SVN Stroke & Vascular Neurology

Discontinuation of antiplatelet therapy after stent-assisted coil embolisation of cerebral aneurysm: a nationwide cohort study

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To cite: Baik M, Jeon J, Kim J, *et al*. Discontinuation of antiplatelet therapy after stent-assisted coil embolisation of cerebral aneurysm: a nationwide cohort study. *Stroke & Vascular Neurology* 2024;**9**: e002882. doi:10.1136/svn-2023-002882

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2023-002882).

Received 1 October 2023
Accepted 7 December 2023
Published Online First 29 January 2024

Check for updates

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ABSTRACT

Introduction Stent-assisted coil embolisation (SACE) for the treatment of unruptured cerebral aneurysms has been increasingly used. Long-term advantages of antiplatelet therapy (APT) post-SACE treatment are still not well understood. We investigated the long-term effects of APT on clinical prognosis after SACE.

Patients and methods We conducted a retrospective study using nationwide health insurance claims data from South Korea, including patients with cerebral aneurysm treated with SACE from January 2009 to December 2020. The study outcomes consisted of the occurrence of cerebral infarction and major haemorrhage. To evaluate the impact of APT, we employed a multivariable time-dependent Cox proportional hazards regression model for each of the three distinct periods: 1–12 months, 12–24 months and >24 months after SACE.

Results This study included 17 692 unruptured cerebral aneurysm patients treated with SACE. During the mean follow-up of 4.2 years, there were 379 (2.1%) patients with cerebral infarction and 190 (1.1%) patients with major haemorrhage. The percentage of patients receiving APT was 79.5% at 1 year, which gradually decreased to 58.3% at 2 years after SACE. APT was beneficial in preventing cerebral infarction within 12 months after SACE (adjusted HR (aHR) 0.56; 95% CI, 0.35 to 0.89; p=0.014). After 12 months, this association was not evident. APT increased the risk of haemorrhage after 24 months (aHR 1.76; 95% CI 1.11 to 2.87; p=0.016).

Discussion and conclusion Our findings suggest that in patients with unruptured cerebral aneurysm treated with SACE, the reasonable duration of APT for preventing cerebral infarction might be 1 year after SACE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ After the insertion of an endovascular stent, antiplatelet therapy (APT) is a fundamental component and duration of APT after stent implantation is determined according to both thromboembolic and haemorrhagic risk. However, the effect of long-term APT in patients with unruptured cerebral aneurysm treated with stent-assisted coil embolisation (SACE) remains unclear.

WHAT THIS STUDY ADDS

⇒ In this nationwide health claims-based cohort study, APT was associated with a reduced risk of cerebral infarction only within the 12 months, while APT increased the risk of haemorrhage after 24 months from SACE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Among patients with unruptured cerebral aneurysm treated with SACE, a reasonable duration of APT for preventing cerebral infarction might be 1 year after SACE.

INTRODUCTION

Antiplatelet therapy (APT) is an essential treatment strategy used in the prevention of thromboembolic complications following endovascular stent implantation.[1] The guidelines for APT during endovascular stent implantation in atherosclerotic stenosis of coronary and intra/extracranial arteries recommend the administration of dual APT (DAPT) for 1–12 months and followed by maintenance with lifelong single APT (SAPT), taking into account the thromboembolic and haemorrhagic risks.[2–5]

Stent-assisted coil embolisation (SACE) is an effective method for assisting optimal coil placements and preventing recanalisation during endovascular coil of unruptured cerebral aneurysms.[6 7] Unlike other endovascular stent implantation procedures, stent implantation during SACE for cerebral aneurysm is unique because it is usually performed in normal, non-atherosclerotic arteries. Stent implantation in normal arteries, as opposed to atherosclerotic arteries, might carry a lower risk of thromboembolic events and require a less invasive APT strategy. Based on the aforementioned assumption, several clinicians advocate the discontinuation of APT 3–36 months after SACE in clinical practice[8–12]; however, the duration for which APT should be maintained after SACE remains largely unexplored.[13] Although determining the optimal duration of APT necessitates finding a balance between thromboembolic

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and haemorrhagic risks, no guidelines currently exist for patients with unruptured cerebral aneurysm after SACE that address this issue.[5 14]

This study used a comprehensive nationwide health claims database to explore the following aspects, (1) the duration for which APT should be continued after SACE for unruptured cerebral aneurysm in real-world settings and (2) the potential temporal impact of APT on the risk of cerebral infarction and major haemorrhage during different time periods beyond the acute phase following SACE. Based on these findings, we aimed to determine the ideal length of time for APT after SACE in patients with unruptured cerebral aneurysm.

METHODS

Data source and study participants

This retrospective cohort study used data from the nationwide health insurance claims database. South Korea operates a public single-payer health insurance system, the National Health Insurance Service (NHIS), which covers the entire population (approximately 50 million people).[15] The Health Insurance Review and Assessment Service (HIRA) service is responsible for the review of all health insurance claims and quality assessments. The HIRA database collects insurance claims data, including information on demographics, hospital visits, medical procedures, prescriptions and diagnoses, based on the International Classification of Diseases, 10th revision (ICD-10) coding.

We selected patients diagnosed with unruptured cerebral aneurysm who underwent SACE from January 2009 to December 2020, using data from the HIRA database. The criteria for inclusion were as follows: (1) hospitalisation with a diagnostic code for unruptured cerebral aneurysm (I67.1), (2) coil embolisation of cerebral aneurysms and (3) cerebral stents for SACE. The date on which the SACE procedure was performed was designated as the index date. To include patients who had newly received SACE, those who underwent SACE during the washout period (2008) were excluded from the analyses. We excluded individuals younger than 20 years or those with a history of conditions such as myocardial infarction, stroke, thromboembolism of venous system, cardiovascular intervention, atrial fibrillation, end-stage kidney disease or gastrointestinal haemorrhage. Patients with multiple stents or those admitted more than 30 days after SACE were excluded. To investigate the benefits and risks of long-term APT after SACE, patients who experienced primary outcomes within 30 days or those followed up for less than 30 days were excluded from this study.[11–13] Comprehensive information derived from the is thoroughly outlined in online supplemental methods and table S1.

Outcomes

The primary outcomes were cerebral infarction development and occurrence of major haemorrhage beyond 1 month following SACE. The occurrence of cerebral infarction was identified hospitalisation with a primary diagnosis for ICD-10 code I63, and the patient underwent brain CT or MRI during admission. Major haemorrhage was defined as haemorrhagic stroke or gastrointestinal haemorrhage, which was determined based on the related diagnostic codes and claims data (online supplemental methods and table S1). After SACE, each patient was followed up until the development of each ischaemic or haemorrhagic outcome event, loss of eligibility for the NHIS owing to emigration, death or the end of the study period (30 June 2021), whichever came first. The risk of stent thrombosis and ischaemic complications after stenting is initially high and gradually declines,[16 17] and the duration for maintaining APT was most commonly considered to be 12 months after SACE according to a previous survey.[13] Hence, we evaluated the ischaemic and haemorrhagic risks according to APT in three different time periods: (1) 1–12, (2) 12–24 and (3) >24 months after SACE.

Antiplatelet therapy

In each patient, we collected prescription records for antiplatelet drugs, which were classified into three categories: aspirin; P2Y12 inhibitor (clopidogrel, ticlopidine, prasugrel and ticagrelor); and others (triflusal and cilostazol). To accurately capture the fluctuating patterns of medication usage, we assessed the daily use of antiplatelet drugs during the study period following SACE based on whether the prescriptions covered each day. DAPT was defined as the concomitant use of aspirin and another antiplatelet, which is the only regimen covered by insurance through the NHIS in Korea. SAPT was defined as the use of any single antiplatelet drug. APT was defined as either DAPT or SAPT. To focus on the impact of discontinuing versus and maintaining antiplatelet drugs, the main independent variable was set as APT (vs no APT), and further analysis differentiated between no APT, SAPT and DAPT.

Statistical analyses

Throughout the study period, we evaluated the proportion of patients who received APT and those who did not. We assessed the trend of APT by calculating the ratio of at-risk patients receiving APT to the total at-risk patients each day and illustrating the patterns throughout the study period. Given the time-dependent characteristics of APT, we employed the Simon and Makuch method to generate an estimated cumulative incidence curve during the follow-up period.[18] The difference between the curves according to APT was evaluated by Mantel-Byar test, a method for comparison of survival data with a time-dependent variable.[19]

Two separate time-dependent Cox regression models were constructed for each primary outcome: cerebral infarction and major haemorrhage. We assessed the proportional hazard assumption of the models using the Schoenfeld test. To explore the temporal impact of APT on the risk of each

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primary outcome, we computed estimated simulated time-varying HR with 50 and 95% CI for APT based on multivariable Cox regression model, which were graphed across a continuous time period.[20] Given that the proportional hazard assumption for APT was not met, we determined the adjusted HR (aHR) and 95% CI for APT across three distinct periods after SACE. Based on multivariable time-dependent Cox proportional hazards regression models, we derived the aHR and 95% CI for APT during the three distinct time periods following SACE: 1–12, 12–24 and >24 months. Adjustments were made for age; sex; type of insurance; history of hypertension, diabetes, congestive heart failure, chronic renal disease, hepatic disease, chronic obstructive lung disease and cancer; and use of statin. To investigate differential effects of DAPT and SAPT, with no APT as the reference, we plotted event-free survival curves, depicted estimated simulated time-varying aHR with CI, and analysed multivariable time-dependent Cox regression for primary outcomes. Statistical analyses were performed using SAS (V.9.4.2; SAS Institute) and R (V.3.5.1; R Foundation for Statistical Computing, http://www.R-project.org/). Statistical significance was set at p<0.05. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

RESULTS

From January 2009 to December 2020, we initially screened 115 761 patients diagnosed with unruptured cerebral aneurysm. Of these, 32 198 underwent SACE as shown in figure 1. After applying the study criteria, 14 506 patients were excluded, resulting in a final cohort of

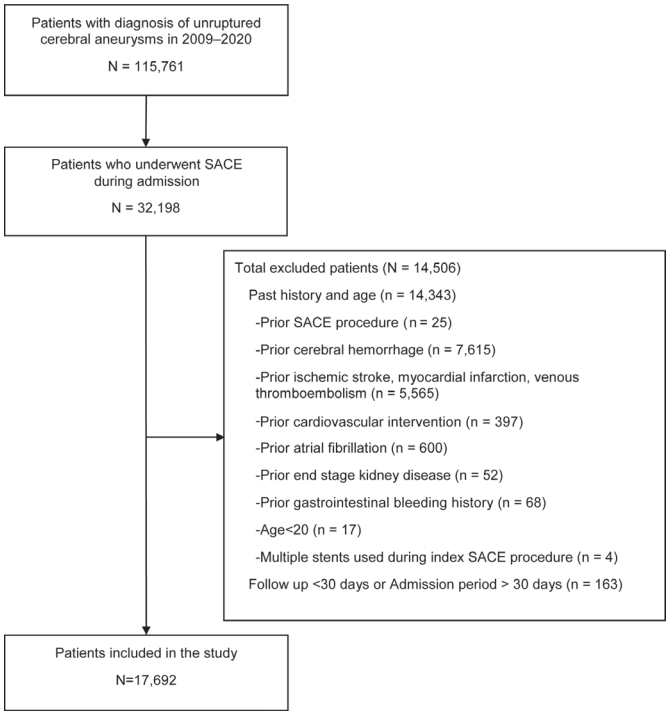

Figure 1 Flow chart describing the patient inclusion criteria. SACE, stent-assisted coil embolisation.

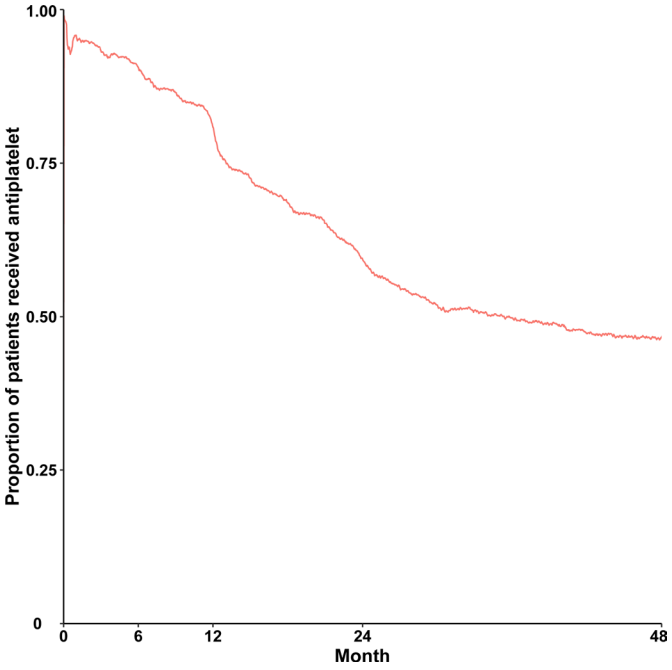

Figure 2 Daily antiplatelet use since stent-assisted coil embolisation.

17 692 patients with unruptured cerebral aneurysm who received SACE treatment. The mean age of the included patients at SACE was 57.7±10.8 years, and 13 523 (76.4%) patients were women (online supplemental table S2). The percentage of patients receiving APT was 90.7, 79.5 and 58.3% at 6 months and 1 and 2 years after SACE, respectively (figure 2). The percentage of patients on DAPT decreased rapidly: 76.8% at 3 months, 56.3% at 6 months and 27.6% at 1 year (online supplemental figure S1). Additionally, most patients (more than 90%) on DAPT were prescribed a regimen of aspirin with a P2Y12 inhibitor (online supplemental table S3). The proportion of patients on SAPT increased steadily until 1 year after SACE and then relatively stabilised: 51.9% (with 69.1% on aspirin and 27.2% on P2Y12 inhibitor) at 1 year, and 50.7% (with 66.8% on aspirin and 28.4% on a P2Y12 inhibitor) at 2 years (online supplemental figure S1 and table S3).

Cerebral infarction

During the mean follow-up period of 4.2±3.0 years after SACE, 379 (2.1%) patients experienced cerebral infarction. Significant differences in the risk of cerebral infarction were not observed in association with APT (p=0.999, figure 3A). In assessing the proportional hazards assumption of APT in the Cox model for cerebral infarction, we identified a tendency of violation via the Schoenfeld test (online supplemental figure S2). The simulated estimates of the multivariable time-varying HR graph showed that APT had a beneficial effect on the primary ischaemic outcome until 2 years after SACE and this effect was attenuated throughout the remainder of the follow-up period (figure 4A). In the time-dependent multivariable Cox regression analysis, we derived the aHR for APT at three

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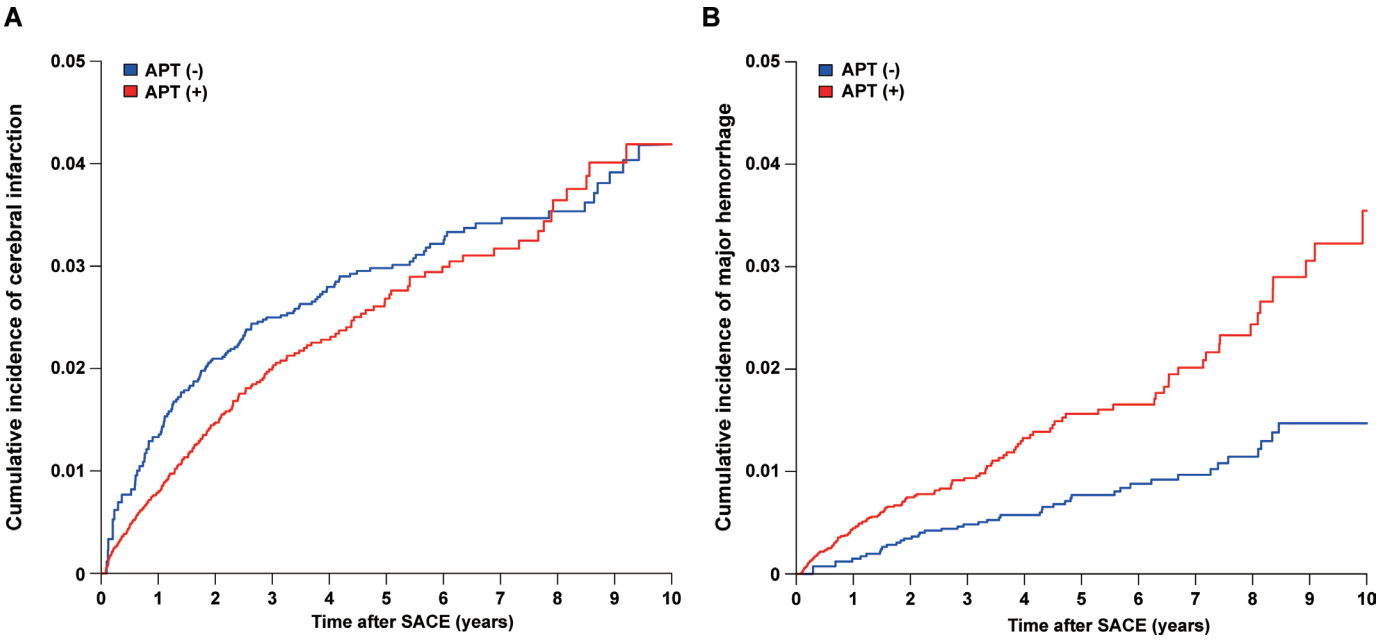

Figure 3 Cumulative incidence of cerebral infarction (A), and major haemorrhage (B) according to APT. Simon and Makuch plot showed no difference in the risk of cerebral infarction according to APT (Mantel-Byar test, p=0.999, A). APT increased the risk of major haemorrhage (Mantel-Byar test, p<0.001, B). APT, antiplatelet therapy; SACE, stent assisted coil embolisation.

different periods (1–12, 12–24 and >24 months) after SACE. APT showed a 44% reduction in cerebral infarction risk during 1–12 months after SACE (aHR 0.56; 95% CI 0.35 to 0.89; p=0.014; table 1). However, 1 year after SACE, APT showed no benefit in preventing cerebral infarction. Old age, medical aid status and the presence of hypertension and diabetes were also linked to an increased risk of cerebral infarction (online supplemental table S4). Compared with no APT, DAPT significantly reduced the risk of cerebral infarction for up to approximately 1 year and offered a stronger protective effect than SAPT (online supplemental figures S3–S4) and online supplemental table S5).

Major haemorrhage

During the mean follow-up period of 4.2±3.0 years after SACE, 190 (1.1%) patients experienced a primary

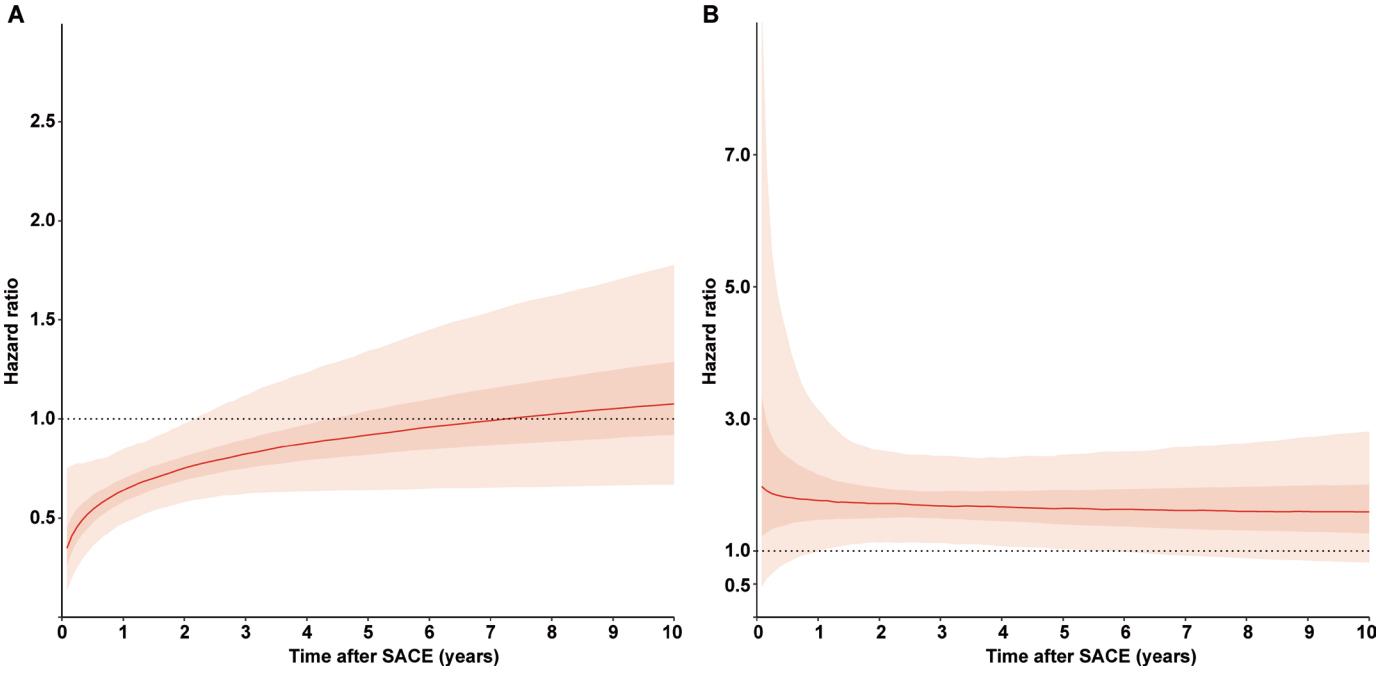

Figure 4 Plot of estimated time-varying HRs of APT for cerebral infarction (A), and major haemorrhage (B) after SACE for unruptured cerebral aneurysm. Plots show simulated time-varying multivariable HRs of APT as a red solid line and the CIs of central 50% (dark red) and 95% (light red) as shaded areas. APT, antiplatelet therapy; SACE, stent-assisted coil embolisation.

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Table 1 Impact of antiplatelet therapy on primary outcomes

	Cerebral infarction (n=379)				Major haemorrhage (n=190)			
	No at risk	Event no	aHR (95% CI)	P value	No at risk	Event no	aHR (95% CI)	P value
1–12 months	17 692	141	0.56 (0.35 to 0.89)	0.014	17 692	68	3.69 (0.89 to 15.36)	0.072
12–24 months	15 679	97	0.73 (0.48 to 1.12)	0.144	15 750	39	1.23 (0.60 to 2.52)	0.568
>24 months	12 333	141	1.01 (0.72 to 1.43)	0.933	12 453	83	1.76 (1.11 to 2.87)	0.016

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 made for age, sex, insurance status, hypertension, diabetes, congestive heart failure, chronic renal disease, hepatic disease, chronic obstructive lung disease, and cancer, and use of statin.
aHR, adjusted HR; APT, antiplatelet therapy.

haemorrhagic outcome (94 with haemorrhagic stroke and 96 with gastrointestinal haemorrhage (online supplemental table S6). APT increased the risk of primary haemorrhagic outcome throughout the study period (p<0.001, figure 3B). In the time-varying estimated multivariable HR model, APT appeared to increase the risk of major haemorrhage during entire follow-up period (figure 4B). In the multivariable time-dependent Cox model according to time periods after SACE, APT indicated a 1.8-fold increased risk of major haemorrhage beyond 24 months after SACE (aHR 1.76, 95% CI 1.11 to 2.87, p=0.016, table 1). The primary haemorrhagic outcomes were also associated with old age (p<0.05, online supplemental table S4). Both DAPT and SAPT consistently showed an increased risk of major haemorrhage, with a higher risk associated with DAPT compared with no APT (online supplemental table S3–S4 and table S5).

DISCUSSION

Using nationwide healthcare claims data, we examined the longitudinal effect of APT on cerebral infarction and major haemorrhage throughout the long-term period following SACE and identified the optimal time to discontinue APT in patients with unruptured cerebral aneurysm treated with SACE. In real-world practice in South Korea, APT was discontinued in only one-fifth of the patients 1 year after SACE. Approximately 2% of patients experienced a cerebral infarction, and 1% suffered major haemorrhage events following SACE. In the multivariable time-dependent model, considering three distinct periods after SACE, APT was associated with a reduced risk of cerebral infarction in the initial 1 year and an increased risk of major haemorrhage 2 years after SACE.

The optimal duration of APT after SACE remains uncertain, particularly regarding its safety in the chronic phase after SACE.[5 14] Balancing thrombosis and haemorrhagic risks is crucial when applying APT after stent implantation. Existing guidelines and studies related to atherosclerotic coronary and intracranial artery diseases recommend lifelong APT poststent implantation.[2 21–24] For stent implantation during SACE for unruptured cerebral aneurysm, which is typically performed in non-atherosclerotic arteries, the risk of thromboembolic risk is lower compared with stent implantation at atherosclerotic arteries, suggesting that a potentially less aggressive strategy of APT might be a reasonable consideration for this population.

Neurointerventionalists generally agree that the use of APT after SACE does not need to be lifelong.[8–13] A French national survey revealed that only 16% of centres prescribed lifelong APT after SACE.[13] Complete endothelialisation of the stent reduces the need for lifelong APT by ensuring a living, non-thrombogenic surface within the lumen of the parent artery and eliminating direct stent-blood flow contact.[25] Given the inherent bleeding risks associated

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with APT, lifelong maintenance of APT might not be a theoretically reasonable approach. A study using rat aneurysm models indicated early neointima formation 4 weeks after SACE,[26] and confirmed complete endothelialisation 4 months after SACE in a post-mortem study.[27] Although previous retrospective studies predominantly relied on descriptive results, they proposed diverse regional protocols (3–24 months) for the safe timing for discontinuation of APT after SACE.[8–12] All of these protocols emphasised the selection of patients with a low risk of ischaemia and documented complete neointimalisation of the parent artery.[8–12] In line with the previous studies, our study findings suggest that APT benefits cerebral infarction prevention until 1 year after SACE,[8–13] making it a reasonable strategy to consider discontinuing APT at that time.

APT is also associated with an increased risk of haemorrhage. Numerous studies have consistently reported that APT is associated with an increased risk of bleeding complications; hence, its routine use for the primary prevention of cardiovascular disease is not recommended.[28–30] As a result, recent studies have emphasised the importance of safety in reducing haemorrhagic events as much as the efficacy of APT in decreasing ischaemic events.[31 32] Similar to the strategy of transition from DAPT to SAPT in patients with stent implantation for atherosclerotic diseases,[2 21 22] temporary APT was a reasonable treatment approach in patients with cerebral aneurysm after SACE, especially considering that stent implantation in SACE typically occurs in non-atherosclerotic parent arteries. Our study findings showed that APT was linked to an increased risk of major haemorrhage beyond 2 years after SACE. Since the benefit of APT in reducing cerebral infarction was observed only until 1 year after SACE in this study, discontinuing APT 1 year after SACE and at least 2 years after SACE is reasonable. Given the wide CI for the risk of major haemorrhage within the 1 year after SACE, as well as an increasing tendency towards major bleeding throughout the study period, it is important to note that the risk of haemorrhage should be considered even in the short-term after SACE, and strategies to minimise the duration of APT should be employed as much as possible.

To date, limited data are available regarding the maintenance of APT after SACE in patients with unruptured cerebral aneurysm in real-world clinical practices. In our study, which included a substantial number of patients with unruptured cerebral aneurysm treated with SACE (n=17 340) and used a nationwide health insurance database, long-term maintenance of APT was common in South Korea. Specifically, 1 year after SACE, only 20% of the patients discontinued APT. Furthermore, approximately half of the patients continued to be treated with APT, even 2 years after SACE. These findings indicate a significantly lower percentage of APT discontinuation compared with the results of the aforementioned French national survey, which reported that APT was maintained for 6, 12 and 12–24 months and lifelong in 16%, 57%, 11% and 16% of centres following SACE for cerebral aneurysm.[13] Considering the potentially increased risk of bleeding complications associated with the prolonged use of APT after SACE, appropriate discontinuation of APT is necessary.

This study had several limitations. First, given the retrospective cohort nature of this study, without direct intervention, there exists a potential for residual confounding. Second, in the claims data, we could not identify the location of the artery where SACE was performed and cerebral infarction occurred; therefore, determining whether the occurrence of cerebral infarction was related to the SACE procedure was impossible. Information regarding aneurysm characteristics, SACE procedure-associated factors including stent type, no recanalisation of the aneurysm, adequate stent apposition without deformity, retreatment, and, most importantly, results of follow-up angiography regarding neointima formation were unavailable,[8–12] given the basis of this study on a nationwide claims-based cohort study. Third, its generalisability may be limited to South Korean cohorts. Fourth, given the extended inclusion period from 2009 to 2020, changes in the devices and techniques may have occurred and influenced the clinical outcomes. Finally, our analysis excluded patients with prior stroke, myocardial infarction, cardiovascular procedures or atrial fibrillation; thus, the findings may not extend to those with a high thromboembolic risk. Nonetheless, this study synthesised real-world data from a substantial cohort of unruptured cerebral aneurysm patients treated with SACE using nationwide healthcare claims data. The utilisation of prescription records enabled us to employ APT as a time-dependent variable, which is more robust than time-fixed model.[33]

CONCLUSIONS

Among patients with unruptured cerebral aneurysm treated with SACE, only one-fifth discontinue APT 1 year after SACE in real clinical practices in South Korea. APT was linked to decreased cerebral infarction risk in the first year, but it correlated with increased major haemorrhage risk beyond 2 years after SACE. Temporal maintenance of APT for 1 year after SACE might be a reasonable strategy to reduce the risk of cerebral infarction and avoid excess risk of haemorrhage. Further randomised trials investigating the optimal timing for APT discontinuation to decrease both ischaemic and haemorrhagic complications in these patients are warranted.

Acknowledgements The Health Insurance Review and Assessment Service (HIRA) database was provided by the HIRA. The authors would like to thank the HIRA for their cooperation.

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Contributors MB and JY contributed to the concept and design of the study. MB, JJ, JK and JY contributed to the data acquisition and analysis. MB, JK and JY drafted the manuscript and prepared the figures. JY had full access to all data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis as guarantor.

Funding This work was supported by the Yonsei University College of Medicine (6-2022-0047) and Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2021R1I1A1A0104944111).

Disclaimer The funders had no role in the study design, data collection, analysis, interpretation, the decision to publish, or preparation of the manuscript.

Competing interests MB received research grants from Daewoong Pharmaceuticals. JY received research grants from Chong Kun Dang Pharmaceuticals. JK received research grants from Chong Kun Dang and Myung In Pharmaceuticals. The authors declare no potential conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this study was approved by the institutional review board of Yongin Severance Hospital, Yonsei University Health System (4-2021-1634).The need for informed consent was waived because of the retrospective nature of this study, which was based on an anonymised health insurance claims database.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data supporting the findings of this study are available from the Health Insurance Review and Assessment Service (HIRA) database. Researchers can gain access by submitting a request with the HIRA Big Data Hub (https://opendata.hira.or.kr)

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