ARIC Manuscript Proposal #4138

PC Reviewed: 10/11/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: 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

b. Abbreviated Title (Length 26 characters): Contralateral differences and mortality

2. Writing Group:
Daniela Charry, Jasper Xu, Michelle Meyer, Kunihiro Matsushita, Hirofumi Tanaka, others welcome

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

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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: Analysis is to begin in the Fall 2022. We plan to complete the manuscript within one year from the release of the data.

4. Rationale:

The prevalence of contralateral differences in arterial blood pressure (i.e., ≥10 and ≥15 mmHg) are common among older adults.[1] Accordingly, hypertension guidelines recommend measuring blood pressure in both arms during an initial visit and subsequently monitoring blood pressure on the higher reading arm.[2,3] Due in part to the intensified effort to screen peripheral artery disease using ankle-brachial index, the ankle has emerged as an additional site for noninvasive blood pressure measurement.[4,5] Several epidemiological studies have found strong associations between large interarm difference in systolic blood pressure (BP) and increased all-cause and cardiovascular disease (CVD) mortality.[6,7] Similarly, interankle difference in systolic BP has been associated with peripheral vascular disease and increased risk for overall and CVD mortality in hemodialysis patients.[8] However, evidence demonstrating whether such association is present in individuals without peripheral vascular disease and kidney disease is scarce. Lately, more attention has been placed in the potential role of arterial stiffness as the stiffening of arteries has been implicated in the pathogenesis of systolic hypertension and CVD.[9] Arterial wave reflection resulting from the stiffened arteries appears to be a primary mechanism responsible for augmenting systolic BP, and the lower body is believed to be an important site of arterial wave reflection.[10] Indeed, individual variabilities in contralateral differences in pulse wave velocity (PWV) have been reported.[11] The magnitude of interankle, but not interarm, differences in SBP is associated with various measures of arterial stiffness in community-dwelling older adults since individuals with interankle systolic BP difference were more likely to have contralateral differences in PWV.[1] Whether contralateral differences in PWV are also associated with increased cardiovascular and all-cause mortality is still unknown. Accordingly, the primary aim of this study is to evaluate whether there is an association between contralateral BP and PWV differences with all-cause and CVD mortality in a sample of community dwelling older adults.

5. Main Hypothesis/Study Questions:

1. Is there an association between contralateral systolic BP and PWV differences with all-cause and CVD mortality?

2. Is there a significant difference in risks for all-cause and CVD mortality among those with arterial stiffness and contralateral BP differences?

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: Cross-sectional analysis of participants at ARIC visit 5 and most updated data on all-cause and CVD mortality events.

Exposure:

Demographic variables: age, sex, race, smoking status, hypertension (prevalent hypertension and/or blood pressure medication use).

Hemodynamic variables: brachial BP, ankle BP, pulse pressure, brachial-ankle pulse wave velocity, augmentation index.

Variables for a descriptive table of participant characteristics: height, body weight, body mass index (BMI), fasting glucose, triglycerides, HDL-cholesterol, LDL-cholesterol concentrations, ankle-brachial index, and diabetes.

Outcome: Contralateral differences in arterial stiffness assessed by PWV between the heart and ankle (haPWV), and brachial artery and ankle (baPWV); contralateral differences in systolic BP; all-cause and CVD mortality (last updated).

The semi-automatic vascular screening device OMRON VP-1000 plus (Kyoto, Japan) was used to measure blood pressure simultaneously in the arms and ankles and arterial stiffness by PWV after participants were in the supine position for 5–10 min. PWV was estimated as the distance between 2 arterial recording sites divided by transit time. Bilateral brachial and 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 arms and ankles. Trained technicians recorded PWV and blood pressures twice, and the results of the two readings were averaged.

For the research question addressed, this system has the advantage of measuring blood pressure in all 4 limbs simultaneously [8]. Thus, beat-by-beat differences in blood pressure between limbs are considered a minimum. Contralateral differences in blood pressure will be defined as interarm and interankle systolic BP difference ≥10 mmHg and ≥15 mmHg. Contralateral differences in PWV will be set at the 90th percentile of the study sample.

Inclusions: All ARIC participants with PWV data obtained at visit 5.

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, and missing covariates of interest.

Statistical Analysis:

Variables will be presented as means ± standard deviation if continuous and as percent if categorical. Baseline characteristics will be compared between individuals with and without interarm and interankle systolic BP difference ≥10 mmHg and ≥15 mmHg using t-tests. Cox proportional hazards modeling will be used to evaluate the association of

contralateral differences in systolic BP and PWV with all-cause and CVD mortality. Variables with skewed distribution will be naturally log transformed for analysis.

Limitations:

- Some PWV measurements were not collected due to technical errors, participant factors, and scheduling conflicts.
- Height-based formulas to calculate baPWV and faPWV were derived and validated in a Japanese population.
- Because of the cross-sectional nature of the study, the assessment of causality cannot be confirmed.

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)?

#1970: Arterial stiffness and contralateral differences in blood pressure: 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__)

___ 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

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