ARIC Manuscript Proposal # 3053

1.a. Full Title: Various blood pressure components and risk of peripheral artery disease (PAD) in the Atherosclerosis Risk in Communities (ARIC) Study

 b. Abbreviated Title (Length 26 characters):
    Blood pressure & PAD

2.   Writing Group:
Writing group members: Yifei Lu, Shoshana Ballew, Hirofumi Tanaka, Moyses Szklo, Gerardo Heiss, Josef Coresh, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _Y.L.____ **[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: 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 the third leading cause of atherosclerotic vascular morbidity after coronary heart disease and stroke[1] and affects more than 200 million individuals around the world.[2] Among traditional atherosclerotic risk factors (i.e. smoking, diabetes, hypertension and dyslipidemia), hypertension is a big contributor to total burden of

PAD given its high prevalence.[3] Individuals with hypertension have ~50% higher risk of developing PAD compared to those without.[1]

Despite this important well-acknowledged contribution of blood pressure (BP) to the development of PAD, most prior studies[4-20] were limited in several aspects. First, several were cross-sectional studies.[4-7] In addition to the lack of temporality, this design has a critical issue for assessing the BP-PAD relationship since brachial BP is not only used as an exposure but also as a part of the outcome variable of ankle-brachial index (the ratio of ankle BP to brachial BP). Previous prospective studies also had some caveats by exploring selected populations (e.g., diabetic patients[8,9]) or evaluating relatively short follow up of <10 years.[8-15] Also, most of those studies investigated a single measure of systolic BP,[4,5,8,14,16] diastolic BP,[12,17] or self-reported hypertension.[18] Moreover, an increasing body of evidence has shown different strength of associations across different BP measures (e.g., systolic BP, diastolic BP, pulse pressure) [21-26] in predicting coronary heart disease, heart failure, and stroke, but such a comparison has not been performed for PAD. Therefore, to overcome these caveats, using data from the Atherosclerosis Risk in Communities (ARIC) Study with over 25 years of follow-up, we aim to explore the relative importance of different BP components (diastolic BP, systolic BP, mean arterial pressure, and pulse pressure) in predicting incident PAD.

5. Main Hypothesis/Study Questions:
Which of the BP components is more strongly associated with risk of incident PAD?

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 prevalent PAD at visit 1 with data on blood pressure, covariates, and incident PAD.

Exclusion criteria:
- Participants who identified themselves as non-white/non-black.
- Participants with prevalent PAD at baseline (i.e., ABI<0.9, self-reported peripheral revascularization, intermittent claudication based on the Rose questionnaire).
- Participants with missing data on BP measurement, covariates of interest, and PAD outcomes.

Exposure:
The sitting arm blood pressure was measured three times, after 5 minutes of quiet rest, with a standardized Hawksley random-zero sphygmomanometer at baseline clinic visit.[27] The average of second and third readings was used for the analysis. The BP components assessed in this study consist of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP). The MAP was calculated as $(SBP + 2 \times DBP)/3$. And PP was defined as the difference between SBP and DBP (SBP-DBP).[28]

Outcome:

- PAD-related hospitalizations will be identified with the following ICD codes based on previous literature[29]: 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); leg artery revascularization (38.18, 39.25, 39.29, 39.50).
- Of PAD cases described 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 as Critical limb ischemia (CLI).

Covariates:
- Sociodemographics: age, race, gender, education level, insurance status
- Physical information: body mass index
- Lifestyle: smoking status and alcohol habit
- Comorbidities: dyslipidemia, diabetes, kidney function, history of coronary heart disease, stroke, and heart failure
- Medication: antihypertensive medication use, cholesterol-lowering medication use

Statistical analysis plan:
- Baseline characteristics will be compared across quartiles as well as clinical categories (e.g., SBP <120, 120-139, and ≥140 mmHg or antihypertensive medication use) of each BP parameter.
- Cox proportional hazards models will be performed to quantify the prospective association of BP parameters with PAD- and CLI-related hospitalizations.

> We first include each single BP parameter (SBP, DBP, MAP, and PP in turn) as both continuous variables with splines and categorical variables (quartiles or clinical categories) into the models;
> The joint influence of all of the possible combinations of 2 BP measures will also be assessed;
> Models will be adjusted for variables listed above.

- For each model, the likelihood ratio $\chi 2$, Akaike information criterion (AIC), and Bayes information criterion (BIC) estimates will be tested to assess model fit. Discriminative ability of each model with different combination of BP components will be evaluated and compared by Harrell C statistics.[30]
- We will perform a few sensitivity analyses.

- We will perform additional analysis using supine brachial BP measurement;
- We will conduct subgroup analysis stratified by age, gender, race, diabetes status, smoking status (current, former, vs. never as well as by pack-years), antihypertensive medication use, and history of cardiovascular disease and evaluate their interactions with BP measures on PAD risk using likelihood ratio test;
- We will evaluate whether each BP component is differently associated with incident PAD vs. its severe form of CLI. We will formally test the difference in strength of association using seemingly unrelated regression;
- 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.[31]

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 specifically exploring the association of different BP components with clinical PAD in ARIC. # 1832 "A risk prediction model for incident PAD in the ARIC cohort" includes systolic BP and diastolic BP as candidate predictors and thus may be closest. However, Dr. Matsushita is the leading author of both #1832 (took over from Dr. Corey A. Kalbaugh) and the current proposal and will be responsible for coordination.

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___)
___ 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.

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