ARIC Manuscript Proposal # 3828

PC Reviewed: 4/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Change in NT-proBNP and Association with Incident Heart Failure from the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Reclassification of Heart Failure Stages in the Community

2. Writing Group:(alphabetical):

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

4. Rationale:

N-terminal B-type natriuretic peptide (NT-proBNP) is a well-established biomarker in the diagnosis and prognosis of patients with heart failure (HF). In the general population, increasing levels of circulating NT-proBNP is associated with increasing risk for future HF events and cardiovascular disease (CVD) mortality (1). Data on the association between change in NT-proBNP over time with HF events is more limited. Analysis from the Cardiovascular Health Study (CHS) by deFilippi et al demonstrated among older adults (mean age 72.7 years) with elevated NT-proBNP at baseline that increase in NT-proBNP at follow-up had increased risk for HF and CVD death while those with decrease in NT-proBNP at follow-up had lower risk for adverse events when compared to individuals with stable values (2). However, how the association between change in NT-proBNP with incident HF may differ by age, race, sex and comorbidities including diabetes, hypertension and obesity is not well understood. Moreover, how changes in modifiable risk factors such as blood pressure, blood glucose or body mass index (BMI) over time associate with changes in NT-proBNP over time is unclear.

Better understanding of how change in biomarkers over time relate to dynamic change cardiovascular risk has important clinical implications. Prior analysis from drug trials have shown association between therapy and reduction of circulating NT-proBNP (3). Thus, NT-proBNP change may prove useful as a surrogate for therapeutic efficacy in CVD risk modification. Our goal in the present analysis is to leverage the data from the Atherosclerosis Risk in Communities (ARIC) study to 1) evaluate the association between NT-proBNP change with HF events and CVD death and explore potential differences by age, race, sex and commodities, 2) assess how change in modifiable risk factors including blood pressure, blood glucose, BMI, lipids and smoking status over time relate to changes in NT-proBNP.

5. Study Aims:

1. Assess the association between change in NT-proBNP over time and future risk for incident HF events and CVD death at middle age (change between visits 2-4) as well as at older age (change between visits 5-6). Assess for potential differences in association of NT-proBNP change with incident HF and CVD death by race, sex, hypertension status, diabetes status, obesity, smoking status and prevalent coronary heart disease status.
2. Assess association between change in modifiable risk factors over time – systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, BMI, lipids and smoking status with changes in NT-proBNP.

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 methodological limitations or challenges if present).

Aim 1:

Study Design:

For analysis of NT-proBNP change in middle age, participants who attended both ARIC visit 2 and visit 4 (~6 years apart) will be included. Participants with prevalent HF by visit 4 and those without NT-proBNP measurements at visit 2 or ARIC visit 4 will be excluded.

For analysis of NT-proBNP change in older adults, participants who attend both ARIC visit 5 and visit 6 (~5 years apart) will be included. Participants with prevalent HF by visit 6 and those without NT-proBNP measurements at visit 5 or ARIC visit 6 will be excluded.

Exposure Variables:

Change in NT-proBNP will be modeled as both continuous variables and categorical variables.

Continuous variable – absolute change and percent change.

Categorical variables as:

Visit 2 (5) <125pg/mL/ Visit 4 (6) <125pg/mL (-/-);
Visit 2 (5) <125pg/mL/ Visit 4 (6) ≥125pg/mL (-/+);
Visit 2 (5) ≥125pg/mL/ Visit 4 (6) <125pg/mL (-/+);
Visit 2 (5) ≥125pg/mL/ Visit 4 (6) ≥125pg/mL (+/+);

As well as:

>25% increase from visit 2 (5) to visit 4 (6);
>25% decrease from visit 2 (5) to visit 4 (6);
≤25% increase or decrease between visits

Outcome Variables:

Incident HF hospitalization and CVD death and all-cause death.

Statistical Analysis:

1. Construct Cox proportional hazard models to estimate association between NT-proBNP change with risk for incident HF hospitalization and CVD death. Adjustment models (using visit 2 or visit 5 covariables depending on the index visit) as follows.
    Model 1: age, sex, race.
    Model 2: model 1 plus systolic blood pressure, diastolic blood pressure, hypertensive medication use, diabetes, A1c, LDL-C, triglyceride, eGFR, BMI, CHD and smoking.

2. Perform stratified analysis by race, sex, hypertension status, diabetes status, obesity status, eGFR (>60 mL/min/1.73m^2 vs ≤60 mL/min/1.73m^2), smoking status, CHD status.

Aim 2:

Study Design:

For analysis of NT-proBNP change in middle age, participants who attended both ARIC visit 2 and visit 4 will be included. Participants with prevalent HF by visit 4 and those without NT-proBNP measurements at visit 2 or ARIC visit 4 will be excluded.

For analysis of NT-proBNP change in older adults, participants who attend both ARIC visit 5 and visit 6 will be included. Participants with prevalent HF by visit 6 and those without NT-proBNP measurements at visit 5 or ARIC visit 6 will be excluded.

Exposure Variables:

Change in modifiable risk factors between visit 2 (5) to visit 4 (6) modeled as absolute and percent change for SBP, DBP, fasting glucose, BMI, LDL-C and change categories for current smoking status (i.e. visit 2 nonsmoker/visit 4 nonsmoker; visit 2 smoker/visit 4 nonsmoker; visit 2 nonsmoker/visit 4 smoker; visit 2 smoker/visit 4 smoker).

Outcome Variables:

Change in NT-proBNP between visit 2 (5) and visit 4 (6) modeled as categorical variables:
    >25% increase from visit 2 (5) to visit 4 (6);
    >25% decrease from visit 2 (5) to visit 4 (6);
    ≤25% increase or decrease between visits (stable)

Statistical Analysis:

Perform multinomial logistic regression analysis assessing association between change in modifiable risk factors with NT-proBNP change categories. We will first assess association between each risk factor and NT-proBNP individually and then perform multivariable analysis.

Limitations:

Though we will adjust for multiple co-variables, we cannot completely exclude residual confounding in this observational study.

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 ICTDER 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 __X_ 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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___X__ Yes ___ No

11.b. If yes, is the proposal
_X__ A. primarily the result of an ancillary study *
___ 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/

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.

References

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2. deFilippi CR, Christenson RH, Gottdiener JS, Kop WJ, Seliger SL. Dynamic cardiovascular risk assessment in elderly people. The role of repeated N-terminal pro-B-type natriuretic peptide testing. J Am Coll Cardiol. 2010;55(5):441-50.
3. Januzzi JL, Jr., Xu J, Li J, Shaw W, Oh R, Pfeifer M, et al. Effects of Canagliflozin on Amino-Terminal Pro-B-Type Natriuretic Peptide: Implications for Cardiovascular Risk Reduction. J Am Coll Cardiol. 2020;76(18):2076-85.