ARIC Manuscript Proposal #2002

PC Reviewed: 9/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of High-Sensitivity Cardiac Troponin T (hs-cTnT) with Cognitive Function: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Troponin and Cognition

2. Writing Group:
Writing group members: Andrea L.C. Schneider, Andreea M. Rawlings, Richey Sharrett, Alvaro Alonso, Thomas Mosley, Ron Hoogeveen, Christie M. Ballantyne, Rebecca Gottesman, Elizabeth Selvin; others welcome

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

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3. Timeline: Data is currently available; plan to submit as abstract to the American Heart Association-Epi/NPAM Conference and to submit for publication by March 2013.

4. Rationale:

Dementia affects approximately 14% of persons aged 70 or older in the United States (1) and this estimate is expected to triple by the year 2030 (2). Overt cardiovascular disease has been shown to be a major risk factor for dementia and cognitive impairment (3-5), however the association of subclinical cardiovascular disease with dementia and cognitive impairment is less well characterized.

Novel highly sensitivity assays for cardiac troponin can detect troponin levels approximately 10-times lower than standard cardiac troponin assays that are currently used in clinical practice to diagnose myocardial infarction (6). These novel highly sensitive assays are not yet approved for clinical use. Recent studies have shown that troponin levels measured using these new ultra highly sensitive assays can improve the prediction of cardiovascular disease and mortality in community-based populations without clinically evident cardiovascular disease (7, 8). Troponin is highly specific to the myocardium and minute levels of circulating troponin that can be detected by novel highly sensitive assays are thought to be a novel marker of subclinical myocardial injury (9, 10). It has been suggested that the association of low level elevations of hs-cTnT with cardiac outcomes may be mediated by non-atherosclerotic mechanisms (7, 8, 11, 12). Although left ventricular mass is independently associated with detectable levels of hs-cTnT, coronary artery calcium (a marker of coronary atherosclerosis) is not independently associated with detectable levels of hs-cTnT (8, 9) and the association of hs-cTnT was stronger for total mortality and heart failure that for CHD (7, 9). It has been hypothesized that small elevations in hs-cTnT may be a marker of subclinical small vessel disease rather than atherosclerosis *per se* (13).

There is some evidence that cognitive function and dementia are associated with subclinical cardiovascular disease as assessed by carotid intima medial thickness (14). Hs-cTnT has been investigated or proposed to be investigated using the ARIC cohort in terms of its relationship to stroke-related mortality (HR: 3.3, 95% CI: 1.3, 8.7) (MSP #1811), in terms of its relationship to incident stroke (MSP #1899), and in terms of its relationship to small vessel disease in the brain (MSP #1856). It has been hypothesized that the same persons with subclinical myocardial injury may also have subclinical small vessel disease in the brain. The subclinical small vessel disease in the brain may manifest as subtle impairment on standardized cognitive tests and may place the person at higher risk for dementia later in life. There are three potential mechanisms whereby subclinical myocardial injury could contribute to cerebrovascular problems or cognitive dysfunction: 1) shared risk factors, 2) subclinical stroke (embolic stroke: MSP #1899, either via left ventricular dysfunction/clot formation or subclinical myocardial injury leading to atrial fibrillation leading to thrombus/stroke), or 3) hypoperfusion from inadequate left ventricular function (7, 8, 11, 12). To our knowledge, no previous studies have examined the possible association of cardiac troponin measured by a novel highly sensitive assay (hs-cTnT) and cognitive function and dementia.

To comprehensively characterize the relationship of hs-cTnT with cognitive function and future dementia risk in a community-based population, we propose to examine the cross-

sectional association between hs-cTnT and cognitive test scores at visit 4 and to examine the prospective relationship between hs-cTnT and incident dementia hospitalization in the ARIC Study.

5. Main Hypothesis/Study Questions:

1. Are there cross-sectional associations between hs-cTnT and Delayed Word Recall (DWR) or Digit Symbol Substitution (DSS) or Word Fluency (WF) Test scores?

   Hypothesis: Higher levels of hs-cTnT will be associated with lower cognitive test performance, independently of known risk factors. Specifically, we expect the strongest relationship with DSS performance.

2. Is there a prospective relationship between hs-cTnT and incident dementia hospitalization?

   Hypothesis: Higher levels of hs-cTnT will be associated with incident dementia hospitalization, independently of known risk factors.

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:
Cross-sectional analysis using data from visit 4 and prospective analysis with visit 4 as baseline.

Study Population (inclusion/exclusion criteria):
All ARIC participants who attended visit 4 and who do not meet any of the following exclusion criteria:

- CHD, CHF and stroke at or before visit 4 (this includes self-reported myocardial infarction or stroke before visit 1, or silent MI (diagnosed by electrocardiographic changes), validated MI and revascularization at or before visit 4)
- Missing hs-cTnT
- Missing any of the cognitive tests at visit 4 (DWR, DSS, WF)
- Missing covariates included in statistical models (see below)

Exposure:
hs-cTnT:
hs-cTnT was measured in 2010 from stored plasma samples originally obtained from participants at visit 4 (1997-99) using a novel pre-commercially available highly sensitive assay, Elecsys Troponin T (Roche Diagnostics, Indianapolis, Indiana), on an automated Cobas e411 analyzer with a lower limit of detection (LOD) of 0.003 µg/L. Between-assay coefficients of variation were 2.6% and 6.9% for control materials with mean troponin concentrations of 2.378 µg/L and 0.029 µg/L, respectively. Measurement repeatability

was assessed using blinded split samples (n=418). The reliability coefficient was 0.98 and the coefficient of variation was 15% after excluding >3 standard deviation outliers (n=3).

Outcomes:

1. Cognition:
In the ARIC Study, cognitive functioning was assessed at visit 4 using three standardized tests: the DSST of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (15), the DWRT (16), and the WFT, also known as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination (17). The DSST is a test of memory, executive function and processing speed, the DWRT is a test of verbal learning and recent memory, and the WFT is a test of executive function and expressive language (15-17). Trained examiners administered the cognitive tests in a standardized order during one session in a quiet room. Examiner performance was monitored by audio tape recording. Recordings were reviewed locally and shared across centers to ensure consistency with testing procedures.

2. Incident Dementia Hospitalization:
The ARIC Study obtains hospitalization information from annual telephone contact with study participants and through active surveillance of all hospitalizations in the study communities. We will define time to first hospitalization with an ICD-9 code for dementia using the following ICD-9 codes (listed anywhere in the hospital discharge record): Alzheimer's disease (331.0), vascular dementia (290.4) or dementia of other etiology, including senile, presenile, and frontotemporal dementias, and dementias secondary to a general medical condition (e.g. Parkinson's disease) (290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, 331.9) (18). We will use incident dementia hospitalization data through 2009 (or most recent data available). We have previously reported age- and race-specific rates of hospitalization with dementia (18).

Covariates:
Age, sex, race/field center, body mass index, income, diabetes, education, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, blood pressure medication use, apoE genotype, smoking, alcohol consumption, physical activity. All covariates listed are from visit 4, except for education level, which is only assessed at visit 1.

Potential effect modifiers:
We will formally test for interaction by age, race, and sex. We will perform stratified analysis if we observe evidence for significant effect modification.

Statistical Analysis:

We will analyze hs-cTnT both continuously and categorically. For the categorical analysis, the 33.5% of the ARIC population with undetectable levels (<0.003 μg/L) will

be the reference group (group 1). The remaining 66.5% of the ARIC population will be split in to approximate thirds: cTnT 0.003 to 0.005 µg/L (group 2), 0.006 to 0.008 µg/L (group 3), and higher levels will be divided at approximately the 90th percentile of the ARIC population (group 4: 0.09 to 0.013 µg/L; group 5: ≥0.014 µg/L). We will also analyze hs-cTnT using two different binary variables: detectable (<0.003 µg/L) versus non-detectable (≥0.003 µg/L) and elevated (>99th percentile from a healthy population ages 20-70 years [Roche Diagnostics, Indianapolis, Indiana]) (>0.014 µg/L) versus non-elevated (≤0.014 µg/L). For the continuous analysis, we will assign undetectable levels of hs-cTnT a value of 0.0015 µg/L (half the lower LOD). These methods have been described previously (7, 9).

We will use linear and logistic regression models to assess the cross-sectional association between hs-cTnT and cognitive test scores (DWR, DSS, WF) (Visit 4). Logistic regression models will be used to estimate odds ratios (95% confidence intervals) for the performing in the bottom quintile on each cognitive test by detectable hs-cTnT (vs no-detectable) and by elevated hs-cTnT (versus not elevated hs-cTnT) category.

We will use Cox proportional hazard models to assess the prospective association between hs-cTnT and incident dementia hospitalization.

We will also model the association of hs-cTnT with cognitive function and incident dementia using piece-wise linear splines (knots at as defined above) and using restricted cubic splines. We will perform the spline analyses both among those with detectable levels only and using the entire population where we will assign undetectable levels of hs-cTnT a value of 0.0015 µg/L (half the lower LOD).

We will perform three statistical models:

- Model 1: adjust for demographic factors (age, gender, race/field center, education, income)
- Model 2: Model 1 + behavioral factors (physical activity, alcohol consumption, smoking)
- Model 3: Model 2 + genetic and cardiovascular risk factors (apoE, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, blood pressure medication use)

We will perform sensitivity analyses using visit 2 cognitive test data to assess the association of hs-cTnT at visit 4 with the past trajectory of cognitive function (change from visit 2 to visit 4). We can also look at the association of hs-cTnT with prospective change in cognitive function among participants who attended visit 4 and either the Brain MRI or Carotid MRI visit (2004-2006). In addition, individuals that attended the Brain MRI visit provided information on dementia, family history of dementia, and neurological function; examining the association of hs-cTnT with cognition in this subset of participants, adjusting for these additional covariates, would be useful. We will also do a sensitivity analysis excluding persons who ever had a stroke as subtle changes in cardiac biomarkers and left ventricular function after large strokes and cerebral hemorrhages.

Limitations:

A major limitation of this study will be the method of dementia ascertainment. Relying on hospital discharge data to define incident cases of dementia will likely underestimate the true incidence of dementia in the study population. However, our definition of dementia is likely to be a highly specific case definition. Additionally, because dementia hospitalization is a heterogeneous outcome, we anticipate that we will not have enough cases to create subgroups by type of dementia (e.g. vascular, Alzheimer's). We also have only single measurements of hs-cTnT and cognitive test performance, both of which can vary over time within individuals (19, 20). Due to the cross-sectional design for examining the possible associations of hs-cTnT and cog function, we will have limited ability to draw any conclusions regarding the temporality of any observed associations. As with any observational study, we will also not be able to rule out the possibility of residual confounding.

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)?

MSP #1211: Cognitive change over 12 years and its relationship to cardiovascular risk factors: the ARIC MRI study (Knopman)
MSP #1973: Cardiovascular exposures, cognitive decline, and depression in whites and blacks (Al Hazzouri)
MSP #969: Impact of coronary artery bypass surgery on cognitive function (Knopman)
MSP #1703: Identification of candidate genes associated with cardiovascular disease that predict cognitive change in mid-life: the ARIC study (Bressler)
MSP #672: Changes in cognitive test scores in the ARIC cohort over a 6-year period (visit 2 to visit 4) and their correlation with vascular risk factors (Knopman)
MSP #1365: Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study (Alonso)
MSP #1856: Cardiac troponin t measured by highly sensitive assay and MRI-defined small vessel disease of the brain in the ARIC study (Dadu)
MSP #1759: Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T (Rubin)
MSP #1899: Troponin T, NT-proBNP, and stroke incidence (Folsom)

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

ARIC Ancillary Study #2008.11, "Measurement of NT-proBNP and troponin T at visit 4 for the full ARIC cohort"

11.b. If yes, is the proposal

x **A. primarily the result of an ancillary study (list number*** 2008.11**)**

___ 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.

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disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation. 2011;123(13):1367-76. PMCID: 3072024.
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