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Original Article

Safety and Efficacy of Prasugrel Administration in Emergent Endovascular Treatment for Intracranial Atherosclerotic Disease

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Objective: Intracranial atherosclerosis disease (ICAD) is one of the most common causes of acute ischemic stroke. In endovascular treatment (EVT) for acute large vessel occlusion stroke-related ICAD, reocclusion of the recanalized artery due to in situ thrombosis is problematic. In this study, the safety and efficacy of prasugrel administration to avoid reocclusion of emergent EVT for ICAD was investigated.

Methods: All consecutive emergent EVTs for ICAD between September 2019 and December 2022 were included in this study. The procedures were divided into two groups as receiving periprocedural prasugrel (*PSG group*) or not (*non-PSG group*). Target vessel patency on follow-up, postprocedural intracranial hemorrhage (ICH), and clinical outcome were compared between PSG and non-PSG groups.

Results: A total of 27 procedures were included in this analysis. Nineteen target vessels were patent on follow-up and eight were non-patent. Fifteen patients received prasugrel (18.75 mg: 11 cases, 11.25 mg: 4 cases), and twelve patients did not receive prasugrel. The target vessel patency rate was better in the PSG group vs. non-PSG group (100% vs. 33.3%, respectively; p = 0.0002). The postprocedural ICH rate was not different between the groups (PSG: 40.0% vs. non-PSG: 25.0%; p = 0.68), and all ICHs were asymptomatic. Good clinical outcome (modified Rankin Scale score of 0 to 3 at discharge) was more frequent in the PSG group than that in the non-PSG group (66.7% vs. 16.7%, respectively; p = 0.019).

Conclusion: Prasugrel administration was significantly associated with target vessel patency and good clinical outcome after emergent EVT for ICAD without increasing the symptomatic ICH rate. Prasugrel administration might be safe and effective to avoid reocclusion during and after emergent EVT for ICAD.

Keywords prasugrel, intracranial atherosclerotic disease, large vessel occlusion, endovascular therapy

Introduction

Intracranial atherosclerosis disease (ICAD) is one of the most common causes of acute ischemic stroke (AIS).[1–3] Large vessel occlusion (LVO)-related ICAD was reported in 17%–30% of patients who underwent endovascular treatment (EVT) in Asia, while the incidence varied depending on race.[2] During EVT for ICAD-related LVO, intraprocedural reocclusion is highly likely.[3] In a systematic review, intraprocedural reocclusion during EVT occurred in 36.9% of LVO patients with underlying ICAD versus 2.7% of those without it.[4] Additionally, 24-hour worsening of arterial patency was significantly associated with mortality and poor functional status.[5] As platelet-mediated thrombotic mechanisms are likely involved in reocclusion, antiplatelet drugs, such as glycoprotein IIb/IIIa inhibitors (GPI), are infused to avoid reocclusion during EVT.[3,6] Antiplatelet therapy during EVT could also improve successful reperfusion rates for tandem occlusion.[7] Baek et al. reported that frontline mechanical thrombectomy was successful in only 9.8% of cases of ICAD-related LVO, and combined rescue

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therapy with stenting and GPI infusion improved the patency rate of arteries and clinical outcomes.[6] However, GPIs are not available in Japan, and as conventionally used oral agents require a long time to become active, they are considered insufficient to prevent acute reocclusion.[3]

Prasugrel, which is an oral P2Y12 inhibitor, has a rapid onset of antiplatelet action. Onset of action is between 15 and 30 min with peak plasma concentration for prasugrel's active metabolite.[8] In this retrospective study, we investigated the safety and efficacy of periprocedural prasugrel administration and evaluated whether prasugrel can be an alternative to GPIs to avoid reocclusion during and after emergent EVT for ICAD.

Material and Methods

Retrospective collection of clinical data from medical records was approved by the Ethics Committee of the Local Institutional Review Board (IRB) (approval number: OR02-3). In Japan, prasugrel loading (20 mg) was only approved for use in acute coronary syndrome patients undergoing percutaneous coronary intervention. In Osaka Neurological Institute, low-dose prasugrel loading during emergent EVT for ICAD was performed under IRB approval in 2021 (approval number: OR03-1).

Patients

Between September 2019 and December 2022, 135 emergent EVT procedures for LVO were performed at Osaka Neurological Institute. Among these, all procedures for ICAD-related LVO were included in this study. Twenty-eight procedures (20.7%) in 27 patients diagnosed as ICAD-related LVO were performed. One patient was excluded because of wire perforation before frontline EVT. This patient did not receive any antiplatelet therapy. Finally, 27 procedures were included in the analysis.

Periprocedural antiplatelet therapy

Antiplatelet therapy was divided into prestroke antiplatelet therapy and periprocedural antiplatelet therapy. Periprocedural antiplatelet therapy comprised three types, as follows: (1) preprocedural therapy: when ICAD was diagnosed before EVT, preprocedural oral antiplatelet therapy was administered; (2) intraprocedural therapy: when reocclusion of the recanalized artery was impending during EVT, intraprocedural oral or intravenous antiplatelet therapy was administered; and (3) postprocedural therapy: postprocedural oral antiplatelet therapy was administered immediately after EVT for residual stenosis. Usage, types, dosages, and timing of antiplatelet therapy were determined at the discretion of the treating physician. The types and dosages of the antiplatelet therapies were oral aspirin (100–300 mg), oral P2Y12 inhibitors (clopidogrel: 75–300 mg and prasugrel 10–20 mg), and intravenous ozagrel (40–80 mg). In patients who could not receive medication orally because of neurological deficits, oral antiplatelet therapy was administered via the nasogastric tube. In cases treated with a stent, dual oral antiplatelet therapy comprising aspirin and a P2Y12 inhibitor was administered before stent placement. When reocclusion occurred despite clopidogrel administration, prasugrel was administrated as add-on use for clopidogrel resistance in some cases. From next day of EVT, at least one antiplatelet agent was given throughout the follow-up period.

EVT

All EVT procedures were performed under local anesthesia. Intravenous heparin was administered during the procedure to maintain the activated coagulation time between 200 and 300 seconds except for cases that received intravenous tissue-type plasminogen activator. Frontline mechanical thrombectomy was performed using stent retrievers (Trevo; Stryker, Kalamazoo, MI, USA, or Solitaire; Medtronic, Dublin, Ireland) with or without aspiration catheters (Catalyst; Stryker or Penumbra, Penumbra, Alameda, CA, USA). Contact aspiration thrombectomy was performed if a microcatheter could not cross the lesion. Rescue balloon angioplasty (Gateway; Stryker) with or without a stent (Wingspan; Stryker) was performed in cases with insufficient reperfusion or impending reocclusion due to residual stenosis. If Wingspan could not be used for some reason, other stent was placed. In cases with nearly complete occlusion or former intracranial stent placement, balloon angioplasty with or without an intracranial stent was used as frontline therapy. Successful recanalization was defined as achieving modified thrombolysis in cerebral infarction grade 2b or 3 and no reocclusion observed at the end of the procedure.[9]

Follow-up examinations

CT was performed immediately after and the day after EVT to identify the presence of intracranial hemorrhage (ICH). ICH was classified according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definitions.[10] Target vessel patency was evaluated using MRA or CTA 6–72 hours after EVT. The artery was considered patent when significant distal flow was observed on time-of-flight MRA. Data for neurological adverse events within 14 days were collected retrospectively.

Table 1 Clinical and procedural characteristics

	Patent (N = 19)	Non-patent (N = 8)	p value
Age, year (mean ± SD)	73.3 ± 10.6	82.0 ± 5.1	0.02
Female sex	11 (57.9%)	4 (50.0%)	>0.99
NIHSS score, median (IQR)	8 (5 to 22)	15 (9 to 21)	0.40
Hypertension	15 (79.0%)	6 (75.0%)	>0.99
Diabetes	6 (31.6%)	5 (62.5%)	0.21
Dyslipidemia	12 (63.2%)	3 (37.5%)	0.40
Current smoking†	4 (23.5%)	1 (16.7%)	>0.99
Prestroke antiplatelet therapy	6 (31.6%)	0 (0.0%)	0.14
Target vessel			
ICA	7 (36.8%)	0 (0.0%)	0.07
MCA M1	8 (42.1%)	6 (75.0%)	0.21
MCA M2	1 (5.3%)	2 (25.0%)	0.20
VA	2 (10.5%)	0 (0.0%)	>0.99
IV-tPA	1 (5.3%)	1 (12.5%)	0.52
Periprocedural antiplatelet therapy			
Any	19 (100%)	4 (50.0%)	<0.01
Prasugrel	15 (79.0%)	0 (0.0%)	<0.01
Clopidogrel	8 (42.1%)	1 (12.5%)	0.20
Aspirin	15 (79.0%)	4 (50.0%)	0.18
Ozagrel	7 (36.8%)	2 (25.0%)	0.68
EVT procedure			
MT	13 (68.4%)	8 (100%)	0.14
BAA w/o stent	4 (21.1%)	2 (25.0%)	>0.99
Stenting	8 (42.1%)	0 (0.0%)	0.06
Intraprocedural reocclusion	8 (42.1%)	2 (25.0%)	0.67
Successful recanalization	19 (100%)	6 (75.0%)	0.08

†Smoking history was unknown in four patients. BAA: balloon angioplasty; EVT: endovascular treatment; ICA: internal carotid artery; IQR: interquartile range; IV-tPA: intravenous tissue-type plasminogen activator; MCA: middle cerebral artery; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation; VA: vertebral artery

Study outcomes

The primary efficacy outcome was target vessel patency at the follow-up examination. The safety outcome was symptomatic ICH related to EVT. ICH was defined as symptomatic if the National Institutes of Health Stroke Scale (NIHSS) increased to ≥4 compared with the pre-EVT score. Clinical outcome was measured using the modified Rankin Scale (mRS) score at discharge from our center. Good clinical outcome was defined as mRS of 0 to 3. First, clinical and treatment factors associated with target vessel patency were investigated. Second, to clarify the efficacy and safety of periprocedural prasugrel administration, outcomes were compared between patients receiving periprocedural prasugrel (*PSG group*) or not (*non-PSG group*).

Statistical analysis

Statistical tests were performed using Prism 6 (GraphPad, San Diego, CA, USA). A p value <0.05 was defined as statistically significant. Data were presented as means ± standard deviation. Univariate analysis was performed using the Fisher's exact probability test for nominal variables and the Mann–Whitney U test for continuous variables.

Results

Clinical and treatment characteristics are shown in **Table 1**. Intraprocedural reocclusion occurred during 10 EVT procedures (37.0%). Among these cases, nine reoccluded vessels were recanalized after additional treatment with antiplatelet therapy and balloon angioplasty with or without stenting. Reoccluded vessels were not recanalized at the end of the procedures in one case who did not receive antiplatelet therapy. In another case, contact aspiration thrombectomy could not achieve recanalization. Successful recanalization was achieved in 25 procedures (92.6%).

In the follow-up examination, 19 (70.4%) recanalized target vessels were patent and six were reoccluded. Overall, eight procedures (29.6%) were judged as non-patent (two

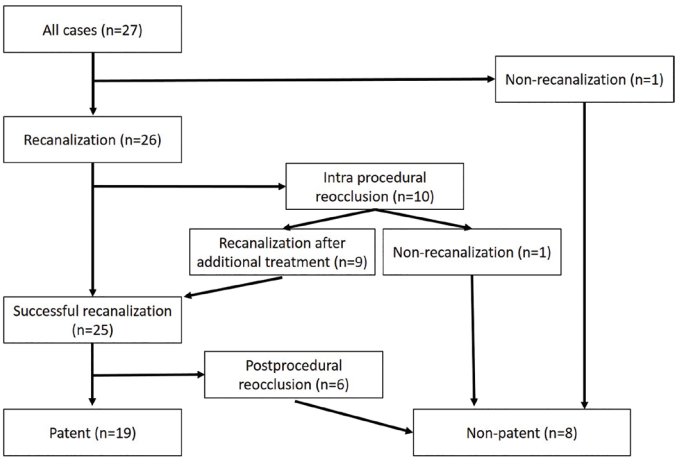

Fig. 1 A flow chart showing the treatment outcomes.

non-recanalizations and six postprocedural reocclusions). A flow chart of the treatment and outcomes is shown in **Fig. 1**.

Primary endpoint

Patients in the patent group were younger than those in the non-patent group (73.3 ± 10.6 vs. 82.0 ± 5.1 years, respectively; p = 0.016). Sex, NIHSS scale before EVT, risk factors, and target vessel location were not different between the patent group and non-patent group. Six cases received prestroke antiplatelet therapy (three cases: aspirin 100 mg, 1 case: aspirin 100 mg with clopidogrel 75 mg, 1 case: clopidogrel 75 mg, and 1 case: cilostazol 200 mg per day). Twenty-three cases (85.2%) received periprocedural antiplatelet therapy. Target vessel patency was associated with young age (p = 0.016), periprocedural antiplatelet therapy (p = 0.0040), and prasugrel administration (p = 0.0002).

Safety and efficacy of prasugrel administration

Fifteen patients (PSG group) received prasugrel (18.75 mg: 11 cases, 11.25 mg: 4 cases), and twelve patients (non-PSG group) did not receive prasugrel. A comparison of the characteristics and clinical endpoints between the two groups is shown in **Table 2**. The PSG group was younger than the non-PSG group (72.0 ± 9.5 vs. 80.8 ± 8.8 years, respectively; p = 0.002). Sex, NIHSS scale before EVT, risk factors, target vessel location, and EVT modality were not different between the two groups. Thirteen cases received prasugrel during the EVT procedure, and two cases received prasugrel just before EVT. In the PSG group, 12 (80%) cases received aspirin as periprocedural antiplatelet therapy. Six cases received clopidogrel (prestroke antiplatelet therapy: 2 cases, periprocedural antiplatelet therapy: 4 cases) and required add-on use of prasugrel for clopidogrel resistance. Three cases received prasugrel as rescue treatment for acute stent thrombosis, which resolved after prasugrel administration (**Fig. 2**). Successful recanalization rates were not different between the two groups (PSG: 100% vs. non-PSG: 83.3%; p = 0.19). In the PSG group, all target vessels were patent on follow-up examination. The target vessel patency rate was better in the PSG group than that in the non-PSG group (100% vs. 33.3%, respectively; p = 0.0002). The postprocedural ICHs were observed in nine patients (subarachnoid hemorrhage: 7 cases, primary intracerebral hemorrhage type 1: 2 cases). All ICHs were asymptomatic. Incidence rates of ICH were not different between the two groups (PSG: 40.0% vs. non-PSG: 25.0%, respectively; p = 0.68).

Neurological events during follow-up

In cases with reoccluded target vessels, infarct volume expanded after EVT. Decompressive craniectomy was required for consecutive brain edema in one case. Rescue bypass surgery was performed in two cases, and additional stenting was required for restenosis 7 days after EVT in a case without stenting during the first EVT. No recurrence of ischemic stroke was observed during the 14 days after EVT in cases with patent target vessels.

Clinical outcome

Good clinical outcome, defined by mRS score 0–3 at discharge, was significantly more frequent in the patent as well as the PSG groups than in the non-patent and the non-PSG groups (63.2% vs. 0.0%; p = 0.003, 66.7% vs. 16.7%; p = 0.019, respectively) (**Fig. 3**).

Table 2 Prasugrel administration and endpoints

	PSG (N = 15)	Non-PSG (N = 12)	p value
Age, year (mean ± SD)	72.0 ± 9.5	80.8 ± 8.8	<0.01
Primary endpoint			
Patent target vessel	15 (100%)	4 (33.3%)	<0.01
Safety endpoint			
Any ICH	6 (40.0%)	3 (25.0%)	0.68
Symptomatic ICH	0	0	–
Periprocedural antiplatelet therapy			
Aspirin	12 (80.0%)	7 (58.3%)	0.40
Clopidogrel	4 (26.7%)	5 (41.7%)	0.45
Ozagrel	6 (40.0%)	3 (33.3%)	0.68
EVT procedure			
MT	11 (73.3%)	11 (91.7%)	0.34
BAA w/o stent	4 (26.7%)	2 (16.7%)	0.66
Stenting	6 (40.0%)	2 (16.7%)	0.24
Successful recanalization	15 (100%)	10 (83.3%)	0.19

BAA: balloon angioplasty; EVT: endovascular treatment; ICH: intracranial hemorrhage; MT: mechanical thrombectomy; PSG: prasugrel; SD: standard deviation

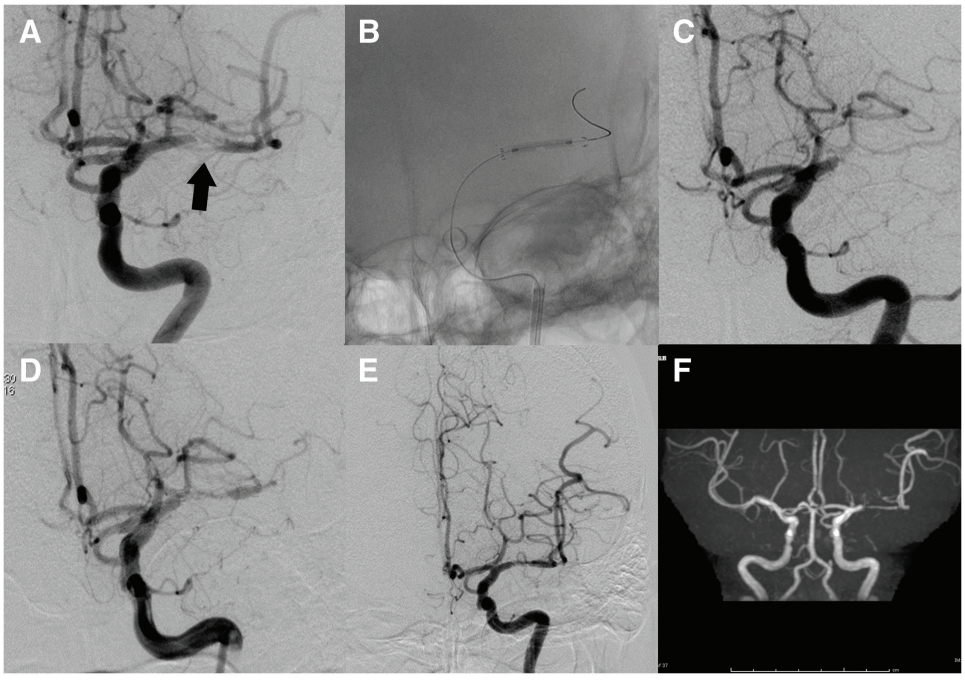

Fig. 2 A case with progressive aphasia who received dual antiplatelet therapy (aspirin 200 mg and clopidogrel 300 mg) before the procedure. (**A**) DSA showing nearly complete occlusion of the M1 segment (arrow). (**B**) Frontline balloon angioplasty with stenting was performed, and the target vessel was recanalized temporarily. (**C**) The target vessel was reoccluded by stent thrombosis 40 minutes after stent placement. (**D**) Intraprocedural stent thrombosis resolved 15 minutes after prasugrel (18.75 mg) loading. (**E**) Successful reperfusion was achieved after additional balloon angioplasty. (**F**) Patency of the target vessel was confirmed on follow-up MRA.

Discussion

In this study, target vessel patency and good clinical outcome were associated with prasugrel administration. Prasugrel administration did not increase symptomatic ICH rates. A previous study showed that a combination of GPI infusion and rescue stenting was associated with target vessel patency and clinical outcomes while solo rescue stenting could not improve procedural outcomes.[6] The present study suggests that oral antiplatelet therapy including prasugrel could be an alternative to GPI infusion for avoiding reocclusion during and after emergent EVT for

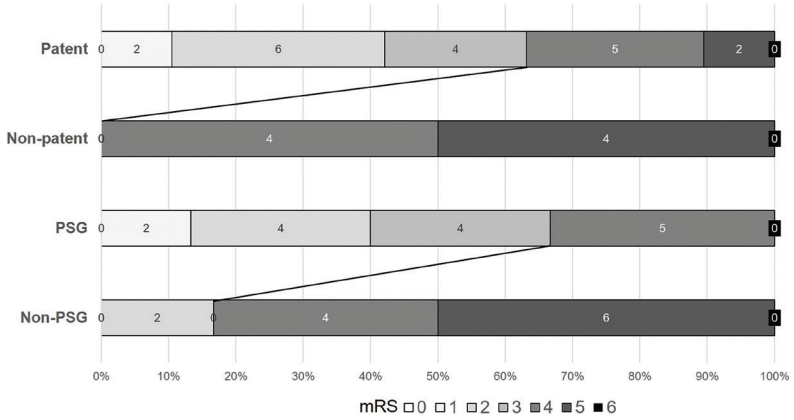

Fig. 3 Good clinical outcome, defined by mRS score 0–3 at discharge, was significantly more frequent in the patent as well as in the PSG groups than the non-patent and the non-PSG groups (63.2% vs. 0.0%; p = 0.003, 66.7% vs. 16.7%; p = 0.019, respectively). mRS: modified Rankin Scale; PSG: prasugrel

ICAD. Moreover, prasugrel administration was effective as rescue treatment for acute stent thrombosis in three cases. The use of GPIs as salvage therapy for acute stent thrombosis during intracranial stenting has also been described.[11)]

P2Y12 inhibitor antiplatelet therapy in EVT for AIS

Other P2Y12 inhibitors, including clopidogrel, ticagrelor, and cangrelor, have been investigated for AIS with intra- and extracranial atherosclerosis disease. Clopidogrel, which is a widely used oral P2Y12 inhibitor, needs 2 hours for onset of action.[8)] Clopidogrel is a prodrug requiring hepatic conversion into its active metabolite, a process that may be influenced by several genetic polymorphisms, including the CYP2C19 genotype. Carriers of the CYP2C19 loss-of-function allele, which is associated with poor response to clopidogrel, account for 50% to 60% of Asian patients.[12)] Prasugrel is unaffected by such CYP2C19 genetic polymorphisms.[13)] In this study, prasugrel was administered as add-on treatment for six patients because of clopidogrel resistance. Because of the high rate of clopidogrel resistance, prasugrel might be more suitable than clopidogrel for emergent EVT for ICAD in Asian patients. Ticagrelor, which is an oral P2Y12 inhibitor, has a faster onset of platelet inhibition compared with clopidogrel.[8)] However, a loading dose of ticagrelor prior to EVT for tandem lesion increased the risk of symptomatic ICH compared with clopidogrel.[14)] Cangrelor, which is an intravenous P2Y12 inhibitor, could achieve near-complete inhibition of platelet aggregation rapidly.[8)] However, postprocedural stent occlusion within the first 24 hours occurred in 7.9% of the patients and symptomatic ICH occurred in 10.5%. Prasugrel might be safer and more effective than the administration of other P2Y12 inhibitors in emergent EVT for AIS patients.

Prasugrel dosage

The optimal prasugrel loading dosage for AIS is not well known. The safety and efficacy of the maintenance dosage of prasugrel (3.75 mg/day) for secondary prevention in Japanese high-risk patients with non-cardioembolic ischemic stroke was demonstrated in a pooled analysis in PRASTRO-I, -II, and -III.[15–17)] In PRASTRO-I, -II, and -III, patients received prasugrel after more than 1 week from ischemic stroke, and prasugrel loading was not performed. In EVT for unruptured aneurysms, a meta-analysis showed that high-dose prasugrel loading (60 mg) was associated with significantly higher periprocedural and early (within 24 hours) hemorrhagic events compared with low-dose prasugrel loading (20 mg).[18)] Low-dose prasugrel loading, which is recommended for acute coronary syndrome in Japan,[19)] was mainly used in this study. Low-dose prasugrel loading in clopidogrel poor responders who received clopidogrel for 14 days achieved insufficient P2Y12 reaction unit (PRU) values in 29.6% of the patients.[20)] A low PRU value was related to hemorrhagic complications[8)]; therefore, the prasugrel dosage as add-on treatment for clopidogrel resistance might need to be reduced. Further investigations are required to clarify the optimal prasugrel dosage for patients with AIS due to ICAD.

Limitations

This study has several limitations, including a lack of randomization and small sample size with short follow-up. In addition, PRU was not measured to evaluate the response

to P2Y12 inhibitor antiplatelet therapies. Aggressive antiplatelet therapy using prasugrel was administered to young patients, and this trend might have influenced the outcome, as the previous retrospective study in which GPI was infused to young patients.[6] Finally, in the PSG group, most patients received aspirin. The efficacy of prasugrel monotherapy for ICAD could not been proven, although prasugrel loading is recommended in combination with aspirin for acute coronary syndrome.[19]

Conclusion

Prasugrel administration was significantly associated with target vessel patency and good clinical outcome after emergent EVT for ICAD without increasing symptomatic ICH rates. Prasugrel administration might be safe and effective to avoid intra- and postprocedural reocclusion during and after emergent EVT for ICAD.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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