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Original Article

Strategies to Prevent Ischemic Complications after Stent-assisted Coil Embolization of Cerebral Aneurysms

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Objective: There have been no delayed ischemic complications related to stent-assisted coil embolization (SACE) of cerebral aneurysms at our institution. We demonstrate our strategies for stent placement and postoperative management of antiplatelet therapy to reduce the risk of ischemic complications.

Methods: We analyzed 57 cases of SACE retrospectively. In the procedure, an appropriate stent was selected and placed to fit the arterial wall without impeding on small arterial branches. Two different antiplatelet drugs, including clopidogrel, were used. Six to twelve months after surgery, follow-up angiography was performed to assess the safety of terminating antiplatelet therapy. In cases in which antiplatelet therapy was tapered, the two antiplatelet drugs were switched to clopidogrel alone, and it was subsequently tapered and finally discontinued.

Results: There were 49 cases of SACE in which postoperative antiplatelet therapy was tapered. Among these cases, antiplatelet therapy was discontinued in 35 cases. The mean duration of dual antiplatelet therapy was 10.6 ± 2.8 months, and the mean duration of total antiplatelet therapy was 15.0 ± 2.1 months. Three patients developed SACE-related ischemic stroke, which developed in the early phase after surgery in all.

Conclusion: Antiplatelet therapy can safely be terminated in most cases of SACE. In order to reduce the risk of ischemic complications, stent selection, stent placement, and management of antiplatelet therapy should be performed appropriately. Furthermore, careful follow-up should be continued even after the termination of antiplatelet therapy.

Keywords ▶ stent-assisted coil embolization, ischemic complications, antiplatelet therapy, clopidogrel

Introduction

Stent-assisted coil embolization (SACE) of cerebral aneurysms has relatively high risk of ischemic complications due to the stent placement in the parent artery, requiring long-term antiplatelet therapy in comparison with standard coil embolization.[1–4] However, long-term antiplatelet therapy may increase the risk of hemorrhage. On the other hand, antiplatelet therapy for SACE can be tapered and finally discontinued during the postoperative course, differing from stenting for arteriosclerotic lesions. Most ischemic complications after SACE develop early after surgery, but delayed complications may develop in some cases.[2,4–9] Therefore, an optimal protocol for antiplatelet therapy following SACE to minimize the risks of ischemic and hemorrhagic complications remains to be clarified. At our institution, there have been no delayed ischemic complications related to SACE. We target the termination of antiplatelet therapy 1 year after surgery, but whether it is appropriate is evaluated in individual patients. We hereby present points to which we have paid much attention in stent selection/placement and dose reduction of antiplatelet drugs to reduce the risk of ischemic complications.

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Materials and Methods

Prior to this study, its protocol was approved by the ethical committee of our institution. Of patients who had undergone SACE at our institution between January 2014 and December 2018, we retrospectively analyzed 57 patients who were able to be followed up (**Table 1**). The aneurysmal

Table 1 Location of aneurysms and placed stent type

	ICA	MCA	BA apex	VA	Acom	PCA
Neuroform EZ, Neuroform Atlas	10	11	3	0	2	0
LVIS	14	0	0	2	0	0
LVIS Jr.	1	1	3	1	1	1
Enterprise, Enterprise 2	3	0	0	3	0	1

Acom: anterior communicating artery; BA: basilar artery; ICA: internal carotid artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VA: vertebral artery

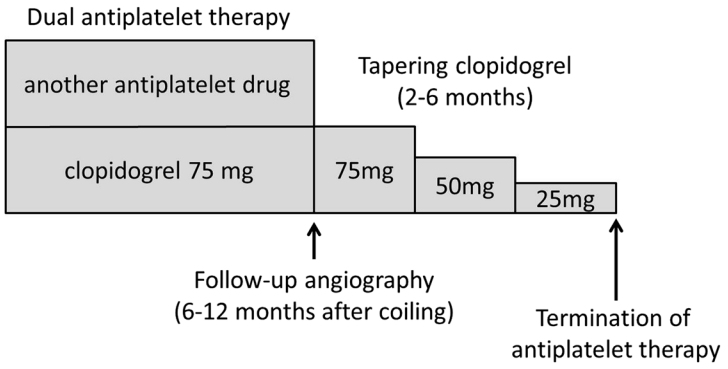

Fig. 1 Protocol for postoperative antiplatelet therapy after SACE for cerebral aneurysms. Following angiography 6 to 12 months after surgery, DAPT is switched to clopidogrel alone. The dose of clopidogrel was subsequently tapered for 2 to 6 months and finally discontinued. DAPT: dual antiplatelet therapy; SACE: stent-assisted coil embolization

sites consisted of the internal carotid artery in 28 patients, middle cerebral artery in 12, basilar artery apex in 6, vertebral artery in 6, anterior communicating artery in 3, and posterior cerebral artery in 2. The subjects included 7 in the acute phase of rupture. The types of stent consisted of LVIS (Terumo, Tokyo, Japan) in 16 patients, Neuroform EZ (Stryker, Kalamazoo, MI, USA) in 13, Neuroform Atlas (Stryker) in 13, LVIS Jr. (Terumo) in 8, Enterprise (Johnson & Johnson, New Brunswick, NJ, USA) in 6, and Enterprise 2 (Johnson & Johnson) in one. Neuroform EZ had been used only in patients before Neuroform Atlas became available. Neuroform stents were primarily selected to be placed in the middle cerebral artery (11/12 patients).

Selection and placement of the stent

For the appropriate selection and placement of the stent, we investigated the presence of important small branch vessels from the parent artery, in addition to the diameter and shape of the parent artery. When the marked difference in the vascular diameter or the marked tortuosity at the site of stent placement was noted, an open-cell stent was selected and placed in order for it to fit the vascular wall. When important small branch vessels, such as perforating arteries or the anterior choroidal artery, bifurcated from the parent artery, attention was paid in order not to cover the bifurcation of the branches by the stent. However, when stent placement at the bifurcation was necessary, an open-cell stent, which is not likely to extend a blood vessel, with a low metallic coverage rate was preferentially selected and placed such that the shape of the parent artery was maintained, not to influence blood flow of the small branch vessels. When the difference in the diameter of the parent artery was small, with low tortuosity and no small branch vessels, closed-cell or braided stents, which have the high metallic coverage rate and the high rectifying effects, were preferentially selected in order to prevent recanalization of the aneurysm.

Antiplatelet therapy

Perioperative dual antiplatelet therapy (DAPT), including clopidogrel, was performed for all patients. In general, 100 mg of aspirin and 75 mg of clopidogrel were used. However, for patients who had received an antiplatelet drug other than clopidogrel, clopidogrel was added for DAPT. Follow-up cerebral angiography was performed 6 to 12 months after surgery to evaluate the states of the embolized aneurysm and the placed stent. When there was no necessity of retreatment for the aneurysm, with favorable patency in the absence of stent deformity or stenosis, the dose reduction of antiplatelet drugs was started. One (other than clopidogrel) of two drugs was initially discontinued,

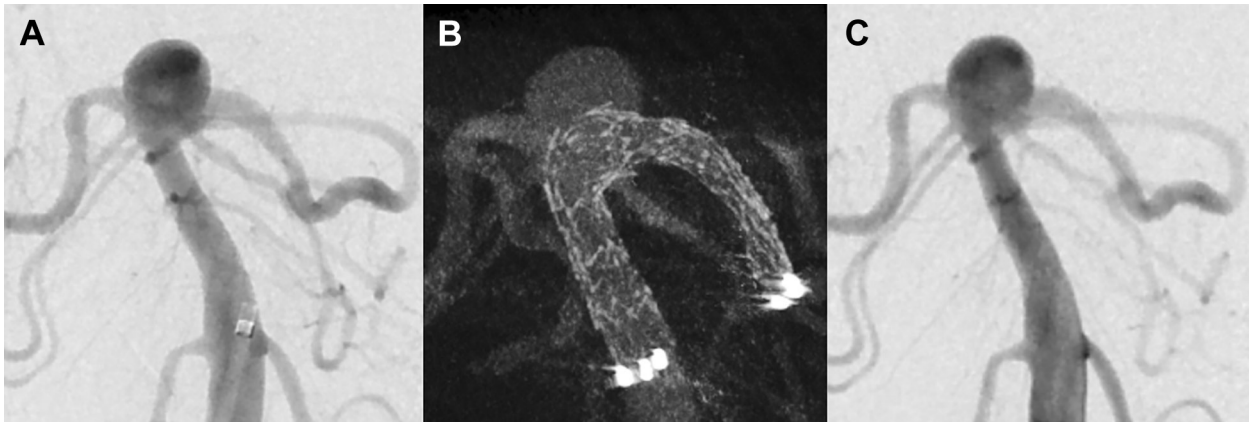

Fig. 2 (**A**) A 65-year-old man with a basilar apex aneurysm. (**B**) Neuroform Atlas (4.5 × 30 mm) was placed in the parent artery for coil embolization of the aneurysm using the trans-cell technique. (**C**) Note that the configuration of arteries was unchanged after stent placement.

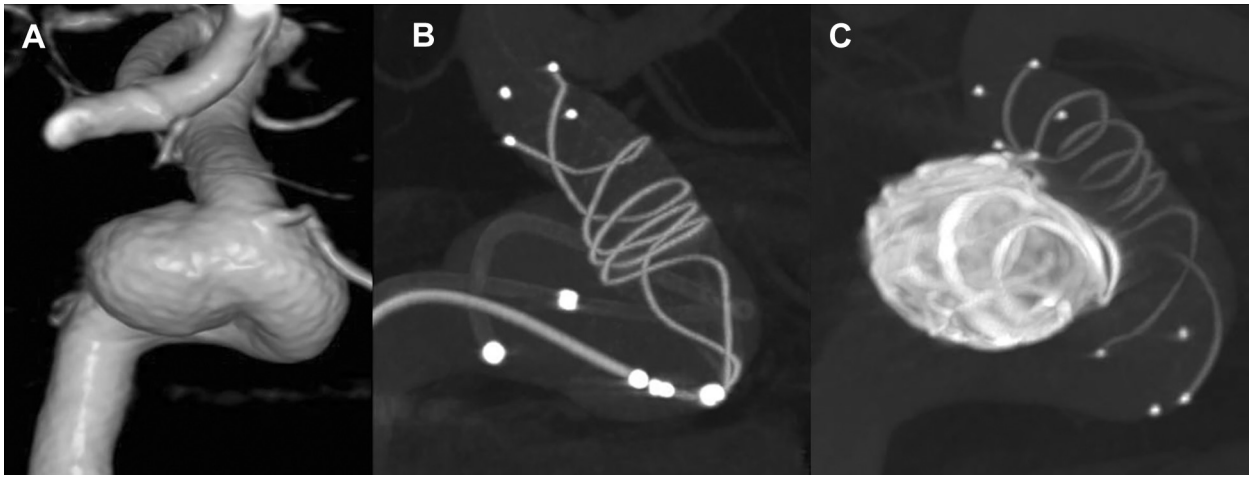

Fig. 3 (**A**) A 68-year-old woman with an aneurysm at the paraclinoid portion of the left internal carotid artery. (**B**) A microcatheter was navigated into the aneurysm, and LVIS (4.5 × 23 mm) was partially deployed. (**C**) After coil embolization of the aneurysm was completed using the semi-jail technique, the stent was fully deployed.

and clopidogrel alone was continued. Subsequently, the dose of clopidogrel was gradually decreased to 50 and 25 mg over 2 to 6 months, and finally discontinued (**Fig. 1**).

Case presentation

Case 1

The patient was a 65-year-old male with a gradually enlarging aneurysm measuring 8 mm in diameter at the apex of the basilar artery (**Fig. 2**). Owing to the wide-neck aneurysm, a stent was considered necessary for coil embolization. The angle between the left posterior cerebral and basilar arteries was sharp, and there was a difference in the vascular diameter. To avoid the influence of changes in the vascular shape on blood flow of perforating arteries from the basilar artery, we selected Neuroform Atlas (an open-cell stent), which was adaptable to the vascular shape, with a low metallic coverage rate. Before surgery, DAPT using 100 mg of aspirin and 75 mg of clopidogrel was introduced. Using Excelsior XT-17 (Stryker), Neuroform Atlas (4.5 × 30 mm) was placed in the left posterior cerebral to basilar arteries, and DynaCT (Siemens Healthineers, Erlangen, Germany) confirmed that the stent fit to the vascular wall. SL-10 (Stryker) was navigated into the aneurysm via a trans-cell route, and sufficient coil embolization was achieved. The postoperative course was favorable. On cerebral angiography 1 year after surgery, no recanalization of the cerebral aneurysm, stent deformity, or in-stent stenosis was observed. The administration of aspirin was discontinued and clopidogrel alone was continued. Subsequently, the dose of clopidogrel was gradually decreased to 50 and 25 mg , and antiplatelet therapy was totally terminated 15 months after surgery. There has been no ischemic complication.

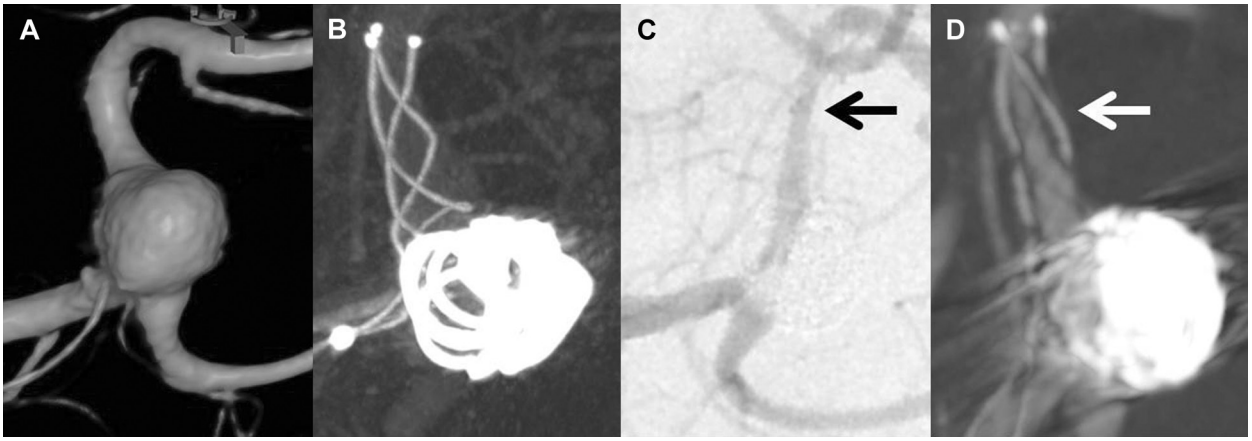

Fig. 4 (**A**) An 82-year-old woman with an aneurysm in the right posterior cerebral artery. (**B**) LVIS Jr. (2.5 × 23 mm) was partially deployed for coil embolization of the aneurysm using the semi-jail technique. (**C** and **D**) As in-stent stenosis was observed on follow-up angiography (arrows), low-dose clopidogrel was continued.

Case 2

The patient was a 68-year-old female with an incidentally detected aneurysm measuring 8 mm in diameter at the paraclinoid portion of the left internal carotid artery (**Fig. 3**). Owing to the wide-neck aneurysm, a stent was considered necessary for coil embolization. There was no small branch vessel other than the ophthalmic artery from the parent artery, and the parent artery did not have marked tortuosity. In addition, the aneurysm was side-wall type. Therefore, LVIS (a braided stent) was selected due to its high metallic coverage rate and high rectifying effects. For stenting, the stent was placed proximally through the C2 segment of the internal carotid artery in order not to cover the bifurcation of the anterior choroidal artery, maintaining blood flow of this artery. Before surgery, DAPT using 100 mg of aspirin and 75 mg of clopidogrel was introduced. Restar (Medico's Hirata, Osaka, Japan) was navigated into the aneurysm, and LVIS (4.5 × 23 mm) was partially deployed to the aneurysmal neck through the C2 segment using Headway 21 (Terumo). DynaCT confirmed that the stent fit to the vascular wall. Using the semi-jail technique, sufficient coil embolization of the aneurysm was achieved. Subsequently, LVIS was completely deployed to the C3 segment. Additional DynaCT confirmed stent fitting to the vascular wall. The postoperative course was favorable. On cerebral angiography 1 year after surgery, no recanalization of the cerebral aneurysm, stent deformity, or in-stent stenosis was observed. The administration of aspirin was discontinued and clopidogrel alone was continued. Subsequently, the dose of clopidogrel was gradually decreased to 50 and 25 mg, and antiplatelet therapy was totally terminated 14 months after surgery. There has been no ischemic complication.

Case 3

The patient is an 82-year-old female with a gradually enlarging right posterior cerebral artery aneurysm measuring 7 mm in diameter (**Fig. 4**). Owing to the wide-neck aneurysm, a stent was considered necessary for coil embolization. Because the parent artery was <2.5 mm in diameter, with no marked diameter difference and no tortuosity, LVIS Jr. was selected. Before surgery, DAPT using 100 mg of aspirin and 75 mg of clopidogrel was introduced. Restar was navigated into the aneurysm, and LVIS Jr. (2.5 × 23 mm) was partially deployed to the aneurysmal neck using Headway 17. Using the semi-jail technique, the first coil was inserted into the aneurysm. DynaCT confirmed stent fitting to the vascular wall and favorable frame arrangement with the first coil. After completely deploying LVIS Jr., another Restar was navigated into the aneurysm via a trans-cell route. Subsequently, coil embolization was continued using the double catheter technique and sufficient embolization was achieved. The postoperative course was favorable. On cerebral angiography 1 year after surgery, no recanalization of the cerebral aneurysm or stent deformity was observed, but in-stent stenosis was noted. It was asymptomatic, and the termination of DAPT was considered possible. The administration of aspirin was discontinued and clopidogrel alone was continued. Subsequently, the dose of clopidogrel was gradually decreased to 50 and 25 mg . However, the administration of clopidogrel at 25 mg

was continued due to in-stent stenosis. There has been no ischemic complication.

Results

Of the 57 patients, it was necessary to continue DAPT due to other diseases such as coronary artery disease in 4, for the retreatment of the embolized aneurysms in 2, and for the treatment of another aneurysm in 1. Furthermore, 1 patient died of cerebral hemorrhage 2 months after surgery. In 49 patients, excluding these 8 patients, dose reduction of antiplatelet drugs was started, but the termination of antiplatelet therapy was considered to be inappropriate due to underlying diseases such as ischemic stroke in 8 patients and due to in-stent stenosis in 1 patient (**Fig. 4**). In the above 49 patients, the mean period of DAPT was 10.6 ± 2.8 months. Of 40 patients in whom the termination of antiplatelet therapy was considered possible, antiplatelet therapy was completely terminated in 35 while the dose of clopidogrel was gradually decreased in 5. The mean period of postoperative antiplatelet therapy was 15.0 ± 2.1 months.

Ischemic stroke was noted in 5 of the 57 patients, with a mean follow-up period of 31.8 ± 15.1 months. In 3 patients, it was possibly associated with SACE, and the interval from surgery until onset was ≤1 week. Two patients had in-stent thrombosis, and one had occlusion of a perforating artery at the site of stent placement. In one of the other 2 patients, mild cerebral infarction developed during orthopedic surgery ≥1 year after the termination of antiplatelet therapy, and its association with the stent was unclear. In 1 patient, cardiogenic cerebral embolism developed at a site that was not related to the artery in which the stent had been placed.

Discussion

Post-SACE ischemic complications may develop in the perioperative and remote phases.[2,4–9] Their etiology is classified into two types: surgical procedures, such as stent selection/placement, and postoperative stent changes, such as in-stent thrombosis/stenosis.

Rectifying effects by stent placement in the parent artery can reduce blood inflow into the aneurysm through coverage of the aneurysmal orifice and extension of the parent artery, improving the embolization efficiency.[10] On the other hand, stent placement in a tortuous blood vessel may markedly change the vascular shape, inducing stent kinking without fitting to the vascular wall.[11,12] Such an event is likely to occur when a closed-cell stent is used and is associated with the development of ischemic complications.[13] Furthermore, stenting at the bifurcation of small branch vessels from the parent artery may lead to occlusion of the branches. In particular, in the presence of stent-related extension of the parent artery, the bifurcating angle of branches from the parent artery may change, influencing blood flow of the branches.[14] Thus, if a marked difference in the vascular diameter or a marked tortuosity is present at the site where stenting is planned or if small branch vessels bifurcate at the site where stenting is planned, an open-cell stent, which is adaptable to the shape of the parent artery, with a low metallic coverage rate may be appropriate. Indeed, we have primarily selected Neuroform stent for middle cerebral artery aneurysms with the above characteristics of the parent artery. However, the main purpose of treatment is obliteration of aneurysms, and there are many situations in which an improvement in the stent-related embolization efficiency should be prioritized. Therefore, closed-cell or braided stents must be adopted in accordance with circumstances. To reduce the risk of ischemic complications, a stent should be carefully placed regardless of the type of stent such that there is no gap between the vascular wall and the stent, and no influence on blood flow of small branch vessels.

Clopidogrel resistance may be involved in early in-stent thrombosis or stenosis. Early dose reduction or discontinuation of antiplatelet drugs, especially clopidogrel, may be highly involved in delayed in-stent thrombosis or stenosis.[5,6,8,15–18] In our patients with in-stent thrombosis early after surgery, it may also have been related to clopidogrel resistance, but these patients were treated before the introduction of a platelet aggregation-measuring device in our institution; whether there was a relationship is unclear. To prevent ischemic complications early after surgery, platelet aggregation should be measured before surgery. If clopidogrel resistance is suspected, it may be managed by increasing the dose of clopidogrel, switching it to another drug, or adding another drug.[19,20] In April 2019 (after the period investigated in this study), a platelet aggregation-measuring device (Hematracer ZEN; LMS, Tokyo, Japan) was introduced at our institution. Since then, platelet aggregation has been measured before surgery in all patients for whom the administration of antiplatelet drugs was started for endovascular treatment. Platelet aggregation is evaluated using 6 grades: +2 to −3. The drug efficacy is classified into three: slight, adequate, and excessive. To date, there has been no patient with marked clopidogrel resistance requiring a switch to another drug. However, when the drug efficacy was classified as "slight," argatroban or ozagrel

sodium was used during surgery and continued for a few days after surgery. We have not encountered a patient with early in-stent thrombosis since the introduction of the measuring device, although it is unclear whether this is associated with management based on the results of platelet aggregation measurement.

To date, we have not encountered a patient with delayed ischemic complications related to SACE. Sufficient postoperative antiplatelet therapy may have played a role in the favorable results. Until the stent surface is covered by the neointima, metal exposure activates platelets, leading to thrombus formation; therefore, to prevent delayed ischemic complications, it is necessary to continue DAPT for a specific period.[2,21,22] Regarding this period, no guidelines or consensus has been established, but a previous study reported that continuous DAPT for 9 months significantly reduced the incidence of ischemic complications without increasing the incidence of hemorrhagic complications.[4] We aim for the termination of antiplatelet therapy approximately 1 year after surgery. However, to terminate this therapy safely, the following preconditions may be necessary: no stent migration from the site of placement or deformity with a damaged tubal structure, adequate stent fitting to the vascular wall, and favorable embolization state with no recanalization of the aneurysm. As it is difficult to evaluate these conditions accurately using MRI or CT angiography, the above preconditions should be confirmed using cerebral angiography. If the stent or aneurysm state is stable in the absence of the above findings on cerebral angiography 6 to 12 months after surgery, antiplatelet therapy can be tapered. The administration of an antiplatelet drug other than clopidogrel should be discontinued to terminate DAPT. The administration of clopidogrel should also be discontinued thereafter. However, clopidogrel exhibits a rebound phenomenon, and sudden discontinuation may cause ischemic complications; therefore, it is important to gradually reduce its dose over a few months.[15,23] When cerebral angiography reveals stent deformity or stenosis, the condition is asymptomatic in many patients. However, the continuation of antiplatelet therapy should be considered in accordance with findings and careful follow-up should be conducted.[9,24]

Lastly, this study does not propose novel findings or an innovative protocol for reducing the incidence of ischemic complications after SACE. However, we demonstrated that antiplatelet therapy can be safely terminated without inducing ischemic complications by paying attention to avoid the reported risk factors for ischemic complications after SACE, carefully selecting/placing a stent, and managing postoperative antiplatelet therapy. This may be epoch-making and significant in a sense.

Conclusion

Antiplatelet therapy for SACE can be safely terminated in most cases. To prevent ischemic complications, the doses of postoperative antiplatelet drugs should be appropriately decreased in addition to appropriate stent selection or placement in accordance with individual patients. Even after the termination of antiplatelet therapy, follow-up must be carefully continued.

Disclosure Statement

The authors declare no conflicts of interest.

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