



Original research

# Relation between duration of dual antiplatelet therapy and risk of ischemic stroke after stent-assisted treatment of cerebral aneurysm (DAPTS ACE-registry)

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## ABSTRACT

**Background** The optimal duration of dual antiplatelet therapy (DAPT) in patients with cerebral aneurysm who undergo stent-assisted coil embolization (SACE) has not been established. We aimed to clarify the association between duration of DAPT and incidence of ischemic stroke in patients with cerebral aneurysm.

**Methods** We registered patients with cerebral aneurysm who underwent SACE in 27 hospitals in Japan. Those treated with DAPT (aspirin and clopidogrel) were eligible for inclusion in a previously reported randomized control trial (RCT). Patients who were ineligible or refused to participate to the RCT were followed-up for 15 months after SACE as the non-RCT cohort. Our study examined both the RCT and non-RCT cohorts. The primary and secondary outcomes were ischemic stroke and hemorrhagic events.

**Results** Among the 313 patients registered, 296 were included for analysis (of these, 136 were RCT patients and 160 were non-RCT patients). Patients who were treated with DAPT for more than 6 months (n=191) were classified as the long-term DAPT group. Those treated less than 6 months (n=105) were classified as the short-term group. The incidence of ischemic stroke did not significantly differ between the long-term group (2.5 per 100 person-years) and the short-term group (3.2 per 100 person-years); nor did incidence of hemorrhagic events (0.8 and 3.2 per 100 person-years, respectively). The period of DAPT was not significantly associated with incidence rates of ischemic stroke or hemorrhagic events.

**Conclusions** Duration of DAPT was not associated with the incidence of ischemic stroke in the first 15 months after SACE.

## INTRODUCTION

The number of cerebral aneurysms treated using an endovascular approach has been increasing since the introduction and approval of cerebrovascular stent use in 2010.<sup>1,2</sup> Dual antiplatelet therapy reduces the incidence of thromboembolic events after stent-assisted coil embolization (SACE);<sup>3,4</sup> however, the optimal duration of therapy is still debated.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although dual antiplatelet therapy with aspirin and clopidogrel has been reported to lower the incidence of thromboembolic events in patients undergoing stent-assisted coil embolization (SACE), the optimal duration of therapy has not been established.

## WHAT THIS STUDY ADDS

⇒ In this multicenter study, there was no significant relationship between duration of dual antiplatelet therapy and incidence of ischemic stroke in the first 15 months after SACE.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Compared with short-term dual antiplatelet therapy after SACE, long-term dual antiplatelet therapy might not reduce ischemic stroke.

Although one study reported that the incidence of delayed ischemic stroke was significantly lower in patients treated with dual therapy for more than 9 months,<sup>5</sup> another reported that dual therapy for 9 months or more only delayed the occurrence of delayed ischemic stroke and did not lower its incidence.<sup>6</sup> In addition, hemorrhagic complications must also be considered. Long-term dual antiplatelet therapy increases the incidence of hemorrhagic complications, especially in patients with a high risk of bleeding.<sup>7,8</sup>

In the Duration of AntiPlatelet Therapy for Stent-Assisted treatment of CErebral aneurysm (DAPTS ACE-RCT) trial, the incidence of ischemic and hemorrhagic complications did not significantly differ between patients treated with dual antiplatelet therapy and those treated with monotherapy between the 3rd and 12th month after SACE.<sup>9</sup> Our study examined patients from the DAPTS ACE registry and aimed to examine the effect of dual therapy duration on incidence of



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ischemic stroke and hemorrhagic events in patients who underwent SACE.

## METHODS

### Study design and participants

The Duration of DAPTS ACE-Registry was a multicenter study conducted in 27 hospitals in Japan from November 2016 to January 2019 and was registered in the UMIN Clinical Trials Registry (UMIN000022463) and the Japan Registry of Clinical Trials (number 051180141). The trial was monitored by an independent data and safety monitoring board. The Steering Committee was responsible for the study design, interpretation, and supervision. The Event Evaluation Committee reviewed any adverse event during the trial. Drug costs were covered by health insurance. The cost of platelet aggregation testing (VerifyNow<sup>TM</sup>; Werfen Inc., Bedford, MA, USA) and cytochrome P450 2C19 (CYP2C19) gene testing were funded by Daiichi Sankyo Co., Ltd.

The trial registered patients with cerebral aneurysm who were  $\geq 20$  years old and who had been treated using SACE. All patients gave their written informed consent to participate in the registry. Those judged as inappropriate by their attending physician were excluded from the trial. Patients in the RCT were randomly assigned to dual antiplatelet therapy (aspirin and clopidogrel) for durations of 3 or 12 months and followed for 15 months after SACE (RCT cohort). Those who were ineligible or refused to participate in the RCT were also followed for 15 months (non-RCT cohort). In the non-RCT cohort, physicians used the patient's clinical information to decide the duration of DAPT for each individual case. In the present study, we investigated both the RCT and non-RCT cohorts. Patients were grouped according to duration of dual antiplatelet therapy (short-term and long-term groups) using the median duration in all patients as a cut-off. In addition, event occurrence was compared between the dual therapy treatment period and the monotherapy treatment period.

### Study procedures

Patients in the 12 month dual therapy group in the RCT received aspirin (100 mg) and clopidogrel (75 mg) daily for 12 months followed by aspirin or clopidogrel alone for 3 months. Those in the 3 month dual therapy group received aspirin (100 mg) and clopidogrel (75 mg) daily for 3 months followed by aspirin or clopidogrel alone for 12 months. Antiplatelet therapy was not standardized in the patients in the non-RCT cohort.

Modified Rankin scale (mRS) score was documented at registration and each follow-up visit. Follow-up was performed 3, 6, 12, and 15 months after SACE. MRI was performed at registration and the 15 month follow-up (fluid attenuated inversion recovery, T2 star-weighted, and angiographic sequences). Platelet aggregation testing was performed at registration and at the 6- and 12 month follow-ups. CYP2C19 gene testing was performed once during the 15 month follow-up period.

### Outcomes

The primary outcome was the incidence of ischemic stroke within 15 months after SACE. Secondary outcomes were incidence of death or any stroke (ischemic stroke, hemorrhagic stroke, transient ischemic attack, aneurysmal rupture), hemorrhagic event, aneurysm retreatment, and stent occlusion or stenosis within 15 months after SACE. Ischemic stroke was defined as a new ischemic lesion on computerized tomography (CT) or magnetic resonance imaging (MRI) with neurological symptoms lasting

$>24$  hours. Hemorrhagic stroke was defined as a new intraparenchymal hemorrhage or subarachnoid hemorrhage on CT or MRI excluding aneurysmal rupture with 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), and hemorrhage resulting in a  $>20$  g/L decrease in hemoglobin concentration or requiring transfusion of more than 2 units of packed red blood cells. Stent stenosis was defined as stenosis  $>50\%$ .

### Statistical analysis

Cumulative event-free survival 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. Survival data were compared using the log-rank test. Propensity scores were estimated in the long- and short-term dual antiplatelet therapy groups with logistic regression using the following variables: study cohort; age; gender; history of subarachnoid hemorrhage, hemorrhagic stroke, and ischemic stroke; comorbidities of hypertension, diabetes mellitus, and dyslipidemia; smoking; mRS score; preoperative aspirin assay value; preoperative P2Y12 assay value; aneurysmal rupture; aneurysm diameter (largest diameter, dome diameter, neck diameter); diameter of stented vessel (minimal, maximal); postoperative embolization; CYP2C19 genotype; aneurysm shape; and type of stent. Patients were divided into five strata according to propensity score for comparison of long- and short-term dual antiplatelet therapy using stratified Cox proportional hazards regression. In addition, proportional hazards regression was used to compare the occurrence of events between the dual and monotherapy patients.

Continuous data are presented as means with standard deviation (SD) and were compared using the Wilcoxon rank-sum test. Categorical data are presented as numbers with percentage and were compared using the Chi-squared test. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.1 (www.r-project.org). Imputation of missing values was not performed. All tests were two-tailed and  $p < 0.05$  was considered significant.

## RESULTS

Among the 313 patients registered in the DAPTS ACE registry, 141 were enrolled in the RCT; 172 patients were enrolled as participants in the non-RCT cohort. Five RCT patients and 11 non-RCT patients were excluded owing to misregistration or withdrawal of consent. One protocol deviation occurred in the non-RCT cohort. Finally, 296 patients were included for analysis (136 RCT patients and 160 non-RCT patients). Patient characteristics according to cohort are summarized in online supplemental table 1). Median duration of dual antiplatelet therapy in all patients and the RCT and non-RCT cohorts was 197, 181.5, and 200 days, respectively (online supplemental figure 1). Considering these results and their clinical significance, 191 patients with duration of dual antiplatelet therapy  $>6$  months were classified to the long-term group, and 105 patients with duration of dual antiplatelet therapy  $\leq 6$  months were classified to the short-term group. Sixty-nine patients in the RCT cohort (50.7%) and 122 patients in the non-RCT cohort (76.3%) received long-term dual therapy (figure 1).

Patient characteristics in the long- and short-term dual antiplatelet therapy groups are summarized in table 1. The duration of DAPT was  $45.0 \pm 15.0$  and  $13.3 \pm 4.6$  weeks (Mean  $\pm$  SD) in

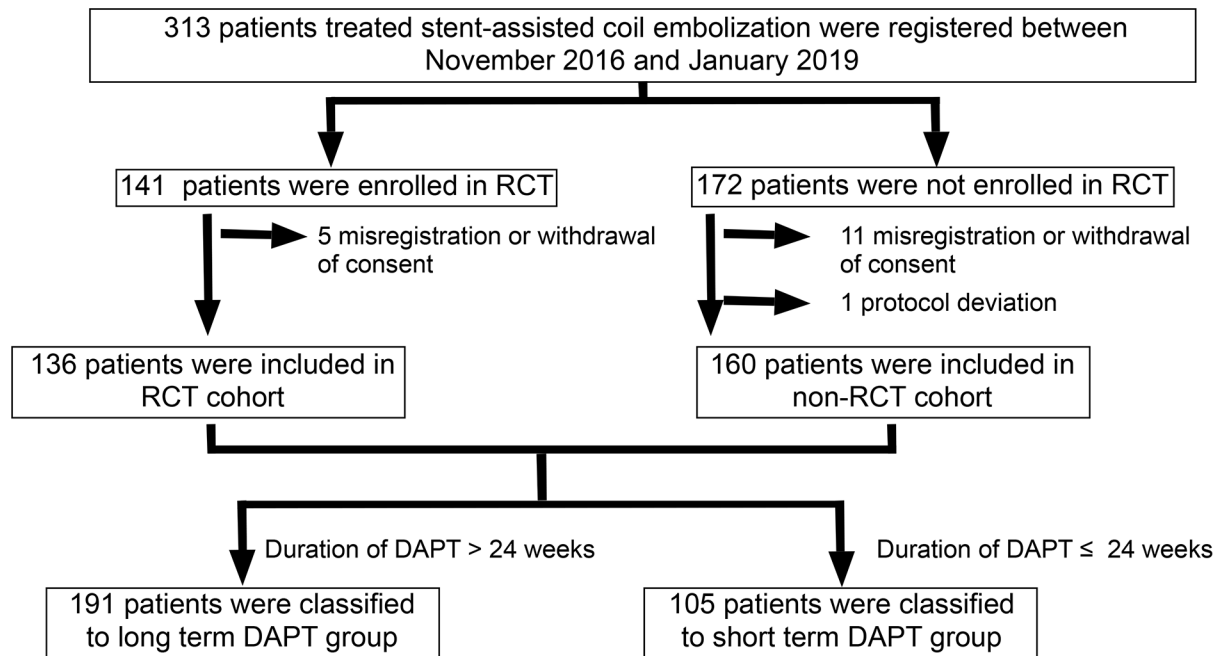


Figure 1 Study flowchart.

the long- and the short-term dual antiplatelet therapy group, respectively ( $p < 0.001$ ). Sex, age, medical history (subarachnoid hemorrhage, hemorrhagic stroke, ischemic stroke, hypertension, diabetes mellitus, dyslipidemia, smoking), and platelet aggregation testing results were similar between the two groups. Prevalence of target aneurysm rupture was higher in the short-term dual therapy group ( $p = 0.030$ ). Aneurysm size and shape, number of stents placed, and angiographic outcomes of SACE were similar.

The antiplatelet agent used for monotherapy after dual therapy had ended did not significantly differ between the groups (online supplemental table 2). Platelet aggregation testing results in the long- and short-term dual antiplatelet therapy groups are shown in online supplemental table 3).

The stents were classified into older stents ( $n = 56$ ; Enterprise VRD, Enterprise two and Neuroform EZ) and newer stents ( $n = 231$ ; Neuroform Atlas, LVIS, LVIS Jr). The duration of DAPT was 31.7 and 33.9 weeks in patients with older and newer stents respectively ( $p = 0.453$ ). There was no difference in the use of newer stents between the long- and short-term dual antiplatelet groups (83.5% vs 75.2%). The ischemic event was occurred in 1 (1.4 per 100 person-years) and 7 (2.5 per 100 person-years) in older stent group and newer stent group respectively ( $p = 0.581$ ).

### Comparison of the long- and short-term dual antiplatelet therapy groups

The comparison of outcomes between the long-term and short-term dual antiplatelet therapy groups is shown in table 2 and the Kaplan–Meier event-free survival curves are shown in figure 2. Within 15 months after SACE, ischemic stroke, the primary outcome, occurred in six patients in the long-term dual antiplatelet therapy group and in four patients in the short-term dual antiplatelet therapy group. The incidence of ischemic stroke did not significantly differ between the groups, (2.5 vs 3.2 per 100 person-years, respectively; HR 0.78,  $p = 0.728$ ). For secondary outcomes, a hemorrhagic event occurred in two patients in the long-term antiplatelet therapy group and in four patients in the short-term dual antiplatelet therapy group (0.8 vs 3.2/100

person-years; HR 0.20,  $p = 0.068$ ). Similarly, the incidence rates of the other secondary outcomes did not significantly differ between the groups.

### Comparison of the dual antiplatelet therapy and monotherapy treatment periods

Hazard ratios comparing the hazard rates for ischemic stroke and the various secondary outcomes in the dual antiplatelet therapy and monotherapy treatment periods are shown in table 2. The HR for ischemic stroke of the dual antiplatelet therapy treatment period was 0.51 compared with the monotherapy treatment period, and it was not significantly different ( $p = 0.533$ ). The risk of the secondary outcomes did not significantly differ between the two periods.

### Relationship between events and the timing of monotherapy initiation

Six ischemic strokes occurred in the long-term dual antiplatelet therapy group and four in the short-term group. Two ischemic strokes in each group occurred within 30 days of initiating monotherapy. Two hemorrhagic events occurred in the long-term group and four in the short-term group; dual therapy was switched to monotherapy within 2 days of the event in one long-term group patient and two short-term group patients (online supplemental table 4).

### DISCUSSION

In our study, rates of ischemic stroke and hemorrhagic events did not significantly differ after SACE between patients who received dual antiplatelet therapy for longer than 6 months and those who received it for less than 6 months. In addition, the risks of ischemic stroke and hemorrhagic events did not significantly differ between the dual therapy and monotherapy treatment periods.

The benefit of long-term dual antiplatelet therapy was not proven in our study. One reason for this was the low rate of delayed thromboembolic events. For the same reason we could

**Table 1** Patient characteristics in the long- and short-term dual antiplatelet therapy groups

	Long-term DAPT (n=191)	Short-term DAPT (n=105)	P value
Age: mean±SD	60.4±13.1	60.1±12.9	0.874
Man: n (%)	51 (26.7)	35 (33.3)	0.285
Previous SAH: n (%)	18 (9.4)	11 (10.5)	0.931
Previous hemorrhagic stroke: n (%)	6 (3.1)	3 (2.9)	1.000
Previous ischemic stroke: n (%)	13 (6.8)	6 (5.7)	0.905
Risk Factors: n (%)			
Hypertension	93 (48.7)	48 (45.7)	0.712
Diabetes	13 (6.8)	3 (2.9)	0.242
Dyslipidemia	67 (35.1)	30 (28.6)	0.312
Smoking habit	27 (14.1)	16 (15.2)	0.932
Target aneurysm, symptoms: n (%)			0.030
Unruptured (asymptomatic)	169 (88.5)	93 (88.6)	
Unruptured (symptomatic)	12 (6.3)	1 (1.0)	
Ruptured (15 days after onset)	10 (5.2)	11 (10.5)	
Target aneurysm, locations: n (%)*			
ICA-paraclinoid	67 (35.1)	41 (39.0)	
ICA-PcomA	20 (10.5)	16 (15.2)	
MCA bifurcation	7 (3.7)	4 (3.8)	
AcomA	25 (13.1)	10 (9.5)	
VA	23 (12.0)	15 (14.3)	
VA-PICA	6 (3.1)	2 (1.9)	
BA bifurcation	19 (9.9)	9 (8.6)	
PCA	1 (0.5)	1 (1.0)	
Others (anterior circulation)	1 (1.5)	2 (1.9)	
Target aneurysm, maximum diameter (mm): mean±SD	8.06±4.32	7.54±3.24	0.280
Target aneurysm, maximum diameter <10mm: no (%)	152 (79.6)	87 (82.9)	0.596
Patients with non-target aneurysm in this study: n (%)	50 (26.2)	17 (16.2)	0.069
Radiographic outcome: n (%)			0.183
Complete occlusion	75 (39.3)	33 (31.4)	
Neck remnant	64 (33.5)	33 (31.4)	
Aneurysm filling	52 (27.2)	39 (37.1)	
Deployed stent: n (%)			0.175
Enterprise VRD	3 (1.6)	0 (0.0)	
Enterprise 2	14 (7.3)	19 (18.1)	
Neuroform EZ	13 (6.8)	7 (6.7)	
Neuroform Atas	57 (29.8)	28 (26.7)	

Continued

**Table 1** Continued

	Long-term DAPT (n=191)	Short-term DAPT (n=105)	P value
LVIS	69 (36.1)	38 (36.2)	
LVIS Jr	26 (13.6)	13 (12.4)	
Double stents†	3 (1.6)	0 (0.0)	
Pipeline	4 (2.1)	0 (0.0)	
Unknown	2 (1.0)	0 (0.0)	
ARU at registration: mean±SD	455.6±73.7	445.9±82.5	0.346
PRU at registration: mean±SD	173.7±75.6	176.4±90.5	0.803
Duration of DAPT (weeks): mean±SD	45.0±15.0	13.3±4.6	<0.001
Characteristics of Long term DAPT group and Short term DAPT group. *includes patients with multiple aneurysms †one patient was treated with Enterprise VRD and Neuroform Atlas stents, one with LVIS Jr and LVIS stents, and one with ELVIS and Neuroform Atlas stentsDAPT, dual antiplatelet therapy AcomA, anterior communicating artery; ARU, aspirin reaction units; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PcomA, posterior communicating artery; PICA, posterior inferior cerebellar artery; PRU, P2Y12 reaction units; SAH, subarachnoid hemorrhage; VA, vertebral artery.			

not prove the superiority of 12 month dual therapy over 3 month dual therapy in the index DAPTS ACE RCT.<sup>9</sup> Even when restricted to the non-RCT cohort, the rate of delayed ischemic stroke events in our study was also low (online supplemental figure 2). In a review article which included 1517 SACE cases, Shapiro *et al* reported a thromboembolic event rate of 9.6%.<sup>10</sup> Mocco *et al* reported a 4% rate in their multicenter study of SACE using the Enterprise stent (Cordis Neurovascular, Miami, FL, USA); mean follow-up in this study was 174.6 days.<sup>11</sup> In contrast, the ischemic stroke rate in the long-term dual antiplatelet therapy group in our study was 2.5 per 100 patient years and 3.2 in the short-term group. With advances in stent quality, thromboembolic event rates have decreased<sup>12–14</sup> and newer stents, such as the Neuroform Atlas (Stryker Neurovascular, Fremont, CA, USA) and LVIS (MicroVention, Tustin, CA, USA), accounted for many of our cases. In particular, the Neuroform Atlas was designed to be used in relatively small arteries than other stents. Its structure enables safe and easy access to distal small vessels and it is compatible with a 0.0165-inch microcatheter, which is the smallest diameter for stent deployment. Daou *et al* reported a 1.3% symptomatic thromboembolic event rate after SACE using the Neuroform Atlas.<sup>15</sup>

Another reason for the low frequency of delayed thromboembolic events in our study is the healthy vascular endothelium on which the stents were deployed. Previous studies of coronary interventions have suggested 1 to 3 months of dual antiplatelet therapy after stenting of stable coronary disease.<sup>16 17</sup> In comparison, 3 to 12 months has been suggested after stenting of acute coronary syndrome.<sup>18 19</sup> Condition of the vascular endothelium and plaque should be considered when determining the duration of dual therapy. Generally, with SACE, the vascular endothelium is normal and significant plaque is not present. Considering this, long-term dual therapy after SACE probably has no advantages over short-term therapy.

Although the thromboembolic event rate after SACE is not generally high, risk factors have been reported.<sup>20–22</sup> Rossen *et al* investigated the incidence of ischemic events after



**Table 2** Primary and secondary outcomes

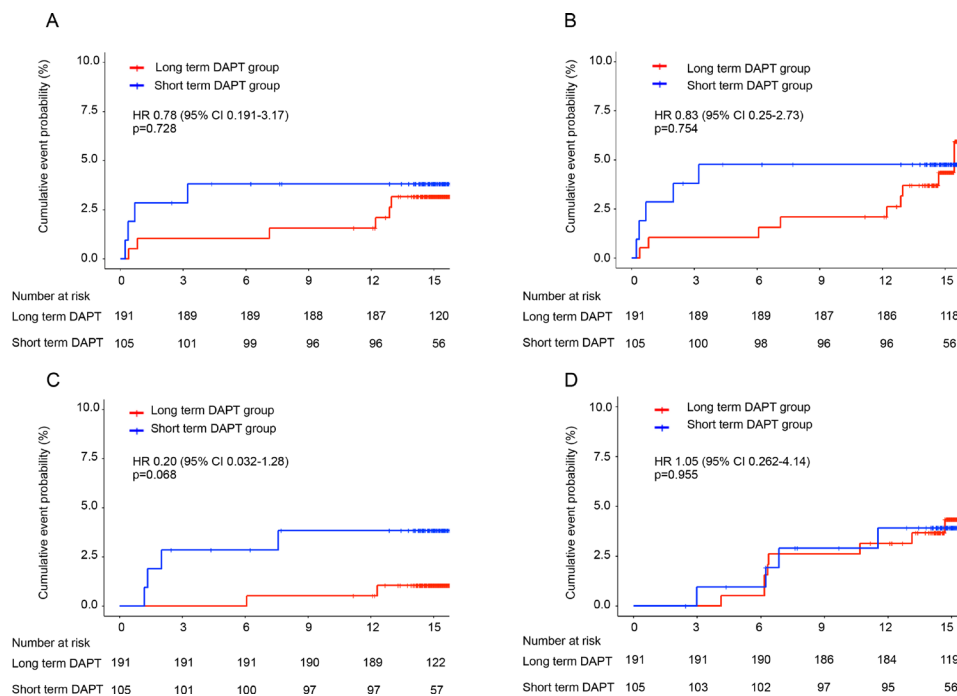
	Long-term DAPT (n=191)	Short-term DAPT (n=105)	Long-term DAPT vs short-term DAPT*		DAPT treatment vs SAPT treatment †	
			Hr (95% CI)	P- value	Hr (95% CI)	P- value
Primary outcome n (per 100 patient-year)						
Ischemic stroke	6 (2.5)	4 (3.2)	0.78 (0.191 to 3.17)	0.728	0.51 (0.059 to 4.31)	0.533
Secondary outcome n (per 100 patient-year)						
Death or any stroke	9 (3.8)	5 (4.1)	0.83 (0.25 to 2.73)	0.754	0.74 (0.135 to 4.11)	0.735
Hemorrhagic event	2 (0.8)	4 (3.2)	0.20 (0.032 to 1.28)	0.068	0.84 (0.085 to 8.38)	0.883
Death, any stroke or hemorrhagic event	10 (4.2)	6 (4.9)	0.77 (0.257 to 2.29)	0.635	1.31 (0.282 to 6.13)	0.728
Retreatment, Stent occlusion/stenosis	8 (3.4)	4 (3.2)	1.04 (0.262 to 4.14)	0.955	2.65 (0.689 to 10.2)	0.156

\*stratified proportional hazards model with patients divided into five strata according to propensity score.  
†proportional hazards model with DAPT and SAPT as time-dependent covariates  
CI, confidence interval; DAPT, dual antiplatelet therapy; Hr, hazard ratio; SAPT, single antiplatelet therapy.

discontinuation of clopidogrel in patients who underwent SACE. Their antiplatelet therapy protocol comprised 6 weeks of aspirin and clopidogrel followed by 3 months of aspirin alone. They reported that patients with cardiovascular risk factors and high-risk aneurysm features and those treated with stent-in-stent flow diversion might benefit the most from longer clopidogrel therapy.<sup>20</sup> Song *et al* investigated 125 patients with unruptured intracranial aneurysms treated with SACE using the Enterprise stent and reported that current smoking and maximum parent artery diameter >4.5 mm were associated with delayed thromboembolic events.<sup>22</sup> Another study reported that the incidence of delayed thromboembolic events after SACE for unruptured intracranial aneurysms was higher in patients with diabetes and dyslipidemia.<sup>21</sup>

Switching from dual therapy to monotherapy requires careful attention. Hwang *et al* reported a delayed ischemic stroke incidence of 3.5% within 2 months of the switch in patients who underwent SACE.<sup>5</sup> In our study, 40% of all ischemic events occurred within 1 month of the switch.

Hemorrhagic complications also have to be considered when determining the optimal duration of dual antiplatelet therapy.<sup>7 8 23</sup> Shoda *et al* reported that long-term dual therapy after SACE in clopidogrel responders (P2Y12 reaction units <208) was related to delayed hemorrhagic events.<sup>23</sup> In our study, 60% of cases experienced a hemorrhagic event and had to be switched from dual therapy to monotherapy. Thus, the duration of dual therapy might have to be determined based on thromboembolic and hemorrhagic risk factors. Costa *et al* proposed the



**Figure 2** Kaplan–Meier curves for ischemic stroke (A), death or any stroke (B), hemorrhagic event (C), and retreatment or stent occlusion/stenosis (D) in the short- and long-term dual antiplatelet therapy groups.

PRECISE-DAPT score, which includes age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding as variables predicting the risk of bleeding after coronary stenting. In their study, longer duration of dual therapy was significantly associated with increased bleeding incidence in patients with a high PRECISE-DAPT score.<sup>8</sup>

### Limitations

The main limitation of our study was that we combined the RCT and non-RCT cohorts. The variety and duration of dual antiplatelet therapy were not defined in more than half of the patients. Second, we chose a dual therapy cut-off duration of 6 months to differentiate short- and long-term therapy; however, the duration did not distribute evenly. Finally, approximately 13% of the non-RCT cohort underwent triple antiplatelet therapy with aspirin, clopidogrel and cilostazol and approximately 7% had aspirin plus prasugrel (online supplemental table 1). One of the main reasons for these results might have been the high prevalence of CYP2C19 polymorphism and the poor metabolizer of the clopidogrel in our country.<sup>24</sup> Physicians added cilostazol or switched from clopidogrel to prasugrel in case they calculated P2Y12 reaction units (PRU) before SACE and found the low response of clopidogrel. In our study, baseline PRU was monitored within 30 days after SACE. Therefore, we did not have the PRU information before SACE and modification of antiplatelet treatment based on the preoperative PRU value.

### Conclusions

This multicenter study found no significant relationship between incidence rates of ischemic stroke and hemorrhagic events and duration of dual antiplatelet therapy within the first 15 months after SACE.

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**Contributors** TO performed the data analysis and drafted the manuscript. HY and NS conceptualized and designed the study. HY is responsible for over all content as guarantor. HY accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish. MM, HI, TH, HO, KH, SY, TS, 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 and KK comprised the independent Event Evaluation Committee. TK contributed to the statistical analyses. All authors reviewed the manuscript and approved the final version.

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