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Effect of Metformin in Diabetic Patients After Treatment of Intracranial Aneurysm: A Nationwide Cohort Study

Minyoul Baik [1] **Jimin Jeon** [1] **Tae-Jin Song** [2] **Joonsang Yoo** [1] and **Jinkwon Kim** [1]

[1]Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea
[2]Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Korea

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Address for Correspondence:
Jinkwon Kim, MD, PhD
Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Republic of Korea.
Email: antithrombus@gmail.com

ORCID iDs
Minyoul Baik
https://orcid.org/0000-0002-6582-0953
Jimin Jeon
https://orcid.org/0000-0003-1497-3914
Tae-Jin Song
https://orcid.org/0000-0002-9937-762X
Joonsang Yoo
https://orcid.org/0000-0003-1169-6798
Jinkwon Kim
https://orcid.org/0000-0003-0156-9736

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ABSTRACT

Background: Intracranial aneurysm (IA) is the most common cause of subarachnoid hemorrhage (SAH), causing high morbidity and mortality. Experimental data have shown that metformin, an antidiabetic agent, has protective effects against IA rupture. This study assessed the effect of metformin on the long-term prognosis of diabetic patients treated for IA.
Methods: This retrospective cohort study included diabetic patients who underwent surgical clipping or endovascular coiling for IA between January 2009 and December 2020, based on Korean health insurance claims data. The primary outcome was the development of SAH. The risk associated with metformin use was evaluated using a multivariable Cox proportional hazards model supplemented with subgroup, propensity score matching, and time-varying Cox regression analyses.
Results: Of 14,086 diabetic patients treated for IA, 9,612 (68.2%) were metformin users. During a mean follow-up of 4.6 years, 120 (0.9%) patients experienced SAH. Metformin use was associated with a reduced risk of SAH (adjusted hazards ratio, 0.63; 95% confidence interval, 0.41–0.95; $P = 0.028$). This finding was consistent in subgroup, propensity score matching, and time-varying Cox regression analyses.
Conclusion: Metformin use in diabetic patients treated with clipping or coiling for IA was associated with reduced risk of SAH. These findings support the use of metformin as the preferred antidiabetic agent for such patients considering these benefits.

Keywords: Metformin; Intracranial Aneurysm; Subarachnoid Hemorrhage; Surgical Clipping; Endovascular Coiling; Type 2 Diabetes Mellitus

INTRODUCTION

Intracranial aneurysms (IAs), which have a prevalence of approximately 3% in the general adult population, are pathological dilatations of intracranial arteries posing risk of rupture.[1,2] IAs are a significant global public health concern, as their potential rupture can cause subarachnoid hemorrhage (SAH), a severe subtype of stroke characterized by high morbidity and mortality.[3] Traditional management strategies for IAs, such as surgical clipping or endovascular coiling, are invasive interventions aimed at preventively occluding

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Data Availability Statement
The data supporting the findings of this study are available from the Health Insurance Review and Assessment Service (HIRA) database, and researchers can gain access by submitting a request for approval from the HIRA Big Data Hub (https://opendata.hira.or.kr).

Author Contributions
Conceptualization: Baik M, Kim J. Data curation: Jeon J. Formal analysis: Baik M, Jeon J, Song TJ, Yoo J, Kim J. Funding acquisition: Song TJ, Kim J. Supervision: Song TJ, Yoo J. Writing - original draft: Baik M. Writing - review & editing: Kim J.

IAs at a high risk of rupture.[4] Considering the high prevalence of IAs and life-threatening outcomes of SAH, non-invasive pharmacological interventions have been increasingly investigated, potentially mitigating the risk of IA formation, growth, and rupture. Currently, no specific medication has been shown to convincingly prevent rupture of IAs.[4-8]

Diabetes mellitus is a common endocrine/metabolic disorder that is involved in the development and progression of various medical conditions including vascular diseases.[9,10] Several studies have shown that antidiabetic agents, primarily used for treating diabetes mellitus, possess the potential to offer cardiovascular and anti-inflammatory benefits beyond the control of hyperglycemia.[11-16] Among these medications, metformin, a well-established first-line biguanide agent for the treatment of type 2 diabetes, has shown a potential protective effect against abdominal aortic aneurysm (AAA), another vascular disorder characterized by abnormal dilatation of arterial vessel; hence, several randomized trials are ongoing.[17] Recently, metformin has also been implicated in preventing IA formation, progression, and rupture in an animal model.[18] Current use of metformin was suggested to be associated with a decreased risk of aneurysmal SAH in a drug-wide association study.[19]

This study aimed to investigate the effect of metformin in type 2 diabetic patients with IAs, particularly those treated with clipping or coiling. By analysing data from a nationwide health claims database, we sought to evaluate the long-term effect of metformin on the risk of SAH in this patient group.

METHODS

Data source and study participants

This retrospective cohort study used Korea's nationwide health insurance claims database from Health Insurance Review and Assessment Service (HIRA). Korea operates a single-payer public health insurance system, the National Health Insurance Service (NHIS), which covers all legal residents (approximately 50 million people) of Republic of Korea.[20] The HIRA is responsible for reviewing all of these health insurance claims and conducting quality assessments. The HIRA database contains insurance claims data for all covered inpatients and outpatients, including visits, procedures, and prescriptions. Hence, it covers the following parameters in a longitudinal manner: demographics, hospital visits, medical procedures, prescriptions, and diagnoses, which are coded according to the International Classification of Diseases, 10^{th} revision (ICD-10).

In this study, we selected type 2 diabetic patients who underwent surgical clipping or endovascular coiling for the treatment of IAs between January 2009 and December 2020 from the HIRA database. The inclusion criteria were as follows: 1) admission for clipping (S4641–2) or coiling (M1661–2) for IAs,[21-23] and 2) history of type 2 diabetes mellitus at admission (**Supplementary Table 1**). The index date was defined as the date of clipping or coiling. To include only patients newly treated for IAs, those who had undergone clipping or coiling during the washout period (2008) were excluded from the analyses. Patients younger than 18 years and those with a follow-up period of less than 1 month were also excluded.

Outcomes and follow-ups

The primary outcome was defined as the development of SAH. The development of SAH was identified by hospital admissions lasting ≥ 3 days with a primary diagnosis of ICD-10 code 'I60' and brain computed tomography or magnetic resonance imaging conducted during the admission.[24] The secondary outcomes were other hemorrhagic stroke; ischemic cardiovascular disease (CVD), including myocardial infarction and ischemic stroke; and all-cause mortality (**Supplementary Table 1**). After the index date of IA treatment, the study patients were followed up until the occurrence of SAH, loss of eligibility for the NHIS due to emigration, death, or until June 30, 2021, whichever occurred first.

Covariates including oral antidiabetic agents

Data on demographics, sex, age at the time of treatment for IA, type of treatment for IA (surgical clipping or endovascular coiling), and type of health insurance were collected. We assessed the presence of comorbidities based on the corresponding ICD-10 codes and health claims data, including prior SAH, hypertension, renal disease, malignancy, and coronary artery disease (**Supplementary Table 1**). Prescription records for statins, antiplatelet agents, insulin, and oral antidiabetic agents were available for individual patients. Treatment with each medication including metformin was identified based on individuals' prescription records, determined by an exposure of at least 1 day to the medication within 30 days from the index date. Oral antidiabetic agents were classified as follows: sulfonylurea or meglitinide (insulin stimulator), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, alpha-glucosidase inhibitors, thiazolidinediones, and metformin (**Supplementary Table 1**).

Statistical analyses

Differences between the groups were evaluated using the independent *t*-test for continuous variables (age) and the χ^2 test for categorical variables. A cumulative incidence curve for the primary outcome, SAH, was plotted according to metformin use, and the differences in the curves were assessed using a log-rank test. To evaluate the relationship between metformin use and the risk of SAH, adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated using a multivariable Cox proportional regression model. Adjustments were made for treatment type (clipping vs. coiling); sex; age; prior SAH; insurance type (medical aid vs. health insurance); hypertension; renal disease; malignancy; coronary artery disease; and the use of statins, antiplatelet agents, insulin, and oral antidiabetic agents. Subgroup analyses were performed to investigate whether the association between metformin use and risk of SAH differed according to sex, age, prior SAH, and renal disease. For secondary outcome analysis, individual Cox proportional hazard models were constructed for each outcome and SAH was treated as a competing risk.

Given the potential confounding effects arising from imbalances in the baseline characteristics between metformin users and non-users, 1:1 propensity score-matched (PSM) samples were selected from both groups. Sensitivity analyses with the matched samples were conducted using Cox regression model (**Supplementary Data 1**). Additionally, since the use of medications can dynamically change for each patient during the follow-up, we constructed a time-varying model that incorporated the use of oral medications, including metformin, as time-varying covariates. In this model, the use of oral medications on each day was determined by exposure to the medications during the preceding 30 days, based on the prescription records of individuals. The estimated cumulative incidence curve according to time-varying use of metformin, was constructed using the Simon and Makuch method.[25] The differences between the curves were evaluated using the Mantel–Byar test for comparing survival data with a time-dependent variable.[26] We evaluated the relationship between metformin use during the follow-up period and SAH using the time-varying Cox regression analysis.

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Statistical analyses were performed using SAS (version 9.4.2; SAS Institute, Cary, NC, USA) and R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Statistical significance was set at *P* value < 0.05.

Ethics statement

This study was approved by the Institutional Review Board of Yongin Severance Hospital, Yonsei University Health System (No. 4-2021-1634). The need for informed consent was waived because of the retrospective nature of this study, which was based on an anonymous health insurance claims database.

RESULTS

Between January 2009 and December 2020, 151,901 patients with IAs treated with clipping or coiling were screened, of whom 25,482 had type 2 diabetes mellitus (**Fig. 1**). After excluding 11,396 patients based on the study criteria, 14,086 type 2 diabetic patients treated with clipping (40.1%) or coiling (59.9%) were included. The mean age of the included patients was 64.3 ± 9.3 years, and 4,880 (34.6%) patients were men. The percentage of patients treated with metformin was 68.2%, making it the most frequently prescribed oral antidiabetic agent. DPP-4 inhibitors were the second most commonly prescribed drugs (40.1%), followed by insulin stimulator (sulfonylurea or meglitinide; 35.0%) (**Table 1**).

During the mean follow-up period of 4.6 ± 3.2 years after clipping or coiling for IAs, 120 (0.9%) patients experienced the primary outcome, SAH. A cumulative incidence curve indicated a decreased risk of SAH with metformin use (log-rank test, *P* < 0.001; **Fig. 2**). In the multivariable Cox regression analysis, metformin use was associated with a 37% decreased risk of SAH (aHR, 0.63; 95% CI, 0.41–0.95; *P* = 0.028; **Table 2**). Other factors associated with an increased risk of SAH were female sex, prior SAH, non-use of statins, and the use of insulin (**Supplementary Table 2**).

Regarding secondary outcomes, 252 (1.8%) patients experienced other hemorrhagic strokes, 851 (6.0%) experienced ischemic CVD, and 935 (6.6%) died from all causes. In the secondary

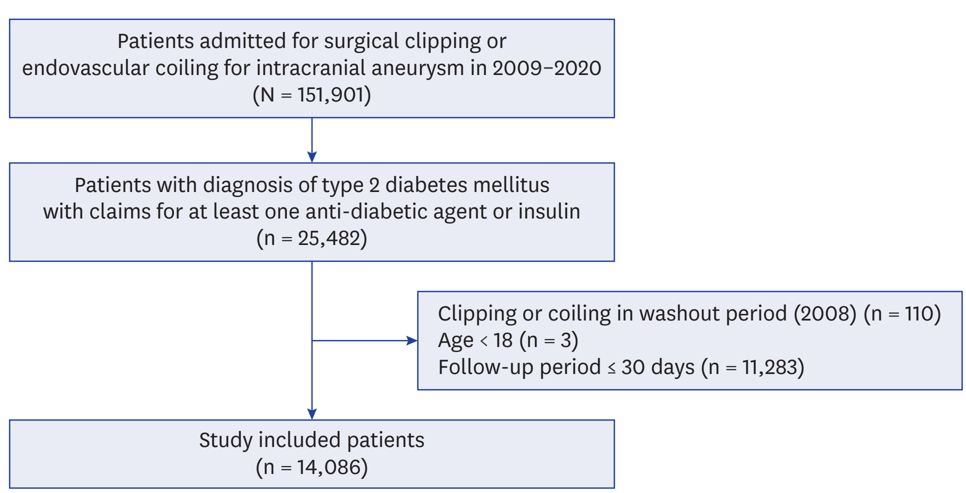

Fig. 1. Flowchart of inclusion and exclusion of study participants.

Table 1. Baseline characteristics of the patients included in the study

Variables	Total (N = 14,086)	Without metformin (n = 4,474)	With metformin (n = 9,612)	*P* value
Sex, male	4,880 (34.6)	1,518 (34.0)	3,362 (35.0)	0.231
Age, yr	64.3 ± 9.3	64.2 ± 10.0	64.3 ± 8.9	0.648
Treatment type				0.174
Surgical clipping	5,644 (40.1)	1,830 (40.9)	3,814 (39.7)	
Endovascular coiling	8,442 (59.9)	2,644 (59.1)	5,798 (60.3)	
Prior SAH	695 (4.9)	304 (6.8)	391 (4.1)	< 0.001
Insurance type				0.007
Health insurance	12,931 (91.8)	4,066 (90.9)	8,865 (92.2)	
Medical aid	1,155 (8.2)	408 (9.1)	747 (7.8)	
Comorbidities				
Hypertension	12,095 (85.9)	3,803 (85.0)	8,292 (86.3)	0.048
Renal disease	3,420 (24.3)	1,061 (23.7)	2,359 (24.5)	0.286
Malignancy	1,224 (8.7)	435 (9.7)	789 (8.2)	0.003
Coronary artery disease	2,997 (21.3)	960 (21.5)	2,037 (21.2)	0.721
Exposure to the medication				
Statin	9,389 (66.7)	2,452 (54.8)	6,937 (72.2)	< 0.001
Antiplatelet agents	10,591 (75.2)	3,198 (71.5)	7,393 (76.9)	< 0.001
Insulin	7,693 (54.6)	2,027 (45.3)	5,666 (59.0)	< 0.001
Sulfonylurea or meglitinide	4,927 (35.0)	1,029 (23.0)	3,898 (40.6)	< 0.001
DPP-4 inhibitor	5,649 (40.1)	746 (16.7)	4,903 (51.0)	< 0.001
SGLT2 inhibitor	524 (3.7)	52 (1.7)	472 (4.9)	< 0.001
Alpha-glucosidase inhibitor	558 (4.0)	168 (3.8)	390 (4.1)	0.418
Thiazolidinedione	848 (6.0)	201 (4.5)	647 (6.7)	< 0.001

The data are represented as numbers (%) or mean ± standard deviation.
SAH = subarachnoid hemorrhage, DPP-4 = dipeptidyl peptidase-4, SGLT2 = sodium-glucose cotransporter-2.

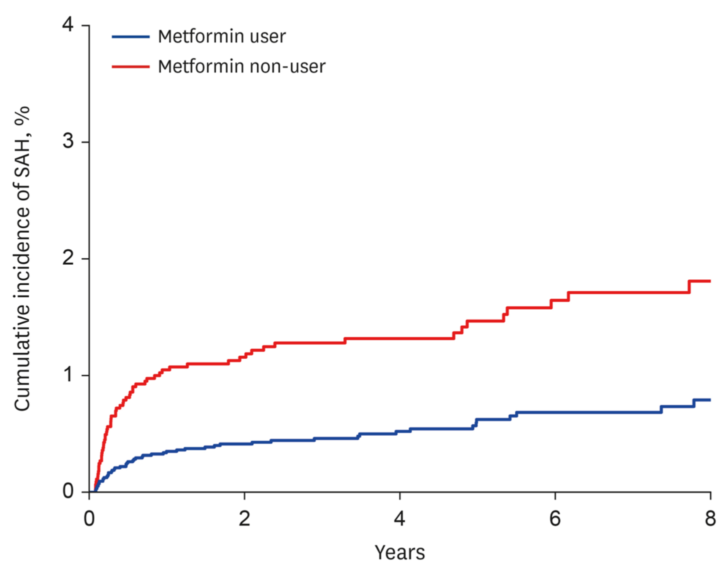

Fig. 2. Cumulative incidence of SAH according to metformin use. The risk of SAH was lower in metformin users than in nonusers (log-rank test, *P* < 0.001).
SAH = subarachnoid hemorrhage.

analyses for individual outcomes, metformin users were at decreased risk of all-cause death (aHR, 0.67; 95% CI, 0.58–0.77; *P* < 0.001; **Table 2**).

Subgroup analysis and sensitivity analysis

We conducted a subgroup analysis to assess the potential differential effects of metformin on baseline characteristics (sex, age, prior SAH, and renal disease). Metformin consistently decreased SAH, in all subgroups and no significant interactions were observed (**Fig. 3**).

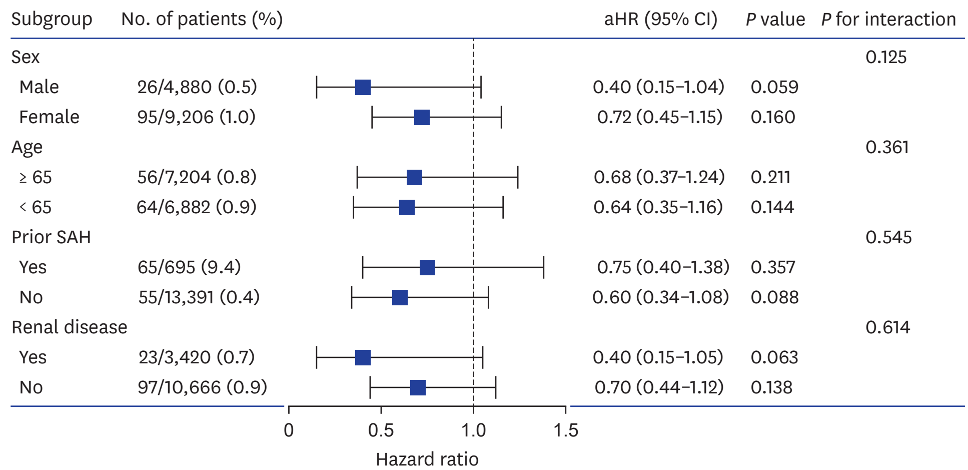

Fig. 3. Subgroup analysis for the effect of metformin on the risk of SAH.
SAH = subarachnoid hemorrhage, aHR = adjusted hazard ratio, CI = confidence interval.

Table 2. Effect of metformin on outcomes after treatment for intracranial aneurysm

Outcomes	Events	aHR (95% CI)	*P* value
Primary outcome			
SAH	120	0.63 (0.41–0.95)	0.028
Secondary outcomes			
All-cause mortality	935	0.67 (0.58–0.77)	< 0.001
Other hemorrhagic stroke	252	0.98 (0.74–1.31)	0.898
Ischemic CVD	851	1.02 (0.87–1.19)	0.845

aHR = adjusted hazard ratio, CI = confidence interval, SAH = subarachnoid hemorrhage, CVD = cardiovascular disease.

To address concerns regarding potential bias owing to differences in baseline characteristics, a sensitivity analysis was performed using PSM between metformin users and non-users. After a 1:1 PSM, 4,058 metformin users and 4,058 non-users were included in the sampled cohort, which was well balanced (**Supplementary Table 3**). In the matched cohort, a cumulative incidence curve indicated a decreased risk of SAH with metformin use (stratified log-rank test, $P = 0.009$; **Supplementary Fig. 1**). A Cox proportional hazard regression analysis with the PSM patients reaffirmed that metformin use was associated with a decreased risk of SAH (hazard ratio, 0.57; 95% CI, 0.37–0.87; $P = 0.010$; **Supplementary Table 4**).

Given the dynamic changes in medication use and its varying effects over time after treatment of IA, we additionally constructed a time-varying model that included the use of oral medications including metformin as time-varying covariates during the follow-up. Simon and Makuch's plot[25] showed that metformin use was associated with decreased risk of SAH (Mantel-Byar test, $P < 0.001$; **Supplementary Fig. 2**). In the time-varying Cox regression analysis, metformin treatment was consistently associated with a lower risk of SAH (aHR, 0.46; 95% CI, 0.29–0.72; $P < 0.001$; **Supplementary Table 4**).

DISCUSSION

Using a nationwide claims-based database, we investigated the long-term prognostic effect of metformin on type 2 diabetic patients with IAs treated with either surgical clipping or endovascular coiling. The primary outcome, SAH, occurred in approximately 0.9% of

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the patients during a mean follow-up period of 4.6 years. More than half of the patients were metformin users, and treatment with metformin was beneficial in reducing the risk of SAH. In patients with type 2 diabetes and IAs, metformin could be primarily recommended, given that it is already the first-line agent for most patients with type 2 diabetes according to the guidelines and has shown potential benefits in this specific population.[27]

To prevent the rupture of IAs and subsequent SAH, traditional treatments have primarily focused on occluding high-risk IAs through invasive interventions such as clipping or coiling.[4] Given the high prevalence of IAs and the devastating outcomes associated with SAH, along with the invasive nature of traditional treatment options, the exploration of non-invasive lifestyle modification, risk factor control, and especially pharmacological interventions to prevent IA formation, growth, and rupture is of significant importance. Typically, smoking and high blood pressure are known to be the most important modifiable risk factors for IA rupture and SAH; hence, smoking cessation and hypertension control are emphasized for SAH prevention.[28] As pharmacological intervention, aspirin and statins, have been identified as potentially reducing the risk of IA rupture in experimental animal models and small human cohort studies.[5-8] Recently, a drug-wide association study involving 4,879 cases of aneurysmal SAH and matched 43,911 controls suggested that the current use of lisinopril, amlodipine, simvastatin, metformin, and tamsulosin is associated with a decreased risk of aneurysmal SAH.[19] However, no drug has been proven to effectively prevent the progression of IA and development of SAH in the randomized trial.

Diabetes mellitus and hyperglycemia have been implicated in their association with SAH.[29] A retrospective multicentre cohort study found that the use of antidiabetic agents was inversely and significantly associated with aneurysmal SAH, whereas glycated hemoglobin levels did not demonstrate such association.[16] Although this study did not individually analyse each antidiabetic agent.[16] the findings suggest that some class of antidiabetic agents, rather diabetes itself, may have a protective effect against the risk of aneurysmal SAH, indicating their potential protective effect against the pathogenesis of IA rupture. In recent years, antidiabetic agents, primarily used for managing diabetes mellitus, have been increasingly studied and applied in diverse medical conditions.[11-15] For instance, thiazolidinediones have been effective in reducing cardiovascular events in patients with ischemic stroke,[11,12] and may offer protection against dementia.[15] Similarly, SGLT2 inhibitors have shown promise in improving cardiovascular outcomes in patients with heart failure.[13]

Metformin, a well-known biguanide antidiabetic agent, has been associated with a decreased risk of aneurysm expansion rate and rupture risk in type 2 diabetic patients with AAA, another life-threating aneurysmal disease caused by weakening of the aortic wall.[17,30] Metformin activates adenosine monophosphate (AMP)-activated protein kinase and inhibits pro-inflammatory cytokines and matrix metalloproteinases, mechanisms that potentially prevent the development, progression, and rupture of AAAs.[31-34] Based on the experimental and epidemiologic evidence for the inhibitory effect of metformin on AAAs, four randomized trials are currently ongoing, comparing a daily dose of 1,500–2,000 mg of metformin with a placebo.[17] Emerging research suggests that metformin also holds potential in inhibiting formation, progression, and rupture of IAs.[18] In an animal study, metformin prevented IA formation and rupture by inhibiting vascular smooth muscle cell phenotype switching and affecting cellular processes such as proliferation, migration, and apoptosis.[18] This effect is also linked to the regulation of the AMP-activated protein kinase/acetyl-CoA carboxylase pathway, essential in vascular smooth muscle cell phenotype

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switching, a key factor in IA development.[18] The aforementioned drug-wide association study also suggested that metformin may decreased the risk of aneurysmal SAH.[19] Our study, utilizing a large nationwide dataset, demonstrated that metformin use reduced the risk of SAH in type 2 diabetic patients with IAs treated with clipping or coiling. This effect was consistent in subgroup, PSM and the time-varying Cox analyses. This study elucidated the effects of metformin in this specific patient population, offering valuable insights into its potential use as a therapeutic agent.

Our study also found that metformin use was also associated with decreased all-cause mortality in patients with IA and type 2 diabetes. This aligns with findings from previous studies that have consistently demonstrated the ability of metformin to reduce all-cause mortality.[9,35-37] Notably, a previous meta-analysis highlighted that diabetic patients on metformin experienced significantly lower all-cause mortality rates than nondiabetic individuals.[36] This suggests that the role of metformin extends beyond primary diabetes management to potentially serve as an effective tool for secondary prevention. Considering that 22–26% of patients with SAH die before reaching the hospital, the preventive effect of metformin against SAH might have partially contributed to the lower all-cause mortality observed among metformin users in our study.[3] These findings, combined with the results of our study, suggest that metformin is a valuable and multifaceted treatment option in the management of patients with IA and diabetes. The ability to decrease all-cause mortality further underscores its potential as a therapeutic agent.

This study has several strengths. We included a large number of type 2 diabetic patients with IAs treated with clipping or coiling using real-world data from a nationwide health claims database. To confirm the association between metformin use and reduced risk of SAH, we performed subgroup and sensitivity analyses, all of which consistently demonstrated the benefits of metformin in patients with IAs and diabetes. This study also has several limitations. Most importantly, certain variables could not be evaluated because the health claims data inherently lacked detailed clinical information, given that this was a nationwide claims-based cohort study. For instance, IA characteristics, including size, location, number of IAs, clipping status, packing density of the aneurysm after coiling, and recanalization of the treated aneurysm were unavailable in the claims database. Data on the control status of glucose, such as glycated hemoglobin levels, as well as information on the dosage and adherence to metformin was also unavailable. It was not possible to ascertain whether the SAH occurred at the treated IA site or another location. Because of the retrospective nature of this observational study without intervention, a causal relationship between metformin use and the occurrence of SAH cannot be established. In addition, the findings may not be generalizable as this study was based solely on a Korean cohort.

Despite these limitations, this study suggests that metformin could be recommended as a first-line antidiabetic agent for type 2 diabetic patients with IAs treated with clipping or coiling. Typically, the choice of a first-line antidiabetic agent for patients with type 2 diabetes depends on the individual comorbidities. In the absence of specific contraindications, metformin has traditionally been the first-line therapy.[27] This research is crucial for understanding the broader implications of metformin therapy, not only as an agent for glycemic control but also as a potential protective intervention for SAH in the context of IAs. The potential effectiveness of metformin in patients with IAs without type 2 diabetes requires further investigation in future randomized clinical trials across multiple ethnicities, using more comprehensive data, similar to ongoing trials in patients with AAAs.

Among type 2 diabetic patients with IAs treated with clipping or coiling, metformin users had reduced risk of SAH. Given that metformin is already a widely used antidiabetic medication, it may be reasonable to consider metformin as a first-line treatment option for patients with diabetes and IAs.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1

Supplemental Methods

Supplementary Table 1

Definition of variables based on health claim data

Supplementary Table 2

Effect of metformin on primary outcome after treatment for intracranial aneurysm

Supplementary Table 3

Baseline characteristics of patients with and without metformin before and after propensity score matching

Supplementary Table 4

Effect of metformin on SAH in sensitivity analyses

Supplementary Fig. 1

Cumulative incidence curve in propensity score matched cohort. A 1:1 propensity score matching is performed using a logistic regression model for the use of metformin (**Supplementary Data 1**) and cumulative incidence curve is plotted in these matched cohort. Metformin use is associated with decreased risk of SAH (stratified log-rank test, $P = 0.009$).

Supplementary Fig. 2

Cumulative incidence curve using the Simon and Makuch method. In this model, metformin use is considered as a time-dependent variable. To plot this cumulative incidence curve for SAH with respect to use of metformin as a time-dependent variable, Simon and Makuch's method is used. Metformin use is associated with the decreased risk of SAH (Mantel-Byar test, $P < 0.001$).

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