ARIC Manuscript Proposal #2192

PC Reviewed: 8/13/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Soluble RAGE and Risk of Kidney Disease Outcomes: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length: 21 characters**)**: sRAGE and Kidney Disease

2. Writing Group:
Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CMR **[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: Since the data are already available for this project, we anticipate being able to submit a manuscript for the Publications Committee to review within six months of manuscript proposal approval.

4. Rationale:

Advanced glycation end products (AGEs) and their cell-bound receptors (RAGE) have been implicated in the pathogenesis of diabetes (Goldin *et al.*, 2006; Goh & Cooper, 2008; Selvin *et al.*, 2013). When stimulated by AGEs, RAGE induces inflammation and is thought to fuel progression of chronic disease through nuclear factor (NF)-kB-mediated signaling (Yan *et al.*, 2008). The soluble form of RAGE (sRAGE) is a cleavage product of RAGE and may prevent the inflammatory processes initiated by RAGE activation (Wautier *et al.*, 1996). Alternatively, high sRAGE levels may simply be reflective of AGE-elicited inflammation. Similar to AGEs, elevated levels of circulating sRAGE may result from decreased renal clearance (Hartog *et al.*, 2005). Inhibition of the renin angiotensin system through the use of angiotensin converting enzyme inhibitors among kidney disease patients may increase the production and secretion of sRAGE (Forbes *et al.*, 2005).

Low levels of sRAGE have been shown to be independently associated with an increased risk of diabetes, coronary heart disease, and mortality in the ARIC Study (Selvin *et al.*, 2013). However, the role of this marker in kidney disease is less well known. A few cross-sectional studies have related higher levels of sRAGE to decline in kidney function, chronic kidney disease (CKD), end-stage renal disease (ESRD), and dialysis (Kalousová *et al.*, 2006; Gohda *et al.*, 2008; Kim *et al.*, 2012; Semba *et al.*, 2008; Basta *et al.*, 2010). In a prospective study of 230 women without kidney disease at baseline, baseline sRAGE level was positively associated with incident CKD (defined as eGFR <60 mL/min/1.73m^2 at the follow-up visit) during 12 months of follow-up (odds ratio: 1.32; 95% confidence interval: 1.01, 1.74; p=0.05) (Semba *et al.*, 2008). However, this study had a relatively short observation time, small sample size, and lacked a control group. Rigorous prospective studies are needed to establish temporality.

Using data from a nested case-cohort study and a nested case-control study in the ARIC cohort, we will conduct prospective analyses to determine whether levels of sRAGE are associated with incident CKD and incident ESRD.

5. Main Hypothesis/Study Questions:

Hypothesis 1: sRAGE is positively and independently associated with incident CKD.
Hypothesis 2: sRAGE is positively and independently associated with incident ESRD.

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).

Unless otherwise specified, the methods below pertain to both study 1 (case-cohort) and study 2 (case-control).

Study Design:

Study 1: Nested case-cohort study with six years of follow-up within the Atherosclerosis Risk in Communities (ARIC) study (N=1,942)

Study 2: Nested, matched case-control study with 18 years of follow-up within the ARIC study (N=302)

Inclusion/Exclusion:
Study 1:
The eligibility criteria for case and control selection were as follows:

1) Estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min/1.73m^2 at ARIC study visit 2
2) Not missing hypertension status, diabetes status, smoking status, and lipid levels (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) at ARIC study visit 2
3) Not missing eGFR at ARIC study visit 4
4) Black in Jackson, white in Minneapolis, white in Washington County, white or black in Forsyth

Study 2:
1) Not missing $eGFR_{SCr}$ at ARIC study visit 2
2) Not missing diabetes status at ARIC study visit 2
3) No ESRD prior to ARIC study visit 2
4) Black in Jackson, white in Minneapolis, white in Washington County, white or black in Forsyth

Case Definition:
Study 1: Incident CKD was defined as not having kidney disease at ARIC study visit 2 (1990-1992, eGFR $\geq$ 60 mL/min/1.73m^2) and developing kidney disease by ARIC study visit 4 (1996-1998, eGFR < 60 mL/min/1.73m^2 and $\geq$ 25% eGFR decline during six years of observation) (n=653). Two case groups will be defined: one based on $eGFR_{SCr}$ and one based on $eGFR_{SCys}$.

Study 2: Incident ESRD was defined as not having ESRD prior to ARIC study visit 2 and developing ESRD by surveillance of hospitalizations and deaths through December 31, 2005 (n=161). ESRD-related hospitalizations and deaths included those with any of the following ICD-9 and ICD-10 codes: 585.5, 585.6, 39.95, 54.98, N18.0, V42.0, V45.1, V56.0, V56.1, V56.2, V56.3, V56.8, Z45.2, Z49.1, Z94.0, and Z99.2.

Selection of Comparison Groups:
Study 1: A random sample of eligible participants was selected to serve as the sub-cohort, AKA cohort random sample (n=1,289).

Study 2: Controls were frequency matched to cases on sex, race, diabetes status, and $eGFR_{SCr}$ categories (per 10 mL/min/1.73m^2 category, i.e. 10-19, 20-29, 30-39, etc.) at ARIC study visit 2 (n=141). Controls did not develop ESRD during follow-up, from ARIC study visit 2 until December 31, 2005.

Exposures: Levels of sRAGE was measured with an ELISA from stored plasma samples that were collected during ARIC study visit 2 (Quantikine® Human RAGE Immunoassay, R&D Systems, Minneapolis, MN).

Other Variables of Interest: C-reactive protein was measured from stored plasma samples using a high-sensitivity immunoturbidimetric assay on the Siemens (Dade Behring, Deerfield, IL) BNII analyzer (Dade Behring). HbA1c was measured from stored whole blood samples using high-performance liquid chromatography, and values were standardized to the Diabetes Control and Complications Trial HbA1c assay.
Two estimates of GFR will be calculated: 1) CKD-EPI equation using serum creatinine only, and 2) CKD-EPI equation using cystatin C only. To examine the independent association of sRAGE with incident CKD and ESRD, the following variables from ARIC study visit 2 will be considered for inclusion in multivariate regression models: age, sex, race, systolic blood pressure, antihypertensive medication use (including angiotensin converting enzyme inhibitors), current smoker, body mass index, low-density lipoprotein, high-density lipoprotein, and triglycerides.

Data Analysis:

Descriptive statistics will be used to describe the study population overall, to compare cases with controls, and to examine differences by sRAGE quartile. For study 1, quartiles will be created based on the distribution of sRAGE in the sub-cohort. In study 2, quartiles will be created based on the distribution of sRAGE in the entire study population. Differences in baseline characteristics by case status will be tested using χ^2 and t tests. Differences in baseline characteristics by sRAGE quartile will be testing using ANOVA, Kruskal-Wallis, and χ^2 tests. sRAGE will be expressed continuously and in quartiles. The correlation between sRAGE, $eGFR_{SCr}$, $eGFR_{SCys}$, ACR, HbA1c, hsCRP, and β_2-microglobulin will be estimated in the sub-cohort in study 1 and in the entire study population in study 2.

Unadjusted and adjusted means (standard deviations) and medians (inter-quartile ranges) will be calculated for sRAGE by case status. Unadjusted and adjusted logistic regression models will be used to examine the association between sRAGE and incident CKD in study 1, using a robust variance estimator and inverse probability weighting. In study 2, we will use conditional logistic regression to examine the association between sRAGE and incident ESRD. Crude and adjusted odds ratios and 95% confidence intervals for incident CKD and incident ESRD will be estimated for an increase of one inter-quartile range, an increase of one standard deviation, and by quartile of sRAGE. Potential covariates for multivariate models include: age, sex, race, systolic blood pressure, antihypertensive medication use, current smoker, body mass index, low-density lipoprotein, high-density lipoprotein, and triglycerides. For race- and gender-stratified analyses, race- and gender-specific quartiles, inter-quartile ranges and standard deviations will be calculated, and regression models will be repeated for the estimation of incident odds ratios and 95% confidence intervals.

Limitations/Challenges: Loss-to-follow up between ARIC study visit 2 and 4 may have introduced selection bias, since individuals with disease may be less likely than healthy individuals to attend follow-up study visits. The plasma specimens may have been

compromised during long-term freezer storage between the time of collection and time of laboratory measurement.

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)?
#1890: Determinants of sRAGE and its Association with Cardiovascular Disease, Diabetes, and Mortality in a Community-based Population

#1905: The Association of Lifestyle Factors with Circulating Levels of the Soluble Receptor for Advanced Glycation End Products (sRAGE)

#2170: sRAGE, progression of subclinical cardiac damage, and risk of heart failure

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* 2006.16, 2009.16**)**

_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.15**)**

*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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