ARIC Manuscript Proposal #2575

PC Reviewed: 7/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Retinal microvascular signs and incidence of abdominal aortic aneurysm

b. Abbreviated Title (Length 26 characters): Retinal signs and AAA

2. Writing Group:

Writing group members: Pamela L. Lutsey, Aaron R. Folsom, Ronald Klein, Barbara E. Klein, Lindsay Bengtson, Weihong Tang, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __PLL__

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Data analyses will begin immediately. Goal completion by Dec. 2015.

4. Rationale:

Abdominal aortic aneurysm (AAA) is a condition in which a portion of the aortic wall undergoes progressive dilation and weakening, potentially leading to aortic rupture if untreated[1]. In the United States in 2009 aortic aneurysms (of which most are abdominal) were the primary cause of 10,597 deaths and a contributing cause in more than 17,215 deaths[2].

Key features thought to underlie the pathogenesis of AAA are the progressive degradation and remodeling of elastin and collagen fibers of the aortic wall[3, 4]. Relatively

little is known about the etiology of AAA, though age, male sex, smoking status and hypertension are important risk factors.

Retinal vessels share similar anatomical and physiological properties with other vessels in the circulatory system, and for decades they have been proposed as an easily and safely measured surrogate for coronary circulation.[5] In ARIC retinal microvascular signs have been associated with numerous outcomes, including stroke,[6, 7] congestive heart failure,[8] coronary heart disease (women only)[9] and brain microvascular disease.[10]

Given that vascular dysfunction is the etiologic foundation of AAA, it is possible that retinal microvascular abnormalities may serve as an early indicator of AAA. To date, no epidemiologic studies have examined the association between retinal microvascular signs and incidence of AAA.

5. Main Hypothesis/Study Questions:

Hypotheses: Presence of retinopathy signs [i.e. retinal microaneurysms, hemorrhages (flame-shaped and blot), and soft exudates], and retinal vessel caliber measurements, specifically, narrower arteriolar and wider venular diameters at ARIC visit 3, will be independently associated with greater risk of incident AAA, and with higher prevalence of AAA by ultrasound at visit 5.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Design: Prospective cohort from visit 3 (when eye measurements took place) through the 2011 event follow-up for ARIC hospitalized AAAs, CMS through 2011 for CMS hospitalized and outpatient AAAs. The visit 5 abdominal aortic ultrasound data will be analyzed separately, and the abdominal aortic ultrasound exam at Visit 5.

Exclusions: We will exclude from the analysis participants who indicated prior surgery on the aorta at ARIC study baseline, and those who developed AAA between Visit 1 and Visit 3.

Exposures:

- retinopathy signs [i.e. retinal microaneurysms, hemorrhages (flame-shaped and blot), and soft exudates]
- retinal vessel caliber measurements
    - arteriolar diameter
    - venular diameter

Outcome: All detected AAAs after Visit 3.
Covariates: age, race-field center, sex, height, weight, smoking status and amount, diabetes, SBP and BP meds, total cholesterol, triglycerides, HDL-C, lipid-lowering medications.

Data analysis: Cox proportional hazards models for clinical/hospital AAA analysis and logistic regression for ultrasound AAA analysis.

Visit 3 will be treated as baseline and AAAs detected before Visit 3 will be excluded. The associations between Visit 3 risk factors and AAA will be examined and reported separately for clinical and ultrasound-detected AAAs. For analyses on hospital AAAs, we will examine the proportionality assumption and use an appropriate form of Cox regression model to examine the association between baseline risk factors and subsequent clinical AAAs. For analyses on ultrasound-detected asymptomatic AAAs, we will exclude participants with known incident clinical AAA, and use logistic regression model to estimate the odds ratios for the associations, on the condition of fixed lengths of follow-up time. We will adjust for potential confounders. We anticipate that model 1 will adjust for age, sex, and race-center. In Model 2 we will further adjust for height, weight, smoking pack years, diabetes, SBP, blood pressure medications, total cholesterol, triglycerides, HDL-C, and lipid medication.

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 ICTDER03 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 ICTDER 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 ICTDER03 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://www.cscc.unc.edu/ARIC/search.php

___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? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* 2009.18**)**

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __X__ Yes ____ No.

References

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