ARIC Manuscript Proposal #2497

PC Reviewed: 2/10/15   **Status:** <u>A</u>   **Priority:** <u>2</u>
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Microvascular disease measures and the risk of peripheral artery disease

  b. Abbreviated Title (Length 26 characters): Microvascular disease and PAD

2.   Writing Group:
    Writing group members: Kunihiro Matsushita, Yuanjie Pang, Shoshana Ballew, Ron C. Hoogeveen, Bernard Jaar, Elizabeth Selvin, Christie M. Ballantyne, Richey Sharrett, Aaron Folsom, Gerardo Heiss, Josef Coresh, Alan Hirsch

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

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3.   Timeline: Data to be used in this proposal are basically available. Analyses and manuscript preparation will be performed over the next 12 months.

4.   Rationale:
Lower extremity peripheral artery disease (PAD) affects 8-10 million individuals in the US and more than 200 million individuals in the globe.[1-3] PAD is a major phenotype of systemic atherosclerotic disease, and persons with PAD have 2- to 5-fold higher risk of

total mortality and cardiovascular events compared to those without.[4] PAD also reduces quality of life due to limited mobility and leg symptoms.[5]

Several prospective studies have demonstrated that traditional atherosclerotic risk factors such as hypertension, diabetes, smoking, and dyslipidemia, account for the majority of PAD risk.[6, 7] However, for critical limb ischemia (CLI), a severe form of PAD characterized by ischemic ulcer, gangrene, or rest pain, clinical investigation of established CLI cases suggests the pathophysiological involvement of microvascular disease, impairing collateral formation and wound healing.[8, 9] However, this concept has not been explored in a prospective community-based cohort, since few cohorts have adequate CLI cases during follow-up. Therefore, using data from the Atherosclerosis Risk in Communities (ARIC) Study with over 25 years of follow-up, we aim to comprehensively study the association of microvascular disease measures with the risk of PAD, under the hypothesis that these measures will be particularly strongly associated with CLI risk.

5.   Main Hypothesis/Study Questions:
Microvascular disease measures will be independently associated with PAD risk, and their associations will be particularly strong for CLI cases.

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).

Inclusions:
-All black and white ARIC subjects with variables of interest

Exclusions:
-Ethnicity other than black or white
-Missing data on variables of interest
-Participants with a clinical history of PAD at baseline visit of interest (determined by self-report leg artery revascularization at visit 1 and any PAD-related hospitalizations prior to the baseline visit of interest [visits 2, 3, or 4])

Exposures:
As measures of microvascular disease, we will use the following variables:
   i.   Retinal findings (visit 3):
          a.   Retinopathy, its severity, and its representative signs (retinal hemorrhage and micro-aneurysms)
          b.   Focal retinal microvascular changes (AV nicking, focal arteriolar narrowing).
          c.   Generalized arteriolar narrowing: central retinal arteriolar equivalent
   ii. Urinary albumin-to-creatinine ratio (ACR) (visit 4)
   iii. High-sensitivity troponin T (hsTnT) (visits 2 and 4): hsTnT is well known as a marker of cardiac injury, but various recent reports suggest its link to

microvascular injury in the heart[10] as well as other organs such as the brain[11] and kidney[12].

iv. Glycemic markers (visits 2) as microvascular disease is a representative clinical manifestation of diabetes and some of these were shown to particularly associate with microvasuclar disease such as lacunar stroke in the ARIC Study[13]:

    a. Hemoglobin A1c
    b. Glycated albumin
    c. Flucosamine
    d. 1-5 anhydroglucitol

Outcomes:

PAD-related hospitalizations will be identified according to the following ICD codes based on previous literature[14, 15]: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); peripheral vascular disease, unspecified (443.9); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, 440.22, 440.23, and 440.24 will be considered CLI. Also, we will consider any cases with the above code as CLI when the following codes coexist: leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4).

Other variables of interest and covariates:

Sociodemographics: age, race, gender, education
Physical information: blood pressure including ankle-brachial index (ABI) obtained at visit 1 (whole study), 3 and 4 (subsample), body mass index, presence/absence of left ventricular hypertrophy by electrocardiogram and carotid atherosclerosis by ultrasound
Lifestyle: smoking status/amount and alcohol habit
Comorbidities: diabetes, dyslipidemia, coronary heart disease, stroke, heart failure, atrial fibrillation

Statistical analysis plan:

The primary analysis will use Cox proportional hazards models to quantify the prospective association of microvascular disease measures with incident PAD- and CLI-related hospitalizations. Whenever possible, microvascular disease measures will be treated as both continuous variables with splines and categorical variables (quantiles and clinical categories) in the models. We will adjust for the covariates listed above. To evaluate whether microvascular disease measures have uniquely strong associations with CLI, differences in log hazard ratios will be obtained by subtracting log-HRs for CLI from the log-HRs for non-CLI PAD.[16] Standard errors for the differences in log-HRs will be estimated by 1,000 bootstraps of the difference of log-HRs.[16]

We will conduct a few sensitivity analyses. Firstly, we will repeat the analysis after stratifying the study sample by key demographic and clinical subgroups according to age, gender, race, smoking status and the presence/absence of diabetes, hypertension, chronic

kidney disease, low ABI, and history of other cardiovascular diseases at baseline. We will formally test interaction using likelihood ratio test. Secondly, we will treat leg artery revascularization as a time-varying covariate. Finally, given the potential impact of the competing risk of death for estimating PAD and CLI risk, we will run Fine and Gray's proportional subhazards models.[17]

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)?
There are several ARIC proposals with PAD as an outcome as listed below (only recent ones are listed), but none of them focus on microvascular disease measures as exposures except #1915 including ACR. However, #1915 does not focus on CLI but overall PAD (CLI is a small part) and key authors of that proposal are in the current proposal as well.

#1832: risk prediction model for incident PAD in the ARIC cohort
#1915: Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population
#2479: Serum 25-hydroxyvitamin D and incident peripheral arterial disease: The Atherosclerosis Risk in Communities Study (ARIC)

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* 2014.05, 2009.16, 2006.16)
        ___   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.

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