ARIC Manuscript Proposal Form

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Publication Committee Review Date: **04/09/24**
ARIC Manuscript Proposal Number: #**4437**

1.a.
Full Title: Orthostatic Hypertension, Standing Hypertension, and Risk of Cardiovascular Disease in the Atherosclerosis Risk in Communities Study (ARIC)

1.b.
Abbreviated Title: OHTN and Outcomes in ARIC

2.
Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Sean W. Dooley, Fredrick Larbi Kwapong, Hannah Col, Ruth-Alma N. Turkson-Ocran, Maruf Khan, Long H. Ngo, Jennifer L. Cluett, Kenneth Mukamal, Lewis A. Lipsitz, Mingyu Zhang, Natalie R. Daya, Elizabeth Selvin, Pamela L. Lutsey, Lynne Wagenknecht, Beverly Gwen Windham, Joseph Coresh, Stephen Juraschek

*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. SWD **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline:

Data analysis will begin once this proposal is approved with the goal of a manuscript draft by December 2023.

4. Rationale:

There is considerable interest in orthostatic hypertension (OHTN), a rise in blood pressure after standing, as a new hypertension phenotype,[1] which has been associated with adverse health outcomes, including cardiovascular disease, stroke, kidney disease, cognitive impairment, and all-cause mortality.[2–5] However, there is no standard definition in the literature. Recent consensus statements advocate that OHTN include both an increase in blood pressure after standing as well as exceed a standing hypertension threshold of systolic blood pressure ≥140 mm Hg.[6] However, this consensus definition could be problematic for both clinical care and future research, if either of these components (i.e., the orthostatic hypertension or standing hypertension) had different risk relationships with cardiovascular (CVD) risk, as the risk attributes of one may be incorrectly attributed to the other.
Our study aims to address this question by examining distinct definitions of OHTN with respect to cardiovascular disease events. We will specifically examine change in systolic or diastolic blood pressure and standing hypertension with respect to incident coronary heart disease, stroke, congestive heart failure, fatal coronary heart disease, and all-cause mortality.
This study will not only seek to refine the definition of OHTN but also aims to differentiate between the risks of cardiovascular disease and mortality associated with orthostatic hypertension and standing hypertension. By achieving these objectives, our study will enhance the understanding of the distinct cardiovascular risks posed by these two conditions, thereby informing the ongoing discussion surrounding the definition of OHTN.
Our objectives are:

1. To determine the prevalence of OHTN (assessed during visit 1) in the ARIC study population by definition.

2. To determine the association between different OHTN definitions and incident coronary heart disease, stroke, congestive heart failure, fatal coronary heart disease, and all-cause mortality.
3. To compare rise in BP with standing BP thresholds in joint models with respect to incident coronary heart disease, stroke, congestive heart failure, fatal coronary heart disease, and all-cause mortality.

5. Main Hypothesis/Study Aims:

1. OHTN and standing hypertension (i.e., a systolic BP ≥140 mm Hg) will be prevalent in the ARIC population (i.e., affect over 10%)
2. OTHN will not be associated with CVD risk, while standing hypertension will be associated with CVD risk
3. Standing HTN will be an important risk factor for CVD events, while OHTN will be inconsistently associated with CVD events

Overall hypothesis: Given differences in their association with CVD events, orthostatic change in BP upon standing should not be combined with standing hypertension in a consensus definition.

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 orthostatic hypertension readings 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
- Prior history of CVD, heart failure, or stroke
- Unknown high blood pressure treatment status (MSRD24A)

Exposure assessment:

Supine, seated and standing BPs were measured during ARIC visit 1 (1987–1989) in over 13,000 ARIC participants. Orthostatic hypertension will be defined as a rise in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg when moving from lying to standing. Additional pertinent exposures include

systolic orthostatic hypertension (standing SBP ≥140 mm Hg), diastolic orthostatic hypertension (standing DBP ≥90 mm Hg), and combinations of systolic orthostatic hypertension with standing SBP ≥140 mm Hg, and diastolic orthostatic hypertension with standing DBP ≥90 mm Hg.

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 orthostatic hypertension, systolic orthostatic hypertension, diastolic orthostatic hypertension, standing systolic BP ≥ 140 mmHg, standing diastolic BP ≥ 90 mm Hg, systolic orthostatic hypertesion and standing systolic BP ≥ 140 mm Hg, and diastolic orthostatic hypertension and standing diastolic BP ≥ 90 mm Hg.
- Association of OHTN by definition with outcomes (CHD, stroke, HF, fatal CHD, all-cause mortality) (**Table 3**)
    - Exposures:
        - OHTN: rise in SBP ≥20 mm Hg or DBP ≥10 mm Hg
        - Systolic OHTN: rise in SBP ≥20 mm Hg

        - Diastolic OHTN: DBP ≥10 mm Hg
        - Standing systolic hypertension: standing SBP ≥140 mm Hg
        - Standing diastolic hypertension: standing DBP ≥90 mm Hg
        - Systolic OH & standing SBP ≥140 mm Hg
        - Diastolic OH & standing DBP ≥90 mm Hg
    - Absolute risk
        - Cumulative incidence plots
    - Relative risk
        - Cox proportional hazard models by outcome (hazard ratios)
        - Adjusted for model covariates (see above)
        - Restricted cubic splines of change in SBP or DBP by standing hypertension status with respect to outcomes
- Comparison of orthostatic changes and standing hypertension in joint models (**Table 4)**
    - Models:
        - Systolic OHTN & systolic standing hypertension
        - Diastolic OHTN & diastolic standing hypertension
    - Cox proportional hazard models by outcome:
        - CHD, HF, stroke, fatal CHD, death
        - Adjusted for model covariates (see above)
- Supplemental analysis: Comparison of seated and standing BP as a scatter plot, using Lowess curves and a linear fit

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.

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3. Rouabhi M, Durieux J, Al-Kindi S, Cohen JB, Townsend RR, Rahman M. Orthostatic Hypertension and Hypotension and Outcomes in CKD: The CRIC (Chronic Renal Insufficiency Cohort) Study. *Kidney Med*. 2021;3(2):206-215.e1. doi:10.1016/j.xkme.2020.10.012
4. Strumia M, Vidal JS, Cestac P, et al. Orthostatic hypotension and orthostatic hypertension are both associated with lower cognitive function: The S.AGES cohort. *J Am Geriatr Soc*. n/a(n/a). doi:10.1111/jgs.18571
5. Kostis WJ, Sargsyan D, Mekkaoui C, et al. Association of orthostatic hypertension with

mortality in the Systolic Hypertension in the Elderly Program. *J Hum Hypertens*. 2019;33(10):735-740. doi:10.1038/s41371-019-0180-4
6. Jordan J, Biaggioni I, Grassi G, Fedorowski A, Kario K. When Blood Pressure Increases with Standing: Consensus Definition for Diagnosing Orthostatic Hypertension. *Blood Press*. 2023;32(1):2161871. doi:10.1080/08037051.2022.2161871