ARIC Manuscript Proposal #3960

PC Reviewed: 6/8/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: **Association between arterial stiffness and acute kidney injury**

1b. Abbreviated Title (Length 26 characters): **PWV and AKI**

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AJ__

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3. Timeline:

Data analysis will begin once the manuscript proposal is approved. The manuscript is expected to be completed within 6 months.

4. Rationale:

Acute kidney injury (AKI) is defined by an abrupt decrease in kidney function. It is very common, occurring in 1 in 7 hospital admissions, and is associated with significant morbidity and mortality.[1] The risk for AKI is determined by an individual's susceptibility to injury and exposure to insults that harm the kidneys. Key risk factors for AKI include

age, preexisting chronic kidney disease (CKD), heart disease, hypertension, and diabetes mellitus.[2] The ability to accurately predict the risk of AKI is poor. Risk assessment instruments have been developed, but they are often poorly validated and specific to AKI post cardiac surgery.[2,3] Given the consequences of AKI, which include prolonged hospitalization and inpatient mortality, additional tools are needed to accurately predict those at risk for AKI.

Greater arterial stiffness is associated with increased risk for kidney function decline and cardiovascular disease.[4,5] Arterial stiffness is influenced by both structural and functional properties of the arterial wall and has significant effects on the ability to conduct blood flow and to mitigate the high pressures that travel through to end-organs.[5] With increasing arterial stiffness, particularly in aging, arterial elasticity and compliance are reduced leading to transmission of high-pressured forces to end-organ microvasculature. These vascular beds are not designed to handle high pressures, resulting in damage.[6-8] The kidneys may be particularly affected given the high volume of flow and the low resistance in the renal afferent arterioles.[8-10] In addition, arterial stiffness increases SBP, which may contribute to decreased renal function.[9] The gold standard for measuring arterial stiffness is carotid-femoral pulse-wave velocity (CFPWV).

Our group has demonstrated a relationship between greater arterial stiffness and risk of incident AKI.[11] Among 613 participants from the Systolic Blood Pressure Lowering Trial (SPRINT) with measurements of arterial stiffness (PWV), there were 20 adjudicated AKI events. Participants with carotid-femoral pulse-wave velocity (CFPWV) ≥ median (≥ 10.4 meters/second [m/s]) had 18 AKI events while participants with CFPWV < median had only 2 events after a median [interquartile range] 453 [289-724] days. There was a 22% greater risk of AKI for each m/s increase in CFPWV (hazard ratio [HR]: 1.22, 95% CI: 1.07-1.39). When adjusted for age, sex, race, treatment randomization, smoking, cardiovascular disease, number of antihypertensives, estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), and systolic blood pressure (SBP), the risk of AKI was 32% higher for each m/s increase in baseline CFPWV (HR: 1.32, 95% CI: 1.13-1.53). When CFPWV was modeled as a categorical variable (≥ median compared to CFPWV < median) results were similar. In the unadjusted model, baseline CFPWV ≥ median was associated with a 9-fold higher risk for AKI (HR: 9.28, 95% CI: 2.15-40.00). After full model adjustment, the risk of AKI was greater by nearly 13-fold (HR: 12.99, 95% CI: 2.87-58.91).

The Atherosclerosis Risk in Communities (ARIC) study provides a unique opportunity to expand upon these results with the carefully collected parameters of kidney function, measurement of CFPWV, active follow-up for AKI, and >1000 AKI events. Approximately 20% of the study population are African American, a subset of the general population that has not been adequately studied. The goal of the proposed analysis is to evaluate the association between CFPWV measured at visit 5 (visit 5 will be considered baseline) and the risk of incident AKI using data collected from the ARIC cohort. We hypothesize greater arterial stiffness as measured by CFPWV will be associated with greater risk of AKI events.

References
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8. Lyle AN, Raaz U. Killing me un-softly: Causes and mechanisms of arterial stiffness Recent Highlights of ATVB: Early Career Committee Contribution. Arterioscler Thromb Vasc Biol. 2017;37(2):e1-e11.
9. Ford ML, Tomlinson LA, Chapman TPE, Rajkumar C, Holt SG. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. Hypertension. 2010;55(5):1110-1115.
10. Townsend RR, Anderson AH, Chirinos JA, et al. Association of Pulse Wave Velocity With Chronic Kidney Disease Progression and Mortality. Hypertension. 2018;71(6):1101-1107.
11. Bispham N, You Z, Supiano MA, Chonchol M, Nowak K, Jovanovich A. Arterial stiffness independently predicts acute kidney injury in SPRINT. 2019 American Society of Nephrology Kidney Week, Washington, DC. SA-OR016.

5. Main Hypothesis/Study Questions:

Higher pulse-wave velocity (greater arterial stiffness) will be associated with acute kidney injury.

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: Prospective study of the ARIC cohort

Inclusion criteria: Participants with measurement of arterial stiffness (pulse-wave velocity) and without end-stage kidney disease (ESKD)

Outcomes: Incident AKI, as defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 584.5 to 584.9 or 10th Revision, Clinical Modification (ICD-10-CM) codes N17.0 to 17.9 among discharge diagnoses [iv]

Predictor: pulse-wave velocity (PWV):

- carotid-femoral (CFPWV) as primary predictor
- heart-femoral (HFPWV)
- heart-carotid (HCPWV)
- heart-ankle (HAPWV)

- brachial-ankle (BAPWV)
- femoral-ankle (FAPWV)

Other variables of interest: Age, sex, race, smoking status, BMI, baseline eGFR, baseline urine albumin-to-creatinine ratio, prevalent cardiovascular disease, prevalent diabetes, prevalent hypertension, systolic blood pressure, diastolic blood pressure, number of antihypertensive medications, total cholesterol, HDL cholesterol, ankle-brachial index

Data analysis:

1. We will evaluate baseline characteristics by quartiles of CFPWV because it is considered the gold-standard measurement for arterial stiffness. Chi-squared test will be used to evaluate differences in categorical variables while independent samples T-test will be used to evaluate difference in continuous variables. Non-normally distributed variables will be log-transformed prior to analysis.

2. We will estimate the association between each measure of PWV (CFPWV, HFPWV, HCPWV, HAPWV, BAPWV, and FAPWV) and incident AKI events using multivariable Cox proportional hazards regression analysis. Since CFPWV is the gold standard measure for arterial stiffness, it will be treated as the primary predictor variable while the other measures of arterial stiffness will be treated as secondary predictor variables. Models will be adjusted for baseline covariates described above under "other variables of interest." PWV will be assessed as a continuous predictor variable and as a categorical predictor variable with quartile 1 as the reference.

3. We will also estimate the association between PWV and incident AKI in pre-specified subgroups including stratification by sex, race, prevalent diabetes, and prevalent cardiovascular disease.

4. In secondary analyses, we will estimate the association of PWV and incident AKI when PWV is dichotomized as $\geq$ and $<$ the median value, and we will explore associations after adjusting for the competing risk of death using the methods of Fine and Gray.

Limitations: Observational study (unable to determine causality or mechanism), possibility of residual confounding variables

7a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes ___X_ No

7b. 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.)

8a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8b. 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)?

"Associations Between Kidney Disease Measures and Regional Pulse Wave Velocity in a Large Community-Based Cohort: The Atherosclerosis Risk in Communities (ARIC) Study" Ester D Kim, Hirofumi Tanka, Shoshana H. Ballew, Yingying Sang, Gerardo Heiss, Josef Coresh, Kunihiro Matsushita

11a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **____ Yes __X__ No**

11b. 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to

publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript **____ Yes __X__ No**