ARIC Manuscript Proposal #3947 (revised)

PC Reviewed: 1/11/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Known biomarkers of CKD progression

b. Abbreviated Title (Length 26 characters): CKD Biomarkers

2. Writing Group:

Writing group members: Carolina Lopez-Silva, Aditya Surapaneni, Josef Coresh, Casey M. Rebholz, Christie M. Ballantyne, Morgan E. Grams, others welcome (order TBD).

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __CLS___ **[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: We will begin analyses 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) is a global health emergency. It is estimated that over 650 million people worldwide and 37 million people in the United States suffer from CKD [1,2]. CKD progression is associated with significant morbidity and mortality; decreasing levels of glomerular filtration rate (GFR) are strongly associated with an increased risk of end-stage renal disease (ESRD), adverse cardiovascular events, hospitalizations, and death[3,4]. In 2017, CKD was responsible for 1.2 million deaths globally, and with increasingly aging populations, this number is expected to rise to 2.2 million by 2040[1,5]. Understanding factors that drive, or protect from, incident kidney disease and CKD progression will allow us to build better

prognostic models for patient management and identify potential therapeutic targets that may ultimately improve patient outcomes.

Plasma levels of the proteins angiopoietin-1 (ANGPT1), tumor necrosis factor ligand superfamily member 12 (TNFSF12), and fibroblast growth factor 20 (FGF20) have been recently found to be associated with a lower risk of incident ESRD among individuals with diabetic kidney disease (DKD) and among diabetic individuals with normal renal function in three cohorts of the Joslin Kidney Study[6]. TNFR1, TNFR2, and KIM-1 have been found to be associated with a higher risk of incident ESRD in several studies. However, whether these proteins have prognostic value for incident kidney disease and CKD progression among non-diabetic individuals and above and beyond existing prognostic tools remains unknown. 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 main hypothesis is that higher blood levels of ANGPT1, TNFSF12, and FGF20 are associated with a lower risk of kidney disease progression and mortality, and that TNFR1, TNR2, and KIM1 are associated with higher risk of kidney disease progression.

Aim: To determine whether blood levels of prior identified proteins are associated with CKD progression, ESRD, and all-cause mortality in ARIC participants, independent of known risk factors.

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, evaluating the short-term prognostic value of the biomarkers as well as the long-term value. As such, we will use visit 2 as a baseline for change in GFR to visit 3, visit 3 for a baseline for change in GFR to visit 4, and Visit 5 (2011-2013) as the baseline visit for change in GFR to visit 6. We will also evaluate the long-term risk associated with these markers using visit 2 as a baseline.

Study Population: The study population will consist of white and African American ARIC participants with SOMAScan data and follow-up through most recent administrative censoring date.

Exposure: Blood ANGPT1, TNFSF12, FGF20, TNFR1, TNFR2, and KIM-1 levels (measured by SomaLogic aptamer platform) at each visit .

Outcomes: 1) Short-term change in GFR; 2) CKD progression; 3) incident ESRD; 4) incident all-cause mortality. Short-term change in GFR will be estimated as a decrease in GFR by >40% over the short-term. In sensitivity analysis, we will also look at 30% decrease in GFR. CKD progression will be defined as 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.[7,8] Incident ESRD as identified by the US Renal Data System (USRDS) registry.[9] Incident all-cause mortality as identified by surveillance of the National Death Index.

Statistical Analysis: We will compare baseline characteristics by tertiles of blood biomarker levels at Visit 2 and 5 using descriptive statistics, including means, medians, and proportions. For formal testing, we will use a student's t-test or Wilcoxon rank-sum test for continuous variables and chi-squared or Fisher's exact test for categorical variables. We will conduct pairwise correlations among Visit 2 and 5 levels of biomarkers using Pearson's correlation coefficient. Cox proportional hazards models will be constructed to study the independent associations of the biomarkers with: 1) GFR decline/CKD progression, 2) incident ESRD and 3) incident all-cause mortality. We will adjust for covariates using three different models: Model 1 will be unadjusted; Model 2 will adjust for age, sex, eGFR, and log-albumin-to-creatinine ratio (ACR) if available. Model 3 will additionally adjust for history of atherosclerotic cardiovascular disease (ASCVD), diabetes, hypertension, smoking and body mass index (BMI). We will construct Kaplan-Meier curves to estimate the risk of incident ESRD and incident mortality by tertiles of biomarker levels. Finally, we will use Harrell's C-statistic to examine the discrimination and improvement in discrimination (using change in C-statistic).

Limitations: One possible limitation of our study is the use of the SOMAscan platform for protein quantification, as aptamer-based measurements are in arbitrary units, not absolute concentrations.

Sensitivity analysis: As more proteomic data becomes available, we will also evaluate the changes in these specific proteins over time and whether changes in protein levels relate to outcomes as well as evaluating relationships using an earlier visit as baseline.

12/07/21 Proposal Amendment: In our analyses, we now plan to include serum levels of tumor necrosis factor receptor 1 (TNFRSF1), tumor necrosis factor receptor 2 (TNFRSF2) and kidney injury molecule-1 (KIM-1) at study visits 2, 3 and 5.

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)?

The most related proposals are ARIC Manuscript Proposal #3533: Proteomics and kidney disease in a community based population and ARIC Proposal #3818: Omic data and adverse kidney outcomes. Both are from our group.

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 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

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