ARIC Manuscript Proposal #1944

PC Reviewed: 5/8/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk factors for acute kidney injury

b. Abbreviated Title (Length 26 characters): AKI risk factors

2. Writing Group:

Writing group members: Morgan Grams, Josef Coresh, W.H. Linda Kao, Mara McAdams-DeMarco, Kunihiro Matsushita. Others are welcome to join.

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 analysis to start after approval of this manuscript proposal, abstract available by June 2012, first draft available by November 2012.

4. Rationale:

Acute kidney injury (AKI) is a common condition – an order of magnitude more common than end stage renal disease, for example – with devastating outcomes.[1-4] Short-term mortality rates in hospitalized AKI can be as high as 40 to 60%,[5-7] and AKI survivors experience twice the long-term mortality of similar patients without AKI.[8] Known risk factors for AKI include age, chronic kidney disease, diabetes, and hypertension; however, other putative determinants of AKI have not been studied.

The relationship between chronic kidney disease (CKD) and AKI is incompletely described: while reduced kidney function at a specific point in time is associated with the subsequent development of AKI, little is known regarding the nature of its association. For example, no population-based studies have explored the relationship between glomerular filtration rate decline and AKI. Similarly, it is not known whether genetic risk factors implicated in the development of CKD – specifically, genetic variants of APOL1 in African-Americans[9, 10] and the E-1 haplotype of the MYH9 gene in European-Americans[11] – hold similar import in AKI development. The association between CKD and AKI may be confounded by several factors, such as serum urate levels, elevated blood pressure, and the use of certain medications. For serum urate, a genetic urate risk score exists, which may help distinguish the confounded relationship of uric acid and CKD.

5. Main Hypothesis/Study Questions:

Specific Aim 1: Estimate the association of eGFR decline and the incidence of AKI.
Hypothesis: Participants with a more rapid decline in eGFR are at higher risk of subsequent AKI.

Specific Aim 2: Explore putative genetic determinants of AKI.
Hypothesis: Known CKD risk variants are also associated with AKI. Genetic urate score is associated with the development of AKI.

Specific Aim 3: Describe additional modifiable and non-modifiable risk factors for the development of AKI.
Hypothesis: Serum urate is associated with the development of AKI, independent of CKD.

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).

We propose to use all ARIC participants free of CKD Stage 5 (eGFR<15 ml/min/1.73 m^2) at visit 1 with measured baseline covariates who consented to the CVD cohort surveillance (and genetic study, for specific aim 2). We will also perform sensitivity analysis excluding participants with CKD Stage 3 and 4 (eGFR<60 ml/min/1.73 m^2). For

Aims 1 & 3 (which will utilize Visit 4 data), participants with an antecedent (between Visits 1 & 4) AKI event will be excluded.

Tested exposures will include serum urate concentration (measured with the uricase method at visits 1, 2, and 4), change in eGFR (estimated between Visits 1 and 4 using the CKD-Epi equation and standardized, calibrated serum creatinine), genetic urate score, genetic CKD score, and previously described CKD genetic risk variants (e.g., APOL1, MYH9). In addition, we will perform a genome-wide association study (GWAS) to assess the association of other regions of genotypic variation with AKI.

The outcome will be incident AKI, defined as the presence of one of the following labels in the diagnosis coding: 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. This definition (used in previous publications[12-14]) encompasses patients who were hospitalized with AKI, by abstracting the candidate ICD codes from the listed discharge diagnoses, as well as those who died with AKI, by abstracting ICD codes from listed causes of death on the death certificate. Dr. Grams is also working on an ancillary study to ARIC to examine the validity of AKI ICD-codes versus hospitalization records.

Data will be analyzed using Cox proportional hazards models; associations will be estimated using adjusted hazard ratios. All analyses will be adjusted for center, demographic variables, as well as baseline diabetes, hypertension, and coronary heart disease. CKD and its key markers (eGFR and albuminuria) will be important risk factors for AKI, which are also strong determinants of hyperuricemia. We will examine associations before and after controlling for these CKD markers. We will explore interactions, including effect modification by sex, race, and medication use.

Potential limitations of this analysis include those inherent in all observational studies of AKI: residual confounding, variable sensitivity and specificity of ICD-9-CM codes for true AKI events, the competing risks of death and end stage renal disease.

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? _x__ 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"?

__x__ 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)?

1681: Uric acid and risk of kidney function decline (2010).
1344: Correlates of gout and its association with kidney function (2008, amended 2012).

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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