Journal of the American Heart Association

RESEARCH LETTER

Retinal Ischemic Perivascular Lesions Are Associated With Stroke in Individuals With Atrial Fibrillation

Christine Y. Bakhoum, MD, MAS; Adrian Au, MD, PhD; Elodie Bousquet, MD, PhD; Mitchelle Matesva, MD; Maxwell B. Singer, MD; Christina Jayaraj, BS; Veronica A. Romero-Morales, MD; Swathi Somisetty, MD; Ahmad Santina, MD; Bryce Bajar, MD, PhD; Anthony N. DeMaria, MD; Michael H. Goldbaum, MD; Judith Meadows, MD, MPH; Erica S. Spatz, MD, MHS; David Sarraf, MD; Mathieu F. Bakhoum, MD, PhD

Atrial fibrillation (AF) is the most common disorder of the heart rhythm in adults.[1] A commonly used tool to identify individuals with AF who are at greatest risk of developing strokes is the CHA_2DS_2-VASc score.[2] Although currently recommended by guidelines, it has modest discrimination for stroke in patients with AF.[3] As such, the development of novel markers and screening tools is necessary to improve tailored anticoagulation strategies.

Patients with AF are also at risk of developing retinal vascular occlusions. Besides retinal artery and vein occlusions, there is evidence of subclinical retinal ischemia in individuals with AF.[4] We recently demonstrated that retinal ischemic perivascular lesions (RIPLs), which are anatomical biomarkers of subclinical retinal ischemia,[5] are significantly associated with AF.[4] RIPLs are observed at the outer plexiform layer of the retina and represent aftereffects of previous microinfarcts arising from ischemia or microemboli. Here, within a cross-sectional cohort of individuals with AF, we sought to determine whether the presence of RIPLs is associated with ischemic stroke. We examined whether the addition of RIPLs to the CHA_2DS_2-VASc score would improve discrimination of patients who have stroke.

This is a retrospective, cross-sectional study that adhered to the tenets of the Declaration of Helsinki. Institutional review board approval was obtained from Yale University, the University of California San Diego (UCSD), and the University of California Los Angeles (UCLA). Informed consent was not required. The data that support the findings of this study are available from the corresponding author upon reasonable request. We identified patients through Epic's Slicer Dicer tool using *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes of AF (I48.0–I48.4, I48.91–I48.92) and presence of a macular optical coherence tomography scan. We included patients who were aged 50 to 90 years. Exclusion criteria included a history of retinal vessel occlusions, diabetic retinopathy, pars plana vitrectomy, retinal laser photocoagulation, or intravitreal injections. Additional exclusion criteria were macular pathology on optical coherence tomography such as significant epiretinal membrane, advanced macular degeneration, or choroidal neovascularization. Individuals with poor-quality scans were excluded. We also excluded individuals with transient ischemic attack based on chart review, given we did not have a specialist for adjudication of these cases. Scans were

Key Words: atrial fibrillation ■ optical coherence tomography ■ retinal ischemic perivascular lesion ■ RIPLs ■ stroke

Correspondence to: Mathieu F. Bakhoum, MD, PhD, Yale University School of Medicine, 300 George Street, #8107B, New Haven, CT 06511. Email: mathieu.bakhoum@gmail.com and Christine Y. Bakhoum, MD, MAS, Yale University School of Medicine, 333 Cedar Street, 3086 LMP, New Haven, CT 06520. Email: christine.bakhoum@yale.edu

This article was sent to Shu-Fen Wung, PhD, RN, Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 2.

JAHA is available at: www.ahajournals.org/journal/jaha

Table. Firth Bias-Reduced Multivariable Logistic Regression Model Evaluating the Relationship of the Presence of RIPLs and CHA_2D-VASc Score With Ischemic Stroke in Patients With AF

Variable	Summary statistic*	Multivariable estimate (95% CI)	*P* value multivariable model
Presence of RIPLs	67 (39.6%)	2.59 (1.04–6.79)	0.04†
CHA_2D-VASc score	3.38 (1.37)	1.36 (0.96–1.96)	0.09

*Frequency (percentage) is presented for the categorical variable, and mean (SD) is presented for the continuous variable. AF indicates atrial fibrillation; CHA_2D-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, vascular disease, age 65 to 74 years, sex category; and RIPL, retinal ischemic perivascular lesion.

†$p<0.05$.

reviewed for RIPLs by three independent and masked observers. A consensus agreement was required to document RIPLs within each patient. Because this is a cross-sectional study evaluating stroke as the outcome, we calculated a modified CHA_2DS_2-VASc score, which we termed CHA_2D-VASc, in which we excluded history of stroke, transient ischemic attack, or thromboembolism as a risk factor. Firth bias-reduced multivariable logistic regression model was utilized to evaluate the relationship between RIPLs and stroke, after adjustment for CHA_2D-VASc score. All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing).

We identified 169 individuals with AF who met all criteria. Within the cohort, 67 patients (39.6%) had RIPLs. There were 21 patients overall (11.8%) who had a history of stroke. Patients with stroke had significantly higher rates of hypertension (95.2% versus 71.6%, *P*=0.016) and a RIPL diagnosis (61.9% versus 36.5%, *P*=0.03) compared with those without stroke. Overall, 116 patients (68.6%) were undergoing anticoagulation therapy, and there was no significant difference in anticoagulation use in those who did (66.7%) or did not (68.9%) have stroke.

In a univariable model, the presence of RIPLs was significantly associated with stroke (*P*=0.03), with an odds ratio (OR) of 2.75 (95% CI, 1.11–7.17). We then tested the association between RIPLs and stroke in a multivariable model that included CHA_2D-VASc score (Table). We determined that each additional CHA_2D-VASc point was associated with an OR of 1.36 (95% CI, 0.96–1.96) of stroke and presence of RIPLs was associated with an OR of 2.59 (95% CI, 1.04–6.79) of stroke (*P*=0.09 and *P*=0.04, respectively). When combining the presence of RIPLs with CHA_2D-VASc in a receiver operating curve analysis, the area under the curve in determining stroke was 0.69, which was an increase from 0.61 when using CHA_2D-VASc alone.

In this cross-sectional study, we identified that the presence of RIPLs was significantly associated with stroke in individuals with AF, after adjustment for established risk factors. The addition of RIPLs to a CHA_2D-VASc score improved the area under the curve of the model for stroke. These findings suggest that the presence of subclinical retinal ischemia in patients with AF may indicate an increased risk of stroke. Our study has limitations to note. First, we conducted a retrospective, cross-sectional analysis, so we cannot determine whether RIPLs precede the development of stroke. In addition, the outcome of stroke was determined through chart review and not adjudicated by a neurologist. Second, our sample size limits our ability to detect small effect sizes. Third, individuals in this analysis were followed at only 2 academic centers, which limits generalizability. Future, prospective studies are needed to validate the predictive ability of RIPLs as either a modifier or additional risk factor to the CHA_2DS_2-VASc score in diverse cohorts.

ARTICLE INFORMATION

Received March 6, 2024; accepted May 15, 2024.

Affiliations

Section of Nephrology, Department of Pediatrics (C.Y.B.) and Clinical and Translational Research Accelerator, Department of Medicine (C.Y.B.), Yale University School of Medicine, New Haven, CT; Department of Ophthalmology, David Geffen School of Medicine, Stein Eye Institute, University of California Los Angeles, CA (A.A., E.B., V.A.R., S.S., A.S., B.B., D.S.); Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, CT (M.M., M.B.S., C.J., M.F.B.); Division of Cardiology, Department of Medicine, Sulpizio Cardiovascular Center, University of California, San Diego, La Jolla, CA (A.N.D.); Department of Ophthalmology, University of California San Diego, La Jolla, CA (M.H.G.); Division of Cardiology, Department of Medicine, Yale University School of Medicine, New Haven, CT (J.M., E.S.S.); Greater Los Angeles VA Healthcare Center, Los Angeles, CA (D.S.); Department of Pathology, Yale University School of Medicine, New Haven, CT (M.F.B.); and Yale Cancer Center, Yale University, New Haven, CT (M.F.B.).

Sources of Funding

C.Y.B. is funded by American Heart Association Award 857722 and K23 DK129836 from the National Institute of Diabetes and Digestive and Kidney Diseases. M.F.B. is supported by National Institutes of Health Research Grant P30CA016359 from the National Cancer Institute, R21EY035090 from the National Eye Institute, by the Office of the Assistant Secretary of Defense for Health Affairs through the Melanoma Research Program under award number HT9425-23-1-1070, and a grant from the Connecticut Lions Eye Research Foundation.

Disclosures

D.S. is a consultant for Heidelberg, Topcon, Amgen, Bayer, Iveric Bio, Novartis, and Optovue, and receives equipment for research from Heidelberg, Optovue, and Topcon. The remaining authors have no disclosures to report.

REFERENCES

1. Brundel B, Ai X, Hills MT, Kuipers MF, Lip GY, de Groot NM. Atrial fibrillation. *Nat Rev Dis Primers*. 2022;8:21. doi: 10.1038/s41572-022-00347-9

2. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584
3. Chen LY, Norby FL, Chamberlain AM, MacLehose RF, Bengtson LG, Lutsey PL, Alonso A. CHA_2DS_2-VASc score and stroke prediction in atrial fibrillation in whites, blacks, and Hispanics. *Stroke*. 2019;50:28–33. doi: 10.1161/STROKEAHA.118.021453
4. Bakhoum CY, Madala S, Lando L, Yarmohammadi A, Long CP, Miguez S, Chan AX, Singer M, Jin A, Steren BJ, et al. Retinal ischemic perivascular lesions in individuals with atrial fibrillation. *J Am Heart Assoc*. 2023;12:e028853. doi: 10.1161/JAHA.122.028853
5. Long CP, Chan AX, Bakhoum CY, Toomey CB, Madala S, Garg AK, Freeman WR, Goldbaum MH, DeMaria AN, Bakhoum MF. Prevalence of subclinical retinal ischemia in patients with cardiovascular disease-a hypothesis driven study. *E Clin Med*. 2021;33:100775. doi: 10.1016/j.eclinm.2021.100775