ARIC Manuscript Proposal #3945

PC Reviewed: 10/12/21	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Elevated NT-proBNP as a cardiovascular risk equivalent: Evidence from the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group: Justin Echouffo-Tcheugui, Sui Zhang, Chiadi Ndumele, William McEvoy, Ron Hoogeveen, Josef Coresh, Christie Ballantyne, Elizabeth Selvin; others welcome

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

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee < one year from the date of approval of this manuscript proposal.

4. Rationale:
N-terminal pro-brain-type natriuretic peptide (NT-proBNP) is a stable amino acid fragment co-secreted with BNP from the ventricular cardiac myocytes in response to left ventricular strain or ischemia.[1,2] NT-proBNP is routinely used in clinical settings as a risk stratification marker in the management of congestive heart failure (HF).[1,2] Community-based studies have also demonstrated that NT-proBNP is associated with an increased risk of mortality and incident cardiovascular disease (CVD) in community-based populations.[3–6]

A number of studies have shown that NT-proBNP improves risk discrimination in the general population. However, until recently, clinical guidelines had not incorporated biomarkers such as NT-proBNP in CVD risk assessment, especially for HF risk. [7] Furthermore, NT-proBNP is not used to guide care among individuals not hospitalized for heart failure.[7,8] Until recently, the American College of Cardiology (ACC)/American Heart Association (AHA) classification of HF risk stages did not include cardiac biomarkers (such as NT-proBNP or troponin). Individuals with a history of atherosclerotic cardiovascular disease (coronary heart disease or stroke) but without any evidence of structural heart disease or symptoms are classified as having stage A HF. The stage B HF definition has been that of asymptomatic structural heart disease based echocardiographic data, and not including biomarkers data.[7] More recently in 2021, a new definition of HF stages has been proposed by some professional societies (the Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society), , and included the evidence of elevated biomarkers (NT-proBNP [≥125 pg/mL] or cardiac troponin) as an alternative approach to define stage B HF.[8]

No current guidelines for HF risk assessment or management address the possibility of having levels of NT-proBNP among asymptomatic individuals without a history of HF (or CVD).[7,8] We hypothesize that there is an important fraction of individuals in the community without history or symptoms of HF or evidence of structural heart disease who have an increased risk of mortality and adverse cardiovascular outcomes and that these individuals can be efficiently identified on the basis of NT-proBNP. Establishing that certain levels of NT-proBNP are 'risk equivalent' for CVD could identify a very high-risk group of otherwise asymptomatic individuals. This group could potentially benefit from appropriate preventative therapy (such as statins, angiotensin receptor blockers or angiotensin converting enzyme inhibitors, which can slow cardiac remodeling.[9]).

We will use data from the community-based Atherosclerosis Risk in Communities Study (ARIC) study to compare the risks of mortality and cardiovascular outcomes (CVD or cardiovascular mortality) in individuals without a prior history of clinical CVD (including HF) but with elevated NT-proBNP to those with a prior history of CVD. We hypothesize that these two groups will have equivalent risks of death and adverse cardiovascular outcomes, suggesting that NTproBNP can serve as a 'risk equivalent' in some individuals.

5. **Main Hypothesis/Study Questions**:

Aims:

To evaluate the risks mortality and cardiovascular outcomes (mortality and events including coronary artery disease [CHD], stroke and HF) among individuals without CVD (including CHD, stroke, or HF) but with elevated NT-proBNP vs. those with a prior history of CVD.

Hypothesis:
We hypothesize that individuals without CVD (including HF) but with elevated NT-proBNP will have a risk of adverse outcomes equivalent to that of individuals with a history of CVD (including CHD, stroke, or HF).

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:
We will perform a prospective cohort analysis of the joint associations of CVD status (yes vs. no) and NT-proBNP (at Visit 4 – baseline) with incident mortality and cardiovascular outcomes (mortality and cardiovascular events), occurring after Visit 4.

Exposures:
The exposures will include NT-proBNP (measured in stored blood samples collected at Visit 4) and the CVD status at Visit 4.
Prevalent CVD at Visit 4, which will be defined as a history of CHD, stroke, or HF.
We will use two approach to define NT-proBNP categories as follows:

- First approach: low: <100 pg/mL, moderate: 100 to less than 300 pg/mL, and elevated: ≥300 pg/mL. This categorization will only be applied to individuals without any history CVD at Visit 4.
- Second approach: low: <125 pg/mL, moderate: 125 to less than 450 pg/mL, and elevated: ≥450 pg/mL. This categorization will also apply to individuals without any history of CVD at Visit 4.

Outcomes:
The outcomes will include the following incident events after Visit 4: overall mortality, cardiovascular-related mortality, atherosclerotic cardiovascular disease (ASCVD – including CHD and/or stroke), and HF. Incident HF will be defined as HF hospitalization or death after Visit 4.

Exclusions:
We will exclude individuals of non-Black or non-White race/ethnicity due to small numbers, and those missing data on the exposure variables, covariates, and outcome variables. For the exploration of the ASCVD outcomes (CHD and/or stroke), we will exclude individuals with prevalent CHD or stroke at Visit 4. For the analysis of the HF outcome, we will exclude individuals with prevalent HF at Visit 4.

Covariates:
Age, sex, race-center, smoking status, alcohol use, systolic blood pressure, anti-hypertensive medications use, LDL-cholesterol, HDL-cholesterol, cholesterol lowering medications, body mass index, diabetes status, and estimated glomerular filtration rate (eGFR)

Main Analyses:
We will compare the participants' characteristics by categories of prevalent CVD status and NTpro-BNP at Visit 4, with those without prevalent CVD further stratified by NT-proBNP: low (<100 pg/mL), moderate (100 to less than 300 pg/mL) and elevated (≥300 pg/mL). We will also examine baseline characteristics using the alternative NT-proBNP categorization (low: <125 pg/mL, moderate: 125 to less than 450 pg/mL, and elevated: ≥450 pg/mL) among those without prevalent CVD.

We will examine the association of risk categories defined using NT-proBNP and prevalent CVD status (low NT-proBNP & no CVD [reference], moderate NT-proBNP & no CVD, elevated NT-proBNP & no CVD, and prevalent CVD), and incident outcomes (all-cause deaths, cardiovascular mortality, ASCVD, CHD, stroke, and HF), using Cox regression to model the time to event data. We will also analyze NT-proBNP as a continuous variable and evaluate at which level of NT-proBNP the absolute risk (incidence rate) and hazard ratio for adverse outcomes are similar to persons with a history of CVD.

For cardiovascular mortality and incident CVD outcomes, mortality due to other causes will be modeled as a competing risk using the Fine and Gray approach.[10] For the incident ASCVD outcome, incident heart failure will not be considered a competing risk, or vice versa.

The models will be adjusted for age, male sex, race-center (Model 1), with additional adjustment for current smoking, alcohol use, systolic blood pressure, hypertension medication use, total cholesterol, HDL-cholesterol, cholesterol-lowering medication use, diabetes, and eGFR (Model 2).

We will conduct separate analyses using each of the two categorizations of NT-proBNP among individuals without any history of CVD at Visit 4.

In additional prospective analyses, we use the prevalent CVD instead as the reference group for comparisons.

Limitations:

1. Residual confounding due to the observational nature of the study.
2. We will not evaluate the changes in NT-proBNP over time in relation to incident outcomes.

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)?

Manuscript Number: 3770 - NT-proBNP as a Univariate Predictor of All-Cause Mortality in Elderly People in The Community

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 (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.

References:

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10. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.