ARIC Manuscript Proposal # 1063r

PC Reviewed: _05/13/05	**Status: __A__**	**Priority: __2__**
SC Reviewed: _05/13/05	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Retinal Arteriolar Changes and Left Ventricular Hypertrophy in African-Americans.

b. Abbreviated Title (Length 26 characters): Retinal Disease and LVH

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

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3. Timeline:

The intent of this analysis is to investigate the association of the retinal arteriolar disease and left ventricular hypertrophy in Jackson site participants of the ARIC study at Visit 3. Initial analyses and writing will take place between April and June 2005, and final writing and manuscript submission between July 2005 and Nov 2005.

4. Rationale:

Left ventricular hypertrophy (LVH) is recognized as an important risk factor for cardiovascular morbidity and mortality, independent of standard risk factors (1-4). Regression of LVH has been associated with reduction in all cause and cardiovascular mortality, independent of the effects of blood pressure reduction (5).

Despite much research, the underlying pathophysiological mechanisms of LVH development are not well understood (6-8). One of the key risk factors of LVH is sustained elevated blood pressure (6-8). In persons with hypertension, LVH is regarded as a key marker of "end organ damage", and its presence is an indication for pharmaceutical treatment even in mild hypertension (9). However, the existence of LVH in apparently healthy people without hypertension suggests that other risk mechanisms may also play a role in its development (10,11). Moreover, differentiating a threshold cutoff (pathological versus physiological) for LVH is not always straightforward (11).

Microvascular disease has been suggested as one possible risk factor in LVH development (12-18). In support of such a hypothesis are observations of changes in myocardial microvessel structure and density in people with hypertension (12), and the demonstration of abnormal coronary microvascular response in individuals with LVH (19,20). However, many of these studies have been concentrated on small numbers of high-risk patients conducted in experimental settings. Key questions that remain unanswered include the following: Are microvascular processes associated with LVH in the general population, and is this association independent of blood pressure? Does the presence of microvascular disease in patients with LVH help identify those with "pathological" disease with its implications of

poorer prognosis (e.g., might these patients have a greater reduction in ejection fraction for a given degree of hypertrophy?)

Recent analyses in the ARIC study have demonstrated that retinal microvascular changes are strongly related to blood pressure. Narrowed retinal vessel diameters are not only associated with concurrent blood pressure levels (21), but also with past (22) and future (23) blood pressure levels independent of the concurrent measurements. Retinal microvascular signs have been further shown to predict incident congestive heart failure (24), independent of standard risk factors. These results support a role of microvascular processes in the development of clinical cardiovascular events.

Furthermore, data from the ARIC study, amongst others, have shown that African-Americans are more likely to have hypertension (25,26), and more likely to develop complications, such as LVH (27) and hypertensive retinopathy (28) than whites. It is possible that the contribution of microvascular disease to LVH development in African-Americans may be more prominent (29).

In the current analyses, we will explore the association between retinal arteriolar signs and LVH as assessed by echocardiography among African-American participants in Jackson, Mississippi.

5. Main Hypothesis/Study Questions:

To describe the association of retinal microvascular changes with LVH, and other measures of LV structure (e.g., posterior and septal wall thickness) and function (e.g., ejection fraction), and to determine whether this association is independent of current and past blood pressure, use of anti-hypertensive medication, and other vascular risk factors, and whether this association is present in people without hypertension.

- Hypothesis: Various measures of LVH are related to retinal microvascular signs independent of blood pressure and other factors.

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

(1) Retinal variables: retinopathy, focal arteriolar narrowing, arterio-venous nicking, arteriolar and venular diameters (CRAE and CRVE), AV ratio
(2) Echocardiogram variables: LVH, posterior and septal wall thickness, LV internal diameter in diastole; relative wall thickness; LV mass, LV mass index, LV geometry
(3) Covariates: age, sex, prevalent CHD and MI, diabetes and hypertension status, blood pressure at visit 1, 2, 3 and 4, HBA1C, cigarette smoking, alcohol consumption, body mass index
(4) Exclusion criteria: From Jackson, MS cohort at ARIC visit 3, exclude persons with no echocardiogram, no retinal photographs or ungradeable photographs.

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

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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