ARIC Manuscript Proposal #3582

PC Reviewed: 3/10/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The association of regional pulse wave velocity with vascular calcification: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Arterial stiffness & vascular calcification

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

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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).

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3. Timeline:

Analysis will begin following proposal approval and completion of visit 7 data cleaning. A manuscript will be completed within 6 months after receiving necessary data for this proposal.

4. Rationale:

Arterial stiffness refers to a pathophysiological process of arteries that involves hardening or stiffening of the arterial walls.[1] Arterial stiffness is commonly measured using pulse wave velocity (PWV), which is a noninvasive, zero-radiation, semi-automated, inexpensive, and readily available measure that represents the speed at which the pressure waves travel a certain segment of the aorta and/or other arteries.[2] Carotid-femoral PWV is generally considered the standard measurement of central artery stiffness;[2, 3] however, other regional PWVs can be measured. Of note, several regional PWVs have been shown as strong independent predictors of mortality and cardiovascular disease.[2]

Recently, several studies have proposed a relationship between arterial stiffness and coronary atherosclerosis including coronary artery calcium (CAC).[1, 2, 4-8] CAC also strongly predicts coronary heart disease and all-cause mortality,[9-11] and has been shown to provide additional information beyond those provided by traditional risk factors in estimating the risk of clinical outcomes.[12, 13] CAC is also recommended for further risk assessment in current US guidelines while PWV is not.[14] However, as CAC measurement involves computed tomography methods, with radiation exposure (although relatively low), further examining the association between arterial stiffness and CAC can provide more insights into the value of using PWV to identify individuals with high CAC and a better understanding of the mechanisms linking the two phenomena. If we find an association between the two, this could inform the use of PWV to identify individuals who could benefit from more aggressive lifestyle interventions and individuals who might benefit most from CAC testing.

Past studies examining this particular relationship have been limited by focusing mainly on one type of PWV, brachial-ankle PWV, and its relationship with total CAC score.[1, 2, 4-8] Using the most recent visit 7 data from the Atherosclerosis Risk in Communities (ARIC) Study, we can better investigate the association of arterial stiffness with CAC as well as extra-coronary calcium (ECC including ascending/descending aorta, aortic valve, and mitral valve).

5. Main Hypothesis/Study Questions:

1) To quantify the associations of regional (various segmental) PWVs with CAC and ECC beyond traditional risk factors

2) To develop prediction models for high CAC and ECC scores using regional PWVs and traditional risk factors

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).

Inclusions:
All black and white ARIC participants with data on PWV, CAC, and ECC scores at visit 7

Exclusions:
- Ethnicity other than black or white
- Missing data on PWV, CAC, or ECC

Exposure (independent variables):
PWV measured at the following segments:
- Carotid-femoral
- Heart-femoral
- Brachial-ankle
- Heart-ankle
- Femoral-ankle

Outcome (dependent variables):
CAC scores evaluated at the following segments:
- Overall/total
- Left main
- Left anterior descending
- Left circumflex
- Right coronary artery

ECC scores at:
- Ascending aorta
- Aortic valve ring
- Aortic valve
- Descending aorta
- Mitral valve

Other variables of interest and covariates:
- Sociodemographics: age, race, gender, education level, study site
- Physical information: body mass index, waist circumference, blood pressure, heart rate
- Lifestyle: smoking status, alcohol habit, and physical activity
- Comorbidities: diabetes, SBP, DBP, dyslipidemia, kidney disease measures (eGFR, albuminuria), history of cardiovascular disease (coronary heart disease, stroke, and heart failure)

Statistical Analysis Plan:
1) To quantify the associations of regional PWVs with CAC and ECC, we will use linear or logistic regression models. CAC and ECC scores will be treated as the dependent variables while PWV measures will be the independent variables. CAC and ECC scores

will be treated as continuous variables after log-transformation and as categorical variables using quartiles as cutoffs in the models. We will adjust for the covariates listed above.

We will also repeat the analyses after stratifying the study population by age, gender, race, and presence/absence of comorbidities such as diabetes and cardiovascular disease (including ASCVD) to check for potential effect measure modification.

2) To develop prediction models for high CAC and ECC, we will follow these steps:

- High CAC and ECC will be primarily defined using a more clinically relevant cutoff of 300; however, we will also try using alternative definitions based on the distributions of the data, such as the age-, gender-, and race-specific upper 25th percentile.[15]
- We will perform variable selection using both elastic net regularization and lasso, and choose the model with the lowest test error using cross-validation. The advantage of using elastic net or lasso as a method of penalization over just a conventional model with a full set of covariates are that conventional models can have low bias but high variance; however, penalized models can trade off a small increase in bias for a large decrease in variance. For the elastic net and lasso models, we will choose the optimal tuning parameters using cross-validation.
- To build the final prediction models, we will try a few classification models (logistic regression [parametric] and tree-based algorithms including random forest [non-parametric] and boosted trees [non-parametric]). For all approaches, we will use internal cross-validation to pick the optimal tuning parameters. We will evaluate the performance of the models based on discrimination metrics (accuracy, test error, area under the receiver operating characteristic curve) and calibration (calibration plot, observed to expected outcomes ratio) using cross-validation.

Limitations:

A cross-sectional design will not allow us to evaluate causality of the associations. As with any observational study, we will not be able to rule out the possibility of residual confounding. The results may not be generalizable to younger population or ethnic groups other than whites and blacks.

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 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?

____ 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)?
There are no proposals looking at the association between CKD and measures of atrial stiffness in ARIC using visit 5 PWV/ABI data.

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.

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