ARIC Manuscript Proposal #2177

PC Reviewed: 7/9/13  Status: A  Priority: 2
SC Reviewed:  _________  Status:  _____  Priority:  _____

1.a. Full Title: Association of urinary biomarkers with the risk of end-stage renal disease in the general population: CKD Biomarkers Consortium

b. Abbreviated Title (Length 26 characters): Urinary biomarkers and ESRD

2. Writing Group: Meredith C. Foster, Josef Coresh, Joseph V. Bonventre, Chi-yuan Hsu, Paul L. Kimmel, Theodore Mifflin, Robert G. Nelson, Vasan S. Ramachandran, Venkata S. Sabbisetti, Sushrut S. Waikar, Kathleen D. Liu, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MF [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 analysis and drafting of manuscript to begin immediately, with anticipated draft for ARIC review within 3-6 months of proposal approval.

4. Rationale: Chronic kidney disease (CKD) is common in the United States and is associated with increased risk of mortality, cardiovascular disease, and progression to end-stage renal disease (ESRD).1-4 The number of well-established biomarkers for CKD in clinical practice is limited (e.g. serum creatinine, cystatin C and urinary albumin to creatinine ratio [UACR]) and may not adequately capture early stages of disease. Risk of mortality, cardiovascular disease, and end-stage renal disease (ESRD) outcomes associated with creatinine-based estimated glomerular filtration rate (eGFRcrea) begins to rise as eGFRcrea declines below 75-60 mL/min/1.73m²,3,4 levels at which substantial declines in kidney function have already occurred. Increased mortality, cardiovascular disease, ESRD risk is observed even at low levels of albuminuria,3,4 but may only reflect early stages of kidney disease due to glomerular damage.
Several urinary markers of tubular injury associated with acute kidney injury, such as specifically liver fatty acid binding protein (L-FABP), kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL),\textsuperscript{5} are also currently under investigation as early markers of CKD and CKD progression.\textsuperscript{6-9} Earlier work in ARIC suggests that urinary NGAL, but not KIM-1, is associated with incident stage 3 CKD, defined as developing an eGFRcrea < 60 mL/min/1.73m\textsuperscript{2} with at least a 25% decrease in eGFRcrea.\textsuperscript{7} As part of analyses within the CKD Biomarkers Consortium (CKD Biocon), we are interested in determining whether L-FABP, KIM-1, NAG, and NGAL are associated with incident ESRD, independent of known clinical risk factors for CKD progression (e.g., baseline glomerular filtration rate, albuminuria, blood pressure, race, diabetes) in adults in ARIC.

5. **Main Hypothesis/Study Questions**: Are levels of the urinary biomarkers NGAL, L-FABP, KIM-1 and NAG associated with incident ESRD, independent of known clinical risk factors for CKD progression in adults from ARIC?

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**: Nested case-control study of 185 incident ESRD cases and 260 frequency matched controls.

**Eligibility Criteria**: Cases and controls for this study were selected from Visit 4 (1996-98). Participants were eligible for this case-control study if:

1. Non-missing creatinine-based eGFR (defined using the CKD-EPI equation) at Visit 4
2. Non-missing diabetes status at Visit 4
3. Non-missing values for UACR
4. Free of ESRD at Visit 4 and non-missing follow-up for ESRD events from Visit 4 through December 31, 2008
5. African Americans at centers in Minneapolis, MN and Washington County, MD and Whites in Jackson, MS were excluded from the analysis.

**ESRD Case definition**: Cases included incident ESRD events after Visit 4 (1996-98) identified through hospitalization surveillance through December 31, 2008. Incident ESRD cases included:

1. AKI codes (584-584.9, 586, N17.0-N17.0) as an underlying cause of death and with a prior history of CKD as indicated by creatinine rise, eGFR MDRD or surveillance ICD code; OR
2. Hospitalizations with ICD codes specified for kidney transplant, dialysis or procedural code indicating dialysis, except:
   a. ICD code of traumatic anuria (958.5) with the same event date
   b. ICD code of AKI (586.x and 788.9x) with same event date and without any prior CKD events as indicated by creatinine rise, eGFR MDRD, or surveillance ICD code

**Control Selection**: Controls were frequency matched to cases (2:1, when possible) based on the following criteria

1. CKD-EPI estimated glomerular filtration rate (eGFR) category (<45, 45-59, 60-74, 75-89, 90-105, ≥105 mL/min/1.73 m\textsuperscript{2})
2. UACR category (<30, 30-299, ≥300 mg/g)
3. Diabetes status (fasting glucose >126 mg/DL, self-reported diabetes medication use in the past two weeks, or self-reported diagnosed diabetes)
Sex
Race (African American, White)

**Exposures:** Urinary biomarker assays were/will be performed for CKD Biocon analyses in this case-control study using pH-adjusted urine samples collected during Visit 4. L-FABP was measured at the University of Pennsylvania; NAG and KIM-1 were measured at Brigham and Women’s Hospital; NAGL measurements are planned. Markers will be standardized to urinary creatinine at Visit 4 if needed. If necessary for normality, we will apply an appropriate transformation to urinary markers (e.g. log10[X], ln[X], log10[X+1])

**Other variables of interest:** Other variables of interest were assessed at Visit 4 and include the matching factors listed above (eGFRcrea, UACR, diabetes, sex, race), urinary creatinine (used as an index for the urinary exposure of interest), and potential covariates in our multivariable adjusted models (e.g. age, systolic blood pressure, diastolic blood pressure, hypertension medication use, body mass index, smoking status).

**Statistical Analyses:** We will evaluate the differences in continuous and categorical characteristics of cases and controls with t-tests and chi-squared tests, respectively. Correlations of the continuous markers (with transformations for normality, if needed) will be assessed using Pearson correlations. Conditional logistic regression (accounting for strata based on matching factors) will be used to estimate the incidence odds ratio (OR) of ESRD separately for each urinary marker. Models will be adjusted for baseline age; additional adjustment for matching factors (such as continuous eGFRcrea or UACR) to account for potential residual confounding. Exposures of interest will be evaluated continuously and categorically based on quantiles.

**Anticipated methodologic limitations or challenges if present:**
This is a small case-control study, so markers are only available in ~400 ARIC participants who attended Visit 4 with follow-up for ESRD. Urine samples were collected at Visit 4 (1996-98) with long-term storage prior to laboratory assays (assays performed in 2012-2013). Thus samples may have degraded with long-term storage; however, this would likely be non-differential based on case status.

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)?

MS1544 – Urinary proteins and incident chronic kidney disease
MS1692 – Identification of urinary biomarkers for incident chronic kidney disease

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
    ___ 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


