ARIC Manuscript Proposal #2358

PC Reviewed: 5/13/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Association of posture-dependent changes in blood pressure with cerebral vascular lesions: the ARIC Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Postural BP and Infarcts

2. Writing Group:
Writing group members: Anna Poon, Clifford Jack, David Knopman, Richey Sharrett, Tom Mosley, David Couper, Alvaro Alonso, Rebecca Gottesman, Laura Loehr, Gerardo Heiss, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AP [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: Analysis is to start once approval is obtained. We plan to complete the manuscript within eight months from approval of the proposal.
4. **Rationale:**

Orthostatic hypotension is defined as a decrease in systolic blood pressure (BP) ≥20 mmHg and/or decrease in diastolic BP ≥10 mmHg following a change in position from supine to standing. Posture-dependent changes in BP provide a measure of cardiovascular reactivity (1). Large changes in posture-dependent BP are related to altered circadian BP patterns, including limited nocturnal dipping and morning surges (2,3). This trait has also been shown to be associated with incident hypertension (4), coronary heart disease (5), all-cause mortality (6), and stroke (7).

To our knowledge, an association between changes in orthostatic BP in middle age and cerebral vascular lesions has not been described. The rationale for consideration of this outcome in the proposed analyses is based on the associations of posture-related increases and decreases in systolic BP with clinically manifest lacunar, non-lacunar thrombotic, and cardioembolic strokes observed by Eigenbrodt et al. and Yatsuya et al. (8,9). Based on this evidence, there is reason to believe that changes in postural BP may be associated with smaller infarcts. The goal of our analysis is to examine the association of changes in postural BP with cerebral vascular lesions on MRI. We will examine decreases and increases in postural BP both as a continuous trait and as categorically defined orthostatic hypotension.

5. **Main Hypothesis/Study Questions:**

**Aim:** To examine the association of postural changes in blood pressure and orthostatic hypotension at Visit 1 (1987-1989) with cerebrovascular brain abnormalities on MRI at Visit 5 (2011-2013) among participants 45-64 years old at baseline.

- **Hypothesis 1:** A U-shaped association will be observed between postural changes in systolic blood pressure (defined as a continuous variable) at ARIC’s Visit 1 with risk of large cortical non-lacunar, small cortical non-lacunar, and subcortical lacunar infarcts assessed at Visit 5.

- **Hypothesis 2:** The risk of cerebrovascular brain abnormalities on MRI (defined categorically as large cortical non-lacunar, small cortical non-lacunar, and subcortical lacunar infarcts) will be greater in individuals who manifest orthostatic hypotension (defined as a categorical variable) compared to individuals without orthostatic hypotension.

- **Hypothesis 3:** The association between postural changes in blood pressure with cerebrovascular brain abnormalities on MRI will differ according to gender, race, hypertension, diabetes, and smoking status.
Hypothesis 4: Postural changes in systolic blood pressure at ARIC’s Visit 1 will be associated with increased risk of large cortical non-lacunar, small cortical non-lacunar, and subcortical lacunar infarcts in persons without clinical stroke at Visit 5.
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 methodological limitations or challenges if present).

Study design: Prospective cohort. The study population will include ARIC participants with postural blood pressure change measurements in ARIC Visit 1 (1987-1989) and cerebral MRI measurements in ARIC NCS Visit 5 (2011-2013).

Exclusion: Participants with a history of stroke or transient ischemic (TIA) attack prior to Visit 1; race other than black or white, blacks from Minneapolis and Washington County; participants with missing exposure, outcome, and covariates of interest

Exposure: Postural blood pressure change was measured in ARIC at Visit 1. Supine blood pressure was measured every 30 seconds for 2 minutes after 20 minutes of rest in the supine position; standing blood pressure was measured for 2 minutes every 30 seconds after standing. Both measurements were taken with the Dinamap 1846 SX device. Because rapid homeostasis of blood pressure occurs within 30 seconds after standing, the first standing blood pressure measurement was excluded from the average.

We will examine change in postural blood pressure for both systolic and diastolic blood pressure as a continuous variable, defined as the difference between average supine blood pressure and average standing blood pressure. We will also examine postural blood pressure change as a categorical variable, according to the conventional definition of orthostatic hypotension as a decrease in systolic blood pressure ≥20 mmHg and/or a decrease in diastolic blood pressure ≥10 mmHg.

Outcomes: Proxy measures for cerebrovascular brain abnormalities on MRI will include small cortical non-lacunar, large cortical non-lacunar, and subcortical lacunar infarcts measured via magnetic resonance imaging in ARIC NCS Visit 5 (2011-2013). Definitions for each MRI outcome were developed by ARIC NCS and include the following: (1) large cortical infarction (non-lacunar) – hyperintense lesions ≥10mm in diameter including grey matter and underlying white matter; (2) small cortical infarction (non-lacunar) - hyperintense lesions <10 mm in diameter including cortical grey matter and underlying white matter; and (3) subcortical infarction (lacunar) - hyperintense lesions with a dark center ≥3mm in diameter in white matter, infratentorial regions, and central gray/capsular regions;

We will examine infarcts as a categorical variable (large cortical non-lacunar infarcts, small cortical non-lacunar infarcts, subcortical lacunar infarcts, and none). Note: Our analysis will not include white matter hyperintensities. We will also reference work conducted by Bryan et al (10) and Bezerra et al (11) regarding infarct-like lesions.

Covariates: Covariates measured at baseline Visit 1 include age, gender, race, study center, education, cholesterol (total, LDL, HDL), BMI, hypertension, diabetes, smoking status, resting
heart rate, stroke prior to Visit 1, coronary heart disease prior to Visit 1, and medications that may induce orthostatic hypotension (anti-hypertensives, anti-depressants, anti-psychotics, anti-cholinergics, sedatives, narcotics, and nitro compounds). Other covariates include APOE e4 and incident stroke after Visit 1.

High school will be categorized as <high school or >high school. Body mass index (kg/m$^2$) will be calculated from measured weight and height. Hypertension will be defined as mean systolic blood pressure $\geq$140 mmHg, mean diastolic blood pressure $\geq$90, and/or use of blood pressure lowering treatment in the past four weeks. Diabetes will be defined based on self-reported physician diagnosis or current use of diabetes medication. Smoking status will be categorized as former, current, or never.

**Statistical Analysis:**

(a) **Baseline characteristics:** Associations of baseline characteristics with infarct categories will be assessed using ANOVA for continuous variables and chi-squared test for categorical variables.

(b) **Hypothesis 1:** Multivariable regression will be used to estimate absolute risks, relative risks, and their respective 95% confidence intervals for the associations of orthostatic changes in systolic blood pressure with large cortical non-lacunar, small cortical non-lacunar, and subcortical lacunar infarcts (SAS PROC GENMOD (LINK=log)). Linear regression with restricted cubic splines will be used to visualize the association of orthostatic changes in systolic blood pressure with risk of large cortical non-lacunar, small cortical non-lacunar, and subcortical lacunar infarcts. We will examine unadjusted associations (model 1), associations adjusted for age, race, gender, study center, BMI, and resting heart rate (model 2), and associations additionally adjusted for diabetes, hypertension, and smoking (model 3: model 2 + additional covariates).

(c) **Hypothesis 2:** Multivariable regression will be used to separately estimate absolute risks, relative risks, and their respective 95% confidence intervals for the associations of orthostatic hypotension (yes or no) with infarcts (large cortical non-lacunar vs none, small cortical non-lacunar vs none, subcortical lacunar vs none) (SAS PROC GENMOD (LINK=log)). Risk differences and 95% confidence intervals will be estimated as well (SAS PROC GENMOD (LINK=identity)). We will examine unadjusted associations (model 1), associations adjusted for age, race, gender, study center, BMI, and resting heart rate (model 2), and associations additionally adjusted for diabetes, hypertension, and smoking (model 3: model 2 + additional covariates).

(d) **Hypothesis 3:** Stratify analyses for Hypothesis 2 by gender, race, hypertension, diabetes, and smoking status. For each subgroup, we will examine unadjusted associations (model 1), associations adjusted for age, race, gender, study center, BMI, and resting heart rate (model 2), associations additionally adjusted for diabetes, hypertension, and smoking (model 3: model 2 + additional covariates), and formally test for interaction (model 4: model 3 + interaction term). **Note:** In stratified analyses, we will not adjust and stratify on the same variable.

(e) **Hypothesis 4:** Repeat analyses excluding persons with incident stroke.
(e) Sensitivity Analysis: Repeat separate analyses excluding persons with medications that may induce orthostatic hypotension at Visit 1 and persons with coronary heart disease prior to Visit 1.

Limitations and solutions

Exposure: The analyses are limited to a single measurement of postural change in blood pressure, which assumes that posture-dependent blood pressure regulation indexed by a single postural change measurement in middle age represents a trait that is characteristic of the individual (within-person, between-person, and between-visit variability is unknown without repeated measurements). This assumption is plausible based on the literature on posture-dependent blood pressure regulation and short-term studies, but we are unaware of empirical data to confirm a long-term “tracking” of orthostatic hypotension.

The intra- and inter-individual variability of the postural change measurements in ARIC are not known. This suggests that postural change in blood pressure should be analyzed as a continuous response, and that large changes in blood pressure on standing up should be analyzed as a categorical variable. This is consistent with the definitions of orthostatic increases/decreases and orthostatic hypotension currently recommended in the literature, which we propose to adopt for our analyses. The latter have also been used in prior work in ARIC, as summarized under Rationale.

Outcomes: Informative censoring is a significant concern as a potential source of bias, given the long-term follow-up of this closed cohort. We will be guided by the NCS analysis group on the use of the most effective analytic approach to identify, and reduce the impact of attrition on our estimates. The study population was also selected for Stage 3 at Visit 5 based on several factors; the subset of with MRI outcomes is therefore not a simple random sample of those who attended Visit 5. Unless advised differently we propose to apply inverse-probability weighting. Also, although participants with prior history of stroke or TIA will be excluded from analyses, we are not able to exclude those with prevalent infarcts at baseline.

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 ICTDER03 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](http://www.cscc.unc.edu/ARIC/search.php)  

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<td>1387</td>
<td>2005</td>
<td>Temporal <strong>changes in blood pressure</strong> and cerebral <strong>white matter lesions</strong> in a biethnic sample: The ARIC MRI study – Rebecca Gottesman (includes <strong>orthostatic hypotension</strong>)</td>
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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)?

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<td>2072</td>
<td>2013</td>
<td><strong>Orthostatic Hypotension</strong> and Risk of Venous Thromboembolism - Liz Bell</td>
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<td><strong>Postural changes in blood pressure</strong> and incidence of ischemic stroke subtype in the ARIC study - Hiroshi Yatsuya</td>
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<td>2008</td>
<td><strong>Orthostatic hypotension</strong> and incident chronic kidney disease: the Atherosclerosis Risk in Communities study – Nora Franceschini</td>
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<td>1334</td>
<td>2008</td>
<td>Does <strong>Orthostatic Hypotension</strong> Predict Diabetes: The ARIC Study – Kathryn Rose</td>
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<td>1352</td>
<td>2008</td>
<td>The association of <strong>orthostatic hypotension</strong> with incident heart failure – Laura Loehr</td>
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<td>1104</td>
<td>2005</td>
<td><strong>Orthostatic Hypotension</strong> and Cognitive Function: the ARIC Study - Kathryn Rose</td>
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<td>768</td>
<td>2001</td>
<td><strong>Postural Blood Pressure Change</strong> and Incident Stroke, Coronary Heart Disease, and All-cause Mortality - Marsha Eigenbrodt</td>
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<td>270A</td>
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<td><strong>Postural change and blood pressure</strong>, variation due to gender and race: The ARIC study - Christopher Nardo</td>
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<td>270C</td>
<td>NA</td>
<td>Relationship between <strong>postural change in blood pressure</strong> and three-year incidence of hypertension – I. Holme</td>
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<td><strong>Postural Change in Blood Pressure</strong> Predicts Incident Coronary Heart Disease: The ARIC Study – Christopher Nardo</td>
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<td>507</td>
<td>NA</td>
<td>Is <strong>Postural Change in Blood Pressure</strong> Associated with Stroke/TIA’s? - Marsha Eigenbrodt</td>
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11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

___ Yes   ___ No

*ancillary studies are listed by number at [http://www.cscc.unc.edu/aric/forms/](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.cscce.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


