ARIC Manuscript Proposal #1966

PC Reviewed: 7/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The association between NT-proBNP with incident diabetes

b. Abbreviated Title (Length 26 characters):
NT-proBNP and DM

2. Writing Group:
Writing group members:
Mariana Lazo, Frederick L. Brancati, Seamus Whelton, Josef Coresh, Chiadi E. Ndumele, Ron Hoogeveen, Christie M. Ballantyne, J. Hunter Young, 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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3. Timeline:
Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next six months.

4. Rationale:

Pro-brain natriuretic peptide (proBNP) is one of the three natriuretic peptides released by the heart in response to hemodynamic stress (e.g. increased volume or high blood pressure)[1]. Furthermore, BNP is closely associated with left ventricular mass index[2] and accurately detects heart failure.[3] Moreover, elevated levels of BNP are associated with an increased risk of mortality and cardiovascular disease (CVD), especially heart failure.[3]

Diabetes and obesity are associated with increased risk of CVD morbidity and mortality[4, 5], thus people with these conditions would be expected to have higher BNP levels. Paradoxically, cross-sectional studies have shown lower levels of BNP with increasing body mass index (BMI) [6-8] and, in some studies, lower NT-proBNP among people with diabetes and metabolic syndrome[9-12]. The reasons for these paradoxical associations are not fully understood.

Widely known effects of BNP include cardiovascular (vasodilation) and renal (natriuresis) effects, which confer protection against fluid overload and hypertension[1]. However, putative metabolic effects of BNP have recently been observed in animal and human experimental studies. BNP transgenic mice with overexpression of BNP, had decreased risk of obesity and insulin resistance after receiving a high-fat diet and, the mechanisms involved in this protective effect include: increased mitochondrial content and fat oxidation[13]. In humans, intravenous administration of BNP was shown to lower circulating glucose after a glucose tolerance test, without affecting insulin secretion and tolerance, and the authors hypothesize that the mechanisms by which BNP induces a decrease in blood glucose is due to increased vasodilatation and increased glucose distribution throughout the body[14].

To our knowledge, the prospective association between BNP levels and the risk of diabetes in humans has not been fully characterized. Therefore, the objective of this study is to determine the independent association between BNP levels and risk of diabetes in a community based sample without diabetes or cardiovascular disease at baseline. We hypothesized that lower levels of N-terminal (NT)-proBNP, a stable cleavage product of proBNP, would be associated with an increased risk of diabetes.

5. Main Hypothesis/Study Questions:

Are levels of N-terminal (NT)-proBNP, a more stable cleavage product of proBNP, associated with the risk of diabetes? We hypothesize that lower levels of NT-proBNP will be associated with increased risk of diabetes.

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 with baseline values measured at Visit 4 and annual follow up via telephone for assessment of physician diagnosis of diabetes or use of medications for diabetes.

Inclusion criteria:
- Participants in whom a plasma NT-proBNP was measured at Visit 4 who provided annual follow up (AFU) information on diabetes.

Exclusion criteria:
- Participants with: known coronary artery disease (history, EKG evidence of angina or myocardial infarction), history of heart failure, diabetes (self-report or undiagnosed) or with low kidney function (estimated GFR <60 mL/min/1.73 m^2).
- Participants missing NT-proBNP .
- Participants with missing data on covariates of interest.
- Participants with race/ethnicity other than black or white.
- Participants who were fasting <8 hours at visit 4

Exposure Variable:
- NT-proBNP measured from stored plasma samples (visit 4, 1996-1998) using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics) with lower limit of detection ≤5 pg/mL and coefficient of variation 3.5–4.7%.
- NT-proBNP will be analyzed categorically (quartiles) and continuously (log-transformed). For the categorical analyses, those with undetectable levels (≤5 pg/mL) will be the included in the lowest quartile. For the continuous analyses, those with undetectable levels will be assigned a value of 2.5 pg/mL (i.e., half the lower limit of detection).

Potential Confounders:
-Age, sex, race, cholesterol levels (total, LDL- and HDL-cholesterol), systolic blood pressure, serum glucose, hypertension medication use, waist to hip ratio, height, estimated glomerular filtration rate, smoking (current, former, never), hs-C-reactive protein, alcohol consumption, plasma lactate, family history of diabetes, use of ACE inhibitors

Potential Effect Modifiers:
- Body mass index, sex, race.

Outcome Variables:
Incident diabetes, defined as self-report physician diagnosis or medication use identified during AFU phone calls through April 2011 [or most recent datafiles available]

Analysis plan and methods:
To compare baseline characteristics by categories (quartiles) of NT-proBNP we will use ANOVA or chi-squared tests as appropriate. To estimate the risk of diabetes by

categories (quartiles) of NT-proBNP we will use cox proportional hazards regression models and we will build models with progressive degrees of adjustment. Model 1: Sociodemographics, Model 2: Model 1 + BMI, Model 3: Model 2+ height and cardiovascular risk factors (SBP, DBP, Smoking, LDL, HDL, hs-CRP), Model 4: Model 3 + Fasting glucose and family history of diabetes.
Additionally, Kaplan –Meier survival analysis will be used to assess the unadjusted association between NT-proBNP quartiles and incidence of diabetes.

NT-proBNP will also be modeled as a continuous variables and we will test the significance of deviation from linearity by comparing a linear model to spline models including a spline model with knots at the 33rd and 67th percentiles.

Sensitivity analyses:
Sensitivity analyses will be conducted excluding participants who presented the outcome during the first 5 years of follow-up.
We will also perform analyses for NT-proBNP excluding individuals who develop heart failure and participants with impaired fasting glucose at baseline.

Limitations
Only single measurements of pro-BNP are available.
The primary outcome is self-reported diabetes.
As with any observational study, the possibility residual confounding cannot be completely eliminated

Summary/conclusion:
We will prospectively investigate the association of NT-proBNP and incident diabetes among a group of participants without a history of cardiovascular disease at baseline. If our hypothesis is correct, the results will extend compelling evidence from animal studies suggesting a causal role of BNP in the development of diabetes.

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.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)?

MP# 1811 Association of high sensitive Troponin T (hs-cTnT),N- Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study

MP# 1596 Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT

MP# 1734 Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T

MP# 1564: Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association withMortality and Adverse Cardiovascular Events

MP# 1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study

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/

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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(2) Nishikimi T, Yoshihara F, Morimoto A et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension* 1996 July;28(1):22-30.

(3) Cowie MR, Struthers AD, Wood DA et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997 November 8;350(9088):1349-53.

(4) Sarwar N, Gao P, Seshasai SR et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010 June 26;375(9733):2215-22.

(5) Selvin E, Marinopoulos S, Berkenblit G et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004 September 21;141(6):421-31.

(6) Bayes-Genis A, DeFilippi C, Januzzi JL, Jr. Understanding amino-terminal pro-B-type natriuretic peptide in obesity. *Am J Cardiol* 2008 February 4;101(3A):89-94.

(7) Das SR, Drazner MH, Dries DL et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation* 2005 October 4;112(14):2163-8.

(8) Wang TJ, Larson MG, Levy D et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004 February 10;109(5):594-600.

(9) Khan AM, Cheng S, Magnusson M et al. Cardiac natriuretic peptides, obesity, and insulin resistance: evidence from two community-based studies. *J Clin Endocrinol Metab* 2011 October;96(10):3242-9.

(10) Olsen MH, Hansen TW, Christensen MK et al. N-terminal pro brain natriuretic peptide is inversely related to metabolic cardiovascular risk factors and the metabolic syndrome. *Hypertension* 2005 October;46(4):660-6.

(11) Pfister R, Sharp S, Luben R et al. Mendelian randomization study of B-type natriuretic peptide and type 2 diabetes: evidence of causal association from population studies. *PLoS Med* 2011 October;8(10):e1001112.

(12) 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 March;%20;115(11):1345-53.

(13) Miyashita K, Itoh H, Tsujimoto H et al. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. *Diabetes* 2009 December;58(12):2880-92.

(14) Heinisch BB, Vila G, Resl M et al. B-type natriuretic peptide (BNP) affects the initial response to intravenous glucose: a randomised placebo-controlled cross-over study in healthy men. *Diabetologia* 2012 May;55(5):1400-5.