ARIC Manuscript Proposal #2983

1.a. Full Title: Ankle-brachial index and subsequent risk of clinical ischemic leg outcomes in the community: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): ABI & ischemic leg outcomes

2. Writing Group:
  Writing group members: Kunihiro Matsushita, Chao Yang, Shoshana Ballew, Corey A. Kalbaugh, Elizabeth Selvin, Maya Salameh, Gerardo Heiss, Josef Coresh

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __K.M.__ [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).

  Name:
  Address:

  Phone:  Fax:
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3. Timeline: The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 12 months.

4. Rationale:
Ankle-brachial index (ABI: ratio of ankle to brachial blood pressure) is considered as the first-line noninvasive test for diagnosing lower-extremity peripheral artery disease (PAD).\(^1\) This is primarily based on its validity to detect leg artery stenosis. Indeed, among individuals with
suspected PAD, ABI, with thresholds around 0.9, demonstrated sensitivity of 63%-82% and specificity of 84%-99% with imaging modalities (e.g., angiography or ultrasound) as a gold standard,\(^2\) although a few old studies combining PAD patients and healthy controls reported much higher sensitivity of >95%.\(^6\)-\(^10\) The potent association of ABI with cardiovascular outcomes (e.g., cardiovascular mortality, coronary heart disease, and stroke) further support the clinical usefulness of ABI.\(^11\),\(^12\) Accordingly, the American Heart Association and the American College of Cardiology recommend using ABI, coronary artery calcium, or high-sensitivity C-reactive protein to refine cardiovascular risk prediction beyond traditional cardiovascular risk factors, when needed.\(^13\) However, interestingly, despite its main purpose of detecting PAD, to our knowledge, no studies have quantified the association of ABI with subsequent risk of clinical ischemic leg outcomes, including leg amputation, in the community. We are particularly interested in whether and if so to what extent borderline ABI (0.9-1, currently considered normal) and high ABI (>1.3, indicating uncompressible artery) will be associated with clinical ischemic leg outcomes compared to normal ABI.\(^14\)

5. **Main Hypothesis/Study Questions:**
Lower ABI (even within a normal range) is associated with the risk of incident clinical ischemic leg outcomes.

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).**

**Study design:** prospective cohort study

**Inclusion criteria:** All black and white ARIC study participants free of clinical manifestations of PAD at baseline examination (visit 1) with data of ABI.

**Exclusion criteria:**
- Participants who identified themselves as non-white/non-black.
- Participants with clinical manifestations of PAD at baseline (i.e., self-reported history of leg revascularization or intermittent claudication based on the Rose questionnaire).
- Participants with missing variables of interest.

**Exposure:** ABI at visit 1: The blood pressure of the upper extremity and lower extremity were measured by automated oscillometric device Dinamap Model 1846 SX according to ARIC Ultrasound Assessment Scanning Procedures.\(^15\) Ankle systolic blood pressure was measured four times in a single leg and the last non-missing value was used as the numerator of ABI and brachial systolic blood pressure was measured twice and the last non-missing value was used as the denominator of ABI.\(^16\)

**Outcome:**
- Clinical PAD: PAD-related hospitalizations will be identified according to the following ICD codes based on previous literature\(^17,18\): 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).

-Critical limb ischemia (CLI): Of PAD cases defined above, those with 440.22, 440.23, and 440.24 as well as any cases with the coexisting code of leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4) will be considered CLI.

Covariates:
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index, systolic blood pressure, diastolic blood pressure
- Lifestyle: smoking status and alcohol habit
- Comorbidities: obesity, dyslipidemia, diabetes, hypertension including, antihypertensive medication use, cholesterol-lowering medication use, kidney function, and history of coronary heart disease or stroke

Statistical analysis plan:
The primary analysis will use Cox proportional hazards models to quantify the prospective association of ABI with incident PAD- and CLI-related hospitalizations. ABI will be treated as both continuous variables with splines and categorical variables (based on clinical categories \([\leq0.9, 0.9-1.1, 1.01-1.1, 1.11-1.2, 1.21-1.3, \text{and } >1.3]^{11,14}\) in the models. We will adjust for the covariates listed above. To evaluate whether ABI has different associations with PAD without CLI vs. CLI, log hazard ratios for these two outcomes will be compared using seemingly unrelated regressions.\(^{19}\)

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, reduced kidney function, and history of other cardiovascular diseases at baseline. We will formally test interaction using likelihood ratio test. Secondly, 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.\(^{20}\) Finally, we will check the consistency of results using ABI data at visits 3 and 4.

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 no proposals exploring the association of ABI with clinical PAD in ARIC. #1832 “A risk prediction model for incident PAD in the ARIC cohort” may be closest, but ABI was not included as a predictor in that proposal. Nonetheless, Dr. Matsushita is the leading author of both #1832 (took over from Dr. Corey A. Kalbaugh) and the current proposal.

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___)  ____ Yes  ____ No
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, approved manuscripts using 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 ____ No.
References


16. The ARIC investigators. ARIC Data Book: Ankle Brachial Index Data.


