Online June 22, 2024
Journal of Neuroendovascular Therapy 2025; 19: 2024-0016 DOI: 10.5797/jnet.ra.2024-0016

Review Article

Antiplatelet Therapy in Endovascular Treatment of Cerebral Aneurysms

Hirofumi Matsubara, Yusuke Egashira, and Yukiko Enomoto

Thromboembolism is one of the main causes of severe complications in the endovascular treatment of cerebral aneurysms, and antiplatelet therapy (APT) is necessary to prevent such complications. Conversely, prolonged APT has the potential risk of hemorrhagic complications; therefore, the timing of dose reduction or discontinuation is an important aspect of periprocedural APT. However, no clinical evidence of an optimal regimen of APT for cerebral aneurysms exists, and the selection, dosage, duration, or combination of antiplatelets has been dependent on physicians for unruptured or ruptured cerebral aneurysms. Many reports have shown that preoperative APT can reduce ischemic complications without increasing hemorrhagic complications, and some reports have shown that the P2Y12 reaction unit (PRU) value measured using the VerifyNow (Werfen, Barcelona, Spain) system is associated with periprocedural ischemic and hemorrhagic complications. Appropriate dose and duration management adjustments based on the platelet reactivity test, aneurysm morphology, treatment, and patient background may contribute to good outcomes. Although accumulating evidence exists regarding the efficacy of preoperative APT, there is no evidence regarding the optimal duration or discontinuation of APT.

Keywords cerebral aneurysm, antiplatelet therapy, flow-diverter, stent-assisted coil

Introduction

Endovascular treatment of cerebral aneurysms is now widely performed as a less invasive and effective treatment, with markedly developed techniques and devices, such as balloon assist,[1] stent assist,[2] and flow-diverter (FD).[3,4] These techniques have enabled the treatment of aneurysms with a complex form (wide neck, large size, and incorporated branches); however, the rate of thromboembolic complication has increased.[5,6] Thromboembolism is a major cause of serious complications in the endovascular treatment of cerebral aneurysms and is directly related to poor outcomes.[7,8] Although perioperative antiplatelet therapy (APT) has been administered to prevent thromboembolism, clinical evidence of its effectiveness is scarce. Current perioperative APT has been derived from cardiological evidence; however, the optimal dose or duration remains controversial because patient characteristics differ between cerebral aneurysms and cardiovascular disease. In this article, we review previous reports on APT in the endovascular treatment of cerebral aneurysms and discuss the current optimal APT.

Department of Neurosurgery, Gifu University Graduate School of Medicine, Gifu, Gifu, Japan

Received: February 14, 2024; Accepted: May 17, 2024
Corresponding author: Yukiko Enomoto. Department of Neurosurgery, Gifu University Graduate School of Medicine, 1-1 Yanagito, Gifu, Gifu 501-1194, Japan
Email: enomoto.yukiko.k1@f.gifu-u.ac.jp

1 Unruptured Aneurysms

1-1 Preoperative APT

Endovascular coil embolization for cerebral aneurysms is a less invasive treatment than direct surgery and is therefore preferred. Endovascular treatment for cerebral aneurysms used simple coiling two decades ago; the rate of severe ischemic complications was 3.7%–6.8%.[7,9–12] Preoperative APT was initiated to prevent these complications.[7,8] In 2006, Ries et al.[7] reported the efficacy of intravenous administration of acetylsalicylic acid (ASA) in preventing intraoperative thromboembolic events. They administered 250 mg ASA after the first coil placement and investigated the incidence of intraoperative thromboembolic events in

patients with or without ASA. The incidence was lower in the ASA group than in the non-ASA group (8.8% vs. 17.6%, p = 0.047). Yamada et al.[13] investigated the rates of thromboembolic and hemorrhagic complications in patients without APT, with APT after coiling, and with APT before coiling. The patients who underwent APT before and after coiling showed the lowest rate of perioperative thromboembolic complications compared with those without APT. Hemorrhagic complications increased slightly, but the authors concluded that the benefits of APT outweigh the risks. These reports led to the development of perioperative APT for coil embolization of unruptured cerebral aneurysms, which has become the standard treatment.

1-1-1 Preprocedural evaluation using platelet function tests

Individual differences exist in responsiveness to antiplatelet agents, and platelet reactivity evaluated using platelet function tests is associated with perioperative ischemic and hemorrhagic complications.[14,15] Many platelet function tests, such as light-transmission aggregometry, several point-of-care analyses, and flow cytometry, are available; however, VerifyNow (Werfen, Barcelona, Spain), a point-of-care analysis that can evaluate the effect of clopidogrel (CLP) as a P2Y12 reaction unit (PRU) value, is the most common tool. Fujita et al.[14] reported that a high preoperative PRU (>212) was associated with symptomatic ischemic complications and a low PRU (<46) was associated with major bleeding complications. Higashiguchi et al.[15] adjusted APT by switching from CLP to prasugrel when the PRU value exceeded 240 and compared the rate of ischemic complications with or without APT adjustment; ischemic complications were significantly decreased in the adjustment group (p = 0.048). These reports analyzed patients with unruptured cerebral aneurysms, including those with balloon-assisted coiling, stent-assisted coiling, and FDs. Hyporesponders to CLP are more frequently observed in Asians than in Europeans and Americans due to polymorphisms of CYP2C19[16]; therefore, many Japanese neuroendovascular surgeons have recognized the importance of preoperative platelet function tests, and in over 90% of cases, the platelet function test was performed before stent-assisted coil (SAC) embolization or FD placement and the APT.[17] However, the optimal timing to start APT remains controversial because the duration of APT before surgery differs between these reports.[7,13,15] A questionnaire survey showed that most patients started APT within 1 month before treatment. Based on these reports, administering antiplatelet agents for a sufficient duration before surgery and evaluating platelet reactivity with a reliable test are important.

1-1-2 For wide-neck aneurysm

Several reports have shown differences in ischemic complications after coil embolization based on aneurysm morphological features and procedure type. Nishikawa et al. analyzed 154 patients with unruptured cerebral aneurysms and reported that symptomatic ischemic complications were significantly higher with single APT (SAPT) than with dual APT (DAPT) for wide-neck aneurysms. They concluded that DAPT might be better for preventing ischemic complications in coil embolization of wide-neck aneurysms.[5] Another report showed that the risk factor for ischemic complications in basilar artery aneurysm coiling was the size ratio between the maximum diameter of the aneurysm and that of the parent artery.[6] These reports focused on the association with aneurysm morphology and suggested that ischemic complications increase when the coil area in contact with the parent artery is large.

Mo et al.[18] reported a difference in diffusion-weighted imaging of lesions due to endovascular treatment techniques. This study analyzed 18 reports, including 1843 patients with unruptured aneurysms, and compared postoperative diffusion-weighted imaging lesions using each technique. The incidence of diffusion-weighted imaging lesions was 66.1% in FDs, 37.6% in SAC, 31.1% in balloon-assisted coil embolization, and 25.6% in coil embolization alone, and FD was significantly higher than other techniques. The incidences of diffusion-weighted imaging lesions in the SAC, balloon-assisted coil embolization, and coil embolization alone groups were not significantly different; however, the incidence tended to increase with the use of adjunctive techniques. Therefore, adjunctive techniques require effective APT compared to simple techniques.

1-1-3 For stent-assisted coiling

SAC has been used to treat complex aneurysms such as those with a wide neck; however, ischemic complications have increased because stents are deployed in the parent artery.[19–21] Currently, Codman Enterprise 2 (Johnson & Johnson Medical Ltd., Wokingham, UK), Neuroform Atlas (Stryker, Portage, MI, CA, USA), and LVIS stents (MicroVention Inc., Aliso Viejo, CA, USA) are available in Japan. DAPT is the standard periprocedural management for SAC.[22–25] In SAC, severe ischemic complications

due to in-stent thrombotic occlusion are problematic, particularly in PRU hyporesponders.[3,26] Some studies have demonstrated the efficacy of prasugrel and ticagrelor as alternatives to CLP before SAC. Sadat et al. investigated the safety and efficacy of prasugrel in SAC.[27] Hemorrhagic and ischemic complications were not significantly different between the ASA and CLP groups or ASA and prasugrel groups. However, complicated aneurysms were more frequently observed in the ASA + prasugrel group. Therefore, this report concluded that prasugrel was more effective than CLP in treating SAC. Other studies have investigated the safety and efficacy of ticagrelor in SAC.[22,26] These reports showed that ticagrelor made no significant differences in hemorrhagic and ischemic complications compared to CLP. Indication of prasugrel for cerebral infarction in Japan is limited. The dose of prasugrel is different from that used in previous reports, and ticagrelor can be used only in patients with coronary artery disease. Previous reports have shown an increase in hemorrhagic complications, although not statistically significant, and it is reasonable to refrain from easily using these drugs.

1-1-4 For FD

FD was approved in Japan in 2015, and the number of procedures has dramatically increased. Preoperative APT is more important for preventing ischemic complications in patients with FD than with coil embolization with or without an assist stent because FD has high metal coverage.[18,28] Japanese guidelines emphasize that dual or more APT is a standard periprocedural antiplatelet regimen, and its evaluation before the procedure using a platelet function test is required.[28–31] The PRU measured using VerifyNow was associated with ischemic and hemorrhagic complications in FD.[28,32,33] Delgado et al. reported an association between PRU and complications in 48 patients treated with a pipeline embolization device; the rate of ischemic and hemorrhagic complications was both 8.3%, and they concluded that PRU <60 or >240 was an independent predictor of perioperative ischemic and hemorrhagic complications.[33] Alternative P2Y12 inhibitors such as prasugrel or ticagrelor could be an option to avoid insufficient P2Y12 inhibition. Suyama et al.[34] reported the clinical results of 110 patients who underwent FD with periprocedural APT using ASA and prasugrel and reported that the rates of ischemic and hemorrhagic complications were 6.4% and 0.9%, respectively. Other studies have investigated the safety and efficacy of ticagrelor for FD.[35,36] Park et al.[36] reported no significant differences in ischemic and hemorrhagic complications between CLP and ticagrelor; however, another report showed that ticagrelor is an independent risk factor for hemorrhagic complications.[35]

1-2 Duration of Postoperative APT

Reports on preoperative APT for coil embolization are numerous; however, there are few reports on postoperative APT. Although some reports have investigated postoperative APT for the SAC and FD, we could not find any reports of postoperative APT for coil embolization without stenting. Therefore, we provide an overview of postoperative APT on SAC and FD in this section.

1-2-1 Stent-assisted coiling

The standard strategy for postoperative APT after SAC is the continuation of DAPT. Hwang et al.[37] included 403 aneurysms treated with SAC and compared the rate of delayed ischemic complications after SAC between three groups: early (3 months), midterm (6 months), and late (9 months), stratified according to the duration of DAPT. Delayed ischemic complications after switching from DAPT to SAPT occurred in 5.6% of the early, 4.6% of the midterm, and 0% of the late groups, and the hemorrhagic complications rate showed no significant difference between the groups. Therefore, DAPT for >9 months after SAC is recommended to prevent ischemic complications. Rossen et al. reported delayed ischemic complications following SAC. The postoperative APT protocol included 81 mg ASA and 75 mg CLP daily for 6 weeks, followed by 325 mg daily, and 5% of ischemic complications occurred within 2 weeks after cessation of CLP.[38] Another report investigated the rate of delayed ischemic complications between a short-term DAPT (9 months) group and a long-term DAPT group (9 months); 507 procedures were included, and all cases involved unruptured aneurysms with single stent use.[20] Delayed thromboembolic events, including transit ischemic attack, occurred in 25 patients (4.9%), and 22 of them (88%) occurred after switching from DAPT to SAPT. The majority (52%) of delayed thromboembolic events occurred within 1 month after the switch, and there was no significant difference in delayed thromboembolic and hemorrhagic complications between the short and long term. They concluded that long-term DAPT delayed the occurrence of delayed thromboembolic events but did not reduce their incidence. However, its long-term efficacy remains unclear. The short- vs. long-term Dual Antiplatelet Therapy for Stent-Assisted

Table 1 Summary of flow-diverter placement study

Study	N	Flow-diverter	Follow up	APT	Duration of DAPT	Ischemic complication
Rice et al.[40]	204	Pipeline	12 months	Aspirin Clopidogrel	3 months	2.9%
Hanel et al.[41]	144	Pipeline	12 months	Aspirin (81–325 mg) Clopidogrel (75 mg)	6 months	2.1%
Guimaraens et al.[29]	185	FRED	19 months	Aspirin (300 mg) Clopidogrel (75 mg)	6 months	4.8%
Meyers et al.[31]	180	Surpass	12 months	Aspirin (75–325 mg) Clopidogrel (75 mg)	>6 months	8.3%

Postoperative antiplatelet therapy was more than 3 months, and the major ischemic complication rate was 1.9%–8.3%.
APT: antiplatelet therapy; DAPT: dual antiplatelet therapy

treatment of cerebral aneurysms (DAPTS ACE study), the only randomized clinical trial comparing the duration of DAPT after SAC with short- (3 months) and long-term (12 months) DAPT,[24] showed no differences in either ischemic or hemorrhagic complications between the groups and concluded that the benefit of long-term DAPT after SAC might be lower than expected. A limitation of this study is the rare complication rate: ischemic complications occurred in 0% of long-term and 2.1% of short-term DAPT patients, and the number of patients enrolled was lower than originally planned (44%). However, this is the only randomized controlled trial (RCT) investigating the optimal duration of DAPT after SAC, and it is crucial to note the limited benefits of long-term DAPT. Ozaki et al.[25] also reported the rates of ischemic and hemorrhagic complications between long-term (>6 months) and short-term (<6 months) DAPT by examining both RCT and non-RCT cohorts. A total of 313 patients were followed up for 15 months and analyzed. This report showed no significant differences in the ischemic and hemorrhagic complications between the groups. Shoda et al.[39] reported that long-term use of DAPT after SAC was associated with hemorrhagic complications in the delayed phase, particularly in responders (PRU <208). Therefore, prolonged DAPT should be avoided to prevent hemorrhagic complications. However, determining the appropriate duration of DAPT based on previous reports is difficult.

1-2-2 FD

The Japanese guidelines for FD recommend postoperative DAPT with ASA and CLP for more than 6 months. However, this recommendation is not based on evidence; therefore, the duration of DAPT is decided and administered at the physician's discretion in the real world. Three FDs (Pipeline, FRED, and Surpass) were launched in Japan, and the ischemic complications and postoperative APT for each FD are summarized above (**Table 1**).

Rice et al.[40] reported the outcomes after pipeline placement in 204 patients. Postoperative DAPT was interrupted within 3 months (20%), major ischemic complications in the territory supplied by the treated artery occurred in 2.9%, and neurological death occurred in 1%. Hanel et al.[41] reported the outcomes of 204 patients after pipeline placement. Postoperative DAPT was maintained for at least 3 months, followed by ASA monotherapy for at least 3 months; major ischemic complications in the territory supplied by the treated artery occurred in 2.1%, and neurological death occurred in 0.7%.

Guimaraens et al.[29] reported the treatment outcome of 185 cases using FRED; postoperative DAPT was maintained for at least 6 months and CLP or ASA for 12–18 months, and major ischemic complications occurred in 4.8% and 1.6% of cases 1–2 weeks after antiplatelet cessation.

Meyers et al.[31] reported on surpassing placement and analyzed 180 patients. Postoperative DAPT was recommended to be continued for a lifetime and required at least 6 months, and major ischemic complications occurred in 8.3% of patients.

To summarize the above reports, postoperative DAPT was continued for at least 3 months, and the major ischemic complication rate was 1.9%–8.3% within 12 months after FD placement. Since the postoperative DAPT was not based on evidence, further studies are necessary, and careful cessation or interruption of APT is needed.

Enomoto et al.[23] reported long-term ischemic and hemorrhagic complications after SAC and FD placement in a multicenter cohort study that enrolled 632 patients treated with SAC or FD in Japan. The median observation period was 646 days, and the average duration of DAPT was 125

days (SAC) and 198 days (FD). The event-free survival rates at 30 days and 1 year after the procedure were 93.3% and 91.5%, respectively, and both complications occurred more frequently within 30 days. No significant differences were observed between short-term (<90 days) and long-term (>90 days) DAPT (p = 0.84). However, the real-world duration of DAPT, assessed using a questionnaire, was slightly longer.[17,42] Caroff et al.[42] reported the questionnaire in France, and in this report, the duration of DAPT was 3 months (62%) and 6 months (38%) for single SAC and 3 months (39%), 6 months (53%), and 12 months (8%) for FD. Matsubara et al.[17] reported that the most common duration of DAPT for SAC was 6 months in Japan. Duration of DAPT after SAC and FD ranges from 3 to 9 mon ths,[29,37,40] and recent reports have tended to show few benefits of long-term DAPT.[20,24]

Most previous studies have described postoperative DAPT; however, little is known about the SAPT regimen after DAPT. The duration of SAPT varied from 9 to 18 months in previous reports.[29,40] In Japan, the most common duration of SAPT is 12 months, followed by a lifetime. The optimal duration of APT remains controversial. Some reports have investigated monotherapy with a P2Y12 inhibitor or ASA for secondary prevention in patients with atherosclerosis,[43–45] and these reports concluded that monotherapy with a P2Y12 inhibitor significantly reduced atherosclerotic events without an increase in major bleeding events compared to ASA. These results do not apply to APT after SAC or FD, and poor CLP metabolism persists. Maintaining P2Y12 inhibitors for SAPT may be vital, and the use of prasugrel or ticagrelor may resolve the poor metabolism in CLP.

2 Ruptured aneurysms

The efficacy of coil embolization for ruptured cerebral aneurysms has been demonstrated in the International Subarachnoid Aneurysm Trial (ISAT),[46] and the number of endovascular treatments for subarachnoid hemorrhage (SAH) is increasing in Japan.[47] Thromboembolism in endovascular treatment for ruptured aneurysms is a major complication similar to that in unruptured endovascular therapy. In the early era, APT was not routinely administered, and thromboembolism occurred in 5%–11% of patients.[48,49] The use of APT for preventing thromboembolism requires careful consideration because it can lead to the exacerbation of SAH and increase the bleeding complications of drainage and craniotomy that may be needed after embolization. Ries et al.[7] also reported that intravenous ASA for ruptured cases effectively prevents thromboembolism. ASA 250 mg was administered after the first coil placement, and thromboembolic events occurred in 10.1% and 20% of patients in the +ASA and −ASA groups, respectively (p = 0.047). Shimamura et al.[49] reported on preprocedural APT-ruptured aneurysms; 200 mg ASA and 150 mg CLP were administered 2 h before the procedure and hemorrhagic and ischemic complications were investigated.[49] A total of 35 patients were enrolled; asymptomatic thrombosis occurred in only 2.9% of patients, and no hemorrhagic complications were reported. Another study reported an association between preprocedural APT for coil embolization of ruptured aneurysms and clinical outcomes.[50] In this study, 110 patients were enrolled; 73% were medicated with multiple APTs, 20% were treated with a single APT, and 7% were treated without APT. APT was administered 2 h before the procedure, and the selection of medication depended on the aneurysm features (atypical location: without APT; narrow neck: ASA 200 mg; wide neck: ASA 200 mg and CLP 150–300 mg; large size: ASA 200 mg, CLP 150–300 mg, and cilostazol 200 mg). Intraoperative thromboembolic complications decreased significantly according to the number of APTs, whereas hemorrhagic complications did not increase with APTs. These reports demonstrate the effectiveness of preoperative APT in cases of ruptured aneurysms, in which simple coil embolization is the basic strategy. Ryu et al.[51] conducted a systematic review of the complications after SAC for ruptured aneurysms. Thirty-three studies with 1090 patients were analyzed, and the event rates of thromboembolism and periprocedural hemorrhage were 11.2% and 9.0%, respectively. This study performed subgroup analyses; patients were divided into preprocedural, modified method, and postprocedural APT administration groups, and the rate of thromboembolism and periprocedural hemorrhage were compared. The loading dose of DAPT (ASA and CLP) was administered at least 2 h before the procedure in the preprocedural group (331 patients), a glycoprotein IIb/IIIa inhibitor was intravenously administered after stent deployment in the modified method group (199 patients), and the loading dose of DAPT was administered after completion of the endovascular procedure with intraprocedural administration of a kind of APT in the postprocedural group (560 patients). The thromboembolism rates in the preprocedural, modified, and postprocedural groups were 7.4%, 13.9%, and 12.3%, respectively, and there was no significant difference in periprocedural hemorrhage among the groups. This

report concluded that complications of SAC for ruptured intracranial aneurysms may be affected by the method of antiplatelet administration. Another systematic review investigated the association between clinical outcomes and APT in patients with SAH,[52] and this report showed that APT after SAH was associated with functional outcomes improvement, but not with delayed cerebral ischemia or intracranial hemorrhage. As mentioned above, the use of APT in patients with SAH is not generally considered to contribute to bleeding or worsen the prognosis, and it is necessary to prevent ischemic complications associated with coil embolization. However, careful consideration is essential when using APT in patients with SAH.

Conclusion

We reviewed previous reports on the use of APT in the endovascular treatment of cerebral aneurysms. Since there is still little evidence in this area and APT is an off-label therapy, evidence of APT for aneurysms will hopefully be established. An RCT is currently planned to examine the frequency of bleeding complications in the chronic phase in patients with FD divided into short- and long-term DAPT groups, and the results of this RCT are expected. Regardless of the indication, APT ensures patient safety, and it is important to ensure appropriate dose and duration management adjustments preoperatively according to platelet reactivity and postoperatively according to aneurysm morphology, treatment device, and patient background, avoiding unnecessarily prolonged administration.

Disclosure Statement

Yukiko Enomoto received research grants from Sysmex and Medtronic and lecture fees from Daiichi Sankyo, Otsuka Pharmaceutical Co. Ltd., and Medtronic. Matsubara Hirofumi and Egashira Yusuke declare no conflicts of interest.

References

1) Wallace AN, Samaniego E, Kayan Y, et al. Balloon-assisted coiling of cerebral aneurysms with the dual-lumen Scepter XC balloon catheter: experience at two-volume centers. *Interv Neuroradiol* 2019; 25: 414–418.
2) Oushy S, Rinaldo L, Brinjikji W, et al. Recent advances in stent-assisted coiling of cerebral aneurysms. *Expert Rev Med Devices* 2020; 17: 519–532.
3) Hong Y, Wang YJ, Deng Z, et al. Stent-assisted coiling versus coiling in treatment of intracranial aneurysm: a systematic review and meta-analysis. *PLoS One* 2014; 9: e82311.
4) Yan Y, Zhu D, Tang H, et al. Safety and efficacy of flow diverter treatment for aneurysm in small cerebral vessels: a systematic review and meta-analysis. *World Neurosurg* 2018; 115: 54–64.
5) Nishikawa Y, Satow T, Takagi T, et al. Efficacy and safety of single versus dual antiplatelet therapy for coiling of unruptured aneurysms. *J Stroke Cerebrovasc Dis* 2013; 22: 650–655.
6) Suzuki R, Takigawa T, Nagaishi M, et al. Impact of size ratio on thromboembolic events based on diffusion-weighted imaging after coil embolization for unruptured basilar apex aneurysm. *Clin Neurol Neurosurg* 2023; 228: 107699.
7) Ries T, Buhk JH, Kucinski T, et al. Intravenous administration of acetylsalicylic acid during endovascular treatment of cerebral aneurysms reduces the rate of thromboembolic events. *Stroke* 2006; 37: 1816–1821.
8) Kang HS, Han MH, Kwon BJ, et al. Is clopidogrel premedication useful to reduce thromboembolic events during coil embolization for unruptured intracranial aneurysms? *Neurosurgery* 2010; 67: 1371–1376; discussion, 1376.
9) Groden C, Kremer C, Regelsberger J, et al. Comparison of operative and endovascular treatment of anterior circulation aneurysms in patients in poor grades. *Neuroradiology* 2001; 43: 778–783.
10) Henkes H, Fischer S, Weber W, et al. Endovascular coil occlusion of 1811 intracranial aneurysms: early angiographic and clinical results. *Neurosurgery* 2004; 54: 268–285; discussion, 280–285.
11) Murayama Y, Nien YL, Duckwiler G, et al. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg* 2003; 98: 959–966.
12) Gallas S, Pasco A, Cottier JP, et al. A multicenter study of 705 ruptured intracranial aneurysms treated with Guglielmi detachable coils. *AJNR Am J Neuroradiol* 2005; 26: 1723–1731.
13) Yamada NK, Cross DT 3rd, Pilgram TK, et al. Effect of antiplatelet therapy on thromboembolic complications of elective coil embolization of cerebral aneurysms. *AJNR Am J Neuroradiol* 2007; 28: 1778–1782.
14) Fujita K, Fujii S, Hirai S, et al. P2Y12 reaction units and ischemic and bleeding events after neuro-endovascular treatment. *J Stroke Cerebrovasc Dis* 2022; 31: 106631.
15) Higashiguchi S, Sadato A, Nakahara I, et al. Reduction of thromboembolic complications during the endovascular treatment of unruptured aneurysms by employing a tailored dual antiplatelet regimen using aspirin and prasugrel. *J Neurointerv Surg* 2021; 13: 1044–1048.
16) Nakamura K, Goto F, Ray WA, et al. Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. *Clin Pharmacol Ther* 1985; 38: 402–408.

17) Matsubara H, Mizutani D, Egashira Y, et al. Perioperative antiplatelet therapy for the stent-assisted coil embolization: results of the questionnaire survey. *J Neuroendovasc Ther* 2023; 17: 56–60.
18) Mo L, Yue J, Yu W, et al. Diffusion-weighted imaging lesions after endovascular treatment of cerebral aneurysms: a network meta-analysis. *Front Surg* 2023; 9: 964191.
19) Song J, Yeon JY, Kim JS, et al. Delayed thromboembolic events more than 30 days after self expandable intracranial stent-assisted embolization of unruptured intracranial aneurysms. *Clin Neurol Neurosurg* 2015; 135: 73–78.
20) Kim T, Kim CH, Kang SH, et al. Relevance of antiplatelet therapy duration after stent-assisted coil embolization for unruptured intracranial aneurysms. *World Neurosurg* 2018; 116: e699–e708.
21) Piotin M, Blanc R, Spelle L, et al. Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. *Stroke* 2010; 41: 110–115.
22) Narata AP, Amelot A, Bibi R, et al. Dual antiplatelet therapy combining aspirin and ticagrelor for intracranial stenting procedures: a retrospective single center study of 154 consecutive patients with unruptured aneurysms. *Neurosurgery* 2019; 84: 77–83.
23) Enomoto Y, Matsubara H, Ishihara T, et al. Optimal duration of dual antiplatelet therapy for stent-assisted coiling or flow diverter placement. *J Neurointerv Surg* 2024; 16: 491–497.
24) Ozaki T, Yamagami H, Morimoto M, et al. Short- versus long-term dual antiplatelet therapy for stent-assisted treatment of cerebral aneurysm (DAPTS ACE): a multicenter, open-label, randomized clinical trial. *J Neurointerv Surg* 2024; 16: 171–176.
25) Ozaki T, Yamagami H, Morimoto M, et al. Relation between duration of dual antiplatelet therapy and risk of ischemic stroke after stent-assisted treatment of cerebral aneurysm (DAPTS ACE-registry). *J Neurointerv Surg* 2023; jnis–2023-020495. [Epub ahead of print]
26) Chien SC, Chen CC, Chen CT, et al. Ticagrelor versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. *Interv Neuroradiol* 2022; 28: 568–574.
27) Sedat J, Chau Y, Gaudart J, et al. Prasugrel versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. *Interv Neuroradiol* 2017; 23: 52–59.
28) Tonetti DA, Jankowitz BT, Gross BA. Antiplatelet therapy in flow diversion. *Neurosurgery* 2020; 86(Suppl 1): S47–S52.
29) Guimaraens L, Vivas E, Saldaña J, et al. Efficacy and safety of the dual-layer flow-diverting stent (FRED) for the treatment of intracranial aneurysms. *J Neurointerv Surg* 2020; 12: 521–525.
30) Szikora I, Marosfoi M, Salomváry B, et al. Resolution of mass effect and compression symptoms following endoluminal flow diversion for the treatment of intracranial aneurysms. *AJNR Am J Neuroradiol* 2013; 34: 935–939.
31) Meyers PM, Coon AL, Kan PT, et al. SCENT trial. *Stroke* 2019; 50: 1473–1479.
32) Delgado Almandoz JE, Crandall BM, Scholz JM, et al. Last-recorded P2Y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. *AJNR Am J Neuroradiol* 2014; 35: 128–135.
33) Delgado Almandoz JE, Crandall BM, Scholz JM, et al. Pre-procedure P2Y12 reaction units value predicts periprocedural thromboembolic and hemorrhagic complications in patients with cerebral aneurysms treated with the Pipeline Embolization Device. *J Neurointerv Surg* 2013; 5(Suppl 3): iii3–iii10.
34) Suyama K, Nakahara I, Matsumoto S, et al. Efficacy and safety of dual antiplatelet therapy with the routine use of prasugrel for flow diversion of cerebral unruptured aneurysms. *Clin Neuroradiol* 2024; 34: 201–208.
35) Liu L, Xu L, Guo N, et al. Ticagrelor is related to nuisance bleeding after flow diversion of unruptured intracranial aneurysms. *Neurosurg Rev* 2023; 46: 134.
36) Park KY, Ozaki T, Kostynskyy A, et al. Ticagrelor versus clopidogrel in the dual antiplatelet regimen for intracranial stenting or flow-diverter treatment for unruptured cerebral aneurysms: a single-center cohort study. *AJNR Am J Neuroradiol* 2021; 42: 1638–1644.
37) Hwang G, Kim JG, Song KS, et al. Delayed ischemic stroke after stent-assisted coil placement in cerebral aneurysm: characteristics and optimal duration of preventative dual antiplatelet therapy. *Radiology* 2014; 273: 194–201.
38) Rossen JD, Chalouhi N, Wassef SN, et al. Incidence of cerebral ischemic events after discontinuation of clopidogrel in patients with intracranial aneurysms treated with stent-assisted techniques. *J Neurosurg* 2012; 117: 929–933.
39) Shoda K, Enomoto Y, Egashira Y, et al. Long-term complications after stent assist coiling dependent on clopidogrel response. *BMC Neurol* 2021; 21: 247.
40) Rice H, Martínez Galdámez M, Holtmannspötter M, et al. Periprocedural to 1-year safety and efficacy outcomes with the Pipeline Embolization Device with Shield technology for intracranial aneurysms: a prospective, postmarket, multi-center study. *J Neurointerv Surg* 2020; 12: 1107–1112.
41) Hanel RA, Kallmes DF, Lopes DK, et al. Prospective study on embolization of intracranial aneurysms with the pipeline device: the PREMIER study 1 year results. *J Neurointerv Surg* 2020; 12: 62–66.

42) Caroff J, Aubert L, Lavenu-Bombled C, et al. Antithrombotic therapies for neurointerventional surgery: a 2021 French comprehensive national survey. *J Neurointerv Surg* 2023; 15: 402–407.
43) Chiarito M, Sanz-Sánchez J, Cannata F, et al. Monotherapy with a $P2Y_{12}$ inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020; 395: 1487–1495.
44) Aggarwal D, Bhatia K, Chunawala ZS, et al. $P2Y_{12}$ inhibitor versus aspirin monotherapy for secondary prevention of cardiovascular events: meta-analysis of randomized trials. *Eur Heart J Open* 2022; 2: oeac019.
45) Al-Abdouh A, Abusnina W, Mhanna M, et al. P2Y12 inhibitors versus aspirin monotherapy for long-term secondary prevention of atherosclerotic cardiovascular disease events: a systematic review and meta-analysis. *Curr Probl Cardiol* 2022; 47: 101292.
46) Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005; 366: 809–817.
47) Sakai N, Uchida K, Iihara K, et al. Japanese surveillance of neuroendovascular therapy in J.R.,-NET - Part II. Japanese registry of neuroendovascular treatment 3. Main report. *Neurol Med Chir (Tokyo)* 2019; 59: 106–115.
48) van Rooij WJ, Sluzewski M. Procedural morbidity and mortality of elective coil treatment of unruptured intracranial aneurysms. *AJNR Am J Neuroradiol* 2006; 27: 1678–1680.
49) Shimamura N, Naraoka M, Matsuda N, et al. Safety of preprocedural antiplatelet medication in coil embolization of ruptured cerebral aneurysms at the acute stage. *Interv Neuroradiol* 2014; 20: 413–417.
50) Shimamura N, Naraoka M, Matsuda N, et al. Use of preprocedural, multiple antiplatelet medications for coil embolization of ruptured cerebral aneurysm in the acute stage improved clinical outcome and reduced thromboembolic complications without hemorrhagic complications. *World Neurosurg* 2020; 133: e751–e756.
51) Ryu CW, Park S, Shin HS, et al. Complications in stent-assisted endovascular therapy of ruptured intracranial aneurysms and relevance to antiplatelet administration: a systematic review. *AJNR Am J Neuroradiol* 2015; 36: 1682–1688.
52) Nagahama Y, Allan L, Nakagawa D, et al. Dual antiplatelet therapy in aneurysmal subarachnoid hemorrhage: association with reduced risk of clinical vasospasm and delayed cerebral ischemia. *J Neurosurg* 2018; 129: 702–710.