ARIC Manuscript Proposal #2555

PC Reviewed: 5/12/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lipoprotein(a) and incident heart failure hospitalization: ARIC study
b. Abbreviated Title (Length 26 characters): Lp(a) and heart failure

2. Writing Group:
Anandita Agarwala, MD
Yashashwi Pokharel, MD, MSCR
Wensheng Sun, MPH
Salim Virani, MD
Chiadi Ndumele, MD, MHS
Eyal Shahar, MD, MPH
Gerardo Heiss, MD, MSc, PhD
Eric Boerwinkle, PhD
Suma Konety, MD
Ron Hoogeveen, PhD
Christie Ballantyne, MD
Additional interested authors to be added.

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

First author: Anandita Agarwala
Address: Baylor College of Medicine
6565 Fannin Street
MS A601/ STE B160
Houston, TX 77030
Phone: 713-798-5800 Fax: 713-798-7885
E-mail: anandita.kulkarni@bcm.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Christie Ballantyne
Address: Baylor College of Medicine
6565 Fannin Street
MS A601/ STE B160
Houston, TX 77030
Phone: 713-798-7545 Fax: 713-798-7885
E-mail: cmb@bcm.edu

3. Timeline: Analysis will start as soon as approval is obtained. Manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. Rationale:

Heart failure affects roughly 5.7 million Americans and the total cost of treatment in 2012 was estimated to be $30.7 billion[1]. The clinical burden of heart failure necessitates additional methods of prevention. Lipoprotein (a) [Lp(a)] is a structurally heterogeneous proatherogenic lipoprotein composed of an LDL-like moiety to which a unique glycoprotein, apolipoprotein (a) [apo(a)], is covalently linked to a single molecule of apolipoprotein B-100 (apoB-100). Apo(a) also contains a variable number of kringle repeats that affects characteristics such as isoform size, plasma levels, and synthetic rate[2, 3]. Elevated plasma levels of Lp(a) are a significant risk factor for atherosclerotic cardiovascular disease[4-9]. Plasma levels of Lp(a) vary widely among individuals and recent studies have shown that common genetic variants in the *LPA* gene such as rs10455872 and rs3798220 are associated with elevated levels of Lp(a) and with an increased risk of coronary artery disease that is independent of traditional risk factors[10]. Given its proatherogenic properties, Lp(a) may be a risk factor for heart failure that is predominantly ischemic in origin. The association between Lp(a) levels and heart failure, however, has yet to be elucidated. In this study, we plan to examine the association of Lp(a) levels with incident heart failure hospitalization in the ARIC study. We hypothesize that higher levels of Lp(a) and genetic variants associated with increased Lp(a) levels will be associated with greater risk for incident heart failure hospitalization.

5. Main Hypothesis/Study Questions:

We hypothesize that higher levels of Lp(a) and genetic variants associated with increased Lp(a) levels will be associated with greater risk for incident heart failure hospitalization.

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).

In the primary analysis, data on Lp(a) from ARIC visit 4 will be used. Lp(a) will serve as the exposure variable and incident heart failure hospitalization will be the outcome. Covariates will include age, gender, race, body mass index (BMI), current smoking, diabetes, total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C), and hypertension.
The association between Lp(a) data from ARIC visit 1 and incident heart failure hospitalization will be determined as a secondary analysis as the Lp(a) data from ARIC visit 4 assay, which is not influenced by the number of kringle repeats.

Finally, we will assess whether Lp(a) levels and high risk genotypes of *LPA*, rs3798220 and rs10455872, are associated with increased risk for incident heart failure hospitalization.

Inclusion/ exclusion criteria:

All eligible ARIC participants will be included in the study. The major exclusion criteria include a preexisting diagnosis of heart failure (prior to visit 1 and visit 4, respectively for each analysis), participants without data on exposure, outcome, or covariates. We will also exclude race other than African American or white and African American participants from Minnesota and Washington field centers. Participants with a diagnosis of CHD will be included.

Analysis:

The following analyses will be conducted:

1. Lp(a) values from visits 1 and 4 will be divided into appropriate quintiles based on Lp(a) levels in each visit respectively. The association of Lp(a) with incident heart failure hospitalization will be assessed by quintiles. We will also examine the association of incident heart failure hospitalization per 1 standard deviation increase in Lp(a) levels separately using visits 1 and 4. Cox proportional hazard regression models will be developed. Model 1 will adjust for age, gender, and race. Model 2 will adjust for covariates in model 1 as well as systolic blood pressure, history of hypertension, diabetes, current smoking status, body mass index, and heart rate. Model 3 will adjust for variables in model 2 plus HDL-C and non HDL-C (to examine if the association of Lp(a) with heart failure hospitalization holds after adjusting for traditional lipids). Model 4 will adjust for covariates in model 3 as well as prevalent CHD at visit 4 and incident CHD after visit 4 to assess if there will be attenuation of the association of Lp(a) levels with heart failure hospitalization. We will assess for possible interactions of Lp(a) on incident heart failure by race, gender, and diabetes. If significant interactions are noted, a subgroup analysis will be performed.
2. In the sensitivity analyses, we will identify the top and bottom 5% of the extremes of Lp(a) from each visit (1 and 4) respectively. The association with incident heart failure hospitalization will be compared between the top and bottom 5% of Lp(a) values using similar adjustment models.
3. The association between the presence of high risk genotypes of *LPA*, rs3798220 and rs10455872, and incident heart failure hospitalization will be assessed using similar models as described above.

Methodological limitations or challenges

1. Two different assays were used to measure Lp(a) levels in visits 1 and 4. For the visit 1 Lp(a) assay, we will correct for the units as was performed in the previously published paper from the ARIC study[4].
2. The definition of heart failure is based on ICD codes only.

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

_____ Yes __x__ 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)?

Nambi V, Liu X, Chambless LE, et al. Troponin t and n-terminal pro-b-type natriuretic peptide: A biomarker approach to predict heart failure risk--the atherosclerosis risk in communities study. *Clinical chemistry*.

Agarwal SK, Chambless LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: The atherosclerosis risk in communities (aric) study. *Circulation. Heart failure*. 2012;5:422-429

Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, Coresh J, Mosley TH, Morrisett JD, Catellier DJ, Folsom AR, Boerwinkle E, Ballantyne CM. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: The atherosclerosis risk in communities (aric) study. *Circulation*. 2012;125:241-249

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* _____)

___ 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.

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