ARIC Manuscript Proposal # 3056

PC Reviewed: 10/3/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Ankle-brachial index and short-term risk of cardiovascular events in older adults

b. Abbreviated Title (Length 26 characters): ABI & CVD risk in elderly

2. Writing Group:

Writing group members: Kunihiro Matsushita, Chao Yang, 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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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:
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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:

The American Heart Association and the American College of Cardiology Guideline recommends ankle-brachial index (ABI) for refining the predicted risk of cardiovascular events among older adults (together with coronary artery calcium and high-sensitivity C-reactive protein) since prognostic values of traditional cardiovascular risk factors are attenuated in this

population.[1] However, the data regarding ABI as a predictor of cardiovascular outcomes in older adults are almost exclusively from studies conducted in 1980s or 1990s.[2-6] Since medical environments and incidence of cardiovascular disease have changed considerably in the last few decades,[7-9] a contemporary investigation is necessary. Therefore, using data from visit 5 (2011-13) of the Atherosclerosis Risk in Communities Study, we will quantify ABI and short-term risk of cardiovascular outcomes among community-dwelling older adults.

5. Main Hypothesis/Study Questions:
Abnormal ABI is associated with increased risk of cardiovascular events.

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 at baseline examination (visit 5) with data of ABI.

Exclusion criteria:
- Participants who identified themselves as non-white/non-black.
- Participants with missing variables of interest.

Exposure: ABI at visit 5: The systolic blood pressure of both upper and lower extremity was measured simultaneously using an automated oscillometric device OMRON VP-1000 plus (Kyoto, Japan) by trained technicians twice (five minutes apart) according to ARIC Protocol.[10] At each measurement, an ABI was calculated for both sides, and the greater value of the right or left brachial systolic blood pressure was used as the denominator. The mean ABI of the two measurements was recorded for each leg. For this analysis, we used the lower value of the right and left ABI. However, the higher value was used when the higher ABI exceeded 1.3 and the lower ABI was normal (1.0-1.3), to avoid eluding potential pathophysiological information, since an extraordinary high ABI (>1.3-1.4) indicates arterial non-compressibility. [11-13]

Outcome:
The first cardiovascular event, after visit through December 31 2014, of the following:
- Coronary heart disease: a definite or probable myocardial infarction, definite coronary death, or coronary revascularization procedure.
- Stroke: definite or probable cases of sudden or rapid onset of neurologic symptoms lasting for 24 hours or leading to death in the absence of another cause.
- Heart failure: a definite or probable acute decompensated HF.
- Composite of cardiovascular disease: coronary heart disease, stroke, or heart failure.
- All-cause mortality: Since cardiovascular disease is a leading cause of death, we will also analyze all-cause mortality.

Covariates:
- Sociodemographics: age, race, gender, education level

- Physical information: body mass index, systolic blood pressure, diastolic blood pressure
- Lifestyle: smoking status and alcohol drinking habit
- Comorbidities: diabetes, dyslipidemia, hypertension including, antihypertensive medication use, cholesterol-lowering medication use, kidney function, and history of coronary heart disease, stroke, or heart failure.

Statistical analysis plan:
The primary analysis is to use Cox proportional hazards models to quantify the prospective association of ABI at visit 5 with each of the outcomes after baseline. ABI will be analyzed as both continuous variables with splines and categorical variables, based on clinical categories of ≤0.9, 0.9-1, 1.01-1.1, 1.11-1.2, 1.21-1.3, and >1.3 in the models (if there are too few outcomes in some categories, we will merge some of them). We will build several models to assess confounding by adjusting for the covariates listed above.

We also evaluate a few risk prediction statistics such as Hosmer-Lemeshow $\chi 2$, Harrell's c-statistics, and categorical net reclassification improvement by adding ABI beyond known predictors.

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, use of statins, and the presence/absence of diabetes, hypertension, reduced kidney function, and a history of cardiovascular diseases at visit 5. Given clinical implications, we are particularly interested in the subgroups by a history of cardiovascular disease. We will test interaction formally using likelihood ratio test. Secondly, given the potential competing risk of death in estimating the risk of cardiovascular outcomes, we will run Fine and Gray's proportional subhazards models.[14]

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 proposals for visit 1 ABI and cardiovascular events (i.e., #325, #575, #2022, #2505, #2683), but to our knowledge, this is the first proposal to explore visit 5 ABI as a predictor of subsequent cardiovascular events.

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, 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

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