**ARIC Manuscript Proposal # 3448 (Revised)**

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| **PC Reviewed: 5/19/21** | **Status: _____** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Clinical Utility of Small Dense Low-Density Lipoprotein (sdLDL-C) and Lipoprotein(a) [Lp(a)] Measurements in the Prediction of Atherosclerotic Cardiovascular Disease, Coronary Heart Disease, and Stroke and Heart Failure in the Atherosclerosis Risk in Communities Study (ARIC), the Framingham Offspring Study (FOS), and the Multi-Ethnic Study of Atherosclerosis (MESA)

**b. Abbreviated Title (Length 26 characters)**: sdLDL-C, Lp(a), and ASCVD & HF

**2. Writing Group**:

Writing group members:

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


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**3. Timeline**: within 12 months of approval

**4. Rationale**:

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death and disability (1). Major risk factors for CVD based on guidelines for the United States population include gender, age, race, total cholesterol, HDL-C, systolic blood pressure, treatment for hypertension, diabetes, and current smoking (1). It has been recommended that 10-year ASCVD risk should be assessed based on these risk factors using the pooled cohort equation (PCE) for men and women between the ages of 40 and 79 years (1). ASCVD endpoints in this analysis were defined as fatal and non-fatal myocardial infarction and stroke (1). The PCE was developed based on data from the Atherosclerosis Risk in Communities Study (ARIC), the Coronary Artery Risk Development in Young Adults (CARDIA) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (Original Cohort), and the Framingham Offspring Study (FOS) (1). Subjects with established CVD, diabetes, LDL-C $\geq$ 190 mg/dL, and those with a 10-year CVD risk $\geq$ 7.5% between the ages of 40 and 79 years have been recommended to receive statin therapy, as well as potentially other LDL-C lowering therapies (2).

Moreover, one can calculate non-HDL-C by subtracting HDL-C from total cholesterol. In addition, one can calculate low-density lipoprotein cholesterol (LDL-C) using either the Friedewald formula or the Martin-Hopkins equations, provided subjects have been sampled after an overnight fast, and the triglyceride levels are < 400 mg/dL (3-5). Also, automated assays have been developed for directly measuring LDL-C and small dense LDL-C (sdLDL-C) (6-8). In FOS, ARIC, and the Multi-ethnic Study of Atherosclerosis (MESA), sdLDL-C was reported to be more strongly related to CVD than was calculated LDL-C (9-11). Most recently, direct LDL-C measured by two different methods was compared with calculated LDL-C using both the Friedewald and the Martin formulas, and only one of the direct LDL-C added significant information about prospective CVD risk in FOS (12).

Another lipoprotein associated with increased CVD risk is Lp(a). This lipoprotein is generally an LDL-like lipoprotein particle with a protein known as apo(a) bound to the apoB component of LDL. An elevated level of Lp(a) has long been known to be a significant independent CVD risk factor (13-15). Elevated Lp(a) is also a risk factor for congestive heart failure and aortic valve disease (16,17). In this pooling project our goal is to examine the clinical utility of sdLDL-C, and Lp(a) levels as compared to the PCE as well as other models which only include the lipid markers total cholesterol, HDL-C, and calculated non-HDL-C, for predicting fatal and non-fatal ASCVD, ASCVD with coronary revascularization, coronary heart disease (CHD), CHD with revascularization procedures, stroke, and stroke excluding hemorrhagic stroke in all subjects, and in men and women in ARIC, FOS, and MESA using multivariate modeling analysis.

A third project is to investigate whether Lp(a) levels are associated with HF incidence overall, or HF ejection fraction subtypes (HFpEF, HFrEF) in collaboration with the MESA, Framingham Offspring Cohort (FOS), and Atherosclerotic Risk in Communities Study (ARIC). Heart failure (HF) is a major public health burden in the United States that is expected to

increase due to the aging population and improvements in treating coronary heart disease (CHD), which has resulted in higher initial survival after a CHD event, but lingering damage to heart tissue (18-21) (20-22). The pathophysiology of HF varies from patient to patient with about half of HF patients diagnosed with reduced ejection faction (HFrEF) (≤40-50%) and half presenting with preserved ejection faction (HFpEF) (>40-50%) (20, 22, 23). Binary cut-points are often used for defining HF subtypes, but the difference between an EF of 45% vs. 46% is unlikely to be substantial, highlighting the benefit of evaluating three categories of HF: HF with preserved EF (≥40%); HF with intermediate EF (HFiEF) (41%-49%); and EF with reduced EF (≤40%) (24). Risk factors vary by ejection fraction (EF) subtypes and include history of coronary artery disease, body composition, hypertension and diabetes (20, 25). While several risk factors have been identified, research is generally still lacking on factors that could be monitored for identifying individuals at risk for developing HF or that elucidate targets for therapeutic intervention in HF risk reduction. One potential risk factor that warrants additional research is lipoprotein(a) [Lp(a)]. Since its discovery in 1963, Lp(a) has been investigated as a potential risk factor for numerous cardiovascular-related diseases, including more recently with heart failure (HF) (16, 26, 27). To our knowledge, only one prior study has evaluated the association between Lp(a) and HF by EF subtypes and no studies have evaluated HF with intermediate EF subtype. Given current knowledge of differences in risk factors by EF subtype this would provide important information, particularly for HFpEF which is less well understood. Additionally, both Lp(a) levels and HF risk have been shown to differ by race/ethnicity, but large studies evaluating the relationship between these factors are lacking (27). We previously observed a difference in the Multi-Ethnic Study of Atherosclerosis (MESA), but findings need to be confirmed in a larger study (28). Given the limitations of using a binary cut-point to define ejection fraction, if there is a sufficient number of cases with EF data to evaluate HFpEF, HFrEF and HFiEF separately, we would also evaluate HFiEF. We additionally propose to investigate whether associations differ by race/ethnicity. We hypothesize that elevated Lp(a) will be associated with HF incidence overall and all EF subtypes, and associations will be attenuated for HF overall, HFrEF and HFiEF, but not HFpEF, after excluding for prior cardiovascular events

**5. Main Hypothesis/Study Questions**:

1. Small dense LDL-C analysis will provide additional benefit to the current Pooled Cohort Equations (PCE) risk model for CVD risk prediction in all subjects, in men, and in women.
2. Lp(a) analysis will provide additional benefit to the current PCE risk model for CVD risk prediction in all subjects, in men, and in women.
3. Both sdLDL-C and Lp(a) analysis will provide additional benefit to the current PCE risk model for CVD risk prediction in all subjects, in men, and in women.
4. Adding sdLDL-C and Lp(a) results to standard risk factors will provide a better model in terms of the C statistic and net reclassification statistic than the variables used in the PCE in terms of both CVD, CHD, and stroke risk prediction in all subjects, in men, and in women.
5. To assess whether Lp(a) levels are associated with incidence of HF overall, or incidence of preserved or reduced ejection fraction HF (primary outcomes).
6. To evaluate whether associations between Lp(a) and HF differ by race/ethnicity

**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).**

1. The populations to be studied will be participants in ARIC (Visit 4), FOS (cycle 6), and MESA (Exam 1) who are free of all evidence of CVD at the time at which sdLDL-C and Lp(a) was measured at the beginning of the follow up period. For the first two projects: (1) sdLDL and ASCVD outcomes and (2) Lp(a) and ASCVD outcomes, all subjects must have the covariates for the PCE model plus sdLDL-C and Lp(a); that is, no missing data.
2. The outcome to be assessed initially will be the same as for the PCE, which was 10-year risk of atherosclerotic cardiovascular disease (ASCVD) defined as nonfatal and fatal myocardial infarction or stroke, starting from the examination at which sdLDL-C and Lp(a) were measured to the event or to the last follow up, if no event.
3. Another endpoint to be assessed will be hard CHD, defined as nonfatal and fatal myocardial infarction, defined as new development of MI, recognized with diagnostic electrocardiogram (ECG), recognized without diagnostic ECG, but including enzymes and history, recognized without diagnostic ECG, but with autopsy evidence, or recognized at autopsy, and/or death from MI or CHD.
4. Another endpoint to be assessed will be hard CHD as defined above, as well as those that have had cardiac revascularization procedures, specifically coronary angioplasty and or coronary artery bypass grafting procedures.
5. Another endpoint to be assessed will be hard ASCVD as defined above (#2) plus procedures (angioplasty, coronary artery bypass, carotid artery surgery, and/or peripheral arterial surgery).
6. Another endpoint to be assessed will be all fatal and non-fatal stroke.
7. Another endpoint to be assessed will be fatal and non-fatal stroke, excluding hemorrhagic stroke.
8. Subjects will be excluded if they were sampled in the non-fasting state or if they were not free of ASCVD (defined prior myocardial infarction or stroke or prior revacularization procedure (angioplasty and/or coronary artery bypass surgery) at the time of the baseline examination. Only the first ASCVD event will be used in the analyses where comparisons with 10- year ASCVD risk is assessed over a follow-up of 10 years to match the PCE.
9. For Project 3, Lp(a) and HF project, the primary analytic cohort includes all ARIC, FOS, and MESA cohort participants with measurements of Lp(a) and HF outcome data. As timing of Lp(a) measurement varies across cohorts, HF cases prior to Lp(a) measurement will be excluded from analyses.
10. For project 3, Lp(a) and HF, potential covariates include age, sex, race/ethnicity, family history, alcohol, hypertension, diabetes, smoking, socioeconomic status, BMI, WHR, physical activity, heart rate, creatinine, urinary albumin, interleukin-6, c-reactive protein, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglycerides, estimated glomerular filtration rate, study population.
11. We will conduct proportional hazards regression models for all analyses in the three projects, using survival time as the outcome. Separate analyses will be conducted for each outcome event. For Projects 1 and 2, primary Analyses: all subjects (men and women, all races) using Cox analysis estimating regression coefficients for the PCE Model, including covariates at time of sdLDL and Lp(a) measurements: 1) Sex (0=Male,

1=Female), 2) Race (0=European Ancestry (White), 1=African American Ancestry, 2=Hispanic Ancestry, 3=Other), 3) ln age – (ln = natural logarithm), 4) ln age^2, 5) ln Total Cholesterol (TC), 6) ln HDL-C, 7) ln age * ln HDL-C, 8) ln treated SBP (SBP among those treated, 0 otherwise), 9) ln age * ln treated SBP, 10) ln untreated SBP (SBP among those untreated, 0 otherwise), 11) ln age * ln untreated SBP, 12) current smoker (0=not current smoker, 1=current smoker), 13) ln age * current smoker, 14) diabetes (0=not diabetic, 1=diabetic (treated for diabetes or fasting glucose > 125)

12. For Projects 1 and 2 we will conduct Cox analysis with only one covariate, the weighted sum of the covariates based on the PCE model presented in the 2013 ACC/AHA Guidelines, page S72. Note that the PCE is race and sex-specific. The weighted sum will use the regression coefficients reported on page S72 of reference 1 with the covariates for each subject in the analysis.
13. The analyses for Projects 1 and 2 are detailed as follows
    a. Conduct Cox analysis of PCE Model estimating the regression coefficients from this dataset for the PCE covariates (specified in #9)
    b. Conduct Cox analysis of PCE Model using a single covariate, the weighted PCE sum based on the estimated regression coefficients for the PCE project. (specified in #10)
    c. Conduct Cox analysis of PCE Model as defined in 11.a + sdLDL
    d. Conduct Cox analysis of PCE Model as defined in 11.b + sdLDL
    e. Conduct Cox analysis of PCE Model as defined in 11.a + sdLDL and dropping TC from the model
    f. Conduct Cox analysis of PCE Model as defined in 11.a + Lp(a)
    g. Conduct Cox analysis of PCE Model as defined in 11.b + Lp(a)
    h. Conduct Cox analysis of PCE Model as defined in 11.a + Lp(a) and dropping TC from the model
    i. Conduct Cox analysis of PCE Model as defined in 11.a + Lp(a) + sdLDL-C
    j. Conduct Cox analysis of PCE Model as defined in 11.b + Lp(a) + sdLDL-C
    k. Conduct Cox analysis of PCE Model as defined in 11.a + Lp(a) + sdLDL-C and dropping TC from the model
14. Secondary Analyses:
    a. Repeat analyses excluding diabetic subjects (fasting glucose ≥ 126 mg/dl or on treatment) and those with LDL-C ≥ 190 mg/dL and those outside the age range 40-75
    b. Analyses in those ages 40-75 with 70 mg/dl ≤ LDL-C< 190 mg/dl and no diabetes.
    c. Conduct separate analyses for subjects of European ancestry, African American ancestry, Hispanic ancestry, and potentially Asian ancestry.
    d. Conduct separate analysis for subjects with ≤7.5% 10-year risk of ASCVD calculated by current PCE (Low and/or Borderline risk group in ACC/AHA 2018 primary prevention guideline), to assess clinical utility of sdLDL-C as a risk enhancing factor.

15. For Project 3, Cox Proportional Hazard Models will be performed (1) unadjusted; (2) age, sex, race/ethnicity-adjusted and (3) multivariable-adjusted. For the third model, factors known to be associated with exposure and/or outcome will be selected a priori for

evaluation. All potential covariates with be evaluated in the model and remain in final model if they are associated with outcomes in the fully adjusted model or if they change the association between Lp(a) and the outcome(s). To evaluate potential racial/ethnic differences, models will be additionally run stratified by race/ethnicity and tests for interaction will be assessed using cross-product terms included in models. Models will also be replicated after excluding participants with a history of potential mediating variables (MI, coronary artery bypass grafting, or transluminal coronary angioplasty). Sensitivity analyses will be conducted by excluding subjects with the following: a. Myocardial infarction (MI) and b. MI, coronary artery bypass grafting, or transluminal coronary angioplasty

16. Measures of Evaluation: C-statistic (discrimination), Calibration chi-square (Hosmer-Lemeshow statistic), and net reclassification index as previously described (29,30). Models will be compared using these statistics.

**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/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)?** MS#1827

**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**
**__X_ A. primarily the result of an ancillary study (list number* __**AS#2010.12**___)**

**___ 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 https://www2.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.

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