ARIC Manuscript Proposal #2835

PC Reviewed: 09/13/16 **Status:** _____ **Priority: 2**
SC Reviewed: _____ **Status:** _____ **Priority:** ____

1.a. Full Title: Plasma Concentrations of Galectin-3 and Subsequent Risk of Kidney Disease

b. Abbreviated Title (Length 26 characters): Galectin-3 and Kidney Disease

2.   Writing Group:
Writing group members: Casey M. Rebholz, Elizabeth Selvin, Christie M. Ballantyne, Ron C. Hoogeveen, Morgan E. Grams, Josef Coresh, *others welcome* (order TBD)

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]**

First author: Casey M. Rebholz
Address: 2024 East Monument Street, Suite 2-600
                  Baltimore, Maryland 21287
                  Phone: 410-502-2049   Fax: 410-955-0476
                  E-mail: crebhol1@jhu.edu

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).

Name: Josef Coresh
Address: 2024 East Monument Street, Suite 2-600
               Baltimore, Maryland 21287
               Phone: 410-955-0495   Fax: 410-955-0476
               E-mail: coresh@jhu.edu

3.   Timeline: Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

4.   Rationale:

Galectin-3 is a ~35-kDa β-galactoside-binding lectin which has been proposed as a novel biomarker of heart failure due to its involvement in myocardial fibrosis in addition to inflammation, immunity, and adhesion.[1-3] Elevated levels of galectin-3 may be associated with fibrosis of other organ tissues, such as the kidney, and increase the risk of developing kidney disease through its other mechanisms of action.

In an animal study, it was suggested that galectin-3 is secreted by macrophages, and, through this pathway, leads to the promotion of renal fibrosis.[4] Subsequently, a few papers have been published on galectin-3 measured in humans in relation to kidney disease outcomes. In 2,450 Framingham Offspring study participants followed for approximately 10 years, higher levels of galectin-3 were associated with rapid eGFR decline ($\geq$3 mL/min/1.73 m^2 per year) and incident chronic kidney disease (eGFR<60 mL/min/1.73 m^2).[5] In an accompanying editorial, it was stated that "Although promising, the associations found in this study between levels of galectin-3 and distant renal events need to be confirmed in different populations and settings to be generalizable."[6] In a cross-sectional analysis of the German Diabetes mellitus Dialysis (4D) study (n=1,168 dialysis patients with type 2 diabetes) and the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (n=2,579 patients with coronary angiograms), galectin-3 levels progressively increased across categories of declining kidney function.[7] In contrast, galectin-3 was not associated with kidney function decline in adjusted analyses using data from the Cardiovascular Health Study (CHS), a community-based population of older adults (n=2,763).[8] Given the promising yet inconsistent evidence and the novelty of this biomarker, further research is warranted to better understand the association between galectin-3 and kidney disease outcomes.

5.   Main Hypothesis/Study Questions:

The main hypothesis is that galectin-3 will be positively and independently associated with risk of incident chronic kidney disease, eGFR decline, and incident end-stage renal disease.

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: We will conduct a prospective analysis of the ARIC cohort, using study visit 4 as baseline with follow-up through December 31, 2013 (or the most recent surveillance year).

Study Population: We will exclude study participants with missing data for galectin-3 and those who developed chronic kidney disease or end-stage renal disease prior to study visit 4.

Exposure: The primary exposure is plasma levels of galectin-3. Galectin-3 concentrations were measured in plasma EDTA specimens collected from study participants at study visit 4 (1996-1998). The ARCHITECT galectin-3 assay is a chemiluminescent micro-particle immunoassay (CMIA) that was used on the ARCHITECT automated immunoassay analyzer.

Outcomes:
The main outcomes are incident chronic kidney disease, eGFR decline, and incident end-stage renal disease. Estimated glomerular filtration rate (eGFR) will be calculated using the creatinine-based Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation, incorporating serum creatinine measurements at visit 4 and visit 5.[9] Incident chronic kidney disease will be defined as meeting any of the following criteria: 1) development of eGFR<60 mL/min/1.73 m^2 at follow-up (visit 5) accompanied by $\geq$25% eGFR decline relative to baseline

(visit 4); 2) chronic kidney disease-related hospitalization or death based on ICD-9/10 codes; 3) development of end-stage renal disease, as defined below.[10] Given that biochemical measures of kidney function are available only at visit 4 and visit 5 (for the purpose of this analysis), the visit-based measures are supplemented with surveillance-based measures (USRDS registry, hospitalizations, deaths). As a sensitivity analysis, chronic kidney disease will be defined using the visit-based measures only [i.e. development of eGFR<60 mL/min/1.73 m^2 at follow-up (visit 5) accompanied by ≥25% eGFR decline relative to baseline (visit 4)].

In accordance with recent proposals for quantifying kidney disease progression, we will investigate eGFR decline defined as ≥30% eGFR decline.[11] To mirror the analysis conducted in the Framingham Offspring study, we will define rapid eGFR decline as ≥3 mL/min/1.73 m^2 per year.

Incident end-stage renal disease will be defined as the initiation of renal replacement therapy (either dialysis or transplant) and cases will be defined through linkage of the ARIC study with the United States Renal Data System (USRDS) registry. As a sensitivity analysis, we will use a composite outcome of kidney failure defined as meeting any of the following criteria: 1) USRDS-identified end-stage renal disease; 2) eGFR <15 mL/min/1.73 m^2 at follow-up (visit 5); or 3) ICD-9/10 code for a kidney failure-related hospitalization or death.[12]

Statistical Analysis:
Descriptive statistics (means, proportions, etc.) will be used to examine baseline characteristics of the study participants according to quantiles of galectin-3 and test for differences using χ^2 tests and linear regression. The cross-sectional association between eGFR and galectin-3 will be investigated using scatterplots and correlation coefficients. The distribution of galectin-3 will be examined using a histogram and tests of normality. If the distribution is skewed, transformations will be considered, such as logarithmic transformation and categorization using quantiles.

Cox proportional hazards regression will be used to estimate the association (hazard ratios, 95% confidence intervals) between galectin-3 and risk of kidney disease during follow-up, incorporating time to the development of kidney disease and accounting for censoring. Cubic splines will be used to visually depict the association between galectin-3 and kidney disease risk. In a sensitivity analysis, we will evaluate the associations taking into account the competing risk of death.

Stratified analyses and test for interaction will be conducted by race, sex, diabetes, and baseline kidney function (eGFR <60 mL/min/1.73 m^2 vs. eGFR ≥60 mL/min/1.73 m^2). In addition, we will investigate differences in the association between galectin-3 and kidney disease outcomes according to *APOL1* genetic variants by including an interaction term in the regression model.

Potential covariates for multivariable regression models include: age, sex, race-center, body mass index, systolic blood pressure, anti-hypertensive medication use, hypertension status, hemoglobin A1c, diabetes status, physical activity, history of cardiovascular disease, cigarette smoking status, education level, eGFR, and albuminuria.

Limitations:

We acknowledge that there are a few study limitations including the availability of biochemical measures of kidney function only at visit 4 and visit 5 (for the purpose of this analysis); the measurement of galectin-3 at a single time point; and the potential interrelationship between kidney filtration and circulating levels of galectin-3. These limitations will be addressed in the analysis and acknowledged in the discussion section within the context of the study strengths. For example, we will supplement visit-based measures of kidney function with surveillance-based measures (USRDS registry, hospitalizations, deaths). We could assess change in galectin-3 for participants with measures at the CARMRI visit in addition to visit 4, and, when the data are available, for participants with measures at visit 5 in addition to visit 4. Lastly, the cross-sectional association between eGFR and galectin-3 will be investigated and the prospective analyses will adjust for baseline kidney measures (eGFR as well as UACR).

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? __ 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)?

#2771 – Galectin-3 and Cardiovascular Outcomes; first author: David Aguilar; ARIC and corresponding author: Christie Ballantyne

   This manuscript proposal is the primary manuscript from this ancillary study, which focuses on cardiovascular outcomes (primarily, heart failure). We will collaborate with Dr. Ballantyne.

#2805 – Galectin-3 and Atrial Fibrillation Incidence; first author: Aaron Folsom

This manuscript proposal focuses on the outcome of atrial fibrillation exclusively.

#2436 – Galectin-3 and risk of heart failure and death in a subsample of the Atherosclerosis Risk in Communities (ARIC) study

This manuscript proposal used galectin-3 measurements of specimens collected during the CARMRI visit, and focuses on the outcomes of heart failure and death. The manuscript based on this proposal was recently published.[3]

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* 2013.21)
  ___   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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References

1.	de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med.* 2011;43(1):60-68.
2.	de Boer RA, Voors AA, Muntendam P, van Gilst WH, van Veldhuisen DJ. Galectin-3: a novel mediator of heart failure development and progression. *Eur J Heart Fail.* 2009;11(9):811-817.
3.	McEvoy JW, Chen Y, Halushka MK, et al. Galectin-3 and Risk of Heart Failure and Death in Blacks and Whites. *Journal of the American Heart Association.* 2016;5(5).
4.	Henderson NC, Mackinnon AC, Farnworth SL, et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. *The American journal of pathology.* 2008;172(2):288-298.
5.	O'Seaghdha CM, Hwang SJ, Ho JE, Vasan RS, Levy D, Fox CS. Elevated galectin-3 precedes the development of CKD. *Journal of the American Society of Nephrology : JASN.* 2013;24(9):1470-1477.
6.	Ravani P, Barrett BJ. Galectin-3 and new-onset CKD: marker or mediator? *Journal of the American Society of Nephrology : JASN.* 2013;24(9):1342-1344.
7.	Drechsler C, Delgado G, Wanner C, et al. Galectin-3, Renal Function, and Clinical Outcomes: Results from the LURIC and 4D Studies. *Journal of the American Society of Nephrology : JASN.* 2015;26(9):2213-2221.
8.	Bansal N, Katz R, Seliger S, et al. Galectin-3 and Soluble ST2 and Kidney Function Decline in Older Adults: The Cardiovascular Health Study (CHS). *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2016;67(6):994-996.
9.	Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Annals of internal medicine.* 2009;150(9):604-612.
10.	Grams ME, Rebholz CM, McMahon B, et al. Identification of incident CKD stage 3 in research studies. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2014;64(2):214-221.
11.	Levey AS, Inker LA, Matsushita K, et al. GFR decline as an endpoint for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2014.
12.	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. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2015;66(2):231-239.