

**ARIC Manuscript Proposal #1570**

**PC Reviewed:** 11/10/ 09

**Status:** 2

**Priority:** A

**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_

**Priority:** \_\_\_\_\_

- 1 **a. Full Title:** Retinal microvascular abnormalities and lacunar stroke incidence in the ARIC study
- b. Abbreviated Title:** Retinal findings and risk of lacunar stroke

**2 Writing Group:**

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. HY

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- 3 **Timeline:** Analysis will begin immediately, once the proposal is accepted, using surveillance data files through 2005 or the latest available. A draft will be prepared within four months and will be submitted to the Publications committee by 6 months.

#### **4 Rationale:**

Retinal microvascular abnormalities have been associated with an increased incidence of ischemic stroke,<sup>1</sup> and cross-sectionally with greater prevalence of MRI-defined subclinical cerebral infarction<sup>2</sup> and white matter lesions<sup>3</sup> in the ARIC and other populations.<sup>4-7</sup> Other cross-sectional studies of stroke patients found a positive association between acute lacunar stroke and retinal microvascular abnormalities.<sup>8</sup> However, no previous studies have prospectively examined whether retinal microvascular abnormalities are associated with incidence of clinical lacunar stroke in comparison with other subtypes of ischemic stroke. Since the retinal vasculature shares embryologic and anatomic characteristics with that of the cerebral vasculature, an association, if documented prospectively, would reinforce our understanding of the underlying pathology of stroke and its subtypes, in particular lacunar stroke and small vessel disease of the brain.

Retinal microvascular abnormalities are also associated with diabetes and hypertension,<sup>9-11</sup> which are major ischemic stroke risk factors. It therefore would be clinically informative to know whether or not retinal microvascular abnormalities are associated with the incidence of clinically apparent lacunar stroke independently of these risk factors, and if so, whether addition of retinal information will improve prediction of lacunar stroke incidence beyond conventional risk factors.

#### **5 Main Hypothesis/Study Questions:**

a. Incidence of lacunar stroke, but not of nonlacunar or cardioembolic stroke, is positively related to the presence of retinal microvascular abnormalities (focal arteriolar narrowing, arteriovenous nicking, generalized arteriolar narrowing, generalized venular widening). Retinopathy signs, including microaneurysms, retinal hemorrhage, soft and hard exudates, and optic disc swelling, are associated with lacunar as well as nonlacunar ischemic and cardioembolic stroke incidence. Adjustment for carotid IMT as a measure of atherosclerosis will attenuate positive associations between incidence of nonlacunar ischemic stroke and retinal arteriolar signs.

Age-related macular degeneration will not be addressed in the present manuscript.

b. The association of retinal microvascular abnormalities, especially generalized arteriolar narrowing and generalized venular widening, with lacunar stroke incidence is independent of hypertension, diabetes and other established risk factors. A significant association will be observed in subjects with or without these risk factors.

**6 Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).**

*Study design:* A prospective cohort study

***Inclusion/Exclusion:***

Inclusion: all black and white, ARIC visit 3 participants with no missing independent variable data, without a self-reported history of stroke at visit 1 or ascertained incident stroke from visit 1 to visit 3 (n=59). Subjects who, after visit 3, developed hemorrhagic stroke before the onset of ischemic stroke will be censored at the time of hemorrhagic stroke.

***Dependent variables:*** incident stroke, incident ischemic stroke subtypes (lacunar, nonlacunar and cardioembolic) measured through 2005 or the latest available. Details on ascertainment and classification of stroke are described elsewhere.<sup>12</sup> Briefly, a stroke was classified as “lacunar” on the basis of the recorded neuroimaging results when two criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of  $\leq 2$  cm or unstated size. Definite or probable “cardioembolic” stroke required the same criteria as ischemic infarction, plus either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain or (2) medical record evidence of a possible source of embolus such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure, or intracardiac thrombus. Definite or probable ischemic strokes that were not deemed lacunar or embolic were labeled “nonlacunar.” CT or MRI was available for 90% of the ischemic stroke cases.

***Independent variable:*** presence/absence or the degree of retinal microvascular abnormalities obtained at visit 3. Variables are arteriolar caliber (CRAE), venular caliber (CRVE), arteriovenous nicking and focal arteriolar narrowing. Other abnormalities to be included in the analysis are hemorrhages, microaneurysms, soft and hard exudates, and other retinal photography findings.

***Covariates:*** age at visit 3, sex, race, smoking status, usual alcohol consumption, physical activity, education level, mean systolic blood pressure (visit 1 and visit 3), use of antihypertensive medication, prevalent diabetes, waist circumference, and blood levels of HDL cholesterol at visit 3. Each covariate will preliminarily be examined for its confounding effect separately.

***Modeling:***

1. Hazard ratios for each ischemic stroke subtype by the presence of arteriovenous nicking, focal arteriolar narrowing, and other retinal lesions and the degree of generalized arteriolar narrowing (quintiles of CRAE) and degree of generalized venular widening (quintiles of CRVE) will be assessed by Cox proportional hazards model. Because of a positive

correlation between CRAE and CRVE, these variables will be examined simultaneously.<sup>13</sup> In addition, the variability in grading focal narrowing and arteriolar nicking will statistically be adjusted.

***Analysis plan:***

Assumption of hazards proportionality will be assessed by examining the parallelness of the ln (-ln) survival curves for groups defined each abnormality. A formal test will be carried out by including an interaction term between each abnormality and time (continuous or dichotomous at median (10-year)) in the Cox model.

***Stratified analyses:***

Analyses will be performed by stratified by (1) hypertension (2) diabetes (3) smoking (4) aspirin and other anticoagulant use, (5) past history of CVD

***Analysis comparing prediction equations:***

Area under the receiver operating curves for two models with or without retinal microvascular abnormalities will be compared. The base model includes age, sex, race, smoking status, alcohol consumption, physical activity, education level, systolic blood pressure, use of antihypertensive medication, prevalent diabetes, waist circumference, and blood levels of HDL cholesterol.

**7 Will the data be used for non-CVD analysis in this manuscript?**

\_\_\_\_\_ Yes     No

**8 a. Will the DNA data be used in this manuscript?**

\_\_\_\_\_ Yes     No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA="No use/storage DNA"?

c. If yes, is the author aware that the participants with RES\_DNA ="not for profit" restriction must be excluded if the data used by a for profit group?

**9 The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.**

Yes    \_\_\_\_\_ No

**10 What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

**MS# 334, Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study**

Retinal microvascular abnormalities were associated with increased prevalence of MRI-defined subclinical cerebral infarcts independent of stroke risk factors.<sup>2</sup> (Cooper LS, *Stroke*, 2006)

**MS#553, Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study**

Arteriovenous nicking and any retinopathy were associated with increased incidence of ischemic stroke independent of age, sex, race, mean arterial blood pressure over three ARIC examinations, hypertensive medication, diabetes status, smoking status and total and HDL cholesterol, triglyceride, and fasting glucose.<sup>1</sup> (Wong TY, *Lancet*, 2001).

**MS#753, Cerebral white matter lesions, retinopathy, and incident clinical stroke**

Focal arteriolar narrowing, arteriovenous nicking and other retinopathies but not generalized arteriolar narrowing were associated with increased prevalence of MRI-defined white matter lesions independent of age, sex, race, 6-year mean arterial blood pressure, hypertensive medication, diabetes status, smoking status and total cholesterol, fasting glucose, and carotid intima-media thickness. Retinopathy (microaneurysm, retinal hemorrhage, soft exudates) were associated positively with incident stroke independent of white matter lesions, ant relative risk representing joint effect of retinopathy and white matter lesions was 19.8 (95% confidence interval: 6.4-61.3) after adjusting for age, sex, race, 6-year mean arterial blood pressure, diabetes status, and carotid intima-media thickness.<sup>14</sup> (Wong TY, *JAMA* 2002)

**MS#1110, Risk Prediction of Coronary Heart Disease and Stroke using Retinal Arteriolar and Venular Signs**

In women but not men, wider retinal venular caliber and narrower retinal arteriolar caliber were associated with higher risk of incident CHD after adjusting for Framingham risk score variables. Area under the receiver operator curve increase from 0.695 to 0.706 (1.7% increase) with the addition of retinal vascular caliber to the Framingham risk model in women.<sup>15</sup> (McGeechan K. *Am J Cardiol*, 2008) (Despite proposal listed both CHD and stroke, the published article included only CHD.)

**11** Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

\_\_\_\_\_ Yes     No

- 12 Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

## References

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