ARIC Manuscript Proposal # 1608

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

1.a. Full Title: Single nucleotide polymorphisms in the *LPA* gene region, lipoprotein a levels, and cardiovascular events in The Atherosclerosis Risk In Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters)*:* *LPA* SNPs and CVD events.

2. Writing Group:
Writing group members: Christie M. Ballantyne MD, Salim S. Virani Vijay Nambi MD, MD, Ariel Brautbar MD, Ron C. Hoogeveen PhD, Eric Boerwinkle PhD, Gerardo Heiss MD Ph D, Josef Coresh MD PhD, Thomas H. Mosley MD, Joel D Morrisett PhD, Aaron R Folsom MD.

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

Ariel Brautbar MD
Address: Ariel Brautbar, Baylor College of Medicine 6565 Fannin, M.S. A656,

Houston, TX 77030
Phone: 713-798-5321 Fax: 713-798-3057
E-mail: brautbar@bcm.tmc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Christie M. Ballantyne, MD
Christie Ballantyne
Address: Baylor College of Medicine, 6565 Fannin, M.S. A656, Houston, TX 77030
Phone: 713-798-5034 Fax: 713-798-3057
E-mail: cmb@bcm.tmc.edu

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:

Recent publications demonstrated new associations between single nucleotide polymorphisms (SNP's) in the *LPA* gene, Lp(a) levels, coronary heart disease(CHD) and stroke. It is well established that Lp(a) levels are associated with CHD events [Sharrett AC, Circulation 2001:104:1108-113]. However, the extent of influence of *LPA* gene SNP's on Lp(a) levels in whites, and indirectly on CHD , has been emphasized in recent publications [Clark R, N Engl J Med; 126:2518-28; Shiffman D, PLoSONE 2008; Shiffman D Arterioscler Thromb Vasc Biol. 2008 Jan;28(1):173-9.]. In one of the largest studies conducted by Clark et al, several SNP's were shown to be associated with CHD with variable degrees of odds ratios, most of which were associated as well with Lp(a) levels. In particular, two SNP's (rs3798220 and rs10455872) had the strongest association with CHD, (odds ratio 1.92 and 1.7 respectively) and were associated Lp(a) levels as well. The association of these two SNP's with CHD was canceled by adjustment for Lp(a) levels suggesting the association to CHD was via Lp(a) levels. One of the limitations of the above studies was that these analyses were done in white subjects only which limit their generalizability to other ethnic groups. We propose to examine the associations between SNP's in the *LPA* region, Lp(a) levels, and Cardiovascular events (CVD) in African Americans. We will further examine these associations in ARIC whites and compare our results to associations identified in African Americans in emphasis on SNP frequency and association with CVD events. We propose to conduct this study in ARIC by means of Mendelian randomization approach.

5. Main Hypothesis/Study Questions:

1. Which SNPs in the *LPA* gene region are associated with CHD and stroke events in African American and whites in ARIC ?
2. Which SNPs in the *LPA* gene region are associated with Lp(a) levels in African American and whites in ARIC.
3. Are the associations observed in 1 persist after adjusting for traditional risk factors ands Lp(a) levels. .
4. Does the presence of risk allele (single or multiple) identified in 1 predict incident CVD events in African Americans and whites in the ARIC study

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 use Lp(a) levels as measured in ARIC first visit and genotype data available from Affymetrix 6.0 chip. Lp (a) in ARIC 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. 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].

The below analysis 1-8 will be preformed separately for African Americans and whites in ARIC. Because of reported differences between the association of Lp(a) levels and CHD for men and women[Sharrett AC, Circulation 2001:104:1108-113], analysis 1-8 will be preformed for men and women combined (for increased sample size) and then separately(for each ethnicity examined).

1. Subjects in ARIC visit 1 that have *LPA* genotype data and CHD follow up data will be included in the analyses.
2. Analysis of *LPA* genotypes (for the different SNP's) and baseline characteristics will be preformed to demonstrate no associations.
3. Frequencies of all SNP's in the *LPA* (available from affi 6.0 data) region ±10kb will be determined.
4. Testing for association of SNP's in *LPA* with prevalent CHD, prevalent stroke and prevalent stroke plus CHD, will be preformed separately.
5. Testing for association of SNP's in *LPA* with Lp(a) levels will be preformed.
6. Using traditional risk factors (age, sex, smoking, LDL-C, HDL-C, diabetes, hypertension, hypertension medication, triglicerides) we will describe predictors of incident CHD/stroke using Cox proportional hazards model. We will repeat Cox proportional hazard model calculation with the addition of associated SNP's (identified in 4) to predict risk.
7. Haplotype analysis will be preformed for SNP's in *LPA* associated with either Lp(a) levels and/or CHD events/stroke events.
8. Based on the analysis results the most significant SNP's associated with Lp(a) levels will be combined in an additive model to examine association with CHD and or stroke.

LIMITATIONS: Sample size may limit the ability to identify significant associations especially for the separate analysis of African American men and women. In that regard analysis of prevalent CVD events may be helpful in increasing available sample size. Other then sample size, SNP frequency, and available follow up period may also limit the ability to identify significant associations.

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. Virani et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in African Americans: 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.