ARIC Manuscript Proposal #2973

PC Reviewed: 5/9/16 **Status:** _____ **Priority: 2**
SC Reviewed: _____ **Status:** _____ **Priority:** ____

1.a. Full Title: Association of NT-proBNP change with the risk of atrial fibrillation in the ARIC cohort

  b. Abbreviated Title (Length 26 characters):

2. Writing Group:
    Writing group members: Linzi Li, Alvaro Alonso, Wesley T. O'Neal, Elsayed Soliman, Lin Yee Chen, Liz Selvin, Pam Lutsey, Ron Hoogeveen

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

First author: **Linzi Li**
Address: Dept of Health Policy and Management, Rollins School of Public Health
        Emory University
        1518 Clifton Rd NE
        Phone: 404-513-9466
        E-mail: linzi.li@emory.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: Dept of Epidemiology, Rollins School of Public Health
        Emory University
        1518 Clifton Rd NE, CNR 3051
        Atlanta, GA 30322
        Phone: 404-727-8714
        E-mail: alvaro.alonso@emory.edu

3. Timeline:
A draft manuscript will be ready to submit for Publications Committee Review in summer 2017.

4. Rationale:
    Atrial fibrillation (AF) is a common chronic cardiac arrhythmia. It is associated with a 5-fold increase in the risk of ischemic stroke, accounting for approximately 15% of all strokes

nationally.[1] In the United States, the prevalence of AF, which rises substantially with age, is likely to increase 2.5-fold during the next 50 years.[2] The increasing prevalence will result in reduced quality of life and higher burden of medical costs. AF is commonly asymptomatic and paroxysmal, likely resulting in an underestimate of its prevalence and reduced opportunities for the prevention of AF-related complications (such as stroke). [3] Due to this limitation, risk scores for predicting AF have been developed, with the hope that they can contribute to identify high-risk individuals that may benefit from AF screening. [4,5]

Biomarkers can potentially contribute to the characterization of the risk of developing AF. N-terminal pro B-type natriuretic peptide (NT-proBNP) is an established biomarker of volume overload and myocardial stretch. NT-proBNP plays an important role in cardiovascular remodeling, volume homeostasis, and response to ischemia.[6,7]

Prior studies have described the association between circulating NT-proBNP and the risk of developing AF. In two Swedish cohorts, using a multimarker approach, NT-proBNP was a strong predictor of incident AF, and improved risk prediction when added to traditional risk factors.[8] Investigators in the Multi-Ethic Study of Atherosclerosis (MESA) found that NT-proBNP was a robust predictor of incident AF, with differences in the prognosis and predictive value of this biomarker across age groups and ethnic groups. [9] In addition, we have demonstrated previously in ARIC and other cohorts that concentrations of circulating NT-proBNP improve our ability to predict AF beyond information provided by clinical factors. [10,11] To our knowledge, however, no prior studies have specifically assessed whether changes in circulating NT-proBNP over time are associated with the risk of AF.

Therefore, taking advantage of the repeated measurements of NT-proBNP in ARIC, we seek to assess the change of plasma NT-proBNP as a predictor of incident AF in the ARIC cohort study.

5. Main Hypothesis/Study Questions:

Question: Is there an independent association between changes in circulating NT-proBNP and the risk of developing AF?

Hypothesis: Increase in plasma NT-proBNP concentration is associated with and predicts higher risk of 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).

- Study design

  Prospective cohort study

- Inclusion/Exclusion criteria

  o Inclusion: ARIC participants with available circulating NT-proBNP concentrations at visit 2 and 4 (about 11,000 individuals).

  o Exclusion: those with missing circulating NT-proBNP levels at visit 2 or 4, and participants who had developed AF by visit 4. We will also exclude non-whites from the Minneapolis and Washington County field centers, and individuals other than white or African American in the Forsyth County field center.

- Exposures

  The change of circulating NT-proBNP concentration between visit 2 and visit 4.

- Outcome

  Incident AF from the end of visit 4 through the end of 2013.

- Covariates

  Sex, age, race, study center, height, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, alcohol using status, diabetes, use of antihypertensive medications, heart failure (HF), myocardial infarction (MI), ECG p wave terminal force in V1. We will also run separate models that adjust for the variables included in the CHARGE-AF model: age, race, height, BMI, SBP and DBP, smoking status, diabetes, use of antihypertensive medications, HF, MI and visit 4 values of NT-proBNP.

- Analysis

  Concentrations of NT-proBNP will be natural logarithm-transformed (ln-transformed) and the main independent variable will be the difference between the two log-transformed variables, which corresponds to the logarithm of the ratio $[\ln(\frac{NT-proBNP4}{NT-proBNP2})]$. After exploring the distribution of this variable in the final sample and its association with AF

incidence, we will model it as a continuous variable or in categories defined either based on the distribution of the data or by change crossing clinically meaningful threshold.

We will calculate hazard ratios of AF and their 95% confidence intervals by change in NT-proBNP using Cox proportional hazards models. We will adjust for the variable shown above and for visit 4 NT-proBNP (to determine the association of change in NT-proBNP beyond visit 4 values). We will conduct sensitivity analyses excluding participants with prevalent heart failure at visit 4. Based on a calibration study performed in ARIC (Parrinello et al.),[12] we will add 9 pg/mL to the visit 4 plasma measurements to make then comparable with serum measurements (used at visit 2).

Finally, we will explore the predictive value of change in NT-proBNP by adding it to the CHARGE-AF predictive model and calculating the change in the c-statistic and the net reclassification index (Sinner et al, Europace 2014). [10]

As a limitation, we recognize that survival bias may occur since we will be limiting the analysis to participant who lived through visit 4. However, this sample is still relevant to answer questions on the predictive value of repeated NT-proBNP measurements conditional on survival.

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)?

MS #1578: Prediction of atrial fibrillation in the community: the CHARGE consortium (Alonso)
MS #2140: 6-year changes in NT-proBNP and metabolic change: the ARIC study (Lazo)

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* 2009.16 and 2008.10_____)**
    ___   **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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _X__ No.

[1] Atrial Fibrillation Investigators. (1994). Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch. Intern. Med.*, *154*, 1449.

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[7] Levin, Ellis R., David G. Gardner, and Willis K. Samson. "Natriuretic peptides." *New England Journal of Medicine* 339.5 (1998): 321-328.

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[10] Sinner, M. F., Stepas, K. A., Moser, C. B., Krijthe, B. P., Aspelund, T., Sotoodehnia, N., ... & Witteman, J. C. (2014). B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies. *Europace*, *16*(10), 1426-1433.

[11] Alonso, A., Roetker, N. S., Soliman, E. Z., Chen, L. Y., Greenland, P., & Heckbert, S. R. (2016). Prediction of Atrial Fibrillation in a Racially Diverse Cohort: The Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of the American Heart Association*, *5*(2), e003077.

[12] Parrinello, Christina M., et al. "Recalibration of blood analytes over 25 years in the Atherosclerosis Risk in Communities Study: impact of recalibration on chronic kidney disease prevalence and incidence." *Clinical chemistry* 61.7 (2015): 938-947.