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Review Article

Antithrombotic Therapy in Carotid Artery and Intracranial Artery Stent

Ichiro Nakagawa, Masashi Kotsugi, Shohei Yokoyama, Ryosuke Maeoka, Hiromitsu Sasaki, Ai Okamoto, Yudai Morisaki, Tomoya Okamoto, Kengo Yamada, and Ryosuke Matsuda

Optimal platelet inhibition is critical in patients with carotid and intracranial artery stenosis undergoing carotid artery stenting (CAS) and intracranial artery stenting (ICS). Many reports have highlighted the importance of dual antiplatelet therapy (DAPT) in reducing adverse neurological outcomes without a significant increase in bleeding complications during CAS. DAPT has commonly used CAS and ICS, typically with aspirin and clopidogrel, but clopidogrel resistance occurs in approximately 20% of Japanese and other Asian populations. One solution to clopidogrel resistance is using adjunctive cilostazol to suppress the frequency of stroke events and in-stent restenosis after CAS. Other antiplatelet agents such as prasugrel, ticagrelor, cangrelor, and glycoprotein (GP) IIb/IIIa inhibitors are under investigation. The duration of DAPT after CAS remains controversial, as a longer duration of DAPT after CAS is associated with lower rates of readmission for stroke, but increased risk of hemorrhagic complications. Regarding antithrombotic therapy in CAS with concomitant atrial fibrillation, the use of direct oral anticoagulants plus a P2Y12 inhibitor may be suggested for the optimal safety and efficacy of antithrombotic management. For emergent CAS in acute ischemic stroke (AIS), intraprocedural DAPT loading and GP IIb/IIIa inhibitors, as necessary, may improve stent patency without increasing the risk of intracranial hemorrhage. In ICS, aggressive antiplatelet therapy based on an assessment of platelet aggregation is also important to improve clinical outcomes. In addition, rescue stenting for AIS caused by intracranial atherosclerotic stenosis-related large vessel occlusion is gaining attention. GP IIb/IIIa inhibitors have shown promise, but are not approved in Japan. In conclusion, DAPT is essential for the perioperative management of CAS and ICS. Specific perioperative antithrombotic management remains unclear, but the potential benefits of antithrombotic agents must be weighed against the corresponding increased risk of bleeding complications.

Keywords ▶ antiplatelet therapy, carotid artery stenting, intracranial artery stenting

Introduction

Optimal platelet inhibition represents an important therapeutic adjunct in patients with carotid artery or intracranial artery stenosis undergoing carotid artery stenting (CAS) and intracranial artery stenting (ICS). Many reports have shown that the efficacy of dual antiplatelet therapy (DAPT) during CAS treatment determines the success or failure of treatment.[1–4] With respect to ICS, no evidence currently suggests that ICS is superior to the best medical treatment, but well-functioning DAPT has been noted as important for reducing the perioperative complications of ICS. Although DAPT has become the standard pretreatment pharmacotherapy for CAS and ICS and oral aspirin and clopidogrel have been the standard regimen in most previous reports, clopidogrel shows wide interindividual variation in its antiplatelet effects.[5,6] Several studies have reported periprocedural thromboembolic complications in neurovascular and cardiovascular stent placement in patients with clopidogrel resistance.[7] Furthermore, there is no standardized approach to antithrombotic drug management in various situations, such as the specific types of DAPT for combined administration, when to start and when to stop DAPT, combination

Department of Neurosurgery, Nara Medical University, Kashihara, Nara, Japan

Received: February 10, 2024; Accepted: March 26, 2024
Corresponding author: Ichiro Nakagawa. Department of Neurosurgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
Email: nakagawa@naramed-u.ac.jp

with direct oral anticoagulants (DOACs) in patients with non-valvular atrial fibrillation (NVAF), effectiveness in preventing in-stent restenosis (ISR), and more recently, antithrombotic drug management during emergency CAS in acute ischemic stroke (AIS). This review discusses the current status and future prospects for antithrombotic therapy in CAS and ICS.

DAPT in CAS

DAPT is known to reduce ischemic complications in percutaneous coronary intervention with bare metal stents compared to aspirin alone or aspirin plus anticoagulant[8] and has also been shown to reduce ischemic complications in CAS treatment compared to aspirin alone.[1,9] Mckevitt et al.[10] reported that hemorrhagic complications (groin hematoma or excessive bleeding at the groin site) within 30 days after CAS occurred in 17% of an aspirin plus heparin group and 9% of an aspirin plus clopidogrel group (p = 0.35) and the incidence of neurological complications in the 24-h aspirin and heparin group was 25%, compared with 0% in the aspirin and clopidogrel group (p = 0.02). They concluded that DAPT has a significant impact in reducing adverse neurological outcomes without an additional increase in bleeding complications.[10] A study on the real-world experience of CAS from the Japanese Registry of NeuroEndovascular Therapy (JR-NET3) reported that 7581 patients (94.8%) undergoing CAS received dual or triple antiplatelet therapy, and aspirin (85.8%) and clopidogrel (79.7%) were commonly used among those antiplatelet agents.[11] The ACCF/SCAI/SVMB/SIR/ASITN clinical expert consensus document recommended that the patient should be treated with aspirin and clopidogrel for at least 24 h before the procedure, and preferably for 4 days.[12] In contrast, the effectiveness of cilostazol in improving clinical outcomes has been reported. Sakai et al. reported that the incidence of the first event of death, ischemic stroke, hemorrhagic stroke, transient ischemic attack, myocardial infarction, or serious hemorrhage for aspirin plus cilostazol was significantly lower than that for aspirin plus clopidogrel (p = 0.01) and antiplatelet monotherapy (p < 0.01), suggesting an additional effect of cilostazol. We have also shown that DAPT of cilostazol and clopidogrel reduces the rate of clopidogrel resistance (5% versus 16%, p <0.001) and suppresses new ischemic lesions (8% versus 25%, p <0.047) without hemorrhagic complications compared with standard DAPT of aspirin plus clopidogrel.[4] Cilostazol enhances cAMP within platelets by blocking phosphodiesterase-3A. Since both clopidogrel and cilostazol augment cAMP levels in the signal transduction pathway from P2Y12 receptors, the combined use of these two drugs augments the inhibition of ADP-induced platelet aggregation.[13] Furthermore, the effect of cilostazol in reducing ISR has also been reported.[14,15] Takayama et al.[16] reported that the restenosis rate in the non-cilostazol group was 15.6% (5/32), while the restenosis rate in the cilostazol group was 0% (0/30) (p = 0.024). These ISR-suppressing effects of cilostazol have been attributed to the prevention of intimal hyperplasia after stent placement, inhibition of smooth-muscle cell proliferation, and actions on endothelial cells.[17,18]

Several studies have examined the duration of DAPT after CAS. Although the ACCF/SCAI/SVMB/SIR/ASITN clinical expert consensus document recommended that aspirin should be continued for life and clopidogrel should be given for at least 4 weeks,[12] the mean duration of DAPT after CAS was observed to be 3 months in the Asymptomatic Carotid Surgery Trial, and the frequency of stroke events with long-term DAPT after CAS appears similar to that of short-term DAPT.[19] Jhang et al. reported that the use of aspirin plus clopidogrel for longer than 42 days after CAS did not decrease the risks of ischemic stroke, composite vascular events, or death during 6 months of follow-up.[20] On the other hand, a recent study suggested that a longer duration of DAPT after CAS is associated with lower rates of readmission for stroke, but an increased risk of hemorrhagic complications (particularly extracranial hemorrhage).[2] The potential benefits of prolonged DAPT for ischemic complications must be balanced against the corresponding increased risk of hemorrhagic complications.

Clopidogrel Resistance in CAS

As mentioned above, DAPT using a combination of two aspirin, clopidogrel, or cilostazol is the most common perioperative antiplatelet therapy in CAS. However, clopidogrel resistance is known to occur in approximately 20% of Japanese and other Asian populations.[21] Clopidogrel is a prodrug that requires metabolic conversion to an active metabolite by several cytochrome P450 (CYP) isoenzymes, and one of these isoenzymes, CYP2C19, is known to inhibit ADP-induced platelet activation and aggregation.[22] VerifyNow assay (Accumetrics, San Diego, CA), light transmission aggregometry, platelet function analyzer (PFA-100), and thromboelastography are currently

available; however, no single test is clearly superior as it targets specific pathways in the multi-step process of platelet adhesion, activation, and aggregation.[23] In the coronary artery literature, several studies have reported an optimal cutoff value for thromboembolic complications for PCI under DAPT (e.g., P2Y12 reaction units (PRU) ≤178 or ≤189)[24,25]; however, the optimal cutoff value in CAS is unknown. Sorkin et al.[26] reported that platelet aggregation assessment showing ≤198 PRU by VerifyNow assay may be associated with a lower incidence of ischemic neurological sequela and death after CAS. A recent study also demonstrated that patients identified as clopidogrel nonresponders were at increased risk of developing thromboembolic events.[27] Such reports indicate that clopidogrel resistance influences clinical outcomes among patients who have undergone CAS.

Various potential solutions to clopidogrel resistance have been reported. A study using double doses of clopidogrel (150 mg/day) found no significant inhibition of platelet aggregation at 30 days after CAS and showed that incidences of transient ischemic attack, stroke, and death at up to 30 days after CAS were similar to those with the standard dose of clopidogrel (75 mg/day).[28] In contrast, we have previously reported that adjunctive cilostazol in patients with clopidogrel resistance suppressed the frequency of new cerebral ischemic lesions without increasing hemorrhagic complications, decreased PRU values, and intensified platelet inhibition as compared with aspirin plus clopidogrel DAPT.[13] In recent years, ticagrelor has been attracting attention in Western countries because its non-responsiveness appears practically absent, compared to 20%–25% for clopidogrel and 10% for prasugrel.[29] Recent reports have suggested that ticagrelor as part of DAPT is safe and efficacious in both symptomatic and asymptomatic carotid artery stenosis in patients undergoing trans-carotid artery revascularization[30] and CAS.[31] However, ticagrelor has not yet been approved for use in Japan, so prasugrel would be expected as an alternative to clopidogrel to avoid resistance issues.

Antithrombotic Therapy in CAS with Concomitant Atrial Fibrillation

NVAF and carotid artery stenosis are major risk factors for stroke. CAS is recommended for patients with symptomatic high-grade carotid stenosis, but the optimal medical management of patients with NVAF after CAS remains unclear.[32] Huang et al. reported that a group with a combination of a single antiplatelet agent and an anticoagulant and a group with anticoagulant alone showed significantly lower mortality rates than a group with only a single antiplatelet agent, with no significant differences in major bleeding, ischemic stroke, or vascular events.[33] Furthermore, a recent study showed that among NVAF patients with large vessel occlusion stroke treated by endovascular thrombectomy and emergent CAS, the 90-day mortality rate was significantly higher in patients not receiving oral anticoagulation.[34] Those reports suggested a need for anticoagulation therapy in CAS with NVAF, but Pardo-Galiana et al.[35] demonstrated that triple therapy, as a combination of anticoagulation and DAPT, confers a significantly high risk of bleeding among CAS patients with NVAF compared to patients with DOACs plus clopidogrel or those with DAPT. A regimen of DOACs plus a P2Y12 inhibitor could provide a good safety profile with significantly lower bleeding rates and optimal efficacy but requires further investigation.

Antithrombotic Therapy in Emergent CAS for AIS

Acute stroke from the tandem extracranial carotid artery and intracranial large vessel occlusion poses challenges for emergency endovascular treatment. Establishing and maintaining patency of the carotid artery and avoiding intracranial hemorrhage (ICH) are competing concerns. A recent study suggested that emergent CAS (eCAS) combined with intracranial mechanical thrombectomy represents an effective treatment for tandem occlusions that can be performed with a high technical success rate and can achieve good clinical outcomes.[36] Although periprocedural antithrombotic treatment is a key determinant for the risk–benefit balance of eCAS during stroke thrombectomy, no consensus has yet been reached on optimal antithrombotic therapy for eCAS.[37] Early reports have suggested that the administration of heparin 3000 IU, the administration of glycoprotein (GP) IIb/IIIa inhibitors, and DAPT during eCAS increased the risk of ICH.[38,39] Regarding rescue treatment during eCAS, cangrelor and aspirin presented a better safety profile than abciximab, a GP IIb/IIIa inhibitor, with a lower risk of ICH and a higher rate of good clinical outcomes.[40] However, more recently, reports have been increasing that intraprocedural DAPT loading and the use of a GP IIb/IIIa inhibitor, when necessary, increase stent patency without increasing symptomatic ICH compared to aspirin alone or aspirin plus heparin.[41,42] Although

there are no standardized criteria yet for the duration of DAPT after eCAS, it may be advisable to refrain from prolonged DAPT, as it has been reported that consecutive GP IIb/IIIa inhibitor or DAPT suffered from an increased risk of relevant secondary ICH[43] and discontinuation of DAPT was not associated with any increase in the risk of stent thrombosis after eCAS.[44] Recently, urgent CAS with crash-loaded antiplatelet therapy (comprising 500 mg of intravenous aspirin and 600 mg of oral clopidogrel) on the day of CAS did not produce any more ischemic, thrombotic, or hemorrhagic complications than conventional longer loading times.[45] Further studies are warranted to assess the presence of any additional benefit better and clarify the optimal duration of DAPT after tandem lesion stroke thrombectomy.

Antithrombotic Therapy in Intracranial Artery Stent Therapy

Although ICS for atherosclerotic lesions has been reported to offer better clinical outcomes with the use of self-expandable wingspan stents,[46] the SAMMPRIS randomized controlled trial (RCT) showed that aggressive medical therapy was superior to stenting.[47] Subsequently, in the WEAVE/WOVEN trials with strict eligibility criteria, including platelet aggregation control (>80 PRU but <237 PRU), wingspan stenting outcomes were better than in the medical group of the SAMMPRIS study.[48,49] A recent CASSIS RCT was therefore performed to demonstrate the superiority of ICS but failed to show any benefit of ICS despite strict perioperative platelet aggregation control.[50] The Japanese wingspan stent post-marketing study showed frequencies of 3.9% for ischemic events, 7.9% for total stroke events, and 9.2% for total stroke and death at 1 year, representing a good result comparable to WEAVE/WOVEN, which may be due to the strict use of antiplatelet drugs and patient selection criteria.[51] In a sub-analysis of the SAMMPRIS study regarding the duration of DAPT to determine whether DAPT beyond 90 days affects the risk of bleeding, the major bleeding rate tended to be high in both the augmented medical therapy-alone arm (DAPT >90 days = 4.0% versus DAPT ≤90 days = 2.5%; $p = 0.67$) and the ICS arm (DAPT >90 days = 10.9% versus DAPT ≤90 days = 3.5%; $p = 0.08$).[3] Long-term use of DAPT may reduce the risk of stroke among patients receiving medical therapy for intracranial stenosis but may increase the risk of major bleeding.

On the other hand, rescue stenting of AIS caused by intracranial atherosclerotic stenosis-related large vessel occlusion, especially in the internal carotid artery and M1 portion of the middle cerebral artery, has recently received attention.[52] Intravenous administration of GP IIb/IIIa inhibitor has been reported to significantly improve functional outcomes and death at 90 days without increasing symptomatic ICH,[53] and several similar reports have been presented.[54] However, GP IIb/IIIa inhibitor has not yet been approved for use in Japan and this gap in drug approval between Western countries and Japan, as the so-called "drug lag," needs to be resolved.

Conclusions

Although DAPT is an essential perioperative management in CAS and ICS, many issues remain to be addressed. The potential benefits of antithrombotic drugs must be weighed against the corresponding increases in the risk of bleeding complications.

Disclosure Statement

The authors have no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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