ARIC Manuscript Proposal #2981

PC Reviewed: 5/9/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: ***APOL1* renal-risk variants, cardiovascular disease, and all-cause mortality in African-Americans**

b. Abbreviated Title (Length 26 characters): **APOL1, CVD, and death**

2. Writing Group:

Writing group members: Barry I. Freedman, Nicholas M. Pajewski, Morgan Grams, Shoshana Ballew, Yingying Sang, and Joe Coresh

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MG **[please confirm with your initials electronically or in writing]**

First author: **Morgan Grams and Nicholas Pajewski**
2024 E. Monument Street, Rm 2-638
Baltimore, MD 21287
Phone: 443-287-1827 Fax: 410-955-0485
E-mail: mgrams2@jhmi.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: **Morgan Grams, MD, PhD**
Address: 2024 E. Monument Street, Rm 2-638
Baltimore, MD 21287
Phone: 443-287-1827 Fax: 410-955-0485
E-mail: mgrams2@jhmi.edu

3. Timeline:

Data analysis will start immediately. A manuscript is expected to be prepared within 12 months.

4. Rationale:

Apolipoprotein L1 gene (*APOL1*) G1 and G2 renal-risk variants (RRVs) are powerfully associated with a spectrum of progressive non-diabetic forms of nephropathy in individuals who possess recent African ancestry.[1] However, it remains controversial whether the *APOL1* RRVs are also independently associated with incident cardiovascular

disease (CVD) and all-cause mortality. While several studies have examined this issue,[2–5] statistical power is an overarching concern, given that only 13% of African Americans in the general population possess two *APOL1* RRVs. Therefore, we propose to conduct a comprehensive meta-analysis to definitively address whether *APOL1* RRVs confer risk for CVD, independent of their association with chronic kidney disease.

5. Main Hypothesis/Study Questions:
To conduct a comprehensive meta-analysis to definitively address whether *APOL1* RRVs confer risk for CVD, independent of their association with chronic kidney 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 populations. Potential studies to be included include: ARIC, JHS, REGARDS, CHS, SPRINT, Look Ahead, ARIC, AASK, CRIC, REGARDS, CARDIA, and MESA. Analyses will be restricted to African-American study participants aged 18 years or older.

Study Variables at Baseline. Age, sex, genetically defined proportion of African ancestry, systolic and diastolic blood pressure, medication use (ACE inhibitors, Angiotensin II Receptor Blockers, other anti-hypertensive medications, and statins), total and high-density lipoprotein cholesterols, smoking status (Current versus Not), diabetes (defined as fasting glucose ≥ 7.0 mmol/L, non-fasting glucose ≥ 11.0 mmol/L, hemoglobin A1c≥6.5%, use of glucose lowering drugs, or self-reported diabetes), estimated GFR based on the CKD-EPI equation, urine albumin-to-creatinine ratio (UACR), and a history of CVD (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, stroke, or peripheral artery disease).

Cardiovascular Outcomes. We plan to examine prevalent CVD, as well as the incidence of CVD and all-cause mortality. To the extent possible, definitions for incident CVD outcomes will mimic previous analyses from the CKD Prognosis Consortium, for example including the incidence of CVD mortality, coronary heart disease, stroke, and heart failure.[6] We expect that some upfront discussion will be required to in order to harmonize CVD outcome definitions.

Statistical Analyses. The primary analytic approach for prevalent CVD will be logistic regression models including the traditional CVD risk factors described above as covariates. Analyses for incident CVD will analogously be conducted using Cox proportional hazards regression models, excluding individuals with prevalent CVD at baseline. For incident outcomes within clinical trial cohorts, randomized intervention group will also be included as a covariate in analyses under an intent-to-treat approach. Both eGFR and log-transformed UACR will be modeled using linear splines, with knots at 30, 45, 60, 75, 90, 105 ml/min/1.73 m^2 and 10, 30, and 300 mg/g, respectively. The number of knots will be adjusted as necessary, for example in cohorts that exclusively include participants with chronic kidney disease. The primary analysis will consider *APOL1* RRVs parameterized under a recessive model. Summary effect estimates (hazard ratios) will be pooled from each study, weighting by the number of events, using a

random-effects meta-analysis. Sensitivity analyses will include considering the effect of *APOL1* RRVs under an additive genetic model, as well as accounting for the competing risk of non-CVD death using the of approach of Fine and Gray.[7] Missing covariate information will be addressed using multiple imputation techniques.

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)?

MP2003 – Association of APOL1 variants with microvascular and cardiovascular disease in African Americans

(This is mostly looking at microvascular outcomes, so no real overlap. The association between APOL1 and cardiovascular disease and mortality has already been published in PMID: 26966015)

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 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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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.