

# Retinal Vein Occlusion and the Risk of Stroke Development

## A 9-Year Nationwide Population-Based Study

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**Purpose:** To evaluate the risk of stroke development after retinal vein occlusion (RVO).

**Design:** Nationwide, population-based 9-year longitudinal study.

**Participants:** National registry data were collected from the Korean National Health Insurance Research Database, comprising 1 025 340 (~2.2%) random subjects who were selected from 46 605 433 Korean residents in 2002.

**Methods:** Patients diagnosed with RVO or stroke in 2002 were excluded. The RVO group was composed of patients with an initial diagnosis of central or branch RVO between January 2003 and December 2005 (n = 344 in 2003, 375 in 2004, and 312 in 2005). The comparison group was composed of randomly selected patients (5 per patient with RVO; n = 1696 in 2003, 1854 in 2004, and 1524 in 2005) who were matched to the RVO group according to age, sex, residential area, household income, and year of RVO diagnosis. Each sampled patient was tracked until 2010. Cox proportional hazard regressions were used to calculate the overall survival rate for stroke development after adjusting for potential confounders, including hypertension, diabetes mellitus, and chronic kidney disease.

**Main Outcome Measures:** Retinal vein occlusion and ischemic or hemorrhagic stroke based on the International Classification of Disease codes.

**Results:** Stroke developed in 16.8% of the RVO group and in 10.7% of the comparison group. Retinal vein occlusion was associated with an increased risk of stroke development (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.24–1.76). Hypertension, diabetes mellitus, and chronic kidney disease also increased the risk of stroke development. In addition, RVO increased the risk of both ischemic stroke (HR, 1.51; 95% CI, 1.24–1.84) and hemorrhagic stroke (HR, 1.30; 95% CI, 0.83–2.05), although this result was not significant for hemorrhagic stroke. In terms of age, the effect size of the HR was largest among younger adults, aged <50 years (HR, 2.69), compared with middle-aged adults, aged 50 to 69 years (HR, 1.33), and older adults, aged ≥70 years (HR, 1.46).

**Conclusions:** Retinal vein occlusion was significantly associated with stroke development after adjusting for potential confounders. These findings are limited by uncontrolled confounding and need to be replicated by other observational studies. *Ophthalmology* 2015;122:1187–1194 © 2015 by the American Academy of Ophthalmology.

Retinal vein occlusion (RVO) is classified into central RVO (CRVO) and branch RVO (BRVO) and is a common cause of severe visual impairment.<sup>1</sup> Recently, the retinal vasculature has gained attention because traditional risk factors,<sup>2</sup> such as hypertension, diabetes, and cigarette smoking, are insufficient to fully explain stroke development.<sup>3</sup> The vasculature of the retina in the human eye is unique in that the retinal vessel can be directly and noninvasively visualized via indirect ophthalmoscopy. On the basis of the Atherosclerosis Risk in Communities study, retinal conditions, including signs of hypertensive retinopathy<sup>4</sup> and mild nonproliferative diabetic retinopathy,<sup>5</sup> were reported as risk factors for stroke. The retinal blood vessels display similar embryologic, anatomic, and physiologic characteristics as the cerebral vessels in the brain<sup>6</sup>; also, RVO has been reported as a

risk factor for stroke.<sup>7</sup> Several studies have examined the association between RVO and stroke, and the results have been inconsistent.<sup>8–15</sup> A large population-based study in the United States recently found that the event rate for cerebral vascular accidents in patients with RVO was increased approximately 2-fold relative to controls.<sup>16</sup> However, another nationwide population-based cohort study in Taiwan on the incidence of cerebrovascular disease observed no overall association between RVO and stroke.<sup>17</sup>

In this study, we investigated the association between RVO and the prospective risk of stroke development using this nationwide representative sample of 1 025 340 adults using the National Health Insurance Service National Sample Cohort 2002–2010 (NHIS-NSC 2002–2010) in South Korea.

## Methods

### Statement of Ethics

This study adhered to the tenets of the Declaration of Helsinki, and the NHIS-NSC 2002–2010 project was approved by the Institutional Review Board of the Korean National Health Insurance Service (KNHIS). This study design was reviewed and approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital, Gyeonggi-do, Korea. Written informed consent was waived.

### Database

In Korea, all nationals are obligated to enroll in the KNHIS. A total of 97% and 3% of the Korean population is covered by the Medical Assistance Program and the Medical Care for Patriots and Veterans Affairs Scheme, respectively. Thus, nearly all of the data in the health system are centralized in large databases. In Korea, patients with KNHIS pay approximately 30% of their total medical expenses when using medical facilities, and medical providers are required to submit claims for the remaining 70% of the medical expenses. Claims are accompanied by data regarding diagnostic codes, procedures, prescription drugs, personal information about the patient, information about the hospital, the direct medical costs of both inpatient and outpatient care, and dental services. No health care records of the patients were duplicated or omitted because all Korean residents have received a unique identification number at birth. This number is used by the Korean government for purposes related to the health care system. Further, the KNHIS uses the Korean Classification of Diseases (KCD), which is a similar system to the International Classification of Diseases (ICD).

### Study Sample

This study used an NHIS-NSC 2002–2010, which was released by the KNHIS in 2014. The data comprise 1 025 340 nationally representative random subjects, amounting to approximately 2.2% of the entire population in the KNHIS in 2002. The data were produced by the KNHIS using a systematic sampling method to generate a representative sample from all 46 605 433 Korean residents in 2002. This database includes all medical claims filed from January 2002 to December 2010.

An RVO group and a comparison group matched to age, gender, residential area, and household income were generated. The RVO group included all patients who received inpatient and outpatient care between January 2003 and December 2005 for an initial diagnosis of RVO (KCD code H34.8, corresponding to International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 362.35, CRVO, or 362.36, venous tributary [branch] occlusion). We excluded subjects who had been treated for RVO in ambulatory and inpatient care in 2002 ( $n = 586$ ) to exclude patients with chronic conditions and to ensure that the RVO group included subjects with new episodes only. For the same reason, patients who had a diagnosis of stroke in 2002 (KCD codes I60–I69, corresponding to ICD-9-CM codes 430–438, cerebrovascular disease) were also considered to have chronic conditions and were excluded (8549 subjects). We included the patients who were diagnosed with RVO before their stroke on the basis of the index date, which considers the incident date. Finally, 344, 375, and 312 eligible patients with RVO in 2003, 2004, and 2005, respectively, were identified after excluding potential pre-existing cases of both RVO and stroke. These cases were regarded as new incident cases of RVO. We selected 5074 patients (5 per patient with RVO; 1696 in 2003, 1854 in 2004, and 1524 in 2005) from the database of 1 025 340 patients who were matched to the

RVO group in terms of age, gender, residential area, and household income.

### Definition of Stroke

Each patient was tracked on the basis of his or her index dates of ambulatory and inpatient care visits over the 8 years from 2003 to 2010 to detect those patients who developed stroke (KCD codes I60–63, corresponding to ICD-9-CM codes 430–438, cerebrovascular disease). For subgroup analysis, stroke was categorized into 2 types: ischemic stroke (KCD code I63, corresponding to ICD-9-CM codes 433–434, occlusion and stenosis of precerebral arteries, and occlusion of cerebral arteries) and hemorrhagic stroke (KCD codes I60–I62, corresponding to ICD-9-CM codes 430–432, subarachnoid hemorrhage, intracerebral hemorrhage, and other and unspecified intracranial hemorrhage).

### Independent Variables

The regression models were adjusted for the patient's age (<40, 40–49, 50–59, 60–69, 70–79, or  $\geq 80$  years), sex, household income ( $\leq 30\%$ , 30%–60%, 60%–90%,  $> 90\%$  of the median), and geographic location according to 4 regions (Seoul, a metropolitan area in Korea; large city; small city; and rural area). Comorbidities, such as hypertension, diabetes mellitus, and chronic kidney disease, diagnosed on the basis of the KCD, may be associated with an increased risk of stroke.<sup>18–21</sup> We defined these comorbidities as any diagnoses between 2003 and 2010.

### Statistical Analysis

Descriptive statistics of the study population are presented, and chi-square tests were performed to examine the differences between the 2 groups. A 2-step, multidimensional approach was used to identify the association between RVO and the prospective development of stroke. First, to identify the hazards associated with stroke, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated via univariate Cox proportional hazard regression. Second, multivariate Cox proportional hazard regression was performed to determine the adjusted HR of prospective stroke development after adjusting for confounding comorbidities and sociodemographic characteristics. The overall survival rate was calculated using the Kaplan–Meier curve for the 8-year follow-up period, and the log-rank test was performed to examine the differences in stroke development between the RVO and comparison groups. A significance level of 0.05 was selected. The statistical packages SAS System for Windows, version 9.4 (SAS Inc, Cary, NC), and Stata/SE version 13.1 (StataCorp LP, College Station, TX) were used to perform the analyses in this study.

## Results

**Table 1** displays the characteristics of the study population for the 2 cohorts: the RVO group and the comparison group. The subjects with RVO were more likely to experience stroke ( $P < 0.001$ ), hypertension ( $P < 0.001$ ), diabetes mellitus ( $P < 0.001$ ), and chronic kidney disease ( $P < 0.001$ ) compared with the comparison group. No significant difference in year of RVO diagnosis, age, sex, residential area, or household income was detected between the 2 groups; because these variables were used for sample matching, this finding indicates that the matching was appropriately performed.

**Table 2** displays the HR for stroke during the 8-year follow-up period using univariate and multivariate Cox regression models.

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