ARIC Manuscript Proposal # 3615

PC Reviewed: 5/12/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Racial differences in plasma renin activity and renal outcomes

b. Abbreviated Title (Length 26 characters): Renin and renal outcomes

2. Writing Group:
Matthew Blum, Jingsha Chen, Josef Coresh, Anna Kottgen, Paul Welling, Christie Ballantyne, Stephen Turner, Morgan Grams, *others welcome*

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

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3. Timeline: Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

4. Rationale:

The renin-angiotensin-aldosterone system (RAAS) regulates electrolytes, intravascular volume, and systemic blood pressure, and in doing so, both reflects and influences renal health. Increased renin levels have been shown to be a negative prognostic factor in various conditions including heart failure (1–4) and coronary artery disease (5). Given its role in blood pressure regulation, renin has been studied as a risk factor for cardiovascular disease among hypertensive

and non-hypertensive patients. Among hypertensive patients, increased renin has been associated with incident ischemic heart disease (6–10), heart failure (6,10), and mortality (11). In mixed hypertensive and non-hypertensive cohorts, higher renin levels have been associated with incident cardiovascular disease and mortality (12,13). In a study of normotensive adults, no significant association was seen between renin and myocardial infarction and sudden cardiac death (14). Fewer studies have explored renin as a risk factor for kidney disease. In a cohort of hypertensive patients within the Kaiser health system, renin was positively associated with the odds of prevalent chronic kidney disease (CKD) (15). An electronic medical records cohort such as this, however, is limited by confounding by indication. Analysis of a prospective cohort of 689 adults not receiving antihypertensive agents found renin to be negatively associated with the risk of CKD (16). The role of renin, along with its downstream enzymes, in the development of CKD and end stage renal disease (ESRD) in hypertensive and non-hypertensive adults deserves further study.

Beyond renin's role as a risk factor for disease, there have been efforts over the last four decades to phenotypically characterize RAAS physiology and hypertension, especially with regards to race. Repeated studies have shown that compared to white participants, black particpants tend to have lower renin levels in both hypertensive (17–19) and non-hypertensive cohorts (20–26). It is thought that hypertensive black patiens are more likely to manifest a salt-sensitive hypertensive phenotype (25,27,28), which has been attributed to Liddle syndrome-like phenomenon (29) where activation of the epithelial sodium channel drives sodium retention independent of renin. Though now a standard teaching, this race-based association has not been universally seen when studied (30–33) and was not observed in a large, adjusted analysis in the MESA cohort (34). Furthermore, those with *APOL1* high risk alleles have been shown to have a paradoxically greater response to angiotensin receptor blockers, suggesting a potential link between RAAS and *APOL1* (35,36).

We will evaluate the cross-sectional association of renin and race, stratified by hypertension status, to determine if this race-based hypertensive phenotype persists in a large research cohort with adjustment for relevant confounding variables. We will test for an association between renin levels and *APOL1* high risk alleles. We will also evaluate the association of baseline renin levels with incident CKD, ESRD, cardiovascular disease (CVD), and mortality in the ARIC cohort. We plan to stratify our analysis by the presence and absence of baseline hypertension and race. To further understand how the RAAS pathway influences these associations, we will also assess angiotensinogen, ACE, and ACE-2 levels and their association with these outcomes.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the baseline associations of renin with race, APOL1 high risk alleles, and percent European ancestry in adults with and without hypertension.

Hypothesis 1: Renin is not significantly different in black and white adults, and there is no association of renin with number of APOL1 alleles and percent European ancestry, regardless of hypertension status.

Aim 2: Evaluate the association of baseline renin levels with the risk of CKD, ESRD, CVD, and mortality in adults with and without hypertension.

Hypothesis 2: Higher renin levels in adults is associated with a higher risk of CKD, ESRD, CVD, and mortality, regardless of hypertension status.

Aim 3: Evaluate the association of angiotensinogen, ACE, and ACE-2 levels with race and the risk of CKD, ESRD, CVD, and mortality in adults with and without hypertension.

Hypothesis 3: Angiotensinogen, ACE, and ACE-2 levels are not significantly in white and black adults; higher angiotensinogen, ACE, and ACE-2 levels in adults are associated with a higher risk of CKD, ESRD, CVD, and mortality, regardless of hypertension status.

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: We will conduct a prospective analysis of the ARIC cohort, using study visit 3 as baseline with follow-up through December 31, 2018 (or the most recent surveillance year).

Study Population: The study population will include all members of the ARIC cohort with available creatinine and renin levels at visit 3. We will exclude those with baseline eGFR<60 ml/min per 1.73 m^2 at visit 3. Incident cardiovascular disease analysis will exclude those with a history of cardiovascular disease at visit 3.

Exposure: We will use renin levels obtained using SOMAscan apatamer-based measurements from blood obtained at visit for our primary analysis. For additional analyses, and to evaluate the correlation between renin levels and the clinically use plasma renin activity, we will look at visit 5 plasma renin activity and SOMAscan-derived renin levels from visit 5, along with visits 3 and 5 angiotensinogen, ACE, and ACE-2 levels.

Outcomes:

The main outcomes are incident CKD, incident ESRD, incident CVD, and mortality. Estimated glomerular filtration rate (eGFR) will be calculated using the creatinine-based Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation, incorporating serum creatinine measurements at visits 3, 4, 5, and 6 (37). Incident CKD will be defined as meeting any of the following criteria: 1) development of eGFR<60 mL/min/1.73 m^2 at follow-up accompanied by ≥25% eGFR decline relative to baseline; 2) CKD-related hospitalization or death based on ICD-9/10 codes; 3) development of ESRD, as defined below (38).

Incident ESRD will be defined as the initiation of renal replacement therapy (either dialysis or transplant) and cases will be defined through linkage of the ARIC study with the United States Renal Data System (USRDS) registry. As a sensitivity analysis, we will use a composite outcome of kidney failure defined as meeting any of the following criteria: 1) USRDS-identified

end-stage renal disease; 2) eGFR <15 mL/min/1.73 m^2 at follow-up (visit 5); or 3) ICD-9/10 code for a kidney failure-related hospitalization or death (39).

Incident CVD will be definied as incident coronary heart disease (myocardial infarction, fatal coronary heart disease, or cardiac procedure) or stroke (40). Mortality will be determined through linkage to the National Death Index and through active surveillance.

Statistical Analysis:

Renin, angiotensinogen, ACE, and ACE-2 levels will be compared using correlations stratified by race and inter-protein correlation will be compared to previously published data using gold-standard assays. Visit 3 and visit 5 SOMAscan renin levels will be correlated to visit 5 plasma renin activity measured in a previous ancillary study performed by Dr. Stephen Turner. Descriptive statistics (means, proportions, etc.) will be used to examine baseline characteristics of the study participants, stratified by race and hypertension status, and according to tertiles of renin levels.

Cox proportional hazards regression will be used to estimate the association (hazard ratios, 95% confidence intervals) between visit 3 renin levels, modeled as a cubic spline, and risk of the outcomes described above during follow-up, incorporating time to the development of the outcome and accounting for censoring. Regression models will be stratified by history of hypertension. Analagous models will be performed for angiotensinogen, ACE, and ACE-2 levels as exposures.

Potential covariates for multivariable regression models include: age, sex, estimated glomerular filtration rate, systolic blood pressure, diabetes mellitus, cardiovascular disease, body mass index, smoking status, dietary intake (food frequency questionnaire), and medication use including ACE inhibitors/ARBs, beta blockers, and diuretics. Other models will additionally adjust for long-transformed urine albumin to creatinine ratio; adjust for age, sex, and race-center; and stratify by race. Multiple imputation will be explored for imputation of missing covariate values. We will test interactions between serum renin levels and race. We will perform sensitivity analyses using visit 5 SOMAscan renin, angiotensinogen, ACE, and ACE-2 levels and visit 5 plasma renin activity.

Limitations:

Renin levels vary depending on positioning during phlebotomy, time of day, fluid and sodium consumption, and medications, especially anti-hypertensive medications. These conditions were not uniform in ARIC. We lack 24-hour urine sodium and serum aldosterone levels, which could be used to index renin levels. By using SOMAscan renin levels, our study will deviate from the historic practice of measuring renin through plasma renin activity. There is the potential for residual confounding.

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)?

2183 - Progression of CKD focusing on kidney function (Coresh)
2715- Racial differences in serum potassium and associated outcomes in the Atherosclerosis Risk in Communities Study (Grams)
3597: The Association of Non-Alcoholic Hepatic Steatosis as determined by FIB-4 index and Risk of Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study (Ballantyne). We will work in conjunction with the authors of this mansucript, a study looking at similar markers but different outcomes, to minimize overlap.

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* 2017.27, 2013.21)
___ 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.

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