ARIC Manuscript Proposal # 1899

PC Reviewed: 2/14/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Troponin T, NT-proBNP and stroke incidence

b. Abbreviated Title (Length 26 characters): TnT, NT-proBNP and stroke

2. Writing Group:

Writing group members: Aaron Folsom, Oludamilola Oluleye, Elizabeth Bell, Vijay Nambi, Christie Ballantyne, Rachel Huxley, Rebecca Gottesman, Pam Lutsey

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

First author: Aaron Folsom
Address:

Phone: 612-626-8862 Fax:
E-mail: folso001@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name:
Address:

Phone: Fax:
E-mail:

3. Timeline: Finish by summer 2012

4. Rationale: This is an offshoot of ARIC proposal 1811.

HS-TnT and NT-proBNP have been shown in ARIC to be important biomarkers for CHD and HF risk. Manuscript 1811 is relating these markers to cause-specific mortality. One finding of 1811 is that TnT and NT-proBNP are positively associated with stroke mortality, with HR=3.3 (1.26-8.7) for highest vs lowest categories of TnT and 10.4 (2.26-

47.7) for highest vs lowest quintiles of NT-proBNP. Thus, we want to determine whether the association exists between these biomarkers and stroke incidence in addition to stroke mortality.

Generally TnT is considered a marker of ischemic cardiac myo-necrosis and NT-proBNP is a marker of volume overload. These underlying conditions could contribute to stroke risk, as the heart can be a source of thromboemboli to cerebral vessels and volume overload could lead to stasis and thromboemboli as well. Other mechanisms can be postulated, such as vascular inflammation, given that Ballantyne showed CRP was related to stroke in ARIC. However, it is also possible that these two markers would not reflect any causal process, but would rather be markers of general stroke risk or the result of uncontrolled confounding.

5. Main Hypothesis/Study Questions:
TnT and NT-proBNP are independently and positively associated with stroke incidence.

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 analysis of participants who attended ARIC visit 4

Exclusion
-Participants with missing data for hs-cTnT, NT-proBNP at visit 4; participants who report a race other than Caucasian or African American; participants with stroke prior to visit 4

Exposure
Hs-cTnT, NT-proBNP measured from plasma samples during the ARIC visit 4

Outcome
-Incident stroke after visit 4

Other variables (confounders, mediators, or potential effect modifiers)
-Stroke risk factors identified in other ARIC reports, including age, race, sex, lipids, BP and antihypertensive use, BMI, diabetes, smoking, CRP, LpPLA2, atrial fib, eGFR, etc.

Statistical analysis
Hs-cTnT will be modeled as both a continuous and as a categorical variable reported in categories from undetectable levels to $\geq$ 0.014ug/L. NT-proBNP will also be modeled as both continuous and categorical variable reported in quintiles.

Cox proportional hazards regression will be used to determine the hazard ratios of

incident stroke by hs-cTnT or NT-proBNP. Analysis will first test for interactions by gender, race or hypertension status; 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 will be adjusted for. We will also run models considering both markers together, to test for synergy, in relation to stroke incidence.

In addition to total stroke, we will also examine ischemic stroke as a subset. If numbers permit, we will examine lacunar/nonlacunar, embolic, and hemorrhagic subtypes also. Rebecca's hypothesis is that they will relate strongest to embolic stroke, if numbers are adequate and that there may be an interaction with atrial fib.

If there is an association of significance for either biomarker, we will consider examining if they improve the ARIC risk prediction score (AUC/NRI, etc.).

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)?

1811: 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

1563: Saunders et al. Cardiac Troponin T Measured by a Highly Sensitive Assay Predicts Coronary Heart...*Circulation.*2011; 123: 1367-1376

MS1856: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI-Defined Small Vessel Disease of the Brain in the Atherosclerosis Risk in Community 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/

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.