ARIC Manuscript Proposal #3853

PC Reviewed: 6/8/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Testican-2 and CKD progression

b. Abbreviated Title (Length 26 characters): Testican-2 and CKD

2. Writing Group:

Writing group members: Donghai Wen, Linda Zhou, Aditya Surapaneni, Christy Ballantyne, Ron Hoogeveen, Josef Coresh, Eugene P. Rhee, Morgan E. Grams, others welcome (order TBD).

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __DW___ **[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: Analyses will begin once the manuscript proposal has been approved. We anticipate that the manuscript will be written and submitted to the ARIC Publications Committee within one year of the manuscript proposal being approved.

4. Rationale: Chronic kidney disease (CKD) disproportionately affects older adults. The prevalence of CKD, defined by estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or urine albumin-to-creatinine ratio (ACR) >30 mg/g ,[1] was nearly 50% in persons older than 70 years in the National Health and Nutrition Examination Survey (1999-2004).[2] CKD is associated with myriad morbidity and mortality, including end-stage renal disease (ESRD),[3,4] cardiovascular disease,[5] heart failure, and all-cause and cardiovascular mortality.[6] Still, the progression of CKD is quite variable; identifying factors associated with poor (or improved) prognosis could help accurately risk stratify as well as identify potential targets for intervention.

Plasma levels of the protein testican-2 has been found to be positively correlated with eGFR and to be associated with reduced eGFR loss over time among individuals with normal kidney function at baseline in two community-based cohort studies (Jackson Heart Study and Framingham Heart Study). [7] However, the relationship between circulating levels of testican-2 and the risk of CKD progression, including ESRD, is not known. This study is proposed as a replication of findings in the African American Study of Kidney Disease and Hypertension.

5. Main Hypothesis/Study Questions:

Our overarching hypothesis is that higher blood testican-2 levels are associated with better kidney health.

Aim: To determine whether blood testican-2 levels are associated with CKD progression in ARIC participants, as defined by incident ESRD or 50% decline in eGFR.

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 analyses of the ARIC cohort, treating Visit 5 (2011-2013) as the baseline visit, through 2017.

Study Population: The study population will consist of white and African-American ARIC participants with testican-2 data from Visit 5 through most recent administrative censoring date.

Exposure: Blood testican-2 levels (measured by SomaLogic aptamer platform) at Visit 5.

Outcomes: 1) incident ESRD; 2) CKD progression. Incident ESRD as identified by the US Renal Data System (USRDS) registry.[8] CKD progression will be defined as ESRD or a decline in eGFR by 50% from Visit 5 through 2017, where eGFR is calculated from serum creatinine and serum cystatin using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equations.[9,10]

Statistical Analysis: We will use descriptive statistics, including means, medians, and proportions to compare baseline characteristics by blood testican-2 levels at Visit 5. Formal testing will be performed using student's t-test or Wilcoxon rank-sum test for continuous variables and chi-squared for categorical variables. Cox proportional hazards models will be constructed to study the associations of testican-2 at Visit 5 with: 1) incident ESRD; and 2) CKD progression. We will adjust for the covariates using three different models: Model 1 will be unadjusted; Model 2 will adjust for age, sex, eGFR, history of atherosclerotic cardiovascular disease (ASCVD), smoking and body mass index (BMI); Model 3 will add log-transformed urine albumin creatinine ratio (LogACR) to Model 2.

Limitations: Based on our prior publication,[7] we are confident that the protein identification for the testican-2 aptamer is accurate (a GWAS hit in the cognate gene was confirmed in both the Framingham Heart Study and the Jackson Heart Study). However, a key limitation is that these

aptamer-based measurements are in arbitrary units, not absolute concentrations, and the linear dynamic range for this protein assay has not been established. An additional limitation is the absence of simultaneous urine measurements, which would provide additional insight on testican-2 expression and kidney health.

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/mantrack/maintain/search/dtSearch.html

___**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)?

"Proteomics and kidney disease in a community based population"

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*__ 2017.27**____)**
_ _ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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. Kidney Disease: Improving Global O. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.Suppl.* 2013;3:1-150.

2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007;298(17):2038-2047.

3. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int.* 2011;79(12):1331-1340.

4. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int.* 2011;80(1):93-104.

5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296-1305.

6. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375(9731):2073-2081.

7. Ngo D, Wen D, Gao Y, et al. Circulating testican-2 is a podocyte-derived marker of kidney health. *Proc Natl Acad Sci U S A.* 2020;117(40):25026-25035.

8. www.usrds.org.

9. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* May 5 2009;150(9):604-612.

10. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20-29.