Supplemental Material

Discontinuation of Antiplatelet Therapy After Stent-Assisted Coil Embolization of Cerebral Aneurysm: A Nationwide Cohort Study

Supplemental Methods

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Supplemental Methods

The Health Insurance Review and Assessment Service (HIRA) database contains the following information: sociodemographic details, reimbursement claims for hospital visits, prescriptions, procedures, diagnosis based on International Classification of Disease, 10th revision (ICD-10) coding, and the death records of the entire South Korean population. Researchers can gain access to the HIRA database by submitting a request to the Korean Health Insurance Review Health Bigdata Hub (https://opendata.hira.or.kr).

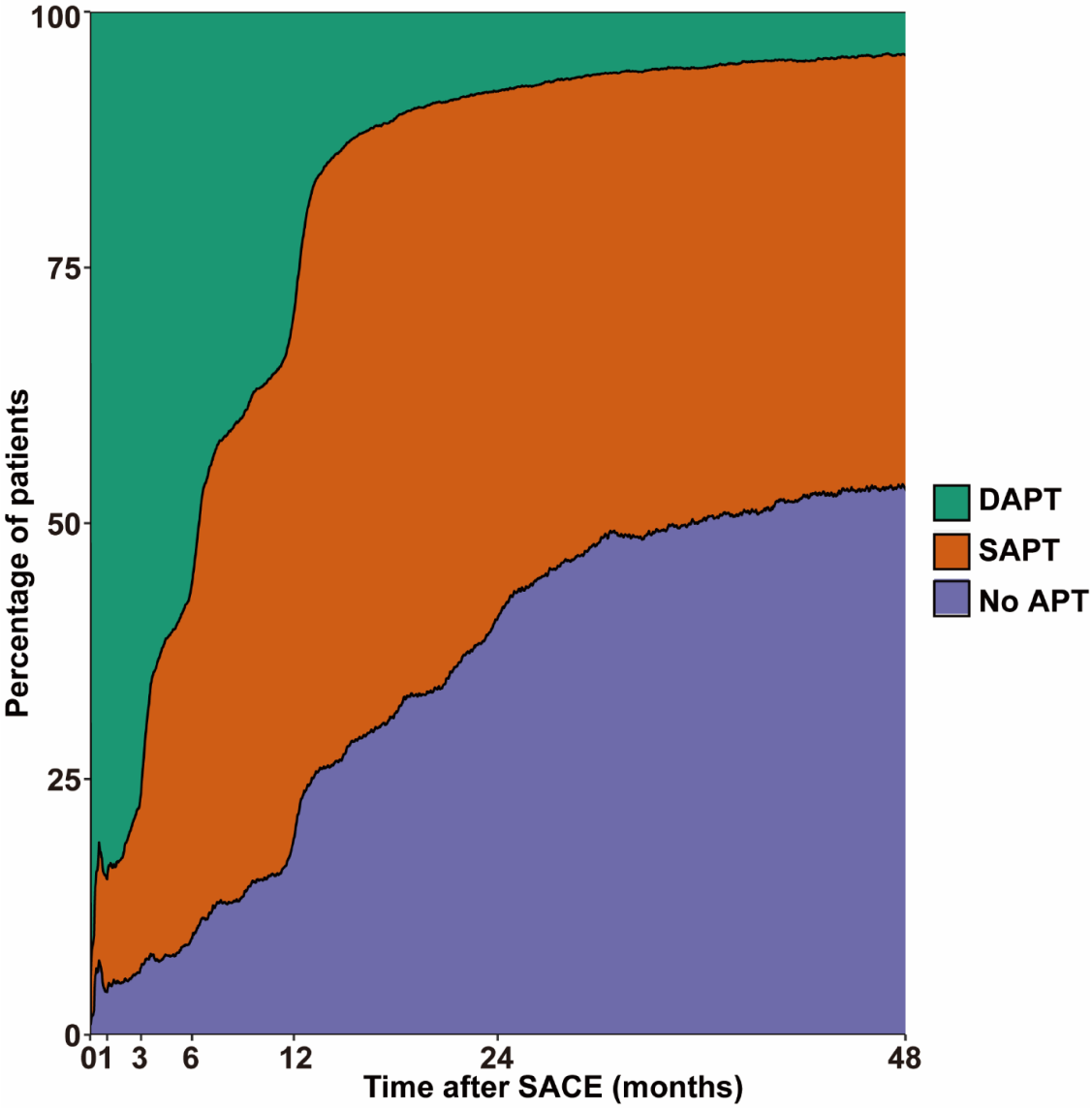
Based on the healthcare claim database, we identified patients with unruptured cerebral aneurysm (ICD-10 code of 'I67.1') who underwent endovascular coil embolization (M1661 and M1662) and intracranial stent implantation for stent-assisted coil embolization (SACE) (J5236). Insurance claims of intracranial stents for SACE are anonymized as J5236 (Enterprise [Cordis Neurovascular, Miami, FL, USA; J5236013], Neuroform [Stryker Neurovascular, Fremont, California, USA; J5236021], Neuroform EZ [Stryker Neurovascular, Fremont, California, USA; J5236031], Alpha [CGBio, Seongnam, Korea; J5236024], Solitaire AB [Medtronic, Irvine, CA, USA; J5236073], LVIS or LVIS Jr [MicroVention, Tustin, California, USA; J5236173], Acclino Flex plus [J5236174], Acclino Flex [Acandis, Pforzheim, Germany; J5236027], and Accero [Acandis, Pforzheim, Germany; J5236175]). Index date was the claim date for the SACE procedure.

We excluded patients with history of myocardial infarction (I21), stroke (I60-63, I69, S06.5, S06.6), thromboembolism of venous system (I26, I67.7, I80.2, I80.3, O22.5, O87.3, G08), cardiovascular intervention (claim for coronary intervention [M6551-2, M6561-4, M6571-2], coronary artery bypass graft [O1641-2, O1647, OA641-2, OA647], carotid endarterectomy [O0226, O0227, O2066], carotid/cerebral stent [M6601, M6602, M6605] and bypass surgery [S4661, S4662]), atrial fibrillation (I48), valvular heart disease (I05.0, I05.2, I05.9, Z95.2-Z95.4), end stage renal disease (N18.5, N18.6), hemodialysis (O7020, O7021, O9991), peritoneal dialysis (O2016, O7061), and kidney transplantation (R3280) before and at the index date.

Regarding comorbidities, we analyzed the presence of hypertension, diabetes mellitus, congestive heart failure, chronic renal disease, hepatic disease, chronic obstruction lung disease, and cancer. Hypertension and diabetes mellitus were ascertained as relevant only if the participants were prescribed anti-hypertensive or anti-diabetic agents with the related diagnostic codes (hypertension: I10-13, I15; diabetes mellitus, E10-14). Congestive heart failure was defined as the presence of diagnostic code of 'I50'. Chronic renal disease (N18–19, except N18.5, N18.6), hepatic disease (C22, K70.2, K70.3, K70.4, and K74.6, K70.1, B18.0-2) and chronic obstructive lung disease (J42–44, except J43.0) were identified when the patients received the diagnostic codes at least two times. Cancer was evaluated as the diagnostic code of malignancy (C00-C97) with cancer-specific registration codes (V027, V193-4).[1]
Regarding outcomes, we analyzed the presence of cerebral infarction and major hemorrhage. Cerebral infarction was defined as admitted with the primary diagnosis of I63 and underwent brain computed tomography (CT) or magnetic resonance imaging (MRI) at the hospital visit.[2]
Major hemorrhage is a composite of hemorrhagic stroke or gastrointestinal bleeding. Hemorrhagic stroke was defined as admitted with the primary diagnosis of I60-62 and underwent brain CT or MRI at the hospital visit.[3] Gastrointestinal bleeding was defined as admission with

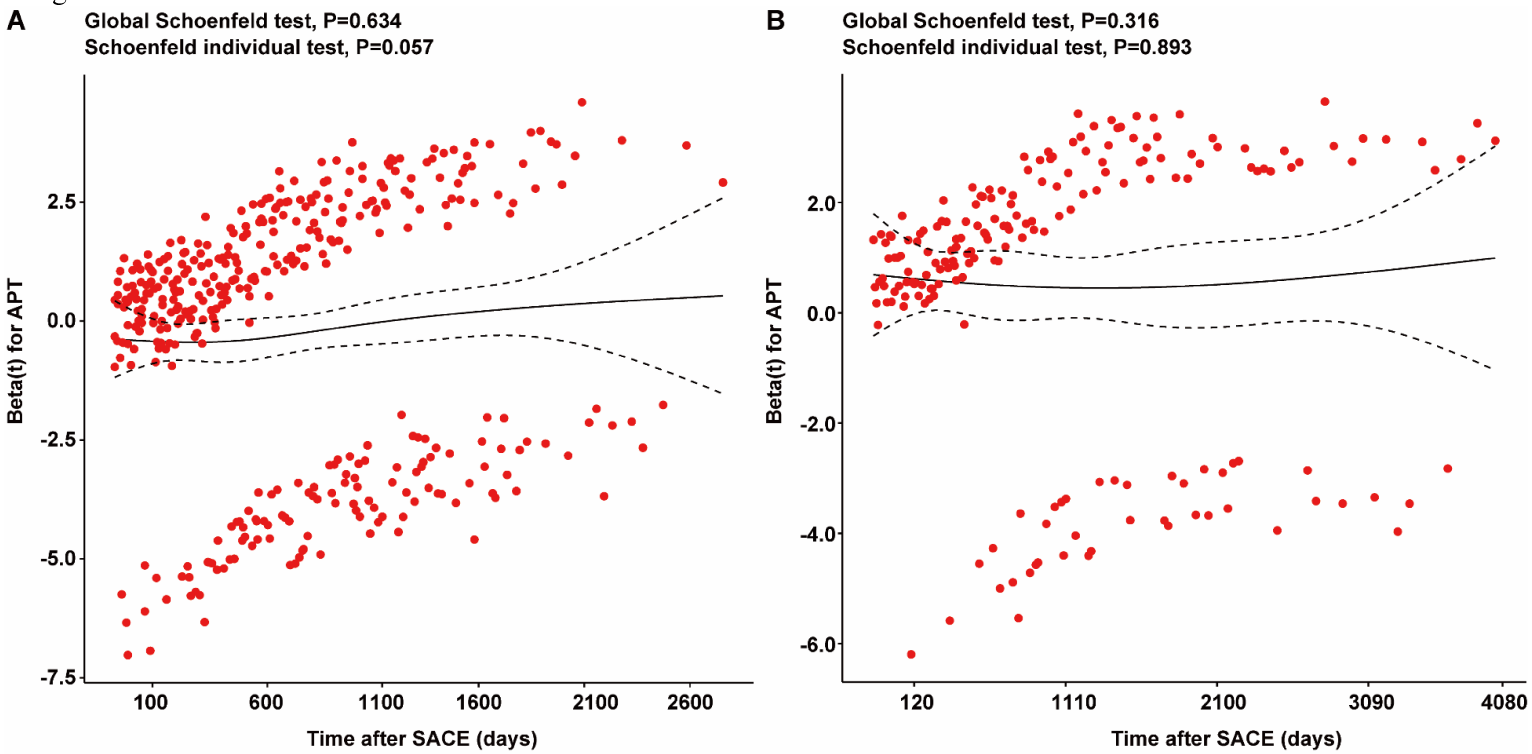
the related codes and receiving red blood cell transfusion during the admission.[4] Detailed definitions are described in Table S1.

Figure S1. Daily antiplatelet regimen since stent-assisted coil embolization



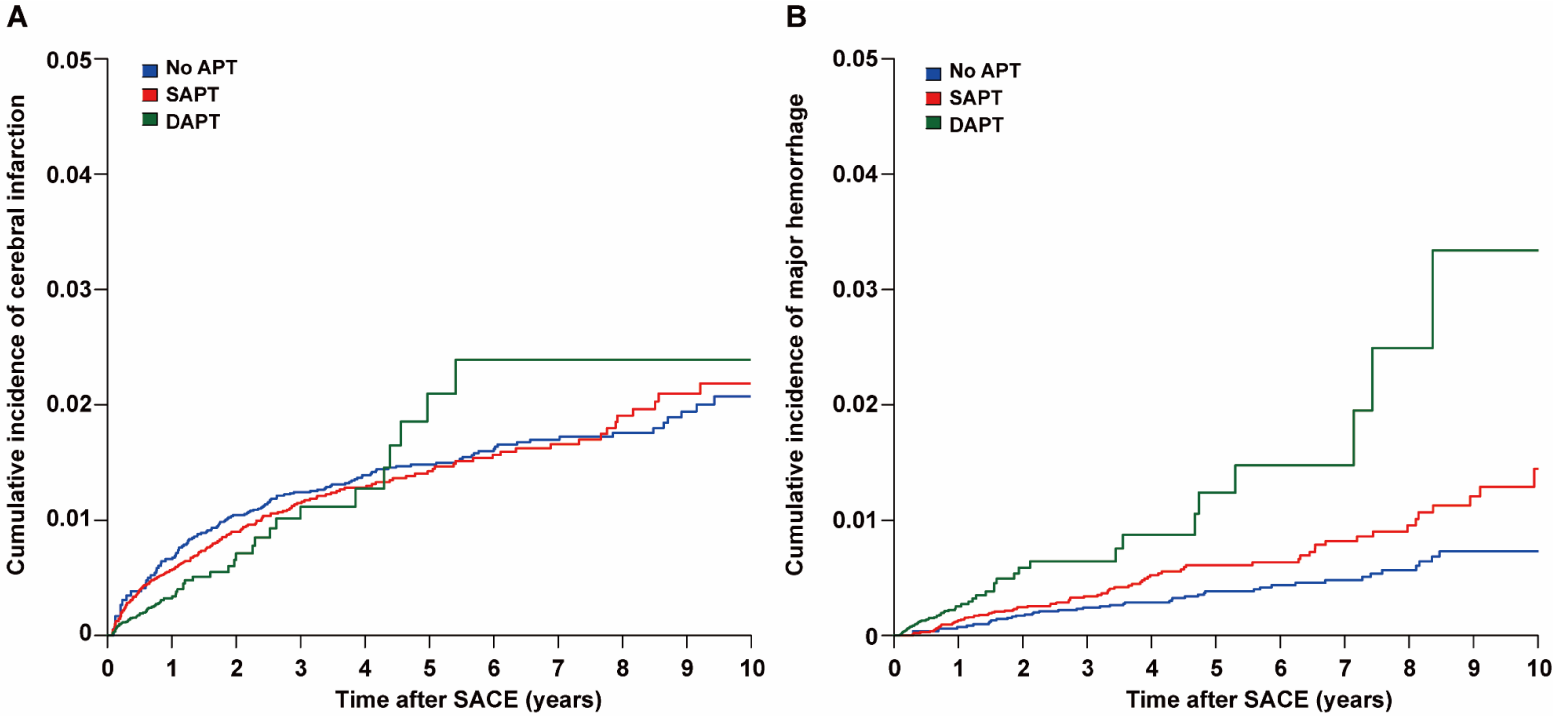
The diagram depicts the regimen of antiplatelet therapy (APT) on a daily basis since stent-assisted coil embolization. The green section illustrates the period and percentage of patients on dual APT (DAPT), the orange section represents the period and percentage of patients on single APT (SAPT), and the purple section indicates the period and percentage of patients without APT. APT, antiplatelet therapy; DAPT, dual APT; SACE, stent-assisted coil embolization; SAPT, single APT.

Figure S2. Diagnostics for the proportional hazards assumption of the Cox proportional hazards model for the primary outcomes using Schoenfeld residuals



Models were adjusted for age, sex, type of insurance, hypertension, diabetes mellitus, congestive heart failure, chronic renal disease, hepatic disease, chronic obstructive lung disease, cancer, and use of statin.
APT, antiplatelet therapy; SACE, stent-assisted coil embolization .

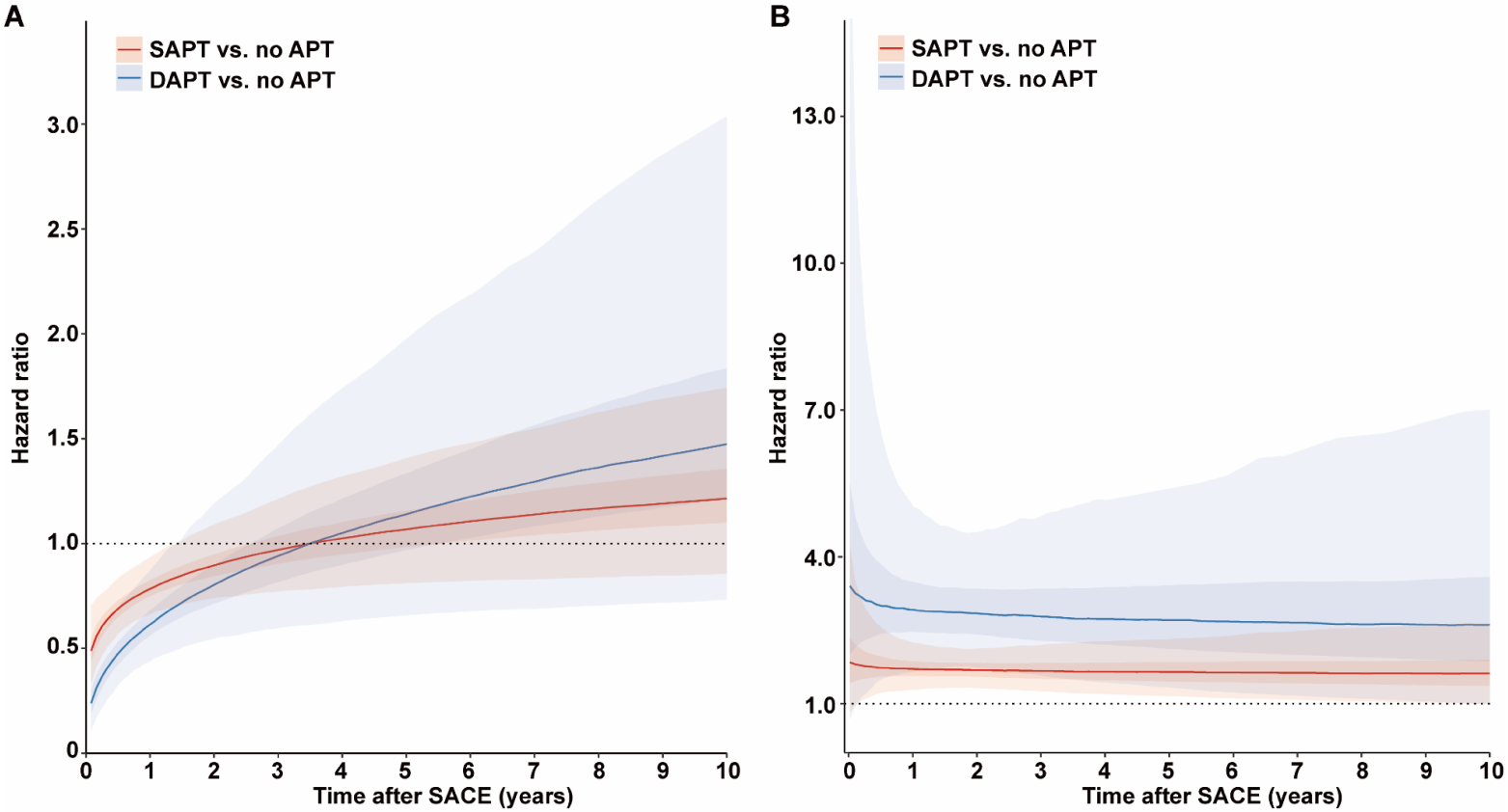
Figure S3. Cumulative incidence of cerebral infarction (A), and major hemorrhage (B) according to antiplatelet therapy regimen.



Cumulative incidence curves are illustrated using the Simon and Makuch method regarding the time-varying characteristic of antiplatelet therapy regimen. In the comparison between no APT, SAPT and DAPT, there was no significant difference in the risk of cerebral infarction (Mantel–Byar test, $P > 0.999$, Figure S3A). However, a notable difference was observed in the risk of major hemorrhage (Mantel–Byar test, $P < 0.001$, Figure S3B).

APT, antiplatelet therapy; DAPT, dual APT; SACE, stent-assisted coil embolization; SAPT, single APT.

Figure S4. Plot of estimated time-varying hazard ratios of antiplatelet therapy regimen for cerebral infarction (A), and major hemorrhage (B) after stent-assisted coil embolization for unruptured cerebral aneurysm.



Plots show simulated time-varying hazard ratios of antiplatelet regimens based on the multivariable Cox model: no APT, SAPT, and DAPT, as a red solid line and the confidence intervals of central 50% (dark red) and 95% (light red) as shaded areas.
APT, antiplatelet therapy; DAPT, dual APT; SACE, stent-assisted coil embolization; SAPT, single APT.

Table S1. Definition of variables based on health claim data

	ICD-10 and claim codes
Inclusion/exclusion criteria	
Unruptured cerebral aneurysm	I67.1
Stent-assisted coil embolization	Claim for assisted coil embolization (M1661, M1662) and claim for intracranial stent (Enterprise [J5236013], Neuroform [J5236021], Neuroform EZ [J5236031], Alpha [J5236024], Solitaire AB [J5236073], LVIS or LVIS Jr [J5236173], Acclino Flex plus [J5236174], Acclino Flex [J5236027], and Accero [J5236175])
Prior stroke	I60-63, S06.5, S06.6, I69
Prior myocardial infarction	I21
Prior venous thromboembolism	I26, I80.2, I80.3, O22.5, O87.3, I67.6, G08
Prior cardiovascular intervention	Claim for coronary intervention (M6551-2, M6561-4, M6571-2), coronary artery bypass graft (O1641-2, O1647, OA641-2, OA647), carotid endarterectomy (O0226, O0227, O2066), carotid/cerebral stent (M6601, M6605, M6602) and bypass surgery (S4661, S4662)
Atrial fibrillation	I48
Valvular heart disease	I05.0, I05.2, I05.9, Z95.2-Z95.4
End stage kindey disease	N185, N186; or claim for hemodialysis (O7020, O7021, O9991), peritoneal dialysis (O2016, O7061), or kidney transplantation (R3280)
Comorbidities	
Hypertension	I10-I13, I15; and prescription of antihypertensive drug
Diabetes mellitus	E10-E14; and prescription of antidiabetic drugs
Congestive heart failure	I50
Chronic renal disease	N18-19, except N18.5, N18.6 at least 2 times
Hepatic disease	C22, K70.2, K70.3, K70.4, and K74.6, K70.1, B18.0-2 at least 2 times
Chronic obstructive lung disease	J42-J44, except J43.0 at least 2 times
Cancer	C00-97; and cancer registration code (V193, V027, V194)
Outcome	
Cerebral infarction	Admission with primary diagnosis of I63; and brain CT or MRI
Hemorrhagic stroke	Admission with primary diagnosis of I60-62; and brain CT or MRI
Gastrointestinal hemorrhage	Admission with primary diagnosis of K22.6, K25.0, K25.2. K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K92.0, K92.1, I85.0, I98.3, K22.11, K31.81; and claims of red blood cell transfusion (X2021, X2022, X2031, X2032, X2131, X2132, X2091, X2092, X2111, X2112, X2515, X2512)
Major hemorrhage	Hemorrhagic stroke or gastrointestinal hemorrhage

Table S2. Baseline characteristics of the patients included in the study

Variable	Total (n = 17692)
Sex, female	13523 (76.44)
Age, years	57.66 ± 10.81
Insurance type	
Health insurance	17096 (96.63)
Medical aid	596 (3.37)
Comorbidity	
Hypertension	10097 (57.07)
Diabetes mellitus	2559 (14.46)
Congestive heart failure	898 (5.05)
Chronic renal disease	263 (1.49)
Hepatic disease	1012 (5.72)
Chronic obstructive lung disease	2572 (14.54)
Cancer	1200 (6.76)

The data are represented as numbers (%) or mean ± standard deviation.

Table S3. Antiplatelet regimen changes after stent-assisted coil embolization

	1 month	3 months	6 months	12 months	24 months
Number at risk	17692	17597	17348	15619	12259
Antiplatelet regimen					
No APT	740 (4.2)	1144 (6.5)	1618 (9.3)	3201 (20.5)	5109 (41.7)
APT	16952 (95.8)	16453 (93.5)	15730 (90.7)	12418 (79.5)	7150 (58.3)
SAPT	1962 (11.1)	2933 (16.7)	5972 (34.4)	8102 (51.9)	6218 (50.7)
Aspirin	886 (45.2)	1576 (53.7)	3966 (66.4)	5597 (69.1)	4155 (66.8)
P2Y12 inhibitor*	1020 (52.0)	1277 (43.5)	1783 (29.9)	2200 (27.2)	1769 (28.4)
Other†	56 (2.9)	80 (2.7)	223 (3.7)	305 (3.8)	294 (4.7)
DAPT	14990 (84.7)	13520 (76.8)	9758 (56.3)	4316 (27.6)	932 (7.6)
Aspirin + P2Y12 inhibitor*	13773 (91.9)	12525 (92.6)	8948 (91.7)	3819 (88.5)	770 (82.6)
Aspirin + Other†	1217 (8.1)	995 (7.4)	810 (8.3)	497 (11.5)	162 (17.4)

*P2Y12 inhibitors include clopidogrel, ticlopidine, prasugrel, and ticagrelor; †other antiplatelet agents include triflusal and cilostazol.
APT, antiplatelet therapy; DAPT, dual APT; SAPT, single APT.

Table S4. Multivariable time-dependent Cox regression for primary outcomes after stent-assisted coil embolization for unruptured cerebral aneurysm

	Cerebral infarction		Major hemorrhage	
Variable	**Adjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)**	***P*-value**
Sex, male	1.06 [0.83–1.35]	0.657	1.38 [1.00–1.90]	0.049
Age, years	1.04 [1.03–1.05]	<.001	1.04 [1.03–1.06]	<.001
Insurance type				
Health insurance	1 (ref)		1 (ref)	
Medical aid	1.67 [1.11–2.51]	0.014	0.65 [0.26–1.61]	0.353
Comorbidity				
Hypertension	1.45 [1.13–1.86]	0.003	1.05 [0.76–1.45]	0.762
Diabetes mellitus	1.47 [1.15–1.87]	0.002	1.41 [0.99–2.02]	0.058
Congestive heart failure	1.35 [0.92–1.97]	0.126	0.64 [0.30–1.37]	0.255
Chronic renal disease	0.93 [0.43–2.01]	0.863	1.37 [0.50–3.73]	0.539
Hepatic disease	0.65 [0.39–1.09]	0.105	1.00 [0.55–1.82]	0.999
Chronic obstructive lung disease	1.10 [0.84–1.45]	0.480	1.13 [0.76–1.67]	0.551
Cancer	0.96 [0.64–1.45]	0.842	1.02 [0.58–1.79]	0.953
Medication				
Statin	0.93 [0.74–1.17]	0.539	0.72 [0.52–0.99]	0.040
APT*				
1 to 12 months	0.56 [0.35–0.89]	0.014	3.69 [0.89–15.36]	0.072
12 to 24 months	0.73 [0.48–1.12]	0.144	1.23 [0.60–2.52]	0.568
> 24 months	1.01 [0.72–1.43]	0.933	1.76 [1.11–2.77]	0.016

Data were obtained from multivariable time-dependent Cox proportional hazards regression model for the development of outcome. Reference is absence of APT at the time period. Adjustments were done for age, sex, insurance type, hypertension, diabetes mellitus, congestive heart failure, chronic renal disease, hepatic disease, chronic obstructive lung disease, cancer, and use of statin.
APT, antiplatelet therapy; CI, confidence interval.

Table S5. Effect of antiplatelet therapy regimens on individual outcomes according to the exposure period after stent-assisted coil embolization for unruptured cerebral aneurysm

		Cerebral infarction (n=379)				Major hemorrhage (n=190)			
Exposure period	**Regimen**	**Number at risk**	**Event number**	**aHR (95% CI)**	**P value**	**Number at risk**	**Event number**	**aHR (95% CI)**	**P value**
1 to 12 months	**No APT**	740	21	Ref		740	2	Ref	
	SAPT	1962	54	0.74 [0.45–1.23]	0.250	1962	17	2.69 [0.60–12.01]	0.194
	DAPT	14990	66	0.42 [0.25–0.69]	<0.001	14990	49	4.65 [1.09–19.85]	0.038
12 to 24 months	**No APT**	3221	33	Ref		3217	10	Ref	
	SAPT	8130	54	0.77 [0.50–1.21]	0.250	8145	20	1.09 [0.52–2.29]	0.813
	DAPT	4328	10	0.62 [0.30–1.26]	0.186	4388	9	2.26 [0.95–5.40]	0.067
>24 months	**No APT**	5147	64	Ref		5130	30	Ref	
	SAPT	6248	63	0.90 [0.62–1.32]	0.603	6302	43	1.59 [0.98–2.58]	0.059
	DAPT	938	14	1.66 [0.90–3.04]	0.102	1021	10	3.79 [1.77–8.11]	<0.001

Data were obtained from multivariable time-dependent Cox proportional hazards regression model for the development of outcome. The reference is the absence of APT during this period. Adjustments were done for age, sex, insurance type, hypertension, diabetes mellitus, congestive heart failure, chronic renal disease, hepatic disease, chronic obstructive lung disease, cancer, and use of statin.
aHR, adjusted hazard ratio; APT, antiplatelet therapy; CI, confidence interval; DAPT, dual APT; SAPT, single APT.

Table S6. Hemorrhage outcomes according to the exposure period after stent-assisted coil embolization for unruptured cerebral aneurysm

	Number at risk	Major hemorrhage (n=190)	Hemorrhagic stroke (n=94)	Gastrointestinal hemorrhage (n=96)
1 to 12 months	17692	68	32	36
12 to 24 months	15619	39	22	17
>24 months	12259	83	40	43

Supplemental Reference

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