

## ARIC Manuscript Proposal #1560

PC Reviewed: 10/13/ 09

Status: A

Priority: 2

SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_

Priority: \_\_\_\_\_

- 1    **a. Full Title:** Postural changes in blood pressure and incidence of ischemic stroke subtype in the ARIC study
- b. Abbreviated Title:** Orthostatic hypotension and risk of ischemic stroke subtypes in ARIC

### 2    **Writing Group:**

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. HY

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- 3    **Timeline:** Analysis will begin immediately, once the proposal is accepted, using surveillance data files through 2005 or the latest available. A draft will be prepared within four months and will be submitted to the Publications committee by 6 months.

#### **4 Rationale:**

Orthostatic hypotension (OH) has been defined as a persistent, consistent, orthostatic decrease in systolic blood pressure of  $\geq 20$  mmHg or diastolic pressure of  $\geq 10$  mmHg within 3 minutes of standing up.<sup>1</sup> OH has been associated with incidence of hypertension<sup>2</sup> and coronary heart disease,<sup>3</sup> and all-cause mortality<sup>4</sup> in middle-aged as well as older men and women.<sup>5</sup> OH was also associated with ischemic stroke incidence (178 cases) in ARIC through 7.9 years of follow-up (by the end of 1996).<sup>6</sup> However, no previous studies have examined whether or not the associations are similar across all the ischemic stroke subtypes (lacunar, nonlacunar atherothrombotic, and cardioembolic).

Previous ARIC investigation found that those with OH were more likely to be older, black, and have diabetes and hypertension.<sup>7</sup> The prevalence of low ankle-brachial index (ABI  $< 0.9$ ), history of CHD, and current smoking were also higher in subjects with OH, suggesting OH may be etiologically diverse. However, a significantly higher prevalence of hypertension with OH implies an unspecified autonomic dysfunction is likely to operate. Indeed, OH has been associated with supine hypertension in other studies.<sup>8</sup> On the other hand, a population-based case-series study of ischemic stroke in Greece reported that autonomic dysfunction may be involved in the etiology of different subtypes of ischemic stroke; lacunar stroke occurred more often than other stroke subtypes during sleep.<sup>9</sup> Thus, exploring the subtype-specific association of ischemic stroke incidence with OH may be etiologically important.

In addition, a previous ARIC investigation found that there were subtype-specific risk factors for ischemic stroke, that is, although age, current smoking, systolic blood pressure, and diabetes mellitus were significantly positively associated with incidence of all stroke subtypes, black race, lower education level and low high density lipoprotein cholesterol were positively associated only with incidence of lacunar stroke; history of coronary heart disease and Lp(a) were positively associated only with incidence of nonlacunar atherothrombotic stroke.<sup>10</sup> Identifying subtype-specific associations would be valuable for further development of more efficient prevention strategy.

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

- a. Incidence of lacunar stroke, but not of nonlacunar or cardioembolic is positively related to the presence of OH.
- b. Updating hypertension information using time-varying covariate will not eliminate OH-lacunar stroke association.

#### **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:** A prospective cohort study

**Inclusion/Exclusion:**

Inclusion: all ARIC visit 1 participants with no missing independent variable data, without a history of stroke. Subjects who had hemorrhagic stroke before the onset of ischemic stroke will also be censored at the time of hemorrhagic stroke.

**Dependent variables:** incident stroke (measured through 2005 or the latest available), incident ischemic stroke subtypes (measured through 2005)

**Independent variable:** presence of orthostatic hypotension (OH) available for 13,152 participants. Blood pressure change was defined as the difference between the supine and the average of the standing blood pressure measurements, excluding the first standing measurement, taken within approximately 30 seconds after standing, during which blood pressure restabilization is still occurring. OH is defined as a decrease of at least 20 mmHg systolic blood pressure (SBP) or a decrease of at least 10 mmHg diastolic blood pressure (DBP).

**Covariates:** age, sex, race, smoking status, alcohol consumption, physical activity, education level

**Additional covariates:** systolic blood pressure, use of antihypertensive and other medications (e.g, anti-Parkinsonian drugs, psychotropic medications, etc.), prevalent diabetes, body mass index (BMI), waist circumference, blood levels of HDL cholesterol, von Willebrand factor and albumin,<sup>12</sup> white blood cell count,<sup>10</sup> intima-media thickness (IMT), ankle-brachial index (ABI), and self-rated health status.

**Modeling:**

1. Hazard ratios for each ischemic stroke subtype by OH status will be assessed by Cox proportional hazards model.

**Analysis plan:**

Assumption of the hazards proportionality will be assessed by examining the parallelness of the ln (-ln) survival curves for the 2 OH groups. A formal test will be carried out by including an interaction term between OH and time (continuous or dichotomous at median (10-year)) in the Cox model.

**Subanalyses:**

Subanalyses will be performed by excluding (1) those with a history of CHD, (2) those on antihypertensive and other potentially OH-causative medications.

In light of the previous findings of OH in the ARIC Study and others, several additional

analyses are also planned.

- 1) Since OH was associated with hypertension incidence in ARIC,<sup>2</sup> blood pressure or hypertension will be adjusted using time-varying covariates in order to more clearly show an independent association of OH with ischemic stroke subtype incidence.
- 2) Since OH was associated with lower ABI,<sup>7</sup> greater IMT<sup>3</sup> in ARIC and greater arterial stiffness in the Rotterdam Study,<sup>11</sup> stratified analysis by the degree of IMT (taking it as a general measure of atherosclerosis in upper body large arteries) will be performed in an attempt to identify any association between OH and ischemic stroke subtype incidence independent of confounding by atherosclerosis, or to see whether the association of OH with stroke subtype is conditional to the presence of preexisting atherosclerosis.
- 3) Diabetes mellitus and age are also considered to be important confounding factors, for which stratified analyses will be conducted.
- 4) Since OH was inversely associated with general well-being at baseline,<sup>4</sup> analyses excluding stroke within one year of baseline will also be carried out.

If it is not considered feasible to carry out these stratified analyses due to small number of subjects in some strata, an alternate approach excluding those with hypertension, diabetes, or fair/poor perceived health at baseline will be employed.

**7 Will the data be used for non-CVD analysis in this manuscript?**

\_\_\_\_\_Yes    ☒ No

**8 a. Will the DNA data be used in this manuscript?**

\_\_\_\_\_Yes    ☒ No

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"?

c. If yes, is the author aware that the participants with RES\_DNA ="not for profit" restriction must be excluded if the data used by a for profit group?

**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.**

☒ 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)?

**MS# 270,** Association between the blood pressure response to a change in posture and the 6-year incidence of hypertension: prospective findings from the ARIC Study

OH was associated with incident hypertension, and this increased risk was found to be highest among those with the lowest levels of baseline, resting systolic blood pressure (SBP) (Rose KM, *J Hum Hypertens*, 2002).<sup>2</sup>

**MS#270A,** Descriptive epidemiology of blood pressure response to change in body position: the ARIC Study

The paper found that study participants who exhibited a decrease in SBP on standing were older, more likely to be black, and had more age-adjusted prevalence of hypertension, diabetes, and history of CHD (Nardo CJ, *Hypertension*, 1999).<sup>7</sup>

**MS#361A,** Orthostatic hypotension and the incidence of coronary heart disease: The Atherosclerosis Risk in Communities Study

The paper found that subjects with OH had an increased risk of CHD (hazard ratio (HR): 3.49, 95% confidence interval (CI): 2.58-4.73). The adjustment for age, ethnicity, gender, comorbid conditions (SBP, antihypertensive medication use, diabetes, ABI and IMT), and CVD risk factors (HDL and LDL cholesterol and smoking) attenuated but did not eliminate the association (HR: 1.85, 95% CI: 1.31-2.63). (Rose KM, *Am J Hypertens* 2000).<sup>3</sup>

**MS#507,** Orthostatic hypotension as a risk factor for stroke: The Atherosclerosis Risk in Communities (ARIC) Study, 1987-1996

OH was predictive of ischemic stroke incidence independent of age, ethnicity, sex, center, education level, mean arterial pressure, general antihypertensive medication use (yes/no), diabetes (yes/no), ABI, IMT, current smoking status, and WBC (HR: 2.0, 95% CI: 1.2-3.2). (Eigenbrodt ML. *Stroke*, 2000).<sup>6</sup>

**MS# 768** Postural blood pressure change and incident stroke, coronary heart disease, and all-cause mortality

OH was associated with 13-year all-cause mortality (HR: 2.41, 95% CI: 2.08-2.78) after controlling for ethnicity, gender, and age. Further adjustment for education, SBP, smoking status, alcohol use, HDL and LDL cholesterol, physical activity, BMI, low ABI, IMT, glucose, resting heart rate, dizziness on standing, selected medications (antihypertensive, anti-Parkinsonism, drugs, tricyclic antidepressants, benzodiazepines, phenothiazines), and selected health conditions (diabetes, CHD, stroke, cancer, and fair/poor perceived health) did not eliminate the association (HR: 1.71, 95% CI: 1.44-2.04) (Rose KM. *Circulation*, 2006).<sup>4</sup>

- 11 Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

\_\_\_\_\_Yes      x  No

- 12 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.

## References

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underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. *J Hypertens* 2006;24:339-44.

12. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2004;160:259-69.