ARIC Manuscript Proposal # 3044

PC Reviewed: 9/12/17  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. **Full Title**: Quantification of the prevalence of older adults potentially benefitting from the detection of peripheral artery disease (PAD): the Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: benefits of PAD detection

2. **Writing Group**: Kunihiro Matsushita, Shoshana Ballew, Corey A. Kalbaugh, Michelle Meyer, Hirofumi Tanaka, Gerardo Heiss, Matthew Allison, Maya Salameh, 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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3. **Timeline**: The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 9 months.

4. **Rationale**: Lower-extremity peripheral artery disease (PAD) is an important clinical condition affecting more than 200 million adults worldwide¹ and increases the risk of mortality and cardiovascular outcomes². However, it is controversial whether individuals at high risk (e.g., older ages) should
be screened for PAD using ankle-brachial index (ABI).\textsuperscript{3,4} This controversy mainly stems from the lack of robust evidence regarding risk prediction improvement with ABI beyond traditional risk factors.\textsuperscript{4} However, this argument does not take into account a few other important aspects of detecting PAD. Specifically, ABI \( \leq 0.9 \) itself indicates PAD and is an indication for cardiovascular preventive therapy (e.g., statin and aspirin).\textsuperscript{3} A previous study using data from NHANES reported that \( \sim 10\% \) of adults with new identification of PAD are not taking statin and aspirin and may optimize their preventive therapies.\textsuperscript{5} However, this report was based on data in 1999-2004, and given changes in clinical practice, contemporary data are needed. Also, to our knowledge, no studies have quantified the burden of individuals with newly identified PAD with reduced leg function who may benefit from exercise therapy. This burden is important since the Centers of Medicare and Medicaid Services (CMS) recently decided to reimburse supervised exercise therapy among patients with PAD.\textsuperscript{6} Therefore, using visit 5 data from the Atherosclerosis Risk in Communities Study, we will quantify the comprehensive and contemporary prevalence of community-dwelling older adults who may benefit from PAD identification with ABI.

5. **Main Hypothesis/Study Questions:**
What is the proportion of community-dwelling older adults who may benefit from the identification of PAD? We believe there will be potential benefits in the following two scenarios:
1. Optimizing preventive therapy with statin and aspirin and
2. Recognizing PAD as a potential cause of reduced leg function.

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:**
Cross-sectional study

**Inclusion criteria:**
- All black and white ARIC study participants
- Those without a clinical history of PAD
- Those with data on ABI, medication use, and the Short Physical Performance Battery (SPPB) at visit 5

**Exclusion criteria:**
- Participants who identified themselves as non-white/non-black
- Participants with a clinical history of PAD at visit 5 (i.e., PAD-related ICD codes in discharge diagnosis or CMS data or self-reported peripheral revascularization at any previous visits or annual follow-up data)
- Participants with missing data on ABI, medication use, and the SPPB at visit 5

**Exposure:**
- ABI measured at visit 5: We will test both lowest value and mean value of ABI from both legs. We will primarily define PAD as ABI \( \leq 0.9 \) according to the AHA/ACC 2016 guideline.\textsuperscript{3} Since ABI 0.91-1.0 is considered as borderline low ABI\textsuperscript{7} and some investigators
consider high ABI >1.3-1.4 equivalent to PAD\textsuperscript{8}, we will secondarily evaluate the proportion of older adults who may benefit from recognizing these “abnormal” categories as well.

**Outcome (cases potentially benefitting from the detection of PAD):**
- As noted in the section of Study Question, we think the following two scenarios for the detection of PAD to be beneficial: 1. Optimizing preventive therapy with statin and aspirin (i.e., newly detected PAD but not taking statin and aspirin) and 2. Recognizing PAD as a potential cause of reduced leg function (i.e., newly detected PAD and having reduced leg function). We will test a few thresholds of SPPB for reduced leg function such as ≤6 and ≤9.\textsuperscript{9}

**Covariates:**
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index
- Lifestyle: smoking status, alcohol habit, physical activity based on questionnaire
- Comorbidities: dyslipidemia, diabetes, kidney function, history of coronary heart disease, stroke, and heart failure, cognitive function
- Medication: antihypertensive medication use, anti-diabetic medication use

**Statistical analysis plan:**
- Baseline characteristics will be compared across clinical categories of ABI (e.g., ≤0.90, 0.91-1.00, 1.01-1.30, and >1.30).
- We will describe the proportion of participants who would benefit from the detection of PAD overall and in the subgroups by age, gender, race, and the status of clinical conditions like history of other cardiovascular disease (i.e., coronary heart disease, stroke, and heart failure), diabetes, hypertension, chronic kidney disease, and cognitive impairment (mild cognitive impairment and dementia).
- Using logistic regression models, we will identify factors strongly associated with higher odds of potentially benefitting from the detection of PAD with covariates listed above as candidate independent variables.
- We will run this analysis in the overall study population as well as in those with ABI indicative of PAD (i.e., ≤0.90 for primary analysis and ABI ≤ plus 0.90-1.00 and >1.3 for secondary analysis). The former analysis will have implications on who should be screened with ABI, and the latter will inform us of demographic and clinical traits behind underuse of preventive therapy and/or likelihood of reduced leg function in those with PAD.
- We will perform a few sensitivity analyses:
  - As noted above, we will explore a few different thresholds of abnormal ABI
  - As noted above, we will explore a few different thresholds of SPPB for reduced leg function
  - We will evaluate statin and aspirin separately
  - We will analyze two beneficial scenarios of 1. optimizing preventive therapies and 2. recognizing PAD as a potential cause of reduced leg function separately

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    ____ 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)?
To our knowledge, there are no proposals specifically aiming to quantify the burden of older adults who may benefit from the detection of PAD.

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

_____ A. primarily the result of an ancillary study (list number*______)  
____X____ 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