ARIC Manuscript Proposal # 1667r

PC Reviewed: 8/10/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lipid levels, lipid lowering medications, and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities study

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

2. Writing Group:

Faye L. Lopez, Sunil K. Agarwal, Richard F. Maclehose, Rachel Huxley, Suma Konety, Christie M. Ballantyne, A. Richey Sharrett, 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 2010)

4. Rationale:

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, with a projected prevalence of 2.66 million Americans in 2010 [1]. In the US, as the population ages and rates of cardiovascular disease increase, the prevalence of AF is also increasing. AF is associated with increased risks of heart failure, stroke and cardiovascular death [2], including a 9-fold higher risk of mortality within the first 4 months after AF, compared to those without AF [3]. 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 [4-6]. These predictors are similar to the risk factors for cardiovascular disease in general, which often precede an AF event [2].

The metabolic syndrome, which is characterized by a group of metabolic risk factors linked to overweight and obesity, is known to be associated with a higher incidence of AF [7,8]. Two of the components include elevated triglycerides (≥150 mg/dL) and low levels of HDLc (men< 40 mg/dL and women <50mg/dL). Specifically, it has been shown that low HDLc levels are associated with a 20-40% increased risk of AF, but elevated triglyceride levels have not yet shown an association with the risk of AF [7,9]. Since low HDL cholesterol is associated with higher risk of coronary heart disease (CHD), and CHD is a risk factor for AF, this association is expected. However, few other studies have assessed whether levels of total cholesterol and LDLc are associated with AF occurring.

Numerous studies have provided evidence of statins in the prevention and treatment of cardiovascular diseases [10]. There is interest in determining whether the incidence of AF is also lowered when patients are treated by statins. Some randomized controlled trials have found that use of statins was significantly associated with a decreased risk of post-operative AF, and a decreased recurrence of AF [11]. Similarly, an observational study reported statin use reduced the risk of developing AF independently of the reduction in serum cholesterol levels [12]. However, a large clinical trial (ALLHAT) showed no relationship between statin use (pravastatin) and a reduction in incident AF, after a follow-up time of six years [9]. Similarly, no information exists on the effect of other lipid lowering medications on the risk of AF.

This study would be the first large cohort study to estimate the association of participants' lipid profile and changes in lipids over time with the incidence of AF. This study would also provide an opportunity to compare those taking statins to those taking other cholesterol-lowering medications, taking advantage of the large number of incident AF cases and ample follow-up time in the ARIC cohort.

5. Main Hypothesis/Study Questions:

i. To determine whether lipid levels (total cholesterol, HDLc, LDLc, triglycerides) are associated with the incidence of atrial fibrillation in ARIC participants
ii. To determine whether lipid medication (statins, other lipid-lowering medications) is associated with the incidence of atrial fibrillation in ARIC participants

We hypothesize an inverse relationship between HDLc levels and the incidence of AF, and a positive relationship between LDL, total cholesterol, triglycerides and the ratio of total/HDL cholesterol with the incidence of AF.
Also, we hypothesize that participants taking statins have a lower incidence of AF when compared to those not taking statins.

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 lipid levels, lipid medications and the incidence of AF using a longitudinal data analysis. Data will first be obtained from the baseline exam on those participants who have measures of all lipid levels. For all analyses, we will exclude individuals with prevalent AF at baseline, those not fasting for 8 hours, and those with missing variables in any of the covariates. We will also exclude the small number of participants who reported a race other than white or black. For Aim 1, we will exclude individuals using medications that affect blood lipid levels.

Covariates:
Main outcome variable is the time to AF from baseline through 2007.

Main independent variable (Aim 1): lipid levels, which include HDLc, LDLc, total cholesterol, triglycerides and the ratio of total/HDL cholesterol over time (visit 1-visit 4).

Main independent variables (Aim 2): Lipid medications: statins, vitamin B-3 (niacin), antihyperlipidemics, bile sequestrants, and fibrates over time (visit 1-visit 4)

Covariates measured at baseline (visit 1): gender, race, center, education, height, and income

Covariates measured at all visits: age, smoking status, cigarette years, alcohol intake, waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, prevalent stroke, prevalent heart failure,

prevalent coronary heart disease (including silent myocardial infarction (MI) detected by ECG), electrocardiograph based left-ventricular hypertrophy.

Statistical Analysis

For all participants, we will examine the means and standard deviations for the continuous variables and percentages for the categorical variables. We will stratify by lipid levels, which will be categorized by quartiles to examine demographic characteristics.

Aim 1:

We will assess the association between baseline lipid levels and AF incidence with Cox proportional hazards models. First, we will explore the shape of the association of lipid fractions with AF incidence using restricted cubic splines. Based on this analysis, we will decide whether to model lipids as continuous or categorical variables (e.g. quartiles or clinically significant categories).

We will take into account changes in lipid levels over time by using a Cox proportional hazards model with time-varying covariates and a marginal structural Cox model. The following 3 models will be used to assess the association between lipid levels and incident AF cases:

Models:

1: adjust for age, gender and race

2: adjust for age, gender, race, height, center, education, income, smoking status, cigarette years, waist circumference, alcohol intake, BMI, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus.

3: model 2, and additionally adjust for stroke, heart failure, and CHD (including silent MI), both baseline and incident.

Aim 2:

We will assess the association between lipid medication use and incidence of AF with Cox proportional hazards models time-varying covariates and/or a marginal structural Cox model to take into account changes in medication use over time, along with time-varying confounders. Lipid medications will be divided into 2 categories: Statins and Other Lipid Medications. Included in the "other" category will be vitamin B-3, antihyperlipidemics, bile sequestrants, and fibrates. Analyses will compare risk of AF in those taking statins versus those taking other lipid lowering medications, and those taking lipid lowering medications (statins or other, as separate levels of exposure) versus those not taking these drugs. The same three models as used in Aim 1 will be used to assess the association between lipid medication use and incidence of AF. In addition to the multivariable analyses, a secondary analysis will be performed using a propensity score approach to adjust for measured confounders, to ensure we adjust for confounding as properly as possible. Specifically, we will create a propensity score as the inverse of the probability of receiving treatment given baseline covariates (previously mentioned). Secondly, we will do two different analyses: (1) we will match treated and untreated on their propensity score, and (2) we will conduct a standard Cox model adjusting for propensity score. Follow-up for this analysis will start in visit 2 in order to adjust for

lipid levels and other covariates measured in the previous visit. We will also test for interactions between lipid levels and medication use.

Limitations:
Misclassification of the outcome is possible, with AF diagnosis having a positive predictive value of ~90% [4]. Misclassifications of the exposures, both lipids and medication, are possible due to unmeasured changes over time between visits. The ARIC study does not contain information on thyroid profiles, which would potentially be a strong confounder in this study. An additional limitation is the lack of information on the dose of statins or other lipid medications. Higher doses have more impact on cholesterol levels and other processes (such as inflammation in the case of statins), and therefore different doses may affect the incidence of AF.

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? ____ 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

___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)?

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* 2008.09, 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.

Reference list:

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2. Benjamin EJ, Levy D, Vaziri SM. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271(11):840-4.
3. Miyaska Y, Barnes ME, Bailey KR et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study*. J AM Coll Cardiol.* 2007;49:986-92.
4. Alonso A, Agarwal SK, Soliman EZ et al. Incidence of atrial fibrillation in whites and African-Americans: the atherosclerosis risk in communities (ARIC) study. *Am Heart J.* 2009;158:111-7.
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7. Chamberlain AM, Agarwal SK, Ambrose M, et al. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the atherosclerosis risk in communities (ARIC) study. *Am Heart J.* 2010;159:850-6.
8. Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation*. 2008;117:1255-60.
9. Haywood LJ, Ford CE, Crow RS, et al. Atrial fibrialltion at baseline and during follow-up in ALLHAT (Antihypertensive and lipid-lowering treatment to prevent heart attack trial). *J Am Coll Cardiol*. 2009;54:2023-31.
10. Banach M, Mikhailidis DP, Kjeldsen SE et al. Time for new indications for statins? *Med Sci Moni.* 2009;15(12)MS1-5.
11. Fauchier L, Pierre B, de Labriolle A, et al. Antiarrhythmic effect of statin therapy and atrial fibrillation. A meta-analysis of randomized controlled trials. *J Am Coll Caridiol.* 2008;51:828-35.
12. Young-Xu Y, Jabbour S, Goldberg R, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. *Am J Cardiol.* 2003;92:1379-83.