ARIC Manuscript Proposal # 1104

PC Reviewed: 09/20/05	**Status: __A__**	**Priority: _2__**
SC Reviewed: __09/21/05	**Status: __A__**	**Priority: _2__**

1.a. Full Title:

b. Abbreviated Title (Length 26 characters):

Orthostatic Hypotension and Cognitive Function: the ARIC Study

2. Writing Group:
Writing group members:

David Couper, Marsha Eigenbrodt, Gerardo Heiss, Richey Sharrett, others welcome

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

F**irst author**: Kathryn Rose
Bank of America Center
Address: 137 E Franklin St, Ste 306
Chapel Hill, NC 27514

Phone: 919-966-4596 Fax: 919-966-9800

E-mail: kathryn_rose@unc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author): Same

3. Timeline:

Analyses to begin in Fall 2005. Draft of manuscript is expected during Summer 2006.

5. Rationale:

Orthostatic hypotension (OH) occurs when there is a marked decrease in blood pressure after assuming the upright posture. While not consistently defined in the past, guidelines established in the mid 1990's suggested defining OH as a decrease in

SBP $\geq$ 20 mmHg and /or a decrease in DBP $\geq$ 10 mmHg. [1] Most of the research on OH is based on elderly, frail populations in which OH is accompanied by symptoms of dizziness and syncope and is associated with falls, fractures, and potential serious morbidity. Orthostatic hypotension is consistently associated with older age, elevated blood pressure [2-6] and thicker carotid arterial walls. [3,4] Inconsistent associations have been noted between OH and body mass index (BMI), [3-7]diabetes [3-5] and cigarette smoking. [3,4] Several studies have examined the association between OH and mortality in the elderly or other high risk populations. Some have reported modest increased risk of mortality among those with OH, [8-11] while others have reported the absence of an association. [12]

In the Atherosclerosis Risk in Communities (ARIC) Study, OH has been foundassociated with incident hypertension, [13] coronary heart disease (CHD), [3] stroke, [14] and mortality (Rose, unpublished manuscript). An intriguing finding with respect to mortality was the persistence of this association in the absence of selected known co morbid conditions and the effect modification of the association by age such that the strongest association was among the youngest participants. Similarly, in both the ARIC study and other populations, cognitive function and/or decline has been associated with a variety of cardiovascular outcomes including diabetes, [15-17] hypertension, [16,17] CHD, [17,18] stroke, [17,18] and microvascular disease. [19,20]

There are suggestions in the literature that repeated episodes of OH may produce some structural cerebral deterioration that could potentially impact cognitive function. In one study of 55-74 year olds, most of whom had non-insulin-dependent diabetes, those with asymptomatic OH had lower level of cognitive function than did those without the condition. [21] However, in a second study of elderly Finnish persons there were no differences in cognitive function by OH status nor was there evidence of greater cognitive decline over two years of follow-up. [22] Given that the research to date on this topic is limited and inconclusive and based on elderly and other high risk populations, we propose examining the association between OH and cognitive function in The ARIC cohort.

5. Main Hypothesis/Study Questions:

1. Those with OH have lower levels of cognitive function than those without OH
    - This association is mediated but not accounted for by age, education, and CVD risk factors
    - This association varies by presence/absence of co morbid vascular conditions (hypertension, diabetes, microvascular retinal abnormalities)
    - This association is stronger in younger than in older participants

2. Change in cognitive function over time (V2 to V4) will be greater among those with OH at baseline than among those without OH

Data:

Postural blood pressure change data is available from ARIC V1. Orthostatic hypotension will be classified using standardized criteria that have been used in earlier ARIC publications: a decrease in SBP $\geq$ 20 mm Hg and/or a decrease in DBP $\geq$ 10 mm Hg associated with changing from the supine to the standing position.

Measures of cognitive function – measured at Visits 2 and 4 – will include the following neuropsychological tests: the Delayed Word Recall test, the Digit Symbol Subtest of the WAIS-R, and the Word Fluency test of the Multilingual Aphasia Examination. Covariates, from V1 and/or V2 will include age, race, educational attainment, center, standard coronary risk factors (e.g., SBP, IMT, ABI, indicators of retinal vascular abnormalities (e.g., retinopathy, focal and generalized arteriolar narrowing), alcohol use, smoking status and pack years, BMI, LDL-C, HDL-C, fibrinogen, glucose, antihypertensive medication use), diabetes, and self-reported health status.

Exclusions:

Those who did not undergo the postural BP examination, those with prevalent stroke, CHD, or atrial fibrillation at baseline, those who had an incident stroke or CHD event between V1-V2, and those not attending Visit 2 / participating in the V2 cognitive testing will be excluded. For analyses of changes in cognitive function, those not attending V4/participating in V4 cognitive testing will also be excluded.

Analyses:

Descriptive analyses will include age and race/center adjusted mean levels of measures of cognitive function by OH status. Linear regression analyses will be the main analytic technique employed. The timing of the ascertainment of the exposure (OH, ascertained at V1) in relation to the first assessment of cognitive function (V2) is not optimal. Thus, we will create a variable to be included as a covariate that considers the lag time between V1 and V2 and explore methods to take into account risk factor levels at both visits. All analyses will be done including and then excluding those who at baseline, had selected health conditions (hypertension, diabetes, retinal vascular disease) or were users of drugs with potential CNS effects (e.g., antipsychotics, antidepressants).

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"? n/a

____ 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)?

MS 270 (Rose), MS 361 (Rose), MS 507 (Eigenbrodt), MS 768 (Rose), MS 734 (Alves de Moreas), MS762 (Alves de Moares)

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*)

3. **___ B. primiarly 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

1. 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*. 1996;46:1470.
2. Applegate WB, Davis BR, Black HR, Smith WM, Miller ST, Burlando AJ. Prevalence of postural hypotension at baseline in the Systolic Hypertension in the Elderly Program (SHEP) cohort. *Am Geriatr Soc*. 1991;39:1057-1064.
3. Rose KM, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, Sharrett AR, Szklo M. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. *Am J Hypertens*. 2000;13:571-8.
4. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension*. 1992;19:508-19.
5. Shin C, Abbott RD, Lee H, Kim J, Kimm K. Prevalence and correlates of orthostatic hypotension in middle-aged men and women in Korea: the Korean Health and Genome Study. *J Hum Hypertens*. 2004;Apr 29 [Epub ahead of print].
6. Strogatz DS, Keenan NL, Barnett EM, Wagner EH. Correlates of postural hypotension in a community sample of elderly blacks and whites. *J Am Geriatr Soc*. 1991;39:562-6.
7. Davis BR, Langford HG, Blaufox MD, Curb JD, Polk BF, Shulman NB. The association of postural changes in systolic blood pressure and mortality in persons with hypertension: the Hypertension Detection and Follow-up Program experience. *Circulation*. 1987;75:340-6.
8. Luukinen H, Koski K, Laippala P, Airaksinen KE. Orthostatic hypotension and the risk of myocardial infarction in the home-dwelling elderly. *J Intern Med*. 2004;255:486-493.
9. Luukinen H, Airaksinen K. Orthostatic hypotension predicts vascular death in older diabetic patients. *Diabetes Res Clin Pract*. 2005;67:163-166.
10. Masaki KH, Schatz IJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, Curb JD. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation*. 1998;98:2290-5.
11. Sasak iO, Nakahama H, Nakamura S, Yoshihara F, Inenaga T, Yoshii M, Kohno S, Kawano Y. Orthostatic hypotension at the introductory phase of haemodialysis predicts all-cause mortality. *Nephrol Dial Transplant*. 2005;20:377-81.
12. Raiha I, Luutonen S, Piha J, Seppanen A, Toikka T, Sourander L. Prevalence, predisposing factors, and prognostic importance of postural hypotension. *Arch Intern Med*. 1995;155:930-5.
13. Rose KM, Holme I, Light KC, Sharrett AR, Tyroler HA, Heiss G. 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*. 2002;16:771-7.
14. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996. *Stroke*. 2000;31:2307-13.

15. Geroldi C, Frisoni G, Paolisso G, Bandinelli S, Lamponi M, Abbatecola A, Zanetti O, Guralnik J, Ferrucci L, Jul;62(7):1067-72 AN. Insulin resistance in cognitive impairment: the InCHIANTI study. *Arch Neurol*. 2005;62:1067-1072.
16. Kuo H, Jones R, Milberg W, Tennstedt S, Talbot L, Morris J, Lipsitz L. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. *J Am Geriatr Soc*. 2005;53:1154-1161.
17. Knopman D, Boland L, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom A, Investigators. ARiCAS. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology*. 2001;56:42-48.
18. Skoog I, Lithell H, Hansson L, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, Group. SS. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). *Am J Hypertens*. 2005;18:1052-1059.
19. Wong T, Klein R, Sharrett A, Nieto F, Boland L, Couper D, Mosley T, Klein B, Hubbard L, Szklo M. Retinal microvascular abnormalities and cognitive impairment in middle-aged
persons: the Atherosclerosis Risk in Communities Study. *Stroke*. 2002;33:1487-1492.
20. Wong T, Klein R, Nieto F, Moraes S, Mosley T, Couper D, Klein B, Boland L, LD. H, AR. S. Is early age-related maculopathy related to cognitive function? The atherosclerosis risk in
communities study. *Am J Ophthalmol*. 2002;134:828-835.
21. Perlmutter L, Greenberg J. Do you mind standing?: cognitive changes in orthostasis. *Exp Aging Res*. 1996;4:325-341.
22. Viramo P, Luukinen H, Koski K, Laippala P, Sulkava R, Kivela SL. Orthostatic hypotension and cognitive decline in older people. *J Am Geriatr Soc*. 1999;47:600-604.