ARIC Manuscript Proposal #2539

PC Reviewed: 4/14/15   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title:
Mid-Life Long-term Blood Pressure Variability and Late-Life Cognitive Decline: The ARIC Neurocognitive Study.

b.   Abbreviated Title (Length 26 characters):
BPV and Cognition Decline

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. __YY__ **[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:
November 2014: Submit proposal.
November-December 2014: Perform analysis.
December 2014-January 2015: Prepare manuscript.
February-March 2015: Send draft to co-authors and submit to journal.

4.   Rationale:
The association between higher blood pressure (BP) and lower cognitive function has been well established.[1-4] In addition to average BP values, BP variability (BPV) may be

associated with cognitive function.[5] BPV consists of the short-term BPV (e.g., beat-to-beat and within 24 hours) and long-term BPV (e.g., day-by-day and visit-to-visit BPV).[6,7] The implications of long-term BPV are less defined, particularly its effects on cognition.

The association between higher long-term BPV and lower cognitive function has recently been reported.[8-11] Most of the studies were conducted on middle-aged/older persons and/or high-risk populations, in which participants without dementia or with a Mini-Mental State Examination (MMSE) score of 24 points and over were recruited.[8-11] We recently reported that long-term BPV even during young adulthood is associated with lower cognitive function in midlife; the baseline cognitive function was not assessed.[11] No convincing evidence exists assessing the association between long-term BPV and quantitative cognitive change over the long-term. BPV itself could be influenced substantially by comorbidities including individual atherosclerotic changes (e.g., [silent] cerebrovascular diseases), so that baseline cognitive function might contribute to both long-term BPV and future cognitive function.

The Atherosclerosis Risk in Communities (ARIC) Study provides a unique opportunity to potentially resolve these issues, since analyses using ARIC data can evaluate cognitive change. We will focus on the effects of exposure to long-term BPV from visit 1 to visit 4 on cognitive function and decline from visit 4 to visit 5, avoiding the inclusion of late assessments of BP at the end of follow-up (i.e., visit 5 BP) that already might have been affected by comorbidities.

5.   Main Hypothesis/Study Questions:
The main study question is to examine whether higher long-term BPV from visit 1 to visit 4 is associated with cognitive function and decline from visit 4 to visit 5.

Hypotheses:
#1. Participants who have higher long-term BPV will have greater cognitive decline, as assessed by scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), World Fluency (WF) tests, standardized versions of these scores and the standardized global Z-score as used in previous ARIC examinations.
#2. Contributions to cognitive decline will be greater for long-term BPV than for standardly used mean BP measures.
#3. The association of long-term BPV with cognitive function change will remain even after adjustment for other potential confounders (e.g., smoking, alcohol, physical activity, fasting glucose, total cholesterol, HDL, use of antihypertensive drugs, incidence of stroke).
4. The association between long-term BPV and cognitive function change may differ by race (/site).

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 analyses.
Inclusion: Those who have available ~~complete~~ data   shown in the table below.

ARIC data to be used	Visit (V)
Education	V1
Resting BP	V1, V2, V3, V4, V5
BMI	V1, V2, V3, V4, V5
Fasting glucose	V1, V2, V3, V4, V5
Lipid	V1, V2, V3, V4, V5
Anti-HTN Meds	V1, V2, V3, V4, V5
Diabetic Meds	V1, V2, V3, V4, V5
Physical activity (Sports\Leisure\Work scores)	V1, V3, V5
Prevalent/Incidence of stroke	V1, V2, V3, V4, V5
Cognitive function (DWRT, DSST, WFT)	V2, V3, V4, Brain MRI, Carotid MRI, V5

Exclusion:
Not white or African-American and stroke prior to baseline (stroke information prior to each visit will be used for time-varying exclusions as appropriate). We will also exclude from analysis any cognitive tests at visits when the participant was taking CNS-altering medications (e.g. neuroleptics or benzodiazepines). Interim incident strokes will be excluded in a secondary analysis. Sensitivity analyses will also include exclusion of individuals with depression and stratified examination of antihypertensive medication \use

Outcome:
Cognitive function measures (DWRT, DSST, WFT), related Z-scores and the global cognitive Z-score as previously defined in ARIC publications will be used to examine cognitive change using appropriate data where available (we note that cognitive function measures were only collected on subsets of participants at V3, brain MRI, and Carotid MRI).

Primary exposure:
Long-term BPV from (e.g. from <u>visit 1 to visit 4</u>, defined by standard deviation, coefficient of variation, difference between maximum and minimum BP, average real variability and or estimated variance components from a longitudinal mixed model for SBP). A graphical depiction of BPV calculations is shown in the included Figure 1 on the following page.

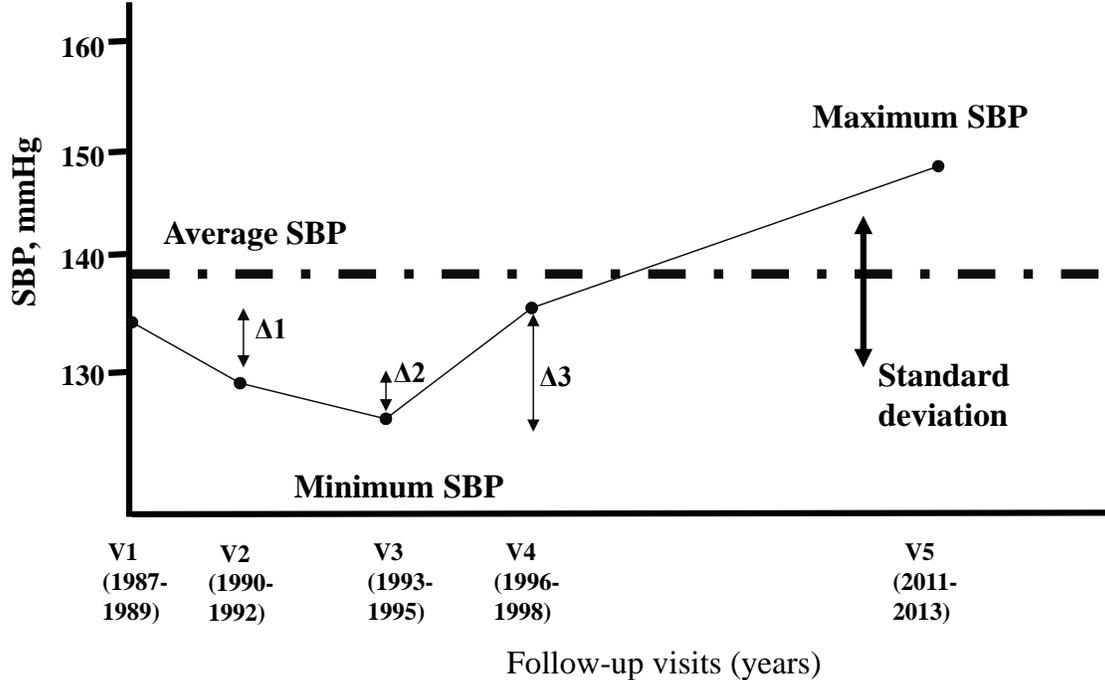**Figure 1: Visual Description of Long-Term Blood Pressure Variablitiy (BPV) measures**

Figure 1 Description: The figure shows one example of individual follow-up data of BP across 5 visits (V1-V5). The **absolute** differences of BP between successive BP measurements are shown as Δ1-Δ3. For example, Δ1 represents the absolute difference in SBP between the V1 and V2 BP values. Average real variability (ARV) is calculated as (Δ1+Δ2+Δ3)/3. Maximum and minimum BP difference (MMD) was calculated as maximum BP minus minimum BP from visit 1 to visit 4. Average BP and standard deviation (SD) were calculated from 4 BP values from visit 1 to visit 4 for each individual, and coefficient of variation was calculated as SD/average BP.[11]

Covariates:
Potential adjustment variables: age, sex, educational attainment, clinical characteristics at visit 4 (body mass index (BMI), smoking, alcohol, physical activity, fasting glucose, total cholesterol, HDL, use of antihypertensive drugs, incidence of stroke), and mean BP from visit 1 to visit 4.

Analyses will include race-stratified and race-combined models (the latter including a race-center variable with appropriate time interaction terms). Unadjusted and multivariable-adjusted longitudinal regression models (see below) will be used to assess the association of long-term BPV and with cognitive function and decline. In the first step, we will carry out unadjusted analyses (Model 1). In the second step, we will add age (visit 4), sex, race, and educational attainment (years) as adjustment covariates (Model 2). In the last step, we will further adjust for clinical characteristics at visit 4 (i.e., BMI, smoking, alcohol, physical activity, glucose and lipid parameters, use of antihypertensive drugs, and incidence of stroke) plus mean BP from visit 1 to visit 4 (Model 3).

We will also examine for race-BPV interaction. If significant, we will perform race-specific models to examine overall patterns of associations. Similarly, we will examine for sex-BPV interaction.

Interim incident strokes or antihypertensive medication use during follow-up periods will be excluded as a sensitivity analysis.

Analyses:
Initial longitudinal models will be fit using GEE on visit 4 and visit 5 cognitive data. To examine and account for potential biases arising from informative missingness effects due to death, incident dementia, and dropout, we will include models using (**a**) standard GEE approaches (Missing Completely At Random assumption; MCAR) (**b**) GEE with inverse probability of weighting for attrition (IPAW) where weights include death, dropout and dementia probabilities (Missing At Random assumption; MAR). In addition, we will fit(**c**) standard GLMMs (MAR) (**d**) Shared Parameter Model which combine the longitudinal cognitive decline GLMM models with a competing risks survival model for incident death and dementia in a joint formulation (Missing Not At Random assumption; MNAR), using visit 4 and visit 5 data alone (to match the GEE results), and then expand to include the Brain MRI and Carotid MRI study data, which are more naturally includable in a GLMM context given the differential administrative versus informative missingness mechanisms at work.

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 ICTDER 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)?

#1121: Cognitive change over 12 years and its relationship to cardiovascular risk factors ARIC MRI Study   (Knopman et al.)
#1982: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS (Gottesman et al.)
#2115: Sensitivity analyses with shared-parameter models for studying cognitive change of potentially informative dropout—the ARIC neurocognitive study (Griswold et al)
#1387: Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI study (Gottesman et al)

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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