ARIC Manuscript Proposal # 1811

PC Reviewed: 7/12/ 11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of high sensitive Troponin T (hs-cTnT),N- Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause-specific mortality: ARIC study

b. Abbreviated Title (Length 26 characters):cTnT, BNP, CRP& mortality

2. Writing Group:

Writing group members: Oludamilola W. Oluleye, Aaron R. Folsom, Vijay Nambi and Christie Ballantyne.

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

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3. Timeline:

Data analysis - 3 months
Writing the manuscript - 3 months
Coauthor review and revisions - 3 months

4. Rationale:

Recently identified biomarkers have increased understanding of the pathophysiology of disease, accuracy of diagnosis and disease prognosis.

Troponin proteins are used as biomarkers because they are released into the blood stream as a result of cardiomyocytenecrosis. Troponin T determination is a widely pertinent and economical

method for risk assessment in patients with unstable coronary heart disease[1]. It provides prognostic information based on the maximum TnT obtained during the first 24hours[1]after an episode of acute coronary syndrome. Hs-c TnT, a novel cardiac troponin-T marker, detects a 10-fold lower concentration of Troponin T and has proven to be more sensitive than the conventional fourth generation assay (cTnT) [2, 3]. Hs- cTnT is positively associated with incident coronary heart disease, all- cause mortality and heart failure in individuals without known CHD or stroke[3](ARIC). It has also shown to be positively associated with cardiovascular events and all-cause death in individuals with heart failure[4] and stable coronary heart disease[5].

Brain (B- type) natriuretic peptide is predominantly synthesized in the ventricular myocardium as a neurohormone in response to cardiac wall stress in conditions associated with volume overload. Cardiac hormone B- type natriuretic peptide (BNP) has been useful in the diagnosis of heart failure [6]; it is a predictor of short- and medium- term prognosis across the spectrum of acute coronary syndromes[7]. N- Terminal pro- brain natriuretic peptide (NT-proBNP) has also been demonstrated to predict cardiovascular disease and mortality[8] in addition to its provision of prognostic information on total mortality[9]. NT-proBNP is a stronger prognostic marker of all-cause death in the general population than BNP[10].

C reactive protein (CRP) is an acute phase reactant produced by the liver due to inflammation.It serves as a systemic marker of inflammation used to monitor patients with overwhelming infections. Recent studies have however shown that individuals with ischemia and myocardial infarction have elevated serum CRP levels[11, 12] because inflammation takes place during atherogenesis and acute events. CRP was found to be a moderately strong marker of risk for subsequent CHD using baseline CRP data in ARIC[13]. High sensitivity CRP however helps to detect lower CRP levels in otherwise healthy individuals[14]. Hs- CRP has been found to be positively associated with an increased risk of heart attack, restenosis of coronary arteries after angioplasty, stroke and peripheral vascular disease[15]. It has added more prognostic information to that available from LDL cholesterol in the prevention of cardiovascular disease because these two biomarkers represent different components of the disease process[15]. Hs- CRP has also been found to be positively associated with the risk of developing type 2 diabetes and has not been shown to predict cancer and all other major disorders[15].

A comparison between hs-cTnT, NT-proBNP and hs-CRP by Saunders et al in the ARIC study suggested an improvement in risk prediction for CHD, heart failure and total mortality when hs-cTnT was added to the risk prediction model. This was however similar to that provided by NT-proBNP and bigger than that by hs-CRP[2].

The association of hs-cTnT, NT-proBNP and hs-CRP with cause- specific mortality in the general population is however unknown. This study will address this question using measurements of NT- proBNP,hs-cTnT and hs-CRP on participants who attended the fourth ARIC visit.

5. Main Hypothesis/Study Questions:

a. What is the association of hs-cTnT with cause specific mortality (coronary heart disease (CHD), stroke, diabetes, cancer, respiratory diseases, external cause of mortality, and all other causes) among Caucasians and African Americans in the ARIC cohort?
b. What is the association of NT-proBNP with cause specific mortality (coronary heart disease, stroke, diabetes, cancer, respiratory diseases, external cause of mortality, and all other causes) among Caucasians and African Americans in the ARIC cohort?
c. What is the association of hs-CRP with cause specific mortality (coronary heart disease, stroke, diabetes, cancer, respiratory diseases, external cause of mortality, and all other causes) among Caucasians and African Americans in the ARIC cohort?

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

- A cohort study of participants who attended ARIC visit 4

Exclusion

- Participants with missing data for hs-cTnT, NT-proBNP and hs-CRP at visit 4; participants who report a race other than Caucasian or African American. Participants with evidence of a history of CHD, stroke,diabetes mellitus (DM), cancer or respiratory disease at visit 4 will be excluded from the study.

Inclusion

- All Caucasians and African Americans ARIC subjects with data on hs-cTnT, NT-proBNP and hs- CRP at visit 4.

Exposure

- Hs-cTnT, NT-proBNPand hs- CRP measured from plasma samples during the ARIC visit 4

Outcome

Cause specific mortality will be defined using the underlying cause of death on the death certificate (ICD-9 code or ICD-10 code). Participants will be considered if the underlying cause of death is CHD (ICD 9code 410- 414 or ICD-10 code I20- I25), stroke (ICD 9code 430- 438 or ICD-10 code I60- I69), DM (ICD 9code 249-250 or ICD-10 code E10- E14), cancer (ICD 9code 140- 239 or ICD-10 code C00- D48), respiratory disease (ICD 9code 460- 519 or ICD-10 code J00- J98), external causes (accidents, suicide, violence) (ICD 9 code E000- E999 or ICD-10 code V01- Y89); in addition to mortality from all other causes of death.

Statistical analysis

Hs-cTnT will be modeled as both a continuous and as a categorical variable reported in quintiles from undetectable levels to ≥ 0.014ug/L. The lowest quintile for hs-cTnT will serve as the referent group. NT-proBNP will also be modeled as both continuous and categorical variable reported in quintiles. The lowest quintile will serve as the referent group.Hs-CRP will also be modeled as both continuous and categorical variable reported in quintiles. The lowest quintile

will serve as the referent group.

Cox proportional hazards regression will be used to determine the hazard ratios of cause specific mortality by hs-cTnT, NT-proBNP and hs-CRP. Analysis will first test for interactions by age, gender or race; stratified results will be presented if there is interaction. If effect modification is absent; age, gender and race will be adjusted for as confounders in a minimally adjusted model 1. In the 2nd model, other covariates at baseline will be adjusted for: level of education, diet, forced expiratory volume (FEV_1), total cholesterol, use of blood cholesterol lowering medication, systolic blood pressure, use of antihypertensive medication, hormone replacement therapy, smoking status and number of pack years, BMI, alcohol, physical activity and renal function (eGFR). Kaplan- Meier survival curves assessing time to each cause specific death across hs-TnT, NT-proBNP and hs-CRP categories will also be obtained. Due to possible confounding; age, gender and race adjusted survival curves will be presented.

A final model will assess all three biomarkers together.

Limitations
The follow up period will be restricted to 1996-1998 to 2011 since the baseline of this study is ARIC visit 4. The study will be restricted to Caucasians and African Americans; thus the results cannot be generalized to other races. There might be some confounding factors our study failed to identify; this will lead to residual confounding, thus giving a biased estimate of association.

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)?
-ARIC Manuscript Proposal #1564: : Correlation of High Sensitivity Troponin-T (hs-cTnT) and

Amino Terminal proBrain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events.
- ARIC Manuscript Proposal # 1759: Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T.
- ARIC Manuscript Proposal # 1596: Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT.
- ARIC Manuscript Proposal # 1776: High-Sensitivity Cardiac Troponin T and the Risk of Incident Atrial Fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study.
- ARIC Manuscript proposal 1711: High-sensitivity C-reactive protein and family history and the classification of risk for coronary heart disease: The Atherosclerosis Risk in Communities Study

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* _2006.16_____)
___ 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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