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Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion

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Purpose: To investigate the risk of stroke and acute myocardial infarction (AMI) in patients with incident central retinal artery occlusion (CRAO).

Design: A self-controlled case series (SCCS) study.

Participants: Patients with incident CRAO from the entire Korean population of 48 million individuals.

Methods: We used the Korean national claim database (2007–2011) for analyses. After identifying patients with incident CRAO, the relative incidence rate ratios (IRRs) for stroke and AMI in risk periods were measured in these patients using a SCCS method.

Main Outcome Measures: The IRRs of stroke and AMI by risk periods.

Results: Of 1655 patients with incident CRAO in 2009–2010, 165 had stroke/AMI (ischemic stroke in 139, hemorrhagic stroke in 13, and AMI in 15) in the observation period spanning 365 days before and after the occurrence of CRAO. The IRR of stroke/AMI 1 to 30 days after CRAO occurrence significantly increased (14.0; 95% confidence interval [CI], 8.90–22.00); the IRR peaked during the 1 to 7 days after CRAO occurrence (44.51; 95% CI, 27.07–73.20), and the increased risk was present for the first 30 days. The IRR of stroke/AMI also significantly increased 1 to 30 days (6.82; 95% CI, 4.01–11.60) and 31 to 90 days (2.86; 95% CI, 1.66–4.93) before CRAO occurrence. Subanalysis for only ischemic stroke showed similar, magnified IRRs in the risk periods compared with all events. The IRRs were not significantly different between sexes or age groups (<65 vs. ≥65 years).

Conclusions: Patients with incident CRAO are at increased risk of ischemic stroke just after CRAO occurrence, and the risk is particularly increased during the first week immediately after the CRAO occurrence. The results suggest that patients with incident CRAO require immediate neurologic evaluation and preventive treatment to reduce mortality and morbidity. *Ophthalmology 2015;■:1–8 © 2015 by the American Academy of Ophthalmology.*

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Central retinal artery occlusion (CRAO), an ocular analogue of stroke, typically presents as sudden, severe, and painless visual loss.[1,2] In addition to the similarities in pathogenesis, CRAO and stroke share risk factors[3] and show similar incidence patterns with respect to age (incidence increases with increasing age and peaks at age 80–84 years) and sex (predominance of men).[2,4,5] Therefore, several studies have reported an association between retinal artery occlusion (RAO) and stroke.[3,6–8] An association between CRAO and acute myocardial infarction (AMI) also has been suggested[3,9,10] because they share risk factors,[3] pathogenesis (e.g., atherosclerosis and thromboemboli lodged in the lumen of coronary arteries),[11] and incidence pattern characteristics.[2,4,5]

However, data are scarce regarding the temporal characteristics of the risk for stroke and AMI in patients with CRAO, which is essential to reduce mortality and morbidity.[12] Central retinal artery occlusion is a rare condition,[2] and longitudinal databases containing sufficient information regarding stroke and AMI events and comorbidities are scarce. Despite recommendations by guidelines that patients with retinal ischemia should have immediate brain imaging and sufficient evaluation for modifiable conditions to reduce mortality and morbidities,[13] only one-third of ophthalmologists transfer patients with incident CRAO to an emergency department for immediate evaluation.[14]

Therefore, this study aimed at evaluating the risk for stroke and AMI and the temporal characteristics of that risk in patients with CRAO using a self-controlled case series (SCCS) design with data from the national claims database covering the entire Korean population of 48 million individuals, with which we previously conducted a study regarding CRAO incidence.[2]

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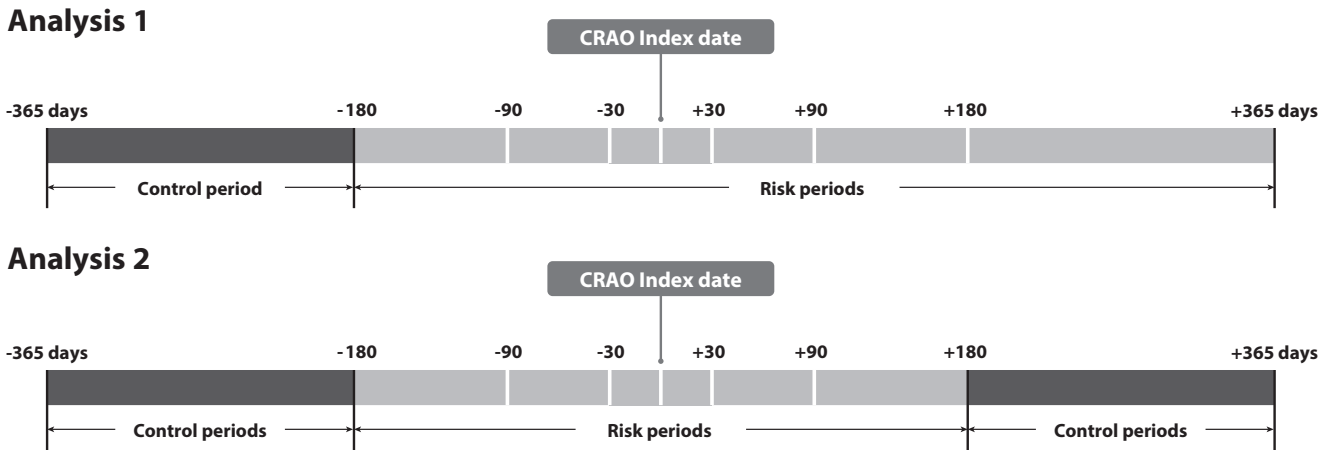

Figure 1. Self-controlled case series analyzing the association between central retinal artery occlusion (CRAO) and stroke or acute myocardial infarction. The incidence rate ratio was measured using 2 different analyses. Both analyses included days 181−365 before the index date as a control period. Analysis 2 also included days 181−365 after the index date as a control period.

Methods

Database and Participants

We accessed health claims from the years 2007−2011 in the database of the national Health Insurance Review and Assessment (HIRA) service of Korea; results from this data set have also been published for incidence studies of rhegmatogenous retinal detachment,[15] retinal vein occlusion,[16] and CRAO.[2] In brief, the HIRA reviews all of the health claims in Korea, including those submitted through the Korean National Health Insurance scheme, which covers 97% of the population, and the other available medical assistance programs (e.g., the Medical Assistance Program), which cover the remaining 3% of the population. Subsequently, the HIRA database stores data for the entire Korean population and their medical claims (including diagnoses, procedures, prescription records, and demographic information). The database provides a sufficient number of CRAO cases for statistical power and allows tracking of these cases across all health care use in Korea over a period of 5 years. Individuals in the HIRA database can be easily identified by their unique Korean Resident Registration Number, which is assigned to each Korean resident at birth; therefore, there are no duplications or omissions when accessing the data.[2,15,16] The HIRA Deliberative Committee approved the conditional use of the database from the years 2007−2011.[2] Institutional review board/ethics committee approval was obtained from the Seoul National Bundang Hospital.

Case Identification and Statistical Analyses

We identified CRAO cases using the first occurrence of a CRAO diagnostic code (H34.1) according to the Korean Classification of Diseases 6th edition, a version of the International Classification of Diseases 10th edition adapted for the Korean health care system. Potential preexisting CRAO cases were removed by excluding cases that had a CRAO diagnostic code during the first 2 years of the study period (2007−2008); all remaining cases had a disease-free period of at least 2 to 4 years, which is sufficient to identify incident cases.[2,16] The index date was defined as the date of the earliest claim with a CRAO diagnostic code; this was also considered the incident time.

For statistical analyses, we set the observation period, consisting of control period(s) and risk periods in each incident CRAO case, as ±365 days from the index date (index date was defined as +1 day). Then, we identified stroke/AMI cases using their first occurrence of stroke/AMI-related hospitalization (ischemic stroke [I63 Korean Classification of Diseases codes, 6th edition {KCD-6}], hemorrhagic stroke [I60−62 KCD-6], and AMI [I21KCD-6]) during the observation period.[17−19] To remove preexisting stroke/AMI cases, we excluded those with their first occurrence of stroke/AMI-related hospitalization during the year preceding the observation period. Therefore, all included cases had a period of at least 1 year free from a stroke/AMI attack before the observation period. To summarize, the study included the CRAO cases with an index date within 2009−2010 who had a stroke/AMI during their observation period.

The relative incidence rate ratios (IRRs) for stroke/AMI were measured in 2 separate ways to avoid immortal time bias and the issue of chronological aging: analysis 1 and analysis 2[20] (Fig 1). In both analyses, the control period was considered as 181−365 days before the index date; in analysis 2, the 181−365 days after the index date were also considered a control period. In both analyses, the 6 risk periods were defined as days 1−30, days 31−90, and days 91−180 before and after the index date, and in analysis 1, an additional risk period was defined as days 181−365 after the index date. The IRR was calculated using the SCCS method, which is a conditional Poisson regression method that compares the risk of stroke/AMI during the different time periods (control period vs. risk period) for each individual with reference to the index date.[21]

In addition, we estimated the IRRs in a more granular fashion: days 1−30 were subdivided to days 1−7, 8−14, and 15−30, and days 31−180 were subdivided to days 31−60, 61−90, 91−120, 121−150, and 151−180. We also performed subgroup analyses by sex and age (individuals aged <65 years and ≥65 years). Last, subgroup analyses were conducted on the basis of the 3 different cardiovascular attacks: ischemic stroke (I63), hemorrhagic stroke (I60−62), and AMI (I21). We adjusted the year when estimating the IRRs. We used SAS version 9.3 (SAS Inc, Cary, NC) for all analyses. The 95% confidence intervals (CIs) were also calculated.

Results

Of the 1655 individuals with incident CRAO and an index date between 2009 and 2010, 1585 (932 men, 653 women; mean age, 61.6±15.0 years) were included after the exclusion of 70 patients for a history of stroke or AMI before the observation period. Of the 1585 patients, 165 (115 men, 50 women; mean age, 66.2±13.1