ARIC Manuscript Proposal #2605

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Impact of serum potassium on kidney outcomes and mortality in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): K^+, kidney outcomes and mortality

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

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _YC_ **[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:
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 crucial in many physiological functions. Normal serum potassium levels of 3.5-5.5 mmol are maintained by extrarenal and distinct renal mechanisms.[1] By regulating potassium secretion, reabsorption and excretion, the kidney plays an important role in potassium homeostasis.[2] The deviation of serum potassium from normal range could be both a manifestation and predictor of decreased renal function.

Hyperkalemia and hypokalemia have been shown to be related to kidney outcomes and mortality in populations with comorbidities such as heart failure and chronic kidney disease (CKD). Wang et al found that both hypokalemia and hyperkalemia were associated with elevated risk of end-stage renal disease (ESRD) in CKD patients.[3] Hayes et al. suggested that hypokalemia and hyperkalemia were associated with increased mortality in a CKD population and that hypokalemia was associated with faster CKD progression.[4] Furthermore, among patients with heart failure, hypokalemia was associated with increased mortality.[5] However, little is known about whether extreme values of serum potassium are associated with incident renal outcomes and mortality in the general population.

Many medications can influence serum potassium levels. Kaliuretic diuretics are common causes of hypokalemia while the use of renin–angiotensin–aldosterone system (RAAS) inhibitors can cause hyperkalemia.[6][7][8] β blockers and potassium sparing diuretics also have the potential to increase serum potassium levels.[9][10] Few studies have looked into how these medication can change the association between extreme values of serum potassium and renal outcomes and mortality.

The aim of this study is to investigate the relationship between serum potassium and renal outcomes/mortality as well as the role of relevant medications as a possible modifier of this relationship, by using data from the Atherosclerosis Risk in Communities study.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association of extreme serum potassium levels with renal outcomes and mortality.

Hypothesis 1: Both hyperkalemia and hypokalemia will be risk factors for mortality in the general population. Extreme levels of serum potassium will also associate with acute kidney injury, incident CKD, and ESRD.

Aim 2: Evaluate whether relevant medications can alter the association between serum potassium levels and outcomes.

Hypothesis 1: Concomitant use of cardioprotective medications that increase levels of potassium (e.g., RAAS-inhibitors and B-blockers) will attenuate the association between hyperkalemia and mortality.

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; in evaluating the risk of incident CKD, we will exclude participants with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.

Outcome variables: **Mortality** and incident renal outcomes including **chronic kidney disease** (defined as baseline $eGFR_{CKD\text{-}Epi}$ >= 60 ml/min/1.73 m^2 and at least one follow-up $eGFR_{CKD\text{-}Epi}$ <60 mL/min/1.73m^2 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 m2 during a planned study visit, USRDS registry identification, or a relevant ICD-9-CM/ICD-10-CM code).[11][12][13]

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). In sensitivity analysis, we will also evaluate serum potassium levels at visit 2, categorizing levels by average potassium levels as well as patterns of nominal variables (e.g., high-high, high-normal, low-low).

Summary of data analysis: We will use ANOVA F-test and chi-square tests to examine the difference in potential confounders by baseline serum potassium levels. Kaplan-Meier curves will be used to assess the cumulative survival during follow-up and the log-rank test will be used to test the overall survival experience by different potassium groups. We will use Cox proportional hazard regression to evaluate the relationship between serum potassium and outcomes (mortality and kidney outcomes). In sensitivity analysis, hyperkalemia will be redefined as serum potassium level $\geq$ 5mmol to examine the dependence of the association in primary analysis on the choice of cutoff point. Results will also be shared with broader subsequent meta-analyses in the CKD Prognosis Consortium.

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. Only two measures of serum potassium during follow-up.

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 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 __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)?
#328 Analysis of the relationship between potassium and incidence of cardiovascular diseases

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.

References:

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