ARIC Manuscript Proposal #2077

PC Reviewed: 2/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Functional Status Moderates Mortality Risk Associated with Blood Pressure: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Function and BP-Mortality Risk

2. Writing Group:

B. Gwen Windham, Michael E. Griswold, Seth Lirette, Anna Kucharska-Newton, Randi Foraker, Wayne Rosamond, Thomas H Mosley, Jr., PhD, Others welcome

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

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3. Timeline:

Analysis to begin upon receipt of data
Anticipate abstract will be submitted to a national meeting 2013
Manuscript to ARIC manuscript review committee: Summer/Fall 2013

4. Rationale:

The association between blood pressure (BP) and mortality in older adults remains controversial, with epidemiologic studies reporting U-shaped relationships between BP and mortality, and among the oldest old, a greater chance of survival among those with high blood pressures compared to those with normal blood pressures.[1-4] Although some randomized controlled trials have demonstrated benefits of lowering blood pressure in

hypertensive persons >60 years old,[5-7] and recently ≥80 years,[8] the optimal blood pressure in older adults, particularly those over 80 years old, remains a source of contention.[9,10] The crux of the controversy generally relates to findings of attenuated or lack of benefit, or even increased overall mortality among participants >80 years of age in hypertension treatment arms.[5-7,11,12] Although the Hypertension in the Very Elderly Trial (HYVET) demonstrated reduced risk of stroke, heart failure, death from stroke and all-cause mortality in persons ≥80 years, criticisms of that study included the healthy status of the population, a large proportion of whom were not living in the US. Therefore, findings may not be generalizable to clinical practice typical in the US.[13](See letters to the editor, reference #14)

Identifying subgroups of patients who will potentially achieve limited or no benefit, or even harm, from having lower BP, has important clinical implications in BP management. Functional status may help define such subgroups. Self-reported walking speed (fast, medium, slow) was recently reported to modify the relationship between BP and mortality in Latino persons 60 – 101 years old.[14] No relationship between higher BP and mortality was observed among self-identified "slow walkers" in this study while faster walkers had increased mortality risk with higher BP. It is well-known that subjective and objective measures of functional status are associated with risk of death, disability (prevalent and incident), nursing home admission, and other adverse outcomes in older adults[15-20] and moderates life expectancy.[21] However, the moderating effect of functional status on the blood pressure-mortality relationship has not been reported in other populations in the US, nor has any study examined this relationship in a middle- and older-aged community dwelling cohort or in a large population of African Americans (AA).

Factors such as shorter life expectancies may result in adults with poor functional status achieving less benefit from having lower blood pressure. Adults with good functional status adults may achieve marked benefit from attaining lower BP. Defining such subpopulations could guide clinical decision making through the development of individualized treatment regimens that will maximize benefit and minimize risk. To this end, we propose to examine functional status as a moderator of the relationship between blood pressure and mortality in the ARIC cohort.

5. Main Hypothesis/Study Question:
Does self-reported functional status moderate the relationship of blood pressure to cardiovascular and all-cause mortality?

Secondary Question: Does self-reported functional status moderate the relationship of blood pressure to cardiovascular 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).

Statistical Analysis

Overall:

The analysis will use visit 4 data (1996-1998) for self-reported functional status and covariates and subsequent surveillance/event data through 2009 to define mortality and cardiovascular event outcome variables.

Predictor variables:

The primary independent predictors will be continuous systolic blood pressure and functional status, with an interaction term between blood pressure and functional status; this interaction term comprises the focus of our investigations. Systolic blood pressure will also be categorized using standard cutpoints, e.g. $\geq$140/90, as well as thresholds identified in exploratory analysis of non-linear relationships. Functional status will be defined from the Physical Ability Questionnaire (PAQ) initially using dichotomous variables:

i. Functional impairment
   = '0' if reports "No Difficulty" on all items 1-12 of the Physical Activity Questionnaire (PAQ)
   = '1' if reports with Some, Much, or Unable to Do" response on any one of PAQ questions 1-12
ii. Disability
   = '0' if reports "No" for all questions 13-17 on
   = '1' if reports "Yes" for any q 13-17

We will also examine diastolic blood pressure in separate and combined predictor models.

Outcome variables:

Primary outcome variables will be all-cause mortality and cardiovascular mortality, which will be defined as mortality due to stroke, heart failure, or coronary heart disease.

Secondary outcome variables will be cardiovascular non-fatal events: stroke, heart failure, coronary heart disease. We anticipate also using a composite outcome incorporating both fatal and non-fatal events.

Covariates

Visit 4 covariates to be considered in full or parsimonious models include:
age, sex, race, field center, education, prevalent hypertension, prevalent diabetes, prevalent coronary heart disease, prevalent heart failure, prevalent stroke, body mass index, smoking, physical activity, total cholesterol, LDL, HDL, triglycerides, use of hypertension medications, use of statin medications.

Analysis

Cox Proportional Hazards Models will be used to assess risk in all-cause mortality over time from visit 4 to 2009. Outcomes of cardiovascular mortality and non-fatal events will incorporate a competing risks framework.[22]

Non-linear relationships will be assessed using loess smoothers and spline terms.

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

__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)?

	Manuscript #	Title
a.	1697	Functional Status and Cardiovascular Disease. Drs. Kucharska-Newton, Foraker, and Rosamond are included as co-authors

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/

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.

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