

ARIC Manuscript Proposal #2142

PC Reviewed: 5/14/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Obesity and the Use of NT-proBNP for Heart Failure Prediction: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Obesity, NT-proBNP and HF

2. Writing Group: Chiadi E. Ndumele; Kunihiro Matsushita; Yingying Sang; Mariana Lazo; Sunil K. Agarwal; Vijay Nambi; Roger S. Blumenthal; 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. CN [please confirm with your initials electronically or in writing]

First author: Chiadi E. Ndumele, MD, MHS
Address: Assistant Professor of Medicine
Johns Hopkins University School of Medicine
600 North Wolfe Street
Carnegie 568
Baltimore MD 21287

Phone: 410-502-2319 Fax: 410-614-8882
E-mail: cndumel2@jhmi.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: Elizabeth Selvin, PhD
Address: Associate Professor of Epidemiology
Johns Hopkins University
2024 E. Monument Street, Suite 2-600
Baltimore MD 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: lselvin@jhsph.edu

3. Timeline: We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. Rationale:

Brain Natriuretic Peptide (BNP) is a hormone with natriuretic properties that is secreted by ventricular myocytes in response to elevated ventricular filling pressures and increased wall stress¹. The N-terminal fragment of the prohormone of BNP (NT-proBNP) is a marker for the severity of heart failure (HF)^{2, 3} and is also associated with subclinical left ventricular dysfunction among asymptomatic individuals⁴. Elevated NT-proBNP levels predict incident HF among apparently healthy individuals in the general population⁵⁻⁷. A recent analysis demonstrated that the addition of NT-proBNP to traditional risk factors significantly improved HF risk discrimination⁸.

Individuals with obesity are also at increased risk for the development of HF⁹, but an inverse association has previously been noted between adiposity and NT-proBNP levels among individuals with stable HF^{10, 11}, acute decompensated HF^{12, 13} and among those in the general population¹⁴. Physiologic studies have demonstrated a poor correlation between BNP levels and left ventricular filling pressures among individuals with obesity, in contrast to strong correlations among lean individuals¹⁵⁻¹⁷. It has been suggested that lower cutpoints for “high” NT-proBNP may be appropriate among obese HF patients to maximize sensitivity^{10, 12}. However, the appropriate use of NT-proBNP for HF risk prediction according to obesity status among individuals in the general population is presently unknown.

In this analysis of asymptomatic participants in the Atherosclerosis Risk in Communities (ARIC) study, we will evaluate the utility of NT-proBNP for HF risk prediction among individuals with different obesity status, in order to further inform its clinical use among obese and overweight individuals in the general population.

5. Main Hypothesis/Study Questions:

Aims:

- 1) To evaluate whether the association of NT-proBNP with HF differs according to obesity status
- 2) To evaluate the use of NT-proBNP for HF risk prediction among individuals within different obesity categories in the general 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: We will evaluate whether the prospective association of NT-proBNP levels with incident HF varies according to obesity status. The utility of NT-proBNP for risk prediction across within different obesity categories will also be evaluated. To

maximize the number of HF cases, ARIC Visit 2 (1990-1992), at which NT-proBNP levels have recently been measured on all participants, will be used as the baseline for this analysis.

Exposures: The exposure of interest will be NT-proBNP levels measured at ARIC Visit 2. NT-proBNP will be evaluated continuously and also categorized (initially using cutpoints of 100 pg/mL, 200 pg/mL, 300 pg/mL and 400 pg/mL, with other cutpoint schemes likely to be defined by percentiles).

Potential effect modifier: Body-mass index (BMI) (height in kilograms divided by meters squared) measured at ARIC Visit 2 will be used as a measure of adiposity and will be the potential effect modifier in this study. BMI will also be assessed continuously and categorically as normal (BMI 18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), obese (30-34.9 kg/m²) and severely obese (>35 kg/m²).

Outcomes: The primary outcome will be incident HF, defined as a HF-related hospitalization or death occurring after Visit 2 through January 1, 2010 (or most current follow-up available). Secondary outcomes will be cardiovascular and all-cause mortality.

Exclusions: We will also exclude the small number of participants at Visit 2 who are not black or white, and those participants missing covariates of interest at baseline.

Covariates: Variables within the ARIC HF risk factor score: age, sex, race, smoking status, heart rate, systolic blood pressure, use of anti-hypertensive medications, diabetes and prevalent CVD. Additional variables of interest include LDL-cholesterol, HDL-cholesterol, triglycerides, alcohol intake and estimated GFR.

Main Analyses: We will evaluate the prospective association of NT-proBNP with the risk of incident HF among participants within each BMI category and formally test their interaction.

- 1) We will compare baseline characteristics across BMI and NT-proBNP categories.
- 2) We will use Poisson-regression models with linear spline terms to estimate the association of higher NT-proBNP with HF incident rates within each BMI category.
- 3) We will construct Cox proportional hazards models to estimate the hazard ratios for incident HF and related 95% confidence intervals associated with higher NT-proBNP within each BMI category. NT-proBNP will be modeled categorically using the cutpoints described above and will also be modeled continuously using restricted cubic spline models. The interaction between NT-proBNP and BMI (both as categorical and continuous variables) will be tested with likelihood ratio tests.
- 4) We evaluate changes in the net reclassification index (NRI) associated with the addition of NT-proBNP to traditional HF risk factors (using variables included in the ARIC HF risk score) within each BMI category, using methods accounting for censoring. We will use cutpoints for 10-year risk of incident HF of <5%, 5 to

- <10%, 10 to <20%, and \geq 20%. NT-proBNP will be modeled both categorically (assessing different cutpoints for “high” BNP) and continuously. We will also evaluate changes in the continuous NRI with the addition of NT-proBNP.
- 5) We will also assess changes in integrated discrimination improvement (IDI) associated with the addition of NT-proBNP to traditional risk factors within each BMI category, using methods accounting for censoring. NT-proBNP will be modeled both categorically and continuously.
 - 6) We will evaluate changes in the c-statistic associated with the addition of NT-proBNP to traditional HF risk factors among individuals with different baseline BMIs, modeling BMI and NT-proBNP both categorically and continuously. We will again utilize methods that account for censoring.
 - 7) We will perform analyses stratified by race, gender and age (\geq or < than 60 years) and test for their three-way interactions with NT-proBNP and BMI.
 - 8) We will perform additional analyses substituting waist circumference (assessed categorically, by dividing into quartiles) for BMI as the metric for adiposity.

Subgroup Analysis: We will repeat the above analyses within the subgroup of individuals without known CVD prior to Visit 2 (defined as self reported CVD at Visit 1, or incident HF or adjudicated CHD events at or prior to Visit 2).

Sensitivity Analysis: We will perform a sensitivity analysis using NT-proBNP at ARIC Visit 4 (1996-1998) as a secondary baseline, which will allow us to account for some unique confounders only evaluated at visit 4 (e.g., albuminuria).

Limitations:

- There is the likelihood for some residual confounding in our efforts to assess differences in the relationship between NT-proBNP and incident HF within different BMI categories
- The use of hospitalization and discharge codes for the diagnosis of incident HF may have resulted in some misclassification

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 ICTDER03 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.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)?

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

Agarwal SK, Chambless LE, Ballantyne CM, Astor B, Bertoni AG, Chang PP, Folsom AR, He M, Hoogeveen RC, Ni H, Quibrera PM, Rosamond WD, Russell SD, Shahar E, Gerardo Heiss G. Prediction of Incident Heart Failure in General Practice: The Atherosclerosis Risk in Communities (ARIC) Study. *Circ Heart Fail*. 2012;5:422-429.

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? Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* [2009.16](#))

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/>

12. 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.

Reference List

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- (7) Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006 December 21;355(25):2631-9.
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- (9) Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002 August 1;347(5):305-13.
- (10) Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *J Am Coll Cardiol* 2006 January 3;47(1):85-90.
- (11) Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, Frohlich ED. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol* 2004 May 5;43(9):1590-5.
- (12) Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Maisel AS. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *Am Heart J* 2006 May;151(5):999-1005.
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