ARIC Manuscript Proposal # 1673

PC Reviewed: 7/13/10	**Status: <u>A</u>**	**Priority: <u>2</u>**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a.   Full Title: Association between apolipoprotein B and A1 and declining GFR and incident CKD from ARIC visit 4 to the ARIC Carotid MRI visit

  b. Abbreviated Title (Length 26 characters): Apolipoproteins and incident CKD

2.   Writing Group:

Writing group members: O.N. Goek, J. Coresh, Ballantyne C.M., Hoogeveen R.C., A. Kottgen, B.C. Astor, others welcome

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

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3.   Timeline: Analyses to start immediately after approval, completion of analyses and writing of a manuscript projected within 6 months.

4.   Rationale: Chronic kidney disease (CKD) is a growing epidemic in the United States and worldwide.[1-2] For the purpose of risk stratification and early prevention, it would be useful to identify patients at high risk for CKD progression. Currently, there is insufficient knowledge about risk factors for CKD progression.[3] Discovering risk

factors and markers for CKD progression at an early stage will likely be instrumental for targeted preventive efforts against the increasing CKD burden worldwide.

CKD has been associated with significant changes in lipid profile and specifically serum concentrations of apolipoproteins.[4-22] Several studies have highlighted an association between elevated triglycerides or low HDL levels and incident or progressing CKD[18, 23-25]. Few studies, mostly with small sample sizes, have prospectively illuminated the potential relationship between apolipoprotein concentrations and incidence or progression of CKD.[4-9, 17-18, 26-27] Even fewer studies have examined these relationships in non-Caucasian populations, such as African American or Asian populations.[13-16]

In this respect, the ARIC Study cohort is uniquely positioned as a large, prospective observational study including a significant population of African American participants. Furthermore, the availability of apolipoprotein measurements from ARIC visits one, two and four allows one to study potential associations between CKD incidence and progression over very long periods of time. Moreover, the very well characterized ARIC study population, which underwent four examinations between 1987/89 and 1996/98, allows to adjust for repeated measurements of multiple confounding factors.[28] For example, it will be possible to integrate information on cumulative blood pressure measurements and fasting glucose levels.

Irrespective of their design, not all studies showed significant associations between apolipoproteins and CKD incidence or progression after confounding variables were adjusted for.[26, 29-32] Based on most of the prior studies, however, we would expect to observe a significant association between reduced apolipoprotein A1 and elevated apolipoprotein B serum concentrations with increased CKD incidence and a decline in estimated glomerular filtration rate (eGFR).[4-8, 10, 12-22, 26, 30]

5. Main Hypothesis/Study Questions:

Main hypothesis: Serum concentrations of apolipoprotein associate with incident CKD and GFR decline.

Study questions:
1. Is there an association between apolipoprotein A1 and B serum concentrations and incident CKD and GFR decline?
2. Is such an association observed for both increased albuminuria and reduced eGFR as different renal phenotypes, potentially providing insight into the pathophysiologic mechanisms involved?
3. How will such associations be influenced by adjustment for or stratification on other risk factors for kidney disease such as diabetes mellitus and hypertension? For example, will accounting for cumulative blood pressure and fasting glucose measurements impact any potential associations between apolipoproteins and CKD?

4. Will the association of apolipoproteins and renal phenotypes be present in both African American and Caucasian individuals?

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: Prospective: apolipoproteins are measured at ARIC visit 4, incident CKD status and GFR decline will be evaluated at the ARIC Carotid MRI Study visit. Therefore, the study sample will consist of the 2066 selected participants in the ARIC Carotid MRI Study visit, which is a substudy among of the ARIC Cohort.

Inclusions/exclusions: Individuals missing variables needed to calculate eGFR and urine albumin-to-creatinine ratio as a measure of albuminuria will be excluded. Further exclusions will be made for missing apolipoprotein measurements, important covariates (such as hypertension and diabetes), and more specialized exclusions may be made for analyses of different subgroups. For analysis of incident CKD and albuminuria, we will exclude participants with prevalent CKD and albuminuria.

Outcomes:

There will be three primary outcomes:

1. Incident CKD will be defined as eGFR <60 ml/min based on the CKDepi equation at the ARIC Carotid MRI visit and/or any hospitalizations or death events related to CKD between ARIC visit four and the ARIC Carotid MRI visit.[33-34] Secondary definitions may be explored such as incident CKD defined as described previously by this group [33].

2. Decline in GFR will be examined continuously as well as categorized into rapid and slow decline. Rapid GFR decline will be defined as more than 3 ml/min/1.73m^2 per year.[35]

3. Incident microalbuminuria, defined as >25 mg Albumin/g Creatinine in females, >18 mg Albumin/g Creatinine in males, or change in UACR. This will be of interest particularly among individuals with diabetes, as albuminuria could be useful as surrogate marker for early diabetic nephropathy with hyperfiltration and therefore without GFR decline until the later stages. A sensitivity analysis will be conducted defining albuminuria as more than 30 mg/g Creatinine for both sexes to assess the stability of findings.

Other variables of interest: Age, sex, study center, race, CKD risk factors (hypertension and/or blood pressure, diabetes mellitus and/or fasting glucose, obesity, serum total cholesterol, serum LDL and HDL, serum triglycerides, smoking, alcohol use,

socioeconomic status, prevalent coronary heart disease), treatment with ACE inhibitors and ARBs will be considered in analyses of ACR as they reduce albuminuria. Analytical approaches to address this issue include adjustments for intake of these medications, as well as secondary analyses excluding individuals taking these medications. Adjustments for other lipid parameters will include serum total cholesterol, and log transformed triglycerides. Adjustments for specific subclasses of cholesterol, i.e. lipoprotein containing HDL and LDL, will be considered after potential co-linearity with apolipoproteins has been determined. All variables will be used from ARIC visit 4 as baseline as well as the ARIC-MRI visit as follow-up.

Data analysis:

Variables will be transformed to approximate a normal distribution. Previous analyses used natural logarithmic transformations of eGFR and UACR.

Descriptive statistics comparing will be generated using t-tests and chi-squared tests as appropriate and will compare individuals across categories of exposure (such as tertiles or quartiles of the apolipoprotein distributions) and outcome (incident CKD status, rapid GFR decline, incident microalbuminuria).

Linear and logistic regression will be conducted as appropriate to relate the renal phenotypes to apolipoprotein levels. Apolipoprotein concentrations will be examined continuously as well as in tertile or quartiles, depending on their distribution and on previous literature. A linear relationship between apolipoprotein and renal outcomes will be evaluated by the incorporation and testing of spline terms. Interactions will be evaluated for race as well as diabetes and hypertension status by incorporating an interaction term into the regression models. Stratified analyses for these variables will be conducted as secondary analyses. The apolipoprotein B/A1 ratio will also be evaluated as an exposure. Lastly, cumulative measures of (visit 1 to 4) serum cholesterol, triglycerides will be incorporated as covariates as well as cumulative apolipoproteins A1 and B as exposures. These results of the cumulative analyses will be compared to those using cross-sectional measurements from visit 4.

Covariates will be used from ARIC visit 4, when the baseline measurement of renal function measures for these analyses took place. In secondary analyses, we will explore potential differences arising from accounting for cumulative exposures to covariates across ARIC visits 1-4, for example for blood pressure or fasting glucose, instead of accounting for the cross-sectional measurement from ARIC visit 4.

A special question of interest will be if and how accounting for the probability of being selected into the ARIC MRI Study will influence the results. Analyses will be repeated incorporating the weights generated for this purpose by the ARIC Coordinating Center. If differences exist, weights will be incorporated in all analyses or at a minimum, we will adjust for variables which define the sampling strata (age, sex, race and IMT stratum).

All analyses will be conducted using Stata v11 and R.

Limitations: Possibility of survival bias impacting the results, since ARIC-MRI participants were selected among survivors. Only one urine measurement for albumin was done at both visits, which slightly limits its use as surrogate marker for incident CKD stages 1 and 2.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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/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)?

ARIC Manuscript Proposal # 868
Full Title: Lipid-related genetic risk factors for decline in renal function in African-Americans in the ARIC Study

ARIC Manuscript Proposal # 1623
Full Title: Apolipoprotein B, Apolipoprotein A1 and Standard Lipid Measures in the Prediction of Incident Coronary Heart Disease: The Atherosclerosis Risk in

Communities (ARIC) Study

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* 2006.16)
    ___ 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/

12. 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.

References:

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