ARIC Manuscript Proposal #1991

PC Reviewed: 9/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lipid gene scores and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Lipid gene score and AF

2. Writing Group:

Faye L. Lopez, Sunil K. Agarwal, Lin Y. Chen, Pam L. Lutsey, Dan E. Arking, James S. Pankow, Alvaro Alonso, others welcome

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

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3. Timeline:

Data analysis: 2 months

First draft of the manuscript: 3 months

We expect to submit an abstract with preliminary results to the AHA Epi conference (submission deadline Oct 2012)

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with increased risks of heart failure, stroke and cardiovascular death,[1] including a 9-fold higher risk of mortality within the first four months after AF, compared to those without AF.[2] Some major predictors for AF include age, white race, obesity, heart failure, coronary heart disease, left ventricular hypertrophy, and hypertension, along with certain lifestyle factors.[3-5] These predictors are similar to the risk factors for cardiovascular disease (CVD) in general, which often precede an AF event.[1]

High levels of total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDLc) and low levels of high-density lipoprotein cholesterol (HDLc) have long been associated with CVD in general. We have shown recently, however, that *lower* levels of LDLc and total cholesterol were associated with incident AF, with no association seen in HDLc and triglycerides in the ARIC study.[6] Other studies have found a similar paradoxical association.[6-9] Reasons for this inverse association are not clear, but some potential mechanisms include confounding by subclinical hyperthyroidism or a direct effect of cholesterol on myocardial cell membranes.

One approach to evaluate whether lipid levels are causally associated with AF risk is to use Mendelian randomization.[10] In fact, several genome-wide association studies (GWAS) have identified genes associated with blood lipoprotein levels,[11-13] including a meta-analysis of > 100,000 Caucasians, published by Teslovich, *et al*. that identified 95 loci significantly associated with lipid phenotypes.[14] Using data from the Teslovich manuscript, phenotype-specific lipid gene scores have been calculated to estimate the effect of lipid genes on lipid levels in the ARIC cohort.[15]

We propose to determine whether the previously developed lipid gene scores are associated with the incidence of AF. Ours will be the first study to look at the effect of recently identified lipid genes and their association with the incidence of AF.

5. Main Hypothesis/Study Questions:

Main aim: To determine whether lipid gene scores are associated with the incidence of AF in ARIC participants
Secondary aim: To determine if the association between lipid gene scores and incident AF is independent of covariates.

We hypothesize that lipid gene scores will be associated with the risk of incident AF similarly to the associations seen between lipid levels and AF. We hypothesize this relationship will be independent of other covariates.

As an exploratory aim, we will examine if adding serum lipid levels to the model with the lipid gene score mediates the association between the lipid gene score and AF risk. We hypothesize that the association between lipid gene scores and AF risk will disappear after adjusting for lipid levels.

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).

This study will assess the association between the lipid gene score and the incidence of AF using a longitudinal data analysis approach. Data will first be obtained from the baseline exam on those participants who have measures of lipid levels, who gave consent for genetic analyses and had successful GWAS genotyping. For this analysis, we will exclude individuals with a race/ethnicity other than white, those with prevalent AF at baseline, those not fasting for 8 hours, and those with missing variables in any of the covariates.

Variables:
Main outcome variable: time to AF from baseline through 2009.

Main independent variable: Lipid gene scores for HDLc, LDLc, triglycerides, and total cholesterol

Covariates: measured at baseline (visit 1): age, gender, center, education, height, smoking status, BMI, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, HDLc, LDLc, triglycerides, total cholesterol, ECG based left-ventricular hypertrophy, prevalent stroke, prevalent heart failure, prevalent coronary heart disease and lipid medication use.

Statistical Analysis

First, we will explore the correlations between lipid levels and the lipid gene scores. Then we will assess the association between lipid gene scores and AF incidence using Cox proportional hazards models.

Effect-size weighted lipid gene scores for HDLc, LDLc, triglycerides and total cholesterol will be calculated as published by Lutsey et. al,[15] using SNPs identified in the Teslovich GWAS.[14] They will be used as a continuous variable per 1 standard deviation.

The following models will be used to assess the association between lipid gene scores and incident AF cases:

Models:

1: adjust for age, gender and center

2: adjust for age, gender, center, education, height, smoking status, BMI, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, ECG based left-ventricular hypertrophy.

3: model 2, and additionally adjust for prevalent stroke, heart failure, and CHD

4: model 3, and additionally adjust for lipid levels and lipid medication use

Interactions between lipid gene scores and sex will be examined.

Finally, we will conduct a similar analysis using gene scores including only SNPs exclusively associated with specific cholesterol fractions (LDLc, HDLc) to assess potential causal effects of each fraction without including indirect effects through other cholesterol fractions, as recently described.[16]

Limitations:

Misclassification of the outcome is possible, with AF diagnosis having a positive predictive value of ~90%.[3] Misclassification of lipid levels is also possible due to variations in serum levels. Some SNPs in the GWAS score were imputed, and the genes scores only explain a portion of the variation seen in lipid levels.[15]

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 ICTDER03 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?
__X_ 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
_X_ 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

_X_ Yes no overlap found _____ 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 #1482 Lutsey, Lipid gene score and lipid trends. This paper examined the association of lipid gene scores with trends in lipid levels. Dr. Lutsey will be a coauthor in this manuscript and she will provide the lipid gene scores used in her manuscript.

10. 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* 2008.12)
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 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.

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