ARIC Manuscript Proposal #2140

PC Reviewed: 5/14/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: 6-year changes in n-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and metabolic changes: The Atherosclerosis Risk in Community Study

b. Abbreviated Title (Length 26 characters): Change in NT-proBNP, obesity, insulinemia and diabetes

2. Writing Group:

Writing group members: Mariana Lazo; Andreea Rawlings; Chiadi Ndumele; Dhananjay Vaidya; Hunter Young; Ron C. Hoogeveen; Christie M. Ballantyne; Josef Coresh; Elizabeth Selvin; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ML__ **[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: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

NT-pro BNP is a hormone released by the heart in response to increased wall stress (i.e. hypertension, heart failure). It has well established cardiovascular effects including natriuresis and vasodilatation.

More recently, it has been postulated that the effects of natriuretic peptides extend beyond the cardiovascular system and that they may play a role in metabolic regulation, lipolysis, and the development of insulin resistance(1-3). The mechanisms for these metabolic effects are not well understood but likely involve an increase in the mitochondrial biogenesis, adipose tissue lipolysis, and the "browning" of white adipocytes (inducing energy expenditure)(2, 4, 5). Receptors for natriuretic peptides have been found in cells of tissues other than the classical cardiovascular and renal systems, including adipose tissue(6). Cross-sectional studies have shown low levels of BNP among persons who are overweight or obese (7-10) and, in some studies, lower BNP among adults with diabetes or the metabolic syndrome(8, 9). A prospective analysis using ARIC data showed an inverse association between levels of NT-proBNP and incidence of diabetes, among persons without evidence of coronary heart disease or heart failure (MSP# 1966, submitted for publication).

Very few prospective studies are available to examine if levels of BNP predate changes in obesity and insulin resistance, or if levels of obesity and insulin resistance predate changes in NT-proBNP.

The availability of two measurements of NT-proBNP along with metabolic features six years apart in ARIC provides a unique opportunity to more fully characterize the association.

5. Main Hypothesis/Study Questions:

Aims :
Aim 1: To identify metabolic risk factors that correlate with change in NT-proBNP in a community-based population.

Aim 2: To characterize the association of six-year change in NT-proBNP with change in BMI, waist to hip ratio, A1C, fasting glucose, fasting insulin and lipids in a community-based population.

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 analysis of the changes in NT-proBNP from visit 2 (1990-1992) to visit 4 (1996-1998), and baseline levels as well as changes in metabolic risk factors.

NT-proBNP: NT-proBNP was measured at two time points

Visit 2: NT-proBNP levels were measured from stored (visit 2) serum samples using a sandwich immunoassay method (Roche Diagnostics) implemented on a Roche Elecys 2010 Analyzer in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study.

Visit 4: NT-proBNP levels were measured from stored (visit 4) plasma samples using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics) at the Baylor College of Medicine as part of Dr. Ballantyne's ancillary study.

Calibration of visit 2 and 4 measurements: A calibration study is currently underway to test the comparability of different laboratory assays between different ARIC visits (V1-V5), including the Roche NT-proBNP assay at visit 2 (serum, Roche Elecsys2010 at UMN) and visit 4 (plasma, Cobas e411 at Baylor). Anticipated completion date of the calibration study is ~May 2013. If systematic differences are observed between NT-proBNP values obtained using the method at UMN in serum compared to the method used at Baylor in plasma, we will use a statistical calibration to align the measurements and correct for the bias ("drift").

Exposure/Outcomes:

Change of NT-proBNP:
We will model NT-proBNP change in different ways: 1) Absolute change, 2) Percent Change, 3) Categorically: we will split the sample into 2 groups (below median, above median) and will define groups based on changes across groups from visit 2 to visit 4 (2X2 grid).

Metabolic factors:

BMI, waist to hip ratio, A1c, fasting glucose, fasting insulin and lipids. Changes in these factors will be also modeled as absolute and percent change.

Exclusions: Persons who did not attend visits 2 and 4, were missing information on exposures or covariates of interest, persons whose race was reported to be other than white or black, and blacks in the Minneapolis and Washington County cohorts.

Statistical analyses:
All analyses will be stratified by history of CVD status.

Aim 1: To identify metabolic risk factors that correlate with change in NT-proBNP in a community-based population

For analyses of percent or absolute change of NT-proBNP we will use multivariable linear regression models. We will consider the following models:

Model 1: age, sex, race-center.
Model 2: Model 1 + baseline systolic blood pressure, diastolic blood pressure, hypertension medication use.
Model 3: Model 1+ baseline BMI
Model 4: Model 1+ baseline waist circumference
Model 5: Model 1+ baseline waist to hip ratio
Model 6: Model 1+ baseline HDL, LDL, tryglycerides.
Model 7: Model 1+ baseline A1c (or diabetes)
Model 8: Model 1+ all anthropometrics measures, systolic blood pressure, diastolic blood pressure, hypertension medication use, BMI, HDL, LDL, triglycerides, diabetes.

For the analyses based on changes across categories : High→High, High→Low, Low→High, we will compare the metabolic characteristics across groups using ANOVA test.

Aim 2: To characterize the association of six-year change in NT-proBNP with change in BMI, waist to hip ratio, A1C, fasting glucose, fasting insulin and lipids in a community-based population.

We will use linear regression model to examine correlates of change of NT-proBNP, and 6-year change of obesity status, progression of dysglycemia, and lipids.

Limitations:

- Different assays and sample type (serum vs. plasma) were used to measure NT-proBNP at visits 2 and 4. Results of the calibration study will inform of any drift, and if needed we will use statistical methods to account for the drift and align the measures.
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

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)?

Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, Huxley RR, Ballantyne CM. Troponin T, N-Terminal Pro-B-Type Natriuretic Peptide, and Incidence of Stroke: The Atherosclerosis Risk in Communities Study.
Stroke. 2013 Mar 7. [Epub ahead of print] PMID: 23471272

MSP# 1966. Mariana Lazo, Frederick L. Brancati, Seamus Whelton, Josef Coresh, Chiadi E. Ndumele, Ron Hoogeveen, Christie M. Ballantyne, J. Hunter Young, Elizabeth Selvin. The association between NT-proBNP with incident diabetes

MSP# 1614. Avery CL, Hoogeveen RC, Catellier D, Shahar E, Heiss G, Rhodes CE, Agarwal SK, Ballantyne CM. Components of variability in the measurement of NT-pro BNP. 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

___ 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.

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2. Miyashita K, Itoh H, Tsujimoto H, Tamura N, Fukunaga Y, Sone M, et al. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. Diabetes. 2009;58(12):2880-92.
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6. Sarzani R, ssi-Fulgheri P, Paci VM, Espinosa E, Rappelli A. Expression of natriuretic peptide receptors in human adipose and other tissues. JEndocrinolInvest. 1996;19(9):581-5.
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8. Khan AM, Cheng S, Magnusson M, Larson MG, Newton-Cheh C, McCabe EL, et al. Cardiac natriuretic peptides, obesity, and insulin resistance: evidence from two community-based studies. JClinEndocrinolMetab. 2011;96(10):3242-9.
9. Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. Circulation. 2007;%20;115(11):1345-53.
10. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation. 2004;109(5):594-600.