ARIC Manuscript Proposal # 3049

PC Reviewed: 10/3/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lipoprotein(a) and family history of myocardial infarction: insights from the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Lipoprotein(a) and family history of myocardial infarction

2. Writing Group: Anurag Mehta, Salim Virani, Christie Ballantyne, Colby Ayers, Parag Joshi, Jarett Berry, Anand Rohatgi, and Amit Khera

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

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3. Timeline: 9/2017 – 12/2017

4. Rationale:

Cardiovascular disease is the leading cause of morbidity and mortality in the United States. (1) Primary prevention of cardiovascular disease is a public health priority and cardiovascular biomarkers are useful tools that enhance a clinician's ability to identify apparently healthy patients at risk for future cardiovascular disease events. (2) Lipoprotein(a) level [Lp(a)] in the blood is one such biomarker associated with major adverse cardiovascular events (MACE) independent of traditional cardiovascular risk factors (TRF). (3, 4) Circulating Lp(a) levels are largely determined by a variety of differences in the LPA gene, including biochemical influences on transcription factors, variations in LPA single nucleotide polymorphisms (SNPs) and the inter- and intra-individual heterogeneity in kringle IV type 2 (KIV-2) repeats. (5) Two large Mendelian randomization studies support the causal relationship between genetically elevated levels of Lp(a) and the risk of MACE. (6, 7) Family history of Myocardial Infarction (FHMI) by itself is also an independent risk factor for developing MACE in the general population. (8) Despite a strong genetic basis that determine Lp(a) concentration in the blood, there is a paucity of literature regarding the association between Lp(a) levels and family history of myocardial infarction(FHMI). Additionally, the interaction between these two non-traditional cardiovascular risk factors (non-TRF) for predicting incident MACE in a multi-ethnic cohort free of cardiovascular disease has not been evaluated. In the proposed project, we wish to explore the independent and joint associations between Lp(a) and FHMI for predicting MACE among participants enrolled in the ARIC Study.

References:

1. Writing Group M, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):e38-360.
2. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation.* 2006;113(19):2335-2362.
3. Emerging Risk Factors C, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA.* 2009;302(4):412-423.
4. Willeit P, Kiechl S, Kronenberg F, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. *J Am Coll Cardiol.* 2014;64(9):851-860.
5. Lee SR, Prasad A, Choi YS, et al. The LPA Gene, Ethnicity, and Cardiovascular Events. *Circulation.* 2016.
6. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA.* 2009;301(22):2331-2339.
7. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med.* 2009;361(26):2518-2528.
8. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA.* 2004;291(18):2204-2211.

5. Main Hypothesis/Study Questions:

Lipoprotein(a) levels and family history of myocardial infarction are both predictors of incident MACE, but interact with each other in a manner that Black and White ARIC participants with high Lp(a) and FHMI have the highest incidence of MACE.

1. To establish the relationship between race-specific Lp(a) levels and FHMI in the ARIC study
2. To investigate the independent association between race-specific Lp(a) levels and FHMI with incident MACE.
3. To investigate the joint association and interaction between race-specific Lp(a) levels and FHMI for incident MACE.

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 cohort study

Inclusion criteria:
Participants of the ARIC Study with information available for lipoprotein(a) concentration in mg/dl, family history of myocardial infarction (any family history – defined as the presence of history of a heart attack in parents which was assessed by means of interviewer-administered, standardized questionnaires during ARIC study visit; and premature family history of myocardial infarction – defined as a parent who had a heart attack occurring in a father before the age of 55 years or in a mother before the age of 60 years), 10-year ASCVD risk estimator variables (age, gender, race, diabetes, systolic blood pressure, antihypertensive use, smoking, total cholesterol, high density lipoprotein-cholesterol) as well as diastolic blood pressure, body mass index, statin use, non-HDL cholesterol, low density lipoprotein-cholesterol, and triglycerides will be included. The data from baseline ARIC examination will be used.

Exclusion criteria:
Participants who have a history of cardiovascular disease at ARIC visit 1 (MI, stroke, heart failure, or atrial fibrillation) or renal failure at baseline will be excluded.

Outcomes:
The study participants will be assessed for MACE outcomes at the time of latest ARIC follow up: incident CHD events (myocardial infarction, silent infarction identified by ECG, coronary artery bypass surgery, and coronary angioplasty), CHD death (death lacking a probable non-CHD cause and with a recent myocardial infarction, chest pain within 72 hours of death, or a history of CHD), heart failure hospitalization (defined by International Statistical Classification of Diseases and Related Health Problems codes of 428. x [9th Revision] or I50 [10th Revision] in any position on the hospital discharge list or on a death certificate with death from heart failure in any position), and stroke.

Data analysis:
The distribution of Lp(a) levels among participants of the ARIC cohort will be described using median (interquartile range) and mean (SD) levels. We will use standardized values of Lp(a) from ARIC visit 1 during our analyses. These standardized values were obtained by using a conversion equation derived from a comparison between samples measured using the double-antibody enzyme-linked immunosorbent assay technique (used in ARIC visit 1) and a commercially available automated immunoturbidimetric assay (Denka Seiken Co. Ltd., Tokyo, Japan; used in ARIC visit 4). Given marked racial variation in Lp(a) levels, with Blacks having higher levels than Whites, race-specific Lp(a) concentrations will be evaluated.

The baseline characteristics of participants with and without family history of MI will be compared. The characteristics will include: median age, gender proportion, race proportion, proportion with diabetes, median systolic blood pressure, proportion with antihypertensive use,

proportion with smoking, median total cholesterol, median HDL-C, median diastolic blood pressure, median BMI, proportion with statin use, median non-HDL cholesterol, median LDL-C, median triglycerides, median race-specific Lp(a) concentration, and proportion of participants with Lp(a) >30 mg/dl.

A. The cumulative incidence curves of MACE for Lp(a) greater and lesser than 30 mg/dl in Black and White participants, with and without a family history of MI, will be constructed. These curves will be compared by using the log rank test. Similar cumulative incidence curves for race-specific quintiles of Lp(a) concentration in participants with and without a family history of MI will be constructed and compared using the log rank test.

B. Race-specific univariate and multivariate-adjusted Cox proportional hazards models will be used to assess the association between Lp(a) levels and incident MACE. Univariate models will use Lp(a) in different ways: as greater or less than 30 mg/dl, race-specific log Lp(a) concentration (per 1-unit SD), and race-specific Lp(a) concentration quintiles. The race-specific univariate models will be stratified by those with and without FHMI. The race-specific multivariate models will use Lp(a) in the above three ways and adjust for age, gender, race, diabetes, SBP, antihypertensive use, smoking, total cholesterol, HDL, BMI, statin use, and triglycerides. Multivariate models will be stratified by those with and without FHMI. The interaction between FHMI and Lp(a) will be evaluated by using the multiplicative variable in the fully adjusted Cox model.

Analyses A and B will be repeated after stratifying participants by history of premature FHMI.

Sensitivity analysis: During ARIC visit 4, Lp(a) levels were measured using a commercially available automated immunoturbidimetric assay (Denka Seiken Co. Ltd., Tokyo, Japan). This assay is less sensitive to isoform sizes as compared to the double-antibody enzyme-linked immunosorbent assay used in ARIC visit 1. We plan to use the standardized values of Lp(a) from ARIC visit 1 during our analyses. These values will be obtained from the conversion equation described above. In order to account for the potential differences in association with MACE that arise by using standardized Lp(a) values at ARIC visit 1, we will repeat analyses A and B in the study population after participants that developed MACE between ARIC visits 1 and 4 are further excluded.

All statistical analyses will be performed using SAS.

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/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)?

1. Association between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study.
2. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study.

We are including Dr. Virani and Dr. Ballantyne in our present project

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*_Carotid MRI Study)

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, 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.