

**ARIC Manuscript Proposal #2290**

**PC Reviewed:** 1/14/13  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1. a. Full Title:** Association of Obesity, Smoking and Alcohol Consumption with Ischemic Stroke in Atrial Fibrillation: The ARIC Study

**b. Abbreviated Title (Length 26 characters):** Obesity and Ischemic Stroke in Atrial Fibrillation

**2. Writing Group:**

Writing group members: Younghoon Kwon, Faye L. Lopez, Sunil K. Agarwal, Elsayed Z. Soliman, Gregory Lip, Alvaro Alonso, Lin Y. Chen, and others welcome

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

**First author:** Younghoon Kwon

Address: Division of Cardiology, University of Minnesota Medical School  
420 Delaware Street SE, MMC 508  
Minneapolis, MN 55455

Phone: 612-625-4401

Fax: 612-624-4937

E-mail: [kwonx208@umn.edu](mailto:kwonx208@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).

Lin Y. Chen, MD, MS  
Cardiac Arrhythmia Center, Cardiovascular Division  
Department of Medicine,  
University of Minnesota Medical School,  
420 Delaware Street SE, MMC 508,  
Minneapolis, MN 55455.

Phone: 612-625-4401

Fax: 612-624-4937

E-mail: [chenx484@umn.edu](mailto:chenx484@umn.edu)

OR

Alvaro Alonso, MD, PhD  
Division of Epidemiology and Community Health  
School of Public Health, University Of Minnesota  
1300 S. 2<sup>nd</sup> Street, Suite 300  
Minneapolis, MN 55416

Phone: 612-626-859      Fax: 612-624-0315  
E-mail: [alonso@umn.edu](mailto:alonso@umn.edu)

### **3. Timeline:**

Statistical analysis: 3 months

Manuscript preparation: 4 months

### **4. Rationale:**

Atrial fibrillation (AF) is a major and growing public health concern<sup>1</sup>. Ischemic stroke (IS) is the most serious complication of AF, and one quarter of IS are attributed to AF. Much effort has been put forth to identify risk factors defining high likelihood of incident IS in AF. In this context, IS predicting tools such as CHADS2 and CHA2DS2-VASC scoring systems have been developed and are increasingly used in clinical practice<sup>2-4</sup>. These risk scores, derived and validated in various randomized AF trials or cohort studies, incorporate variables significantly associated with the risk of IS. However, most of the variables considered in these schemes are not modifiable risk factors. The identification of additional modifiable risk factors for stroke in AF patients may enhance risk prediction of stroke, and importantly, inform novel prevention strategies.

Obesity is associated with higher incidence of both AF and IS in the general population<sup>5,6</sup>. Whether obesity is associated with higher risk of IS in patients with AF remains unclear as this was not specifically evaluated in the derivation of the aforementioned risk stratification schemes<sup>7-9</sup>. A post hoc analyses of Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial suggested an ‘obesity paradox’ with lower CVD risks in AF patients<sup>10,11</sup>. In contrast, a Danish National cohort study reported a higher risk of IS/ thromboembolism (TE) among obese patients with incident AF<sup>12</sup>.

Given the conflicting findings from limited number of studies above, we aim to examine the association of obesity with IS in AF patients in the ARIC cohort. In addition, we are interested in exploring associations of other lifestyle modifiable risk factors including smoking and alcohol consumption with IS in the setting of AF. Both smoking and excessive use of alcohol have previously been associated with increased risk of IS in general population but to our knowledge, this remains unstudied in AF patients<sup>13,14</sup>. Exploring association of these variables with IS in AF patients will have important public health implications as they may represent potentially modifiable risk factors.

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

### Aims:

1. Examine the association of obesity, smoking status, and alcohol consumption with incident IS among AF patients.
2. Explore whether obesity as measured by body mass index (BMI), smoking status, and alcohol consumption provide incremental value for prediction of IS beyond CHADS2 and CHA2DS2-VASC risk factors.

We hypothesize that:

1. Higher BMI, current smoking and heavy alcohol use will be associated with higher incidence of IS among participants with incident AF.
2. Higher BMI, current smoking, and heavy alcohol consumption will improve risk prediction of IS in AF, over and above the CHADS2 and CHA2DS2-VASC risk scores.

## **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 population**

ARIC participants with incident AF from baseline (1987-89) through the end of 2010 will be included.

\* Exclusion criteria: Participants with prevalent AF or atrial flutter at baseline, prevalent stroke at baseline, missing data on weight, height, smoking status, and alcohol consumption, missing covariates, and race/ethnicity other than white or black. Incident AF diagnoses will be obtained from 2 sources: ECGs at study exams and hospital discharge records (ICD-9 code 427.31 and 427.32 – Atrial fibrillation/flutter) as previously described<sup>15</sup>.

### **Exposure variable**

Information on BMI, cigarette smoking and alcohol consumption will be obtained from the visit before AF ascertainment.

#### 1. BMI

Height and weight will be used to derive BMI, calculated as weight in kilograms divided by height in meters squared. Subjects will be divided into three BMI categories, normal: 18.5-24.9; overweight: 25-29.9; obese: 30 and above.

#### 2. Smoking habits

Subjects will be classified into three groups. No smoking; past smoking; current smoking.

#### 3. Alcohol consumption

In ARIC, alcohol consumption was ascertained by means of an interviewer-administered dietary questionnaire. We will adopt similar criteria used in previous ARIC study<sup>16</sup>.

Subjects will be classified into three groups, no use; light to moderate use: 1-98 g per week for women and 1-196 g per week for men; heavy use: more than 98 gram per week for women and 196 g per week for men. In calculating the amount of alcohol consumed (in grams per week), it will be assumed that 4 oz of wine contains 10.8 g, 12 oz of beer contains 13.2 g, and 1.5 oz of liquor contains 15.1 g of ethanol<sup>16</sup>.

### **Outcome measurement**

Incident IS events were identified in ARIC from annual telephone interviews, study visits, surveillance of the ARIC community hospitals for all participants' hospitalizations, review of death certificates, physician questionnaires, coroner/medical examiner reports, and informant interviews. Hospital reports were reviewed if the discharge diagnosis included a cerebrovascular disease code (ICD-9 codes 430 to 438), if a cerebrovascular procedure was mentioned in the summary, or if the CT or MR report showed evidence of cerebrovascular disease. ARIC adapted the National Survey of Stroke criteria for its stroke definition. A computerized algorithm and physician reviewer independently confirmed the diagnosis of stroke. We will include definite and probable ischemic strokes. **Only incident IS events that occurred after ascertainment of AF will be included in our analyses.**

### **Covariates**

Covariates will be measured at the visit before AF ascertainment. These include age at time of AF ascertainment, sex, race, BMI, smoking status, alcohol consumption, systolic blood pressure, use of anti-hypertensive medications, eGFR, heart failure, diabetes, coronary heart disease, previous MI, peripheral arterial disease, aspirin use, and warfarin use.

### **Statistical Analysis**

Descriptive statistics will be used to compare baseline characteristics between a group with and without IS. Incidence rate will be expressed as number of events per 1,000 person-years.

Each exposure variable (BMI, smoking and alcohol consumption) will be separately added into a multivariable Cox proportional hazards model in relation to incident IS. Participants who developed stroke before incident AF will be censored. Hazard ratio and 95% CI will be calculated in the following models:

Model 1 will adjust for age, sex, race, and study center.

Model 2: Model 1 + BMI,\* smoking status,\* alcohol consumption,\* systolic blood pressure, use of anti-hypertensive medications, heart failure, diabetes, eGFR,

coronary heart disease, previous MI, peripheral arterial disease, aspirin use, and warfarin use

\*The relevant covariate will be excluded if it is also the exposure variable of interest.

Interaction with race and sex will be tested by including cross-product terms.

Any variable with significant association (“X variable” hereafter) will be added to CHADS2 and CHA2DS2-VASC scheme to test for any improvement in prediction of 5-year IS risk. For this purpose, the following strategies will be employed.

1) C-statistics (Discrimination)

To test any improvement in the model discrimination, Harrell’s C-statistic will be calculated for the established schemes, CHADS2 and CHA2DS2-VASC and new schemes, CHADS2 + X variable and CHA2DS2-VASC + X variable using survival model based receiving operator characteristics curve analysis (designating IS vs. no IS as a binary outcome). Bootstrapping will be used for an internal validation of the expanded models and for estimation of confidence intervals<sup>17</sup>.

2) Net Reclassification Improvement (NRI)

The proportion of individuals reclassified from risk stratum based on estimated annual stroke risk provided from CHADS2 and CHA2DS2-VASC to a new risk stratum ((CHADS2 + X variable and CHA2DS2-VASC + X variable) will be calculated<sup>18</sup>. A value of  $P < 0.05$  would suggest that a significantly greater number are being reclassified appropriately than are being reclassified inappropriately<sup>19</sup>. The risk categories will be  $< 5\%$ , 5 to  $< 10\%$ ,  $\geq 10\%$  for 5-year risk.

3) Integrated Discrimination Improvement (IDI)

Difference in  $R^2$ -like statistics between (CHADS2 and CHA2DS2-VASC) and (CHADS2 + X variable and CHA2DS2-VASC + X variable) will be calculated<sup>18</sup>.

**Limitation**

- 1) Subclinical AF or AF managed in the outpatient setting would be missed by our method of ascertainment. However, the AF ascertainment method in ARIC has been shown to have 84% sensitivity and 98% specificity<sup>15</sup>. In addition, incidence of AF in ARIC is also similar to those reported from other cohort studies<sup>20</sup>.
- 2) Through the end of 2010, approximately 1,996 participants developed AF of who approximately 169 developed ischemic stroke after ascertainment of AF. We will consider meta-analyzing the results from ARIC with results from CHS and the RS to optimize statistical power.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**     Yes  
 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  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.csc.unc.edu/ARIC/search.php>**

**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 #1897: Chen - Improving Prediction of Atrial Fibrillation Using Carotid Intima-Media Thickness and Carotid Distensibility: The ARIC Study

The authors of the above manuscript proposal are included in the current proposal.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? \_\_\_\_\_ Yes  No**

**11.b. If yes, is the proposal**

**\_\_\_\_\_ A. primarily the result of an ancillary study (list number\* \_\_\_\_\_)**

**\_\_\_\_\_ 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.csc.unc.edu/aric/forms/>

**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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

### Reference

1. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circulation. Cardiovascular quality and outcomes*. Jan 2012;5(1):85-93.
2. Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *Journal of the American College of Cardiology*. Feb 26 2008;51(8):810-815.
3. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA : the journal of the American Medical Association*. Nov 26 2003;290(20):2685-2692.
4. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. Feb 2010;137(2):263-272.
5. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity--results of a meta-analysis. *American heart journal*. Feb 2008;155(2):310-315.
6. Suk SH, Sacco RL, Boden-Albala B, et al. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke; a journal of cerebral circulation*. Jul 2003;34(7):1586-1592.
7. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. *JAMA : the journal of the American Medical Association*. Apr 22-29 1998;279(16):1273-1277.
8. Ezekowitz MD, Levine JA. Preventing stroke in patients with atrial fibrillation. *JAMA : the journal of the American Medical Association*. May 19 1999;281(19):1830-1835.
9. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA : the journal of the American Medical Association*. Aug 27 2003;290(8):1049-1056.

10. Ardestani A, Hoffman HJ, Cooper HA. Obesity and outcomes among patients with established atrial fibrillation. *The American journal of cardiology*. Aug 1 2010;106(3):369-373.
11. Badheka AO, Rathod A, Kizilbash MA, et al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *The American journal of medicine*. Jul 2010;123(7):646-651.
12. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Lip GY, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. *The American journal of medicine*. Jul 2013;126(7):640 e649-617.
13. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *Bmj*. Mar 25 1989;298(6676):789-794.
14. Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. *The New England journal of medicine*. Oct 23 1986;315(17):1041-1046.
15. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *American heart journal*. Jul 2009;158(1):111-117.
16. Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G. Alcohol consumption and the incidence of hypertension: The Atherosclerosis Risk in Communities Study. *Hypertension*. May 2001;37(5):1242-1250.
17. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *Journal of clinical epidemiology*. Aug 2001;54(8):774-781.
18. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Statistics in medicine*. Jan 30 2008;27(2):157-172; discussion 207-112.
19. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Statistics in medicine*. Jan 15 2011;30(1):11-21.
20. 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 : the journal of the American Medical Association*. Mar 16 1994;271(11):840-844.