ARIC Manuscript Proposal #2992

PC Reviewed: 06/06/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Orthostatic Hypotension and Subclinical and Clinical Cardiovascular Disease in the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Orthostatic Hypotension and Cardiovascular Disease in ARIC

2. Writing Group:

Writing group members: Stephen P Juraschek, Natalie Daya, Lawrence Appel, Edgar Miller, John William (Bill) McEvoy; Kunihiro Matsushita, Christie M. Ballantyne, Elizabeth Selvin, others welcome

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]**

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3. Timeline: Data analysis to begin after approval of this manuscript proposal. First draft should be available October, 2017.

4. Rationale:

Orthostatic hypotension (OH) is common in the elderly[1] as well as those treated for hypertension[2] and is associated with a number of adverse health outcomes, including falls, syncope, cardiovascular disease, stroke, and death.[3–5] Whether OH contributes to the development of cardiovascular disease is unclear, however. While OH has been associated with change in heart structure over time, suggestive of a causal relationship,[13] the association between OH and cardiovascular disease in the literature is contradictory. Several prospective studies reported no association between OH and myocardial infarction,[14] coronary heart disease,[15,16] or cardiovascular disease mortality.[17] Similarly, a recent secondary study of the ACCORD trial, a trial of blood pressure reduction in a population with diabetes, found that while OH was associated with death and heart failure, it was not associated with atherosclerotic events.[18] In contrast, a large number of studies have shown that OH is associated with history of myocardial infarction,[3] coronary artery disease,[19–21] cardiovascular disease events,[5,22] and cardiovascular disease morality.[20,23]

The ARIC Study affords a unique opportunity to examine the relationship between orthostatic hypotension and subclinical and clinical cardiovascular disease in more detail. OH was assessed via high quality, standardized protocols during visit 1 and was derived using standard clinical definition (a decrease of at least 20 mmHg SBP or a decrease of at least 10 mmHg DBP when changing positions from supine to standing) in 681/13,191 (5.2%) of participants. Furthermore, covariates known to be associated with OH and cardiovascular disease were also assessed at baseline, affording an opportunity to rigorously address confounding. We will examine the cross-sectional association of OH with carotid intimal thickness and plaque at visit 1 in middle-aged adults. We will also examine the association with hs-troponin (measured at visits 2, 4, and 5) as well as proBNP (measured at visits 2, 4, 5) along with incident CHD, CVD subtypes (heart failure, fatal and nonfatal CHD), and mortality.

5. Main Hypothesis/Study Questions:

Primary study questions:

1. Is orthostatic hypotension as assessed at visit 1 (using a traditional definition) associated with plaque presence and carotid intimal thickness at visit 1?
2. Is orthostatic hypotension associated with subclinical myocardial damage at visit 2, 4, 5 as measured by hs-troponin or pro-BNP as well as changes in troponin between visits?
3. Is orthostatic hypotension associated with incident CHD, CVD subtypes (heart failure, fatal and nonfatal CHD), or death (update/extension to prior analysis)?

Hypotheses:

1. Orthostatic hypotension will be associated with carotid intimal medial thickness and the presence of carotid plaque.

2. Orthostatic hypotension will be associated with detectable and elevated hs-cTnT at visit 2, change between visits, and detection at 4 or 5 as well.
3. Orthostatic hypotension will be associated with incident coronary heart disease and mortality (both proximal and distal 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 and including cross-sectional analyses of measures of subclinical cardiovascular disease (carotid plaque, carotid intima medial thickness, high sensitivity cardiac troponin T)

Exclusions:

- ARIC participants without an OH assessment at visit 1
- For analyses of hs-cTnT, missing hs-cTnT at visit 2
- For analyses of proBNP, missing proBNP at visit 2
- Missing covariates of interest
- No prior history of CHD, CHF, or stroke

Exposure assessment:

Systolic blood pressure and diastolic blood pressure were measured up to 5 times in supine and standing positions at baseline. Orthostatic hypotension will be defined as a dichotomous variable, using the traditional definition of a 20 mm Hg drop in systolic blood pressure or 10 mm Hg drop in diastolic blood pressure upon changing from a supine to standing position.[24] The drops in SBP or DBP will be based on an average of up to 5 measurements. We will look at look at individual measurements in sensitivity analyses.

In addition, we will look at continuous changes in SBP and DBP upon standing per 5 mm Hg or per standard deviation.

Primary outcome:

The primary outcomes in this study are (1) carotid plaque or carotid intimal thickness assessed at visit 1, (2) high sensitivity troponin measured at visit 2/4/5 or proBNP at visits 2/4/5, and (3) incident CHD (and its subtypes) and mortality (through December 31, 2014 or most recent data available). We will use the following variables for these outcomes: “mnb45_1s” for carotid thickness, “plaque03” for carotid plaque, and “c7_in_13sp” for CHD. The detection of high sensitivity troponin measures in stored specimens of visit 2, will be defined as a value >= 3 ng/dL.

Other variables of interest:

Models will be adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, eGFR, BMI, lipids (LDL, HDL,

triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.

Data analysis:

Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics by orthostatic hypotension status (**Table 1**).
    - Means, proportions
- Cross-sectional examination of orthostatic hypotension (dichotomous, continuous SBP per 5 mmHg, continuous DBP per 5 mmHg) with carotid plaque (logistic regression/ORs) and carotid intimal thickness (linear regression per 1 unit of thickness) (**Table 2**).
    - Models adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, egfr, BMI, lipids (LDL, HDL, triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.
    - **Figure 1 A-D**: restricted cubic spline of plaque (proportion from logistic regression) for continuous SBP or DBP; restricted cubic spline of thickness (linear regression) for continuous SBP or DBP; 4 knots will be selected via Harrell's method
- Association of OH (dichotomous, continuous SBP per 5 mmHg, continuous DBP per 5 mmHg) with detectable visit 2 (or visit 4 or visit 5) high sensitivity troponin (>=3 ng/L) via logistic regression (**Table 3**)
    - Models adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, eGFR, BMI, lipids (LDL, HDL, triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.
    - Figure 2 A-B: fully adjusted restricted cubic splines (4 knots, Harrell's method) of continuous SBP or DBP with hazard of CHD
    - We will also examine change in troponin between visits via linear regression adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, egfr, BMI, lipids (LDL, HDL, triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.
- Association of OH (dichotomous, continuous SBP per 5 mmHg, continuous DBP per 5 mmHg) with detectable visit 2 (or visit 4 or visit 5) proBNP via logistic regression (**Table 3**)

    - Models adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, egfr, BMI, lipids (LDL, HDL, triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.
    - Figure 2 A-B: fully adjusted restricted cubic splines (4 knots, Harrell's method) of continuous SBP or DBP with hazard of CHD
    - We will also examine change in proBNP between visits via linear regression adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, egfr, BMI, lipids (LDL, HDL, triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.
- Sensitivity analysis
    - Models repeated in strata of visit 1 hypertension status
- Association of OH (dichotomous, continuous SBP per 5 mmHg, continuous DBP per 5 mmHg) with incident CHD and death) via Cox proportional Hazards models
    - Models adjusted for the following covariates assessed at visit 1: age, sex, race-center, sitting SBP, sitting DBP, sitting heart rate, egfr, BMI, lipids (LDL, HDL, triglycerides), smoking status, alcohol use, education level, leisure index, cholesterol lowering medication use, antihypertensive medication use within the last 2 weeks, hypertension status, and diabetes status.

Limitations:

- Temporal discrepancy between visit 1 OH and visit 2 hs-troponin; cannot differentiate temporal association in absence of baseline troponin measures
- OH data not available on all participants
- Residual confounding is always a concern with observational studies.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X___ 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 __x__ 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.cscc.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)?

Orthostatic change in blood pressure and incidence of atrial fibrillation: results from a bi-ethnic population based study. Agarwal SK, Alonso A, Whelton SP, Soliman EZ, Rose KM, Chamberlain AM, Simpson RJ Jr, Coresh J, Heiss G. PLoS One. 2013 Nov 11;8(11):e79030.

Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities study. Jones CD, Loehr L, Franceschini N, Rosamond WD, Chang PP, Shahar E, Couper DJ, Rose KM. Hypertension. 2012 May;59(5):913-8.

Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM; ARIC Study Investigators. Hypertension. 2011 Feb;57(2):167-73.

Orthostatic hypotension and incident chronic kidney disease: the atherosclerosis risk in communities study. Franceschini N, Rose KM, Astor BC, Couper D, Vupputuri S. Hypertension. 2010 Dec;56(6):1054-9.

Orthostatic hypotension and cognitive function: the Atherosclerosis Risk in Communities Study. Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Neuroepidemiology. 2010;34(1):1-7.

Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, Heiss G. Circulation. 2006 Aug 15;114(7):630-6. Epub 2006 Aug 7.

Association between the blood pressure response to a change in posture and the 6-year incidence of hypertension: prospective findings from the ARIC study. Rose KM, Holme

I, Light KC, Sharrett AR, Tyroler HA, Heiss G. J Hum Hypertens. 2002 Nov;16(11):771-7.

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

Orthostatic blood pressure responses as a function of ethnicity and socioeconomic status: the ARIC study. Clark R, Tyroler HA, Heiss G. Ann N Y Acad Sci. 1999;896:316-7. No abstract available.

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

___ 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.cscc.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.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.

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 __x__ Yes ____ No.

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