ARIC Manuscript Proposal #2627

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Retinal Vessel Caliber and Cardiac Risk Reclassification: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Sara B. Seidelmann, Brian Claggett, Venkatesh Murthy, Paco Bravo, Marcelo Di Carli, [Others welcome], Scott D. Solomon

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SBS **[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 6 months of data availability.

4. Rationale:

Coronary heart disease (CHD) and congestive heart failure (CHF) represent the most important causes of death and disability in the developed world. The lifetime risk of developing CHD after age 40 is 49% for men and 32% for women(1) and CHF is a high volume indication for hospital visits in our aging population(2). Identifying individuals at low to moderate risk that may benefit from aggressive medical therapy and lifestyle modification is imperative. Widespread assessment of CHD risk is based on clinical, multivariate predictive models derived from large-scale epidemiological studies. CHD risk scores such as the Framingham CHD Risk Score (FRS) have greatly contributed to the prevention of CHD but are imperfect. Previous studies in the ARIC cohort have shown that FRS was significantly associated with CHD events with an AUC of 0.77, however, using a "high risk" definition of greater than or equal to a 20% 10-year risk of disease, the sensitivity of FRS was only 13% [Table 1 (3)]. In fact, 75% of CHD events occurred in those not categorized as "high" risk by FRS. Therefore, most individuals who experienced a CHD event would not have been acknowledged to be in need of intensive medical intervention by their physician.

Table 1.
Observed CHD (fatal or non-fatal myocardial infarction (MI)) incidence rate based on FRS categories in subjects without known CHD, stroke, TIA, or DM at baseline. Adapted from Murphy et al (3).

	Low FRS (FRS <6%)	Int FRS (FRS 6–19%)	High FRS (FRS ≥20%)	Total	Chi square *p*-value
ARIC: *n* = 11,436; 438 CHD events during 10-year follow-up					
No CHD event; no. (% within FRS categories)	7309 (98.5%)	3409 (92.6%)	280 (83.3%)	10,998	<0.0001
CHD event; no. (% within FRS categories)	110 (1.5%)	272 (7.4%)	56 (16.7%)	438	
Total	7419	3681	338	11,436	

In the 2013 Guideline on the Assessment of Cardiovascular Risk, the American College of Cardiology/American Heart Association (ACC/AHA) released Pooled Cohort Equations, derived using data from multiple cohort studies including ARIC (Atherosclerosis Risk in Communities), CARDIA (Coronary Artery Risk Development in Young Adults) and CHS (Cardiovascular Health Study). They are multivariable risk equations developed to predict 10-year risk of atherosclerotic cardiovascular disease (ASCVD) event (4). ASCVD was defined as non-fatal MI and CHD death, in addition to nonfatal or fatal stroke. The 2013 Guidelines were created to address the limitations of FRS and its application to the Adult Treatment Panel Guidelines (III).

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(5), endothelial dysfunction(6), diabetes(7), stroke, and CHD and its risk factors (5, 7, 8). Imaging of the fundus, including the retinal artery and vein has historically been performed using a fundus machine costing tens of thousands of dollars. In 2010, was the first report of using a smartphone for the purpose of fundus photography and since then, the technology has been rapidly advancing. It is reasonable to expect that a cheap, simple, repeatable method for using smartphones for fundus photography will be available in the near future, making imaging of the retinal vessel feasible on a large scale. We hypothesize that utilizing retinal vessel caliber to re-classify patients as "high," "intermediate" and "low" risk for ASCVD will more accurately predict outcomes.

5. Main Hypothesis/Study Questions:

The retinal vasculature is easily imaged and alterations in vessel caliber may be associated with ASCVD. We propose to apply the 2013 AHA/ACC pooled cohort equation to calculate 10-year ASCVD risk in the

ARIC cohort. We will then use retinal vessel caliber to re-categorize ASCVD risk. We hypothesize that utilizing retinal vessel caliber may significantly re-categorize ASCVD risk in subjects in the ARIC cohort, more precisely identifying those at high risk or low risk for disease above and beyond the 2013 AHA/ACC 10-year risk equation. Additionally, we propose to describe the value of using retinal vessel caliber to assess risk for the development of CHF.

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:

Data from the ARIC will be used for the proposed investigations. Retinal vessel calibers were measured from retinal fundus photographs taken at the third examination (in which 12,887 subjects attended). Other considered risk factors were also from the third examination, and the 10+ year-ASCVD events were taken at the fifth examination.

Exposures and their measurement:

Central retinal arteriolar equivalent (CRAE), Central retinal venular equivalent (CRVE), arteriolar-to-venular ratio (AVR) = CRAE/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 (9).

Outcomes and their measurement:

The outcomes studied will be incident stroke and cardiovascular events (including death) since the third visit. We define incidence ASCVD as new stroke (fatal or non-fatal) or incident CHD (fatal or non-fatal MI or CHD death) since the third visits (1993-95) to the fifth visits (2011-2013) among subjects who were free of these outcomes at the beginning of visit three when retinal photography was performed. CHF, including both systolic heart failure and heart failure with preserved ejection fraction will also be evaluated both independently and as a composite outcome with ASCVD.

Confounders and their measurement (Variables for calculating AHA/ACC risk categories):

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), diabetes mellitus status (categorical variable).

Analysis plan:

Separate models of ASCVD risk will be created. We will calculate the 10-year risk of CHD or stroke for each ARIC individual that attended visit 3 using the algorithm published in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (age, gender, race, smoking, diabetes, SBP, DBP, hypertension treatment, HDL, and TChol) as well as for the FRS (10). The subsequent models will include the base model plus AVR and we will evaluate and compare the various models with respect to discrimination, calibration and reclassification. We will also analyze the association between retinal artery caliber and risk for CHF and death.

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:
ARIC Manuscript Proposal #1630 Direct and Indirect Effects of Retinal Vascular Caliber, Cardiovascular Risk Factors on CVD Outcomes. 4/13/10

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

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