ARIC Manuscript Proposal #2301

PC Reviewed: 2/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiovascular risk factor profile in atrial fibrillation patients and its association with NT-proBNP: the ARIC study

b. Abbreviated Title (Length 26 characters): Risk factors in AF patients

2. Writing Group:

Writing group members: Lindsay Bengtson, Elsayed Soliman, Sunil Agarwal, Ron Hoogeveen, Laura Loehr, Lin Chen, Alvaro Alonso, Scott Solomon, others welcome

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

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3. Timeline: This project should be submitted to a journal within 6 – 9 months of proposal submission.

4. Rationale:

Atrial fibrillation (AF) and other cardiovascular diseases (CVDs) share many common risk factors, including age, hypertension, diabetes, obesity, and prior coronary

heart disease.[1,2] Among US adults aged 20 and older in 2009-2010, 46.5% had at least one of the three following CVD risk factors: uncontrolled high blood pressure, uncontrolled high low density lipoprotein cholesterol, and current smoking.[3] Furthermore, the prevalence of cardiovascular comorbidities among those with AF is high; more than half of the AF burden can be explained by having at least one non-optimal risk factor.[4] In the ARIC study, we previously have shown that healthcare utilization, especially non-AF CVD-related utilization, was higher among participants with compared to those without AF, even after adjustment for CVD risk factors.[5]

Information on the prevalence and control of CVD risk factors in community-based samples of AF patients and how AF patients compare with the general population is limited. A repeat cross-sectional study performed in Spain in 1999 and 2009 reported an increase in the prevalence of AF and CVD comorbidities among AF patients as well as increased pharmaceutical treatment.[6] However, there was no control group so it is unknown how the CVD comorbidity and treatment trends compare to the general adult population. No similar report exists in the United States. Moreover, how control of cardiovascular risk factors in AF patients relates to N-terminal prohormone of brain natriuretic peptide (NT-proBNP), a biomarker of heart failure and a prognostic biomarker in AF patients,[7,8] is unclear.

Therefore, the aim of this study is to describe the prevalence, treatment, and control of CVD risk factors among those with compared to those without AF and to assess the association between CVD risk factor control and NT-proBNP.

5. Main Hypothesis/Study Questions: The specific aims and hypotheses are as follows:

Aim 1: Compare treatment and control of each CVD risk factor (hypertension, hyperlipidemia, and diabetes) among those with and without AF.

Hypothesis 1: Treatment and control of each CVD risk factor will be lower among those with compared to those without AF.

Aim 2: Among AF patients, evaluate the association between control of CVD risk factors and NT-proBNP.

Hypothesis 2: Atrial fibrillation patients with worse control of CVD risk factors will have higher NT-proBNP 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).

Study design

A cross-sectional analysis of visit 5 data will be performed.

Inclusion/exclusion

ARIC cohort participants who attended the 5th study visit (2011 – 2013) will be eligible for inclusion. Participants whose race is not white or black and nonwhites from

the Minneapolis and Washington County field centers will be excluded. Participants with missing risk factor, NT-proBNP or other covariate data from visit 5 will be excluded.

Atrial fibrillation

An AF diagnosis before or during the fifth study visit, from hospital discharge codes or study ECG, will be considered evidence of AF. Of the 6,538 participants who attended visit five, 557 had diagnosed AF or atrial flutter, 468 based on annual follow-up through 2010 and an additional 89 identified during the visit five ECG.

Risk factors

Hypertension

At visit five, seated blood pressure (BP) was measured three times following a five minute rest.

Definition: The mean of the BP readings will be used to define hypertension; systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, or self-reported use of antihypertensive medications, confirmed based on medication brought to the study visit.

Treatment: Self-reported use of antihypertensive medication. Participant self-report was confirmed based on medication bottles at the study visit.

Control: According to the Joint National Committee (JNC)-7 guidelines, participants on antihypertensive medications will be defined as having controlled high blood pressure if SBP < 140 mm Hg and DBP < 90 mm Hg or for those with diabetes or chronic kidney disease if SBP < 130 mm Hg and DBP < 80 mm Hg.[9] Additional analyses will be performed using the recently published JNC-8 guidelines.[10]

Hyperlipidemia

At visit five, blood samples were collected after a fast of at least eight hours and sent to the ARIC Central Lipid Laboratory for processing.

Definition: Hyperlipidemia will be defined based on low-density lipoprotein (LDL) cholesterol; an LDL-cholesterol level ≥ 100 mg/dL or self-reported use of lipid-lower medications, confirmed based on medications brought to the study visit.

Treatment: Self-reported use of lipid-lowering medications, confirmed based on medications brought to the study visit. Lipid-lowering medications were classified as statins as other lipid medications.

Control: According to the Adult Treatment Panel III guidelines, which were the current guidelines during ARIC study visit 5, participants on lipid-lowering medications will be defined as having controlled hyperlipidemia according to the LDL-C levels; participants will be considered controlled with LDL-C < 100 mg/dL for those with coronary heart disease (CHD) or a CHD risk equivalent, < 130 mg/dL for those with two or more risk factors, and < 160 mg/dL for those with 0-1 risk factor.[11] Additional analyses will be performed using the current guidelines.[12]

Diabetes

At visit five, blood samples were collected after a fast of at least eight hours and sent to the ARIC Clinical Research Laboratory.

Definition: Diabetes will be defined as fasting glucose ≥ 126 mg/dL, non-fasting glucose of ≥ 200 mg/dL, A1C ≥ 6.5%, self-reported physician diagnosis or self-reported current use of glucose lowering medications, including oral agents and insulin.
Treatment: Self-reported use of diabetes medication, confirmed based on medications brought to the study visit; use of diabetes medication includes oral agents and insulin.
Control: According to the American Diabetes Association participants on glucose lowering medication will be defined as having controlled diabetes with a fasting glucose < 126 mg/dL, non-fasting glucose of < 200 mg/dL or A1C of < 6.5%.[13]

Obesity
At visit five, standing height and weight were collected. Body mass index (BMI) was determined from these measurements.
Definition: Obesity will be defined, according to expert panel guidelines, as BMI ≥ 30 kg/m^2.[14]

Current smoking
At visit five, participants were asked, "Do you now smoke cigarettes?" and could answer "Yes" or "No."
Definition: Those who responded affirmatively will be classified as current smokers.

N-terminal prohormone of brain natriuretic peptide
Participants underwent venipuncture during visit 5; NT-proBNP was measured on the automated Cobas e433 analyzer (Roche Diagnostics) using an electrochemiluminescent immunoassay with a measurement range of 5-35,000 pg/mL and a limit of quantification of 35 pg/mL.

Other covariates

Standardized methods were used to collect data on age, race, sex, and educational achievement during the baseline visit, and data on smoking, body mass index, prior coronary heart disease, and prior heart failure were updated at each study visit, including visit 5.[15]

Statistical analysis

Participants with prevalent AF at visit 5 will be matched to up to three ARIC participants without AF based on age (within two years), sex, race and field center. Matching will be utilized to account for strong confounders and to obtain a balanced sample, and will be performed with the SAS macro, *gmatch*.[16] Characteristics of the study sample will be presented stratified by AF status. The prevalence of each CVD risk factor will be presented as the percent with the condition, stratified by AF status; multivariable adjusted logistic regression models will be used to assess if there are differences in the prevalence of each risk factor among those with compared to those without AF. For analyses involving NT-proBNP, log transformation will be explored; participants with values lower than the level of detection will be assigned the mean value between zero and the lower limit of detection.

Aim 1

Treatment and control of each CVD risk factor will be presented as the percent with the condition, stratified by AF status. Logistic regression models will be used to determine if there are differences in treatment and control of each risk factor among those with compared to those without AF, after adjustment for potential confounders. Logistic regression models will be used to identify independent factors associated with control of each CVD risk factor.

Aim 2

Among participants with AF and without prevalent heart failure, linear regression models will be used to determine if poor CVD risk factor control is independently associated with NT-proBNP.

Potential covariates

Statistical models will be adjusted for matching criteria (age, sex, race, and field center) to account for imbalances after matching. For Aim 1 models will be additionally adjusted for education, prior coronary heart disease, prior heart failure, prior stroke, and each of the other risk factors (hypertension, hyperlipidemia, diabetes, obesity and current smoking). For Aim 2 models will be adjusted for education, prior coronary heart disease, all of the risk factors examined in Aim 1.

Limitations

This is a cross-sectional analysis so we will not be able to determine the temporality of associations with echo measurements. However, it is unlikely that NT-proBNP would affect the CVD risk factors under examination in this study.

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/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)?

- **MS2097**—First and senior author, as well as some writing group members, are involved with this project

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ 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.cscc.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.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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