with an increased risk of subsequent stroke in model 1 (crude analysis; hazard ratio [HR] = 1.31; 95% confidence interval [CI], 0.89–1.92), model 2 (adjusted analysis for demographics; HR = 1.19; 95% CI, 0.81–1.75), and model 3 (adjusted analysis for demographics, comorbidity, co-medication, and the Charlson index score; HR = 1.10; 95% CI, 0.75–1.62), respectively. Because neither of these Cox regression models reached statistical significance, the authors concluded that NAION per se is not associated with a subsequent risk of stroke in the general population.

The statistical power of this study may be reduced by combining different types of stroke as a single outcome measurement. In our previous study[2] consisting of 414 NAION patients and 789 controls based on the National Health Insurance Research Database (NHIRD) of Taiwan, including 1 million beneficiaries' random samples, the risk of ischemic stroke among the subjects with NAION was significantly higher than in those without NAION (HR = 2.03; 95% CI, 1.26–3.25). On the contrary, the risk of hemorrhagic stroke among the subjects with NAION was not statistically different from those without NAION (HR = 1.24; 95% CI, 0.43–3.57). Combining ischemic stroke and hemorrhagic stroke, the risk of all strokes among the subjects with NAION was 1.9 times higher than in those without NAION (95% CI: 1.26–2.96). For ischemic stroke, which accounts for 82.9% of all kinds of stroke in our study, we interpreted the relationship between NAION and all kinds of strokes as a diluted effect of ischemic stroke. However, according to the study design by Park and associates, stroke was defined as patient's first hospital admission with any of the following International Classification of Diseases (ICD)-10 codes: I60 (subarachnoid hemorrhage, I61 (intracerebral hemorrhage), I62 (other nontraumatic intracranial hemorrhage), I63 (cerebral infarction), and I64 (stroke, not specified as hemorrhage or infarction).[3] Although the proportion of ischemic stroke admissions increased from 64.7% in 2000 to 76.1% in 2009 in Korea,[4] the risk of stroke in this study was derived from a combined result of both ischemic stroke and hemorrhagic stroke, which shared different pathogenesis. Our observations already showed that the NAION is a risk factor in subsequent ischemic stroke attack, but not for a hemorrhagic stroke.[2] We do suggest that the hemorrhagic stroke should be separated from ischemic stroke in the investigation of risk of stroke in patients with NAION. Without knowing they are using all strokes as an outcome measurement in this NAION study, care must be taken when interpreting the results offered here.

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Reply

EDITOR:

WE THANK DR. TSAI FOR HIS INTEREST IN OUR PAPER.[1] DR. Tsai and associates already published a study which showed that nonarteritic anterior ischemic optic neuropathy (NAION) is a risk factor for subsequent ischemic stroke but not for hemorrhagic stroke.[2] They suggested that we should separate hemorrhagic stroke from ischemic stroke in the investigation of risk of stroke after NAION. We deeply appreciate Dr. Tsai and associates for pointing out that we should take another opportunity to further analyze our data and clarify the risk of ischemic and hemorrhagic stroke separately after NAION. Based on their suggestion, we divided the outcome according to the type of stroke, ischemic and hemorrhagic stroke, which was defined as the time to first hospital admission with diagnostic codes of ischemic stroke (I60–I62) and hemorrhagic stroke (I63) after entering the cohort, respectively. For each of the types of stroke, we performed the same set of analyses using the 3 time-varying covariate Cox regression models, as we did in our previous article.[1] The results of all three models showed that incident NAION was not associated with an increased risk of subsequent ischemic stroke (hazard ratio [HR] = 1.16; 95% confidence interval [CI], 0.52–2.59 in model 1; HR = 1.10; 95% CI, 0.49–2.45 in model 2; and HR = 1.05; 95% CI, 0.47–2.34 in model 3) and hemorrhagic stroke (HR = 1.44; 95% CI, 0.96–2.17 in model 1; HR = 1.30; 95% CI, 0.86–1.95 in model 2; and HR = 1.19; 95% CI, 0.79–1.80 in model 3). In addition, we performed a sensitivity analysis by using propensity score-based matching in the defined cohort in the same way as previously mentioned. We matched 10 controls to each NAION patient, and details regarding the estimation and

assessment of propensity scores are described in our previous article.[1] The demographics, comorbidities, and use of comedications were comparable between subjects with NAION and their matched controls when they entered the cohort. The results of sensitivity analyses also showed that incident NAION was not associated with an increased risk of ischemic stroke (HR = 1.10; 95% CI, 0.48–2.53 in model 1; HR = 1.06; 95% CI, 0.46–2.42 in model 2; and HR = 1.03; 95% CI, 0.45–2.35 in model 3) and hemorrhagic stroke (HR = 1.40; 95% CI, 0.91–2.14 in model 1; HR = 1.31; 95% CI, 0.85–2.00 in model 2; and HR = 1.27; 95% CI, 0.83–1.95 in model 3). We used SAS software version 9.3 (SAS Inc., Cary, North Carolina) and R programming version 3.1.0 (R Foundation, Vienna, Austria) for all analyses. In conclusion, NAION is not associated with a subsequent risk of both hemorrhagic and ischemic stroke in the general population of South Korea.

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CONFLICT OF INTEREST DISCLOSURES: THE AUTHORS declare that they have no competing interests.

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1. Park SJ, Yang HK, Byun SJ, Park KH, Hwang JM. Risk of stroke after nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 2019;200:123–129.
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Reply

EDITOR:

WE THANK AWASTHI AND ASSOCIATES FOR THEIR INTEREST and positive comments on our paper.[1] We are pleased to provide clarifications on some of the points they raised.

We agree that choroidal neovascularization (CNV) were detected in only 6 patients using optical coherence tomography angiography. In the Method section, we pointed out that the presence of CNV detected by optical coherence tomography angiography was not an exclusion criterion. The presence of subretinal fluid in cases of CSC complicated by CNV could be considered a sign of CSC activity, and these CNV might have been "quiescent."[2] Thus, it was interesting to evaluate the effect of ARM in these cases. In addition, the presence of CNV was found to be a factor of poor response to ARM treatment in the publication by Sacconi and associates.[3] Our results support those findings.

Furthermore, the authors raised a concern over the lack of discussion about switching eplerenone to spironolactone. In our study, only 3 patients were switched from eplerenone to spironolactone therapy after 3 months because of a lack of efficacy. In those 3 patients, the treatment with spironolactone was also not effective and those patients were included in the "nonresponder" group. Additionally, the side effects occurred 3 to 6 months after the initiation of treatment (only the patients treated for at least 3 months were included in our study).

However, the aim of the study was to identify potential predictive factors for short-term (3 to 6 months) response to ARM treatment and not to evaluate or compare the clinical efficacy of both drugs and to evaluate the efficacy of a rescue therapy. We agree that these questions are very interesting and useful in clinical practice. Thus, further studies are needed to evaluate the effect of the switch or the rescue therapy.

We thank the authors for their insight into the possible role of corticosteroids on Bruch's membrane structure.

Finally, as stated by the authors, we fully agree that the term "clinical study" would have been more appropriate than the term "clinical trial." As a point of clarification, in Table 1, 23 of 60 patients achieved a complete resolution of subretinal fluid at 3 months (38.3%).[1]

Again we thank Awasthi and associates for their interest, encouraging comments, and careful analysis of our study.

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