ARIC Manuscript Proposal # 1460

PC Reviewed: 12/9/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Smoking and Risk of Incident Atrial Fibrillation in the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

Writing group members: Alanna Chamberlain, MPH
Sunil K. Agarwal, MD, MPH
Marietta Ambrose, MD
Aaron Folsom, MD
Elsayed Z. Soliman, MD, MSc, MS
Alvaro Alonso, MD, PhD

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

First author: Alanna Chamberlain
Address: 1300 S. 2nd Street, Suite 300
Minneapolis, MN 55454

Phone: 612-625-5352 Fax: 612-624-0315
E-mail: gram0119@umn.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: Alvaro Alonso
Address: 1300 S. 2nd Street, Suite 300
Minneapolis, MN 55454

Phone: 612-626-8597 Fax: 612-624-0315
E-mail: alonso@umn.edu

3. Timeline:

Statistical Analysis:	February 2009 – May 2009
Manuscript Preparation:	June 2009
Manuscript Revision:	July 2009
Manuscript Submission:	August 2009

4. Rationale:

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, and is associated with increased stroke and cardiovascular morbidity and mortality[1]. AF currently affects more than 2.2 million Americans, and the lifetime risk for development of AF in men and women over 40 years of age is 1 in 4[2].

It is well known that cigarette smoking increases the risk of cardiovascular disease. Potential mechanisms by which cigarette smoke contributes to acute vascular events, such as myocardial infarction, include induction of a hypercoagulable state, increased myocardial work, carbon monoxide-mediated reduced oxygen-carrying capacity of the blood, coronary vasoconstriction, and catecholamine release[3]. Furthermore, cigarette smoking likely promotes atherosclerosis through adverse effects on lipids, endothelial damage or dysfunction, hemodynamic stress, oxidant injury, neutrophil activation, enhanced thrombosis, and increased fibrinogen and blood viscosity[3]. However, knowledge on the mechanism and association between smoking and AF is limited. Smoking, through the effects of nicotine, has been reported to contribute to the development of atrial fibrosis, which in turn may predispose to developing AF[4].

Only a few studies have reported on the association between smoking and AF. In a study on rats given nicotine at concentrations found in the blood of human smokers, nicotine was associated with increased atrial vulnerability to inducible AF in young rats, but not old rats[5]. In the Framingham Heart Study, cigarette smoking was associated with a 40% increased odds of developing AF among women, but no association between smoking and AF was found in men[6]. A study including hospitalizations for AF among men in Sweden reported no association between smoking and AF, even among men who smoked more than 15 cigarettes a day[7]. The limited and inconsistent data on the association between smoking and AF warrants further investigation. Therefore, we propose to determine the risk of incident AF in relation to smoking status and amount using the ARIC study. We will additionally conduct a systematic review of the literature and a meta-analysis on the association between smoking and AF.

5. Main Hypothesis/Study Questions:

We hypothesize that the incidence of AF will be higher among those who were current smokers at baseline compared to those who never smoked, and we also expect a dose-response relationship where incidence of AF increases with increasing pack-years of smoking. These associations will be independent of other known and measured risk factors for AF.

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).

Individuals without ECG or who had diagnosed AF or atrial flutter at baseline will be excluded from analyses. Independent variables in our analysis include smoking status and pack-years of smoking. The dependent variable is incident AF. Incident cases of atrial fibrillation will be identified through hospital discharge codes (ICD-9 code 427.31), death certificates (underlying cause of death ICD-9 code I48 or 427.3), and ECG's performed during follow-up visits. Individuals who develop both atrial flutter and AF during follow-up will be considered as having an event, and follow-up will be censored at the first occurrence of either AF or atrial flutter. Those that develop atrial flutter only will not be considered as having an event, and will be censored at the date of diagnosed atrial flutter.

First, we will assess pooled, as well as race- and/or sex-specific rates of AF incidence by smoking status at baseline using Poisson regression. Then, Cox proportional hazards regression will be used to determine the hazard ratios of AF by smoking status at baseline (current, former, or never smoker). The associations will be adjusted for age, sex, race, field center, education, drinking status and amount of alcohol consumed, body mass index, hypertension, diabetes, height, ECG-defined left ventricular hypertrophy, and presence of CHD and heart failure at baseline. We will repeat the Poisson and Cox regression analyses using pack-years of smoking after creating a categorical variable for pack-years using tertiles or quartiles. Interaction tests by race and sex will be conducted, and analyses will be reported separately by race and/or sex if evidence of heterogeneity by these variables is present. We will also categorize individuals according to change in smoking status from visit 1 to visit 2 and run Cox regression analyses (with follow-up starting at visit 2) comparing individuals who were smokers at both visits 1 and 2, those who smoked at visit 1 but quit by visit 2, those who did not smoke at visit 1 but had taken up smoking by visit 2, and those who were nonsmokers at both visits. Additionally, time-dependent Cox regression analyses will be run using smoking status as the time-dependent variable. We may also use inverse probability weighting to adjust for censoring in our data.

A systematic literature review on smoking and AF will also be conducted, and a meta-analysis using all publications on smoking and AF will be run. For the systematic literature review, we will search the Medline, CINAHL, and ISI Web of Science databases for the following terms: atrial fibrillation, atrial arrhythmia, arrhythmia, tachyarrhythmia, smoking, smoke, tobacco, and cigarette. A secondary search for additional articles will be done by reviewing the reference lists of papers identified through our database search. For non-English papers and abstracts where a full manuscript was not published, we will contact the authors in an attempt to gather all relevant information so that these studies may also be included in the meta-analysis. After all possible studies are identified and reviewed, those not related to smoking and AF, and those with an outcome other than AF will be excluded. We will report individual study results, results stratified by study design (cohort, cross-sectional, case-control), results stratified by exposure representation (smoking status, pack-years of smoking), and an overall pooled association between smoking at atrial fibrillation. If we do not find evidence of heterogeneity among studies, we will use fixed-effects models**.** However, if evidence of heterogeneity exists, we may use random-effects models and further explore possible sources for the heterogeneity. We additionally may run a meta-

regression analysis in order to estimate dose-response relationships between pack-years of smoking and incidence of atrial fibrillation. Finally, a funnel plot will be plotted to identify possible publication bias, which is identified by asymmetry in the funnel plot.

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 ICTDER02 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 ICTDER02 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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

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 # 1351: Incidence of atrial fibrillation in a bi-racial cohort: the ARIC study

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__)

___ 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.

References:

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The framingham heart study. *Circulation*. 1998;98:946-952.

2. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: A report from the american heart association statistics committee and stroke statistics subcommittee. *Circulation*. 2008;117:e25-146.

3. Benowitz M,Neal L., Gourlay, MB, BS, PhD,Steven G. Cardiovascular toxicity of nicotine: Implications for nicotine replacement therapy. *Journal of the American College of Cardiology*. 1997;29:1422-1431.

4. Goette A, Lendeckel U, Kuchenbecker A, et al. Cigarette smoking induces atrial fibrosis in humans via nicotine. *Heart*. 2007;93:1056-1063.

5. Hayashi H, Omichi C, Miyauchi Y, et al. Age-related sensitivity to nicotine for inducible atrial tachycardia and atrial fibrillation. *Am J Physiol Heart Circ Physiol*. 2003;285:H2091-2098.

6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. the framingham heart study. *JAMA*. 1994;271:840-844.

7. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: Morbidity and risk factors. *J Intern Med*. 2001;250:382-389.