ARIC Manuscript Proposal #2896

PC Reviewed: 11/08/16	**Status: ____**	**Priority: 2**
SC Reviewed: _____	**Status: ____**	**Priority: ___**

1.a. Full Title: Retinal Vessels Calibers in the Long-term prediction of Cardiac Structure and Function

b. Abbreviated Title (Length 26 characters): Retinal vessels and echo

2. Writing Group:

Writing group members: Sara B. Seidelmann, Brian Claggett, Amil Shah, [OTHERS WELCOME], Barbara E. Klein, Ronald Klein, Scott D. Solomon

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SS_ **[please confirm with your initials electronically or in writing]**

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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: Analysis will begin following proposal approval with the aim of completing the analysis and associated manuscript(s) within 1 year of data availability.

4. Rationale:

Fundus photography provides a noninvasive method of visualizing the microvasculature. Alterations in the caliber of the retinal artery and vein have been associated with inflammation[1], endothelial dysfunction[2], diabetes[3], stroke, and CHD and its risk factors [1, 3, 4]. Most recently, our group has shown that narrower retinal arterioles and wider retinal venules conferred long-term risk of mortality and ischemic stroke in both genders and CHD in women[5]. Further, retinal vessel caliber provided incremental value over the 2013 American College of Cardiology/American Heart Association pooled cohort equations (PCE) in predicting Atherosclerotic Cardiovascular Disease Events (ASCVE) in low risk women[5]. In this study, we aim to further characterize the association of retinal vessel calibers with long-term functional and structural cardiovascular effects through the use of echocardiography. We hypothesize that retinal vessel calibers will be vastly predictive of measures of cardiac structure and function obtained 18 years later.

5. Main Hypothesis/Study Questions:
1) We hypothesize that retinal vessel calibers, measured at Visit 3, will be predictive of echocardiographic measures of cardiac structure and function, measured 18 years later.
2) We hypothesize that retinal vessel calibers will be independently predictive of cardiac structure and function over traditional cardiovascular risk factors such as blood pressure and hypertension.

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).

Basic Study Design and study population:

Retinal vessel calibers were measured from retinal fundus photographs taken at the third examination (in which 12,887 subjects attended). Other considered risk factors will also be from the third examination, and the echocardiographic measures taken at the fifth examination.

Exposures and their measurement:

Exposures are Central retinal arteriolar equivalent (CRAE) and Central retinal venular equivalent (CRVE). Retinal photographs were captured and digitized. CRAE and CRVE were calculated, representing the average of estimated calibers for the central retinal vessels. The reproducibility statistics for CRAE and CRVE were high, reflecting repeat readings of the same fundal photograph [6].

Outcomes and their measurement:

Echocardiographic measures--Left ventricular dimensions and volume, systolic function, LV diastolic measures, LA dimensions and function, tissue Doppler and speckle tracking based strain (longitudinal, circumferential and radial), RV dimension, volumes, and function.
ECG measures—heart rate, PR, QRS, and QT interval, RBBB and LBBB
Plasma measures—brain natriuretic peptide levels
Confounders and their measurement:
Age, gender, race (self reported "African American" or "other"), Total cholesterol (TChol, continuous variable measured by blood plasma assay), high density lipoprotein (HDL, continuous variable measured by blood plasma assay), systolic and diastolic blood pressure (SBP, DBP continuous variable was measured 3 times using a random-zero sphygmomanometer and the average of the 2nd and 3rd measurements used for analysis), hypertension status (categorical variable defined as antihypertensive medications within the past 2 weeks of examination were self-reported or taken from prescription bottles or BP> 140/90), diabetes mellitus status (categorical variable), body mass index, estimated Glomerular Filtration Rate.
Analysis plan:
Visit 3 will serve as the baseline for these analyses. Data will be reported as frequencies and percentages and compared by chi-squared or Fisher exact tests. Mean and standard deviation will be used to summarize continuous, normally distributed data; non-normally distributed data will be summarized as median and 25^{th} -75^{th} percentile. Interactions between age, sex, and/or race and the relationship between CRAE/CRVE and echocardiographic outcomes will be assessed. Stratified analysis by age, sex and/or race strata will be performed if a significant interaction is apparent. The association between CRAE/CRVE and echocardiography measures will be analyzed with multivariable linear regression controlling for potential confounders such as age, sex, race, BMI, ARIC center, and diabetes mellitus. Inverse probability weighting will be used to account for the non-randomness of missing echocardiographic data at Visit 5.

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)?**

Past (inactive) proposals:

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/

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 ____ Yes __x__ No.

References:

1. Wong, T.Y., et al., *Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA).* Invest Ophthalmol Vis Sci, 2006. **47**(6): p. 2341-50.
2. Delles, C., et al., *Impaired endothelial function of the retinal vasculature in hypertensive patients.* Stroke, 2004. **35**(6): p. 1289-93.
3. Wong, T.Y., et al., *Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons.* JAMA, 2002. **287**(19): p. 2528-33.
4. Wong, T.Y., et al., *Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study.* JAMA, 2002. **287**(9): p. 1153-9.
5. Seidelmann, S.B., et al., *Retinal Vessel Calibers in Predicting Long-term Cardiovascular Outcomes: The Atherosclerosis Risk in Communities Study.* Circulation, 2016.
6. Couper, D.J., et al., *Reliability of retinal photography in the assessment of retinal microvascular characteristics: the Atherosclerosis Risk in Communities Study.* Am J Ophthalmol, 2002. **133**(1): p. 78-88.