Association of Retinal Microvascular Signs with Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

Gen-Min Lin, *Northwestern University*
Laura A Colangelo, *Northwestern University*
Barbara EK Klein, *University of Wisconsin School of Medicine and Public Health*
Mary Frances Cotch, *National Eye Institute (NEI)*
Tien Y Wong, *National University of Singapore*
CarolY Cheung, *Chinese University of Hong Kong*
Susan R Heckbert, *University of Washington*
Alvaro Alonso, *Emory University*
Younghoon Kwon, *University of Virginia School of Medicine*
Richard A Kronmal, *University of Washington*

Only first 10 authors above; see publication for full author list.

Journal Title: Ophthalmology Retina

Volume: Volume 5, Number 1

Publisher: (publisher) | 2021-01-01, Pages 78-85

Type of Work: Article | Post-print: After Peer Review

Publisher DOI: 10.1016/j.oret.2020.06.019

Permanent URL: https://pid.emory.edu/ark:/25593/w2hbz

Final published version: http://dx.doi.org/10.1016/j.oret.2020.06.019

HHS Public Access

Author manuscript

Ophthalmol Retina. Author manuscript; available in PMC 2022 August 11.

Published in final edited form as:

Ophthalmol Retina. 2021 January ; 5(1): 78–85. doi:10.1016/j.oret.2020.06.019.

Association of Retinal Microvascular Signs With Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

Gen-Min Lin, MD, PhD[a,b,*], **Laura A. Colangelo, MS**[a], **Barbara E.K. Klein, MD, MPH**[c], **Mary Frances Cotch, PhD**[d], **Tien Y Wong, MD, PhD**[e], **Carol Y Cheung, PhD**[f], **Susan R. Heckbert, MD, PhD**[g], **Alvaro Alonso, MD. PhD**[h], **Younghoon Kwon, MD**[i,j], **Richard A. Kronmal, PhD**[k], **Donald M. Lloyd-Jones, MD, ScM**[a], **Kiang Liu, PhD**[a]

[a.]Department of Preventive Medicine, Northwestern University, Chicago, IL, USA

[b.]Departments of Medicine, Hualien Armed Forces General Hospital, Hualien; Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

[c.]Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, Madison, WS, USA

[d.]Division of Epidemiology and Clinical Applications, NIH Intramural Research Program, National Eye Institute, National Institutes of Health, Bethesda, MD, USA.

[e.]Singapore Eye Research Institute, Singapore National Eye Centre, Duke-NUS Medical School, National University of Singapore, Singapore

[f.]Department of Ophthalmology and Visual Sciences, Chinese University of Hong Kong, China

[g.]Department of Epidemiology, University of Washington. Seattle, WA, USA

[h.]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

[i.]Department of Medicine, University of Virginia, Charlottesville, VA, USA

[j.]Department of Medicine, University of Washington, Seattle, WA, USA

[k.]Department of Biostatistics, University of Washington, Seattle, WA, USA

Abstract

[*]**Corresponding author:** Gen-Min Lin; Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 North Lake Shore Drive, Suite 1400, Chicago, IL 60611, gen-min.lin@northwestern.edu, Tel: 312-908-5749; Fax: 312-908-9588.

Authors' contributions: GML wrote and corresponded to the paper; LAC made the present analyses; BEK, MFC, TYW, CYC, SRH, AA, YK, RAK, and DLJ interpreted the data and made intellectual contributions to the writing of the final version of the manuscript; KL was the senior author. All authors have read and approved the manuscript.

Declaration

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of each MESA participating institution, and written informed consent was obtained from all participants.

Consent for publication: All authors and participants agreed the publication in the Journal.

Availability of data and materials: As the study materials were obtained from the MESA study, the majority of which was funded by NHLBI under U.S. government contract, the data are confidential and not open to the public. If there are any needs for clarification, the readers can contact Dr. Gen-Min Lin, the corresponding author, for further information.

Competing interests: None

Objective—Microvascular diseases may contribute to occurrence of atrial fibrillation (AF). Retinal microvascular signs which are similar to other microvasculature in the body and can be directly visualized via ophthalmoscopy may provide insights into such a relationship.

Participants—We examined the association between retinal microvascular signs and incident AF in 4994 participants, aged 47–86 years and free of prior AF, who underwent fundus photography in 2002–2004, and were followed through 2015 in the Multi- Ethnic Study of Atherosclerosis (MESA).

Design—A prospective longitudinal multiethnic study.

Methods—Retinal microvascular signs evaluated include central retinal arteriolar and venular equivalents (CRAE and CRVE, respectively), and presence of any retinopathy signs (e.g. retinal microaneurysms or hemorrhages). A multivariable Cox regression analysis was used to determine the relationship while adjusting for traditional risk factors, alcohol intake, body mass index, diabetes status, chronic kidney disease status, HbA1c, C-reactive protein, medications and prevalent cardiovascular diseases or heart failure.

Main Outcome and Measures—Incident AF events were identified using 12-lead electrocardiographic findings, hospital discharge records and Medicare claimed data.

Results—During a median follow-up of 14.1 years, 643 AF events were identified. There was no association of any retinal microvascular signs with incident AF except retinal focal arteriolar narrowing (hazard ratio: 1.75 (95% confidence intervals (CI): 1.06–2.87) in the overall population. However, in the subgroup analyses by sex, wider CRVE was associated with higher risk of incident AF in women but not in men (hazard ratios for every 10-μm increase in CRVE: 1.08 (95%CI: 1.01–1.15) and 0.97 (95% CI: 0.92–1.03), respectively, *P* for interaction =0.041).

Conclusions—There was no consistent pattern of association between retinal microvascular signs and incident AF. We observed an association in women but not men of wider retinal venular calibers with incidence of AF. The reasons for a possible interaction are incompletely understood.

Keywords

Atrial fibrillation; retinal vascular calibers; retinopathy; sex difference

INTRODUCTION

Atrial fibrillation (AF), one of the most prevalent cardiac arrhythmia among elderly individuals, is associated with a wide range of cardiovascular disease (CVD) and heart failure.[1] Risk factors of AF such as age, hypertension, obesity, diabetes mellitus, inflammation, and obstructive sleep apnea have been identified.[2, 3] Microvascular disease may lead to the occurrence of clinical CVD,[4] whereas the relationship of microvascular characteristics with AF is unclear. Some cross-sectional cardiac perfusion imaging studies revealed that AF might relate to myocardial microvascular dysfunction, but evidence for the temporal association remains lacking.[5, 6]

The retinal vasculature, similar to microvasculature elsewhere in the body, is a unique biological model to study microvascular abnormalities and pathology associated

with CVD.[7, 8] Retinal arteriolar narrowing has been shown to be strongly related to age and hypertension,[9–11] while retinal venular widening has been related to metabolic abnormalities, obesity, cigarette smoking, inflammation and atherosclerosis.[11, 12] Retinopathy signs, specifically retinal microaneurysms, hemorrhages, and cotton wool spots found in patients with diabetes, are also prevalent in the general population (5–10%), and related to age, obesity, hyperglycemia, inflammation, and elevated blood pressure.[9] Many studies have demonstrated the association between retinal microvascular signs and clinical CVD,[13–21] supporting a concept that changes seen in the retinal vasculature likely reflect similar changes in the systemic peripheral, cerebral and coronary microcirculation (e.g. intimal thickening, vasoconstriction). However, few studies have directly examined their association with AF, with conflicting results.[22–24] To address this gap, we prospectively investigated the association between retinal microvascular signs and incident AF in a large multiethnic population.

METHODS

Study population and data collection

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study[25] designed to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without clinical CVD at baseline. In brief, there were 6814 women and men aged 45–84 years old recruited from 6 U.S. communities at the first examination (July 2000 to July 2002). The participants were 38% white, 28% black, 22% Hispanic and 12% Chinese. At the second examination of MESA (August 2002 to January 2004), 6237 participants (92%) returned, 6112 underwent fundus photography, and 5583 had gradable retinal photographs. Of these, we excluded those with incident AF events at or prior to the second examination (N=95) as well as those missing covariates (N=494), leaving 4,994 participants for the present analysis. This study was approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from all participants.

Retinal photography and retinal grading

Fundus photography was performed in both eyes of each participant according to a standardized protocol using a 45° digital nonmydriatic camera.[26] All retinal images were sent to the Ocular Epidemiology Reading Center at the University of Wisconsin (Madison, WI) and were evaluated by trained graders masked to participants' characteristics.[26] Retinopathy signs were defined according to the Early Treatment Diabetic Retinopathy Study severity scale, including retinal microaneurysms, retinal hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, retinal neovascularization, venous beading, hard exudates, and other lesions of proliferative diabetic retinopathy.[27] Participants without diabetes in the eye examination with retinopathy greater than level 13 were considered to have non-diabetic retinopathy. In addition, retinal arteriolar wall signs such as retinal arteriovenous nicking and retinal focal arteriolar narrowing were also included. Retinal vascular caliber was measured with a computer-based program following a detailed protocol.[27, 28] For each fundus photograph, all retinal arterioles and venules coursing through a zone between 0.5- and 1-disc diameters away from the optic disc margin were measured as the central retinal arteriolar equivalents (CRAE) and venular equivalents

(CRVE).[29] The average of the right and left eye measurements was taken for both CRAE and CRVE in each participant. If retinal vascular caliber could not be measured in both eyes, the eye with the available fundus photograph was used. The reproducibility of retinal vascular measurements has been reported previously with intra- and inter-grader intraclass correlation coefficients ranging from 0.78 to 0.99.[10, 11]

Ascertainment of incident AF events

Self-reported AF was an exclusion criterion for recruitment in MESA and participants received standard 12-lead electrocardiography (ECG) at the first visit (2000–2002). Incident AF events were identified post-study enrollment from hospital discharge diagnosis codes for AF or atrial flutter (according to International Classification of Diseases, Ninth Revision diagnosis codes 427.31 and 427.32; and Tenth Revision, code I48) as ascertained by the MESA events detection protocol, from Medicare claims data for participants enrolled in fee-for-service Medicare, and from the study 12-lead ECG conducted at the fifth visit (2010–2012).[30] A validation substudy[2] reviewing a random sample of 45 of 185 MESA participants with hospital discharge diagnosis codes for AF showed that AF was confirmed in 93% of hospitalizations, implying a high positive predictive value for the diagnosis.

Assessment of risk factors for AF and retinal microvascular signs

All participants underwent an interview and were assessed for cardiovascular risk factors at the second visit of MESA (2002–2004), and updated at later visits. Risk factors related to AF or retinal microvascular signs were defined as follows. Cigarette smoking status was defined as current, former and never. Alcohol intake status was classified into current and noncurrent (never and former). Body mass index (BMI) was calculated as weight (kg)/height squared (m^2). Blood pressure (BP) level was ascertained as the mean of the last 2 of 3 seated measurements. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg and/or the use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose ≥126 mg/dl and/or the use of hypoglycemic medications. HbA1c levels were measured on the Tosoh A1c 2.2 Plus Glyco- hemoglobin Analyzer (Tosoh Medics, Inc., CA, USA) using automated HPLC. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/minute/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration equation which was obtained at the MESA first visit.[31] Total cholesterol and high-density lipoprotein cholesterol concentrations were measured from blood samples obtained after a 12-hour fast. The Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont) measured serum high-sensitivity C-reactive protein (hs-CRP) using the BN II nephelometer (N High Sensitivity CRP, Dade Behring Inc., Deerfield, Illinois) in 2000–2002.[32] Medication use was assessed by reviewing participants' medication containers.

Statistical analysis

Baseline demographic characteristics of participants with gradable retinal photographs taken at the second MESA examination were reported as mean ± standard deviation or as percentages for continuous and categorical variables, respectively.

The analysis used the calendar time for follow-up since the second MESA visit with censoring at first occurrence of incident AF event, death, loss to follow-up, or end of follow-up (December 31, 2015). Cox proportional hazard regression analyses were used to determine the multivariable association for retinal microvascular signs (CRAE (each 10-μm increase), CRVE (each 10-μm increase), and presence of any retinopathy signs or specific retinopathy sign, (e.g. retinal hemorrhages and microaneuryms) with incident AF, adjusting for potential confounders. Subgroup analyses for the association according to sex, age, race/ethnicity, diabetes status, and hypertension status were performed. In model 1, age, sex and race/ethnicity were adjusted. In model 2, BMI, cigarette smoking status, alcohol consumption status, chronic kidney disease status, diabetes status, HbA1c levels, systolic BP, total cholesterol, high-density lipoprotein cholesterol, antihypertensive therapy, lipid-lowering therapy, hs-CRP concentrations ($\log_e$ transformation), and baseline CVD or heart failure were additionally adjusted. CRAE, CRVE, and any retinopathy signs (or respective specific retinopathy signs) were included together in the models. These potential confounders in models were chosen according to prior published associations with AF or retinal vascular signs.[2, 3, 7] Formal testing for multiplicative interactions and subgroup analyses for the associations of retinal microvascular signs with incident AF were performed. In addition, since there was a relatively long follow-up period in this study, we considered the possibility that the status of some covariates may change with time before the development of AF. We, therefore, conducted a “time-updated” analysis adjusting for the covariates included in model 2 to clarify the association between retinal microvascular signs and incident AF using as time–dependent covariates data on BMI, kidney function, diabetes status, systolic BP, total cholesterol, high-density lipoprotein cholesterol, anti- hypertensive therapy, and lipid-lowering therapy collected at a subsequent MESA visit (exam visit 3 or later). A 2-tailed value of $p < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, N.C.).

RESULTS

Baseline characteristics of participants with gradable retinal photographs at the second MESA examination were shown in table 1. The participants ranged between 47 and 86 years, with a mean of 62.6 years. Of the participants, 52.3% were women, 11.6% were current smokers, 13.9% had diabetes mellitus, and 11.3% were found with any retinopathy signs.

Table 2 shows the results of the Cox proportional hazard regression model of the relationship of CRAE, CRVE, and any retinopathy signs with incident AF. There were 643 AF events (12.9%) during the study period. The associations of retinal vascular calibers and any retinopathy signs with incident AF were not statistically significant after adjustment in model 1 and model 2, as well as in time-updated analysis (supplemental table 1). The associations of specific retinopathy signs with incident AF are shown in table 3. After adjusting for all of the covariates in model 2, only retinal focal arteriolar narrowing was associated with higher risk of incident AF (hazard ratio (HR): 1.75, 95% confidence intervals (CI): 1.06–2.87), whereas no statistically significant relationship was observed between retinal hemorrhages, microaneurysms, soft exudates, arteriovenous nicking and incident AF.

Table 4 shows the results of subgroup analyses regarding the Cox regression model of the relationship of CRAE, CRVE, and any retinopathy signs with incident AF. In the subgroup analysis by sex, 287 and 356 incident AF events occurred in women and men respectively. In women, wider CRVE (per each 10-μm higher) was associated with higher risk of incident AF (HR: 1.08, 95% CI: 1.01–1.15) after adjusting for age, race/ethnicity, BMI, cigarette smoking status, current alcohol intake, diabetes status, systolic BP, total cholesterol, high-density lipoprotein, HbA1c, $\log_e$ hs-CRP, antihypertensive therapy, lipid-lowering therapy, chronic kidney disease, and baseline CVD and heart failure, whereas in men, the association between CRVE and incident AF was not statistically significant (HR: 0.97, 95% CI: 0.92–1.03). There was a possible sex difference in the association between CRVE and incident AF (p for interaction =0.041). For CRAE and any retinopathy signs, the sex-specific associations with incident AF were not significant. Exploratory analyses were conducted examining associations for specific retinopathy signs in men and women in supplemental table 2. In general, these results did not differ by sex in model 2. Regarding other subgroup analyses according to age, race/ethnicity, diabetes status and hypertension status, all of the associations were not significant in each subgroup and without interactions.

DISCUSSION

The incidence of AF in this study was 11.8 per 1,000 person-years which was 2.2, 7.7, 18.2, and 32.5 per 1,000 person-years, respectively, for those aged 45–54, 55–64, 65–74 and ≥75 years. This rate was comparable to 8.2 – 12.1 per 1,000 person-years in other cohort studies of middle- and old-aged general populations including 12.1, 8.5 and 8.2 per 1000 person-years in the Framingham Heart Study, the Atherosclerosis Risk in Communities (ARIC) study and the UK Clinical Research Datalink Study, respectively.[33–35] Our principal finding was that in a general multi-ethnic population, retinal vascular calibers and any retinopathy signs except focal arteriolar narrowing at baseline were not associated with incident AF. In subgroup analyses, there was a suggestion of a possible sex difference in the association of retinal venular calibers with incident AF, where wider retinal venular calibers in women were associated with higher incidence of AF independent of multiple potential confounders, but that was not seen in men. There was no evidence of an association of retinal arteriolar calibers or any retinopathy signs with incident AF in either men or women. In addition, there were no interactions within age status, race/ethnicity, diabetes status, and hypertension status for the association between retinal microvascular signs and incident AF.

To our best knowledge, there have been only three published studies examining the association of retinopathy microvascular signs with AF.[22–24] In the ARIC study,[22] Agarwal *et al.* reported a relationship of any retinopathy, specifically retinal hemorrhages and retinal microaneurysms, with incident AF in the general population. In a cross-sectional analysis for the Australian Heart Eye Study,[23] Phan *et al.* revealed no association between diabetic retinopathy and prevalent AF in a clinic-based cohort with high vascular risk profiles. In a nationwide Korean diabetic cohort,[24] Lee *et al.* uncovered that those with diabetic retinopathy had higher risk of incident AF. Retinopathy signs related to age, metabolic disorders, and hypertension has been associated with sleep apnea, clinical CVD, and heart failure.[9, 20, 36] However, the risk ratios for any or diabetic retinopathy with AF in the studies were relatively low, ranging from 1.14 to 1.37 regardless of whether the result

was statistically significant.[22–24] Our study participants had similar baseline demographics, incidence of AF, and follow-up time compared with that of ARIC,[22] but reported conflicting results for various retinopathy lesions in association with incident AF. Since ARIC and MESA each utilized different methods of retinal image acquisition in that ARIC took film-based photographic images from a single eye whereas MESA took digital images of both eyes with immediate retakes possible if image quality was determined to be subpar, it is possible that improvement in photographic technique, in conjunction with other unmeasured differences in the two cohorts studied decades apart, could account for observed differences. Retinal focal arteriolar narrowing sign has been shown with an association with aortic stiffness, left ventricular hypertrophy, and lacunar stroke.[37–39] Therefore, the finding of such a relationship with incident AF in our study is likely related to concomitant subclinical cardiac remodeling and vascular pathology.

Previous studies have found retinal vascular caliber changes (narrower arteriolar calibers and wider venular calibers) associated with incident coronary heart disease and stroke.[14, 16–18] Although clinical CVD shares similar risk factors with AF, current evidence consistently showed no relationship between retinal arteriolar calibers and prevalent or incident AF events after controlling age and several CVD risk factors.[22–24] The relationship between retinal arteriolar calibers and incident AF were not significant after an adjustment of age, sex, and race/ethnicity where age is closely associated with both retinal arteriolar calibers and AF events.[9–11] Interestingly, we found a sex difference in the association of retinal venular calibers with incident AF. As is known, women's microvessels appear to be more frequently dysfunctional compared with men.[40] Several studies have revealed that microvascular abnormalities including retinal venular widening may play a more important role in the pathogenesis of myocardial ischemia in women,[21, 41, 42] which could be a possible mechanism for a higher risk of AF in women as well. In addition, cardiac structure and the relationship with retinal venular calibers may differ by sex.[43] A previous MESA study has shown a correlation between wider retinal venular calibers and greater left ventricular mass index in women but not in men, which could be consistent with the observed higher risk of AF associated with CRVE in women.[43] It is notable that despite statistical significance in the CRVE association in women, the strength of the relationship with incident AF was weak (HR: 1.08, per each 10-μm higher), which might not be clinically meaningful.

The strengths of our study include the carefully conducted adjudications for incident CVD and a validation for incident AF, the ethnic diversity of the MESA cohort, the availability of digitally acquired retinal data on a variety of retinal signs, and the availability of a wide range of data on other covariates. Additionally, given its longitudinal design and good response rate, there was sufficient sample size and follow-up time in MESA in which to interrogate several subgroup interactions. However, we tested for 5 interactions for each of 3 retinal measures, therefore the statistically significant interaction by sex for the association between retinal venular calibers and incident AF may be due to chance alone. Residual confounding may be present despite the large array of covariates in the multivariable adjustment models. In addition, incident AF events were mainly identified in symptomatic participants based on hospital discharge records from Medicare claims data, and those with asymptomatic AF such as paroxysmal AF might be underestimated.

CONCLUSIONS

We found that retinal vascular calibers and any retinopathy signs except focal arteriolar narrowing were not associated with incident AF in a multi-ethnic cohort. However, there was an association of wider retinal venular calibers in women at baseline with the incidence of AF but with no evidence of such a relationship in men. The reasons for a possible interaction are not understood completely and its clinical relevance needs to be determined. We hope our study prompts ophthalmologists to pay closer attention to patients who have specific retinal signs and were at higher risk for incident AF and to cooperate with internists and geriatricians to take preventive action on controlling common risk factors, such as smoking, alcohol use, diet, hypertension and metabolic disorders, and to coordinate medical management, as necessary. Finally, this study reminds ophthalmologists to reinforce to their patients the notion that pathologic changes occurring in one organ of the body may have multi-organ effects and encourage them to divulge symptoms that may inform their care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank the investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Funding:

T This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute at the National Institutes of Health and by grants UL1-RR-024156 and UL1-RR-025005 from National Center for Research Resources (NCRR). Retinal data were collected under an Intramural Research Award ZIAEY000403 by the National Eye Institute, National Institutes of Health. Identification of atrial fibrillation was supported by R01HL127659 from the National Heart, Lung, and Blood Institute. Additional supports were provided by grant 16EIA26410001 from the American Heart Association (AHA) and by grant 805C-109–07 from the Hualien Armed Forces General Hospital, Taiwan.

REFERENCES

1. Melgaard L, Gorst-Rasmussen A, Lane DA, et al. Assessment of the CHA2DS2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. JAMA 2015;314:1030–1038. [PubMed: 26318604]
2. Lin GM, Colangelo LA, Lloyd-Jones DM, et al. Association of Sleep Apnea and Snoring With Incident Atrial Fibrillation in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2015;182:49–57. [PubMed: 25977516]
3. Vlachos K, Letsas KP, Korantzopoulos P, et al. Prediction of atrial fibrillation development and progression: Current perspectives. World J Cardiol 2016;8:267–276. [PubMed: 27022458]
4. Guo L, Cheng Y, Wang X, et al. Association between microalbuminuria and cardiovascular disease in type 2 diabetes mellitus of the Beijing Han nationality. Acta Diabetol 2012;49 (Suppl 1):S65–71. [PubMed: 20593206]
5. Skalidis EI, Hamilos MI, Karalis IK, et al. Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. J Am Coll Cardiol 2008;51:2053–2057. [PubMed: 18498961]

6. Sciagrà R, Sotgia B, Olivotto I, et al. Relationship between atrial fibrillation and blunted hyperemic myocardial blood flow in patients with hypertrophic cardiomyopathy. J Nucl Cardiol 2009;16:92–96. [PubMed: 19152133]
7. Liew G, Wang JJ, Mitchell P, et al. Retinal vascular imaging: a new tool in microvascular disease research. Circ Cardiovasc Imaging 2008;1:156–161. [PubMed: 19808533]
8. Cheung CY, Ikram MK, Sabanayagam C, et al. Retinal microvasculature as a model to study the manifestations of hypertension. Hypertension 2012;60:1094–1103. [PubMed: 23045470]
9. Nguyen TT, Wang JJ, Wong TY. Retinal vascular changes in pre-diabetes and prehypertension: new findings and their research and clinical implications. Diabetes Care 2007;30:2708–2715. [PubMed: 17595350]
10. Cheung N, Sharrett AR, Klein R, et al. Aortic distensibility and retinal arteriolar narrowing: The Multi-Ethnic Study of Atherosclerosis. Hypertension 2007;50:617–622. [PubMed: 17698721]
11. Cheung N, Islam FM, Jacobs DR Jr, et al. Arterial compliance and retinal vascular caliber in cerebrovascular disease. Annals of Neurology 2007;62:618–624. [PubMed: 17918248]
12. Myers CE, Klein R, Knudtson MD, et al. Determinants of retinal venular diameter: the Beaver Dam Eye Study. Ophthalmology 2012;119:2563–2571. [PubMed: 22917892]
13. Cheung CY, Tay WT, Ikram MK, et al. Retinal microvascular changes and risk of stroke: the Singapore Malay Eye Study. Stroke 2013;44:2402–2408. [PubMed: 23868266]
14. McGeechan K, Liew G, Macaskill P, et al. Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis. Am J Epidemiol 2009;170:1323–1332. [PubMed: 19884126]
15. Wieberdink RG, Ikram MK, Koudstaal PJ, et al. Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: the Rotterdam Study. Stroke 2010;41:2757–2761. [PubMed: 21030694]
16. McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. Ann Intern Med 2009;151:404–413. [PubMed: 19755365]
17. Seidelmann SB, Claggett B, Bravo PE, et al. Retinal Vessel Calibers in Predicting Long-Term Cardiovascular Outcomes: The Atherosclerosis Risk in Communities Study. Circulation 2016;134:1328–1338. [PubMed: 27682886]
18. Ong YT, Wong TY, Klein R, et al. Hypertensive retinopathy and risk of stroke. Hypertension 2013;62:706–711. [PubMed: 23940194]
19. Mitchell P, Wang JJ, Wong TY, et al. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology 2005;65:1005–1009. [PubMed: 16217050]
20. Wong TY, Rosamond W, Chang PP, et al. Retinopathy and risk of congestive heart failure. JAMA 2005;293:63–69. [PubMed: 15632337]
21. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA 2002;287:1153–1159. [PubMed: 11879113]
22. Agarwal S, Shah T, Lopez F, et al. Retinal Microvascular Abnormalities, Albuminaria, and Atrial Fibrillation Incidence: the ARIC study. Circulation 2013;128 (suppl 22):A13405
23. Phan K, Mitchell P, Liew G, et al. Relationship between macular and retinal diseases with prevalent atrial fibrillation - an analysis of the Australian Heart Eye Study. Int J Cardiol 2015;178:96–98. [PubMed: 25464229]
24. Lee SR, Choi EK, Rhee TM, et al. Evaluation of the association between diabetic retinopathy and the incidence of atrial fibrillation: A nationwide population-based study. Int J Cardiol 2016;223:953–957. [PubMed: 27589043]
25. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881. [PubMed: 12397006]
26. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the united states. Am J Ophthalmol 2006;141:446–455. [PubMed: 16490489]
27. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified airlie house classification. Etdrs report number 10. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98 (5 Suppl):786–806. [PubMed: 2062513]

28. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/ sclerosis in the atherosclerosis risk in communities study. Ophthalmology 1999;106:2269–2280. [PubMed: 10599656]
29. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. Curr Eye Res 2003;27:143–149. [PubMed: 14562179]
30. Heckbert SR, Wiggins KL, Blackshear C, et al. Pericardial fat volume and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study. Obesity (Silver Spring) 2017;25:1115–1121. [PubMed: 28452401]
31. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis 2010;55: 622–627. [PubMed: 20338463]
32. Lin GM, Liu K, Colangelo LA, et al. Low-Density Lipoprotein Cholesterol Concentrations and Association of High-Sensitivity C-Reactive Protein Concentrations With Incident Coronary Heart Disease in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2016;183:46–52. [PubMed: 26597828]
33. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet 2015;386:154–162. [PubMed: 25960110]
34. Mou L, Norby FL, Chen LY, et al. Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status: ARIC Study (Atherosclerosis Risk in Communities). Circ Arrhythm Electrophysiol 2018;11:e006350. [PubMed: 30002066]
35. Martinez C, Katholing A, Wallenhorst C, et al. Increasing incidence of non-valvular atrial fibrillation in the UK from 2001 to 2013. Heart 2015;101:1748–1754. [PubMed: 26307057]
36. Lin GM, Redline S, Klein R, et al. Sex-Specific Association of Obstructive Sleep Apnea With Retinal Microvascular Signs: The Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2016;5:e003598. [PubMed: 27451457]
37. De Silva DA, Woon FP, Manzano JJ, et al. The relationship between aortic stiffness and changes in retinal microvessels among Asian ischemic stroke patients. J Hum Hypertens 2012;26:716–722. [PubMed: 21975690]
38. Tikellis G, Arnett DK, Skelton TN, et al. Retinal arteriolar narrowing and left ventricular hypertrophy in African Americans. the Atherosclerosis Risk in Communities (ARIC) study. Am J Hypertens 2008;21:352–359. [PubMed: 18246060]
39. Cooper LS, Wong TY, Klein R, et al. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. Stroke 2006;37:82–86. [PubMed: 16306463]
40. Cankar K, Finderle Z, Strucl M. Gender differences in cutaneous laser Doppler flow response to local direct and contralateral cooling. J Vasc Res 2000;37:183–188. [PubMed: 10859476]
41. McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. Ann Intern Med 2009;151:404–413. [PubMed: 19755365]
42. Pepine CJ, Kerensky RA, Lambert CR, et al. Some thoughts on the vasculopathy of women with ischemic heart disease. J Am Coll Cardiol 2006;47:S30–35. [PubMed: 16458168]
43. Cheung N, Bluemke DA, Klein R, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol 2007;50:48–55. [PubMed: 17601545]

In this prospective cohort study, there were suggestions that women might have a stronger association between wider retinal venules and incident AF and retinal signs for focal arteriolar narrowing was associated with higher risk of incident AF.

Table 1

Baseline Characteristics of the Cohort by Those with Gradable Retinal Images at the Second MESA Examination (2002–2004)

Characteristics	Retinal Image Available at 2nd MESA Visit N =4,994
Age, y	62.6 (9.7)
Female Sex, %	2,612 (52.3)
Race/ethnicity, %	
White	1,943 (38.9)
Black	1,334 (26.7)
Hispanic	1,094 (21.9)
Chinese	623 (12.5)
Smoking status, %	
Current	579 (11.6)
Former	2,092 (41.9)
Never	2,323 (46.5)
Current alcohol intake, %	2,574 (51.5)
Diabetes mellitus, %	696 (13.9)
BMI, kg/m^2	28.4 (5.5)
Systolic BP, mmHg	123.6 (20.5)
Diastolic BP, mmHg	70.6 (10.1)
Total cholesterol, mg/dL	191.9 (35.7)
HDL-cholesterol, mg/dL	51.7 (15.1)
HbA1c, %	5.70 (0.98)
hs-CRP, mg/L	1.87 (0.82 – 4.20) *
Antihypertensive therapy, %	2,004 (40.1)
Lipid-lowering therapy, %	1,079 (21.6)
CRAE, μm	144.41 (13.92)
CRVE, μm	214.11 (21.77)
Any retinopathy signs, %	565 (11.3)
Chronic kidney disease, %	417 (8.4)
CVD or heart failure, %	61 (1.2)

Continuous variables are expressed as mean (SD) and categorical variables as number (percentage). Abbreviations: BMI, body mass index (defined as weight in kilograms divided by height in meters squared); BP, blood pressure; CRAE, central retinal arteriolar equivalents; CRVE, central retinal venular equivalents; CVD, cardiovascular disease; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; MESA, the Multi-Ethnic Study of Atherosclerosis

* Median (Interquartile range)

Table 2.

Association of Retinal Microvascular Signs With Incident Atrial Fibrillation, 2002–2015

Variables	Hazard Ratio	95% confidence intervals	*P* value
CRAE, each +10 μm higher			
Unadjusted	0.90	(0.85–0.96)	0.002
Model 1	0.97	(0.91–1.04)	0.438
Model 2	0.99	(0.93–1.06)	0.791
CRVE, each +10 μm higher			
Unadjusted	0.97	(0.93–1.01)	0.189
Model 1	1.03	(0.99–1.08)	0.183
Model 2	1.01	(0.97–1.06)	0.541
Any retinopathy signs			
Unadjusted	1.25	(0.99–1.57)	0.060
Model 1	1.22	(0.97–1.54)	0.087
Model 2	1.10	(0.80–1.39)	0.449

Abbreviations: CRAE, central retinal arteriolar equivalents; CRVE, central retinal venular equivalents

Multivariable Cox Proportional Hazard Regression Model 1, adjusting for age, sex, and race/ethnicity; Model 2 adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus status, HbA1c, cigarette smoking status, current alcohol intake, systolic blood pressure, antihypertensive therapy, total cholesterol, high-density lipoprotein, lipid-lowering therapy, high-sensitivity C-reactive protein, chronic kidney disease, and baseline cardiovascular disease and heart failure

Table 3.

Association of Specific Retinopathy Signs With Incident Atrial Fibrillation, 2002–2015

Variables	Hazard Ratio	95% confidence intervals	*P* value
Retinal hemorrhages			
Unadjusted	1.51	(1.06–2.16)	0.023
Model 1	1.12	(0.78–1.59)	0.548
Model 2	1.08	(0.76–1.56)	0.660
Retinal microaneurysms			
Unadjusted	0.89	(0.64–1.23)	0.470
Model 1	1.05	(0.76–1.46)	0.774
Model 2	0.95	(0.68–1.33)	0.776
Retinal soft exudate			
Unadjusted	1.73	(1.08–2.77)	0.023
Model 1	1.58	(0.99–2.54)	0.057
Model 2	1.33	(0.82–2.17)	0.240
Retinal arteriovenous nicking			
Unadjusted	1.45	(1.02–2.06)	0.040
Model 1	1.11	(0.78–1.59)	0.552
Model 2	1.00	(0.70–1.43)	0.993
Retinal focal arteriolar narrowing			
Crude	3.30	(2.02–5.38)	<0.001
Model 1	1.73	(1.06–2.84)	0.030
Model 2	1.75	(1.06–2.87)	0.028

Multivariable Cox Proportional Hazard Regression Model 1, adjusting for age, sex, and race/ethnicity; Model 2 adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus status, HbA1c, cigarette smoking status, current alcohol intake, systolic blood pressure, antihypertensive therapy, total cholesterol, high-density lipoprotein, lipid-lowering therapy, high-sensitivity C-reactive protein, chronic kidney disease, and baseline cardiovascular disease and heart failure, along with central retinal arteriolar equivalents (CRAE) and central retinal venular equivalents (CRVE)

Table 4.

Association of Retinal Microvascular Signs With Incident Atrial Fibrillation by Subgroup Analyses for Sex, Age, Race, Diabetes, and Hypertension Status, 2002–2015

Variables	AF events	CRAE, each +10 μm	CRVE, each +10 μm	Any retinopathy
Sex				
Women (N=2,612)	287	0.96 (0.87–1.06)	1.08 (1.01–1.15) *	1.10 (0.77–1.57)
Men (N=2,382)	356	1.01 (0.93–1.11)	0.97 (0.92–1.03)	1.11 (0.82–1.52)
P for interaction		0.421	0.041	0.952
Age				
≥65 y (N=2,165)	472	1.02 (0.94–1.10)	0.99 (0.94–1.04)	1.14 (0.87–1.49)
<65 y (N=2,829)	171	0.89 (0.781.01)	1.04 (0.96–1.13)	0.91 (0.57–1.47)
P for interaction		0.061	0.264	0.422
Race/ethnicity				
White (N=1,943)	306	0.99 (0.89–1.09)	1.02 (0.96–1.09)	1.13 (0.78–1.65)
Black (N=1,334)	139	0.97 (0.85–1.11)	1.08 (1.00–1.18)	0.79 (0.48–1.30)
Hispanic (N=1,094)	119	1.00 (0.86–1.17)	0.96 (0.88–1.06)	1.52 (0.97–2.40)
Chinese (N=623)	79	1.03 (0.87–1.21)	0.93 (0.82–1.05)	0.94 (0.48–1.30)
P for interaction		0.960	0.145	0.253
Diabetes mellitus				
Presence (N=696)	111	1.01 (0.87–1.19)	1.00 (0.92–1.10)	1.37 (0.92–2.04)
Absence (N=4,298)	532	1.00 (0.93–1.07)	0.98 (0.94–1.03)	0.96 (0.70–1.30)
P for interaction		0.849	0.711	0.161
Hypertension				
Presence (N=2,424)	431	1.02 (0.94–1.10)	0.98 (0.94–1.03)	1.01 (0.77–1.33)
Absence (N=2,570)	212	0.96 (0.86–1.08)	1.01 (0.93–1.09)	1.32 (0.84–2.05)
P for interaction		0.412	0.612	0.316

Data are expressed as hazard ratio and 95% confidence intervals. Model 2 was used and adjusted for the covariates of age, sex, race/ethnicity, body mass index, diabetes mellitus status, HbA1c, cigarette smoking status, current alcohol intake, systolic blood pressure, antihypertensive therapy, total cholesterol, high-density lipoprotein, lipid-lowering therapy, high-sensitivity C-reactive protein, chronic kidney disease, and baseline cardiovascular disease and heart failure.

Abbreviations: CRAE, central retinal arteriolar equivalents; CRVE, central retinal venular equivalents

* p =0.028