ARIC Manuscript Proposal # 1332r

PC Reviewed: _2_/_12_/08	**Status: ___A_**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Orthostatic hypotension and incident chronic kidney disease: the Atherosclerosis in Communities study

b. Abbreviated Title (Length 26 characters): orthostatic hypotension and kidney disease

2. Writing Group: Kathryn M Rose, Suma Vupputuri, Nora Franceschini, Marsha Eigenbrodt, David Couper, Brad Astor

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NF____ **[please confirm with your initials electronically or in writing]**

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3. Timeline: 1 to 2 years

4. Rationale: Orthostatic hypotension (OH), a manifestation of autonomic dysfunction, has been associated with incident hypertension (Rose, Holme et al. 2002),

coronary heart disease(Rose, Tyroler et al. 2000), stroke (Eigenbrodt, Rose et al. 2000) and increased mortality (Rose, Eigenbrodt et al. 2006) among ARIC participants. For example, ARIC participants with OH at baseline had a 2-fold increase in risk of dying from cardiovascular disease (CVD) and a 2-fold increase in risk of dying of other causes, unrelated to cancer, including kidney diseases (Rose, Eigenbrodt et al. 2006). Most previous studies of OH are based on the elderly and other high risk populations that are often symptomatic. In contrast, ARIC participants were middle-aged and largely asymptomatic for OH. Further, the associations of OH with CVD-related outcomes often persisted in apparently healthy subgroups of the population (Rose, Tyroler et al. 2000; Rose, Eigenbrodt et al. 2006). Thus, the findings from ARIC, a middle-aged and ostensibly healthy population are of particular interest as they suggest that OH may be a marker of subclinical autonomic dysfunction.

Kidney disease may result from episodic hypoperfusion leading to renal ischemia during orthostasis and/or diseases affecting autonomic innervation in large vessels as well as in the renal microcirculation. Therefore, mechanisms related to kidney perfusion or adaptation to hypoperfusion during orthostasis may be causally linked to the development of kidney disease. For example, among hemodialysis patients OH was a significant and independent predictor of all cause mortality (Sasaki, Nakahama et al. 2005).

In this study, we will explore the association of OH and the development/progression of chronic kidney disease (CKD) among middle age participants of the ARIC study.

5. Main Hypothesis/Study Questions:

Orthostatic hypotension among middle age men and women is independently associated with incident CKD.

- This association will be attenuated but not explained by traditional CKD risk factors.

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 analysis of incident CKD and CKD mortality associated with OH.

Inclusion/exclusion criteria: Exclusion: ethnicity other than black or white; black individuals from Minneapolis and Washington County; lack of serum creatinine at baseline; or a serum creatinine at visit 1 of 2 mg/dl or higher.

Exposure definition: Postural BP measurements were taken with a DINAMAP automated device during the carotid ultrasound exam. Orthostatic hypotension will be defined as a decrease in systolic blood pressure of 20 mm Hg or more, or a decrease in

diastolic blood pressure of 10 mm Hg or more upon changing from the supine to the standing position per established guidelines (1996).

Outcome: Incident CKD will be defined as an increase in serum creatinine of at least 0.4 mg/dL over follow-up or a hospitalization (discharge or death) coded for chronic renal disease (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 581-583 or 585-588), hypertensive renal disease (*ICD-9* code 403), hypertensive heart and renal disease (*ICD-9* code 404), unspecified disorder of kidney and ureter (*ICD-9* code 593.9), diabetes with renal manifestations (*ICD-9* code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (*ICD-9* codes V42.0, V45.1, or V56), hemodialysis (*ICD-9* code 39.95) or peritoneal dialysis (*ICD-9* code 54.98), without acute renal failure (*ICD-9* codes 584, 586, 788.9, and 958.5) as the primary or secondary hospitalization code (Muntner, Coresh et al. 2000; Hsu, Kao et al. 2005).

Covariates: age, sex and race, education, systolic blood pressure, smoking status, alcohol use, HDL and LDL cholesterol, physical activity, BMI, resting heart rate, medications (antihypertensive, tricyclic antidepressants, benzodiazepines, phenothiazines), and history of diabetes, CHD, and stroke.

Statistical analysis: The association between postural blood pressure change and incident CKD will be modeled using proportional hazards regression. The proportional hazards assumption will be tested by comparing estimated −ln(−ln) survivor curves of those with and without OH. Crude and age-, gender-, and ethnicity-adjusted PH models will be performed. Potential confounders will be included in the models.

We will also evaluate whether the association between OH and CKD differed between those with and without comorbid conditions (eg, diabetes, hypertension, smoking status, peripheral vascular disease [low ABI], atherosclerosis [thick IMT]). Stratified analyses will be done to compare hazard ratios between those with and without each comorbid condition. In addition, we will test for effect measure modification by including interaction terms of OH with covariates included in the final model using a Likelihood Ratio Test. The likelihood estimate from the model with interaction terms is compared to the model without interaction terms using an alpha=0 .10.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

ARIC manuscript #361A, Rose K. Orthostatic hypotension and the incidence of coronary heart disease: The Atherosclerosis Risk in Communities Study.
ARIC manuscript # 1104. Rose, K. Orthostatic Hypotension Predicts Mortality in Middle-Aged Adults.The Atherosclerosis Risk in Communities (ARIC) Study

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 at http://www.cscc.unc.edu/aric/forms/

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:

(1996). "Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology." Neurology **46**(5): 1470.

Eigenbrodt, M. L., K. M. Rose, et al. (2000). "Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996." Stroke **31**(10): 2307-13.

Hsu, C. C., W. H. Kao, et al. (2005). "Apolipoprotein E and progression of chronic kidney disease." JAMA **293**(23): 2892-9.

Muntner, P., J. Coresh, et al. (2000). "Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study." Kidney Int **58**(1): 293-301.

Rose, K. M., M. L. Eigenbrodt, et al. (2006). "Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study." Circulation **114**(7): 630-6.

Rose, K. M., I. Holme, et al. (2002). "Association between the blood pressure response to a change in posture and the 6-year incidence of hypertension: prospective findings from the ARIC study." J Hum Hypertens **16**(11): 771-7.

Rose, K. M., H. A. Tyroler, et al. (2000). "Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study." Am J Hypertens **13**(6 Pt 1): 571-8.

Sasaki, O., H. Nakahama, et al. (2005). "Orthostatic hypotension at the introductory phase of haemodialysis predicts all-cause mortality." Nephrol Dial Transplant **20**(2): 377-81.