ARIC Manuscript Proposal #2353

PC Reviewed: 5/13/14	**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

2. Writing Group:

Writing group members: Patricia Metcalf, Michelle Snyder, Hirofumi Tanaka, Gerardo Heiss, Sunil Agarwal [invited but has not responded yet], Aaron Folsom, Gwen Windham, David Couper [to be invited] others 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]**

First author: Patricia Metcalf
Address: University of North Carolina at Chapel Hill
Bank of America Center
137 E. Franklin St., Suite 306
Chapel Hill, NC, USA 27514

Phone: 919-966-2068 Fax: 919-966-9800
E-mail: p.metcalf@auckland.ac.nz

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).
Name: Gerardo Heiss
Address: University of North Carolina at Chapel Hill
Bank of America Center
137 E. Franklin St., Suite 306
Chapel Hill, NC, USA 27514

Phone: 919-962-3253 Fax: 919-966-9800
E-mail: gerardo_heiss@unc.edu

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

4. Rationale:

Pulse wave velocity (PWV) is a reliable measure of arterial stiffness that predicts cardiovascular disease events and all-cause mortality in clinical and community based studies [1]. Carotid-femoral PWV (cfPWV) reflects central arterial stiffness and is the most commonly PWV used measure in research studies. Brachial-ankle PWV (baPWV) represents a composite measure of central and peripheral arterial stiffness and is commonly used in clinical settings in East Asian countries because of its ease of implementation. Little information is available on the longitudinal relationship of blood pressure with these two measures of arterial stiffness.

Given that the structural and functional propoerties of arteries vary by anatomical location [2-6], the process of arterial stiffening can plausibly differ by arterial segment. Some reports suggest that segment-specific PWV is not homogeneous, e.g., baPWV was not associated with known risk factors [7] and did not increase with age [8, 9], contrasting with associations well documented for arterial stiffening [10]. On the other hand studies in Asian populations have shown that baPWV is comparable to cfPWV [11, 12] and correlated to CVD risk factors [13, 14]. Such inconsistencies in the literature may be due in part to small sample sizes, various participant exclusions (excluding participants with hypertension, diabetes, dyslipidemia and obesity) and t o variations in the protocol for PWV.

Few studies of PWV have included both peripheral and central PWV despite the potential importance of both sites in measuring segment-specific arterial stiffness. The Atherosclerosis Risk in Communities (ARIC) Study cohort is a community-based study which will allow us to evaluate the longitudinal relationship of central and peripheral arterial stiffness and in a well characterized population of African American and Caucasian men and women. In Visit 5 of ARIC, PWV was measured using the Colin VP-1000 Plus device. Femoral-ankle PWV (faPWV) is an additional measure in ARIC that represent arterial stiffness.

The aim of this report is to characterize the longitudinal relationships between average sitting blood pressure (over the 5 ARIC visits) and central and peripheral arterial stiffness estimated from PWV in the ARIC Study at Visit 5. A second aim is to determine whether cfPWV, baPWV and faPWV have similar longitudinal associations with blood pressure. Understanding these relationships could generate hypotheses regarding its pathogenesis of segment-specific vascular stiffening.

5. Main Hypothesis/Study Questions:

1. Describe the longitudinal relationships of blood pressure variables with central and peripheral arterial stiffness estimated from PWV, considering age (time varying at each visit), gender, ethnicity and heart rate (HR) as covariates. HR has been reported to be an important confounder in PWV analysis and is recommended to be accounted for in any analysis [15, 16].

2. Estimate the hypertension-free probability according to cfPWV, baPWF and faPWV in late life, adjusted for age, gender, ethnicity and heart rate.

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 for blood pressure measurements (visit 1 to visit 5) with cross-sectional PWV measurements at ARIC visit 5.

Exposure:
Carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV) PWV was measured by the Colin VP-1000 plus system (Omron Co., Ltd., Komaki, Japan) and the path length was calculated using the following formula: path length (cm) = (suprasternal notch - carotid distance (cm) - carotid-femoral distance (cm)). A minimum of two measurements were taken per participant and the last two usable measurements (i.e. non-zero values) were averaged. PWV measurements include the following: cfPWV, baPWV, and faPWV).

Outcomes at all visits: Sitting blood pressure variables (SBP, DBP, hypertension (prevalent hypertension and/or blood pressure medication use), MAP and pulse pressure will be calculated.

Covariates
Covariates include gender, race, history of CVD (coronary heart disease, stroke, heart failure), age and heart rate at each visit, current smoking habit, lipids and diabetes status.

Inclusions: All white and black 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 white or African-American; and 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), reported use of antiarrhythmic or vasoactive medications per the ARIC medication survey use (MSR Item 33.g) and/or specific medication codes in the ARIC database.

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. If lack of normality is not a concern and transformation is not required then conventional statistics will be used. If normality is a concern we will use non-parametric methods. A multivariate model for hypertension will be built using PWV, age, gender, ethnicity, body mass index, heart rate, smoking status and systolic blood pressure to see whether all PWV values are similarly associated with hypertension. We will also determine the age, gender, ethnicity and heart rate adjusted relationship between the

hypertension –free probability by year of ARIC visit and the PWV variables.

Limitations:

Some PWV measurements were not collected due to technical errors, participant factors and scheduling conflicts. Despite adjusting for HR, some residual confounding cannot be excluded. Finally, the cross-sectional design limits our ability to determine causality. Mortality or loss to follow-up before visit 5 could be associated with arterial stiffness, leading to potential for informative censoring/selection bias. We cannot examine this possibility as PWV was only measured at visit 5. However, we will calculate the inverse probability weights to account for bias due to selective attrition [17].

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)?

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.

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.

References

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