ARIC Manuscript Proposal #4526

PC Reviewed: 09/17/24 **Status: _____** **Priority: 2**

1.a. Full Title: Longitudinal changes in interankle SBP differences and cardiovascular events and mortality in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Changes in interankle SBP differences and mortality

2. Writing Group:

Daniela Charry, Jasper Xu, Michelle Meyer, Anna Kucharska-Newton, Kunihiro Matsushita, Kenneth Butler, Timothy Hughes, Hirofumi Tanaka, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal **DC**

First author: Daniela Charry
Address: The University of Texas at Austin
Department of Kinesiology and Health Education
2109 San Jacinto Blvd
Austin, TX, USA 78712

Phone: 512-471-8594 Fax: 512-471-8194
E-mail: daniela.charrysegura@austin.utexas.edu

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: Hirofumi Tanaka
Address: The University of Texas at Austin
Department of Kinesiology and Health Education
2109 San Jacinto Blvd, D3700
Austin, TX, USA 78712

Phone: 512-232-4801 Fax: 512-471-8194
E-mail: htanaka@austin.utexas.edu

3. Timeline: Analysis will begin once the proposal is approved. We plan to complete the manuscript within six months of the data release.

4. Rationale:

Derivatives of blood pressure, including ratios and differences between the four limbs, can provide additional information for health appraisal [1,2]. In particular, a large interankle systolic blood pressure (SBP) difference has been investigated as a predictor of adverse cardiovascular and cerebrovascular outcomes, as well as mortality [3-6]. The increased interankle SBP difference has often been attributed to the presence of peripheral artery disease (PAD) in one lower limb [1,7], as PAD decreases blood flow and perfusion pressure in the affected side [8]. The resultant interankle SBP difference might have prognostic value for overall and cardiovascular mortality given the presence of unequal limb atherosclerosis. However, recent evidence from us and others suggests that non-atherosclerotic characteristics of the blood vessels may also contribute to this association [4,6].

Arterial stiffness has emerged as a potential factor in the association between interankle SBP difference and adverse clinical outcomes [9]. Arterial stiffening leads to arterial wave reflection and elevates SBP [10-12]. Peripheral resistance of the lower body is believed to be one of the most important sites of arterial wave reflection [13]. An increase in arterial stiffness leads to greater transmission of pulsatile pressure into the microcirculation, causing subsequent end-organ damage [14]. Differences in arterial stiffness between the two sides of the body may indicate asymmetric or localized arterial stiffening, which might be manifested as an abnormal increase in interankle SBP differences [9].

Previous research demonstrated that large differences in ankle SBP are associated with increased cardiovascular risk and mortality [3-6]. However, these studies have been cross-sectional, providing limited insights into how these differences change over time and into their longitudinal association with cardiovascular outcomes. Accordingly, the primary aim of this proposed study is to examine longitudinal changes in interankle SBP differences and to investigate their relationship with cardiovascular events and mortality.

Longitudinal blood pressure data from Visits 5 and 6 or 7 of the Atherosclerosis Risk in Communities (ARIC) study provide a unique resource to address this gap in knowledge. The semi-automatic vascular screening device OMRON VP-1000 plus (Kyoto, Japan) was used to measure blood pressure simultaneously in the ankles after participants were in the supine position for 5–10 min. Bilateral posterior-tibial arterial pressure waveforms were detected over 10 s by extremity cuffs connected to a plethysmographic and an oscillometric pressure sensor wrapped on both ankles. Trained technicians recorded blood pressures at least twice, and the results of the two closest readings were averaged. This system has the advantage of measuring blood pressure in both ankles simultaneously, ensuring that beat-by-beat differences in blood pressure between limbs are minimized.

5. Main Hypothesis/Study Questions:

The specific aims include:

1. To characterize how interankle SBP differences change at two distinct points: from midlife to older adulthood.
2. To assess whether changes in interankle SBP differences are associated with incident cardiovascular events and all-cause as well as cardiovascular-specific mortality.

Our main hypothesis is that increasing interankle SBP differences over time are independently associated with a higher risk of future cardiovascular events and all-cause and cardiovascular-specific mortality, even after adjusting for traditional cardiovascular risk factors.

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 methodological limitations or challenges if present).

Study design: Observational study utilizing longitudinal data on ankle SBP from ARIC Visits 5 and 6 or 7, and most updated data on all-cause and CVD mortality events.

Inclusions: ARIC participants with available ankle SBP data obtained at both Visits 5 and either 6 or 7. Interankle SBP differences will be calculated as the absolute value of the difference between the right and left sides.

Exclusions: Nonwhite and nonblack participants, BMI ≥40 kg/m^2, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2), aortic aneurysms, history of aortic or peripheral revascularization or aortic graft, aortic stenosis, moderate or greater aortic regurgitation, history of coronary heart disease (CHD), heart failure or stroke for analyses of incident events, and missing covariates of interest.

Exposure: Changes in interankle SBP differences, both as a continuous and as categorical variable (< 10 mmHg and ≥10 mmHg). Our previous study [6] demonstrated that an interankle SBP difference of ≥10 mmHg, was significantly and independently associated with all-cause mortality even after the adjustments for traditional cardiovascular risk factors, and extreme values of ankle-brachial index.

Outcome: Incident cardiovascular disease (CHD, stroke, and heart failure), all-cause and cardiovascular-specific mortality.

Other variables of interest: Age, sex, race, smoking status, hypertension defined as SBP ≥140 mmHg, diastolic BP ≥90 mmHg, or reported use of hypertensive medication, diabetes defined as having a fasting serum glucose concentration of ≥126 mg/dl, a non-fasting glucose of ≥200 mg/dl, a self-reported history of physician-diagnosis of diabetes, or the use of glucose-lowering medication, carotid-femoral pulse wave velocity, brachial-ankle pulse wave velocity, carotid artery augmentation index, blood pressure, body mass index, fasting glucose, triglycerides, HDL-cholesterol, LDL-cholesterol concentrations,

ankle-brachial index, and medication use (aspirin, β-blockers, calcium channel blocker, ACE inhibitors, and diuretics).

Summary of Statistical Analysis: Variables will be presented as means ± standard deviation if continuous and as percent if categorical. Variables with skewed distribution will be naturally log transformed for analysis. Baseline characteristics (Visit 5) will be compared between individuals with and without interankle SBP difference ≥10 mmHg using t-tests and chi-squared test. Reproducibility of absolute interankle SBP difference ≥10 mmHg from Visits 5 to 6/7 will be assessed and correlations between exams will be performed. We will describe the distribution of change in interankle SBP differences as the slope of change from earliest to latest value divided by the time interval between measures. We will analyze the change, both as a continuous and as categorical variable (< 10 mmHg and ≥10 mmHg). Cox proportional hazards modeling will be used to evaluate the association of interankle SBP difference with all-cause and cardiovascular mortality. Multivariable analyses will adjust for age, sex, race, and traditional cardiovascular risk factors (body mass index, smoking status, diabetes, hypertension, triglycerides, HDL-cholesterol, LDL-cholesterol, ankle-brachial index, carotid-femoral pulse wave velocity, and brachial-ankle pulse wave velocity). A two-sided p-value of <0.05 will be considered statistically significant. All analysis will be performed using SAS 9.4 (SAS Institute, Cary, NC).

Limitations:

Non-attendance at Visit 6/7 due to survivor bias and attendance bias may influence our analysis results. We will perform sensitivity analyses using inverse probability of attrition weights to account for non-random Visit 6/7 attendance.

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 ICTDER03 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. 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/mantrack/maintain/search/dtSearch.html

__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)?

#4138: Contralateral differences in arterial blood pressure and pulse wave velocity, and all-cause and cardiovascular disease mortality in the Atherosclerosis Risk in Communities (ARIC) Study

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* __PWV 2015.23 __)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

References

1. Singh S, Sethi A, Singh M, Khosla K, Grewal N, Khosla S. Simultaneously measured inter-arm and inter-leg systolic blood pressure differences and cardiovascular risk stratification: a systemic review and meta-analysis. *J Am Soc Hypertens* 2015; 9: 640–50.
2. Liu S, Li P, Su H. Four-limb blood pressure measurement with an oscillometric device: a tool for diagnosing peripheral vascular disease. *Curr Hypertens Rep* 2019; 21(2): 15.
3. Moon I, Kim HL, Lim WH, Seo JB, Zo JH, Kim MA et al. Association between inter-leg blood pressure difference and cardiovascular outcome in patients undergoing percutaneous coronary intervention. *PLoS One* 2021; 16(10): e0257443.
4. Chen SC, Chang JM, Tsai YC, Tsai JC, Su HM, Hwang SJ et al. Association of interleg BP difference with overall and cardiovascular mortality in hemodialysis. *Clin J Am Soc Nephrol* 2012; 7(10): 1646-1653.
5. Han M, Kim YD, Choi JK, Choi J, Ha J, Park E et al. Predicting stroke outcomes using ankle-brachial index and inter-ankle blood pressure difference. *J Clin Med* 2020; 9(4): 1125.
6. Charry D, Xu J, Meyer ML, Kucharska-Newton A, Matsushita K, Tanaka H. Contralateral differences in ankle SBP and pulse wave velocity: associations with incident heart failure and mortality. *J Hypertens* 2024.
7. Su HM, Lin TH, Hsu PC, Lee WH, Chu CY, Chen SC et al. Association of interankle systolic blood pressure difference with peripheral vascular disease and left ventricular mass index. *Am J Hypertens* 2014; 27(1): 32–37.
8. Zhang Z, Ma J, Tao X, Zhou Y, Liu X, Su H. The prevalence and influence factors of inter-ankle systolic blood pressure difference in community population. *PLoS One* 2013; 8(8): e70777.
9. Yang W, Sun L, He Y, Xu X, Gan L, Guo T et al. Association between four-limb blood pressure differences and arterial stiffness: a cross-sectional study. *Postgrad Med* 2022; 134(3): 309-315.
10. Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H et al. Brachial-ankle pulse wave velocity predicts increase in blood pressure and onset of hypertension. *Am J Hypertens* 2011; 24: 667–673.
11. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. *Hypertension* 2005; 45: 426–431.
12. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012; 308: 875–881.
13. Tarumi T, Sugawara J, Tanaka H. Association between ankle blood pressure and central arterial wave reflection. *J Hum Hypertens* 2011; 25: 539-544.
14. Vasan RS, Pan S, Xanthakis V, Beiser A, Larson MG, Seshadri S et al. Arterial stiffness and long-term risk of health outcomes: The Framingham Heart Study. *Hypertension* 2022; 79(5): 1045-1056.