ARIC Manuscript Proposal # 1759

PC Reviewed: 3/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T.

b. Abbreviated Title (Length 26 characters): Traditional risk factors and hs-cTnT.

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

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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).

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3. Timeline: We aim to complete this manuscript within 6 months of approval.

4. **Rationale**:

Cardiac troponin-T (cTnT) measured in plasma allows for the noninvasive identification of persons at risk for a cardiovascular event [1-5]. A recently developed, high-sensitivity cardiac troponin-T (hs-cTnT) assay allows for the detection of hs-cTnT levels below clinical thresholds or detection levels of earlier cTnT assays. Using this novel pre-commercial assay, troponin levels far below the conventional limit of detection have been shown to predict cardiovascular events and death from any cause in persons with heart failure [6], stable coronary artery disease [7] and in the general population [8, 9]. Unpublished data from ARIC (MS # 1563) suggests that hs-cTnT is also independently associated with heart failure and all-cause mortality.

Various mechanisms have been proposed to explain the release of troponin in persons with and without obstructive coronary heart disease including subendocardial ischemia leading to myocyte necrosis, oxidative stress and ischemia without necrosis [10]. Other potential sources of elevated troponin include left ventricular strain [11], apoptosis [12], vigorous exercise [13] and cardiomyocyte turnover [14].

The determinants of elevated hs-cTnT levels below clinical thresholds in the general population are unknown. Measurement of hs-cTnT from stored samples from participants who attended the fourth ARIC visit provides a community-based sample in which to assess the relationship between traditional cardiovascular risk factors and hs-cTnT.

5. Main Hypothesis/Study Questions:

Aim: To characterize the cross-sectional associations between traditional cardiovascular risk factors and hs-cTnT

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 of participants who attended ARIC visit 4.

Exposure: Traditional cardiovascular risk factors (age, sex, diabetes status (undiagnosed, diagnosed, treated/untreated), race/center, smoking status, body mass index, waist-hip ratio, blood pressure, hypertensive medication use, education, income, triglycerides, total-, HDL- and LDL-cholesterol, metabolic syndrome, kidney function (estimated glomerular filtration rate (GFR) from serum creatinine) and Framingham Risk Score.

Outcome:
hs-cTnT modeled continuously and by categories (as described below in the Statistical Analysis section).

Inclusions

All black and white ARIC subjects with data on high-sensitivity troponin T measured from blood samples (plasma) obtained at visit 4 (n ≈ 11,500).

Exclusions:
Race other than black or white, missing hs-cTnT at visit 4, or missing covariates of interest.

Statistical Analysis

Continuous variables will be reported as means with standard deviations and categorical variables as proportions. We will model hs-cTnT as both a categorical and a continuous variable. For categorical analyses, Group 1 will include all participants with undetectable levels (~30%). The remaining (~70%%) will be categorized into approximate thirds: hs-cTnT 0.003–0.005 μg/L (Group 2), 0.006–0.008 μg/L (Group 3), and higher levels further divided at approximately the 99th percentile value specified by the manufacturer (which corresponded to the ~90th percentile in the ARIC populations into Group 4 (0.009–0.013 μg/L) and Group 5 (≥0.014 μg/L). For continuous models, undetectable levels of hs-cTnT will be assigned a value of 0.0015 μg/L (i.e., half the lower limit of detection).

Statistical comparison of groups will be performed using one-way ANOVA for continuous variables or chi-square tests for categorical variables. Multivariable logistic regression models will be used to identify variables that are independently associated with elevated hs-cTnT. Analyses will be performed separately in persons with no previous clinical or silent CHD. We will also conduct analyses implementing linear splines and restricted cubic splines in multivariable models to characterize the shape of the association of traditional risk factors with hs-cTnT.

Limitations
Because neither echocardiography nor coronary angiographies were available from participants who attended ARIC visit 4, we cannot rule out elevated hs-cTnT due to underlying subclinical cardiovascular disease. Despite adjustment for known risk factors for cardiovascular disease, we will also not be able to rule out the possibility of residual confounding. The association with race cannot be easily separated from geography since the majority of blacks were recruited at the Jackson Field Center. Due to the cross-sectional nature of this investigation, the temporality of any observed associations cannot be established.

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)?

Proposals on the association of hs-cTnT or NT-proBNP to cardiovascular or kidney disease
MP#1564: Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events
MP#1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study
MP##1596: Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT

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-pro-BNP 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 #2006.15 and #2008.10**)**

___ 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.

Reference

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