ARIC Manuscript Proposal #4225

PC Reviewed: 4/11/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Standing, Seated, and Supine Blood Pressure and Risk of 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: Duc Giao, Hannah Col, Fredrick Larbi Kwapong, Ruth-Alma Turkson-Ocran, Long Ngo, Jennifer Cluett, Lynne Wagenknecht, B. Gwen Windham, Elizabeth Selvin, Pamela Lutsey, 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. DG **[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: Data analysis will begin once this proposal is approved with the goal of a manuscript draft by Fall 2023.

4. Rationale:

Blood pressure (BP) is an important modifiable risk factor directly related to cardiovascular disease (CVD), stroke, and mortality.[1] It is normal for BP to decline in the evening hours and elevated BP measures at night are strongly associated with CVD events and all-cause mortality.[2,3] However, most people sleep in the supine position, making it possible that supine hypertension (HTN) is responsible for some of the observed associations between nocturnal hypertension and CVD events. In fact, our group recently found that BP measured in different body positions as part of daytime orthostatic hypertension (OH) protocols was related to nocturnal elevations in BP.[4]

However, it remains unknown whether supine HTN is a risk factor for CVD events independent of seated BP. This could provide a simple and efficient way to identify nocturnal hypertension in a clinical setting. Additionally, this study will directly contribute to future work in ARIC visit 10, which includes collecting supine BP from OH assessments and examining them in relation to sleep-time BP from ambulatory blood pressure monitoring (ABPM).

The ARIC population is an ideal sample for addressing this question because of the availability of supine and seated BP measurements in over 13,000 middle-aged adults at visit 1, combined with ARIC's longitudinal surveillance for CVD.

Thus, our objectives are as follows:

1. To determine the prevalence of supine HTN (assessed during visit 1) in the ARIC study population. (Supine HTN is defined as having a supine systolic blood pressure (SBP) > 130 or diastolic blood pressure (DBP) > 80 mm Hg.)
2. To determine the prevalence of supine HTN in different subgroups of the ARIC population based on their seated blood pressure levels and hypertension treatment status.
3. To determine the relationship between supine HTN and CVD outcomes and by hypertension treatment status.

5. Main Hypothesis/Study Questions:

1. What is prevalence of supine HTN (SBP >130 or DBP >80 mm Hg) in middle-age adult participants of the ARIC population overall and by hypertension treatment status?
2. What is the relationship between supine HTN and CVD outcomes (CAD, stroke, CHF, mortality) overall and by hypertension treatment status?
3. How do sustained or discordant HTN detection (supine only, seated only) compare to confirmed normotension in adults with and without a diagnosis of HTN, with respect to CVD 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 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 (while race/ethnicity are unlikely to impact our analysis, since we will use the Field Center-Race categories this small number of participants, <N=15, will be excluded)
- African Americans from Washington County or Minnesota
- No prior history of CVD, heart failure, or stroke
- Unknown high blood pressure treatment status (MSRD24A)

Exposure assessment:

Seated and supine BPs were measured during ARIC visit 1 (1987-1989) in over 13,000 ARIC participants. Supine BP will be examined in strata of hypertension treatment with the following definitions: (1) Untreated supine HTN: a supine SBP ≥130 or DBP ≥80 mm Hg among adults who were not being treated for hypertension (based on MSRD24A=N; "Were any of the medications you took during the past two weeks for high blood pressure?") and (2) Uncontrolled supine HTN will be defined as a supine SBP ≥130 or DBP ≥80 mm Hg among adults who were being treated for hypertension (based on MSRD24A=Y).

Within categories of adults not being treated for high blood pressure and those treated for high blood pressure (MSRD24A response or Y or N) we will define (1) untreated seated hypertension (seated SBP ≥130 or DBP ≥80 mm Hg and MSRD24A= "N") and (2) treated seated hypertension (seated SBP ≥130 or DBP ≥80 mm Hg and MSRD24A= "Y"). Using these categories, we will determine participants with confirmed normotension in both positions (reference), hypertension in the supine only position, hypertension in the seated only position, and hypertension in both positions.

We will also perform a sensitivity analysis defining hypertension treatment based on actual pill bottle review (HYPTMDCODE01, 0 or 1; indicator of participant taking a hypertension lowering medication nin the last two weeks).

Primary outcomes: CVD, stroke, heart failure, and mortality

The individual primary outcomes in this study are incident (1) coronary heart disease (CHD), (2) heart failure, (3) stroke, (4) fatal coronary heart disease, and (5) all-cause mortality after visit 1 through December 31, 2019 (this end date will be updated as more data is released). All events (except heart failure, which was not adjudicated initially) will be defined as the first occurrence of these adjudicated outcomes after the baseline visit. We will use the following outcome variables with their corresponding follow-up time for these analyses: CHD (c7_in_19sp), heart failure (c7_inchf19), definite/probable stroke (c7_ft19dp), fatal CHD (c7_fatchd19), and all-cause mortality (dead19; censdat7 and dated19 will be used for determining follow-up time for all-cause mortality).

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, education, and smoking status.

Data analysis:

Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics (**Table 1**).
    - Means, proportions
- Prevalence of supine HTN, overall and by HTN treatment status and by seated BP categories (seated SBP ≥130 or DBP ≥80 mm Hg, yes or no) (**Table 2**)
- Association of supine HTN, overall and by HTN treatment status with outcomes (CAD, stroke, HF, fatal CHD, all-cause mortality) (**Table 3**)
    - Exposures:
        - Primary: Supine HTN (vs no supine HTN)
        - Secondary: Continuous supine BP
    - Absolute risk
        - Incidence Rate per 1,000 person-years
    - Relative risk
        - Cox proportional hazard models by outcome (hazard ratios)
        - Adjusted for model covariates (see above)
    - Characterization of association between supine SBP (mm Hg) (supplement DBP) and the 5 outcomes via fully adjusted restricted cubic splines (**Figure 1 A-E)**; 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 supine SBP.
- Association of confirmed hypertension, supine only HTN, and seated only HTN (vs normotension in both positions) and outcomes, overall and by HTN treatment status (**Table 4)**
    - Exposures:
        - Categorical: HTN in both body positions, supine only, or seated only vs normal in both positions (reference)
    - Cox proportional hazard models by outcome:
        - CHD, HF, stroke, fatal CHD, death
        - Adjusted for model covariates (see above)
- Supplemental analysis: Separate systolic and diastolic BP and repeat Table 2-4 looking at these individual components. Consider splines by treatment status if associations appear to differ in pre-specified stratified analyses above.

Limitations:

- Supine BPs are not available on all participants
- Seated and supine BPs were measured with different devices and protocols
- 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)?

05/11/2022	4030	Phenotypes of orthostatic hypotension and their association with adverse clinical outcomes in Middle-Aged Adults	Juraschek, SP	04/12/2022	Approved	PDF	
05/11/2022	4027	Standing Blood Pressure and Risk of Falls, Fracture, Syncope, Cardiovascular Disease and Mortality from the Atherosclerosis Risk in Communities Study (ARIC)	Kondo, J	04/12/2022	Approved	PDF	
11/25/2019	3501	Subclinical and Clinical Cardiovascular Disease and Physical Function in Older Adult Participants of the Atherosclerosis Risk in Communities Study (ARIC)	Juraschek, SP	11/12/2019	Approved	PDF	
08/16/2018	3221	Subclinical Cardiovascular Disease, Falls, and Syncope in the Atherosclerosis Risk in Communities Study (ARIC)	Juraschek, SP	08/14/2018	Approved	31493355 PDF	31493355

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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2. Kario K, Hoshide S, Mizuno H, Kabutoya T, Nishizawa M, Yoshida T, Abe H, Katsuya T, Fujita Y, Okazaki O, Yano Y, Tomitani N, Kanegae H; JAMP Study Group. Nighttime Blood Pressure Phenotype and Cardiovascular Prognosis: Practitioner-Based Nationwide JAMP Study. Circulation. 2020 Nov 10;142(19):1810-1820. doi: 10.1161/CIRCULATIONAHA.120.049730. Epub 2020 Nov 2. Erratum in: Circulation. 2020 Dec 22;142(25):e632. PMID: 33131317; PMCID: PMC7643792.

3. Yang WY, Melgarejo JD, Thijs L, Zhang ZY, Boggia J, Wei FF, Hansen TW, Asayama K, Ohkubo T, Jeppesen J, Dolan E, Stolarz-Skrzypek K, Malyutina S, Casiglia E, Lind L, Filipovský J, Maestre GE, Li Y, Wang JG, Imai Y, Kawecka-Jaszcz K, Sandoya E, Narkiewicz K, O'Brien E, Verhamme P, Staessen JA; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. Association of Office and Ambulatory Blood Pressure With Mortality and Cardiovascular Outcomes. JAMA. 2019 Aug 6;322(5):409-420. doi: 10.1001/jama.2019.9811. PMID: 31386134; PMCID: PMC6822661.

4. Ghazi L, Drawz PE, Pajewski NM, Juraschek SP. The Association of Orthostatic Hypotension With Ambulatory Blood Pressure Phenotypes in SPRINT. Am J Hypertens. 2021 May 22;34(5):511-520. doi: 10.1093/ajh/hpaa184. PMID: 33186448; PMCID: PMC8140655.