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ARIC Manuscript Proposal #769

PC Reviewed: 01/ 16/ 01 **Status: A** **Priority: 2**
SC Reviewed: 01/ 30/ 01 **Status: A** **Priority: 2**

1.a. Full Title: Retinal microvascular abnormalities and its relation to renal dysfunction: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Retinal and renal diseases

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

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3. Timeline:

The intent of this analysis is to investigate the relation of microvascular diseases (as reflected by retinal microvascular abnormalities) to renal dysfunction. Specifically, this proposal will involve a cross-sectional analysis of retinal microvascular changes (graded at visit 3) and renal dysfunction (incident rise in serum creatinine from visit 1 to visit 4).

After approval, the initial analyses and writing will take place between March and May 2001, final analysis between June 2001 and August 2001, and final writing and submission of manuscript between September 2001 and December 2001.

4. Rationale:

Chronic renal failure is a common cause of morbidity and disability in the elderly. A large proportion of renal failure cases do not have evidence of a primary renal disease (e.g. nephritis). In these cases, the etiology remains largely unknown. Epidemiological and clinical data have indicated that “idiopathic” renal failure is more common in persons with atherosclerosis, hypertension, diabetes and hyperlipidemia (Preston, 1997). A microvascular cause has also been suggested, but the exact relation of microvascular diseases to the development of renal failure is not clear, partly due to the difficulties in evaluating the renal microcirculation (Mailloux, 1994).

The retinal arteriole offers an opportunity to explore the relation of microvascular disease to renal dysfunction. The retinal microcirculation is accessible to direct non-invasive visualization, and appears to share similar pathology (e.g. arteriolar wall hyalinization, medial thickening and sclerosis) as the renal microcirculation in persons with hypertension and other vascular diseases (Nag, 1980)(Freedman, 1994)(Tso, 1982). The relation between diabetes-related retinal and renal microvascular changes have been shown consistently in both clinical (DCCT, 1993)(Lovestam-Adrian, 1998) and pathological studies (Schwartz, 1998)(Chavers, 1994). However, few data are

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available regarding the relation between retinal microvascular diseases and renal dysfunction in the non-hypertensive or non-diabetic general population. The ARIC cohort provides a unique opportunity to evaluate this association.

In the ARIC visit 3 examination, focal retinal microvascular abnormalities were quantified based on standardized photographic grading techniques, and retinal arteriolar diameter was further quantified based on computer-assisted measurements of retinal vessel widths (Hubbard, 1999). We have previously found that retinal microvascular abnormalities were related strongly to both current and past blood pressure levels (Sharrett, 1999), with prevalent subclinical cerebral infarcts detected by MRI, and with incident clinical strokes, independent of blood pressure and other stroke risk factors (ARIC MS#334 and 553, both submitted to Lancet).

In ARIC, renal function was quantified at Visit 1, 2 and 4 by serum creatinine levels. A previous paper, with renal dysfunction defined as incident rise in serum creatinine between visits 1 and 2 of >=0.4 mg/dL showed that persons with higher triglycerides and lower HDL cholesterol levels were found to have a higher risk of incident renal dysfunction, even after adjusting for age, gender, race, baseline serum creatinine, systolic blood pressure, anti-hypertensive medication use and diabetes (Muntaner, 2000).

The purpose of this present analysis is to evaluate the relation between retinal microvascular abnormalities at visit 3, and serum creatinine levels at visit 1, 2 and 4, the change in creatinine levels from visit 1 to visit 4, and incident renal dysfunction from visit 1 to visit 4 in the ARIC cohort. This information would provide further understanding of the role of microvascular disease in the development and course of renal dysfunction in middle-aged persons.

5. Main Hypothesis/Study Questions:

(1) After controlling for age, sex, race and examination center, retinal arteriolar diameter (visit 3) is negatively correlated to serum creatinine levels at visit 1, 2 and 4 (i.e. narrower vessels associated with higher creatinine levels), with 9-year change in serum creatinine levels from visit 1 to 4 (i.e. greater 9-year increase in creatinine levels) and incident renal dysfunction (persons with serum creatinine levels >=0.4 mg/dL at visit 2 or 4, in persons free of this at visit 1).

(2) After controlling for age, sex, race and examination center, focal retinal microvascular abnormalities are associated positively with the outcomes in (1)

(3) Associations in (1) and (2) may be attenuated after controlling for hypertension, blood pressure levels, diabetes and other cardiovascular factors (e.g. lipid levels, inflammatory markers)

(4) Associations in (1) and (2) may differ in persons with and without hypertension or diabetes (we will test associations stratified by hypertension and diabetes status)

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. Retinal arteriolar narrowing quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.

(2) Renal function: Serum creatinine at visit 1, 2 and 4, change in serum creatinine between visit 1 and 4, incident rise in serum creatinine >=0.4 mg/dL between visit 1 to 4 (among those free of this at visit 1).

(3) Demographic variables: age at visit 1 to 4, , sex, race, examination center

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(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, and TG), fasting glucose levels, hemostatic function indicators (von Willebrand factor, factor VIIIc, aPTT), fibrinogen, WBC, cigarette smoking indicators (ever/never, current/former/never, pack-years), alcohol indicators, hypertensive medications, diabetic medications

(5) Exclusion criteria: From participants at ARIC third exam, exclude persons whose race is neither black nor white, exclude persons with no retinal photographs or ungradeable photographs, those with retinal venous or artery occlusions and those missing data on creatinine levels at either visits 1, 2 or 4.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X__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 ICTDER02 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 _X__ 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

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