ARIC Manuscript Proposal # 3100

PC Reviewed: 1/9/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The Association between Body mass index and NT-proBNP with the incidence of Atrial Fibrillation in the ARIC Study

 b. Abbreviated Title (Length 26 characters): **BMI, NT-proBNP and AF**

2.   Writing Group:
    Writing group members: Zakaria Almuwaqqat, Wesley O'Neal, Lin Y. Chen, Pamela L. Lutsey, Elizabeth Selvin, Faye Norby, Elsayed Soliman, Alvaro Alonso, others welcome.

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

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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).

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3.   Timeline:
January 2018 – Submit proposal

January-February 2018 – Complete primary data analysis
March-April 2018 –Manuscript preparation and submission

4. **Rationale**:

Obesity and atrial fibrillation (AF) are two major public health problems in the United States that are associated with significant morbidities and increasing risk of adverse cardiovascular events [1, 2]. The prevalence of AF in the US is expected to increase 2.5-fold during the next 50 years [3]. Similarly, the prevalence of obesity was 36.5% (crude estimate) among US adults during 2011–2014 with increasing prevalence over this period according to the US national center for health statistics.

Natriuretic peptides (NP), such as B-type NPs (BNP) and atrial NP are produced by cardiac myocytes in response to stretching of atrial or ventricular walls [4, 5]. BNPs are thought to play an important role in cardiovascular remodeling, volume homeostasis, and response to ischemia [6]. In addition, studies have shown that NPs may enhance lipolysis, and modulate energy expenditures accordingly [7, 8]. BNP and related molecules, such as the N-terminal pro B-type NP (NT-proBNP), are useful as biomarkers in the diagnosis of acute HF decompensation [9].

BNP concentrations are inversely correlated with body mass index (BMI) and total body fat [10]. Different hypotheses have been postulated in an attempt to explain the inverse relationship between obesity and circulating BNP levels. However, to date there has been no strong evidence supporting any of these hypotheses.

Obese and overweight patients with AF may have better prognosis and lower risk of adverse outcomes than leaner AF patients with the same degree of severity of

cardiovascular disease/AF [11]. These observations suggest a complex interplay between adiposity, NP physiology, and the development of AF.

A previous study has demonstrated an inverse relationship between BMI and plasma NT-proBNP concentrations in AF patients without heart failure [12]. While the relationship between NT-proBNP and BMI has been studied previously in ARIC populations with heart failure [8], the interaction between BNP and BMI, and between changes in BNP and BMI, in their association with AF risk has not been studied before.

In this proposal, we take advantage of the repeated measurements of NT-proBNP and BMI in ARIC to assess potential interactions in the association of BMI and NTproBNP (and their change over time) with incident AF in the ARIC cohort study.

5. Main Study Questions:

1) Aim 1: Assess the interaction of NT-proBNP and BMI with AF risk among HF free subjects using visit 4 (1996-98) data as baseline (with incident AF through 2015).

2) Aim 2: Assess the interaction between changes in BMI and changes in NT-proBNP between visits 2 (1990-92) and 4 (1996-98) in the association with incident AF among HF free subjects.

We hypothesize that ARIC participants with high NT-proBNP and BMI will be at the highest risk of developing AF, and that increases in both risk factors between visits 2 and 4 will be associated with increased AF risk. The direction of any identified interaction (i.e. synergistic vs antagonistic) may provide insights into the mechanisms underlying the inverse association between NPs and obesity.

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 participants

Eligible participants will be from the ARIC cohort with baseline examination data and information on NT-proBNP and BMI at visit 2 and 4.

Exclusion criteria

- Participants with AF at visit 4

- Participants with HF at visit 4 as HF would be a major confounder in NT-proBNP association with AF, also HF is going to have a major impact on NTproBNP values, so interpretation of results in a population that includes HF patients is going to be more complicated.

- Participants with race other than white or black, as well as non-whites from the Minnesota and Washington County field sites (because of very small numbers).

- Participants with very high levels of BNP in any of the 2 visits (e.g. >99th percentile)

Main exposure

BMI at visit 4 (Aim 1) and Change in BMI at visits 2 and 4 (Aim 2).

NT-proBNP at visit 4 (Aim 1) and Change in NT-proBNP at at visit 2 and 4 (Aim 2). Based on a calibration study performed in ARIC we will add 9 pg/mL to the visit 4 plasma measurements to make them comparable with serum measurements (used at visit 2). [13]

Outcome definition

Incident AF from the end of visit 4 through the end of 2015.

Other Variables of Interest

Sex, age, race, study center, education, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, alcohol using status, diabetes, use of antihypertensive medications, LVH by ECG, incident HF, and incident myocardial infarction (MI).

Analysis plan

For Aim 1, we will assess the interaction between BMI and concentrations of NT-proBNP in their association with incident AF. Concentrations of NT-proBNP will be natural logarithm-transformed (ln-transformed). We will assess interaction through different approaches (categorizing both BMI and NT-proBNP and using them as continuous variables). We will study association with incident AF using Cox proportional hazards models, adjusting for the variables described above. Interactions will be explored both in the multiplicative and in the additive scales.

For Aim 2, we will assess the interaction between change in BMI and change in NT-proBNP between visits 2 and 4 following a similar approach to Aim 1. In addition, we will

adjust for visit 2 covariates and for visit 2 NT-proBNP. We will explore the best modeling approach for the interaction using different categorizations of NT-proBNP and BMI. As mentioned above, based on a calibration study performed in ARIC we will add 9 pg/mL to the visit 4 plasma measurements to make then comparable with serum measurements (used at visit 2). [13]

As a limitation, we recognize that survival bias may occur since we will be limiting the analysis to participant who lived through visit 4. We will consider using approaches such as inverse probability weighting or multiple imputation to adjust for any selection bias derived from this limitation.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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

   No overlap with existing proposals

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)
- MS #2142: NT-proBNP and Heart Failure Risk Among Individuals With and Without Obesity: The ARIC Study (Ndumele)
- MS #2061: BNP and obesity in acute decompensated heart failure with preserved vs. reduced ejection fraction: The Atherosclerosis Risk in Communities Surveillance Study. Int J Cardiol, 2017. **233**: p. 61-66. (Khalid et al)
- MS #2973: NT-proBNP change and prediction of AF (Li / Alonso). This paper focuses on the added predictive value of NT-proBNP changes between visits 2 and 4, but does not explore interactions with BMI.

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

11.b. If yes, is the proposal
    ___   **A. primarily the result of an ancillary study (list number* _____)**
    _X__   **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _2008.10 and 2009.16)**

*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: No

References:

1.	Allison, D.B., et al., *Annual deaths attributable to obesity in the United States.* JAMA, 1999. **282**(16): p. 1530-8.
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3.	Go, A.S., et al., *Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study.* JAMA, 2001. **285**(18): p. 2370-5.
4.	de Bold, A.J., B.G. Bruneau, and M.L. Kuroski de Bold, *Mechanical and neuroendocrine regulation of the endocrine heart.* Cardiovasc Res, 1996. **31**(1): p. 7-18.
5.	Mukoyama, M., et al., *Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide.* J Clin Invest, 1991. **87**(4): p. 1402-12.
6.	Goetze, J.P., *Biosynthesis of cardiac natriuretic peptides.* Results Probl Cell Differ, 2010. **50**: p. 97-120.
7.	Ricci, M.A., et al., *Determinants of low levels of brain natriuretic peptide in morbid obesity.* Clin Nutr, 2017. **36**(4): p. 1075-1081.
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9.	Hogg, K., K. Swedberg, and J. McMurray, *Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis.* J Am Coll Cardiol, 2004. **43**(3): p. 317-27.
10.	Das, S.R., et al., *Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study.* Circulation, 2005. **112**(14): p. 2163-8.
11.	Lavie, C.J., et al., *Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise.* J Am Coll Cardiol, 2017. **70**(16): p. 2022-2035.
12.	Zheng, L.H., et al., *Impact of body mass index on plasma N-terminal ProB-type natriuretic peptides in Chinese atrial fibrillation patients without heart failure.* PLoS One, 2014. **9**(8): p. e105249.
13.	Parrinello, C.M., et al., *Recalibration of blood analytes over 25 years in the Atherosclerosis Risk in Communities Study: The impact of recalibration on chronic kidney disease prevalence and incidence.* Clinical chemistry, 2015. **61**(7): p. 938-947.