ARIC Manuscript Proposal #4457

PC Reviewed: 05/14/24 **Status: _____** **Priority: 2**

1.a. Full Title: Prevalence and Demographic Characteristics of Hypertension and Orthostatic Hypotension Using Office, Ambulatory, and Home Blood Pressures from the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): OH, ABPM, and HBPM in ARIC

2. Writing Group:

Writing group members: Md Marufuzzaman Khan, Fredrick Larbi Kwapong, Dhrumil Patil, Hannah Col, Ruth-Alma Turkson-Ocran, Mingyu Zhang, Jennifer Cluett, Kenneth Mukamal, Long Ngo, 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. MMK **[please confirm with your initials electronically or in writing]**

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3. Timeline: Data analysis will begin once this proposal is approved with the goal of a manuscript draft by Fall 2024.

4. Rationale:

Hypertension is prevalent in the majority of U.S. adults above the age of 75 and is one of the most important modifiable risk factors for cardiovascular disease, dementia and all-cause mortality.[1–3] The Systolic Blood Pressure Intervention Trial (SPRINT) and a recent meta-analysis have shown cardiovascular benefits, reduced cognitive decline, and improved survival in older adults who underwent more aggressive treatment of clinic-based blood pressure (BP) measures.[4,5]

Despite this evidence, more intensive treatment of elevated BP is avoided in older adults due to concerns that a drop in BP on standing (i.e., orthostatic hypotension [OH]) might be exacerbated by therapy, contributing to falls and dementia.[6] Therefore, there is an urgent need to determine the prevalence and long-term implications of OH in older adults to inform better therapeutic strategies for elevated BP. Furthermore, while elevated BP in older adults is associated with falls, cardiovascular disease (CVD), and dementia, the extent to which it is driven by potential overtreatment of adults with white coat effect (WCE, elevated clinic BP with normal or low wake time BP at home) remains unknown.

Previous studies have reported that older adults tend to have limited mobility and decreased access to transportation, which reduces their ability to reach clinics for BP measurement.[7] These barriers have been amplified during the COVID-19 pandemic, which disproportionately affected older adults and refrained them from clinic visits to avoid coronavirus infection. This reliance on brick-and-mortar facilities delays BP treatment and control, leading to a risk of preventable adverse clinical outcomes. Home blood pressure monitoring (HBPM) is a potential approach to detect uncontrolled hypertension at home and initiate timely BP treatment, which can contribute to reducing the risk of preventable and often devastating clinical events. However, the performance of home BP compared to clinic-based BP and gold-standard 24-hour ambulatory BP monitoring (ABPM) is yet to be established in older U.S. adults.

5. Main Hypothesis/Study Questions

1. What is the prevalence of different types of OH in elderly participants of the ARIC population overall and by different sociodemographic characteristics, comorbid conditions, and medications?
2. Is there any association between different types of OH and falls, and different types of symptoms?
3. What is the prevalence of different clinical definitions of blood pressures based on ABPM in older participants of the ARIC population, overall and by different sociodemographic characteristics, comorbid conditions, and medications?
4. Is there any association between different clinical definitions of blood pressures based on ABPM and falls, and different types of symptoms?
5. What is the impact of HBPM measurement protocols on the prevalence of hypertension (defined by SBP≥130 mm Hg or DBP≥80 mm Hg) in elderly participants of the ARIC population overall and by different sociodemographic characteristics, comorbid conditions, and medications?

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: Cross sectional study with ARIC visit 10

Exclusions:

- Participants who did not complete in-clinic, orthostatic hypotension (OH), ambulatory (ABPM), and home blood pressure monitoring (HBPM) study of ARIC visit 10

Exposure assessment:

The following blood pressures were measured during ARIC visit 10: in-clinic seated blood pressure, supine and standing blood pressure in orthostatic hypotension assessment, and out-of-clinic blood pressures over 24 hours and 8 days in ABPM and HBPM assessment, respectively.

Primary outcomes: Falls, Different symptoms

The primary outcomes in this study are (1) falls, and (2) different symptoms (Light headedness, Fainting, Dizziness, Black out, Imbalance) experienced during the last 30 days or throughout the study.

Participants were asked about falls and different symptoms during ARIC visit 10. Falls were defined based on self-reported responses to the question about whether participants had

experienced a fall in the last 12 months. Similarly, data on different symptoms were obtained from participant responses to the questions about symptoms they had experienced in the last 30 days or at the time of the study when standing up, and whether they had experienced different symptoms during the 26 hours of ABPM monitoring.

Other variables of interest:

The following variables will be used for prevalence estimations and model adjustments: age, sex, race, body mass index, diabetes history, history of cardiovascular disease (coronary heart disease, stroke, congestive heart failure), estimated glomerular filtration rate, chronic kidney disease, hypertension status, hypertension medication use in the past 2 weeks, and medication classes associated with falls (e.g. diuretic, antidepressant, sedative, hypnotic, antipsychotic, and anticholinergic medications). Data for these variables will be obtained from the ARIC visit 1 and visit 9 studies.

Data analysis:

Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics.
    - Means, proportions

- Aim 1:
    - Calculate different types of OH based on the definitions provided in **Table 1**
    - Estimate prevalence
        - Overall
        - By other variables of interest (see above)
    - Logistic models for outcome
        - Exposures: Different types of OH
        - Outcome: Falls, symptoms
        - Adjustment of other variables (see above)

- Aim 2:
    - Calculate different clinical definitions **(Table 2)** of blood pressures based on ABPM
    - Estimate prevalence
        - Overall
        - By other variables of interest (see above)
    - Logistic models for outcome
        - Exposures: Different types of blood pressures based on ABPM
        - Outcome: Falls, symptoms

        - Adjustment of other variables (see above)

- Aim 3:
    - Calculate different HBPM measurement protocols **(Table 3)** and hypertension (defined by SBP≥130 mm Hg or DBP≥80 mm Hg)
    - Estimate prevalence
        - Overall
        - By other variables of interest (see above)

Limitations:

- Self-reported responses of falls and other symptoms
- Residual confounding

Table 1. Definitions of different types of orthostatic hypotension

	Measurements involved						Definitions
OH metric	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	
Primary OH	Y	Y	Y				Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Traditional OH		Y	Y				Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Initial OH	Y	N	N	N	N	N	Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Early OH	Y	Y	Y	N	N	N	Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Delayed OH	N	N	N	Y	Y	Y	Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Sustained OH	Y	Y	Y	Y	Y	Y	Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Mean OH	Average of all measurements from M1 to M6						Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg
Minimum OH	Minimum among all measurements from M1 to M6						Drop in SBP ≤ -20 mm Hg or DBP ≤ -10 mm Hg

Table 2: Clinical definitions of different types of blood pressures based on ABPM

ABPM Protocol	**Definitions**
White coat effect	Drop in ABPM versus clinic SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg
White coat hypertension	Clinic SBP = 140 and/or DBP = 90 mm Hg and wake- time ABPM SBP < 135 mm Hg and DBP < 85 mm Hg
Masked hypertension	Clinic BP < 140 / < 90 mm Hg and wake-time ABPM SBP = 135 or DBP = 85 mm Hg
Average of blood pressures during sleep	mean of all ABPM measurements during sleep
Average of blood pressures during wake	mean of all ABPM measurements during wake
Nocturnal dipping patterns	a ratio of wake-to-night mean SBP: extreme dipping < 0.8, normal dipping 0.8 to < 0.9, non-dipping 0.9-1, and reverse dipping>1

Table 3. Clinical definitions of different types of blood pressures based on HBPM

HBPM Protocol	N of days	AM			PM			N of measurements
		M 1	M 2	M 3	M 1	M 2	M 3	
Mean days 1-8	8	×	×	×	×	×	×	48
Mean of days 1-7	7	×	×	×	×	×	×	42
Exclude first day (mean of days 2-8)	7	×	×	×	×	×	×	42
Morning measures only, days 1-7	7	×	×	×				21
Evening measures only, days 1-8	7				×	×	×	21
Exclude first measurement of each triplet, days 1-7	7		×	×		×	×	28
Exclude last 2 measurement of each triplet, days 1-7	7	×			×			14
3-days of monitoring, morning and evening	3	×	×	×	×	×	×	18
3-days of monitoring, single measurements	3	×			×			6
3-days of monitoring, morning only	3	×	×	×				9
3-days of monitoring, evening only	3				×	×	×	9

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)?

Here are recent proposals using orthostatic data from ARIC visit 1 that are relevant.

4437: Dooley, Orthostatic Hypertension

4225: Giao, Supine Hypertension

4027: Kondo, Standing BP

4030: Juraschek/Earle, OH Phenotypes

Here are relevant ARIC manuscripts:

2023

Kondo, Jordan K., et al. "Standing blood pressure and risk of falls, syncope, coronary heart disease, and mortality." *American journal of hypertension* 36.11 (2023): 593-601.

Earle, William B., et al. "Association of supine hypertension versus standing hypotension with adverse events among middle-aged adults." *Hypertension* 80.11 (2023): 2437-2446.

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.

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* 2019.22/2020.28)

___ 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.

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3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet Lond Engl*. 2002;360(9349):1903-1913. doi:10.1016/s0140-6736(02)11911-8

4. Vaduganathan M, Claggett BL, Juraschek SP, Solomon SD. Assessment of Long-term Benefit of Intensive Blood Pressure Control on Residual Life Span. *JAMA Cardiol*. 2020;5(5):1-6. doi:10.1001/jamacardio.2019.6192

5. Juraschek SP, Hu JR, Cluett JL, et al. Effects of Intensive Blood Pressure Treatment on Orthostatic Hypotension : A Systematic Review and Individual Participant-based Meta-analysis. *Ann Intern Med*. 2021;174(1):58-68. doi:10.7326/M20-4298

6. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res Off J Clin Auton Res Soc*. 2011;21(2):69-72. doi:10.1007/s10286-011-0119-5

7. Wolfe MK, McDonald NC, Holmes GM. Transportation Barriers to Health Care in the United States: Findings From the National Health Interview Survey, 1997–2017. *Am J Public Health*. 2020;110(6):815-822. doi:10.2105/AJPH.2020.305579