ARIC Manuscript Proposal # 2394

PC Reviewed: 7/8/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Determinants of blood pressure trajectories from midlife to older age: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Predictors of BP trajectories

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

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3. Timeline:
Start of analysis: September, 2014
Draft of manuscript: January, 2015

4. Rationale:
Hypertension is defined by systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg. [1] Hypertension is one of the most prevalent modifiable risk factors of cardiovascular disease, affecting 27.8-30.7% – approximately 77.9 million adults in the United States. [1,2] The National Health and Nutrition Examination Survey (NHANES)

2007-2010 found that an additional 6% of adults over 20 years have undiagnosed hypertension. [1] Hypertension is associated with a variety of adverse clinical outcomes including myocardial infarction, congestive heart failure, stroke and kidney disease[3].

Hypertension can be classified into essential (or primary) and secondary hypertension. Secondary hypertension includes hypertensive individuals with a single causative disease like endocrine disorders and accounts for approximately 10% of hypertension cases. [4] The rest of 90% are currently categorized as essential hypertension and thus are multifactorial. Some well-known factors include age, sex, race, geographic location, sodium intake, sedentary lifestyle, obesity, genetic predisposition, and kidney function. [1,5-23]

Previous studies exploring aforementioned risk factors for hypertension investigated the development of hypertension at one time point of life[18,24,25], cross-sectional or baseline blood pressure[6-11,15,21], tracking blood pressure trends in multiple cross-sectional populations[14] or averaged changes in blood pressure over time[23]. These approaches do not necessarily account for tracking the patterns of changes in blood pressure over time. A few studies have demonstrated that blood pressure trajectories from young to middle age differ by age, gender and ethnicity. [5,26-28] Furthermore Allen et al recently reported an association between blood pressure trajectories and the development of coronary artery calcification, with highest risk of coronary calcium development in elevated [baseline]-increasing followed by elevated-stable, moderate-increasing, moderate-stable, and low-stable. [28] Understanding the relative importance of risk factors for different patterns of blood pressure trajectories would have important clinical implications for targeted preventative and treatment strategies. Thus, we first aim to investigate the associations of conventional risk factors with blood pressure trajectories.

Subsequently, we will also investigate metabolites involved in the citric acid cycle (e.g. lactate, alanine, alpha-ketoglutarate, and succinate,) and in the sodium handling pathway (e.g., uromodulin) in this context. Recently, a few studies indicate that metabolites in the citric acid cycle are associated with the development of hypertension and clearly sodium plays a pivotal role in blood pressure control.[20,29,30]

5. Main Hypothesis/Study Questions:

Aim 1. To determine the patterns of blood pressure trajectories from midlife to older age in the ARIC Study.

Aim 2. To characterize the associations of conventional risk factors of hypertension (e.g. sex, race, physical activity, obesity, family history of hypertension and prevalent kidney disease) will be generally associated with blood pressure elevation over time, but will demonstrate distinct blood pressure trajectories determined in Aim 1 (e.g., elevated-increasing, elevated-stable, moderate-increasing, moderate-stable, and low-stable).

Aim 3. To quantify the association of metabolites involved in the citric acid cycle (e.g. lactate, alanine, alpha-ketoglutarate, and succinate,) and in the sodium handling pathway (e.g., uromodulin) with different patterns of blood pressure trajectories.

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
Longitudinal data analysis

Inclusion criteria
All ARIC participants with blood pressure measured in at least any two of visits 1-5 with data on whether participants were taking blood pressure lowering medications (N = 14,665; 10,881 European Americans and 3,784 African Americans).

Outcome
Patterns of blood pressure trajectory over time derived from blood pressure measurements from visits 1-5. Blood pressure measures of interest include systolic and diastolic blood pressure, their mean, their middle value, and pulse pressure. Their trajectories will be categorized by latent class models, as detailed subsequently, and will be investigator-labeled (e.g., elevated- increasing, elevated-stable, moderate-increasing, moderate-stable, and low-stable). As detailed subsequently, for those who were taking antihypertensive drugs, we will calibrate or impute "underlying" blood pressure (blood pressure that the participants would have had if they did not take antihypertensive drugs) accounting for measured blood pressure.

Variables
1. Conventional risk factors for high blood pressure (predictors for Aim 2): sex, race (accounting for field center), socioeconomic status, body mass index, waist circumference, smoking status, alcohol intake, physical activity, family history of hypertension and prevalent kidney disease
2. Metabolites (predictors for Aim3): Lactate, alanine, alpha-ketoglutarate, succinate, uromodulin[20,29]

Statistical analysis
All below statistical analyses will be performed separately for the blood pressure measured described above, but given its stronger association with clinical outcomes, we are primarily interested in systolic blood pressure.[31-33]

1. Calibration or imputation of blood pressure values among those who were on antihypertensive drugs:
Antihypertensive medication certainly influences an individual's blood pressure trajectory. So in order to appropriately assess associations with blood pressure trajectory, the "underlying" blood pressure of individuals on antihypertensive medication needs to be estimated. For this estimation, we will implement three methods recommended in previous reports, as summarized below.[34,35]

A. Calibration using constant values.

a. Add constant to "measured" blood pressure values among those on antihypertensive drug(s). For those individuals taking blood pressure lowering medication, a constant of 10mmHg will be added to the measured systolic blood pressure and a constant of 5mmHg will be added to the measured diastolic blood pressure.[36,37]

b. Add medication class specific constant to "measured" blood pressure values among those on antihypertensive drug(s). This method takes into account that medications and combinations of medications will have different quantitative reductions in blood pressure. In individuals taking blood pressure lowering medication, a medication class specific constant will be added to the systolic and diastolic blood pressure. This class specific constant will be calculated from estimated effect sizes in mmHg from existing literature. In particular, Wu et al. summarize the expected reductions in blood pressure of six major blood pressure medication classes (i.e. ACE inhibitors [+12.5 mmHg SBP/+9.5 mmHg DBP], alpha blockers [+15.5 mmHg SBP/+11.7 mmHg DBP], beta blockers [+14.8 mmHg SBP/+12.2 mmHg DBP], calcium channel blockers [+15.3 mmHg SBP/+10.5 mmHg DBP], diuretics [+15.5 mmHg SBP/+9.0 mmHg DBP], miscellaneous [+14.8 mmHg SBP/+10.5 mmHg DBP]). In cases of combination therapy, the primary medication class is chosen by the largest estimated effect. The effect of any non-primary is estimated as a percentage of the full effects listed above (i.e. if no diuretic in combination therapy [11% of estimated blood pressure reduction effect as summarized above for SBP [e.g., 1.4 mmHg =12.5 mmHg * 11% for ACE inhibitors]/34% for DBP] and if diuretic in combination therapy [50% for SBP/42% for DBP]).[35]

B. Imputation of "underlying" blood pressure values from censored normal distribution. We will impute the "underlying" blood pressure values by utilizing a method proposed by Tobin et al. and Cook.[34,38] The "underlying" blood pressure is sampled from a censored normal distribution with the measured blood pressure under treatment as the censored value. For each subject the parameters from the censored normal distribution are derived from the measured blood pressure under treatment and demographic covariates including age, sex and race.

2. Determining the patterns of blood pressure trajectories (Aim 1):
Individuals will be assigned into categories of blood trajectories via latent class analysis. Latent class models combine individuals into categories with similar patterns of change in the quantitative traits (e.g. systolic and diastolic blood pressure) over time (e.g. age).

Categories of blood pressure trajectories will be built in three steps:

A. *Individuals will be assigned a posterior probability of being in each category of blood trajectory.* Based on previous blood pressure trend research, the number of categories to be assessed in the latent class models will be three to five.[26-28] The optimal number of categories will be determined empirically using a modified Bayesian information criterion (BIC) due to the high sample size and large number of latent classes.[39] As a sensitivity analysis, other methods of choosing the best

model will also be employed including a modified likelihood ratio test (LRT) and modified Akaike information criterion (AIC). The latent class models will generate posterior probabilities of an individual being in each blood pressure category.

B. *Individuals will be assigned into a category of blood pressure trajectory.* Each individual's set of posterior probabilities will be used to assign the individual to a category of blood pressure trajectory. The individual will belong to the category of blood pressure trajectory with the largest posterior probability.

C. *Categories of blood pressure trajectories will be labeled by behavior of change over time.* After assigning each individual to a category of blood pressure trajectory, the category will be assigned a user-defined label (e.g. elevated- increasing, elevated-stable, moderate-increasing, moderate-stable, and low-stable).[26-28] Each individual will now be part of a labeled category of blood pressure trajectory. These categories of trajectories will serve as the outcome for the following analyses.

3. Association of conventional risk factors (Aim 2) and candidate metabolites with blood pressure trajectories (Aim 3):
Using multinomial regression, the blood pressure trajectories from the previous section will be assessed for association with conventional hypertension risk factors and candidate metabolite predictors, listed above. Two sets of models will be constructed for Aim 2; model 1 will assess the association of the demographic risk factors (e.g. sex, race, center, socioeconomic status) and model 2 will incorporate the other conventional risk factors (e.g. body mass index, waist circumference, smoking status, alcohol intake, physical activity, prevalent kidney disease, prevalent cardiovascular disease, family history of hypertension). Two sets of models will be constructed for Aim 3; model 1 will assess the crude association of each metabolite and model 2 will be adjusted for the significant conventional risk factors from Aim 2. Statistical significance will be determined by a p-value threshold of 0.05.

Strengths and Limitations

This study proposes to investigate risk factors for different patterns of blood pressure trajectories from midlife to older age, which has not been previously studied. As Aim 1, we will determine suitable patterns of blood pressure trajectory in ARIC, which can be used in future ARIC projects. We also aim to explore determinants of blood pressure trajectories, with clinical implications. In dealing with calibration for underlying blood pressure due to medication, medication adherence and dosage data is unavailable. Due to the observational nature of the study, residual confounding might be a limitation.

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)?
No previous proposal in ARIC focus specifically on assessing risk factors of categories of blood pressure trajectories. ARIC Manuscript Proposal #2146 (Systolic blood pressure trajectories and incident cardiovascular disease) includes the association of blood pressure trajectories with cardiovascular outcomes. Our proposal aims to further understand the risk factors of the blood pressure trajectories themselves in visits 1-5 as well as investigate novel biomarker predictors. Also, we will account for antihypertensive drugs to determine patterns of blood pressure trajectory.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ X __ Yes ____ No

11.b. If yes, is the proposal
__X __A. primarily the result of an ancillary study (list number * 2006.04)
___ 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.

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