

ARIC Manuscript Proposal #753

PC Reviewed: 11/ 21/ 00
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Priority: 1
Priority: _____

1.a. Full Title: Retinal microvascular abnormalities and its relation to cerebral white matter lesions and atrophy: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Retinal and cerebral lesions

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

This analysis is part of overall objective to investigate the relation of retinal microvascular abnormalities, graded during the ARIC third examination and cerebral diseases. Specifically, this proposal will be similar to ARIC #334 (Retinal microvascular changes and MRI-detected cerebral infarcts), with a new dataset created with white matter lesions (WML) and cerebral atrophy as endpoints. We estimate that there will be approximately 1,800 persons will have both retinal photography and cerebral MRI.

After approval, the initial analyses and writing will take place between Jan and March 2001, final analysis between April 2001 and June 2001, and final writing and submission of manuscript between July 2001 and September 2001.

4. Rationale:

With the introduction of MRI technology, cerebral WML and atrophy are frequently detected in elderly individuals. Although these lesions may be asymptomatic, WML and cerebral atrophy have also been found to be related to cognitive decline, gait disturbance, disability, depression and clinical stroke. The etiology and pathogenesis is not clear. It has been suggested these lesions are the consequence of arteriolosclerosis, microvascular diseases and subsequent ischemia. In this respect, associations between WML and hypertension and other cardiovascular risk factors have been inconsistently reported.

Retinal microvascular changes reflect systemic microvascular damage from aging and hypertension. Because the retinal vasculature are embryologically and anatomically part of the

cerebral vasculature, and are directly accessible to non-invasive evaluation, retinal microvascular lesions have been suggested as markers of cerebral microarteriolar pathology.

In ARIC, retinal microvascular abnormalities were quantified based on standardized photographic grading techniques and on computer-assisted measurements of retinal arteriole calibers (Hubbard, 1999). We have previously found that retinal microvascular abnormalities are related strongly to both current and past blood pressure levels (Sharrett, 1999), with prevalent subclinical cerebral infarcts detected by MRI (Cooper, 2000), and with incident clinical strokes (Wong, 2000), independent of blood pressure and other stroke risk factors.

The prevalence and risk factors of MRI-defined WML in ARIC have also been reported (Liao, 1996, 1997). WML were found in 85% of participants with an MRI, and were related to age, blood pressure, pulse pressure, hypertension status, smoking status, and a history of stroke. The association was stronger in persons with treated uncontrolled hypertension (OR 3.4) compared to persons with treated controlled hypertension (OR 1.94) and untreated hypertension (OR 1.99).

The purpose of this present analysis is to evaluate the relation between retinal microvascular abnormalities and MRI-defined cerebral WML and atrophy in the ARIC cohort. This information would provide further understanding of microvascular contribution of the etiology and pathogenesis of WML and cerebral atrophy.

5. Main Hypothesis/Study Questions:

- (1) After controlling for age, sex, race and examination center, blood pressure, and smoking, among other variables, retinal microvascular abnormalities are associated with MRI-defined cerebral WML.
- (2) After controlling for age, sex, race and examination center, blood pressure, and smoking, among other variables, retinal microvascular abnormalities are associated with MRI-defined cerebral atrophy.
- (3) The association of these abnormalities with cerebral WML is stronger in persons with hypertension than in those without.
- (4) The association of these abnormalities with cerebral atrophy is stronger in persons with hypertension than in those without

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

- (1) Retinal variables: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysm, soft exudates and hard exudates. Generalized arteriolar narrowing quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.
- (2) Cerebral MRI variables: Presence and severity of WML (grade 1 to 9), presence and severity of cerebral atrophy (sulcal widening and ventricular enlargement)
- (3) Demographic variables: age at visit 3, sex, race, examination center
- (4) Other CVD risk factors/potential confounders: Hypertension status, diabetes status, mean arterial BP, systolic and diastolic BP, serum lipids (total, HDL and LDL cholesterol, TG, lp(a), apo A1 and B, fasting glucose levels, hemostatic function indicators (von Willebrand factor, factor VIIIc, fibrinogen, WBC, cigarette smoking indicators (ever/never, current/former/never, pack-years), alcohol indicators,

hypertensive medications, diabetic medications, (variables from ARIC visit 3, except for lp(a), apo A1 and B, von Willebrand factor, factor VIIIc, and cigarette pack-years, available from ARIC visit 1 only)

- (5) Exclusion criteria: From participants at ARIC third exam, exclude persons who did not participate in the second exam, whose race is neither black nor white, if missing data on BP, and hypertension status, at any of the three examinations. Also exclude persons with no retinal photographs or upgradeable photographs and those with retinal venous or artery occlusions.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No