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Short- versus long-term Dual AntiPlatelet Therapy for Stent-Assisted treatment of CErebral aneurysm (DAPTS ACE): a multicenter, open-label, randomized clinical trial

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ABSTRACT

Background The optimal duration of dual antiplatelet therapy (DAPT) after stent-assisted coil embolization (SACE) for cerebral aneurysm remains uncertain. This randomized trial of short- versus long-term Dual AntiPlatelet Therapy for Stent-Assisted treatment of CErebral aneurysm (DAPTS ACE) aimed to clarify whether long-term DAPT can reduce the occurrence of ischemic stroke in patients with cerebral aneurysms treated by SACE compared with short-term DAPT.

Methods Patients treated for cerebral aneurysm with SACE were enrolled from 17 hospitals in Japan. Patients were enrolled within 30 days after SACE and assigned in a 1:1 ratio to receive long-term (12 months) or short-term (3 months) DAPT with aspirin and clopidogrel. Randomization was performed centrally through a web-based system. The primary outcome was the time to ischemic stroke event during 3 to 12 months after SACE. This trial was registered with the Japan Registry of Clinical Trials (jRCTs051180141).

Results A total of 142 patients were recruited from November 4, 2016 to January 7, 2019. Among them, 65 and 68 patients assigned to the long- and short-term DAPT groups, respectively, were included in the full analysis set. Ischemic stroke occurred in no patients in the long-term DAPT group and in one patient in the short-term DAPT group. The incidence rate did not differ between the groups (0.0 vs 2.1/100 person-years; log rank test, P=0.33).

Conclusions In this multicenter randomized controlled trial, there was not a statistically significant difference in the rate of ischemic strokes between long- and short-term DAPT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been reported to lower the incidence of thromboembolic events in stent-assisted coil embolization (SACE), long-term DAPT might increase hemorrhagic complications. The optimal duration of DAPT after SACE is undetermined.

WHAT THIS STUDY ADDS

⇒ In this randomized multicenter study, the ischemic event rate during 3 to 12 months after SACE was similarly low in long- and short-term DAPT with aspirin and clopidogrel.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although the duration of DAPT might have to be determined based on thromboembolic and hemorrhagic risk factors, benefits of long-term DAPT after SACE might be low on the basis of this study.

INTRODUCTION

Since the approval of stents as treatment devices for coil embolization of cerebral aneurysms, wide-necked aneurysms have been managed safely.[1 2] However, thromboembolic complications are a formidable challenge to overcome in stent-assisted coil embolization (SACE).[3 4] Although dual antiplatelet therapy (DAPT) with aspirin and clopidogrel lowers the incidence of thromboembolic events after coil embolization,[5] long-term DAPT might increase the incidence of hemorrhagic complications.[6] To determine the optimal duration of DAPT after SACE, Hwang *et al* assigned patients to three groups (3 months, 6 months, and >9 months) based on the time point of changing DAPT to single antiplatelet therapy (SAPT) after SACE.[7] The authors reported that longer-term DAPT of >9 months significantly decreased the incidence of delayed ischemic stroke.[8] In contrast, Kim *et al* compared short-term DAPT (<9 months) and long-term DAPT (≥9 months) after SACE and reported that long-term DAPT did not lower the incidence of delayed thromboembolic events.[9] As described, there is a paucity of data indicating the suitable duration of DAPT after SACE. Therefore, we performed this randomized clinical trial of short- versus long-term Dual AntiPlatelet Therapy for

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Stent-Assisted treatment of CErebral aneurysm (DAPTS ACE) to clarify whether DAPT with aspirin and clopidogrel for 12 months can reduce the occurrence of ischemic stroke in patients with cerebral aneurysms treated by SACE compared with DAPT for 3 months.

METHODS

Study design and participants

The DAPTS ACE trial was a prospective, multicenter, open-label, parallel-group, randomized controlled trial (RCT) involving 17 hospitals in Japan from November 4, 2016 to January 7, 2019. The trial was monitored by an independent data and safety monitoring board. The Steering Committee was responsible for the design, interpretation, and supervision of the trial, and the Event Evaluation Committee reviewed any event during the trial. The costs for the trial drugs were covered by each patient's health insurance. The costs of platelet aggregation testing (VerifyNow; Werfen Inc, Bedford, MA) and cytochrome P450 2C19 (CYP2C19) gene testing was funded by Daiichi Sankyo Co., Ltd. Japan.

Initially, patients treated with SACE using stents approved in Japan for cerebral aneurysm and aged ≥20 years were registered within 30 days after the procedure. Among them, patients taking DAPT with aspirin and clopidogrel were eligible for this RCT. The exclusion criteria were a history of SACE for target intracranial aneurysms, withdrawal of antiplatelet treatment scheduled during the study period, ruptured aneurysm in the first 14 days, allergy to aspirin or clopidogrel, requiring anticoagulation drugs, platelet count <100 000/mm^3, history of intracranial hemorrhage or bleeding tendency, and clinical evidence indicating a high bleeding risk, assessed by the investigators. The patients who could not be enrolled in the RCT were followed-up for 15 months after SACE as the non-RCT cohort.

Study procedures

Randomization was performed centrally through a web-based system. The patients were randomly assigned to the long-term (12 months) DAPT group or the short-term (3 months) DAPT group in a 1:1 ratio with minimization with three adjustment factors: ruptured or unruptured aneurysm, maximum aneurysmal diameter (≥10 mm or <10 mm), and institution. For patients in the long-term DAPT group, aspirin (100 mg) and clopidogrel (75 mg) once per day were prescribed for 12 months followed by SAPT (aspirin or clopidogrel) for 3 months. For patients in the short-term DAPT group, aspirin (100 mg) and clopidogrel (75 mg) once per day were prescribed for 3 months followed by SAPT (aspirin or clopidogrel) for 12 months (online supplemental figure 1). In-person neurological follow-up was performed at registration and 3, 6, 12, and 15 months after SACE. The score for a standard clinical scale (modified Rankin scale (mRS)) was documented. MRI (fluid attenuated inversion recovery (FLAIR) and T2 star-weighted imaging) and MR angiography were performed at registration and 15 months after SACE. Platelet aggregation testing (VerifyNow) was scheduled at registration and 6 and 12 months after SACE. CYP2C19 gene testing was performed once, within 15 months after SACE.

Outcomes

The primary outcome was the time to first occurrence of ischemic stroke during 3 to 12 months after SACE. Ischemic stroke was defined as a new ischemic lesion on cranial CT or MRI and continuing neurological symptoms lasting >24 hours. The secondary outcomes were as follows: time to death or any stroke (ischemic, hemorrhagic, transient ischemic attack, or aneurysmal rupture); time to hemorrhagic event; time to death, any stroke, or hemorrhagic event; and time to retreatment of the aneurysm, or occlusion or stenosis of the stent. Hemorrhagic stroke was defined as new intraparenchymal hemorrhagic and subarachnoid hemorrhage on cranial CT or MRI, excluding target aneurysmal rupture, and continuing neurological symptoms lasting >24 hours. Hemorrhagic events comprised fatal hemorrhage, symptomatic hemorrhage (intracranial, intrathecal, intraocular, retroperitoneal, intra-articular, intrapericardial hemorrhage, and intramuscular hemorrhage associated with muscle compartment syndrome), or hemorrhage leading to a decrease in hemoglobin level of >20 g/L or requiring blood transfusion of >2 units. Stent stenosis was defined as stenosis of >50%.

Statistical analysis

In accordance with Hwang *et al*'s report,[7] the 1-year incidence of ischemic stroke events in the short-term DAPT group was assumed to be 6%, and the hazard ratio (HR) in the long-term DAPT group versus the short-term DAPT group was assumed as 0.017. Using these conditions, the sample size required to detect a difference with a two-sided significance level of 0.05 and a power of ≥0.8 at the 1-year follow-up was calculated to be 134 patients in each group. Assuming a trial dropout rate of 10%, the target sample size was set at 300 patients (150 in each group).

The full analysis set comprised all patients except those who discontinued follow-up during SAPT treatment within 3 months after SACE. Survival time analysis was a landmark analysis starting 3 months at SAPT switching. The cumulative ischemic stroke event-free survival rate was estimated using the Kaplan-Meier method. Patients who discontinued the study without having an event were analyzed as censored cases at the time of discontinuation. The number of events, incidence (/100 patient-years), and corresponding 95% confidence intervals (95% CI) were calculated for each group. Event-free survival was compared between the groups using the log rank test, and the HRs and 95% CIs for the treatment groups were calculated using proportional hazards analysis. When the number of events was 0, the HR was calculated using Firth's bias correction. As a sensitivity analysis, HRs adjusted for the presence or absence of ruptured cerebral aneurysm, maximum cerebral aneurysmal diameter, and concomitant medications at the start of DAPT were calculated. Secondary endpoints were analyzed as for ischemic stroke event-free survival. All analyses were performed using SAS version 9.4 (Cary, NC). Data are expressed as mean±SD for continuous variables, and frequencies and percentages for discrete variables, unless specifically stated otherwise. Imputation of missing values was not performed for the primary or secondary endpoints. The significance level was set at P<0.05 (two-tailed). The DAPTS ACE trial was registered in the Japan Registry of Clinical Trials (jRCTs; number 051180141).

RESULTS

Participants were recruited from November 4, 2016 to January 7, 2019. Two hundred and sixty-five patients were registered after SACE. Consent for RCT could be acquired in 142 patients, and 114 of remaining 123 patients were followed-up as the non-RCT cohort (figure 1). The minimum, maximum and median number of enrollments per site was 1, 22 and 7, respectively. The enrollment ratio to RCT among initially registered patients in each site (17 sites) varied from 6.7% to 100% (median 50.0%). In each cohort, six and nine patients were excluded because of misregistration or withdrawal of consent, respectively. The baseline characteristics and event rate during 3 to 12 months after

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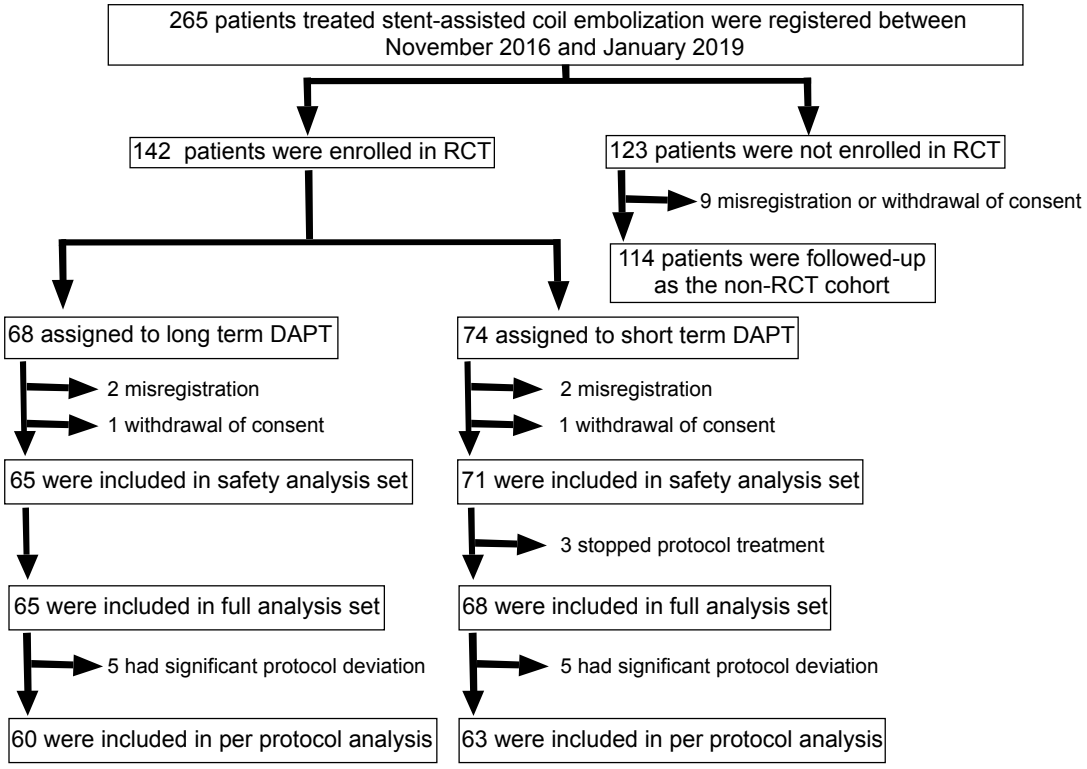

Figure 1 Study flowchart.

SACE in the RCT and non-RCT cohorts are described in online supplemental tables 1 and 2. Patients in the non-RCT had more often histories of previous hemorrhagic and ischemic stroke, and larger size of target aneurysm than those in the RCT cohort. However, event rates during 3 to 12 months after SACE were not statistically different between the two cohorts. The number of enrolled patients in the RCT (142 patients) did not reach the estimated number to reach a power of 80%. Because the incidence rate (per 100 patient-years) of ischemic stroke was much lower than estimated, and the power was much lower than 0.5 even if the target number of patients (300 patients) had been enrolled, the Steering Committee decided to stop enrollment. Of the 142 patients who were enrolled in the RCT, 68 patients were assigned to the long-term DAPT group, and 74 patients were assigned to the short-term DAPT group. In each group, two patients were excluded because of misregistration and one patient withdrew consent. Thus, 136 patients (65 in the long-term DAPT group and 71 in the short-term DAPT group) were included in the safety analysis set. Among these patients, three in the short-term DAPT group discontinued follow-up during the SAPT treatment period. Therefore, 133 patients were included in the final full analysis set; 65 patients were assigned to the long-term DAPT group, and 68 patients were assigned to the short-term DAPT group (figure 1).

The baseline clinical characteristics of the long-term DAPT group and short-term DAPT group are summarized in table 1. The baseline clinical characteristics, which comprised sex, age, medical history (subarachnoid hemorrhage, hemorrhagic stroke, ischemic stroke, hypertension, diabetes mellitus, dyslipidemia, smoking habit), and platelet aggregation (aspirin and P2Y12 assays) calculated by VerifyNow, were well balanced between the two groups. The rate of symptoms due to aneurysm, location, size, and shape of aneurysms, type of stent and obstruction results of the embolization were similar between the two groups.

The selection of continuous antiplatelet drug therapy (SAPT) (aspirin or clopidogrel) after the end of DAPT did not differ between the groups (online supplemental table 3). The median aspirin reaction units (ARU) at registration, and 6 months and 12 months after SACE were 425.0, 432.0 and 412.5, respectively, in the long-term DAPT group, and 429.0, 507.0 and 510.0, respectively, in the short-term DAPT group. The median P2Y12 reaction units (PRU) at registration, and 6 months and 12 months after SACE were 157.0, 165.5 and 169.5, respectively, in the long-term DAPT group, and 162.0, 220.0 and 210.0, respectively, in the short-term DAPT group (online supplemental table 4).

Primary and secondary outcomes

A primary event, ischemic stroke, occurred in one patient in the short-term DAPT group; none occurred in the long-term DAPT group during 3 to 12 months after SACE. The incidence rate of ischemic stroke did not differ between the groups (2.1 vs 0.0/100 person-years, respectively; log rank test, P=0.33, table 2 and figure 2A).

In a predefined secondary analysis, death or any stroke during 3 to 12 months after SACE was seen in one patient in each group (2.2 vs 2.1/100 person-years, long- vs short-term group, respectively; log rank test, P=0.97, table 2 and figure 2B). Two hemorrhagic events occurred in the long-term DAPT group and none occurred in the short-term DAPT group during 3 to 12 months after SACE (4.3 vs 0.0/100 person-years, respectively, P=0.27, table 2 and figure 2C). Specifically, a patient in their 50s suffered putaminal hemorrhage 185 days after SACE, and the final mRS score of this patient was 5. The other patient in their 50s suffered chronic subdural hematoma 375 days after SACE, and the final mRS score of this patient was 0. Death, any stroke, or hemorrhagic event during 3 to 12 months after SACE occurred in two patients in the long-term DAPT group and in one patient

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Table 1 Characteristics of long-term DAPT group and short-term DAPT group

Number of patients	Long-term DAPT (n=65)	Short-term DAPT (n=71)	P value
Age: mean±SD	58.9±12.3	59.2±12.8	0.934
Man: n (%)	15 (23.1)	26 (36.6)	0.086
Previous SAH	3 (4.6)	6 (8.5)	0.369
Previous hemorrhagic stroke	0 (0.0)	1 (1.4)	0.337
Previous ischemic stroke	2 (3.1)	1 (1.4)	0.508
Risk factors: n (%)			
Hypertension	31 (47.7)	29 (40.8)	0.422
Diabetes	6 (9.2)	2 (2.8)	0.112
Dyslipidemia	25 (38.5)	20 (28.2)	0.203
Smoking habit	13 (20.0)	12 (16.9)	0.641
Target aneurysm, symptoms: n (%)			0.118
Asymptomatic	64 (98.5)	66 (93.0)	
Symptomatic	1 (1.5)	5 (7.0)	
Target aneurysm, locations: n (%)*			
ICA-cavernous	0 (0.0)	1 (1.4)	
ICA-paraclinoid	32 (49.2)	29 (40.8)	
ICA-PcomA	6 (9.2)	9 (12.7)	
ICA-bifurcation	1 (1.5)	1 (1.4)	
MCA-bifurcation	2 (3.1)	4 (5.6)	
AcomA	5 (7.7)	7 (9.9)	
VA	9 (13.8)	10 (14.1)	
VA-PICA	2 (3.1)	2 (2.8)	
BA trunk	1 (1.5)	0 (0.0)	
BA-SCA	1 (1.5)	0 (0.0)	
BA bifurcation	7 (10.8)	7 (9.9)	
PCA	0 (0.0)	1 (1.4)	
Others (anterior circulation)	1 (1.5)	1 (1.4)	
Target aneurysm, maximum diameter (mm): mean±SD	6.97±2.84	7.06±2.42	0.494
Target aneurysm, maximum diameter <10 mm: n (%)	56 (86.2)	61 (85.9)	0.968
Target aneurysm, subtype: n (%)			0.713
Saccular	54 (83.1)	55 (77.5)	
Fusiform	7 (10.8)	10 (14.1)	
Dissecting	4 (6.2)	6 (8.5)	
Patients with aneurysm not eligible for inclusion to this trial: n (%)	14 (21.5)	10 (14.1)	0.255
Radiographic outcome: n (%)			0.103
Complete occlusion	28 (43.1)	21 (29.6)	
Neck remnant	24 (36.9)	25 (35.2)	
Aneurysm filling	13 (20.0)	25 (35.2)	
Deployed stent: n (%)			0.836
Enterprise VRD	3 (4.6)	0 (0.0)	
Enterprise 2	8 (12.3)	11 (15.5)	
Neuroform EZ	5 (7.7)	4 (5.6)	
Neuroform Atlas	19 (29.2)	19 (26.8)	
LVIS	21 (32.3)	28 (39.4)	
LVIS Jr	7 (10.8)	7 (9.9)	
Double stents†	2 (3.1)	2 (2.8)	
Pre-procedural ARU: mean±SD	444.6±66.3 (n=55)	445.0±83.7 (n=55)	0.779
Pre-procedural PRU: mean±SD	161.2±75.6 (n=55)	170.7±78.3 (n=55)	0.473

*Target aneurysm, location includes the cases with multiple aneurysm (duplicated aggregation).
†Details of double stents: One case was treated with 2 Neuroform Atlas and the other case was treated with 2 LVIS in long-term DAPT group. One case was treated with 2 LVIS Jr and the other case was treated with Enterprise VRD and Neuroform Atlas in short-term DAPT group.
AcomA, anterior communicating artery; ARU, aspirin reaction units; BA, basilar artery; DAPT, dual antiplatelet therapy; ICA, internal carotid artery; LVIS, Low-profile Visualized Intraluminal Support; MCA, middle cerebral artery; PCA, posterior cerebral artery; PcomA, posterior communicating artery; PICA, posterior inferior cerebellar artery; PRU, P2Y12 reaction units; SAH, subarachnoid hemorrhage; SCA, superior cerebellar artery; VA, vertebral artery.

in the short-term DAPT group (4.3 vs 2.1/100 person-years, respectively; log rank test, P=0.81, table 2). Retreatment of the aneurysm, or occlusion or stenosis of the stent during 3 to 12 months after SACE, occurred in one patient in the long-term DAPT group and in three patients in the short-term DAPT group (2.2 vs 6.4/100 person-years, respectively; log rank test, P=0.36, table 2 and figure 2D). Specifically, stent occlusion occurred in a patient in their 40s 193 days after SACE.

DISCUSSION

In this multicenter RCT, we did not detect a significant difference in the ischemic stroke rate during 3 to 12 months after SACE between long- and short-term DAPT. To the best of our knowledge, this trial, DAPTS ACE, is the first RCT to investigate the duration of DAPT after SACE for intracranial aneurysms.

Neurointerventionalists have been able to expand aneurysmal treatment indications to include wide-necked aneurysms since the approval of stents as treatment devices for coil embolization of cerebral aneurysms[1 2]; however, thromboembolic complications have become a major problem to overcome.[3 4 10] The efficacy of DAPT comprising aspirin and clopidogrel has been reported, and this regimen is generally considered the standard regimen after SACE.[3 8–10] However, evidence supporting the optimal duration of DAPT after SACE has yet to be obtained. Rossen *et al* investigated the risk of ischemic events during 3 months after 6 weeks of DAPT following SACE and reported that clopidogrel discontinuation was associated with a 5% risk of ischemic events.[10]

Table 2 Primary and secondary outcome

	Long-term DAPT (n=65) N (per 100 patient-years)	Short-term DAPT (n=68) N (per 100 patient-years)	HR (95% CI)	P value
Primary outcome				
Ischemic stroke	0 (0.0)	1 (2.1)	0.35 (0.002 to 6.54)	0.328
Secondary outcome				
Death or any stroke	1 (2.2)	1 (2.1)	1.06 (0.09 to 13.0)	0.969
Hemorrhagic event	2 (4.3)	0 (0.0)	3.35 (0.20 to 487.3)	0.273
Death, any stroke or hemorrhagic event	2 (4.3)	1 (2.1)	1.17 (0.13 to 13.9)	0.814
Retreatment, stent occlusion/stenosis	1 (2.2)	3 (6.4)	0.46 (0.04 to 2.81)	0.355

The reference group is short-term DAPT group.
DAPT, dual antiplatelet therapy.

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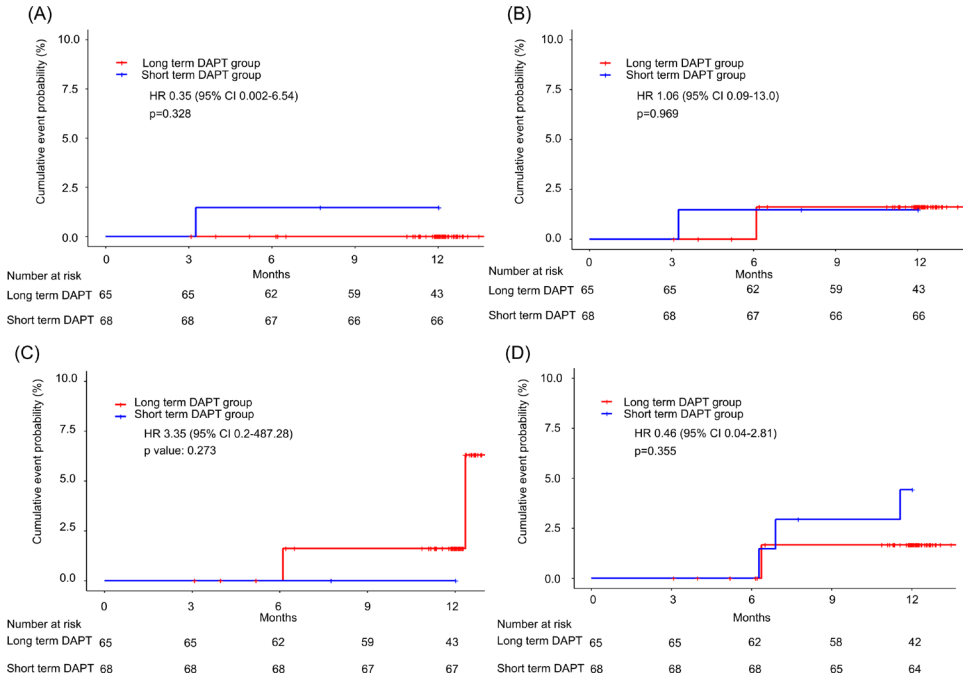

Figure 2 Kaplan-Meier analysis of the primary and secondary outcomes. Kaplan-Meier curves for the time to the first event for the primary outcome, defined as ischemic stroke (A), and for the secondary outcomes, defined as death or any stroke (B), hemorrhagic event (C), and retreatment or stent occlusion/stenosis (D). The reference group is short- term DAPT group. DAPT, dual antiplatelet therapy.

Mocco *et al* reported that among their 219 SACE cases, seven (3%) delayed thromboembolic events occurred at 2 weeks (n=2), 3 weeks (n=1), 4 weeks (n=2), 4 months (n=1), and 6 months (n=1). All events occurred after cessation of DAPT.[3] Based on the above reports, 6 months might be an insufficient duration of DAPT after SACE. Hwang *et al* reported that DAPT for more than 9 months was associated with a significantly lower incidence of ischemic stroke after SACE for unruptured intracranial aneurysms compared with 3 and 6 months of DAPT.[8] Based on these results, Kim *et al* retrospectively divided patients into two groups according to DAPT duration after SACE for unruptured intracranial aneurysms (short-term, <9 months; long-term, ≥9 months) and compared the occurrence of late thromboembolic events.[9] The authors concluded that long-term DAPT delayed the occurrence of late thromboembolic events but did not lower the incidence compared with short-term DAPT.[9] Additionally, a high risk of hemorrhagic complications associated with DAPT has been reported.[6 11] Thus, the benefit of long-term DAPT after SACE is controversial.

The benefit of long-term DAPT was not supported in the present study, similar to findings in previous studies. One of the main reasons for this finding is presumably the low rate of delayed thromboembolic events after SACE because of improvements in stent quality. In a recent study, Fiorella *et al* reported that in their 153 patients with wide-necked cerebral aneurysms, the rate of major stroke within the vascular territory of the low-profile visualized intraluminal support stent (LVIS; Microvention/Terumo, Tustin, CA) after 30 days was equal to the incidence of non-ipsilateral major stroke.[12] The new open-cell laser-cut stent, Neuroform Atlas (Stryker Neurovascular, Fremont, CA) has been associated with a lower frequency of thromboembolic events,[13 14] even when deployed in small vessels measuring <2 mm in diameter, compared with other stents.[15] Kwon *et al* reported that in their 130 patients with unruptured wide-necked intracranial aneurysms treated with the Neuroform Atlas, only one (0.8%) case of delayed ischemia occurred during their patient follow-up (mean 12.4 months).[14] In the present study, the event rate of the non-RCT cohort after SACE was also low and there was no significant difference between the RCT cohort and the non-RCT cohort (online supplemental table 2).

Although there was no significant difference in PRU and ARU values between the long- and short-term DAPT groups in the present study, platelet aggregation testing is generally recommended before SACE because individual variability is high, especially in the case of clopidogrel. Clopidogrel is a prodrug that must be converted into an active metabolite by CYP, especially CYP2C19, to acquire platelet inhibition ability.[16] Genetic polymorphism of the CYP2C19 gene contributes to the metabolism of clopidogrel. Therefore, clopidogrel is less effective in carriers of CYP2C19 loss-of-function alleles, which are present in 25% of people from the West and in 60% of East Asians.[17 18] An association between clopidogrel resistance and a higher risk of thromboembolic events during neuroendovascular procedures has been reported.[19 20] As these facts have become clear, the importance of platelet function testing for neurointerventional procedures has been reported.[21–24] The VerifyNow system is a reliable method to monitor platelet aggregation.[25 26] Shoda *et al* classified 61 patients who underwent SACE for unruptured intracranial aneurysms into a hypo-responder group and a hyper-responder group according to their PRU values, with a cut-off value of 208. The hyper-responder group had a significantly higher incidence of hemorrhagic events, defined as major bleeding events in accordance with the International Society on Thrombosis and Haemostasis,[27] compared with the hypo-responder group between 1 and 6 months after SACE under DAPT (20.0% vs 2.78%, respectively; P=0.037).[22] Delgado *et al* reported that PRU <60 was significantly associated with hemorrhagic complications, and PRU >240 was associated with ischemic complications.[24] Furthermore, Song *et al* reported that diabetes and dyslipidemia showed a significant association with the incidence of delayed symptomatic thromboembolic events after SACE for unruptured intracranial aneurysms. Neither the

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ARU value nor PRU value were associated with the occurrence of delayed thromboembolic events.[21] Further validation of platelet aggregation testing might be necessary to determine suitable cut-off values for PRU and ARU for individualized patient therapy.

Limitations

The main limitation of this trial is that we evaluated only 44% of the planned number of patients and the sample size was quite small. Additionally, the number of patients who achieved the primary endpoint in the short- and long-term DAPT group was much lower than we expected. Larger studies are warranted to evaluate the benefit of long-term DAPT after SACE. Second, the timing of registration was post-procedure. Because of this, physicians could have avoided registration of cases that they considered high-risk cases for thromboembolic events such as Y configured stenting, which may have led to selection bias. In detail, only two cases in both groups (3.1% in the long-term DAPT group and 2.8% in the short-term DAPT group) were treated with two stents. Finally, there might be a difference of discretion about the decision of enrollment in the RCT cohort among physicians and hospitals. However, the event rate in the non-RCT cohort was also low and there were no significant differences between the RCT and non-RCT cohorts (online supplemental tables 1 and 2). Therefore, the difference of discretion about the decision of enrollment between hospitals is considered to be small.

Conclusions

In this multicenter RCT, the ischemic event rate during 3 to 12 months after SACE was low in both long- or short-term DAPT with aspirin and clopidogrel, and there was not a statistically significant difference between the two groups. The duration of DAPT might have to be determined based on thromboembolic and hemorrhagic risk factors.

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Contributors TO performed the data analysis and drafted the manuscript. HY and NS conceptualized and designed the study. MM, TH, HO, KH, SY, KS, YuM, YaM, and MH acquired the data. HY, HO, SY, KS, KI, YuM, and YaM comprised the Steering Committee. TS, MH, and CS assisted in devising the study protocol. SM, KK, and TD comprised the independent Event Evaluation Committee. TK contributed to the statistical analyses. All authors reviewed the manuscript and approved the final version. HY is guarantor of this manuscript.

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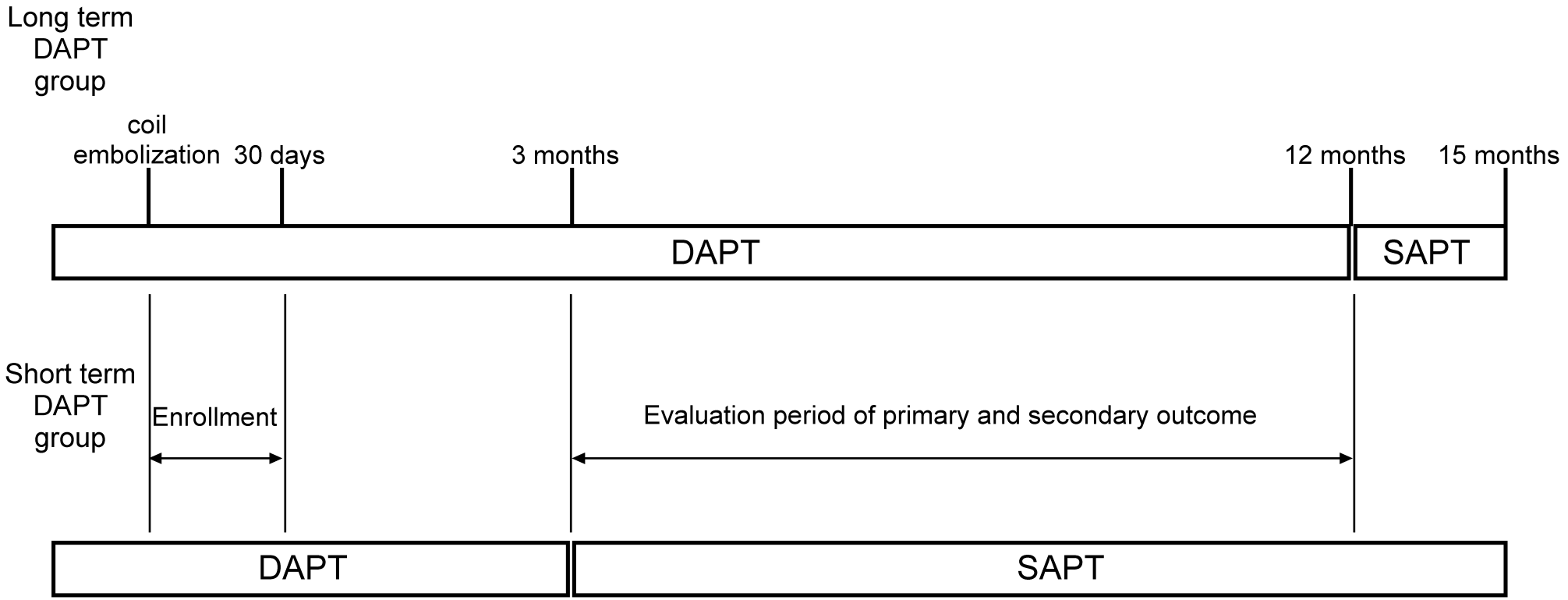


Supplementary Figure 1. Trial schedules for the long- and short-term dual antiplatelet therapy

Supplementary Table 1

Characteristics of RCT and non-RCT cohort

	RCT cohort (n=136)	Non-RCT cohort (n=114)	p value
Background characteristics			
Age: mean ± SD	59.0 ± 12.5	59.8 ± 13.4	0.658
Man: n (%)	41 (30.1)	38 (33.3)	0.687
Previous SAH	9 (6.6)	14 (12.3)	0.186
Previous hemorrhagic stroke	1 (0.7)	8 (7.0)	0.021
Previous ischemic stroke	3 (2.2)	10 (8.8)	0.041
Risk Factors: n (%)			
Hypertension	60 (44.1)	63 (55.3)	0.103
Diabetes	8 (5.9)	8 (7.0)	0.916
Dyslipidemia	45 (33.1)	41 (36.0)	0.731
Smoking habit	25 (18.4)	15 (13.2)	0.343
Target aneurysm, maximum diameter (mm): mean ± SD	7.02 ± 2.62	7.95 ± 4.10	0.030
Radiographic outcome: n (%)			0.257
Complete occlusion	49 (36.0)	35 (30.7)	
Neck remnant	49 (36.0)	36 (31.6)	
Aneurysm filling	38 (27.9)	43 (37.7)	

Abbreviations: RCT, randomized control trial; SD, standard deviation; SAH, subarachnoid hemorrhage

Supplementary Table 2

Event rate of RCT and non-RCT cohort during 3 to 12 months after SACE

	RCT cohort	Non-RCT cohort	HR (95% CI)	p value*
Ischemic stroke	n=133	n=111		
	1 (1.1)	1 (1.2)	1.15 (0.05-29.13)	0.92
Death or any stroke	n=133	n=111		
	2 (2.1)	1 (1.2)	0.58 (0.03-6.02)	0.65
Hemorrhagic event	n=133	n=112		
	2 (2.1)	1 (1.2)	1.14 (0.05-28.76)	0.93
Death, any stroke or hemorrhagic event	n=133	n=110		
	3 (3.2)	1 (1.2)	0.58 (0.03-6.07)	0.65
Retreatment, Stent occlusion/stenosis	n=133	n=114		
	4 (4.3)	5 (6.0)	1.38 (0.37-5.58)	0.63

In the Non-RCT cohort, event occurred in 4 cases within 3 months after SACE. The patients were excluded in each event according to their event types.

The reference group is RCT cohort.

* Event-free survival was compared between the groups using the log-rank test, and the hazard ratios and 95% confidence intervals were calculated using proportional hazards analysis.

Abbreviations: RCT, randomized control trial; SACE, stent-assisted coil embolization; CI, confidence interval

Supplementary Table 3

Continued antiplatelet drug in reducing from DAPT to SAPT

No. of Patients	Long term DAPT (n=65)	Short term DAPT (n=68)	p value
Aspirin: n (%)	42 (64.6)	39 (57.4)	0.273
Clopidogrel: n (%)	21 (32.3)	29 (42.6)	

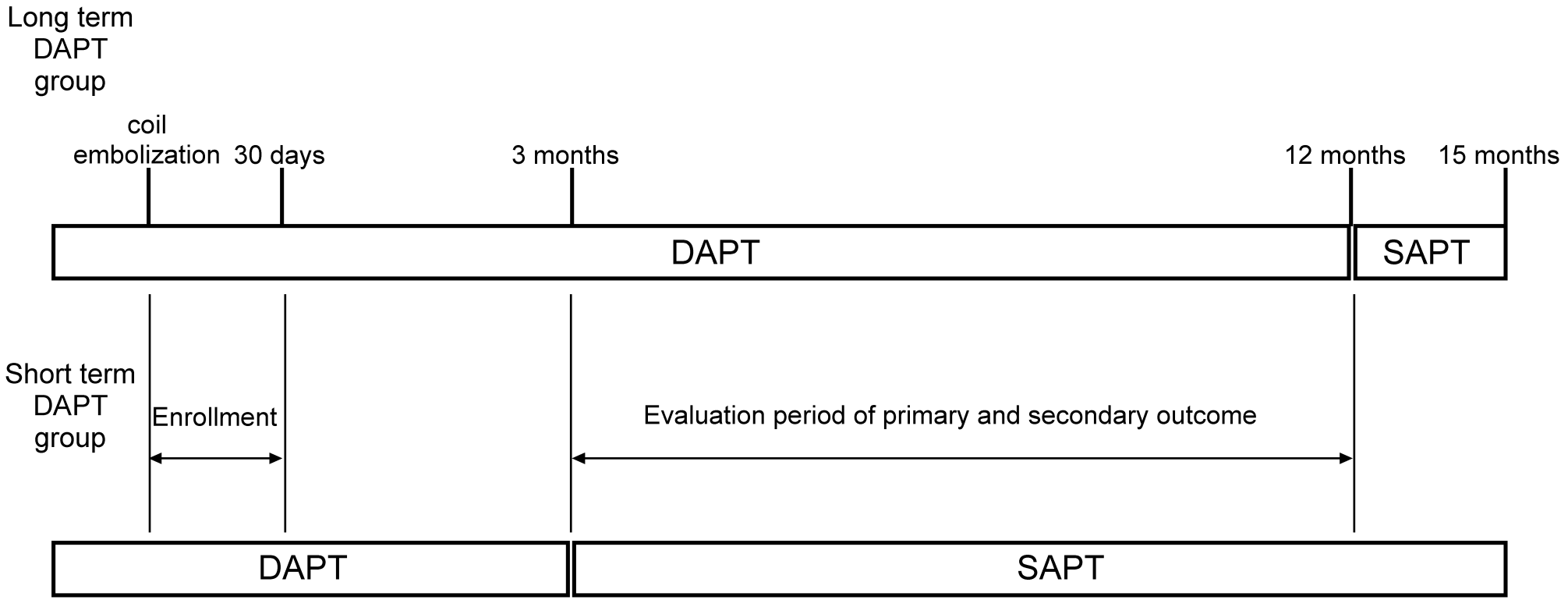
Abbreviations: DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy

Supplementary Table 4

Platelet aggregation study (Verify Now^{TM}) at registration and 6 and 12 months after SACE

	Long term DAPT				Short term DAPT				
	N	Median	Q1	Q3	Continuous drug	N	Median	Q1	Q3
ARU									
Registration	63	425.0	403.0	501.0	Any	70	429.0	395.0	485.0
6 months	54	432.0	394.0	493.0	Any	55	507.0	437.0	616.0
					Aspirin	33	458.0	437.0	616.0
					Clopidogrel	21	615.0	519.0	638.0
12 months	50	412.5	397.0	485.0	Any	51	510.0	428.0	616.0
					Aspirin	29	468.0	418.0	510.0
					Clopidogrel	22	615.0	519.0	638.0
PRU									
Registration	63	157.0	83.0	207.0	Any	70	162.0	114.0	214.0
6 months	54	165.5	119.0	203.0	Any	54	220.0	171.0	260.0
					Aspirin	30	251.5	210.0	294.0
					Clopidogrel	23	174.0	104.0	219.0
12 months	50	169.5	123.0	212.0	Any	53	210.0	176.0	259.0
					Aspirin	28	234.0	205.5	266.5
					Clopidogrel	25	176.0	127.0	211.0

Abbreviations: SACE, stent assisted coil embolization; DAPT, dual antiplatelet therapy; ARU, aspirin reaction units; PRU, P2Y12 reaction units



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