ARIC Manuscript Proposal # 1830

PC Reviewed: 8/9/11 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Chronic kidney disease, plasma lipids and coronary heart disease

b. Abbreviated Title (Length 26 characters): **CKD, Plasma lipids and CHD**

2. Writing Group:
Writing group members:
Julio A Lamprea-Montealegre
Moyses Szklo
Richey Sharrett
Kunihiro Matsushita
Elizabeth Selvin
Brad Astor

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

F**irst author**: **Julio Lamprea**
2024 E. Monument Street
Suite 1-500 Room K
Phone No.443-287-7772
The Johns Hopkins University
Baltimore, MD 21205
Email: jlamprea@jhsph.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Brad Astor, PhD
2024 E. Monument Street
Suite 2-600
Baltimore, MD 21287
(410) 502-2779
bastor@jhsph.edu

3. Timeline: Analysis to start as soon as approval is obtained. We expect that the manuscript will be completed within 6 months from approval of the proposal.

4. Rationale:

Chronic kidney disease (CKD) affects more than 26 million American adults, representing approximately 13% of the adult US population [1]. In CKD, risk factors for coronary heart disease

(CHD) are highly prevalent, and their relationship with CHD largely parallels that of the general population [2]. However, studies that have assessed the relationship between plasma lipids and CHD in individuals with CKD, have found inverse associations, in which higher total cholesterol and LDL cholesterol levels are associated with a lower risk of CHD events [3-5]. These studies have been limited to severe CKD and end stage renal disease (ESRD). Additionally, these studies used serum creatinine to estimate glomerular filtration rate, which may be biased among CKD patients with malnutrition, which may also affect lipid levels.

CKD is associated with abnormalities in lipid particle distributions and apolipoproteins, including high particle counts for small-dense LDL cholesterol and intermediate LDL cholesterol, low counts for large LDL cholesterol, high levels of apolipoprotein B, and low levels of apolipoprotein A-1 [6,7]. To our knowledge, the associations of apolipproteins A-1 and B with CHD risk across CKD status has not been studied.

We, therefore, propose to investigate the association between plasma lipids, including apolipoproteins A-1 and B, and CHD in individuals with CKD and compare these associations to those of individuals without CKD (eGFRcys> 60ml/min/1.73m^2).

5. Main Hypothesis/Study Questions:

Hypothesis: Compared to individuals without CKD, the association between plasma lipids and CHD among individuals with CKD is attenuated. The strength of the association differs by severity of CKD.

1. Compared to individuals without CKD, how are traditionally measured plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol: Total cholesterol-HDL cholesterol –) and the total cholesterol/HDL cholesterol ratio associated with incident CHD in individuals with CKD?
2. Compared to individuals without CKD, how are apolipoprotein A-I, apolipoprotein B, and apolipoprotein B/AI ratio associated with incident CHD in individuals with CKD?
3. Does the strength of the associations differ by severity of CKD, as assessed by cystatin C-estimated glomerular filtration rate (eGFRcys)?

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).

Using survival analysis, participants without CHD at visit 4 will be followed until the onset of a new CHD event or until the last year of follow up (administrative censoring).

I. Inclusions: Visit 4 ARIC participants without a history of CHD.

II. Exclusions: Missing measurements of cystatin C, urinary albumin, or missing plasma lipid measurements including apolipoproteins, or history of CHD.
III. Analysis plan:

1. Description of the distribution of traditionally measured lipids (total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol and non-HDL-cholesterol), and apolipoproteins, in individuals without CKD and across strata of CKD severity (e.g. eGFRcys: 45-59, <45 mL/min/1.73m^2). A Cystatin-C based equation will be used in order to categorize CKD.
2. Evaluation of the crude and adjusted association of baseline (visit 4) lipids and apolipoproteins with incident CHD comparing individuals without CKD with those with CKD and across different severity categories of CKD (Cox proportional hazards regression models or parametric survival models will be used). Covariates that will be

used for adjustment include age, gender, race, blood pressure, diabetes, BMI, smoking, education level and use of a lipid-lowering therapy.

3. Assessment of whether the associations between lipids and incident CHD differ by CKD category (interaction terms between CKD category and lipid levels will be used).

4. In a sensitivity analysis we will determine whether the results of the analysis change by excluding individuals on lipid lowering medications. Furthermore, alternative definitions for the categorization of CKD will be used. Specifically, as was done recently, we will use different markers for CKD separately (Cystatin-C, serum creatinine, urinary albumin-Creatinine ratio) and in combination[8], and assess whether inferences derived from the main analysis (using a Cystatin-C based formula) change.

5. CHD incidence will be defined using a composite variable including definite or probable myocardial infarction, a definite CHD death, or coronary revascularization. However, separate analyses will be conducted using CHD death, and CHD (definite or probable myocardial infarction) with and without coronary revascularization.

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)?

#1623: Apolipoprotein B, Apolipoprotein A1 and Standard Lipid Measures in the Prediction of Incident Coronary Heart Disease: The Atherosclerosis Risk in Communities (ARIC) Study (First author: Ndmulel)

Association between apolipoprotein B and A1 and declining GFR and incident CKD from ARIC visit 4 to the ARIC Carotid MRI visit(First Author: O. Goek)

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. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

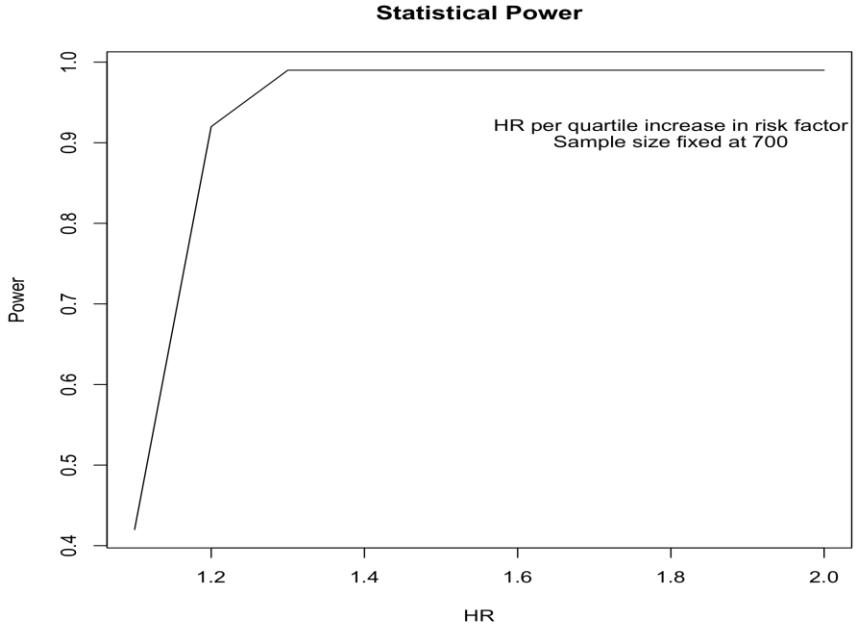
*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

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.

Appendix 1 (Statistical Power)

For a HR of 1.2 in the risk of CHD per quartile increase in plasma lipids with 80% power, we estimate a required sample size of 700 individuals. In ARIC visit 4, 922 individuals had an eGFR of less than 60ml/min/1.73m^2.

The estimation of the statistical power is based on the primary research question: Is the association between plasma lipids and CHD different between individuals with normal kidney function and those with eGFRcys<60/ml/min/m^2. Our study may have a limited statistical power for the comparisons across CKD severity categories (eGFRcys 45-60 and eGFRcys<45).



References

1. Coresh J, Selvin E, Stevens L, Manzi J. Prevalence of chronic kidney disease in the United States. *JAMA* 2007.

2. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108(17):2154-2169.

3. Kovesdy C, Anderson J. Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition- …. *Journal of the American society of Nephrology,* 2007.

4. Chawla V, Greene T, Beck GJ, et al. Hyperlipidemia and long-term outcomes in nondiabetic chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(9):1582-1587.

5. Contreras G, Hu B, Astor BC, et al. Malnutrition-inflammation modifies the relationship of cholesterol with cardiovascular disease. *J. Am. Soc. Nephrol.* 2010;21(12):2131-2142.

6. de Boer I, Astor B, Kramer H. Lipoprotein abnormalities associated with mild impairment of kidney function in the multi-ethnic study of atherosclerosis. *Clinical Journal of the …*. 2008.

7. Muntner P, Hamm LL, Kusek JW, et al. The Prevalence of Nontraditional Risk Factors for Coronary Heart Disease in Patients with Chronic Kidney Disease. *Ann. Intern. Med.* 2004;140(1):9-17.

8. Peralta CA, Shlipack MG, Judd S, et al. Detection of Chronic kidney Disease with Creatinine, Cystatin C, and Urine Albumin-Creatinine ratio and Association with progression to End-Stage renal disease and Mortality. JAMA. 2011;305(15):1545-1552.