Radiology

Delayed Ischemic Stroke after Stent-assisted Coil Placement in Cerebral Aneurysm: Characteristics and Optimal Duration of Preventative Dual Antiplatelet Therapy[1]

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Purpose: To evaluate characteristics of delayed ischemic stroke after stent-assisted coil placement in cerebral aneurysms and to determine the optimal duration of dual antiplatelet therapy for its prevention.

Materials and Methods: This retrospective study was approved by the institutional review board, and the requirement to obtain written informed consent was waived. Of 1579 patients with 1661 aneurysms, 395 patients (25.0%) with 403 aneurysms (24.3%) treated with stent-assisted coil placement were included and assigned to groups stratified as early (126 patients [31.9%]; 3 months of coil placement), midterm (160 patients [40.5%]; 6 months), or late (109 patients [27.6%]; ≥9 months), according to the time points of switching dual antiplatelet therapy to monotherapy from coil placement. Cumulative rates of delayed ischemic stroke in each group were calculated by using Kaplan-Meier estimates that were compared with log-rank tests. Risk factors of delayed ischemic stroke were identified by using Cox proportional hazard analysis.

Results: Delayed ischemic stroke occurred in 3.5% of all cases (embolism, 3.0%; thrombotic occlusion, 0.5%) within 2 months following the switch. Late switch yielded no delayed ischemic stroke, unlike early (seven of 126 patients [5.6%]; $P = .013$) or midterm (seven of 160 patients [4.4%]; $P = .028$) switch. Incomplete occlusion (hazard ratio, 6.68 [95% confidence interval: 1.490, 29.900]) was identified as a risk factor.

Conclusion: Delayed ischemic stroke after stent-assisted coil placement is caused by embolism from or thrombotic occlusion of stent-containing vessels after switching from dual antiplatelet therapy to monotherapy. The stent-containing vessel with incomplete aneurysm occlusion presents as a long-term thromboembolic source. Therefore, dual antiplatelet therapy for more than 9 months and late switch to monotherapy are recommended for its prevention.

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Antiplatelet therapy is recommended for prevention of delayed ischemic stroke after stent-assisted coil placement in cerebral aneurysms. Unlike coronary artery stent placement, the short-term (6 weeks to 3 months) use of initial dual antiplatelet therapy and subsequent switch to monotherapy are generally accepted (1–3). However, previous studies (4,5) reported a delayed ischemic stroke rate of 4%–5% after this antiplatelet therapy protocol that is known to be 80–100 times higher than the stroke rate in general population (5). Therefore, antiplatelet therapy protocol is currently imperfect in stent-assisted coil procedures.

There are patients in our practice who had delayed ischemic stroke during follow-up after stent-assisted coil placement. Therefore, we revised our antiplatelet therapy protocol for stent-assisted coil placement several times by prolonging the duration of dual antiplatelet therapy. The purpose of this retrospective study is to evaluate characteristics of delayed ischemic stroke after stent-assisted coil placement in cerebral aneurysm and to determine the optimal duration of dual antiplatelet therapy for its prevention.

Advances in Knowledge

- Stent-assisted coil placement in cerebral aneurysm is associated with a greater risk of delayed ischemic stroke during follow-up than is standard coil placement (stent-assisted vs standard, 3.5% vs 0.2%, respectively; hazard ratio, 27.69 [95% confidence interval: 6.277, 122.100]; $P < .001$).
- Delayed ischemic stroke after stent-assisted coil placement is mainly caused by embolism from stent-containing vessels after early switch of dual antiplatelet therapy to monotherapy (switch at 3 months of coil placement, 5.6%; switch at 6 months, 4.4%).
- Delayed ischemic stroke can be reduced with long-term dual antiplatelet therapy for more than 9 months and late switch to monotherapy (late switch to monotherapy vs switch at 3 months, $P = .013$; late switch to monotherapy vs switch at 6 months, $P = .028$).

Materials and Methods

Patients

This study was approved by our institutional review board. The requirement to obtain written informed consent to participate in this study was waived. We analyzed the clinical and radiologic data retrieved from a registry obtained from our institute for 1783 patients with cerebral aneurysms who underwent endovascular treatment between May 2003 and December 2011. This study included patients who underwent endosaccular coil embolization and were evaluated with regular follow-up over 1 year. Among them, we excluded 78 patients treated with endovascular trapping of parent artery and 126 patients who did not undergo follow-up over 1 year because of death or poor outcome after subarachnoid hemorrhage. Therefore, 1579 patients with 1661 cerebral aneurysms were included (median follow-up, 54 months [interquartile range, 31–83 months]). Of 1661 aneurysms in 1579 patients enrolled in this study, 403 (24.3%) aneurysms in 395 (25.0%) patients were treated with stent-assisted coil placement. All clinical (J.K.K. and K.S.S., both with 7 years of experience in neurosurgery) and radiologic data (Y.J.L., 4 years of experience in neurointervention, and G.H., 7 years of experience in neurointervention) were analyzed by the authors. Discrepancies were solved by consensus during the research period.

Coil Placement Procedure

All aneurysm coil placement was performed under general anesthesia by using a biplane angiographic unit (Integris Allura; Philips Medical Systems, Best, the Netherlands) operated by one neurointerventionist (O.K.K, 17 years of experience in neurointervention). Systemic heparinization was administered after placement of the femoral introducer sheath. Three-dimensional image reconstruction by volume rendering after rotational angiography was performed before embolization in all patients by using software (Integris 3D-RA, release 3.2; Philips Medical Systems). On the basis of the images generated by using rotational acquisition, at least two working projections that provided the best achievable view of the aneurysm neck were defined. For coil placement in aneurysms with an unfavorable configuration, multiple microcatheter, balloon-assisted coil placement, or stent-assisted coil placement technique was used. All coil embolizations were performed by using detachable bare platinum coils (GDC, Stryker Neurovascular, Fremont, Calif; MicroPlex, MicroVention, Aliso Viejo, Calif; Trufill-DCS, Cordis, Miami Lakes, Fla; Axium, Covidien, Irvine, Calif) coils. Modified coils (Matrix, Stryker Neurovascular; Hydro-Coil, MicroVention; Hydrosoft, MicroVention) were not used. During the coil placement procedure, coil that was suitable for safe packing was selected at every step. We used two types of stents for stent-assisted coil placement (Neuroform, Stryker Neurovascular; Enterprise, Cordis).

Implication for Patient Care

- Longer-term dual antiplatelet therapy for more than 9 months and late switch to monotherapy are recommended to prevent delayed ischemic stroke.

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Conflicts of interest are listed at the end of this article.

They were successfully deployed to cover the aneurysmal neck in all cases. We performed final angiography after embolization at the working projection to evaluate occlusion grade according to the Raymond grade (6) and detect any complications. Frontal and lateral projections were also acquired at the end of the procedures.

Antiplatelet Therapy for Stent-assisted Coil Placement

For all patients with unruptured aneurysms in whom stent-assisted coil placement was considered, dual antiplatelet therapy (aspirin, 100 mg; clopidogrel, 75 mg daily) was administered more than 5 days before stent-assisted coil placement. In stent-assisted coil placement for ruptured aneurysms, loading doses of aspirin (300 mg) and clopidogrel (300 mg) were initiated after the procedure. In the early period of the study, dual antiplatelet therapy was recommended for the first 3 months after stent-assisted coil placement, and patients were then switched to monotherapy. Under this policy, however, several patients experienced delayed ischemic stroke after switching from dual antiplatelet therapy to monotherapy. Therefore, we revised our protocol to prolong duration of dual antiplatelet therapy and delay its switch. For the 1st year after coil placement, we followed up with the patients every 3 months. Accordingly, our duration of dual antiplatelet therapy has been gradually prolonged in this follow-up interval.

Definition of Delayed Ischemic Stroke and Evaluation of Its Cause

Delayed ischemic stroke was defined as a transient ischemic attack or stroke with evidence of infarction on diffusion-weighted images, which resulted in new neurologic deficits that occurred in the vascular territory consistent with stent-containing vessel location after 1 month of stent-assisted coil placement (7).

The cause of delayed ischemic stroke was investigated with routine evaluation for ischemic stroke. Electrocardiography, chest x-ray, and laboratory tests that included electrolyte, glucose, lipid profile, vitamin B12, folate, homocystein, fibrinogen, C-reactive protein, and D-dimer were performed. For routine imaging work-up, we performed brain magnetic resonance (MR) imaging (including diffusion-weighted imaging) and contrast agent–enhanced MR angiography, but conventional cerebral angiography was also performed

Table 1

Baseline Characteristics of Cerebral Aneurysms Treated with Endosaccular Coil Embolization

Parameter	All Cerebral Aneurysms	Nonstent-assisted Coil Placement	Stent-assisted Coil Placement	*P* Value
No. of men	492 (29.6)	393 (31.2)	99 (24.6)	.012
Mean age (y) ± SD	57 ± 12.3	57 ± 12.6	56 ± 11.4	.224
History				
Hypertension	760 (45.8)	566 (45.0)	194 (48.1)	.275
Diabetes mellitus	175 (10.5)	138 (11.0)	37 (9.2)	.351
Hyperlipidemia	346 (20.8)	253 (20.1)	93 (23.1)	.205
Smoking	261 (15.7)	202 (16.1)	59 (14.6)	.529
Cerebrovascular accident	154 (9.3)	112 (8.9)	42 (10.4)	.375
Atrial fibrillation	18 (1.1)	12 (0.9)	6 (1.5)	.406
Coronary heart disease	71 (4.3)	59 (4.7)	12 (3.0)	.158
Ruptured at initial presentation*	457 (27.5)	430 (34.2)	27 (6.7)	<.001
Aneurysm location*				
Anterior cerebral artery	345 (20.8)	327 (26.0)	18 (4.5)	<.001
Internal carotid artery	893 (53.8)	588 (46.7)	305 (75.7)	…
Middle cerebral artery	211 (12.7)	202 (16.1)	9 (2.2)	…
Posterior circulation	212 (12.8)	141 (11.2)	71 (17.6)	…
Mean aneurysm diameter (mm) ± SD	6.5 ± 4.03	6.3 ± 3.82	7.2 ± 4.52	<.001
≤5 mm*	757 (45.6)	604 (48.0)	153 (38)	<.001
5–15 mm*	828 (49.8)	609 (48.4)	219 (54.3)	…
>15 mm*	76 (4.6)	45 (3.6)	31 (7.7)	…
Mean aneurysm neck (mm) ± SD	4.2 ± 2.44	3.9 ± 2.13	5.3 ± 2.97	<.001
≤4 mm*	1008 (60.8)	851 (67.8)	157 (39)	<.001
>4 mm*	651 (39.2)	405 (32.2)	246 (61)	…
Atherosclerotic lesion in cerebral circulation	92 (5.5)	75 (6.0)	17 (4.2)	.211
Coil placement method*				
Single-catheter technique	614 (37.0)	…	…	…
Multiple catheter technique	449 (27.0)	…	…	…
Balloon-assisted coil placement	195 (11.7)	…	…	…
Stent-assisted coil placement	403 (24.3)	…	…	…
Occlusion grade*†				
Complete	673 (40.5)	466 (37.0)	207 (51.4)	<.001
Residual neck	684 (41.2)	555 (44.1)	129 (32)	…
Residual sac	304 (18.3)	237 (18.8)	67 (16.6)	…
No. of thromboembolic complications				
Periprocedural; <1 month after coil placement	50 (3.0)	34 (2.7)	16 (4.0)	.239
Delayed; ≥1 month after coil placement	18 (1.0)	2 (0.2)	14 (3.5)	<.001

Note.—Unless otherwise indicated, data are number of patients. Data in parentheses are percentages. There were 1661 cerebral aneurysms, 1258 (75.7%) of which had nonstent-assisted coil placement and 403 (24.3%) of which had stent-assisted coil placement. SD = standard deviation.

* Data are number of aneurysms.

† Occlusion grade was evaluated on postembolization angiogram according to Raymond grade.

in the patients who were treated with stent-assisted coil placement to evaluate the status of the aneurysm and stent-containing vessel. To evaluate cardioembolic source, transthoracic echocardiography was performed and checked first. If the test result was negative, transesophageal echocardiography was then performed. Holter monitoring was performed when paroxysmal atrial fibrillation was highly suspicious. Patients suspected of having an embolism with negative findings on these cardioembolic work-ups underwent patent foramen ovale test with agitated saline. With these findings and clinical information, we determined the cause of delayed ischemic stroke by using the Causative Classification System for Ischemic Stroke, an automated version of the Stop Stroke Study–Trial of Org 10172 in Acute Stroke Treatment (known as SSS-TOAST) system (8–10). When the Causative Classification System for Ischemic Stroke result indicated that other causes subtype (ie, the stent or stent-containing vessel) was evident, we finally considered stent as a cause of delayed ischemic stroke. These results were re-evaluated (J.K.K. and K.S.S.), and discrepancies were solved by consensus during the research meeting.

Statistical Analyses

Statistical analysis was conducted by using statistical software (R software version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria). Either the *t* test or one-way analysis of variance test were used for continuous variables, and the χ^2 or Fisher exact test was used for nominal factors. Cox proportional hazard analysis with backward elimination was performed to adjust confounders or identify risk factors of delayed ischemic stroke. Variables with an unadjusted effect with a *P* value of less than .15 in bivariate analysis were included in this analysis. The proportional assumption of the fitted models were confirmed by log-log plot and a Schoenfeld residual test.

According to the time point of switching dual antiplatelet therapy to monotherapy from coil placement, 395 patients who underwent stent-assisted

Table 2

Summary of Patients Who Experienced Delayed Ischemic Stroke during Follow-up after Stent-assisted Coil Placement

Patient No.	Stent-assisted Coil-Placement Subgroup*	Sex	Age (y)	Aneurysm Location	Antiplatelet Change to Delayed Ischemic Stroke (d)	Type	Mechanism	NIHSS at Admission	Resistance†		mRS Score
									Aspirin	P2Y12	
1	Early	F	77	Proximal intradural ICA	6	Infarction	Embolism	3	No	Yes	0
2	Early	F	44	BA bifurcation	7	Infarction	Occlusion	15	No	No	3
3	Early	F	58	Proximal intradural ICA	8	TIA	Embolism	0	No	No	1
4	Early	F	56	Proximal intradural ICA	10	Infarction	Occlusion	2	No	Yes	0
5	Early	F	60	BA bifurcation	18	Infarction	Embolism	4	No	No	0
6	Early	F	72	MCA bifurcation	19	Infarction	Embolism	5	No	Yes	1
7	Early	F	56	Proximal intradural ICA	57	Infarction	Embolism	2	No	Yes	1
8	Midterm	M	63	BA bifurcation	8	TIA	Embolism	0	No	Yes	0
9	Midterm	F	70	Proximal intradural ICA	10	TIA	Embolism	0	No	No	0
10	Midterm	F	74	Cavernous ICA	16	Infarction	Embolism	4	No	Yes	0
11	Midterm	M	62	Proximal intradural ICA	25	TIA	Embolism	1	No	No	0
12	Midterm	M	56	Proximal intradural ICA	37	TIA	Embolism	0	No	No	0
13	Midterm	F	59	Proximal intradural ICA	44	TIA	Embolism	0	No	Yes	0
14	Midterm	F	57	Proximal intradural ICA	45	TIA	Embolism	0	No	No	0

Note.—BA = basilar artery, ICA = internal carotid artery, MCA = middle cerebral artery, mRS = modified Rankin scale at last follow-up, NIHSS = National Institutes of Health Stroke Scale score, TIA = transient ischemic attack.

* Stratified by the time point of switching dual antiplatelet therapy to monotherapy from coil placement procedure.Early, 3 months of stent-assisted coil placement; midterm, 6 months; late, ≥9 months or more.

† Antiplatelet resistance was evaluated by using a test (VerifyNow; Accumetrics, San Diego, Calif). Aspirin and P2Y12 resistances were defined as aspirin reaction unit ≥550 and percentage inhibition ≤20%, respectively.

coil placement were divided into switch groups that were classified as early (3 months of stent-assisted coill placement, 126 patients [31.9%]), midterm (6 months of stent-assisted coil placement, 160 patients [40.5%]), and late (9 months of stent-assisted coil placement or more, 109 [27.6%]). Cumulative rates of delayed ischemic stroke in each study group were calculated by using Kaplan-Meier estimates and compared by log-rank tests. Statistical significance was accepted for *P* values less than .05. Collection and summary of all reviewed data were performed by three authors (E.A.J., 11 years of experience, N.M.P., 6 years of experience, and S.J.P., 2 years of experience in medical research).

Results

Baseline characteristics of the 1661 coil-treated aneurysms are summarized in Table 1. Stent-assisted coil placement was mainly applied for aneurysms that were unruptured ($P < .001$), large ($P < .001$), and wide necked ($P < .001$) in a relatively large parent artery (internal carotid artery, $P < .001$). However, stent-assisted coil placement was found to have a significantly greater risk of delayed ischemic stroke than coil placement that was not stent assisted, although baseline differences between these groups were adjusted (stent-assisted vs nonstent-assisted coil placement, 14 of 403 [3.5%] vs two of 1258 [0.2%], respectively; hazard ratio, 27.69 [95% confidence interval: 6.277, 122.100]; $P < .001$).

Among the 395 patients who underwent stent-assisted coil placement, delayed ischemic stroke during follow-up occurred in 14 patients (3.5%; transient ischemic attack in seven patients, infarction in seven patients) (Table 2). In 12 patients, embolic infarction occurred. On their evaluations for ischemic stroke, no possible source of this embolism was detected other than the stent in the affected vascular territory. By using the Causative Classification System for Ischemic Stroke result, we decided that the stent or stent-treated vessel was the cause of embolic infarction. In the remaining two patients, thrombotic occlusion of the stent-treated vessel led to delayed ischemic stroke. All delayed ischemic stroke occurred within 2 months (range, 6–57 days) after we switched dual antiplatelet therapy to monotherapy, but was undetected thereafter. In these 14 patients, no aspirin resistance was found. Two patients underwent intra-arterial thrombolysis, and the remaining patients were treated by conservative therapy, which included intravenous hydration, reinitiation of dual antiplatelet therapy

Table 3

Baseline Characteristics of the Subgroups, Stratified by the Time Point of Switching Dual Antiplatelet Therapy to Monotherapy from Coil Placement

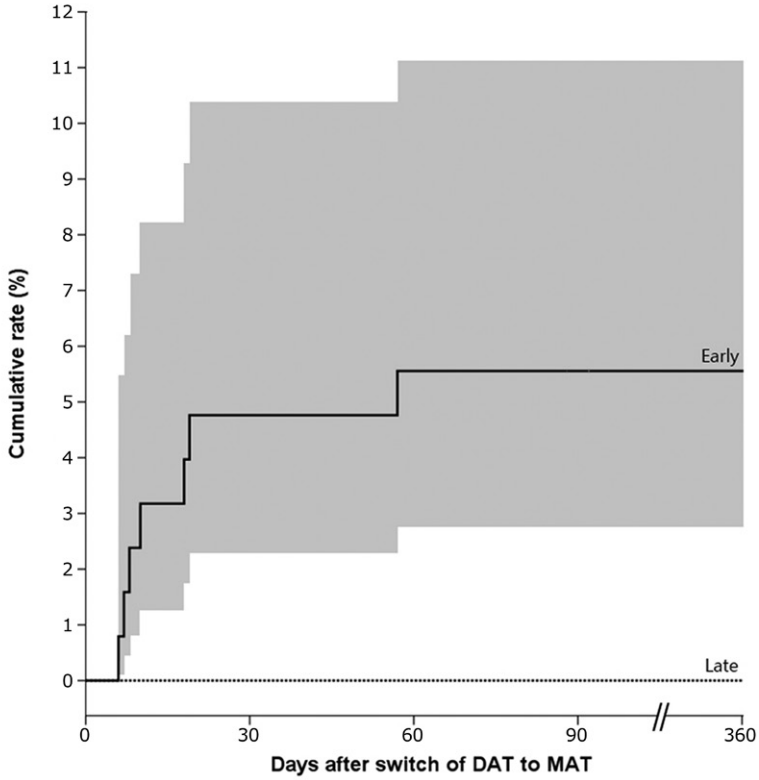
Parameter	Stent-assisted Coil-Placement Subgroups*			*P* Value
	Early Subgroup	Midterm Subgroup	Late Subgroup	
No. of men	25 (19.5)	42 (25.6)	32 (28.8)	.230
Mean age (y) ± SD	54 ± 12.3	57 ± 10.9	57 ± 11.4	.163
Past history				
Hypertension	60 (46.9)	78 (47.6)	56 (50.5)	.843
Diabetes mellitus	11 (8.6)	14 (8.5)	12 (10.8)	.783
Hyperlipidemia	29 (22.7)	39 (23.8)	25 (22.5)	.962
Smoking	15 (11.7)	25 (15.2)	19 (17.1)	.480
Cerebrovascular accident	14 (10.9)	13 (7.9)	15 (13.5)	.322
Atrial fibrillation	1 (0.8)	3 (1.8)	2 (1.8)	.726
Coronary heart disease	4 (3.1)	3 (1.8)	5 (4.5)	.437
Ruptured at initial presentation†	10 (7.8)	7 (4.3)	10 (9.0)	.253
Aneurysm location†				
Anterior cerebral artery	3 (2.3)	11 (6.7)	4 (3.6)	.095
Internal carotid artery	101 (78.9)	127 (77.4)	77 (69.4)	…
Middle cerebral artery	3 (2.3)	1 (0.6)	5 (4.5)	…
Posterior circulation	21 (16.4)	25 (15.2)	25 (22.5)	…
Mean aneurysm diameter (mm) ± SD	7.0 ± 4.18	7.1 ± 4.22	7.7 ± 5.27	.459
≤5 mm†	50 (39.1)	63 (38.4)	40 (36.0)	.964
5–15 mm†	69 (53.9)	87 (53.0)	63 (56.8)	…
>15 mm†	9 (7.0)	14 (8.5)	8 (7.2)	…
Mean aneurysm neck (mm) ± SD	5.2 ± 3.44	5.1 ± 2.37	5.9 ± 3.12	.072
≤4 mm†	57 (44.5)	64 (39.0)	36 (32.4)	.160
>4 mm†	71 (55.5)	100 (61.0)	75 (67.6)	…
No. of atherosclerotic lesions in cerebral circulation	5 (3.9)	5 (3.0)	7 (6.3)	.410
Neuroform stent	26 (20.3)	24 (14.6)	24 (21.6)	.268
Enterprise stent	102 (79.7)	140 (85.4)	87 (78.4)	…
Stent length†				
14–15 mm	12 (9.4)	10 (6.1)	9 (8.1)	.724
20–22 mm	93 (72.7)	128 (78.0)	80 (72.1)	…
28–37 mm	23 (18.0)	26 (15.9)	22 (19.8)	…
Occlusion grade†‡				
Complete	66 (51.6)	85 (51.8)	56 (50.5)	.451
Residual neck	41 (32.0)	57 (34.8)	31 (27.9)	…
Residual sac	21 (16.4)	22 (13.4)	24 (21.6)	…

Note.—Unless otherwise indiated, data are number of patients. Data in parentheses are percentages. There were 403 aneurysms total in the stent-assisted coil-placement subgroups; there were 128 aneurysms in the early group, 164 in the midterm group, and 111 in the late group. SD = standard deviation.

* Early, 3 months of stent-assisted coil placement; midterm, 6 months; late, 9 months or more.

‡ Occlusion grade was evaluated on postembolization angiogram according to Raymond grade.

† Data are number of aneurysms.



Early (3 months of SAC)					
Patients at risk, *n*	126	120	119	118	64
Cumulative event		6	7	7	7
Cumulative rate		4.8%	5.6%	5.6%	5.6%
Late (≥ 9 months of SAC)					
Patients at risk, *n*	109	109	108	103	42
Cumulative event		0	0	0	0
Cumulative rate		0%	0%	0%	0%

a.

(a) Kaplan-Meier curve shows cumulative rates of delayed ischemic stroke after stent-assisted coil placement for early versus late switch, stratified by duration from stent-assisted coil placement to switch from dual antiplatelet therapy to monotherapy. Gray areas indicate 95% confidence intervals of the curves *(continues)*.

(aspirin and clopidogrel), and rehabilitation for neurologic deficit. However, permanent deficit still remained in four patients (1.0% [28.6% of patients with delayed ischemic stroke]) at last follow-up.

No statistically significant difference was found in baseline characteristics among the stent-assisted coil-placement subgroups stratified by the time point of switching dual antiplatelet therapy to monotherapy from coil placement (Table 3). Cumulative rates of delayed ischemic stroke for early and midterm switch groups were, respectively, 5.6% (seven of 126; Fig a) and 4.4% (seven of 160; Fig b) 2 months after the switch. However, none of the patients in the late switch group experienced delayed ischemic stroke after the switch (early vs late switch, P = .013; midterm vs late switch, P = .028; early vs midterm, P = .633).

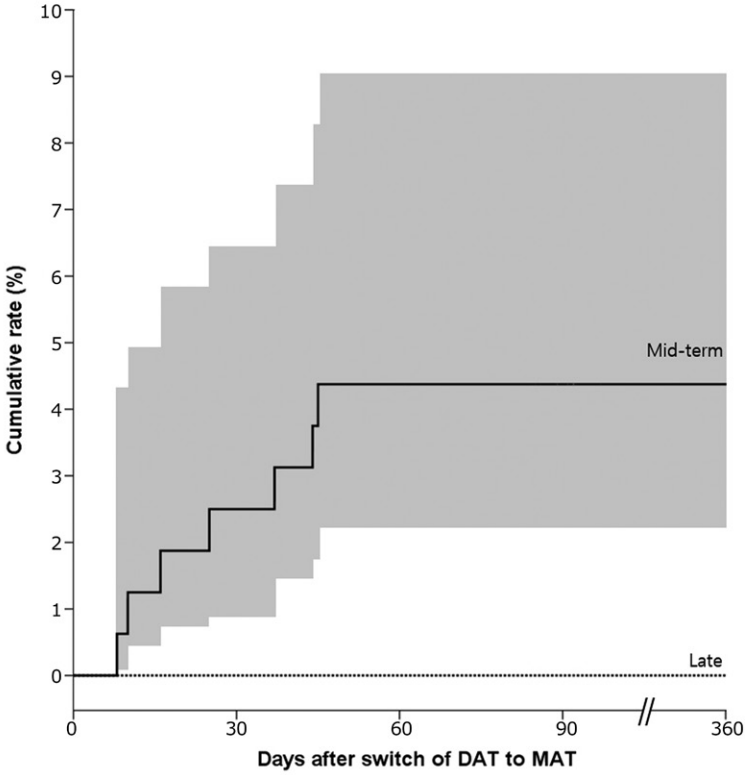
Age (delayed ischemic stroke vs no delayed ischemic stroke group, 61.7 years ± 8.85 vs 55.8 years ± 11.48, respectively; P = .057), diabetes mellitus (three of 14 patients [21.4%] vs 34 of 389 patients [8.7%]; P = .128), wide neck (>4 mm, 12 of 14 patients [85.7%] vs 234 of 389 patients [60.2%]; P = .090), atherosclerotic lesion in cerebral circulation (two of 14 patients [14.3%] vs 15 of 389 patients [3.9%]; P = .113), and incomplete occlusion (residual neck or sac, 12 of 14 patients [85.7%] vs 184 of 389 patients [47.3%]; P = .003) were considered to be candidates for risk factor associated with delayed ischemic stroke after stent-assisted coil placement. Location of aneurysm was also included in this risk-factor analysis. In the Cox proportional hazard analysis with backward elimination of these variables, incomplete occlusion (hazard ratio, 6.68 [95% confidence interval: 1.490, 29.900]; P = .013) was identified as a risk factor of delayed ischemic stroke after stent-assisted coil placement (Table 4). While delayed ischemic stroke occurred in two (1.0%) of 207 stent-assisted coil-placement cases with complete occlusion, it also occurred in 12 (6.1%) of 196 stent-assisted coil-placement cases with incomplete occlusion (P = .003).

During follow-up, easy bruising (201 of 395 patients [50.9%]) and gastric discomfort (98 of 395 patients [24.8%]) were the main adverse effects of antiplatelet therapy. Bleeding complication developed in four patients (1.0%). One patient had epistaxis, one patient had gingival bleeding, and one patient had bleeding from external hemorrhoid during dual antiplatelet therapy. One putaminal hemorrhage occurred 2 years after discontinuation of dual antiplatelet therapy. All adverse effects were treated with conservative care.

Discussion

This study shows a great risk of delayed ischemic stroke in patients treated with stent-assisted coil placement, which was not prevented by the antiplatelet therapy protocol with short-term dual antiplatelet therapy. However, longer-term dual antiplatelet therapy for more than 9 months and late switch to monotherapy were found to significantly reduce delayed ischemic stroke.

(continued)



Mid-term (6 months of SAC)					
Patients at risk, *n*	160	156	153	147	48
Cumulative event		4	7	7	7
Cumulative rate		2.5%	4.4%	4.4%	4.4%
Late (≥ 9 months of SAC)					
Patients at risk, *n*	109	109	108	103	42
Cumulative event		0	0	0	0
Cumulative rate		0%	0%	0%	0%

b.

(continued) **(b)** Kaplan-Meier curve shows cumulative rates of delayed ischemic stroke after stent-assisted coil placement for midterm versus late switch, stratified by durations from stent-assisted coil placement to switch from dual antiplatelet therapy to monotherapy. Gray areas indicate 95% confidence intervals of the curves. *DAT* = dual antiplatelet therapy, *MAT* = monoantiplatelet therapy, *SAC* = stent-assisted coil placement.

Table 4

Delayed Ischemic Stroke after Stent-assisted Coil-Placement Risk Factors

Parameter	Hazard Ratio	95% Confidence Interval	*P* Value
Age	1.05	0.993, 1.099	.088
Incomplete occlusion (residual neck or sac)	6.68	1.490, 29.900	.013

Note.—Risk factors were identified by Cox proportional hazard analysis with backward elimination.

As our study shows, stent-assisted coil placement is mainly used for unruptured aneurysm. Therefore, for the purpose of coil embolization, the complication rate of stent-assisted coil placement should be very low in the treatment of unruptured aneurysm. Although periprocedural complications have been reduced gradually in stent-assisted coil placement, delayed ischemic stroke induces substantial increase in overall rates of complication and resultant permanent neurologic deficit (11–13). Therefore, delayed ischemic stroke after stent-assisted coil placement should be avoided, and for this reason the antiplatelet therapy protocol for stent-assisted coil placement needs to be modified.

The current guidelines for antiplatelet therapy after stent-assisted coil placement in cerebral aneurysm are based on cardiology experience. In stent-assisted coil placement, however, aneurysmal factors should be also considered. Incomplete occlusion, which was identified as a risk factor of delayed ischemic stroke in this study, produces a dead space in combination with the stent. It can induce blood flow disturbance or stagnation continuously and become a long-term source of embolism, which is a cause of delayed ischemic stroke. Therefore, for prevention of embolism from this long-term embolic source, we suggest prolonged use of dual antiplatelet therapy and delayed switch to monotherapy in stent-assisted coil placement in cerebral aneurysm, which was found to be effective in this study.

Recent cardiology guidelines recommend 12 months as an ideal duration of dual antiplatelet therapy even for patients who receive bare metal stent (14). However, long-term dual antiplatelet therapy increases bleeding risk. Therefore, they also recommend that its duration should be tailored to clinical status of each patient. In this study, no serious bleeding complication associated with antiplatelet therapy was found, but a prolonged use of dual antiplatelet therapy after stent-assisted coil placement cannot also be applied to patients who are at high risk for bleeding.

The present study is limited by its retrospective nature. Therefore, the duration of dual antiplatelet therapy of each patient in the same switch group was not strictly identical. Second, data from our registry were based on medical records and images, so several important pieces of information could be omitted. Bleeding complications, especially, may be underestimated. Third, continual increase

in technique and experience of operators with time may affect our outcomes. However, we disclose that annual rate of delayed ischemic stroke in our cases was 4%–5%, and the rate was steady until antiplatelet therapy protocol with long-term dual antiplatelet therapy started. Finally, because a platelet function test was not performed in all patients, the effects of antiplatelet resistance on delayed ischemic stroke could not be evaluated. However, delayed ischemic stroke after stent-assisted coil placement was found to develop after the switch of dual antiplatelet therapy to monotherapy, which is an observation consistent with other studies (2,5,12). Furthermore, no aspirin resistance was detected in patients who experienced delayed ischemic stroke. Therefore, we believe that delayed ischemic stroke after stent-assisted coil placement is mainly associated with insufficient duration of dual antiplatelet therapy rather than inadequate platelet inhibition. In the future, a large prospective study will be necessary to create definite guidelines for antiplatelet therapy in stent-assisted coil placement in cerebral aneurysm.

In summary, delayed ischemic stroke after stent-assisted coil placement in cerebral aneurysm is caused by embolism from the stent or thrombotic occlusion of the stent-containing vessel after early switch of dual antiplatelet therapy to monotherapy, and thus longer-term dual antiplatelet therapy for more than 9 months and late switch to monotherapy are necessary for preventing delayed ischemic stroke.

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