ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #553

1. Full Title: Retinal Arteriosclerosis and Hospitalized Stroke
Abbreviated Title (length 26): Retinal Artrsclrs & Stroke

2. Writing Group (list individual with lead responsibility first):
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3. Timeline:
Analysis request submitted within one month of approval. First draft submitted within 3 months of completion of analysis.

4. Rationale: Small vessel arterial disease, or arteriosclerosis, as assessed qualitatively and quantitatively in retinal vessels, has been found to be a strong predictor of MRI-defined cerebral infarction in the ARIC Study. Most of those MRI-defined infarctions were clinically unrecognized, small in size, and most likely due to small vessel, nonatherosclerotic disease (lacunar infarcts). By contrast, most clinical strokes in ARIC are probably due to large vessel disease, with only about 25% of incident strokes classified as lacunar. Fundoscopic evidence of RA (including arteriolar narrowing and arterio-venous crossing changes) has been shown to predict clinical stroke in rural Japan (Aoki 1975, Okada 1976). It is important to examine whether retinal arteriosclerosis (RA) is associated with clinical stroke in the U.S. population, and how the strength association compares with that for MRI infarcts. ARIC, having both high quality assessment of RA and physician-verified stroke, provides a probably unique opportunity to explore this association.

The chief risk factor for stroke, especially small vessel stroke, is hypertension. However, calculated odds ratios for stroke relative to 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 beyond that of blood pressure alone. For MRI infarcts in ARIC, RA shows an association independent of BP/BP medication use as well as other co-variates; this association is largely limited to hypertensives.

Because retinal photography in ARIC was done during Exam 3, there are not yet enough verified hospitalized incident strokes subsequent to that exam to conduct this analysis. However, it is unlikely that clinical stroke has an impact on RA. While more aggressive BP treatment following a stroke might reduce somewhat the apparent severity of RA, this is unlikely to attenuate the association of RA with stroke to a major degree. For the association of RA and MRI infarcts in ARIC, there is no hint of a difference between hypertensives on BP medication and those not treated. It is therefore proposed to include all incident strokes occurring after each person's Exam 1.

5. Main Hypothesis:
RA is associated with clinical incident stroke (all combined, excluding subarachnoid hemorrhage), independently of blood pressure/hypertensive status, age, and other stroke risk factors. The strength of the relationship is generally weaker than that between RA and MRI-defined cerebral infarcts.

6. Data (variables, time window, source, inclusions/exclusions):
All Definite and Probable Stroke through 1995, excluding Subarachnoid Hemorrhage. Quantitative and qualitative retinal data. Age, gender, race, date of Exam 1 and incident stroke. For cohort Exam 1 through 3 all sitting BP data, derived hypertension status, antihypertensive medication, diabetic status (derived, blood glucose), history of MI/CHD, smoking status, total cholesterol, HDL-C, LDL-C, triglycerides, fibrinogen, BMI. Analysis to be done in Bethesda. Official analysis exemption requested because no new variables used.