ARIC Manuscript Proposal # 1610

PC Reviewed: 2/9/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations between lipoprotein(a) levels and cardiovascular outcomes in African Americans: The Atherosclerosis Risk In Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Lp(a) levels and cardiovascular events in African Americans.

2. Writing Group:
Writing group members: Christie M. Ballantyne MD, Vijay Nambi MD, Salim S. Virani MD, Ariel Brautbar MD, Ron C. Hoogeveen PhD, Eric Boerwinkle PhD, Gerardo Heiss MD Ph D, A. Richey Sharrett MD DrPH, Josef Coresh MD PhD, Thomas H. Mosley MD, Joel D Morrisett PhD, Aaron R Folsom MD, Diane J. Catellier DrPH. Others are welcome

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

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3. Timeline: We plan to analyze the data as soon as approval is obtained. Manuscript will be prepared as soon as analysis is done. We plan to do the analysis, as well as prepare the manuscript for submission within 1 year.

4. Rationale:
Elevated levels of lipoprotein(a) [Lp(a)] have been shown to be associated with an increased risk of coronary heart disease (CHD) and stroke in the ARIC study [Sharrett

AR, Circulation 2001:104:1108-113; Ohira T, Stroke 2006;37:1407-1412] and other studies [Kamstrup PR, JAMA. 2009; 301:2331-39]. In most of these studies, the outcomes with elevated levels of Lp(a) have been studied in Caucasians though the ARIC studies did evaluate outcomes in both Caucasians and African Americans. In the ARIC study [Sharrett AR, Circulation 2001:104:1108-113], though the coefficients for a 1-SD higher Lp(a) levels for incident CHD were significant for Caucasian men and Caucasian women, they were not significant for either African American men or women despite these 2 groups having much higher levels of Lp(a) compared to their Caucasian counterparts. One of the reasons postulated to explain this was that the overall number of CHD events were low in African Americans (out of a total of 725 CHD events, 90 CHD events occurred in African American men and 68 occurred in African American women). Similarly, another manuscript from the ARIC cohort [Ohira T, Stroke 2006;37:1407-1412] showed that although Lp(a) levels were predictive of ischemic strokes in African American women [RR 1.84, 95% CI 1.05-3.07], the results did not reach statistical significance in African American men [RR 1.72, 95% CI 0.86-3.48]. Ascertainment of CHD event and ischemic strokes in the ARIC cohort since these initial publications provides the opportunity to now study the associations between elevated levels of Lp(a) and cardiovascular events in the African American participants of the ARIC cohort with greater statistical power. Since levels of Lp(a) are mostly genetically determined, it could also be argued that elevated levels of Lp(a) may lead to earlier CHD and stroke events. Prior analyses have used prevalent CHD or stroke as an exclusion criteria and this may have also contribute to an apparent lack of association.

Therefore, we propose to study the associations between levels of Lp(a) and cardiovascular disease (CVD) events in the African American participants of the ARIC cohort, and to compare the strength of this association to their Caucasian counterparts.

5. Main Hypothesis/Study Questions:

1. Is Lp(a) an independent predictor of incident CVD events* in African Americans.
2. Does the strength of association between CVD and Lp(a) levels vary between African Americans and Caucasian participants in the ARIC study.

* Incident CVD events will include will include incident CHD and incident ischemic strokes. .

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).

We will request that the analyses be done by the co-ordinating center

Data from ARIC visit 1 will be used for analysis. This includes baseline characteristics of the cohort as well as Lp (a) levels. Lp (a) mass in the ARIC study was measured at visit 1 using a double antibody ELISA technique for *LPA* detection. Lp(a) level was measured

as the total protein component [apolipoprotein (a) + apolipoprotein B]. The protein moiety represented approximately one-third of the total Lp(a) lipoprotein mass. Therefore, an Lp(a) protein value of 10 mg/dL is comparable to a total Lp(a) value of 30 mg/dL. The assay reliability (between-person component of the variance divided by the total variance) was 0.90 [Chambless LE, Am J Epidemiol, 1992;136:1069-1081], with essentially no within-person variability (indicative of a largely genetic predisposition), in a small sample of individuals.

Analyses will be performed in the following order:

1. Participants from ARIC visit 1 will be included in the analyses.
2. All subjects with history or prevalent CVD (prevalent CHD and prevalent ischemic strokes) or on lipid lowering therapy (statins, Niacin, and/or other lipid lowering medications) at visit 1 will be excluded from the analysis.
3. We will describe mean levels of Lp(a) in those with or without any incident CVD event for each of the following groups (a) African American men (b) African American women (c) Caucasian men (d) Caucasian women.
4. Using traditional risk factors from visit 1 data, we will describe predictors of incident CVD in Caucasians and African Americans using Cox proportional hazards model. Relative risk associated with 1 SD increase in Lp(a) in unadjusted models followed by each of the following adjustment models will be calculated. Adjustment models will be as follows:
   Model 1: age, gender.
   Model 2: age, gender, current smoking, systolic blood pressure, use of antihypertensives, diabetes.
   Model 3: Model 2 plus LDL-C, HDL-C, triglycerides.
5. Step 4 will give us relative risk of CVD associated with a 1 SD increase in Lp(a) in Caucasians and African Americans. It is known that a 1 SD change in Lp(a) is much larger in African Americans compared to Caucasians and therefore, the increase in RR per 1 SD increase in Lp(a) for CVD events between African Americans and Caucasians may not be comparable. To circumvent this, we will describe a figure with RR for incident CVD on the y axis and absolute Lp(a) levels in 20 mg/dl increments on the x axis for both African Americans and Caucasians. Please note that this step will only be done if results are positive in step 4. Similarly, separate analyses will be performed for both incident CHD and incident ischemic strokes.

If the number of incident CVD events is low leading to a decrease in power, then we will perform <u>secondary analyses</u> using both incident and prevalent CVD cases to increase power. For these analyses, logistic regression rather than Cox regression will be used using covariates as described above in #4.

LIMITATIONS ANTICIPATED: We have opted to combine both incident and prevalent CVD for secondary analyses to increase power. Since Lp(a) levels are mostly genetically determined, higher levels of Lp(a) may lead to earlier CVD events and this

information is likely important. On the other hand, the method for ascertainment of CVD was likely different for prevalent CVD versus incident CVD events and these two populations therefore might be heterogeneous. For this reason, we propose initially doing analyses for incident CVD events and will perform analyses using both prevalent and incident CVD events only if the number of incident events is low. In this case, we will also determine whether those ARIC participants who had an event between visit 1 and 2 had any systematic rise or fall in the Lp(a) levels. This last step should give us a good idea if the levels of Lp(a) change after a CVD event. This in turn would be important to determine the validity of analyses combining both prevalent and incident CVD cases. In addition, the assay used in the ARIC study uses an antibody towards the kringle IV type 2 domain which is sensitive to the isoform size. Dr. Marcovina and colleagues have developed an assay for Lp(a) using a monoclonal antibody that targets a unique epitope in the apo(a) kringle IV type 9 that does not repeat. This serves as another limitation of the current analyses and will be discussed in the final manuscript. It is important to note that most of the assays used in current clinical practice also use antibodies against the kringle IV type 2 domain and therefore, are sensitive to the Apo(a) isoform size. Future ARIC proposals utilizing the Marcovina assay will likely answer the question whether the older assays or the newer Marcovina assay provide better risk stratification for CHD.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __×__ 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 _×___ 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

____×__ 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. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W; Atherosclerosis Risk in Communities Study Group. 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. Circulation. 2001 Sep 4;104(10):1108-13.

2. Ohira T, Schreiner PJ, Morrisett JD, Chambless LE, Rosamond WD, Folsom AR. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2006 Jun;37(6):1407-12.

3. Brautbar A, et al. Single nucleotide polymorphisms in the *LPA* gene, lipoprotein a levels, and cardiovascular events in 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? ____ Yes ___×_ 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/

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.