

## ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #334

**1. Title:** MRI CeVD and Retinal Art Dis

**2. Writing Group:** Cooper LS (lead), Sharrett AR, Klein R, Bryan RN, Hutchinson RG, Tyroler HA, Hubbard LD, Brothers RJ, Sorlie PD, Cai J

**3. Timeline:**

Analysis to being on available data; publication to follow completion of retinal quantitative readings.

**4. Rationale:**

The retina and its microvasculature are anatomically and embryologically part of the brain. Retinal arteries branch from brain arteries, and retinal and cerebral vessels have similar histology and pathology. It is therefore logical that retinal arteriosclerosis (RA) is associated with cerebrovascular disease (CeVD), and pathologic evidence in Japanese stroke decedents supports this (Goto 1975). Furthermore, fundoscopic evidence of RA (including arteriolar narrowing and arterio-venous crossing changes) has been shown to predict stroke in rural Japan (Aoki 1975, Okada 1976) and in NHANES (results unpublished).

The chief risk factor for stroke, especially small vessel stroke, is hypertension. However, calculated odds ratios for stroke relative hypertensive status likely underestimate the true association, because a small number of blood pressure measurements taken in a research setting give only a small picture of overall lifetime blood pressure status, and the high prevalence of anti-hypertensive medication use in the U.S. population further distorts the picture. RA, itself largely related to hypertension after age adjustment, may provide a "record" of elevated blood pressure, and may therefore add predictive power for stroke and other forms of CeVD beyond that of blood pressure alone.

The potential to show a relationship between RA and CeVD, independent of blood pressure, may well be greater in ARIC than it has been in any previous study. First, qualitative retinal abnormalities, such as arteriolar narrowing and A/V crossing changes, are assessed from fundus photographs, using a standardized grading scale. Second, a quantitative measure of generalized retinal arteriolar narrowing (scaled to venous measurements), based on the method of Parr, has been included in ARIC; preliminary analysis has shown that this measure is associated with blood pressure. Furthermore, during Visit 3 approximately 2000 members of the Forsyth and Jackson cohorts underwent cerebral MRI, which detects clinically silent cerebral infarcts, substantially boosting the statistical power to estimate the association of stroke with retinal findings.

Because arteriosclerosis is by definition a small vessel disease, it is expected that RA will be more strongly associated with MRI lacunar infarct, which involves small cerebral arteries, than with non-lacunar infarct. RA is also expected to be associated with cerebral white matter abnormalities seen on MRI, which are associated with hypertension and are probably related, at least partly, to arteriolar changes. RA may also be associated with cerebral atrophy, which may be associated with small vessel disease.

**5. Main Hypothesis:**

I. RA, as assessed by both qualitative and quantitative methods, is associated with MRI infarct and white matter abnormalities, as well as cerebral atrophy, independently of blood pressure/hypertensive status and

age.

II. RA is more highly associated with MRI lacunar infarct than with non-lacunar infarct.

**6. Data (variables, time frame, source, inclusions/exclusions):**

For members of the Forsyth and Jackson cohorts, all exam 1 through exam 3 sitting, standing and supine BP, derived hypertension status.

Quantitative and qualitative retinal data.

Covariates: age, gender, race, community, exam dates, antihypertensive medication use (for Visit 3 if derived hypertension variable unavailable), diabetes status (derived, blood glucose), medical history, smoking status and history, total cholesterol, HDL-C, LDL-C, triglycerides.

Analysis to be performed in Bethesda. An exemption from Coordinating Center official analysis is requested. Statistical analysis plan to follow.