ARIC Manuscript Proposal #3779

PC Reviewed: 2/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lipoprotein a (Lp(a)) and Coronary Artery Calcium: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Lp(a) and CAC

2. Writing Group:

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

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3. Timeline: Since this analysis will use existing ARIC data, analyses and manuscript preparation will be completed over the next 1 year.

4. Rationale:

Lipoprotein a(Lp(a)) is a plasma lipoprotein that has been established as a potent risk factor for cardiovascular events and mortality.[1–3] Elevated Lp(a) levels have been independently associated with increased atherosclerotic cardiovascular disease (ASCVD) risk, even among individuals on statin therapy and among those with low density lipoprotein (LDL) cholesterol <70 mg/dl.[1,4] The mechanisms via which Lp(a) mediates its effects are, however, largely unknown.[1] Lp(a) has a unique structure which comprises apoB-100, an LDL-like moiety that is thought to mediate atherosclerosis, and an apo(a) moiety, similar to plasminogen, and thought to mediate thrombosis.[3,5] It is unclear if the pathogenicity of Lp(a) and its mediation of ASCVD events occurs via inflammatory, atherogenic or thrombotic mechanisms, or a combination of all three.[1,3,5,6]

The LPA gene that encodes Lp(a) has been identified as one of the strongest indicators for cardiovascular disease, holding promise for potential therapies targeted at lowering Lp(a) levels for the reduction of cardiovascular disease.[6] Several guidelines including the U.S. National Lipid Association and the European Society of Cardiology guidelines currently recommend one time Lp(a) measurement in individuals with intermediate or high ASCVD risk, premature cardiovascular disease and a high chance of exhibiting very high inherited levels of Lp(a).[7,8]

There is, however, currently no uniform method of measuring and reporting Lp(a) values, and so there is no uniform cut-off value above which risk of ASCVD is conferred.[1,6] Nonetheless, one unifying fact through the literature is that higher levels of Lp(a) is associated with higher ASCVD risk,[6] and in the United States, the National Lipid Association has postulated that Lp(a) values ≥50mg/dl is associated with increased risk of ASCVD.[8] Interestingly, Blacks have been shown to have higher Lp(a) levels than Caucasians, and Lp(a) cut-off values for the prediction of ASCVD risk has been demonstrated to be race dependent.[3,6,9,10]

Coronary Artery Calcium (CAC) is an indicator of overall atherosclerotic burden that has been extensively validated for cardiovascular disease risk prediction.[11,12] Unlike other measures of atherosclerosis which are based on population estimates, CAC gives an individualized assessment of atherosclerosis, and is widely used to assess subclinical atherosclerosis among individuals with intermediate cardiovascular disease risk.[11,12]

Studies have examined the relationship between CAC and lipoproteins including high density lipoprotein and LDL, however, few have examined the relationship between CAC and Lp(a).[13–15] The relationship between Lp(a) and CAC is thus, still rather unclear, although it appears to be dependent on race,[16–18] sex,[13,14] and certain comorbidities including diabetes and dyslipidemia.[14,19] Additionally, Lp(a) has been causally linked to some extra-coronary calcification including aortic valve calcification(AVC), which is also thought to be race dependent.[20–22] More research in this field is required to further understand the mechanism via which Lp(a) exerts its effect on the cardiovascular system.

Although Lp(a) has gained increased popularity over the last several years and is recommended by some for inclusion in management guidelines,[3] more information concerning its utility in cardiovascular disease risk assessment is required. Thus, we propose to use the Atherosclerosis Risk in Communities (ARIC) study to evaluate the relationship between Lp(a) in middle age and the presence of CAC in older age. We also plan to use the ARIC dataset to assess the association

between Lp(a) and measures of extra-coronary calcification including AVC and Thoracic Aortic calcification(TAC).

5. Main Hypothesis/Study Questions:

Hypotheses:

- Lipoprotein a(Lp(a)) at middle age is independently associated with coronary artery calcium in older age
- Lp(a) in middle age will also be associated with other measures of extra-coronary calcification (TAC and AVC) in older age.

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: This will be a prospective cohort study examining the association between Lp(a) measurements at visit 4 and CAC score at visit 7

Inclusion criteria: All participants with Lp(a) measurements at visit 4 and CAC measurements at visit 7

Exclusion criteria:

- Individuals who do not have information on Lp(a) values or CAC score
- Individuals with prevalent coronary heart disease at visit 7 (by design of the ARIC CAC ancillary study)
- Individuals with missing covariates of interest

Exposure: Lp(a) at visit 4

Outcome:

- CAC score at visit 7
    - Secondary outcomes: Aortic valve calcification, Thoracic Aortic Calcium

Other variables of interest(Visit 4):

- Cardiometabolic risk factors:
    - Body mass index (BMI)
    - History of hypertension or medication use for hypertension or elevated systolic/diastolic blood pressure (>150/90mmHg)
    - Diabetes, defined as HbA1C≥ 6.5%, fasting glucose level ≥126 mg/dL, non-fasting glucose level ≥200 mg/dL (≥11.1 mmol/L), self-reported physician diagnosis, or use of antidiabetic medications.
    - Laboratory values: Triglycerides, High density lipoprotein cholesterol, Total cholesterol, Lipid lowering medication
- Additional potential confounders: Age, Sex, Race, Family history of coronary heart disease, Income, Smoking history

Data analysis plan:

- Lp(a) will be assessed as a dichotomized variable (normal/elevated) around the clinical cut-off point of 50mg/dl.
- CAC will be dichotomized into (minimal-mild/moderate-extensive) based on the clinically actionable cut-off point of 100.
- Baseline characteristics will be summarized by Lp(a) category. Means and proportions will be reported for continuous and categorical values respectively. Differences between continuous variables will be tested using two sample t-test and differences between categorical values will be tested using χ^2 statistic.
- The association between Lp(a) and CAC will be assessed using logistic regression models with incremental adjustment for confounders as outlined below:
    - Model 1: Crude
    - Model 2: Adjusted for age, sex, race
    - Model 3: Model 2+ all listed potential confounders above
    - Model 4: Model 3+ cardiometabolic factors (excluding lipid lowering medication)
    - Model 5: Model 4 + lipid lowering medication

  *Lipid lowering medication is included separately to explore its importance in modifying lipid parameters and to account for its possible difficult interpretation.
- Interactions between Lp(a) and race, sex and family history of coronary heart disease will be tested, and stratified analyses will be conducted if significant.
- The association between Lp(a) and the secondary outcomes of AVC and TAC will also be explored using the same models outlined above.
- To assess the incremental value of Lp(a) over risk factors for predicting CAC,
    - A base model will be constructed including all the risk factors and confounders listed above (Model 1*)
    - Lp(a) will then be added to Model 1*
    - The area under receiver operating characteristic curves (AUC) for both models will then be compared
- For sensitivity analyses,
    - CAC will be assessed as a continuous variable (log(CAC+1)) and as categories of 0, 1-99, 100-299, 300-1000, and >1000
    - Lp(a) will also be assessed as a continuous log transformed variable and as quartiles or as a categorical variable with thresholds of <=10, 11-20,21-30,31-50 and >50mg/dl, as power allows.
    - Linear and ordinal logistic regressions will be used to evaluate the relationship between Lp(a) and CAC modeled as continuous and categorical variables as outlined above

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No

(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___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)?
Although there are several proposals exploring Lp(a) and CVD outcomes (a few examples listed below), there are no proposals for Lp(a) and CAC.

Proposal # 1827: Relation of Lipoprotein (a) and small dense LDL (sdLDL) to incident CVD: the ARIC study

Proposal # 160: Lipoprotein[a] as a risk factor for incident coronary heart disease

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
___ A. primarily the result of an ancillary study (list number* 2016.06)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

References

1. Wu MF, Xu KZ, Guo YG, Yu J, Wu Y, Lin LM. Lipoprotein(a) and Atherosclerotic Cardiovascular Disease: Current Understanding and Future Perspectives. *Cardiovasc Drugs Ther*. 2019. doi:10.1007/s10557-019-06906-9
2. 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. doi:10.1016/j.jacc.2014.03.061
3. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: Current status. *Eur Heart J*. 2010. doi:10.1093/eurheartj/ehq386
4. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and b, and lipoprotein(a) to cardiovascular outcomes: The aim-high trial (atherothrombosis intervention in metabolic syndrome with low HDL/high triglyceride and impact on global health outcomes). *J Am Coll Cardiol*. 2013;62(17):1575-1579. doi:10.1016/j.jacc.2013.06.051
5. Boffa MB, Koschinsky ML. Thematic review series: Lipoprotein (a): Coming of age at last: Lipoprotein (a): Truly a direct prothrombotic factor in cardiovascular disease? *J Lipid Res*. 2016. doi:10.1194/jlr.R060582
6. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol*. 2017. doi:10.1016/j.jacc.2016.11.042
7. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
8. Wilson DP, Jacobson TA, Jones PH, et al. Scientific Statement Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*. 2019;13:374-392. doi:10.1016/j.jacl.2019.04.010
9. Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: The Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2012. doi:10.1161/CIRCULATIONAHA.111.045120
10. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: The multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015. doi:10.1161/ATVBAHA.114.304785
11. Hecht HS, Cronin P, Blaha MJ, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Cardiovasc Comput Tomogr*. 2017;11(1):74-84. doi:10.1016/j.jcct.2016.11.003
12. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *J Am Coll Cardiol*. 2019.

doi:10.1016/j.jacc.2019.03.010
13. Erbel R, Lehmann N, Churzidse S, et al. Gender-specific association of coronary artery calcium and lipoprotein parameters: The Heinz Nixdorf Recall Study. *Atherosclerosis*. 2013. doi:10.1016/j.atherosclerosis.2013.04.015
14. Qasim AN, Martin SS, Mehta NN, et al. Lipoprotein(a) is strongly associated with coronary artery calcification in type-2 diabetic women. *Int J Cardiol*. 2011. doi:10.1016/j.ijcard.2010.02.021
15. Martin SS, Qasim AN, Wolfe M, et al. Comparison of high-density lipoprotein cholesterol to apolipoprotein A-I and A-II to predict coronary calcium and the effect of insulin resistance. *Am J Cardiol*. 2011. doi:10.1016/j.amjcard.2010.09.033
16. Huffman MD, Kandula NR, Baldridge AS, Tsai MY, Prabhakaran D, Kanaya AM. Evaluating the Potential Association Between Lipoprotein(a) and Atherosclerosis (from the Mediators of Atherosclerosis Among South Asians Living in America Cohort). *Am J Cardiol*. 2019. doi:10.1016/j.amjcard.2018.12.013
17. Guerra R, Yu Z, Marcovina S, Peshock R, Cohen JC, Hobbs HH. Lipoprotein(a) and apolipoprotein(a) isoforms: No association with coronary artery calcification in the Dallas heart study. *Circulation*. 2005. doi:10.1161/01.CIR.0000159263.50305.BD
18. Sharma A, Kasim M, Joshi PH, et al. Abnormal lipoprotein(a) levels predict coronary artery calcification in southeast asians but not in caucasians: Use of noninvasive imaging for evaluation of an emerging risk factor. *J Cardiovasc Transl Res*. 2011. doi:10.1007/s12265-011-9273-3
19. Jug B, Papazian J, Lee R, Budoff MJ. Association of lipoprotein subfractions and coronary artery calcium in patient at intermediate cardiovascular risk. *Am J Cardiol*. 2013. doi:10.1016/j.amjcard.2012.09.016
20. Makshood M, Joshi PH, Kanaya AM, et al. Lipoprotein (a) and aortic valve calcium in South Asians compared to other race/ethnic groups. *Atherosclerosis*. 2020;313:14-19. doi:10.1016/j.atherosclerosis.2020.09.010
21. Schnitzler JG, Ali L, Groenen AG, Kaiser Y, Kroon J. Lipoprotein(A) as orchestrator of calcific aortic valve stenosis. *Biomolecules*. 2019;9(12). doi:10.3390/biom9120760
22. Nanda NC. Genetic associations with valvular calcification and aortic stenosis. *Cardiol Rev*. 2013;29(2):503-515. doi:10.1056/nejmoa1109034