ARIC Manuscript Proposal #4027

PC Reviewed: 4/12/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Standing Blood Pressure and Risk of Falls, Fracture, Syncope, Cardiovascular Disease and Mortality from the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): SBP and Outcomes in ARIC

2. Writing Group:
Writing group members: Jordan Kondo, Julia Wood, Karla Kendrick, Ruth-Alma Turkson-Ocran, Long Ngo, Jennifer Cluett, Lew Lipsitz, Kenneth Mukamal, Gerardo Heiss, Elizabeth Selvin, Pamela Lutsey, Josef Coresh (invited), Beverly Gwen Windham (invited), Natalie Daya Malek (invited). Stephen Juraschek, others welcome

Note this proposal is related to the orthostatic hypotension R01 (PI Juraschek).

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JK **[please confirm with your initials electronically or in writing]**

First author: Jordan Kondo
Address: 259 Kent St
Brookline, MA 02446

Phone: (808) 381-5509 Fax:
E-mail: jordan_kondo@hms.harvard.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: Stephen Juraschek
Address: 330 Brookline Ave, CO-1309
Boston, MA 02215

Phone: Fax:
E-mail: sjurasch@bidmc.harvard.edu

3. Timeline: Data analysis will begin once this proposal is approved with the goal of a manuscript draft by Fall 2022.

4. Rationale:

Blood pressure (BP) is an important modifiable risk factor directly related to cardiovascular disease, stroke and mortality.[1] The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive (systolic BP [SBP] <120 mm Hg) versus moderate (SBP of 135–139 mm Hg) BP treatment reduced the risk of cardiovascular disease in older adults.[2] SPRINT recruited 9,361 adults with age ≥50 years at a high risk for cardiovascular disease (CVD) with a seated SBP 130 to 180 mm Hg, and a standing SBP ≥110 mm Hg. The exclusion of participants with a standing SBP <110 mm Hg has generated discussion regarding the generalizability of the SPRINT findings[3] as the prevalence of standing SBP <110 mm Hg in the general population is not well-known, nor is it routinely measured in the clinical setting.

Orthostatic hypotension (OH) is a predictor of syncope, falls, CVD, and early mortality.[4–9] OH is frequently observed with hypertension treatment,[10] often leading to a down-titration of therapy even when patients are asymptomatic. In SPRINT, however, OH was not associated with injurious falls, syncope, or CVD events, suggesting symptomless OH should not be a reason to reduce antihypertensive treatment.[11] One limitation of the SPRINT cohort is the exclusion of more severe OH phenotypes with standing SBP < 110 mmHg. Thus, further examination of absolute standing SBP and its association with adverse events will help clinicians improve management of hypertensive patients.

We hypothesize that a standing SBP less than 110 mm Hg is not associated with falls, fracture, syncope, CVD, or mortality. The ARIC population is ideal to address this question given visit 1 included a large sample of middle-aged, community-dwelling African American or white adults, a standardized protocol to record OH along with other covariates, and reliable monitoring of long-term outcomes. Furthermore, we will be able to stratify the ARIC population by different stages of hypertension, cardiovascular disease risk (using participants' 10-year ASCVD risk score), and age to evaluate if there is effect modification on an association between low standing SBP and clinical outcomes. As such, our objectives will be to 1) determine the prevalence of standing SBP <110 mm Hg in ARIC overall and by hypertension stage (elevated, stage 1, and stage 2, defined below), 2) determine if there is an association between standing SBP <110 mm Hg and adverse clinical outcomes such as falls, fracture, syncope, CVD, or death, and 3) determine if there is effect modification by hypertension stage, cardiovascular disease risk, or age on the association between standing SBP and adverse clinical outcomes.

5. Main Hypothesis/Study Questions:

1. What is the prevalence of standing SBP <110 mm Hg (the standing exclusion used in SPRINT) in middle-age adult participants of the ARIC population overall and by hypertension stage?
2. Is standing SBP <110 mm Hg associated with falls, fracture, syncope, CVD, or death?
3. Is there effect modification by hypertension stage, cardiovascular disease risk, or age on the association between standing SBP and falls, syncope, CVD, or death?

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 with visit 1 as baseline.

Exclusions:

- ARIC participants without seated or standing BP measured at visit 1
- Missing covariates of interest (listed below)
- Persons of ethnicities other than African American or white
- African Americans from Washington County or Minnesota
- No prior history of falls, syncope, CVD or stroke.

Exposure assessment:
Seated and standing blood pressures were measured during ARIC visit 1 (1987-1989) in over 13,000 ARIC participants.

Primary outcomes: Falls, Fracture, Syncope, CVD, and Mortality
The primary outcomes in this study are (1) falls, (2) fractures, (3) syncope, (4) incident CVD (and its subtypes), and (5) mortality, after visit 1 through December 31, 2019. Falls, fracture, and syncope will be defined as the first occurrence of any related hospitalization or claim for inpatient or outpatient services after the baseline visit. These outcomes were identified via two sources: 1) active surveillance of all hospitalizations for all ARIC participants; and 2) linkage to Centers for Medicare and Medicaid Services (CMS) claims data from 1991-2013.[5,12] For CVD, we will use the variables "C7_IN_19SP," "C7_IN19DP," and "C7_INCHF19." For mortality, we will use the variable "DEAD19."

The ARIC Study obtains hospitalization information from annual telephone contact with study participants and through surveillance of hospitals in the study communities (inpatient hospitalization data currently available from January 1st, 1988, through December 31, 2015). In the original ARIC protocol, surveillance was primarily focused on coronary heart disease, stroke, and heart failure outcomes, but thereafter included other diagnostic codes for hospitalized events, including those attributed to fall, fracture, and syncope.

Participant data were also linked to CMS claims data using a finder file that included participants' social security numbers, sex, and date of birth through a matching process described previously.[5,12] These claims were available for eligible persons derived from two forms of coverage: (1) fee-for-service (FFS) or (2) managed care organizations. CMS data included inpatient and outpatient claims for participants enrolled in FFS continuously after reaching CMS Medicare eligibility and those with intermittent FFS enrollment during the period of observation. While no outpatient claims were available for cohort participants enrolled in managed care programs, inpatient claims were available for all participants with Medicare on a selective basis from the year 2008 onward.

MedPar files were used to identify inpatient CMS records for hospital encounters related to falls, fractures, and syncope. Outpatient falls were identified using the Clinical Classification System

(CCS) category 2603, E codes, which were based on International Classification of Diseases, 9th revision (ICD-9) external cause of injury codes. Falls were identified using the following ICD9 codes: E880.X-E888.X. Fractures were defined by ICD9 codes: 733.10-733.19, 733.93-733.98, and 800-829. Syncope was defined by ICD9 code: 780.2.

Other variables of interest:

Models will be adjusted for age, sex, race-center, non-race adjusted estimated glomerular filtration rate, body mass index, resting heart rate, high density lipoprotein cholesterol, total cholesterol, cholesterol lowering medications, leisure activity, diabetes, prevalent cardiovascular disease, alcohol use, education, smoking status, prior stroke, prior heart failure, antidepressant use, sedative use, hypnotic use, antipsychotic use, anticholinergic use.

Data analysis:

Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics (**Table 1**).
    - Means, proportions
- Association of standing SBP or SBP <110 mm Hg with falls, fracture, syncope, CVD and death (**Table 2**).
    - Exposures:
        - Categorical (2): standing SBP and standing SBP <110 mm Hg
    - Cox proportional hazard models by outcome:
        - Falls, fracture, syncope, CVD, death
        - Adjusted for model covariates (see above)
    - Characterization of association between standing SBP (mm Hg) and falls, fracture, and syncope fully adjusted restricted cubic splines (**Figure 1 A-C)**; standing SBP (mm Hg) and CVD and death (**Figure 2 A-B)**; 4 knots will be selected via Harrell's method; histogram of values by outcome status will overlay each figure; splines will be centered at the median values for standing SBP.
- Association of standing SBP with falls, fracture, syncope, CVD, death, stratified by hypertension stage. (**Table 3)**
    - Exposures:
        - Categorical: standing SBP and standing SBP <110 mm Hg
    - Effect modification strata
        - Hypertension stage (3 strata): No hypertension, Stage 1 (SBP ≥130-139 mm Hg/ Diastolic Blood Pressure (DBP) ≥80-89 mm Hg), Stage 2 (SBP ≥140 mmHg/DBP ≥90 mm Hg)
    - Cox proportional hazard models by outcome:
        - Falls, fracture, syncope, CVD, death
        - Adjusted for model covariates (see above)
- Association of standing SBP with falls, fracture, syncope, CVD, death, stratified by age and CVD risk (**Table 4).**
    - Exposures:
        - Categorical: standing SBP and standing SBP <110 mm Hg
    - Effect modification strata
        - Age (3 strata): <50 years, 50-59 years, ≥60 years

        - Baseline 10-year atherosclerotic cardiovascular disease (ASCVD) risk (3 strata): ASCVD <10%, ASCVD ≥10%, and prior CVD history
            - Baseline 10-year ASCVD risk will be calculated with the U.S.-derived pooled cohort equations.[13]
    - Cox proportional hazard models by outcome:
        - Falls, fracture, syncope, CVD, death
        - Adjusted for model covariates (see above; note history of CVD is not applicable here)
- Supplemental analysis: Characterization of association between standing SBP (mm Hg) and stroke using fully adjusted restricted cubic splines (**Supplemental Figure 1**); 4 knots will be selected via Harrell's method; histogram of values by outcome status will overlay each figure; splines will be centered at the median values for standing SBP.

Limitations:

- Insensitive event ascertainment (falls)
- Standing SBP are not available on all participants
- Residual confounding is always a concern with observational studies.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/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)?

2018
Rawlings AM, Juraschek SP, Heiss G, et al. "Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline." *Neurology*. 2018;91(8):e759-e768.

Juraschek SP, Daya N, Appel LJ, et al. "Orthostatic Hypotension and Risk of Clinical and Subclinical Cardiovascular Disease in Middle-Aged Adults." *J Am Heart Assoc*. 2018;7(10).

2017
Juraschek SP, Daya N, Rawlings AM, et al. "Association of History of Dizziness and Long-term Adverse Outcomes With Early vs Later Orthostatic Hypotension Assessment Times in Middle-aged Adults." *JAMA Intern Med*. 2017;177(9):1316-1323.

Juraschek SP, Daya N, Appel LJ, et al. "Orthostatic Hypotension in Middle-Age and Risk of Falls." *Am J Hypertens*. 2017;30(2):188-195.

2012
Jones CD, Loehr L, Franceschini N, et al. "Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities study." *Hypertension*. 2012;59(5):913-8.

2006
Rose KM, Eigenbrodt ML, Biga RL, et al. "Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study." *Circulation*. 2006;114(7):630-6.

2000
Rose KM, Tyroler HA, Nardo CJ, et al. "Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study." *Am J Hypertens*. 2000;13(6 Pt 1):571-8.

Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. "Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996." *Stroke*. 2000;31(10):2307-13.

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 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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3. Wright JT, Whelton PK, Johnson KC, et al. SPRINT Revisited: Updated Results and Implications. *Hypertension*. 2021;78(6):1701-1710. doi:10.1161/HYPERTENSIONAHA.121.17682

4. Juraschek SP, Daya N, Rawlings AM, et al. Association of History of Dizziness and Long-term Adverse Outcomes With Early vs Later Orthostatic Hypotension Assessment Times in Middle-aged Adults. *JAMA Intern Med*. 2017;177(9):1316-1323. doi:10.1001/jamainternmed.2017.2937

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