Hong et al. 2016²⁸| 753      | Aspirin + Clopidogrel       | SACE                     | N/A                 | 17.6%     |
| Starke et al. 2015²⁷| 120     | Aspirin + Clopidogrel       | SACE                     | 4.17%               | 7.50%     |
| Song et al. 2015²⁹| 125      | Aspirin + Clopidogrel       | SACE                     | 0%                  | 1.6%      |
| Matsumoto et al. 2015³⁰| 51     | Aspirin + Clopidogrel       | SACE                     | 0%                  | 13.73%    |
|                  | 28       | Aspirin + Clopidogrel + Cilostazol | SACE                   | 0%                  | 0%        |
| Ha et al. 2016³¹  | 96       | Clopidogrel                 | Endovascular procedure   | 0%                  | 0%        |
|                  | 98       | Prasugrel                   | Endovascular procedure   | 0%                  | 0%        |
| Kim et al. 2016³⁸ | 246      | Aspirin + Clopidogrel       | SACE                     | N/A                 | 10.16%    |
|                  | 124      | DRT ¹                       | SACE                     | 2.46%               |           |
| Bechan et al. 2016⁹ | 46      | Aspirin + Clopidogrel       | SACE                     | N/A                 | 4.35%     |
| Park et al. 2016³²| 105      | Aspirin + Clopidogrel       | SACE                     | 0%                  | 0.95%     |
|                  | 229      | Aspirin + Clopidogrel + Cilostazol or ticlopidine | SACE                   | 4.8%               | 15.81%    |
|                  | 102      | Aspirin + Clopidogrel       | SACE                     | 3.9%                | 6.86%     |
| Song and Shin 2017⁹³| 99      | Aspirin + Clopidogrel       | SACE                     | 4.04%               | 14.14%    |
| Sedat et al. 2017³⁶| 100     | Aspirin + Clopidogrel       | SACE                     | 3%                  | 20%       |
|                  | 100      | Aspirin + Prasugrel         | SACE                     | 0%                  | 12%       |
| Choi et al. 2018³⁵| 90       | Aspirin + Clopidogrel       | SACE                     | 3.33%               | 6.67%     |
|                  | 207      | Prasugrel                   | SACE                     | 0.48%               | 0.97%     |
| Kim et al. 2018³⁶| 507      | Aspirin + Clopidogrel       | SACE                     | 0.19%               | 1.38%     |
| Soize et al. 2019³⁷| 40       | Aspirin + Clopidogrel       | Flow diverter            | 12.5%               | 20%       |
|                  | 40       | Aspirin + Ticagrelor        | Flow diverter            | 5%                  | 7.5%      |
| Hanel et al. 2016³⁸| 18       | Ticagrelor                  | All stent procedure ⁵    | 0%                  | 0%        |
| Narata et al. 2019³¹| 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.
Early TE: thromboembolic events <3 months or under dual antiplatelets (include in stent thrombosis).
Include SACE, flow diverter, double catheters, etc.
DRT: drug resistant therapy, no detail in the article.
Group for Clopidogrel resistance.
Include carotid stent, intra-, extra-cranial stents, and flow diverter.
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Supplemental Material
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