

ARIC Manuscript Proposal #4030

PC Reviewed: 4/12/22
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Phenotypes of orthostatic hypotension and their association with adverse clinical outcomes in Middle-Aged Adults

b. Abbreviated Title (Length 26 characters): Orthostatic hypotension phenotypes and adverse events

2. Writing Group:

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

Note is 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. ___x___ [**please confirm with your initials electronically or in writing**]

First author:

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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 to begin after approval of this manuscript proposal. First draft should be available August, 2022.

4. Rationale:

Orthostatic hypotension (OH), a drop in standing and supine systolic blood pressure of 20 mm Hg or diastolic blood pressure of 10 mm Hg,^{1,2} is a predictor of cardiovascular disease events, stroke, falls, syncope, and premature death among 40-60 year-old ARIC participants.^{3,4} It has largely been thought that this drop in blood pressure results in organ hypoperfusion and progressive injury. As a result, clinical management of OH focuses on blood pressure augmentation through increased consumption of salt and fluids, de-prescription of antihypertensive therapies, or the introduction of mineralocorticoids to raise blood pressure.⁵ However, given that OH is derived from both supine and standing BP measurements, it is conceivable that either an elevated supine BP (i.e. supine hypertension) or a low standing BP (i.e. standing hypotension) may drive the association of OH with adverse events independent of the difference in BP between the two positions. This could have direct implications for clinical management of OH, as supine hypertension would ideally be lowered with more aggressive BP treatment versus traditional approaches to OH. Indeed, in a recent meta-analysis we demonstrated that more aggressive BP reduction reduced incidence of OH in 9 trials of hypertension treatment.⁶

Study objectives

Our objectives in this proposal are to determine the association between distinct phenotypes of OH, namely, supine hypertension or standing hypotension, with adverse health outcomes. We hypothesize that the underlying OH phenotype will be associated with distinct health outcomes: (1) Supine hypertensive OH will be associated with CVD events and stroke due to high blood pressure (a prominent CVD risk factor), while (2) Standing hypotensive OH will be associated with falls and syncope (due to cerebral hypoperfusion) and (3) either or both will be associated with premature death.

We believe delineating these phenotypes of OH and their associated health implications will inform clinical management decisions for OH.

The ARIC population is ideal to address this question because of the availability of supine and standing BP measurements in over 13,000 middle-aged adults at visit 1 combined with ARIC's longitudinal surveillance for CVD and linkage with CMS claims, which included fall and syncope events. Furthermore, the comprehensive assessments in ARIC afford the opportunity to address numerous confounding variables.

5. Main Hypothesis/Study Questions:

Primary study questions:

1. How many people have hypertensive OH or hypotensive OH?
2. What is the relationship between supine BP, standing BP, or postural change associated with CVD (fatal, all cvd, chf, stroke), falls, syncope, and death? Are they independent of each other? How do the magnitudes of association compare with postural change?

3. Is hypertensive OH or hypotensive OH associated with CVD, dementia, fall, syncope, and death?

Hypotheses:

1. Supine hypertensive OH will be associated with CVD outcomes compared to the population without OH, without supine hypertension, and without standing hypotension.
2. Standing hypotensive OH will be associated with falls and syncope compared to the population without OH, without supine hypertension, and without standing hypotension.
3. Both supine hypertensive OH and/or standing hypotensive OH will be associated with premature 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 supine or standing BP measured at visit 1
- Missing covariates of interest
- Persons of ethnicity other than African American or white
- African-Americans from Washington County or Minnesota

Exposure assessment:

Orthostatic hypotension will be derived from the following equation:

Standing BP – supine BP = Postural change in BP

OH is defined as a postural change in SBP \leq -20 mm Hg or DBP \leq -10 mm Hg.

In addition, we will use the following definitions:

- Supine hypertension: a supine SBP \geq 140 mm Hg or DBP \geq 90 mm Hg
- Standing hypotension: a standing SBP \leq 105 mm Hg or DBP \leq 65 mm Hg

Based on these definitions we will classify the ARIC population, using the following OH phenotypes:

- (1) No OH, no supine hypertension, no standing hypotension (reference group)
- (2) No OH, supine hypertension, no standing hypotension
- (3) No OH, no supine hypertension, standing hypotension
- (4) No OH, both supine hypertension and standing hypotension
- (5) OH, no supine hypertension, no standing hypotension

- (6) OH, supine hypertension, no standing hypotension
- (7) OH, no supine hypertension, standing hypotension
- (8) OH, both supine hypertension and standing hypotension

Outcomes: Any CVD event, fatal CVD, stroke, CHF, falls, syncope, and all-cause mortality

We will examine incident CHD (“c7_in_13sp”), fatal CVD, chf, and stroke through December 31, 2019 or most recent data available

Falls will be defined at 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 1991-2019.^{7,8}

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 falls 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.^{7,8} 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 and syncope. Outpatient falls and syncope 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. Syncope was based on ICD9 code 780.2.

Other variables of interest:

Models will be adjusted for age, sex, race-study center, estimated glomerular filtration rate, body mass index, resting heart rate, history of diabetes, alcohol use, education, leisure activity, smoking status, history of cardiovascular disease, history of stroke, history of heart failure, antidepressant use, sedative use, hypnotic use, antipsychotic use, and anticholinergic use.

Data analysis:

Our primary analyses will be as follows:

- Baseline characteristics by OH phenotype (**Table 1**).
 - Means, proportions
- Association of supine hypertension or standing hypotension with events (**Table 2**)
 - Cox proportional hazards models
 - Model covariates:
 - Unadjusted
 - Minimally adjusted: age/sex/race adjusted
 - Fully adjusted (details above) +/- adjustment for OH
- Association of OH phenotypes with events (**Table 3**)
 - OH phenotypes:
 - No OH with supine HTN without standing hypotension
 - No OH without supine HTN and with standing hypotension
 - No OH with both supine hypertension and standing hypotension
 - OH without supine HTN or standing hypotension
 - OH with supine HTN without standing hypotension
 - OH without supine hypertension with standing hypotension
 - OH with both supine hypertension and standing hypotension
 - Cox proportional hazards models
 - Model covariates:
 - Unadjusted
 - Minimally adjusted: age/sex/race adjusted
 - Fully adjusted (details above)
- Independent and joint models examining the association of supine SBP, standing SBP, the difference in SBP, or mean SBP with respect to outcomes (**Table 4**)
 - Cox proportional hazards models
 - Model covariates:
 - Supine SBP or standing SBP fully adjusted (details above)
 - Supine SBP or standing SBP fully adjusted (details above) + difference in SBP
 - Supine SBP or standing SBP fully adjusted (details above) + mean of supine and standing SBP
 - Difference and mean SBP full adjusted (details above)
- Characterization of association between standing SBP, supine SBP, the difference in SBP, and mean SBP with outcomes using fully adjusted restricted cubic splines (**Figure 1 A-C**); 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 SBP

- Supplement Figure repeating for DBP
- Sensitivity analyses
 - Alternate definitions of supine HTN (130/80) or standing hypotension (110/70)
 - Splines of DBP
 - Models based on OH defined by systolic or diastolic components only
 - Independent and joint models with DBP (instead of SBP)

Limitations:

- Insensitive event ascertainment (falls/syncope)
- Supine and standing BP are not available in all participants
- The number of individuals with some of the OH phenotypes of interest is limited; we may need to aggregate these strata
- Residual confounding is always a concern with observational studies.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes
 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 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 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. 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.csc.unc.edu/ARIC/search.php>
 ____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 the most relevant approved proposal related to our proposed study:

09/28/2021	3927	Maintenance of normal blood pressure from mid- to late-life in the Atherosclerosis Risk in Communities Study: Implications for cardiovascular disease prevention	Foti, K.	09/14/2021	Approved	 PDF
02/02/2022	3979	Sleep medications, physical functioning, and incident injurious falls risk in The Atherosclerosis Risk in Communities (ARIC) Study	Full, K.	12/14/2021	Approved	 PDF

Here are recent ARIC manuscripts, relevant to the current proposal:

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. doi:10.1093/ajh/hpw108

Juraschek SP, Daya N, Appel LJ, et al. Orthostatic Hypotension and Risk of Clinical and Subclinical Cardiovascular Disease in Middle-Aged Adults. *Journal of the American Heart Association*. 2018;7(10):e008884. doi:10.1161/JAHA.118.008884

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 Sep 1;177(9):1316-1323. doi:10.1001/jamainternmed.2017.2937.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes 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 at <http://www.csc.unc.edu/aric/forms/>

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.csc.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.

Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript Yes No.

References

1. Kaufmann H. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. *Clin Auton Res*. 1996;6(2):125-126.
2. 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*. 2011;21(2):69-72. doi:10.1007/s10286-011-0119-5
3. 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). doi:10.1161/JAHA.118.008884
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*. Published online July 24, 2017. doi:10.1001/jamainternmed.2017.2937
5. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. *Cleve Clin J Med*. 2010;77(5):298-306. doi:10.3949/ccjm.77a.09118
6. 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
7. 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. doi:10.1093/ajh/hpw108
8. Kucharska-Newton AM, Heiss G, Ni H, et al. Identification of heart failure events in CMS-Medicare claims. The Atherosclerosis Risk in communities (ARIC) Study. *J Card Fail*. Published online July 23, 2015. doi:10.1016/j.cardfail.2015.07.013