

## ARIC Manuscript Proposal #2715

PC Reviewed: 3/8/16  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Racial differences in serum potassium and associated outcomes in the Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** K<sup>+</sup>, kidney outcomes and mortality

**2. Writing Group:** Josef Coresh, Shoshana Ballew, Morgan Grams, Yan Chen, others welcome

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

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### 3. Timeline:

Data are already available now so analysis will begin as soon as approved. Manuscript preparation will be performed in the next six months.

#### **4. Rationale:**

Potassium is integral to maintaining cell membrane potentials and intracellular osmolarity, and it is affected by multiple types of medications which can both raise and lower potassium concentrations. Recent studies have linked abnormal serum potassium levels to death, major adverse cardiovascular events, hospitalizations, and end-stage renal disease, with possible underlying mechanisms including the discontinuation of valuable medications such as angiotensin converting enzyme-inhibitors and angiotensin receptor blockers<sup>1</sup> (Yan et al; in submission; Chang et al, in submission). An interesting aspect reported in these studies is that there are racial differences in predilection for abnormal levels of hyperkalemia, with African Americans at lower risk for developing hyperkalemia than persons of other ethnicities.<sup>2</sup>

In the United States, there are pervasive racial differences in health outcomes. African Americans have been reported to have higher risks of kidney disease, hypertension, diabetes mellitus, and, in some studies, all-cause mortality compared to other ethnic groups (Grams et al; JASN 2016; in press).<sup>3</sup> While some of these relationships are thought to be mediated by socioeconomic status and quality of medical care, some risk differences are thought to reflect genetic variation.<sup>4-6</sup> The underlying mechanism for racial differences in risk for hyperkalemia, and whether risk associations between potassium levels and adverse outcomes vary by race, is unknown.

To evaluate racial differences in potassium levels, we aim to evaluate the distribution of potassium levels in ARIC participants and determine the extent to which any differences are mediated by racial differences in age, comorbid conditions, or medication use. We will also assess whether race functions as an effect modifier for the association between potassium levels and adverse outcomes including all-cause mortality, end-stage renal disease, and arrhythmias. Finally, we will evaluate the association between percent African ancestry and potassium levels to determine whether there may be a genetic component to potassium levels.

#### **5. Main Hypothesis/Study Questions:**

Aim 1: Evaluate the association of race with serum potassium levels

Hypothesis 1: African American participants will have lower serum potassium levels on average than white participants.

Aim 2: Evaluate for effect modification of the relationship between potassium levels and adverse outcomes by race.

Hypothesis 1: Relationships between potassium and mortality, ESRD, and SCD will be stronger among African Americans.

Aim 3: Assess the association between % African Ancestry and serum potassium levels.

Hypothesis 1: Higher % African ancestry will associate with lower serum potassium levels.

**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 cohort analysis beginning at ARIC visit 1

Inclusion/Exclusion Criteria: All ARIC participants attending visit 1 with measured baseline covariates and serum potassium are included. For analyses of renal outcomes, participants with prevalent renal disease are excluded. For example, in evaluating the risk of ESRD, we will exclude prevalent ESRD.

Outcome variables: **Mortality** and incident renal outcomes including **chronic kidney disease** (defined as baseline  $eGFR_{CKD-Epi} \geq 60$  mL/min/1.73 m<sup>2</sup> and at least one follow-up  $eGFR_{CKD-Epi} < 60$  mL/min/1.73 m<sup>2</sup> with a 25% drop in eGFR, or a CKD-related hospitalization), **acute kidney injury** (defined as a hospitalization or death with the ICD-9-CM code 584.X (ICD-10-CM code N17.x)), **end-stage renal disease** (ESRD, defined as patients on dialysis or receiving transplant through linkage to the US Renal Data System) and **kidney failure** (KF, defined as  $eGFR-Cr < 15$  mL/min/1.73 m<sup>2</sup> during a planned study visit, USRDS registry identification, or a relevant ICD-9-CM/ICD-10-CM code).<sup>7-9</sup>

Exposure variables: Serum potassium concentration at visit 1 will be evaluated as both continuous variable using spline terms (with two knots at 3.5 mmol and 5.5 mmol) and nominal variable (hypokalemia and hyperkalemia vs normokalemia as reference group).

Summary of data analysis: We will plot kernel density graphs stratified by race for the distribution of serum potassium. Assuming a normal distribution, we will use t-tests to compare differences in mean values by race. We will use Cox proportional hazard regression to evaluate the relationship between serum potassium and outcomes (mortality and kidney outcomes) with an interaction term with race. Associations between African ancestry and serum potassium will be evaluated in unadjusted and fully adjusted (including use of medications that affect potassium levels) analyses.

Potential limitations: 1. Modest numbers of certain kidney outcomes such as ESRD, thus the power to detect differences among potassium groups may be limited. 2. African ancestry may correlate with many socioeconomic and environmental factors and thus is an imperfect proxy for genetic determinants.

**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? \_\_x\_\_ 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  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.csc.unc.edu/ARIC/search.php>
- 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)?
- #328  
# 2605 (Same group of investigators but did not ask for genetic data)
- 11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes  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.csc.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.csc.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.

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2. Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron. Clinical practice*. 2012;120(1):c8-16.
3. Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis*. 2013;62(2):245-252.
4. Peralta CA, Bibbins-Domingo K, Vittinghoff E, et al. APOL1 Genotype and Race Differences in Incident Albuminuria and Renal Function Decline. *J Am Soc Nephrol*. Jul 15 2015.
5. Peralta CA, Katz R, DeBoer I, et al. Racial and ethnic differences in kidney function decline among persons without chronic kidney disease. *J Am Soc Nephrol*. 2011;22(7):1327-1334.
6. Foster MC, Coresh J, Fornage M, et al. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol*. 2013;24(9):1484-1491.
7. Grams ME, Rebholz CM, McMahon B, et al. Identification of incident CKD stage 3 in research studies. *Am J Kidney Dis*. Aug 2014;64(2):214-221.
8. Grams ME, Waikar SS, Macmahon B, Whelton S, Ballew SH, Coresh J. Performance and Limitations of Administrative Data in the Identification of AKI. *Clin J Am Soc Nephrol*. 2014;9(4):682-689.
9. Rebholz CM, Coresh J, Ballew SH, et al. Kidney Failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: Comparing Ascertainment of Treated and Untreated Kidney Failure in a Cohort Study. *Am J Kidney Dis*. Aug 2015;66(2):231-239.