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INTRAVITREAL RANIBIZUMAB THERAPY FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AND THE RISK OF STROKE

A National Sample Cohort Study

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Purpose: To evaluate the risk of stroke after ranibizumab treatment for neovascular age-related macular degeneration.

Methods: National registry data for 1,025,340 random subjects in the year 2002 were used. The ranibizumab group comprised patients diagnosed with neovascular age-related macular degeneration and treated with ranibizumab between 2009 and 2013 (n = 467). The two types of comparison groups were defined as comorbidity-matched controls (n = 2,330) comprised of randomly selected patients (5 per age-related macular degeneration patient), who were matched to the ranibizumab group according to sociodemographic factors, hypertension, atrial fibrillation, and the Charlson comorbidities index, and sociodemographic-matched controls (n = 2,331) matched according to sociodemographic factors only. Each sampled patient was tracked until 2013. The Cox proportional hazard regression was used.

Results: Stroke occurred in 6.6% of the ranibizumab group versus 7.0% of the comorbidity-matched controls and 6.7% of the sociodemographic-matched controls; these differences were not statistically significant. The overall incidence of stroke was similar for the ranibizumab group versus the comorbidity-matched controls and sociodemographic-matched controls, based on the multivariable Cox regression (hazard ratio = 0.88; 95% confidence interval, 0.60–1.30; hazard ratio = 0.95, 95% confidence interval, 0.64–1.41, respectively).

Conclusion: Ranibizumab treatment for neovascular age-related macular degeneration did not increase the overall risk of stroke, compared with comorbidity-matched controls or sociodemographic-matched controls.

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Neovascular age-related macular degeneration (AMD) is the leading cause of vision loss. Although neovascular AMD itself has been evaluated as a risk factor for stroke, the link between neovascular AMD (not early AMD) and stroke has not been conclusively established; studies thereon have only been conducted in a small number of patients with neovascular AMD or late AMD.[1,2] A study during 1999 to 2001 in Taiwan, which included 209 patients with neovascular AMD and their controls, reported that the risk of stroke is higher for patients with neovascular AMD than for patients without neovascular AMD. In addition, 15,771 U.S. Medicare beneficiaries with neovascular AMD during 2001 to 2003 had a similar incidence of ischemic stroke compared with 46,408 matched controls.[3] Because anti–vascular endothelial growth factor (VEGF) is the current treatment of choice for neovascular AMD, it is difficult to separately assess anti-VEGF treatment and neovascular AMD.[4] Although severe adverse effects such as stroke are a concern after intravitreal anti-VEGF treatment, previous studies have established the systemic safety of ranibizumab use.[4–10] Nonetheless, evaluation of stroke as an adverse effect of ranibizumab treatment has been difficult, because patients with neovascular AMD can have highly comorbid conditions that are associated with an increasing risk of stroke.[11] To overcome these potential confounding parameters, we chose 2 separate control groups:

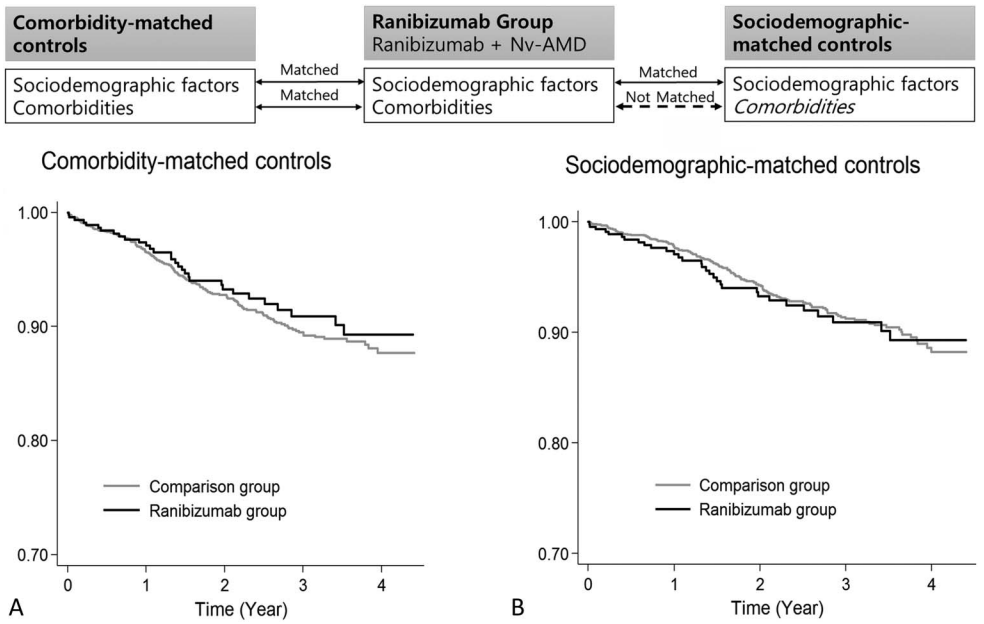

Fig. 1. Stroke-free survival incidences for the ranibizumab group versus the comorbidity-matched controls **(A)** or sociodemographic-matched controls **(B)**. The overall stroke risk for the ranibizumab group was similar to both the comorbidity-matched controls and the sociodemographic-matched controls. Nv-AMD, neovascular age-related macular degeneration.

sociodemographic-matched controls without adjustment for comorbidities, and sociodemographic- and comorbidity-matched controls. In this study, we evaluated the risk of stroke after ranibizumab treatment for neovascular AMD. The cohorts were extracted from a nationwide representative sampling of 1,025,340 subjects documented in the National Health Insurance Service National Sample Cohort 2002 to 2013 (NHIS-NSC 2002 to 2013) of South Korea.

Methods

Statement of Ethics

This study adhered to the tenets of the Declaration of Helsinki, and the NHIS-NSC 2002 to 2013 project was approved by the Institutional Review Board of the Korean National Health Insurance Service (KNHIS). Written informed consent was waived. The design of this study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea.

Database

All individuals in South Korea are required to enroll in the KNHIS. Thus, almost all data in the health insurance system are centralized in large databases. Claims are accompanied by data regarding diagnostic codes, procedures, prescription drugs used, and personal information such as residence, income, age, and gender. All claims are exchanged through the Korean Electronic Data Interchange code. The health care claim data are not duplicated or omitted, because a unique identification number is assigned to for each Korean resident at birth, and this number is used by the Korean government. Furthermore, the KNHIS uses diagnostic codes based on the Korean Classification of Diseases (KCD), which is similar to the International Classification of Diseases (ICD). This study used the NHIS-NSC 2002 to 2013 database, which was released by the KNHIS in 2015.[12] The data comprised 1,025,340 representative random subjects, which was

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S. S. Kim and S. C. Lee had the original idea for this study and contributed to the study design. T. H. Rim contributed to the development of the idea and study design and undertook the primary analysis. T. H. Rim, C. S. Lee, and D. W. Kim reviewed the literature, and wrote the draft of the paper. T. H. Rim, C. S. Lee, S. C. Lee, D. W. Kim, and S. S. Kim interpreted the results. S. C. Lee and S. S. Kim critically reviewed the paper. All authors approved the submitted version.

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approximately 2.2% of the entire population of the KNHIS database in 2002. The data were produced by the KNHIS using a systematic sampling method to generate a representative sampling from all 46,605,433 Korean residents in 2002. Proportionate stratified random sampling was used based on total 1,476 strata (2 categories for gender, 18 categories for age groups, and 41 categories for income). This database included all nationally insured medical claims filed from January 2002 to December 2013.

Ranibizumab Use in South Korea

The use of ranibizumab (0.5 mg only) began in July 2007, after its approval by the Korean Food and Drug Administration for the treatment of patients with neovascular AMD. However, for about 2 years, from July 2007 to July 2009, the national health insurance did not reimburse for ranibizumab treatment; therefore the NHIS-NSC 2002 to 2013 database does not include ranibizumab data during this period. Starting at the end of July 2009, neovascular AMD was classified as a "rare disease" by the Korean Ministry of Health and Welfare. Patients benefited from a "copayment assistance policy" from the national health insurance, and the cost was decreased to a 10% deductible. Before considering the exclusion criteria of this study, Supplementary digital content 1 shows 562 new monthly uses of ranibizumab from August 2009 to December 2013 in our study population. After initiation of a "copayment assistance policy" in August 2009, chronic patients who were diagnosed with neovascular AMD were included, which would explain the slightly higher incidences at the beginning of the study period (see **Figure, Supplemental Digital Content 1**, http://links.lww.com/IAE/A551).

The Korean Health Insurance Review and Assessment Service reviews all ranibizumab use, based on fundus photography and fluorescein angiography, and reimburses the remaining 90% of the ranibizumab cost to the medical provider; therefore ranibizumab use indicates that the patients have active neovascular (wet) AMD. In Korea, bevacizumab use is not approved for neovascular AMD by the Korean Food and Drug Administration. However, off-label intravitreal injections of bevacizumab have been widely used to treat neovascular AMD. Because bevacizumab use is not covered by national insurance, the NHIS-NSC 2002 to 2013 database does not include data on bevacizumab treatment for neovascular AMD.

Study Sample

Inclusion criteria were defined as follows: middle aged and older (≥50 years); all patients who received ranibizumab treatment from inpatient and outpatient care centers between August 2009 and December 2013 (ranibizumab group); randomly selected patients (5 per ranibizumab group patient) who were matched according to sociodemographic factors, hypertension, atrial fibrillation, and the Charlson comorbidity index (comorbidity-matched controls); and randomly selected patients (5 per ranibizumab group) who were matched according to sociodemographic factors only (sociodemographic-matched controls).

Exclusion criteria were defined as follows: patients diagnosed with acute and chronic cerebrovascular disease from 2004 to 2008 (KCD code I60-I69, corresponding to ICD-9-CM code 430–438, cerebrovascular disease including late effects), which were considered as chronic conditions; patients with stroke before ranibizumab treatment based on the patient's date of visit; and patients diagnosed at an eye clinic with "other retinal disorder" (KCD code H34-H36, corresponding to ICD-9-CM code 362, [see **Table, Supplemental Digital Content 2**, http://links.lww.com/IAE/A551] lists the other retinal disorders in detail) to exclude use of bevacizumab in the control group, because bevacizumab use for AMD was not covered by national insurance and not included in the database. Therefore, bevacizumab use for retinal diseases such as AMD, diabetic macular edema, or retinal vein occlusion was excluded from the control group.

Sociodemographic factors included age (50–64, 65–69, 70–74, 75–79, and ≥80 years of age), gender, residential area (1) Seoul, a metropolitan area in Korea; 2) the largest province; 3) the second largest city and second and third largest provinces; and other areas), and 4) household income (≤30%, 30–70%, and ≥70% of the national median income). Hypertension, atrial fibrillation, and the Charlson comorbidity index (including a total of 16 comorbidities, based on KCD) for 5 years (2004–2008). Acquired immune deficiency syndrome was excluded because it is not included in the NHIS-NSC 2002 to 2013 database for privacy protection. **Supplemental Digital Content 3**, (see **Table**, http://links.lww.com/IAE/A551) lists the comorbidities in detail. Finally, 467 eligible ranibizumab-treated patients from August 2009 to December 2013 were identified after excluding potential preexisting cases of stroke. Each patient was tracked until December 2013, to identify patients with newly developed stroke (KCD code I60-I63, corresponding to ICD-9-CM code 430–434, cerebrovascular disease).

Statistical Analysis

Descriptive statistics of the study population were recorded, and the Chi-square test was used to determine

possible differences between the ranibizumab group and the matched control groups. Propensity score matching was performed. We calculated the propensity scores by conducting logistic regression to predict ranibizumab treatment using, and thus controlling for, sociodemographic factors, comorbidities, and year of enrollment. Five-to-one matching was also performed, adjusting for confounders using greedy algorithms (8→1) with the estimated propensity scores. Hazard ratios (HRs) and 95% confidence interval (CIs) were calculated using multivariable Cox proportional hazard regression analyses to determine the adjusted HR of prospective stroke development after adjusting for confounding comorbidities and sociodemographic factors. The proportional hazards assumption was assessed by a Cox model with Schoenfeld residuals, and the assumption was not violated. The overall stroke-free incidence was determined using the Kaplan–Meier curve for the approximate 5 years follow-up period from August 2009 to December 2013. A significance level of 0.05 was selected. The statistical packages SAS System for Windows, version 9.4 (SAS Institute Inc, Cary, NC) and Stata/MP2, version 14.0 (StataCorp, College Station, TX) were used to perform the analyses.

Results

Mean follow-ups for ranibizumab group, comorbidity-matched controls, and sociodemographic-matched controls were 2.13 (1 day–4.40) years, 2.00 (1 day–4.41) years, and 2.06 (1 day–4.40), respectively. There were no differences in follow-up period between the ranibizumab group and comorbidity- and sociodemographic-matched controls (P = 0.175, and 0.760, respectively). In comparison with the comorbidity-matched controls, a total of 5,664 person-years (1,010 person-years for the ranibizumab group and 4,654 person-years for the comorbidity-matched controls) were examined (Table 1). Strokes occurred in 30.7 and 35.2 per 1,000 person-years for the ranibizumab group and the comorbidity-matched controls, respectively. In comparison with the sociodemographic-matched controls, a total of 5,823 person-years (1,010 person-years for the ranibizumab group and 4,813 person-years for the sociodemographic-matched controls) were examined. Stroke occurred in 30.7 and 28.9 per 1,000 person-years for the ranibizumab group and the sociodemographic-matched controls, respectively.

Supplemental Digital Content 4, (see **Table**, http://links.lww.com/IAE/A551) shows the characteristics of the study populations for the 3 cohorts comprised of the ranibizumab group (n = 467), the comorbidity-matched controls (n = 2,330), and the sociodemographic-matched controls (n = 2,331). Stroke occurred in 6.6% of the ranibizumab group versus 7.0% of the comorbidity-matched controls and 6.0% of the sociodemographic-matched controls; these differences were not statistically significant. When comparing the ranibizumab group and the

Table 1. Incidence of Stroke Occurrence in the Ranibizumab Group and the Comparison Group for the Whole Population and Each Subgroup

	Comorbidity-Matched Controls				Sociodemographic-Matched Controls				Ranibizumab Group			
	N	Cases	PY	Incidence	N	Cases	PY	Incidence	N	Cases	PY	Incidence
Whole cohort	2,330	164	4,654	35.2	2,331	139	4,813	28.9	467	31	1,010	30.7
Age group, years												
50–69	1,001	29	2,040	14.2	1,040	39	2,192	17.8	202	9	435	20.7
≥70	1,329	135	2,614	51.6	1,291	100	2,620	38.2	265	22	576	38.2
Gender												
Male	1,459	87	2,863	30.4	1,484	85	2,976	28.6	297	13	643	20.2
Female	871	77	1,791	43.0	847	54	1,836	29.4	170	18	368	49.0
Charlson comorbidity index												
0–1	1,234	81	2,264	35.8	1,553	64	3,116	20.5	251	12	501	23.9
≥2	1,096	83	2,391	34.7	778	75	1,697	44.2	216	19	509	37.3
Hypertension												
No	1,195	64	2,280	28.1	1,444	72	2,835	25.4	252	13	523	24.9
Yes	1,135	100	2,375	42.1	887	67	1,977	33.9	215	18	487	36.9
Diabetes mellitus												
No	1,847	119	3,644	32.7	1,953	103	3,981	25.9	362	22	755	29.2
Yes	483	45	1,011	44.5	378	36	831	43.3	105	9	256	35.2

Incidence rate per 1,000 person-years.
PY, person-years.

sociodemographic-matched controls, patients treated with ranibizumab were more likely to have hypertension ($P = 0.001$), atrial fibrillation ($P = 0.025$), and higher comorbidity index ($P < 0.001$). There were no significant differences in variables between the ranibizumab group and comorbidity-matched controls, and no significant differences in variables except comorbidities between the ranibizumab group and the sociodemographic-matched controls. Because these variables were used for sample matching, the findings indicate that matching was appropriately performed. **Supplemental Digital Content 5** (see **Table**, http://links.lww.com/IAE/A551) lists all comorbidities in detail, and shows no difference between the ranibizumab group and the comorbidity-matched controls in any comorbidity. However, in comparison with the sociodemographic-matched controls, patients in the ranibizumab group were more likely to have myocardial infarction, chronic pulmonary diseases, peptic ulcer, mild liver diseases, uncomplicated diabetes, complicated diabetes, and cancer.

Table 2 shows HRs for overall incidences of stroke, using multivariable Cox regression analysis. After adjusting for age, gender, residence, household income, and comorbidities, the ranibizumab group was not significantly associated with higher subsequent stroke occurrence compared with the comorbidity-matched controls (HR = 0.88; 95% CI, 0.60–1.30). Atrial fibrillation was significantly associated with the occurrence of stroke. Compared with the sociodemographic-matched control group, patients in the ranibizumab group did not have increased risk of prospective occurrence of stroke (HR = 0.95, 95% CI, 0.65–1.41). Atrial fibrillation and an increasing Charlson comorbidity index were also significantly associated with the occurrence of stroke. Using univariable Cox regression analysis, **Supplemental Digital Content 6** (see **Table**, http://links.lww.com/IAE/A551) shows that the ranibizumab group was not associated with higher subsequent stroke occurrence, compared with the comorbidity-matched controls or sociodemographic-matched controls.

Figure 1 shows the results from Kaplan–Meier survival curves. Figure 1A shows that the stroke-free incidence decreased in a similar manner for the ranibizumab group and the comorbidity-matched control group. The cumulative stroke-free incidences for the ranibizumab group in Figure 1, A and B are the same. The curve for stroke-free incidence in the ranibizumab group is slightly higher than the curve for the comorbidity-matched controls in Figure 1A and slightly lower than that for the sociodemographic-matched controls in Figure 1B. However, these differences were not statistically significant, based on the adjusted HRs shown in Table 2.

On subgroup analysis, ranibizumab use was not associated with stroke in all subgroups in Figure 2. The effect sizes (≈HR) were similar to that for the whole cohort (HR = 0.88 based on comorbidity-matched controls and 0.95 based on sociodemographic-matched controls), regardless of the presence of chronic disease (hypertension or diabetes mellitus). The risk of stroke was slightly greater in subjects of 50 to 69 years of age (HR = 1.58) than in subjects of ≥70 years of age (HR = 0.76) in comparisons with comorbidity-matched controls, and was also greater in females (HR = 1.46) than in males (HR = 0.66) in comparisons with sociodemographic-matched controls.

Discussion

In this study, the overall incidence of stroke was similar for the ranibizumab group when compared

Table 2. Multivariable Cox Regression Analyses for Overall Incidences of Stroke Between the Ranibizumab Group and the Comparison Groups After Adjusting for Sociodemographic Factors

	Comorbidity-Matched Controls			Sociodemographic-Matched Controls		
Variables	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Group						
Comparison group	1(ref)			1(ref)		
Ranibizumab group	0.88	0.60–1.30	0.527	0.95	0.65–1.41	0.818
Hypertension						
Not event	1(ref)			1(ref)		
Event	1.08	0.80–1.46	0.627	0.95	0.69–1.31	0.749
Atrial fibrillation						
Not event	1(ref)			1(ref)		
Event	2.79	1.52–5.12	0.001	2.36	1.09–5.12	0.030
Charlson comorbidity index						
1 grade increases	0.98	0.88–1.09	0.687	1.20	1.08–1.35	0.001

Comorbidity-matched controls are the sociodemographic- and comorbidity-matched controls.

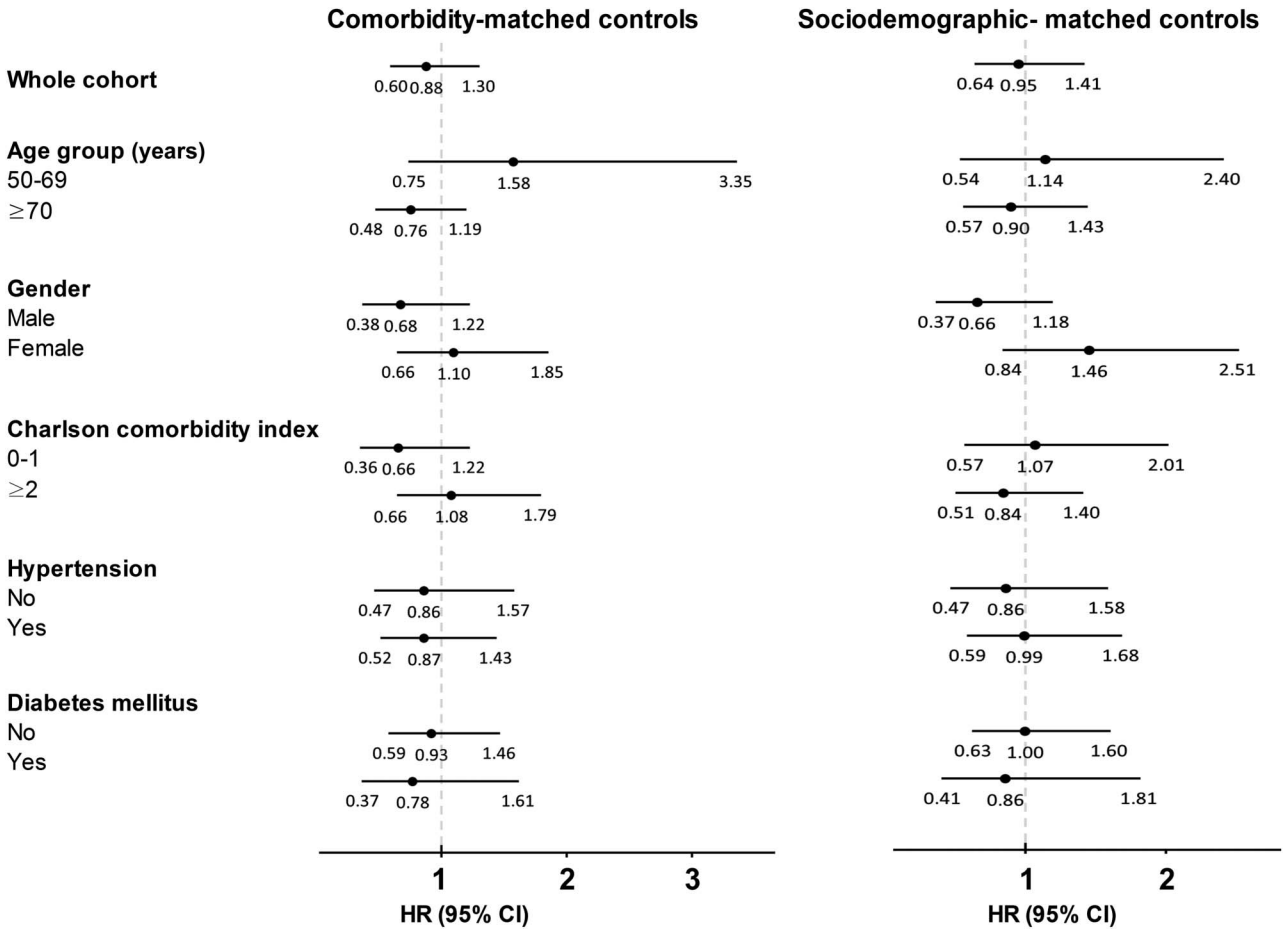

Fig. 2. Risk of stroke occurrence in the ranibizumab group and the comparison group. Hazard ratios (HRs) were calculated based on multivariable Cox regression after adjustment for sociodemographic factors and comorbidities.

with the comorbidity-matched controls and the sociodemographic-matched controls. Patient who underwent ranibizumab treatment were more likely than their sociodemographically matched peers to have comorbidities.

Ranibizumab treatment for neovascular AMD was the only difference between the ranibizumab group and comorbidity-matched controls shown in Figure 1A. Other sociodemographic factors and severities of comorbidities were also matched. In this comparison, stroke-free incidence was similar or slightly lower in the ranibizumab group (30.7 vs. 35.2 per 1,000 person-years, Table 1), suggesting that ranibizumab use and neovascular AMD does not increase the risk of stroke. The observation that "ranibizumab use for neovascular AMD" was not associated with stroke is not the same as "ranibizumab use" was not associated with stroke and "neovascular AMD" was not associated with stroke. However, unless one factor is increasing the risk and the other is decreasing the risk, it would be correct to conclude that neither factor was independently increasing the risk of stroke. Moreover, because anti-VEGF treatments including ranibizumab are considered the first-line treatment for neovascular AMD, it is impossible to separately evaluate whether neovascular AMD or ranibizumab use is associated with stroke risk. Currently, there are no reports that ranibizumab use and/or neovascular AMD is associated with decreased risk of stroke. Therefore, the above interpretation is appropriate. Figure 1B shows possible risk factors for stroke for the ranibizumab group and the sociodemographic-matched controls. Sociodemographic factors including age, gender, income, and residence were matched, whereas comorbidities were not matched. In this comparison, the stroke-free survival curve of the ranibizumab group was slightly lower than that of the comparison group, and these results were consistent with the observation that stroke occurred slightly more frequently in the ranibizumab group than in the sociodemographic-matched controls (30.7 vs. 28.9 per 1,000 person-years, Table 1). However, these differences were not statistically significant on multivariable Cox regression analysis (Table 2).

Comorbidities of hypertension,[13] diabetes mellitus,[14,15] hypercholesterolemia,[15] and myocardial infarction[13,15] have been evaluated as risk factors for neovascular AMD. With the exception of mental disorders, a retrospective case–control study that included 26,057 Medicare beneficiaries reported that patients with neovascular AMD were more likely to be diagnosed with all 13 disease categories, based upon the ICD, ninth Revision, Clinical Modification. High comorbidity was also observed in patients with neovascular AMD in this study (see **Tables, Supplemental Digital Content 4 and 5**; http://links.lww.com/IAE/A551). Atrial fibrillation, one of the most important risk factors for stroke, was almost twice as frequent in the ranibizumab group (2.4%) as in the sociodemographic-matched controls (1.3%, Supplementary digital content 4). Myocardial infarction was also more frequent for the ranibizumab group (1.9% vs. 0.7% in controls, see **Table, Supplemental Digital Content 5**; http://links.lww.com/IAE/A551). Subgroup analysis for stroke risk among subjects with atrial fibrillation or myocardial infarction was impossible, as patients with these diseases were very uncommon (≈2%). For other diseases, such as diabetes mellitus and a higher Charlson comorbidity index of ≥2, the effect sizes (≈HRs) were similar to those of the whole cohort and did not increase the risk of stroke, regardless of the presence of each disease in our subgroup analysis (Figure 2). A relatively small incidence of stroke among individuals 50 to 69 years of age among the comorbidity-matched controls (14.2 per 1,000 person-years) and among females among sociodemographic-matched controls (29.4 per 1,000 person-years) was found to generate slightly higher HRs for stroke, as shown in Figure 2. In our exploratory analysis of p for interaction based on the interaction term (ranibizumab use and age group using comorbidity-matched controls; ranibizumab use and gender using sociodemographic-matched controls) from the multivariable analysis, the *P* for interaction was 0.119 in comparison with comorbidity-matched controls and 0.050 in comparison with sociodemographic-matched controls, respectively. However, the risk of stroke by ranibizumab use was not large enough to compare the comorbidity-matched controls and the sociodemographic-matched controls for younger age group and female with the wide CIs.

In this study, the incidence of stroke of 30.7 per 1,000 person-years for the ranibizumab group was similar to that of controls (35.2 for comorbidity-matched controls, and 28.9 for sociodemographic-matched controls per 1,000 person-years, Table 1); however, the absolute number of strokes was relatively high. This means that in practice, a retinal specialist should see several stroke occurrences within 1 year after the initial neovascular AMD treatment. The well-known traditional risk factor for stroke atrial fibrillation was independently associated with an approximately 3-fold increase in stroke on multivariable analysis (Table 2). An increasing Charlson comorbidity index was also associated with increased stroke risk (HR = 1.20 per 1 grade increases, Table 2). Proper screening for comorbidities, particularly atrial fibrillation in patients with neovascular AMD, is therefore recommended.

A study performed in Taiwan showed an association between neovascular AMD and stroke, but another study performed in the United States with 15,771 Medicare beneficiaries diagnosed with neovascular AMD from 2001 to 2003 showed no association between the 2 diseases.[3] The safety of anti-VEGF use remains a controversial topic. The safety of ranibizumab was evaluated in several studies, and almost all studies reported the systemic safety of ranibizumab use. These studies were originally designed to evaluate the effect of ranibizumab for neovascular AMD; they were not designed to evaluate adverse effects. These studies were limited in their capabilities to evaluate the risk of stroke because of a relatively small number for stroke events during the study period.[4–10] An interim analysis of SAILOR suggested the possibility of an increased risk of cerebrovascular accident (CVA), associated with 0.5 mg ranibizumab treatments than with 0.3 mg treatments, with a higher incidence of stroke in the 0.5 mg treatment group (1.2% in the 0.5 mg group vs. 0.3% in the 0.3 mg group, $P = 0.02$).[16] At the conclusion of the study, the differences were much less pronounced. A brief meta-analysis based on 3 well-known trials (FOCUS, MARINA, and ANCHOR) and a meta-analysis based on 5 well-known trials (FOCUS, MARINA, ANCHOR, PIER, and SAILOR) reported an increased risk of CVA in subjects receiving ranibizumab injections. However, the results were not statistically significant, with a wide range in the CIs as a limitation.[17–19] Recently, another meta-analysis based on 21 trials reported that anti-VEGF treatment does not significantly increase the risk of nonocular hemorrhagic events. However, the authors of this study included anti-VEGF treatment for AMD, diabetic macular edema, and retinal vein occlusion, and emphasized that the meta-analyses were not sufficient to correctly assess these risks because of different comorbidities in the patient population and small sample size. These clinical trials and their meta-analyses were therefore not sufficient to definitively determine whether ranibizumab use was a risk factor for stroke.

In a retrospective cohort study of Medicare patients receiving treatment for AMD, no difference in the risk

of stroke or hemorrhage was observed for bevacizumab- or ranibizumab-treated patients, compared with patients receiving pegaptanib or photodynamic therapy.[20] In addition, a population-based study performed in an Australian cohort comprised of controls and 1,267 patients receiving anti-VEGF treatment reported no difference in the incidence of stroke between the 2 groups.[21] A nested case–control study compared the incidence of stroke during a 180-day period between patients receiving anti-VEGF treatment and controls, and found no difference in the incidence of stroke.[22] A study evaluating trends in the incidence of strokes among patients diagnosed with retinal diseases reported no change in the stroke incidence after the first use of anti-VEGF.[23] A self-controlled case series using 323 patients receiving ranibizumab reported an increased risk of hospitalization for stroke in patients treated with ranibizumab during a 31 to 60 days risk period. Finally, almost all recent, well-designed population-based studies have shown no association between anti-VEGF use, including ranibizumab and bevacizumab, and stroke.

The strengths of this study include 1) a relatively large sample size for a rare disease in South Korea, neovascular AMD; 2) a relatively long follow-up period with more than 5,600 person-years; 3) an analysis performed using nationwide samples rather than a hospital-based study; and 4) two separate control groups through which nonassociation was confirmed (patients with neovascular AMD can have highly comorbid conditions).

Study Limitations

Limitations of this study include 1) the possible use of bevacizumab for patients with neovascular AMD and control group patients was not included in our study, because of unreported data from the national health insurance database; 2) patients with chronic neovascular AMD at the beginning of the study period were included, which might add to the heterogeneity of the disease status that includes both chronic and new diagnoses of neovascular AMD; 3) the possibility of misclassification of disease diagnoses; 4) possible underreporting of asymptomatic neovascular AMD, stroke, or comorbidities; 5) the possibility of delayed visits to the ophthalmologist or physician, and delayed diagnoses of neovascular AMD or stroke; 6) the inability to collect other important health-related information such as smoking; 7) the possibility that the medical claim database might have included biased controls compared with general population-based controls who neither received medical care nor had a specific diagnosis; and 8) the possibility that, cultural differences, or disease pattern differences, such as those for polypoidal choroidal vasculopathy, could exist in the South Korean population.[24]

The most important limitation of this study was that the national insurance only covered the use of ranibizumab that was included in the database; therefore, several different situations are possible: 1) some patients received bevacizumab in 2008, but the regimen changed to ranibizumab in August 2009 when the national health insurance started to cover ranibizumab by the "copayment assistance policy"; 2) only five injections of ranibizumab per person were compensated at the beginning of the "copayment assistance policy" (now 14 injections), therefore, bevacizumab might have been used after five injections; and 3) The Korean Health Insurance Review and Assessment Service reviewed all uses of ranibizumab, and if there was no improvement after three loading injections and no more assistance was possible, bevacizumab might have been used. However, even with respect to these various possibilities, the use of ranibizumab was strictly limited to the active stage of neovascular (wet) AMD, based on fluorescein angiography, and therefore the specificity is very high for ranibizumab-treated neovascular AMD in this study. Nevertheless, bevacizumab use in the ranibizumab group may cause inaccuracies in terms of a mixed effect of bevacizumab and ranibizumab. Because of this uncontrolled bevacizumab use, analysis of the chronic use or duration of use of ranibizumab and/or bevacizumab is a major limitation of this study, although additional analyses showed that the number of ranibizumab injections was not associated with stroke (data not shown). Our results may imply that ranibizumab use, including partial bevacizumab use, does not increase the risk of stroke. To firmly exclude anti-VEGF use in controls, ophthalmology patients with a diagnosis of any "other retinal disorder" were excluded from the control group. "Other retinal disorders" included almost all diseases treated with anti-VEGF, such as AMD, diabetic macular edema, and retinal vein occlusion. By excluding these patients, the likelihood that the control groups included patients treated with anti-VEGF was very small. Immortal time bias might exist, however: there may have been patients who received anti-VEGF therapy before 2009 and started ranibizumab therapy from 2009 as covered by national health insurance. Nevertheless, we excluded patients who were diagnosed with acute and chronic cerebrovascular diseases from 2004 to 2008, for 5 years, in both the ranibizumab and control groups. This relatively long period might reduce immortal time bias. The diagnoses of stroke and comorbidities were defined based on KCD codes, which may be inaccurate compared with the diagnoses obtained from a medical chart, including imaging results. Using the medical insurance claims data, the validity of these data is important in applications of actual clinical practice, even though the possibility of

miscoding for several reasons cannot be excluded. However, the miscoding of diagnoses might occur at similar rates in the ranibizumab group and in the comparison group. In addition, we excluded patients with CVA before enrollment. Therefore, further study is needed to evaluate whether ranibizumab use among patients with prior CVA history increases the risk of newly developed CVA.

In conclusion, we suggest that ranibizumab use and/or neovascular AMD are not associated with an increased risk of stroke, as determined by analyses using sociodemographic-and comorbidity-matched controls. Our data are consistent with other published observations that neovascular AMD is associated with other comorbidities such as hypertension and asymptomatic atrial fibrillation, which are also associated with CVA. Anyone with AMD, regardless of ranibizumab use, should be evaluated for such comorbidities and should understand that, if present, they increase their risk of CVA. Our findings may have been limited by uncontrolled confounding factors and must be replicated by other observational studies.

Key words: age-related macular degeneration, NHIS-NSC 2002 to 2013, ranibizumab, stroke.

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