ARIC Manuscript Proposal #4005

PC Reviewed: 2/8/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Eicosanoids and kidney outcomes in a community-based population

b. Abbreviated Title (Length 26 characters): Eicosanoids and ESKD

2. Writing Group:

Writing group members: Aditya Surapaneni, Pascal Schlosser, Eugene Rhee, Susan Cheng, Mohit Jain, Mona Alotaibi, Josef Coresh, Morgan Grams, *others welcome* (order TBD).

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AS___ **[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: End-stage kidney disease (ESKD) affects more than 700,000 Americans and confers dramatic decrements to quality of life and high risk of premature mortality.[1] Discovering targetable pathways and molecules to forestall or prevent the development of ESKD is of critical importance to improving the health of the US population.

Eicosanoids are molecules derived from fatty acids that are postulated to mediate inflammatory pathways.[2] Metabolites of arachidonic acid (a component of the cell membrane) via cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome p450 (CYP450) enzymes,

specific eicosanoids have been linked to renal vascular tone, the renin-angiotensin system, and endothelial function. One such eicosanoid, 20-hydroxyeicosatetraenoic acid, has also been linked to prevalent hypertension with genetic and animal model data supporting a causal role in disease development.[3-5] Other studies have investigated the use of eicosanoids in risk prediction. A model of 6 eicosanoids developed in FINRISK and validated in the Framingham Heart Study demonstrated an odds ratio of ~2 for the top vs. bottom quartile for hypertension, although Mendelian randomization provided no evidence of a causal role.[6]

Inflammation likely plays a key role in kidney disease as well. Metabolites of arachidonic acid, including thromboxane and leukotrienes have been linked to inflammatory damage in the kidney.[7] Hydroxyeicosatetraenoic acids (HETEs) help regulate ion transport in the kidney. Epoxyeicosatrienoic acids, CYP 450 epoxygenase metabolites, are thought to increase ENaC activity and decrease renal blood flow, leading to hypertension and CKD.[8] To our knowledge, there has been no systematic investigation with respect to the association between eicosanoids and development of adverse kidney outcomes. Identification of key eicosanoid mediators of kidney disease could inform ongoing work in the development of drugs to target arachidonic acid metabolism with the overall goal of reducing the burden of kidney disease.

5. Main Hypothesis/Study Questions:

Our overarching hypothesis is that specific eicosanoids will provide insight on the pathogenesis of CKD-associated outcomes.

Aim 1: To identify eicosanoids associated with eGFR in ARIC participants.

Aim 2: To determine whether levels of eicosanoids are associated with incident CKD, eGFR decline, and ESRD in ARIC participants.

Aim 3: To determine whether eicosanoids associated with adverse kidney outcomes have a possible causal role in disease development. We will perform this analysis by evaluating the genetic determinants of select eicosanoids via genome-wide association study (GWAS) and linking those to summary statistics from external datasets/consortia such as CKD-Gen using Mendelian randomization methods.

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 2 (1991-1993) as the baseline visit.

Study Population: The study population will consist of white and African-American ARIC participants with eicosanoid data from Visits 2 and follow-up for kidney outcomes.

Exposure: For Aim 1, the primary exposure will be baseline eGFR based on creatinine and cystatin. For Aims 2, the exposure of interest will be eicosanoid levels at Visit 2. For Aim 3, the exposures will be genetic markers in the genome (SNP associations with specific eicosanoids).

Outcomes: For Aim 1, the outcome will be individual eicosanoids. For Aim 2, the outcomes will be: 1) incident CKD; 2) eGFR decline; and 3) incident ESRD. Creatinine-based and/or cystatin-based Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equations will be used to estimate GFR.[9,10] Consistent with prior ARIC publications, incident CKD will be defined as having any one of the following: 1) an eGFR <60 ml/min/1.73 m^2 at follow-up (accompanied by a ≥25% eGFR decline relative to baseline; 2) CKD-related hospitalization or death based on the International Classification of Diseases (ICD) 9 or 10 codes; or 3) ESRD as identified by the US Renal Data System (USRDS) registry.[11-13] For exploratory analyses of eGFR decline, at the time of ESRD onset, eGFR will be imputed as 15 ml/min/1.73 m^2. For Aim 3, outcomes will be the SNP associations with renal outcomes derived from external datasets.

Statistical Analysis: We will use descriptive statistics, including means, medians, and proportions to compare baseline characteristics by eGFR categories at Visit 2. Formal testing will be performed using student's t-test or Wilcoxon rank-sum test for continuous variables and chi-squared for categorical variables. We anticipate that the distributions of eicosanoids will be skewed: we plan to transform (e.g., log base-2) to achieve a more normal distribution. For Aim 1 (n~10,400), linear regression models will be used to study the associations of eGFR with eicosanoids. Bonferroni correction will be used to account for multiple comparisons. Model 1 will be unadjusted; Model 2 will adjust for age, sex, and race-center; Model 3 will further adjust for baseline cholesterol, HDLc, diabetes, systolic blood pressure, anti-hypertension medication, CHD, Smoking, and BMI at Visit 2. For Aim 2 (n~10,400), Cox proportional hazards models will be constructed to study the associations of eicosanoids at Visit 2 with: 1) incident CKD; and 2) incident ESRD. We will adjust for the same covariates as in Aim 1 but also add in eGFR to Model 3. To examine the association of eicosanoids with subsequent eGFR decline, we will fit linear mixed-effects models with random intercepts and random slopes, adjusting for the same covariates as above except eGFR, which will be the dependent variable. We will perform these analyses overall and stratified by sex. For Aim 3, we will perform a GWAS to identify genetic markers that are associated with levels of eicosanoids of interest separately within African-American and white ARIC participants. We will use these associations together with published summary statistics to perform bidirectional Mendelian randomization studies.

Limitations: We acknowledge that our proposed study has a few limitations. First, we are only using data from Visit 2 onwards. However, the duration of follow-up for the current proposed study is still long. Second, the accuracy of eicosanoid identification is not always known. Third, power is limited for Mendelian randomization analyses, which requires us to evaluate associations in other, larger datasets such as CKD-Gen and the UK Biobank.

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? __X__ 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)?

Manuscript # 2680: 20-HETE and dementia, Fan Fan, Tom Mosley (genetics rather than biomarkers)

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*__2015.09___)

_ _ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __2011.03_(Selvin for funding on visit 6 labs, Matsushita for funding of visit 3 labs))

*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

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Eicosanoid biosynthesis pathway from arachidonic acid (reference: Wang et al.)