ARIC Manuscript Proposal #3213 rev1

PC Reviewed: 8/11/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: NT-pro B-Type Natriuretic Peptide, Early Menopause and Incident Heart Failure in Postmenopausal Women of the ARIC Study

b. Abbreviated Title: NT-ProBNP, Early menopause 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 B-type 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 (menopause before 45 years of age) 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 goal of our study of our study is to examine the effects of early menopause status on the associations of NT-proBNP and incident HF in postmenopausal women of the ARIC study.

References

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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. We hypothesized that a prior history of early menopause is associated with greater levels of NT-proBNP in postmenopausal women.
2. 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: Postmenopausal women who had measurements of NT-proBNP at ARIC Visit 4 exam. Women were considered to have experienced 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 2 years before ARIC Visit 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 Visit 4. We will also exclude women who had undergone hysterectomy without bilateral oophorectomy due to inability to accurately estimate their menopause age.

Variable types:

Study hypothesis 1:

1. Predictor variable: Early menopause at ARIC Visit 4
2. Outcome variable: NT-proBNP (continuous variable) measured at ARIC Visit 4.

Study hypothesis 2:

1. Predictor variable: NT-proBNP (continuous variable) measured at Visit 4.
2. Outcome variable: Incident HF 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 Visit 4 data):

1. Confounders (exam 5 data): age, race, educational status, cigarette smoking and center
2. Traditional CVD risk factors (exam 5 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 5 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 Visit 4 exam. 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 early menopause categories. Kaplan-Meier plots for incident HF will be presented according to early menopause status and tested with the Log-rank test.

For study hypothesis 1, We will use linear regression methods to model the associations of early menopause with NT-proBNP, adjusting for other covariates.

For study hypothesis 2, we will use Cox Proportional hazards techniques to model the associations of NT-proBNP with incident HF according to early menopause status, adjusting for other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional heart failure risk factors. We will test for the presence of interactions between NT-proBNP and early menopause for our incident heart failure outcome. 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? 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? Not applicable

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"? 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: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html
Yes

10. What are the most related manuscript proposals in ARIC? None

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

NO A. primarily the result of an ancillary study

YES: Number 2008.10 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.