ARIC Manuscript Proposal # 3205

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SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: High-Sensitivity Cardiac Troponin T and the Risk of Heart Failure in Postmenopausal Women of the ARIC Study

b. Abbreviated Title: Menopause and heart failure

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

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

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3. Timeline: 12 -18 months

4. Rationale:

High-sensitivity cardiac troponin T (hs-cTnT) is a subclinical marker of myocardial damage[1,2] and is strongly associated with cardiovascular disease (CVD) events including incident heart failure (HF).[2] In contrast to the conventional cTnT assay which is detectable in 1% of the general population, hs-cTnT is detectable in up to 66% of individuals in the general population.[3] Elevated hs-cTnT concentrations have been associated with a higher prevalence of traditional CVD risk factors such as hypertension and diabetes[4], more cardiac pathology and worse outcomes including HF, coronary heart disease (CHD) and death in adults with known CVD and those with ideal cardiovascular health.[1-3,5]

Early menopause has been identified as a sex specific risk factor for HF in women who experience menopause before the age of forty-five years in prior studies.[6-8] The precise mechanisms that link menopause with HF remain unknown. It is likely that an adverse CVD risk profile in the menopausal state may be partially contributory[9] because the prevalence of CVD risk factors such as hypertension,[10,11] diabetes,[10,12-14] visceral obesity,[12,13,15] insulin resistance,[13,14] dyslipidemia[10,12-14] and endothelial dysfunction are more common after the onset of menopause[12].

Early menopause has also been associated with elevated N-terminal pro brain-type natriuretic peptide levels (NT-proBNP) levels[16] and NT-proBNP is a marker for the diagnosis, prognosis and management of HF.[16] Although it is yet to be studied, hs-cTnT is another biomarker that could also be associated with early menopause and may be an indicator of the risk of future HF in women who experience early menopause. We will evaluate the relationships between early menopause and hs-cTnT in postmenopausal women of the ARIC study. We will investigate the role of hs-cTnT as a predictor of future HF in postmenopausal women according to their early menopause status. Finally, we will explore the implications of a temporal change in hs-cTnT on the risk of future HF in postmenopausal women of the ARIC study.

References

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5a. Main Hypothesis:

1. Early menopause (and age at menopause) are independently associated with measurements of hs-cTnT in postmenopausal women.
2. hs-cTnT is an independent predictor of incident HF in postmenopausal women but this association will vary according to early menopause status being greater in women with early menopause when compared to those without early menopause

5b. Exploratory hypothesis

A temporal increase in hs-cTnT level is associated with an increased risk of incident heart failure in postmenopausal women but this association will also vary according to early menopause status being greater in women with early menopause when compared to those without early menopause

6. Design and analysis:

Study design: Cohort study

Data

Inclusion criteria: Women who had experienced natural menopause and had measurements of hs-cTnT 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 who had undergone hysterectomy without bilateral oophorectomy.

Variable types:
Predictor variables (study hypothesis 1): These will be obtained from exam 4 data. Data related to menopause status of all participants at baseline will also be collected.

1. Early menopause (categorical variable) Early menopause was present if women experienced natural menopause before 45 years
2. Age at menopause (continuous variable)

Menopause related data:

1. Self-report of being postmenopausal
2. Age at menopause
3. Number of periods in last 12 months
4. Date of last menstrual period
5. Self-report of hysterectomy
6. Self-report of bilateral oophorectomy

Outcome variable (study hypothesis 1): hs-cTnT measured at exam 4. We will evaluate hs-cTnT as a categorical variable and continuous variable. For categorical analyses, women will be classified into three groups based on their hs-cTnT levels: undetectable hs-cTnT (<5 ng/l), detectable hs-cTnT (≥5 and <14 ng/l) and elevated hs-cTnT (≥ 14 ng/l) as was done by McEvoy et al.[17] The undetectable hs-cTnT group will be used as baseline. The cutoff value of 14 ng/l for elevated hs-cTnT corresponds to the 99th percentile for a healthy reference population of persons aged 20-70 years.[1] For the continuous analyses, undetectable will be regarded as 0.

Predictor variable (study hypothesis 2): hs-cTnT. We will evaluate hs-cTnT as a categorical variable and continuous variable using the previously defined categorization scheme.

Outcome variable (study hypothesis 2): Incident HF and follow up time in years

Predictor variable (Exploratory hypothesis): Temporal or relative change in hs-cTnT levels between ARIC visit 4 and visit 5. The percent relative change in hs-cTnT is a derived continuous variable which will be calculated as [(Visit 5 hs-cTnT level – Visit 4 hs-cTnT level)/Visit 4 hs-cTnT level X 100]. For our analysis, we will categorize participants as relative change in hs-cTnT <50%, relative increase in hs-cTnT ≥50% and relative decrease in hs-cTnT ≤50% as was previously done done by McEvoy et al in the ARIC study.[17] The group with a relative change in hs-cTnT <50% will be used as baseline.

Outcome variable (Exploratory hypothesis): Incident HF and follow up time in 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. NT-pro BNP levels at ARIC visit 4
5. Prevalent HF at ARIC visit 4

Analytical plan:

This study will include postmenopausal women in the ARIC study with hs-cTnT measurements obtained at study exam 4. Descriptive statistics will be used to present characteristics of study participants according to early menopause status using means ± SD, median (interquartile range) and percentages as appropriate. Comparisons will be made between the groups using Chi-squared test, 2 sample T-test and Mann-Whitney Utest as appropriate. Variables with highly skewed distributions will be log-transformed. We will calculate the incidence rates of HF in each postmenopausal group.

For study hypothesis 1 (cross sectional design at study exam 4), we will analyze our outcome variable, hs-cTnT as a categorical variable using the previously defined categorization scheme by McEvoy et al.[17] We will use unadjusted and multivariable adjusted ordinal logistic regression techniques to model the associations of undetectable, detectable and elevated hs-cTnT levels with early menopause (age at menopause) and other covariates. We will test for the presence of interactions of early menopause (and age at menopause) with race. We will adopt a sequential adjustment process incorporating confounders and traditional CVD risk factors. We will then repeat our analysis modelling hs-CTnT as a continuous variable. For this analysis, we will use unadjusted and multivariable adjusted linear regression techniques in our models.

For study hypothesis 2 (prospective cohort), the predictor variable hs-cTnT will be modelled both as a continuous and categorical variable using the previously defined categorization scheme by McEvoy et al.[17] Kaplan-Meier plots for incident HF will be presented according to hs-cTnT categories and tested with the Log-rank test. We will use Cox Proportional hazards techniques to model the associations of hs-cTnT with incident HF, sequentially adjusting for confounders, traditional CVD risk factors and NT-proBNP. We will check for the presence of interactions of hs-cTnT with early menopause. We will adopt a sequential adjustment process incorporating confounders, traditional CVD risk factors and finally NT-proBNP. We will check for proportionality of

hazards by visually examining the log-log plots. 2-sided p-values of <0.05 will be considered significant.

For our exploratory hypothesis (prospective cohort), the predictor variable relative change in hs-cTnT will be modelled as a categorical variable as previously described by McEvoy et al.[17] Kaplan-Meier plots for incident HF will be presented according to relative changes in hs-cTnT levels and tested with the Log-rank test. We will use Cox Proportional hazards techniques to model the associations of relative changes in hs-cTnT levels with incident HF, sequentially adjusting for confounders, traditional CVD risk factors and NT-proBNP. We will check for the presence of interactions of relative changes in hs-cTnT levels with early menopause. We will adopt a sequential adjustment process incorporating confounders, traditional CVD risk factors and finally NT-proBNP. We will check for proportionality of hazards by visually examining the log-log plots. 2-sided p-values of <0.05 will be considered significant.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? Not applicable

8.a. Will the DNA data be used in this manuscript? 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"? Not applicable

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

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? X Yes

11.b. If yes, is the proposal

No A. primarily the result of an ancillary study

Yes; Number 2013.20 and 2008.10 B. primarily based on ARIC data with ancillary data playing a minor role (Measurement of troponin I at visit 4 and visit 5 for

the full ARIC cohort, Principal Investigator; Christie M. Ballantyne) and (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.
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