ARIC Manuscript Proposal # 3213

PC Reviewed: 8/14/18   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

  1.a.   **Full Title**: NT-proBrain Natriuretic Peptide, Body Fatness and Incident Heart Failure in Postmenopausal Women of the ARIC Study

  b. **Abbreviated Title**: NT-ProBNP and Heart failure

2.   **Writing Group**: Imo Ebong, Duke Appiah, Tamar Polonsky, Patty Chang, Christie Ballantyne, Alain Bertoni

    I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. IAE

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3.   **Timeline**: 12 -18 months

4.   **Rationale**:
Heart failure (HF) is an important cause of morbidity and mortality[1] and is characterized by high prevalence, poor clinical outcomes and significant health care costs.[2] Menopause is associated with adverse changes in cardiac structure and function[3] and postmenopausal women experience a higher burden of HF.[2] Women who experience early menopause are at a greater risk of developing HF when compared to those who transition into menopause at older ages.[4,5] An aging population implies that a greater number of women will be affected by HF in their lifetime. Although there are persisting controversies on the direct causal link between

menopause and HF, it is necessary to understand the mechanisms of HF in the postmenopausal state and identify biomarkers that could reliably predict postmenopausal women who are at an increased risk of developing HF.

NT-pro brain natriuretic peptide (NT-proBNP) is produced from the cleavage of proBNP which is secreted by cardiac myocytes and cleaved into the biologically active fraction, BNP and the inactive fraction, NT-proBNP.[6] NT-proBNP is an established biomarker for the diagnosis, prognosis and management of patients with HF.[7] NT-proBNP is affected by smoking, race and body mass index which are factors that could influence the age at which a woman experiences menopause.[8] Hormonal changes in the postmenopausal state could also affect natriuretic peptide levels.[9] In the MESA study, we showed that an early age at menopause is associated with greater NT-proBNP levels.[8] NT-proBNP can easily be measured by healthcare providers in the clinical setting. Elevated NT-proBNP levels could be an indicator of women who are at increased risk of developing HF after the onset of menopause.

The onset of menopause is commonly associated with an increase in fat mass especially central body fatness.[10] Although obesity is associated with an increased risk of incident HF,[1] NT-proBNP levels are usually lower in individuals with excessive body fat.[11] But, central body fatness has been shown to be a better predictor of incident HF in some studies.[1] The goals of our study are to examine the complex relationships of NT-proBNP, central and generalized body fatness with incident HF in postmenopausal women of the ARIC study.

References

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2.   Agha G, Loucks EB, Tinker LF, et al. Healthy Lifestyle and Risk of Heart Failure in the Women's Health Initiative Observational Study. *J Am Coll Cardiol.* 2014;64:1777-1785.
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5.   Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, Folsom AR. Association of Age at Menopause with Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis. *J Am Heart Assoc.* 2016;5:pii: e003769.
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7.   Palazzuoli A, Gallotta M, Quatrini I, Nuti R. Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure. *Vasc Health Risk Manag.* 2010;6:411-418.
8.   Ebong IA, Watson KE, Goff DC, et al. Association of menopause age and N-terminal pro brain natriuretic peptide: the Multi-Ethnic Study of Atherosclerosis. *Menopause.* 2015;22:527-533.
9.   Lam CSP, Cheng S, Choong K, et al. Influence of Sex and Hormone Status on Circulating natriuretic Peptides. *J Am Coll Cardiol.* 2011;58:618-626.

10.   Ebong IA, Watson KE, Hairston KG, et al. Body fat Distribution, menopausal hormone therapy and incident type 2 diabetes in post menopausal women of the MESA study. *Maturitas.* 2016;91:147-152.

11.   Ndumele CE, Matsushita K, Sang Y, et al. NT-proBNP and Heart Failure Risk Among Individuals With and Without Obesity: The ARIC Study. *Circulation.* 2016;133:631–638.

Design and analysis:
5a. Main Hypothesis:
1. NT-proBNP is associated with incident HF in postmenopausal women but this association will be modified by body fat distribution with the risk of HF due to NT-proBNP being greater in women without central body fatness than those with central body fatness
2. The association of NT-proBNP with incident HF will vary by generalized body fatness with the greatest associations in normal weight women when compared to women who are overweight or obese

5b. Exploratory hypothesis:
We also hypothesized that the association of NT-proBNP with incident HF in postmenopausal women will be greater in women who had experienced early menopause when compared to those who did not

6. Design and analysis:
Study design: Cohort study

Data
Inclusion criteria: Women who had experienced natural menopause and had measurements of NT-proBNP at ARIC visit 4 exam. Women were considered to have experienced natural menopause if they were older than 55 years of age or self-reported being postmenopausal and/or an absence of menstrual periods in the preceding 1 year before ARIC exam 4.

Exclusion criteria: Women who were missing information on age at menopause and HF status at the end of follow up. We will exclude women with prevalent HF at ARIC exam 4. We will also exclude women who were younger than 55 years of age at ARIC exam 4 and those who had undergone hysterectomy without bilateral oophorectomy.

Variable types:
Study hypothesis 1:
1. Predictor variable: NT-proBNP (continuous variable) measured at exam 4 data.
2. Outcome variable: Incident HF and follow up time in years
3. Effect modifier: Central obesity will be indicated by waist circumference (WC). Women will be classified as having central obesity if waist circumference is >88 cm

Study hypothesis 2:
1. Predictor variable: NT-proBNP (continuous variable) measured at exam 4 data.

2. Outcome variable: Incident HF and follow up time in years
3. Effect modifier: Generalized obesity indicated by body mass index (BMI). Women were classified as normal weight if BMI was <25 kg/m^2, overweight if BMI was 25-29.9 kg/m^2, obese if BMI was 30-39.9 kg/m^2 and severely obese if BMI was ≥40 kg/m^2

Exploratory hypothesis:
1. Predictor variable: NT-proBNP (continuous variable) measured at exam 4 data.
2. Outcome variable: Incident HF and follow up time in years
3. Effect modifier: Early menopause (categorical variable). Early menopause was present if women experienced natural menopause before 45 years

Covariates (from exam 4 data):
1. Confounders (exam 4 data): age, race, educational status, cigarette smoking and center
2. Traditional CVD risk factors (exam 4 data): systolic blood pressure, antihypertensive medication use, hypertension, diabetes, total cholesterol, high density lipoprotein-cholesterol, triglyceride, waist circumference, hip circumference, body mass index, sports-index physical activity, hormone therapy use, parity. Waist-hip ratio will be calculated as waist circumference/hip circumference.
3. History of myocardial infarction at ARIC visit 4 and during follow up
4. Menopause related variables:
   a. Self-report of being postmenopausal
   b. Age at menopause
   c. Number of periods in last 12 months
   d. Date of last menstrual period
   e. Self-report of hysterectomy
   f. Self-report of bilateral oophorectomy

Analytical plan:

This study will include postmenopausal women in the ARIC study with NT-proBNP measurements obtained at study exam 4. Descriptive statistics will be used to present characteristics of study participants according to HF status using means ± SD, median (interquartile range) and percentages as appropriate. Comparisons will be made between the HF groups using Chi-squared test, 2 sample T-test and Mann-Whitney U test as appropriate. Variables with highly skewed distributions will be log-transformed. We will calculate the incidence rates of HF according to groups of central and generalized obesity. Kaplan-Meier plots for incident HF will be presented according to quartiles of NT-proBNP and tested with the Log-rank test.

For study hypothesis 1, We will use Cox Proportional hazards techniques to model the associations of NT-proBNP with incident HF and other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional CVD risk factors. We will test for the presence of interactions between NT-proBNP and central obesity.

For study hypothesis 2, We will use Cox Proportional hazards techniques to model the associations of NT-proBNP with incident HF and other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional CVD risk factors. We will test for the presence of interactions between NT-proBNP and generalized obesity.

For our exploratory hypothesis, we will use Cox Proportional hazards techniques to model the associations of NT-proBNP with incident HF and other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional CVD risk factors. We will test for the presence of interactions between NT-proBNP and early menopause. In testing all 3 hypothesis, we will evaluate for the proportionality of hazards assumption by visually examining the log-log plots. Two-sided p-values of <0.05 will be considered significant.

7.a. Will the data be used for non-CVD analysis in this manuscript? <u>No</u>

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? Not applicable

8.a. Will the DNA data be used in this manuscript? <u>No</u>

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"? Not applicable

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: <u>http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html</u>

<u>Yes</u>

10. What are the most related manuscript proposals in ARIC? NT-proBNP and Heart Failure Risk Among Individuals With and Without Obesity: The ARIC Study. Ndumele et al. Circ. 2016

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

11.b. If yes, is the proposal
  <u>NO</u> A. primarily the result of an ancillary study
  <u>YES: Number 2008.10</u> B. primarily based on ARIC data with ancillary data playing a minor role (Measurement of N-pro-BNP and troponin T at visit 4 for the full ARIC cohort, Principal Investigator; Christie M. Ballantyne)

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.