**ARIC Manuscript Proposal #2353**

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| **PC Reviewed: 4/14/15** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Longitudinal associations of blood pressure with pulse wave velocity. The Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters)**: Blood pressure and PWV

**6. Writing Group**:

Writing group members: Patricia Metcalf, Michelle Snyder, Hirofumi Tanaka, Gerardo Heiss, Sunil Agarwal, Aaron Folsom, Gwen Windham, Susan Cheng, David Couper, others are welcome

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


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**7. Timeline**: Analysis can start immediately. We plan to complete the manuscript within one year the start of analyses.

**8. Rationale**:

Pulse wave velocity (PWV) is a reliable measure of arterial stiffness that predicts cardiovascular disease events and all-cause mortality in clinical and population- based studies [1]. Carotid-femoral PWV (cfPWV) reflects central arterial stiffness and is the most commonly used measure of PWV in research studies. PWV measurements simultaneously

measured with cfPWV in ARIC include femoral-ankle PWV (faPWV), a measure of peripheral arterial stiffness, and brachial-ankle PWV (baPWV), a composite measure of central and peripheral stiffness that is widely used in Asian countries. Little information is available on the longitudinal relationship of blood pressure with measures of arterial stiffness, in particular over an extended range of mid-life to older adulthood.

PWV was measured in Visit 5 of ARIC using the VP-1000 Plus device. No pulse wave velocity measures were obtained in ARIC prior to Visit 5. The Visit 5 examination of the ARIC Study cohort allows us however to evaluate the longitudinal relationship of blood pressures antecedent to Visit 5 with central arterial stiffness (cfPWV) and femoral-ankle (faPWV) in a well characterized population of African American and Caucasian men and women.

The aim of this report is thus to characterize the longitudinal relationships between sitting blood pressure measured according to a standardized protocol over the 5 ARIC visits and central arterial stiffness estimated from cfPWV at the ARIC Study at Visit 5. Mean arterial pressure and pulse pressure will also be calculated and their associations with PWV examined. Understanding this relationship can inform the line of research in this area on the long term effects of blood pressure on vascular stiffening.

**9. Main Hypothesis/Study Questions**:

1. Describe the longitudinal relationships of blood pressure variables with central arterial stiffness estimated from cfPWV, considering age, gender, ethnicity and heart rate (HR) as covariates.

**10. 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 for blood pressure measurements (visits 1 to 5); cross-sectional PWV measurements at ARIC visit 5.

**Exposure:**
Carotid-femoral PWV (cfPWV) was measured by the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan) and the path length was calculated as the distance between the suprasternal notch to carotid minus the carotid to femoral distance. A minimum of two measurements were taken per participant and the last two usable measurements (i.e. non-zero values) were averaged. We will treat this variable as the exposure (rather than the outcome) because cfPWV was measured at Visit 5 only. This approach has been applied previously when using repeated measures data in a similar analysis, e.g., Ferreira et al. [2], and has been vetted by the members of this manuscript writing group.

**Outcomes at all visits:** Sitting blood pressure variables at visits 1 through 5 (SBP, DBP, mean arterial pressure (MAP) and pulse pressure (PP).

Covariates

Covariates include gender, race, cardiovascular disease (coronary heart disease, stroke, heart failure) prevalent at baseline, age and heart rate at each visit, smoking habits, blood pressure lowering medication use and diabetes status.

**Inclusions:** African American and Caucasian ARIC participants with PWV data obtained at Visit 5.

**Exclusions:** Missing information on PWV, blood pressure, and antihypertensive medication use or other covariates of interest; not Caucasian or African-American; African American participants at the Minnesota and Maryland sites, and the following exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI>=40 kg/$m^2$, and participants with major arrhythmias (based on ECG data for MN code 8-1-3, 8-3-1 or 8-3-2), self-reported aortic revascularization surgery or aortic graft, aortic aneurysm, abdominal aorta ≥ 5cm, MN codes 8-1-2 with evidence of biased PWV waveforms, aortic stenosis and moderate or greater aortic regurgitation, and PWV values > 3 standard deviations away from the mean.

**Statistical Analysis:**

Participant characteristics will be presented as means and standard errors, or as frequencies and percent, where appropriate and adjusted for age, gender, ethnicity and heart rate. Conventional statistics will be used if lack of normality is not a concern and a transformation is not required. We will use non-parametric methods if normality is a concern. Multivariate models for pressure measurements will be fit using PWV, age, gender, ethnicity, body mass index, heart rate, and smoking status to determine the trajectories of pressure measurements relative to the distribution of cfPWV and faPWV at Visit 5.

**Consideration of selective loss to follow-up/cohort attrition**

Blood pressure levels, and likely several of the covariates to be included in the analyses are associated with loss to follow-up that could potentially bias the estimates of interest. We propose to use the two-step Heckman correction approach to account for selection bias. Coordination with other investigators in ARIC that are implementing the Heckman correction approach has been established.

**Limitations:**

Some PWV measurements were not collected due to sensor equipment failures, representing missing data that are not however systematically related to participant characteristics. Despite adjusting for HR, some residual confounding cannot be excluded. The cross-sectional design limits our ability to determine an antecedent-consequent relation between blood pressure in different life epochs and PWV. A temporal pattern of association between antecedent blood pressure across ARIC examination visits and PWV measured at Visit 5 is informative however, and would contribute novel information.

Mortality or loss to follow-up before Visit 5 may be plausibly associated with arterial stiffness, leading to potential for informative censoring/selection bias. To address this we propose to use the two-step Heckman correction approach to correct for selection bias, as mentioned above.

**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.c. Will the DNA data be used in this manuscript? ___Yes __X__No**

**8.d. 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**

**12. 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**

**13. 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)?**

We have informed investigators that collaborations are welcome.

Previous manuscript proposals include:

MS #1970 Descriptive Epidemiology of Pulse Wave Velocity in the Atherosclerosis Risk in Communities (ARIC) Study.

MS #2241 The association of kidney disease measures with arterial stiffness: The Atherosclerosis Risk in Communities (ARIC) Study.

MS #2246 Pulse Wave Velocity and Retinal Microvascular Characteristics: the Atherosclerosis Risk in Communities (ARIC) Study-Neurocognitive Study (NCS)

MS #2297 The association of diabetes, impaired glucose tolerance, and chronic hyperglycemia with pulse wave velocity: the ARIC study.

**14.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.

**References**


1. Vlachopoulos C, Aznaouridis K, Stefanadis C: **Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis**. *J Am Coll Cardiol* 2010, **55**:1318-1327.
2. Ferriera I, van de Laar R, Prins M, Twisk J, Stehouwer C: **Carotid stiffness in young adults: a life-course analysis of its early determinants: The Amsterdam Growth and Health Longitudinal Study**. *Hypertension* 2012, **59**:54-61.
3. Weuve J, Tchetgen Tchetgen E, Glymour M, Beck T, Aggarwal N, Wilson R, Evans D, Mendos de Leon C: **Accounting for bias due to selective attrition: the example of smoking and cognitive decline**. *Epidemiol* 2012, **23**(1):119-128.