ARIC Manuscript Proposal #3812

PC Reviewed: 4/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Short-term prognostic impact of the aortic-femoral arterial stiffness gradient in older adults without prevalent cardiovascular disease: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Arterial stiffness gradient

2. Writing Group:
Writing group members:
Keeron Stone
Lee Stoner
Michelle Meyer
Gerardo Heiss
Anna Kucharska-Newton
Kevin Heffernan
Simon Fryer
James Faulkner
Kunihiro Matsushita
Hirofumi Tanaka

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

First author: **Keeron Stone**
Address: University of Gloucestershire, School of Sport and Exercise, Gloucester, UK, GL2 9HW.

Phone: 01242715192 Fax: n/a
E-mail: kstone1@glos.ac.uk / keeronstone@hotmail.com

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).
Michelle Meyer

Address: UNC-Chapel Hill
Department of Emeregcy Medicine
170 Manning Dr., CB# 7594
Chapel Hill, NC 27599
Phone: 919 966 6539, E-mail: mlmeyer@med.unc.edu

3. Timeline: We plan to complete the manuscript(s) within 3 years from approval.

4. Rationale:

Increased arterial stiffness is an independent predictor of cardiovascular disease (CVD) [1]. Although several measures of arterial stiffness have been established, carotid-femoral pulse-wave velocity (cfPWV) is the most widely used in clinical and epidemiological studies given its strong association with cardiovascular events and mortality [2]. In contrast, upper extremity (arms) and lower-extremity (legs) peripheral measures of arterial stiffness are used infrequently because of their limited or inconsistent prognostic value [3]. However, assessments of the central to peripheral arterial stiffness gradient have emerged as promising screening tools, with recent studies demonstrating their ability to provide prognostic information beyond regional arterial segment stiffness measures alone [4,5].

To date, the few studies that have investigated the utility of the arterial stiffness gradient measures have focused on the upper extremity derived aortic to brachial SG (ab-SG), defined as the ratio of carotid-radial PWV (crPWV) and cfPWV. An increased ab-SG has been found to be a better a predictor of all-cause mortality than cfPWV in dialysis patients [4], but conferred no unique or additive value in community-dwelling older adults [6]. However, the gradient between the aorta and the lower extremities may provide a more comprehensive picture of hemodynamic integration and be a more sensitive marker of arterial health and CVD risk. Indeed, compared to the upper extremities, the lower extremities make up a significant portion of the arterial tree, are more prone to athero- and arterio-sclerotic processes, and are major sites of wave reflections [7]. As far as we are aware, our group has published the only study to explore the utility of the lower-extremity derived aortic to femoral SG (af-SG), defined as the ratio of femoral-ankle PWV (faPWV) and cfPWV. In the Atherosclerosis Risk in Communities (ARIC) study, we reported a comparable association of af-SG with traditional CVD risk factors when compared to cfPWV[5]. However, we found a unique association with CVD status. Indeed, whilst a high cfPWV was only associated with diabetes, a low af-SG was associated with coronary heart disease, heart failure, stroke and diabetes[5]. However, to confirm its clinical utility the ability of the af-SG to predict incident CVD events and mortality must be identified.

Finally, in order to be of utility, clinical assessments must demonstrate reliability (precision). Indeed, quantifying PWV measurement variation is critical for applications to risk assessment and stratification, and eventual translation to clinical practice. We recently reported that the novel af-SG exhibits good (intra-class correlation coefficient = 0.77) reliability in young healthy adults[8]. But both age and CVD are known to deleteriously impact the precision of PWV measures [9]. The reliability of the af-SG in older adults is not known.

Summary: The ARIC Study cohort is a community-based study, with measures of PWV on over 6,000 older adults. Using data from ARIC Visit 5 and longitudinal data of CVD events and mortality, we plan to address the following questions, which will allow us to generate hypotheses regarding the prognostic implications of a pathological aortic to femoral arterial stiffness gradient (af-SG).

5. Main Hypothesis/Study Questions:

i. A. Does the af-SG predict incident cardiovascular disease or mortality?
   B. Does the af-SG predict incident cardiovascular disease or mortality beyond that of cfPWV?

ii. What is the short-term repeatability of the af-SG in older adults?

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 of data from ARIC visit 5, and longitudinal data of incident CVD events and mortality from Visit 5 assessed through to December 2019.

Inclusions: All white and black ARIC participants with PWV data obtained at visit 5. For repeatability analysis the subgroup (n=79) of visit 5 participants whom agreed to return for a repeat visit 4-8 weeks are the initial visit.

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, participants with major arrhythmias (based on ECG data), 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. To examine incident outcomes, we will exclude those with prevalent coronary heart disease, heart failure, or stroke as well as an ankle-brachial index <0.9.

Exposures: Carotid-femoral PWV (cfPWV), femoral-ankle PWV (faPWV), heart-femoral PWV (hfPWV) and blood pressure (MAP) indices determined using the Omron VP-1000 plus system (Omron Healthcare, Kyoto, Japan) A minimum of two measurements was taken per participant and the last two usable measurements (i.e. non-zero values) were averaged. The af-SG is calculated as faPWV / cfPWV.

Outcomes: The primary outcome of interest will be a composite cardiovascular disease that comprised coronary heart disease, heart failure, and stroke. Secondary outcomes will include coronary heart disease, heart failure, stroke, all examined separately. We will also investigate all-cause mortality since cardiovascular disease is a leading cause of death in the United States. All cardiovascular outcomes (except coronary revascularization) will be adjudicated by physician reviewers [10]. Coronary heart disease will be defined as definite or probable myocardial infarction, coronary heart disease death, or coronary revascularization procedure. Heart failure will be adjudicated as definite or probable acute decompensated heart failure based on hospitalization record review [11]. Stroke will be defined as definite or probable cases of ischemic or hemorrhagic strokes based on stroke hospitalization and death records. All-cause mortality will be defined as death due to any cause and will be ascertained through annual cohort follow-up, hospital surveillance, and linkage to the National Death Index [10]. All outcomes were assessed through December 31, 2019.

Covariate Measurements:
Demographic variables: age, sex, race, field center, education level, body mass index, history of hypertension (prevalent hypertension and/or blood pressure medication use), history of diabetes, history of smoking, history of alcohol consumption, fasting glucose, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, measures of kidney disease (serum creatinine, crystatin C, urine albumin-creatinine ratio).

Hemodynamic variables: resting heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial pressure, central augmentation index, carotid-augmentation index, ankle-brachial index.

Statistical Analysis for predictive value of cfPWV and af-SG.
We will present participant characteristics as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. 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.

The relationship between arterial stiffness measures and the cumulative incidence of the outcomes will be visually assessed using Kaplan-Meier curves. Log-rank tests will be used to compare the survival distributions. Cox proportional hazards models will be used to estimate the associations of cfPWV and derived af-SG measures with cardiovascular events and all-cause mortality after adjusting for confounders based upon their known associations with arterial stiffness, CVD, and mortality. To allow for potential non-linear associations, PWV and derived af-SG measures will be categorized into quartiles. The second lowest quartile (Q2) will serve as the refence category in all analyses.

Sensitivity analyses. For models examining cardiovascular events as the outcome we will conduct a competing risk analysis using sub distribution hazard models that consider death from non-cardiovascular causes as a competing event. Sub-group analysis will be used to examine whether associations with cardiovascular events are modified by sex or race.

Statistical Analysis for Repeatability of af-SG: The analysis will include participants (n=79; mean age 75.7 years) from a repeatability study nested within the ARIC study visit 5 (2011-2013) who underwent two standardized visits, four to eight weeks apart. Trained technicians obtained two PWV measurements at each visit using the VP-1000 Plus system. For af-SG, we will calculate intra-class correlation coefficient (ICC), standard error of measurement (SEM) and the minimal detectable change (MDC) with 95% confidence. The ICC will be calculated according to the formula: $SDb^2/ (SDb^2+SDw^2)$, where SDb^2 and SDw^2 are the between and within-subject variance. In general, ICC values above 0.75 are considered to indicate excellent reproducibility. The SEM will be calculated according to the formula: $SD* \sqrt{(1-ICC)}$. The MDC will be calculated according to the formula: $1.96*SEM*\sqrt{2}$. The MDC is defined as the critical difference in a parameter that must be exceeded between two sequential results for a statistically significant change to occur in an individual.

Limitations: Some PWV measurements were not collected due to technical errors, participant factors and scheduling conflicts. Despite adjusting for heart rate, some residual confounding cannot be excluded.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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? No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

Yes

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)?

Stoner *et al.* (2020). Associations between measures of regional pulse wave velocity: The Atherosclerosis Risk in Communities (ARIC) Study.

MP#3661: Agreement between estimated pulse wave velocity and carotid-femoral pulse wave velocity: The Atherosclerosis Risk in Communities (ARIC) Study (Lee Stoner)

MP#2694: Short-term prognostic impact of cardio-ankle vascular index (CAVI) in community-dwelling older adults (Kunihiro Matsushita)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ ____ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014; 63:636-646.
3. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 2005; 45:592-596.
4. Fortier C, Mac-Way F, Desmeules S, Marquis K, De Serres SA, Lebel M, et al. Aortic-brachial stiffness mismatch and mortality in dialysis population. Hypertension 2015; 65:378-384.
5. Stone K, Fryer S, Meyer M, Kucharska-newton A, Faulkner J, Zieff G, et al. The Aortic-Femoral Arterial Stiffness Gradient: An Atherosclerosis Risk in Communities (ARIC) Study. Journal of Hypertension in press.
6. Niiranen TJ, Kalesan B, Larson MG, Hamburg NM, Benjamin EJ, Mitchell GF, et al. Aortic-Brachial Arterial Stiffness Gradient and Cardiovascular Risk in the Community: The Framingham Heart Study. Hypertension 2017; 69:1022-1028.

7. van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RM, et al. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. J Am Coll Cardiol 2014; 63:1739-1747.
8. Stone K, Fryer S, Faulkner J, Meyer M, Heffernan K, Zieff G, et al. The aortic-femoral arterial stiffness gradient: between-day reliability. Am J Hypertens under review.
9. Meyer ML, Tanaka H, Palta P, Patel MD, Camplain R, Couper D, et al. Repeatability of Central and Peripheral Pulse Wave Velocity Measures: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Hypertens 2016; 29:470-475.
10. The Atherosclerosis Risk in Communities (ARIC) study: Design and Objectives. The ARIC Investigators. American Journal of Epidemiology 1989; 129:687-702.
11. Rosamond WD, Chang PP, Baggett C, Johnson A, Bertoni AG, Shahar E, et al. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. Circ Heart Fail 2012; 5:152-159.