ARIC Manuscript Proposal # 873

PC Reviewed: 03/12/02	**Status: __A__**	**Priority: __K__**
SC Reviewed: 03/19/02	**Status: __A__**	**Priority: __K__**

1.a. Full Title: Incidence, progression and regression of retinal arteriolar disease in the ARIC study

b. Abbreviated Title (Length 26 characters): Incident retinal disease

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

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3. Timeline:

This analysis will investigate the 3-year incidence, progression and regression of retinal microvascular disease, from ARIC visit 3 to visit 4, on a subsample of ARIC participants (n = ± 1,000). Specifically, our proposed study will investigate 1) the development of new focal retinal microvascular lesions (e.g., retinal hemorrhages) at visit 4 in persons without these lesions at visit 3, and 2) the progression or regression of retinal arteriolar narrowing, 3) risk factors associated with incidence and progression of retinal arteriolar disease.

After approval, the initial analyses and writing is anticipated to begin *immediately* on approval (March or April 2002), with preliminary data available for the proposed ARIC visit 5 grant (submission due June 2002). The final analysis and writing will be completed by December 2002.

4. Rationale:

The contribution of microvascular disease to the development and progression of coronary heart disease, stroke and other vascular disorders is not fully understood, but its elucidation will be important from preventive, therapeutic and prognostic perspectives.[1,2] Microvascular disease has been suggested to be a significant risk factor for subclinical and clinical stroke,[3] and has been hypothesized to explain the occurrence of myocardial ischemia without overt coronary artery blockage,[4-8] and risk of left ventricular dysfunction,[9] heart failure,[10] and mortality[11] after a myocardial infarction.

Recent data from the ARIC visit 3 examination indicate that retinal microvascular changes, as assessed via photography, are reliably documented, including computer-based measurements of retinal arteriolar caliber (and summarized as the retinal arteriole / venule ratio [AVR]).[12] Retinal microvascular changes have been found to be strongly associated with

concurrent blood pressure,[13] with past blood pressure independent of current blood pressure[13] and with various systemic markers of inflammation and endothelial dysfunction.[14] Independent of blood pressure, cholesterol, smoking, diabetes, and other risk factors, the ARIC study has shown that baseline retinal arteriolar narrowing was predictive of incident CHD in women, but not in men,[15] which supports a possible microvascular role in the pathogenesis of definite myocardial infarction and CHD death that is more prominent in women than men.

Few data on the incidence and progression of retinal microvascular disease are available. In the Beaver Dam Eye Study, about 6-10% of people developed incident focal retinal changes (focal arteriolar narrowing, arterio-venous nicking, and retinopathy) over a 5-year period.[16]

In the proposed study, we will investigate the 3-year incidence and progression of retinal arteriolar disease in the ARIC study. We will examine traditional (e.g. hypertension) and novel risk factors (e.g., markers of inflammation) for these endpoints. Findings will lead to a clearer understanding of the natural history of microvascular disease, as reflected in the retina, in the general population, and provide a rationale for including retinal photography in ARIC visit 5.

5. Main Hypothesis/Study Questions:

To determine:

(1) The 3-year incidence of focal retinal microvascular lesions (focal arteriolar narrowing, arterio-venous nicking, and retinopathy) at visit 4, in persons without these lesions at visit 3, by age, gender and race

(2) The 3-year progression or regression of retinal arteriolar narrowing (change in retinal AVR), by age, gender and race

(3) Traditional (e.g., blood pressure, hypertension status, cigarette smoking, diabetes) and novel (e.g., inflammatory markers) vascular risk factors for incidence and progression of retinal arteriolar narrowing and other microvascular abnormalities

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

(1) Retinal variables at Visit 3 and 4: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysms and soft exudates. Generalized arteriolar narrowing quantified as retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.

(2) Demographic variables: age, sex, race, center

(3) CVD risk factors/potential confounders: Cardiovascular history status (prevalent CHD and MI), hypertension and diabetes status, BP at visits 1 to 3, serum lipids (total, HDL and LDL cholesterol, TG), fasting glucose levels, hemostatic function (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, hypertensive medications, body mass index, waist to hip ratio, (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, available ARIC visit 1 only)

(4) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white and with no retinal photographs or ungradeable photographs at visit 3 or visit 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 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** _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**

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. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

_X__ **Yes** ____ **No**

References

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