SVN Stroke & Vascular Neurology

Retinal artery/arteriole occlusion risks after endovascular treatment for unruptured intracranial aneurysm

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To cite: Kim HR, Kim MJ, Kim S, *et al*. Retinal artery/arteriole occlusion risks after endovascular treatment for unruptured intracranial aneurysm. *Stroke & Vascular Neurology* 2024;**9**: e002563. doi:10.1136/svn-2023-002563

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2023-002563).

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Received 2 May 2023
Accepted 10 September 2023
Published Online First 4 October 2023

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ABSTRACT

Background To evaluate the association between retinal artery/arteriole occlusion (RAO) and unruptured intracranial aneurysm (UIA).

Methods Incident UIA patients from a nationwide cohort (n=253 240) were categorised into three groups based on subsequent treatment: observation (n=208 993), microsurgical clipping (n=14 168) and endovascular treatment (EVT) groups (n=30 079). The incidence and the incident time of RAO were analysed. HRs of RAO and associated risk factors were evaluated. Additionally, a hospital cohort comprising 2569 consecutive UIA patients treated at a tertiary hospital was analysed with detailed clinical information of UIAs.

Results In the nationwide cohort analysis, the incidence of RAO was significantly higher in EVT group than in observation and clipping groups, especially within 60 days (early RAO (within 60 days): HR=4.00, 95% CI: 2.44 to 6.56); delayed RAO (after 60 days): HR=1.74, 95% CI: 1.13 to 2.68). Multivariable analysis showed that the presence of chronic kidney disease (p=0.009) and use of a balloon microcatheter during the procedure (p=0.013) were associated with a higher risk of RAO. In hospital cohort analysis, 11 (0.8%) cases of RAO occurred after EVT, whereas none occurred after microsurgical clipping (p<0.001). Patients with RAO were younger and received balloon microcatheters more frequently than their counterparts. Ten cases of RAO (90.9%) occurred in paraclinoid aneurysms, where EVT was preferred over microsurgical clipping.

Conclusions Performing EVT for UIA may increase the risk of subsequent RAO. Care should be taken when treating paraclinoid aneurysms with balloon microcatheters.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Case reports on retinal artery/arteriole occlusion occurring after endovascular treatment (EVT) for unruptured intracranial aneurysm.

WHAT THIS STUDY ADDS

⇒ After EVT, retinal artery/arteriole occlusion occurs in 0.8% of cases, with paraclinoid aneurysms and the use of balloon microcatheters being risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Care should be taken when treating paraclinoid aneurysms with balloon microcatheters.

INTRODUCTION

Retinal artery/arteriole occlusion (RAO) is a major cause of sudden painless vision loss that often results in devastating impairment.[1] The disease entity encompasses central RAO (CRAO), branch RAO (BRAO) and RAO. Typical RAO is most commonly caused by an impacted embolus in the narrowest part of the central retinal artery, where it enters the sheath of the optic nerve,[2] or branch retinal arterioles. The main sources of emboli are the carotid artery and heart.[2] Various cardiac conditions or invasive cardiovascular procedures cause RAO.[3] Because the central retinal artery arises from the ophthalmic artery (OphA), the first major branch of the internal carotid artery,[4] significant stenosis of either the OphA or internal carotid artery can result in the development of CRAO. Although much rarer, emboli from other intracranial vascular branches can also result in CRAO due to variations in the origin and course of the OphA.[3] Thus, the presence of intracranial vascular abnormalities, such as unruptured intracranial aneurysm (UIA) and invasive vascular treatment procedures can cause thromboembolic complications in retinal vessels.

A UIA>7 mm has a higher risk of rupture and is warranted for treatment by endovascular treatment (EVT) and surgical clipping.[5] Endovascular coil embolisation is widely practised in cases of UIA given its better safety, anatomical accessibility and higher success rate,[5] whereas the surgical approach outweighs embolisation in complete occlusion and a lower recurrence rate. In cases of paraclinoid aneurysms, which arise from the segment of the internal carotid artery between the distal dural ring and origin of the posterior communicating artery,

endovascular access is preferred over direct surgery because of technical difficulties caused by the anatomical complexity.[6 7] Because paraclinoid aneurysms are located near or contain branches of the OphA, RAO might occur more frequently in paraclinoid aneurysms with or without treatment. In previous studies, most RAO cases were found post-treatment for paraclinoid aneurysms,[8–15] although some have been reported in other types of UIAs.[16–18] Currently, the frequency or risk factors of RAO occurring after EVT remain elusive.[19] In this study, we first analysed a nationwide cohort to investigate the incidence rate of RAO in UIA according to the treatment protocol and to evaluate the risk factors associated with the incidence of RAO in patients with UIA. We further analysed the hospital cohort using detailed clinical information, including the location and size of UIAs.

METHODS

Data source and study population

We used data recorded from January 2016 to July 2022 from the National Health Claims Database of the HIRA service in Korea. The data source has been described in detail elsewhere.[20] Briefly, the HIRA database provides extensive information regarding all health claims in Korea, either submitted through the Korean National Health Insurance scheme or Medical Assistance Programme.[21] This claims database includes direct medical costs, personal information, demographics, diagnoses, procedures and medical prescriptions of all Korean residents. As the database is based on unique identification numbers (Korean Resident Registration Number), that are given to all Korean residents at birth, it can be used to obtain the healthcare records and demographics of patients without duplication or omission.[20]

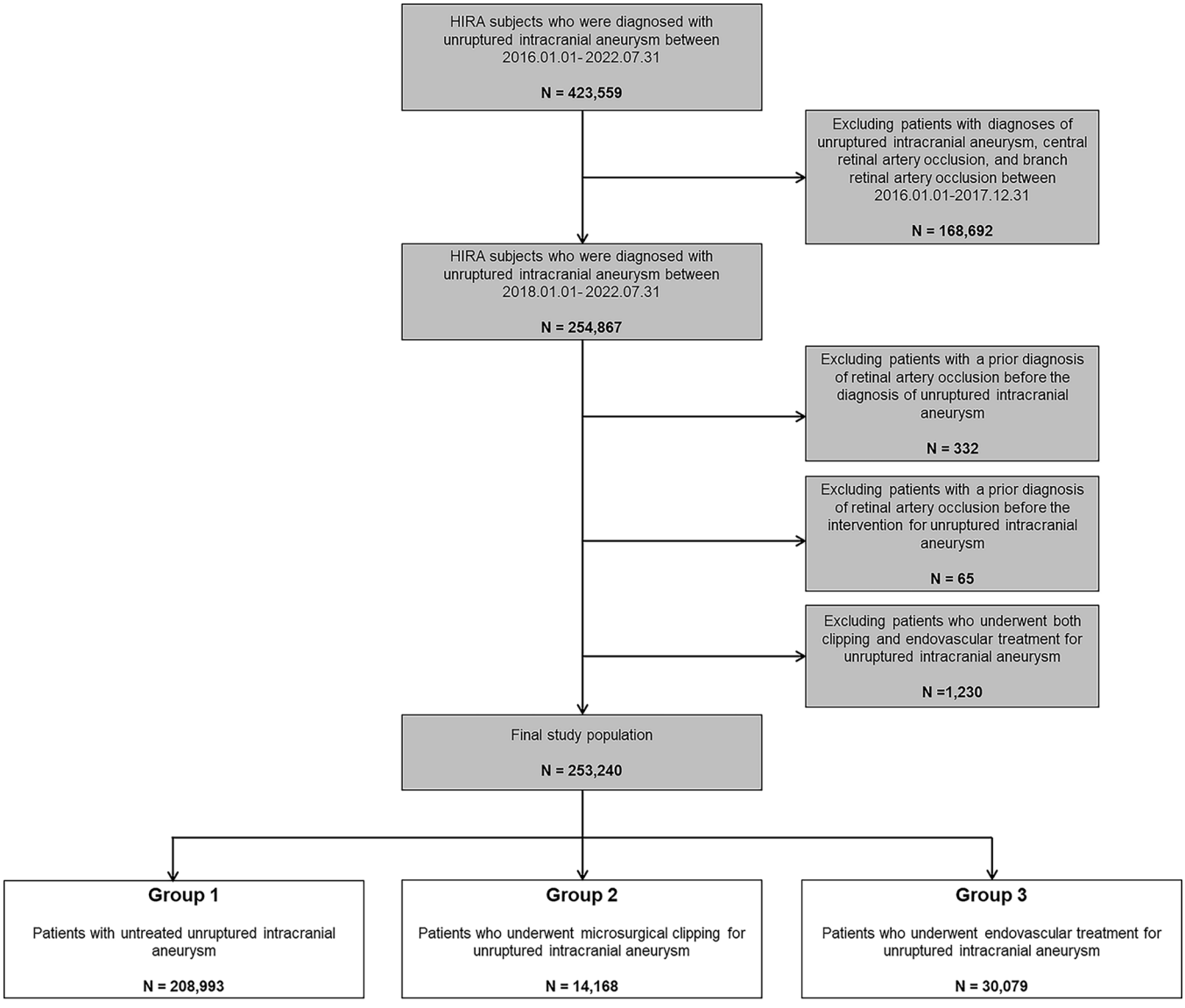


Figure 1 Flow chart of patients excluded and included in the analysis in the current study. HIRA, Health Insurance Review and Assessment.

We identified 423 559 eligible patients diagnosed with UIA between January 2016 and July 2022 (figure 1). All diagnoses were based on the International Classification of Diseases, 10th edition (ICD-10). To clarify the primary risk of UIA on the incidence of RAO, we set a 'washout period' and excluded patients with any previous hospital claims for UIA, CRAO or BRAO between 2016 and 2017 (n=168 692). Patients diagnosed with RAO before the diagnosis of UIA (n=332) or before treatment for UIA (n=65) were excluded. Lastly, patients who underwent both microsurgical clipping and EVT for UIA were excluded (n=1230). Finally, 253 240 participants were included in this analysis.

Exposure

We categorised patients with UIA into three groups based on subsequent treatment: observation (n=208 993), microsurgical clipping (n=14 168) and EVT groups (n=30 079). Patients were considered to have received specific treatment if relevant ICD-10 codes for microsurgical clipping (S4641 or S4642) and EVT (M1661 or M1662) were given after the diagnosis of UIA in the claims data.

Outcome and covariates

The primary outcome was the incidence rate of early (within 60 days) or delayed (after 60 days) RAO and the period from the index date of diagnosis or treatment of UIA to the incidence of RAO. The earliest date of the claim for RAO was considered the incident time of the disease. The secondary outcomes included factors associated with RAO development after EVT.

Baseline patient characteristics, including age, sex, type of medical insurance, residence and medical conditions, such as hypertension, diabetes, dyslipidaemia, transient ischaemic attack, ischaemic stroke, haemorrhagic stroke, myocardial infarction, chronic kidney disease (CKD), malignancy, hyperthyroidism, hypothyroidism, chronic liver disease, chronic obstructive pulmonary disease and Charlson Comorbidity Index (CCI), were collected. To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records with ICD-10 codes in the database. Prescription histories of antithrombotic agents or anticoagulants within 6 months before baseline were obtained from the claims data. Details of the ICD-10 codes used to define the medical conditions, comorbidities, drug treatments and procedures are presented in online supplemental table 1.

Hospital cohort study with detailed clinical information

As the claims data did not include detailed information on UIAs, such as location or size, we conducted additional analyses using a hospital cohort comprising consecutive patients who were treated with microsurgical clipping or EVT for UIAs at a tertiary high-volume hospital between January 2018 and June 2022. In total, 2569 consecutive patients with UIAs (2896 UIAs) treated with microsurgical clipping or EVT were eligible for the study. Patients were categorised based on treatment: 1176 patients with 1369 aneurysms treated with microsurgical clipping, and 1393 patients with 1527 aneurysms treated with EVT. Therapeutic decisions were discussed by a multidisciplinary team of neurosurgeons and neurointerventionists, and a final decision was made by consensus.

The analysed aneurysmal factors included the number of aneurysms, maximum aneurysm diameter, aneurysmal location, accompanying vascular problems and whether re-embolisation was performed. The locations of the aneurysms were classified as the internal carotid artery, which encompasses the distal paraclinoid artery, paraclinoid artery and proximal paraclinoid artery; anterior cerebral artery, including the anterior communicating artery; middle cerebral artery; or posterior circulation, including the vertebral artery, basilar artery, posterior cerebral artery and cerebellar arteries. Considering the proximity of the OphA branch and paraclinoid artery, the risk factors associated with development of RAO in paraclinoid aneurysms were assessed separately. Procedure-related factors included the emboliszation method (single or multiple microcatheter technique) and use of devices (balloon, stent, flow diverter or flow disruptor). For details of the collected data from the retrospective chart review and routine treatment protocols for EVT, seee online supplemental methods.

All patients who had acute-onset vision loss after treatment for UIA underwent complete ophthalmic evaluations, including best-corrected visual acuity, intraocular pressure, slit lamp biomicroscopy, dilated fundoscopic examination, fundus photography and spectral-domain optical coherence tomography. A visual field test and fluorescein angiography were additionally performed, if necessary. The diagnosis of RAO was made clinically by ophthalmologists at the initial assessment and additionally confirmed by two retinal specialists (HRK and YJK) during a retrospective chart review.[3]

Statistical analyses

Baseline characteristics are reported as mean±SD or frequency (per cent). Using the HIRA database, the cumulative incidence of RAO according to the subgroups was calculated using the Kaplan-Meier method. Age-adjusted and sex-adjusted standardised incidence ratios (SIR) of RAO were calculated using the RAO incidence rate in the entire Korean population between 2018 and 2019 as a reference. HRs and 95% CIs based on the Poisson distribution for RAO associated with the subgroups were calculated using Cox proportional hazards models, with untreated UIA as the reference. HRs were adjusted for age, sex and the presence of hypertension, diabetes mellitus or dyslipidaemia. The adequacy of the proportional hazard assumption was confirmed using log-minus-log survival plots and Schoenfeld residuals. Univariable and multivariable analyses of risk factors for RAO in UIA were performed.

For hospital cohort data analysis, Pearson's χ^2 test or Fisher's exact test was used to determine the differences between categorical variables. The means for differences

between continuous variables were analysed using the Student's t-test. A logistic regression model was used to evaluate factors associated with RAO. The results are reported as ORs and 95% CIs.

Statistical analyses were performed using SAS (V.9.4, SAS Institute), SPSS (V.25.0; IBM) and R (V.3.5.3, R Foundation for Statistical Computing, Vienna, Austria). P values <0.050 were considered statistically significant.

RESULTS

Baseline characteristics of the nationwide cohort

Of the 253 240 patients with UIA, 208 993 (82.5%) were observed without further treatment, 14 168 (5.6%) underwent microsurgical clipping and 30 079 (11.9%) underwent EVT. The mean ages were 62.46±13.82, 60.14±9.92 and 60.32±11.76 in the observation, microsurgical clipping and EVT groups, respectively. The three groups differed in age, sex, residence, comorbidities of systemic diseases, CCI and prescription history of antithrombotic agents or anticoagulants. Patients with UIA who required treatment with either microsurgical clipping or EVT were significantly younger, predominantly female and had urban residency than those who were observed without further treatment. The EVT group was more likely to have received aspirin or antiplatelet therapy than the other groups. The general characteristics of the nationwide cohort are presented in table 1.

Risks of RAO

The cumulative incidence of RAO was significantly higher in the EVT group (62.41 per 100 000 person-years) than in the other groups (30.49 and 18.39 per 100 000 person-years in the observation and microsurgical clipping groups, respectively). In the EVT group, early RAO (25 patients (0.08%)) was markedly observed compared with the other groups (observation group: 45 patients (0.02%), microsurgical clipping group: 4 patients (0.03%)) (figure 2 and online supplemental figure 1).

When age, sex and the presence of hypertension, diabetes or dyslipidaemia were adjusted, microsurgical clipping was not associated with higher RAO risks in comparison to conservative treatment (early RAO: HR=1.33, 95% CI: 0.48 to 3.72; delayed RAO: HR=0.45, 95% CI: 0.14 to 1.40). In the EVT group, early RAO developed in 25 (0.1%) patients and delayed RAO developed in another 25 (0.1%), with HRs of 4.00 (95% CI: 2.44 to 6.56) and 1.74 (95% CI: 1.13 to 2.68), respectively (figure 3). The characteristics of the patients who developed early and delayed RAO are presented in online supplemental table 2.

Next, we investigated whether the RAO risk increased when each group was compared with the general population. The incidences of RAO in the general population were 13.96 and 9.40 per 100 000 person-years among men and women, respectively (online supplemental table 3). Age-adjusted and sex-adjusted SIR of RAO was also significantly higher in the EVT group (SIR=2.87, 95% CI: 1.24 to 4.02, p<0.001) than in the entire Korean population, whereas the values in observation (SIR=1.13, 95% CI: 0.93 to 1.19, p=0.120) and microsurgical clipping groups (SIR=0.87, 95% CI: 0.51 to 1.75, p=0.713) were similar to that of the general population (online supplemental table 4).

Risk factors of RAO after EVT for UIA

We assessed the risk factors for RAO after EVT for UIAs. In univariable analysis, female sex (HR=0.58, 95% CI: 0.33 to 1.02, p=0.058), CKD (HR=4.02, 95% CI: 1.45 to 11.17, p=0.022) and the use of a balloon microcatheter (HR=2.93, 95% CI: 1.16 to 7.39, p=0.008) were associated with RAO after EVT. Age, socioeconomic status, residence, hypertension, diabetes, dyslipidaemia, stroke, CCI and the use of anticoagulant/antithrombotic agents were not significantly associated with RAO after EVT. Multivariable analysis revealed that CKD (HR=3.98, 95% CI: 1.42 to 11.19, p=0.009) and the use of a balloon microcatheter (HR=3.33, 95% CI: 1.29 to 8.65, p=0.013) were significantly associated with RAO after EVT (table 2).

Hospital cohort analysis with detailed clinical information

In total, 1393 patients (female=1,075 (77.2%); mean age, 59.5 years) underwent EVT and 1176 patients (female=859 (73.0%); mean age, 60.6 years) underwent microsurgical clipping. Although RAO did not occur after microsurgical clipping, 11 cases (0.8%) occurred after EVT (p<0.001). All RAO cases occurred in the same direction as the right/left positions of the UIAs. Anatomically, RAO appeared to be prevalent after treatment of aneurysms located in the internal carotid artery (paraclinoid aneurysms, 10 (90.9%); and distal paraclinoid aneurysm located at posterior communicating artery, 1 (9.1%)), with borderline statistical significance (p=0.063). Previous studies reported that RAO cases after UIA treatment also occurred after EVT, and most UIAs were paraclinoid aneurysms. The detailed characteristics of the patients who developed RAO after treatment with UIAs are presented in online supplemental table 5. Subjective vision decreases or visual field defects of varying degrees occurred within 1–2 days of treatment. At the last follow-up, three patients (patients 3, 9, 11) had partial vision loss and one patient with CRAO (patient 2) had permanent vision loss. Representative images of RAO after EVT are shown in online supplemental figure 2. Notably, patients with RAO were younger and used balloon microcatheters more frequently than patients without RAO in the EVT group (table 3).

We conducted a subgroup analysis of paraclinoid aneurysms which is close to the OphA. Among the 612 patients with 638 aneurysms, 10 (1.6%) patients developed RAO after EVT. Multivariable logistic regression analysis showed that the independent risk factors for RAO were the use of a balloon microcatheter (OR=7.56, 95% CI: 1.35 to 42.44, p=0.022). The details of the risk factor analysis are presented in table 4.

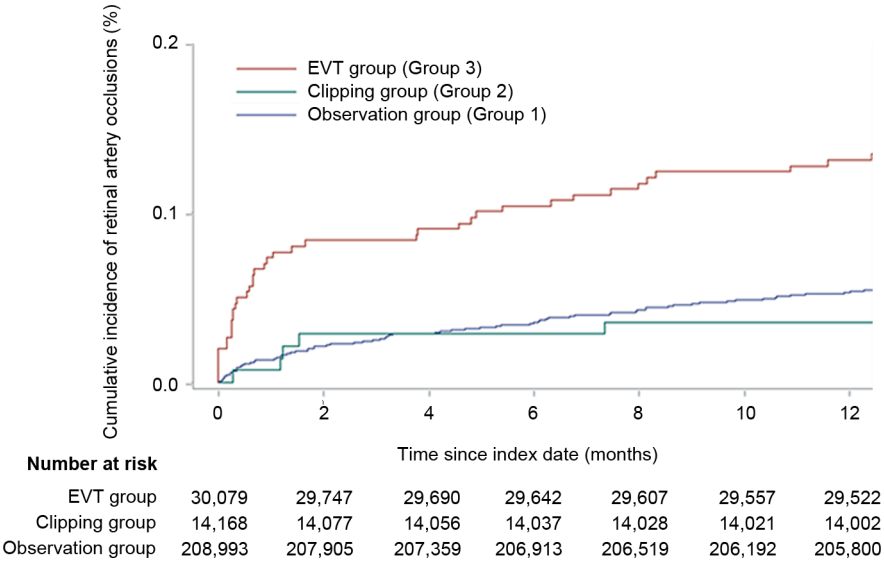
Table 1 Baseline characteristics of the nationwide cohort by subsequent treatment

	Observation group (group 1) N=208 993	Microsurgical clipping group (group 2) N=14 168	EVT group (group 3) N=30 079	P value		
				Group 1 vs 2	Group 1 vs 3	Group 2 vs 3
Age (years)	62.46±13.82	60.14±9.92	60.32±11.76	<0.001	<0.001	0.084
<40	12 876 (6.2%)	418 (3.0%)	1401 (4.7%)			
40–64	100 777 (48.2%)	8883 (62.7%)	17 596 (58.5%)			
65–74	50 481 (24.2%)	3947 (27.9%)	7382 (24.5%)			
≥75	44 859 (21.5%)	920 (6.5%)	3700 (12.3%)			
Sex				<0.001	<0.001	<0.001
Male	74 853 (35.8%)	4439 (31.3%)	8890 (29.6%)			
Female	134 140 (64.2%)	9729 (68.7%)	21 189 (70.4%)			
Socioeconomic status*				0.001	0.209	0.077
Korean National Health Insurance	197 069 (94.3%)	13 466 (95.1%)	28 435 (94.5%)			
Medical Assistance Programme Type1	10 273 (4.9%)	605 (4.3%)	1408 (4.7%)			
Others	1651 (0.8%)	97 (0.7%)	236 (0.8%)			
Residence				<0.001	<0.001	<0.001
Urban	121 019 (57.9%)	10 091 (71.2%)	18 114 (60.2%)			
Rural	87 974 (42.1%)	4077 (28.8%)	11 965 (39.8%)			
Comorbidities						
Hypertension	110 858 (53.0%)	8339 (58.9%)	16 316 (54.2%)	<0.001	<0.001	<0.001
Diabetes	63 692 (30.5%)	3799 (26.8%)	7997 (26.6%)	<0.001	<0.001	0.614
Dyslipidaemia	128 931 (61.7%)	9117 (64.4%)	18 534 (61.6%)	<0.001	0.806	<0.001
Transient ischaemic attack	8387 (4.0%)	593 (4.2%)	1272 (4.2%)	0.312	0.076	0.832
Ischaemic stroke	20 836 (10.0%)	1143 (8.1%)	3067 (10.2%)	<0.001	0.220	<0.001
Haemorrhagic stroke	4482 (2.1%)	425 (3.0%)	974 (3.2%)	<0.001	<0.001	0.181
Myocardial infarction	3551 (1.7%)	134 (1.0%)	390 (1.3%)	<0.001	<0.001	0.002
Chronic kidney disease	6819 (3.3%)	333 (2.4%)	664 (2.2%)	<0.001	<0.001	0.345
Malignancy	18 266 (8.7%)	1069 (7.6%)	2249 (7.5%)	<0.001	<0.001	0.799
Hyperthyroidism	5254 (2.5%)	365 (2.6%)	757 (2.5%)	0.647	0.977	0.710
Hypothyroidism	17 461 (8.4%)	1229 (8.7%)	2353 (7.8%)	0.184	0.002	0.002
Chronic liver disease	24 129 (11.6%)	1767 (12.5%)	3514 (11.7%)	0.001	0.487	0.017
COPD	8484 (4.1%)	440 (3.1%)	979 (3.3%)	<0.001	<0.001	0.406
CCI				<0.001	<0.001	0.029
0	92 683 (44.4%)	6575 (46.4%)	14 367 (47.8%)			
1	49 990 (23.9%)	3491 (24.6%)	7225 (24.0%)			
≥2	66 320 (31.7%)	4102 (29.0%)	8487 (28.2%)			
Drugs						
Aspirin	27 061 (13.0%)	1980 (14.0%)	7409 (24.6%)	<0.001	<0.001	<0.001
Warfarin	905 (0.4%)	46 (0.3%)	96 (0.3%)	0.055	0.004	0.924
NOAC	3343 (1.6%)	152 (1.1%)	456 (1.5%)	<0.001	0.279	<0.001
Antiplatelet	22 519 (10.8%)	1499 (10.6%)	6778 (22.5%)	0.469	<0.001	<0.001

Data are presented as mean±SD or frequency (per cent).
*Socioeconomic status was categorised based on the type of medical insurance received. People who cannot afford 30% of their total medical expenses, which are self-funded under Korean National Health Insurance, are covered by the Medical Assistance Programme.
CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; EVT, endovascular treatment; NOAC, non-vitamin K antagonist oral anticoagulant.

DISCUSSION

In this nationwide, population-based study, we elucidated the risk of RAO in patients with UIA according to subsequent treatment and the associated risk factors for RAO. Few case reports have been published regarding the development of RAO after endovascular



Number at risk							
EVT group	30,079	29,747	29,690	29,642	29,607	29,557	29,522
Clipping group	14,168	14,077	14,056	14,037	14,028	14,021	14,002
Observation group	208,993	207,905	207,359	206,913	206,519	206,192	205,800

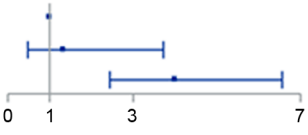
Figure 2 Cumulative incidence of retinal artery occlusion in patients with unruptured intracranial aneurysm according to the Kaplan-Meier method. EVT, endovascular treatment.

coil embolisation for UIA, and there is no evidence regarding the association between RAO and UIA. Our results provide detailed information regarding the increased risk of RAO and the time of incident RAO, especially in patients treated with EVT for UIA. The rapid increase in the incidence of RAO during the first 60 days after treatment of UIA implicates a direct relationship between EVT and RAO. As patent artery occlusion (2%) and thromboembolism (2.4%) are the most common complications of this procedure,[5 16] it is possible that coil embolisation itself may cause RAO. Moreover, the use of certain devices, direct contact with the wall of the intracranial artery or plaque break-off during catheter passage may play a role in the development of thrombus-related RAO.[16 17] In our study, the use of a balloon microcatheter was significantly associated with higher risk of RAO in the HIRA dataset and hospital cohort. In cases of balloon-assisted coil embolisation, intermittent OphA occlusion caused by balloon inflation precedes coil insertion. Previous studies revealed that collateral OphA flow from the external carotid artery was present in 60%–84.6% of cases.[22 23] Usually, distal flow is maintained because of collateral flow, and the possibility of RAO is low. It is assumed that, however, because of this collateral, a thrombus may develop at the proximal segment of the OphA during balloon inflation. Specifically, the usual blood flow from the internal carotid artery to the OphA changes to a flow directed from the external carotid artery to the OphA during balloon inflation, increasing the risk of thrombus formation at the site of flow retention. After balloon deflation, the thrombus may wash out into the OphA, causing RAO.

A

Early retinal artery occlusion events (within 60 days from index date)

Group	Persons	Events	Rates	Hazard ratio	HR (95% CI)
Observation group	208,993	45	131.6		1.00 (ref)
Clipping group	14,168	4	172.7		1.33 (0.48–3.72)
EVT group	30,079	25	510.1		4.00 (2.44–6.56)



B

Late retinal artery occlusion events (> 60 days from index date)

Group	Persons	Events	Rates	Hazard ratio	HR (95% CI)
Observation group	207,905	124	23.8		1.00 (ref)
Clipping group	14,077	3	8.4		0.45 (0.14–1.40)
EVT group	29,747	25	33.2		1.74 (1.13–2.68)

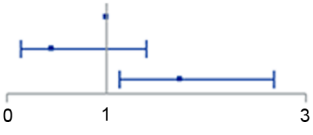


Figure 3 Cox regression analysis of retinal artery occlusion (RAO) risks by onset date. (A) Early RAO, which occurred within 60 days after the diagnosis or treatment of unruptured intracranial aneurysm (UIA), (B) delayed RAO, which occurred after 60 days or longer from the diagnosis or treatment of UIA. Group 1, patients with untreated UIA; Group 2, UIA patients treated with microsurgical clipping and Group 3, UIA patients treated with endovascular treatment. The Cox model was adjusted for age, sex and the presence of hypertension, diabetes mellitus or dyslipidaemia. The incidence rate is per 100 000 person-years.

Table 2 Results of univariable and multivariable analyses for the risk factors of retinal artery occlusion after endovascular treatment for unruptured intracranial aneurysm in the nationwide cohort

	Univariable analysis		Multivariable analysis	
	HR (95% CIs)	P value	HR (95% CIs)	P value
Age	1.00 (0.97 to 1.02)	0.744	1.00 (0.97 to 1.02)	0.762
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	0.58 (0.33 to 1.02)	0.058	0.60 (0.34 to 1.05)	0.075
Socioeconomic status*				
Korean National Health Insurance	1.00 (reference)			
Medical Assistance Programme Type 1	1.31 (0.41 to 4.20)	0.652		
Residence				
Urban	1.00 (reference)			
Rural	1.40 (0.81 to 2.44)	0.232		
Comorbidities				
Hypertension	1.28 (0.73 to 2.25)	0.393		
Diabetes	0.70 (0.35 to 1.40)	0.315		
Dyslipidaemia	1.03 (0.58 to 1.83)	0.914		
Ischaemic stroke	1.22 (0.521 to 2.87)	0.645		
Transient ischaemic attack	0.47 (0.06 to 3.38)	0.450		
Haemorrhagic stroke	1.25 (0.30 to 5.15)	0.757		
Myocardial infarction	0.00	0.981		
Chronic kidney disease	4.02 (1.45 to 11.17)	0.008	3.98 (1.42 to 11.19)	0.009
Malignancy	0.53 (0.13 to 2.16)	0.373		
Hyperthyroidism	0.000	0.983		
Hypothyroidism	1.63 (0.69 to 3.82)	0.264		
Chronic liver disease	1.47 (0.69 to 3.12)	0.321		
COPD	1.26 (0.31 to 5.19)	0.748		
CCI				
0	1.00 (reference)			
1	0.67 (0.30 to 1.49)	0.325		
≥2	1.30 (0.71 to 2.40)	0.397		
Drugs				
Aspirin	0.97 (0.51 to 1.85)	0.918		
Warfarin	0.00	0.986		
NOAC	1.35 (0.19 to 9.78)	0.765		
Antiplatelet	1.21 (0.65 to 2.28)	0.549		
Device				
Balloon microcatheter	2.93 (1.16 to 7.39)	0.022	3.33 (1.29 to 8.65)	0.013
Stent assisted	1.50 (0.83 to 2.71)	0.182		
Flow diverter	1.16 (0.16 to 8.41)	0.883		

*Socioeconomic status was categorised based on the type of medical insurance received. People who cannot afford 30% of their total medical expenses, which are self-funded under Korean National Health Insurance, are covered by the Medical Assistance Programme.
CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; NOAC, non-vitamin K antagonist oral anticoagulant.

The microsurgical treatment of paraclinoid aneurysms remains challenging because of their anatomical features. Meticulous surgical techniques, including anterior clinoidectomy, optic strut removal and dissection of the distal dural ring, are required to fully expose the aneurysm. Simultaneously, surrounding anatomical structures (eg, optic nerves, oculomotor nerves, perforating arteries and cavernous sinuses) should be preserved. In previous

Table 3 Characteristics of patients with hospital-based unruptured intracranial aneurysm (UIA) who underwent microsurgical clipping or endovascular treatment

	Microsurgical clipping	Endovascular treatment		
	Total (N=1176)	Total (N=1393)	Patients with RAO (N=11)	P value
Age (years)	60.6±9.1	59.5±10.9	51.3±7.9	0.011
<40	32 (2.7%)	72 (5.2%)	1 (9.1%)	
40–64	733 (53.5%)	830 (59.6%)	10 (90.9%)	
65–74	368 (31.3%)	396 (28.4%)	0	
≥75	43 (3.7%)	95 (6.8%)	0	
Female	859 (73.0%)	1075 (77.2%)	9 (81.8%)	>0.999
Comorbidities				
Hypertension	619 (52.6%)	669 (48.0%)	5 (45.5%)	0.864
Diabetes mellitus	152 (13.4%)	162 (11.7%)	1 (9.1%)	>0.999
Dyslipidaemia	416 (35.4%)	502 (36.0%)	3 (27.3%)	0.755
Chronic kidney disease	20 (1.7%)	33 (2.4%)	0	>0.999
Multiplicity	522 (38.1%)	599 (39.2%)	5 (45.5%)	0.760
Size of UIA (mm)	4.62	6.21±3.54	5.70±1.67	0.335
<5	935 (68.3%)	652 (42.7%)	3 (27.3%)	
5–10	402 (29.4%)	732 (47.9%)	8 (72.7%)	
10–15	24 (1.8%)	89 (5.8%)	0	
≥15	8 (0.6%)	54 (3.5%)	0	
Direction of UIA				0.197
Central	225 (16.4%)	312 (20.4%)	0	
Left	614 (44.9%)	655 (42.9%)	5 (45.5%)	
Right	530 (38.7%)	560 (36.7%)	6 (54.5%)	
Location of UIA				0.063
Internal carotid artery*	319 (23.3%)	921 (60.3%)	11 (100%)	
Anterior cerebral artery	293 (21.4%)	302 (19.8%)	0	
Middle cerebral artery	749 (54.7%)	129 (8.4%)	0	
Posterior circulation	8 (0.6%)	175 (11.5%)	0	
Associated vascular problems				
Atherosclerosis/stenosis	62 (4.5%)	226 (14.8%)	1 (9.1%)	>0.999
Diffusion restriction	NA	262 (17.2%)	2 (18.2%)	>0.999
Intraoperative carotid artery dissection	NA	7 (0.5%)	0	>0.999
Intraoperative thrombosis	NA	79 (4.8%)	0	>0.999
Device				
Simple coil embolisation	NA	427 (28.0%)	1 (9.1%)	0.307
Balloon microcatheter	NA	92 (5.0%)	3 (27.3%)	0.016
Stent assisted	NA	792 (50.9%)	3 (27.3%)	0.310
Flow diverter	NA	174 (11.4%)	4 (36.4%)	0.132
Flow disruptor	NA	57 (3.7%)	0	>0.999
Post-operative antiplatelet				
None	NA	315 (20.6%)	2 (18.1%)	0.923
Single	NA	184 (12.0%)	1 (9.1%)	
Dual+@	NA	1028 (67.3%)	8 (72.8%)	
Retreatment	57 (4.2%)	97 (6.4%)	0	*>0.999*

*Ten cases of RAO occurred in paraclinoid aneurysm (1.6%, from a total of 622 patients) and one case of RAO occurred in distal paraclinoid aneurysm (0.4%, from a total of 255 patients).
NA, not applicable; RAO, retinal artery occlusion.

Table 4 Risk factors of retinal artery occlusion (RAO) in paraclinoid aneurysm treated with endovascular treatment

	Paraclinoid aneurysm without RAO (638 aneurysms in 612 patients)	Paraclinoid aneurysm with RAO (10 aneurysms in 10 patients)	Univariable analysis		Multivariable analysis	
			OR (95% CIs)	P value	OR (95% CIs)	P value
Age (years)	55.9±10.75	50.5±7.86	0.95 (0.90 to 1.01)	0.088	0.97 (0.91 to 1.02)	0.235
<40	53 (8.7%)	1 (10.0%)				
40–64	418 (68.3%)	9 (90.0%)				
65–74	130 (21.2%)	0				
≥75	11 (1.8%)	0				
Female	524 (85.6%)	9 (90.0%)	1.48 (0.19 to 11.81)	0.713		
Comorbidities						
Hypertension	199 (32.5%)	4 (40.0%)	1.39 (0.39 to 4.98)	0.614		
Diabetes mellitus	45 (7.4%)	1 (10.0%)	1.45 (0.18 to 11.70)	0.729		
Dyslipidaemia	170 (27.8%)	3 (30.0%)	1.08 (0.28 to 4.24)	0.909		
Chronic kidney disease	8 (1.3%)	0	NA	0.999		
Multiplicity	223 (35.0%)	4 (40.0%)	1.37 (0.38 to 4.93)	0.626		
Size of UIA (mm)	6.07±2.90	5.84±1.68	0.99 (0.79 to 1.24)	0.943		
<5	250 (39.2%)	2 (20.0%)				
5–10	339 (53.1%)	8 (80.0%)				
10–15	34 (5.3%)	0				
≥15	15 (2.4%)	0				
Direction of UIA						
Left	358 (56.1%)	4 (40.0%)	1.00 (reference)			
Right	280 (43.9%)	6 (60.0%)	1.14 (0.32 to 4.09)	0.840		
Location of UIA						
ICSHA	413 (64.7%)	4 (40.0%)	1.00 (reference)		1.00 (reference)	
ICC2	167 (26.2%)	4 (40.0%)	3.18 (0.84 to 11.98)	0.069	1.04 (0.10 to 10.52)	0.974
Ophthalmic artery	58 (9.1%)	2 (20.0%)	1.79 (0.20 to 16.33)	0.658	0.97 (0.91 to 1.02)	0.237
Associated vascular problems						
Atherosclerosis/stenosis	65 (10.2%)	1 (9.1%)	0.85 (0.12 to 6.35)	0.878		
Diffusion restriction	82 (12.9%)	2 (18.2%)	2.38 (0.89 to 6.38)	0.886		
Carotid artery dissection	3 (0.5%)	0	NA	>0.999		
Intraoperative thrombosis	15 (2.4%)	0	NA	>0.999		
Device						
Simple coil embolisation	110 (17.2%)	1 (10.0%)	1.11 (0.11 to 10.78)	0.929	1.62 (0.16 to 17.01)	0.686
Balloon microcatheter	55 (8.6%)	3 (30.0%)	6.98 (1.37 to 35.50)	0.019	7.56 (1.35 to 42.44)	0.022
Stent assisted	366 (57.4%)	2 (20.0%)	1.00 (reference)		1.00 (reference)	
Flow diverter	107 (16.8%)	4 (40.0%)	3.49 (0.69 to 17.55)	0.129	2.98 (0.56 to 15.82)	0.201
Post-operative antiplatelet						
None	114 (17.9%)	2 (20.0%)	1.20 (0.25 to 5.90)	0.821		
Single	43 (6.7%)	1 (10.0%)	1.70 (0.20 to 14.13)	0.625		
Dual+@	481 (75.4%)	7 (70.0%)	Reference	>0.999		
Retreatment	13 (2.0%)	0	NA	>0.999		

ICC2, C2 segment of internal carotid artery; ICSHA, internal carotid artery-superior hypophyseal artery; NA, not applicable; UIA, unruptured intracranial aneurysm.

studies, the rate of visual complications after microsurgical clipping was 4.3%–30%.[24–26] Visual dysfunctions included optic neuropathy,[24] visual field defects,[25 26] vision loss of unmentioned cause and oculomotor nerve palsy[25] other than retinal vessel occlusion. The recent introduction of new devices (eg, balloon microcatheter, stent,

flow diverter and flow disruptor) to treat wide-neck aneurysms that are unsuitable for simple coil embolisation has broadened the range of endovascular approaches. Therefore, EVT is widely used for the treatment of paraclinoid aneurysms. In our hospital cohort, RAO did not occur after microsurgical clipping, whereas a few cases occurred after EVT (total EVT group, 0.8%; paraclinoid aneurysms treated with EVT, 1.6%). This implies a higher risk of RAO in cases of paraclinoid aneurysms than in other UIAs. Although the location of the UIA showed borderline significance owing to the small number of RAO cases in the hospital cohort, all RAO cases were reported as internal carotid artery aneurysms, mostly paraclinoid aneurysms. Perhaps the position of the balloon during balloon-assisted coil embolisation might be similar, resulting in a similar risk of consecutive RAO. Interpretations of the results were limited because the number of RAO after EVT was very small and none occurred after microsurgical clipping. Further studies are warranted to recruit a larger cohort encompassing untreated UIAs and the location of the UIAs.

We speculate that the presence of UIA itself might cause thromboembolic complications in the OphA and retinal artery. A comparison of patients with UIA with the general population showed that untreated UIA and microsurgical clipping for UIA did not increase the risk of consecutive RAO. Blood flow from the heart and carotid artery is directed towards the OphA, and emboli from those vessels mainly cause RAO.[2] However, intracranial vessels are located more distal to the OphA branch and have different courses of circulation. Therefore, UIAs other than paraclinoid aneurysms are less likely to cause RAO. Different aetiologies may play a role in the occurrence of RAO in the UIAs located elsewhere. Bae *et al* reported a case of cilioretinal artery occlusion after EVT of the anterior communication artery.[16] Considering the distal location of the aneurysm from the OphA and the direction of blood flow, it is unlikely that the thrombus caused RAO. Air embolism during heparin injection into the catheter may cause microembolism-related retinal infarction.[27] Structural changes in the arterial wall, breakdown of blood products or inflammation due to catheter-induced stimulation of the endothelium may result in vasospasm and then hypoxia.[16 28]

Interestingly, the presence of CKD was significantly associated with an increased risk of RAO in EVT group. The correlation between end-stage renal disease and RAO risk has been well described.[29 30] As RAO and CKD share common risk factors (eg, hypertension, diabetes mellitus, hyperlipidaemia and atherosclerosis), the incidence of RAO can be higher in patients with CKD.[30] Moreover, chronic inflammation, which is prevalent in CKD, may contribute to the development of RAO. However, these studies were limited to patients on dialysis. The relationship between the presence of CKD and RAO needs to be evaluated further.

The strength of this study is that it was based on a nationwide population-based dataset, representative of the entire Korean population. Furthermore, we introduced an inpatient dataset to supplement clinical data that were not provided in the nationwide cohort. However, this study has the following limitations. First, the data were based on diagnostic codes and insurance claims; therefore, it is possible that misclassification or miscategorisation could have occurred. Second, information related to the clinical characteristics of UIA could not be assessed in the nationwide cohort, given that factors other than treatment method might interfere with the risk of RAO. To compensate for this, a comparison with the general population using age-adjusted and sex-adjusted SIR and additional analysis using the hospital cohort were conducted. Third, because not all patients with UIA underwent ophthalmic examinations, asymptomatic patients with RAO were not evaluated. Lastly, confounding factors, such as smoking history and alcohol consumption, which were not available in the HIRA dataset, could not be adjusted.

Because the most dreaded risk of intracranial aneurysms is rupture, which leads to a mortality rate as high as 80%, timely treatment is essential for UIA. However, caution should be exercised when deciding on UIA treatment, as indiscriminate endovascular or surgical treatment may increase the risk of RAO and irreversible vision loss. With the development of EVT, the treatment of UIA, especially paraclinoid aneurysms, has become easier. However, clinicians should be aware of the increased risk of RAO after EVT for paraclinoid aneurysms and the use of balloon-assisted coil embolisation. Also, further studies are warranted to recruit a larger cohort to elucidate associated factors of RAO in patients with UIAs.

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Funding This research was supported by Basic Science Research Program through the National Research Foundation (NRF) of Korea funded by the Ministry of Education (2022R1I1A1A01059209). This research was also supported by grants of the Korea Health Technology R&D Project through the Korea Health Industry

Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI21C1705, HI22C0782).

Disclaimer The funding organisations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. No financial disclosures exists for any author.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Health Insurance Review and Assessment (HIRA) Deliberative Committee (approval number: M20220222838). Use of the national health claims data was approved by the Institutional Review Board (IRB)/Ethics Committee (approval number: 4-2022-1028), which waived the requirement for informed consent owing to the retrospective study design and use of deidentified data. Additional analyses with the hospital cohort were approved by the same IRB (approval number: 4-2022-1025), which also waived the requirement for informed consent because of the retrospective design. This study adhered to the tenets of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All raw data in nationwide cohort can be accessed via the Health Insurance Review and Assessment (HIRA) Healthcare Bigdata Hub server. The application of the claims data submitted through the HIRA Healthcare Bigdata Hub homepage (https://opendata.hira.or.kr/home.do) is reviewed by the deliberative committee of research support, and once approved, raw data are provided to the authorisized researcher at a fee. After obtaining permission, data were analysed using remote access to the HIRA server. The entire dataset can be handled only through a connection to the HIRA server, and the analysed data can be exported with HIRA approval. The anonymised dataset and analytical codes of hospital cohort were available to researchers whose proposed use of the data has been approved by an independent review committee on request to the corresponding author (kyjcolor@yuhs.ac). To gain access, data requestors will need to sign a data access agreement.

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REFERENCES

1 Hayreh SS, Zimmerman MB. Central retinal artery occlusion: visual outcome. *Am J Ophthalmol* 2005;140:376–91.
2 Hayreh SS. Central retinal artery occlusion. *Indian J Ophthalmol* 2018;66:1684–94.
3 Hayreh SS. Acute retinal arterial occlusive disorders. *Prog Retin Eye Res* 2011;30:359–94.
4 Scott IU, Campochiaro PA, Newman NJ, *et al*. Retinal vascular Occlusions. *Lancet* 2020;396:1927–40.
5 Wiebers DO, Whisnant JP, Huston J, *et al*. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and Endovascular treatment. *Lancet* 2003;362:103–10.
6 Park HK, Horowitz M, Jungreis C, *et al*. Endovascular treatment of Paraclinoid aneurysms: experience with 73 patients. *Neurosurgery* 2003;53:14–23;
7 Fulkerson DH, Horner TG, Payner TD, *et al*. Endovascular retrograde suction decompression as an adjunct to surgical treatment of ophthalmic aneurysms: analysis of risks and clinical outcomes. *Neurosurgery* 2009;64(3 Suppl):s107–11.
8 Choudhry N, Brucker AJ. Branch retinal artery occlusion after coil Embolization of a Paraclinoid aneurysm. *Ophthalmic Surg Lasers Imaging Retina* 2014;45 Online:e26–8.
9 Chowdhry S, Sharma J, Blackham K. E-001 partial central retinal artery occlusion following para-ophthalmic artery Embolization: a case report. *Journal of NeuroInterventional Surgery* 2011;3(Suppl_1):A31.
10 Castillo B Jr, De Alba F, Thornton J, *et al*. Retinal artery occlusion following coil Embolization of carotid-ophthalmic aneurysms. *Arch Ophthalmol* 2000;118:851–2.
11 Yoo M, Jin S-C, Kim HY, *et al*. Intra-arterial Thrombolysis for central retinal artery occlusion after the coil Embolization of Paraclinoid aneurysm. *J Cerebrovasc Endovasc Neurosurg* 2016;18:369–72.
12 Wang Y-L, Hui Y-N, Chen R, *et al*. Central retinal artery occlusion after Endovascular coil Embolization for internal carotid artery aneurysm. *Int J Ophthalmol* 2019;12:520–2.
13 Park H, Nakagawa I, Yokoyama S, *et al*. Central retinal artery thromboembolism without ophthalmic artery occlusion during Stent-assisted coil Embolization of ophthalmic artery aneurysm. *World Neurosurg* 2019;121:77–82.
14 Elkordy AM, Sato K, Inoue Y, *et al*. Central retinal artery occlusion after the Endovascular treatment of Unruptured ophthalmic artery aneurysm: A case report and a literature review. *NMC Case Rep J* 2016;3:71–4.
15 Blautain B, Leleu I, Jabbour E, *et al*. Ischemic stroke and retinal artery occlusion after carotid aneurysm Embolization. *Radiol Case Rep* 2021;16:701–3.
16 Bae H, Kang T, Jeong D-E, *et al*. Cilioretinal artery occlusion after Endovascular coil Embolization for anterior communicating artery. *Brain Sci* 2021;11:542.
17 Shin SH, Park SP, Kim YK. Multiple small branch retinal arteriolar Occlusions following coil Embolization of an internal carotid artery aneurysm. *Indian J Ophthalmol* 2018;66:1208–10.
18 Bonnet SEB, Carpenter JS, Nguyen J. Delayed branch retinal artery occlusion and partial Oculomotor nerve palsy following coiling of a giant Intracavernous carotid artery aneurysm. *J Ocular Biol* 2013;1:4.
19 Biberoğlu Çelik E, Haidar H, Eraslan M, *et al*. Choroidal and retinal anatomical response following treatment of carotid-ophthalmic aneurysms with flow Diverter Stents. *Photodiagnosis Photodyn Ther* 2022;40:103117.
20 Park SJ, Choi N-K, Park KH, *et al*. Nationwide incidence of clinically diagnosed retinal vein occlusion in Korea, 2008 through 2011: preponderance of women and the impact of aging. *Ophthalmology* 2014;121:1274–80.
21 Park SJ, Choi N-K, Yang BR, *et al*. Risk and risk periods for stroke and acute myocardial infarction in patients with central retinal artery occlusion. *Ophthalmology* 2015;122:2336–43.
22 Tanaka T, Doijiri R, Saito K, *et al*. Validation of ultrasound parameters to assess collateral flow via ophthalmic artery in internal carotid artery occlusion. *J Stroke Cerebrovasc Dis* 2014;23:1177–82.
23 Ahn JH, Cho YD, Kang H-S, *et al*. Endovascular treatment of ophthalmic artery aneurysms: assessing balloon test occlusion and preservation of vision in coil Embolization. *AJNR Am J Neuroradiol* 2014;35:2146–52.
24 Kanagalingam S, Gailloud P, Tamargo RJ, *et al*. Visual sequelae after consensus-based treatment of ophthalmic artery segment aneurysms: the Johns Hopkins experience. *J Neuroophthalmol* 2012;32:27–32.
25 Kikuta K-I, Kitai R, Kodera T, *et al*. Predictive factors for the occurrence of visual and ischemic complications after open surgery for Paraclinoid aneurysms of the internal carotid artery. *Acta Neurochir Suppl* 2016;123:41–9.
26 Matsukawa H, Tanikawa R, Kamiyama H, *et al*. Risk factors for visual impairments in patients with Unruptured intradural Paraclinoid aneurysms treated by neck Clipping without bypass surgery. *World Neurosurg* 2016;91:183–9.
27 Brisman JL, Song JK, Newell DW. Cerebral aneurysms. *N Engl J Med* 2006;355:928–39.
28 Ahn J-M, Oh J-S, Yoon S-M, *et al*. Procedure-related complications during Endovascular treatment of intracranial Saccular aneurysms. *J Cerebrovasc Endovasc Neurosurg* 2017;19:162–70.
29 Moon TH, Kang M, Lee S, *et al*. The nationwide incidence of retinal artery occlusion following dialysis as a result of end-stage renal disease: 2004 through 2013. *Retina* 2021;41:2140–7.
30 Hsieh T-C, Chou C-L, Chen J-S, *et al*. Risk of mortality and of Atherosclerotic events among patients who underwent Hemodialysis and subsequently developed retinal vascular occlusion: A Taiwanese retrospective cohort study. *JAMA Ophthalmol* 2016;134:196–203.