ARIC Manuscript Proposal # 3050

PC Reviewed: 10/3/17 Status: _____ Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Change in Arterial Stiffness in Older Adults: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Change in PWV

2. Writing Group:
   Writing group members: Michelle L Meyer, Hirofumi Tanaka, Anna Kucharska-Newton, Priya Palta, Jingkai Wei, Ron Hoogeveen, Timothy Hughes, Kunihiro Matsushita, others welcome

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

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3. Timeline: Analysis is to start as soon as approval is obtained. We plan to complete the manuscript within six months from the end of the ARIC-NCS PWV Visit 6/7 study.

4. Rationale:
Pulse wave velocity (PWV) is a non-invasive measure of arteriosclerosis that predicts cardiovascular disease (CVD) events and all-cause mortality in clinical and community based studies.¹ Carotid-femoral PWV (cfPWV) is the reference standard measure of central arterial stiffness.² The value of measuring cfPWV to assess risk of hypertension³ and CVD² has been
established in both vascular laboratory and population-based longitudinal studies. Arterial stiffness may thus be a possible target for intervention intended to prevent and reduce the risk of CVD and arterial stiffness-related end-organ damage. However, arterial stiffness and pulsatility changes over time, as well as factors associated with their change, remain unknown. Therefore, the use of arterial stiffness as a modifiable risk factor is limited. Prior research has been limited to only baseline measures of PWV and pulse pressure (PP). Only one study thus far has included repeat measures of brachial PP. Arteries remodel and stiffen with age, reflecting increases in collagen synthesis, fragmentation of elastin, and thickening of the arterial wall. In cross-sectional studies, central PWV is about 10-15% higher per decade of age,~100 cm/s higher with each 10-year increase in age. Cross-sectional studies also show that PP is about 25% to 40% higher between 30 to 60 years of age. The association between age and cfPWV is stronger among those >50 and >55 years old, and association between age and PP is stronger among those >55 years old compared to younger age groups.

A limited number of prospective studies identified age and systolic blood pressure (SBP) as major determinants of progression of arterial stiffness. Progression of cfPWV is reportedly higher among men than women among non-white persons and among hypertensive individuals. Others have shown that adiposity, heart rate, adiponectin, triglycerides, and fasting insulin are predictive of higher cfPWV at follow-up among men and women. Factors associated with progression of cfPWV are sex-specific and include diastolic blood pressure (DBP) and pulse pressure for women, and pulse pressure, high sensitivity C-reactive protein, and glucose for men. The few longitudinal studies of PWV progression are limited in their assessments of change in PWV among primarily Caucasian adults and do not include measures of central PP.

The aim of this study is to characterize the 5-year change in arterial stiffness and pulsatility and their determinants in older adults. We will use repeat measures of central arterial stiffness and pulsatility from ARIC-NCS Visit 5 and Visit 6/7. Understanding change in arterial stiffness and pulsatility and their demographic variations have the potential to generate avenues for prevention with arterial stiffness and pulsatility as modifiable risk factors for end-organ damage.

5. Main Hypothesis/Study Questions:

1. Characterize the 5-year change and rate of change in arterial stiffness and pulsatility among older adults.
2. Characterize the role of sex and race in the rate of change in arterial stiffness and pulsatility among older adults.

Hypotheses:

a. Increases in central arterial stiffness and pulsatility over the course of 5 years are different by sex and race. Males and black participants have greater increases in central arterial stiffness and pulsatility. Modifiable behavioral, biologic, and metabolic risk attributes influence the rate of change in central arterial stiffness and pulsatility.

b. The rate of change in central arterial stiffness will be higher among those with
higher baseline (Visit 5) PWV measures as compared to those in the lower distribution of PWV.

c. Optimal control of elevated blood pressure is associated with lower changes in arterial stiffness and pulsatility among individuals with hypertension; those with uncontrolled blood pressure have greater changes in arterial stiffness and pulsatility.

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 methodological limitations or challenges if present).

Study design:
This study will include ARIC-NCS participants who had PWV measured at both Visit 5 and Visit 6/7. PWV was measured using a standardized protocol at Visit 5, which is currently being used in Visits 6/7 (VP-1000 Plus; Omron Co., Kyoto, Japan). PWV is estimated from the distance between two arterial recording sites divided by transit time. Distance for cfPWV is measured over the surface of the body with a segmenter (Rosscraft, Surrey, Canada), and calculated as Dcf= [(carotid to femoral artery distance) - (suprasternal notch to the carotid artery distance)]. Transit time is measured as the time delay between the proximal and distal ‘foot’ waveforms, i.e., the commencement of the sharp systolic upstroke. The time delays between carotid and femoral arteries (Tcf) are obtained by the system. PWV is calculated as follows: cfPWV = Dcf / Tcf. Measurements are conducted twice for data quality purposes and averaged. Measures of blood pressure are calculated simultaneously by the VP-1000 Plus to obtain measures of estimated central SBP, central PP and pulse pressure amplification (PPA). The device also calculates segment-specific PWV measures, including brachial-ankle and femoral-ankle PWV. Outliers, defined as values three standard deviations above or below the mean, will be winsorized for the analyses.

Outcome: The 5-year difference and rate of change in PWV and pulsatility.

Arterial stiffness measures include the following:
- Carotid-femoral PWV (cfPWV)
- Brachial-ankle PWV (baPWV)
- Femoral-ankle PWV (faPWV)
- Heart-femoral PWV (hfPWV)

Additional measures include the following:
- Central SBP (cSBP)
- Central pulse pressure (cPP)

Other variables: Age (continuous and categorical), sex, race, hypertension, and use of antiarrhythmic or vasoactive medications.
- Behavioral – physical activity and smoking status
- Biologic – heart rate, systolic blood pressure, mean arterial pressure, and hs-CRP
- Metabolic – fasting glucose, diabetes, and body mass index
- Optimal blood pressure control will be defined as participants with hypertension and with normal (optimal) SBP of less than 120 mm Hg and DBP less than 80 mm Hg DBP at Visits 5-7.
- Uncontrolled blood pressure will be defined as participants with hypertension and with SBP greater than 140 mm Hg and DBP greater than 90 mm Hg DBP at Visits 5-7.

**Inclusions:** All participants who underwent the PWV measurements at ARIC-NCS Visit 5 and Visits 6/7.

**Exclusions:** Missing information on PWV, and exclusions recommended by the ARIC PWV Working group: participants with BMI ≥ 40 kg/m² at Visits 5-7, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2 from Visit 5 ECG), Minnesota code 8-1-2 from Visit 5 ECG with low quality PWV waveforms, aortic aneurysms/abdominal aorta diameter ≥5 cm by ultrasound at Visit 5, self-reported history of aortic or peripheral revascularization or aortic graft at Visits 5-7, echocardiographic evidence of aortic stenosis at Visits 5-7, moderate or greater aortic regurgitation at Visits 5-7, and missing covariates of interest at Visits 5-7. Participants who self-identified as Asian from any site and blacks from Minnesota and Maryland sites will also be excluded due to small numbers.

**Statistical Analysis:**

We will present participant characteristics as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. To characterize the 5-year change in central arterial stiffness and pulsatility in older adults and their determinants, we will first describe change in arterial stiffness and pulsatility over the course of an average five years of follow-up by sex and race, adjusted for age and mean arterial pressure. We will subtract Visit 5 from Visits 6/7 measures to create a change score to compare distinct groups (e.g. sex and race) in terms of their average change over time.

To evaluate whether (1) The rate of change in central arterial stiffness will be higher among those with higher baseline (Visit 5) PWV measures as compared to those in the lower distribution of PWV; and (2) optimal control of elevated blood pressure is associated with lower changes in arterial stiffness and pulsatility among individuals with hypertension; those with uncontrolled blood pressure have greater changes in arterial stiffness and pulsatility. To do this, we will use Visits 6/7 measures as the dependent variable (i.e. not the change) and Visit 5 measures as an independent variable to determine if an individual belonging to one group is expected to change more (or less) than an individual belonging to the other group, given that they have the same baseline response. In our analyses, we will adjust for measurement error in baseline arterial stiffness and pulsatility measures. Measurement error used here includes short-term within-person variability (measurement process variability and within-person biologic variability). Repeatability estimates of cfPWV and cPP are available from Visit 5. These coefficients can be interpreted as 1 minus the measurement variance divided by the total variance, and will be used in model fitting to correct for baseline measurement error. Regression calibration will be used to correct for measurement error. Covariates to be evaluated in multivariable regression models include age, sex, body mass index (BMI), SBP, mean arterial pressure, hypertension, heart rate, type 2 diabetes, and history of cigarette smoking. Additionally, we may consider using distribution-based cut-points for change in arterial stiffness as done
previously with prior ARIC-NCS PWV papers (works in progress).20

**Sensitivity analysis to account for attrition and selection bias.** To account for bias due to attrition, we will use multiple imputation by chained equation (MICE) methods21 for participants not observed at Visit 6/7. We will work with the Coordinating Center and ARIC-NCS working groups using MICE to perform a sensitivity analysis using these methods to account for missingness that may be related to the exposure or outcome.

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 will invite authors from proposals using pulse wave velocity to collaborate on this manuscript proposal.

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* 2015.23 )
____  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.cscce.unc.edu/aric/forms/](http://www.cscce.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/](http://publicaccess.nih.gov/) are posted in [http://www.cscce.unc.edu/aric/index.php](http://www.cscce.unc.edu/aric/index.php) under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

References


