ARIC Manuscript Proposal #2319

PC Reviewed: 2/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Does cardiac troponin T help identify subjects with metabolic syndrome at higher risk of cardiovascular events? An analysis from the ARIC study

b. Abbreviated Title (Length 26 characters): **metabolic syndrome, cardiac troponin T**

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

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3. Timeline: Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation will take place within 1 year from approval of the proposal. Analysis will be done locally at Baylor College of Medicine and co-ordinating center support will not be required.

4. Rationale: Cardiac troponin T (cTnT) is emerging as a biomarker that is strongly associated with incident cardiovascular end points (CVD) including coronary heart disease, heart failure, stroke, and, death with several data from population studies including ARIC demonstrating a robust and strong association (*Saunders J, Circulation 2011; 123: 1367-76, de Lemos JA JAMA. 2010 Dec 8;304(22):2503-12, deFilippi C JAMA. 2010 Dec 8;304(22):2494-502*). Since the initial description of the association of troponin T measured with a high sensitivity assay (hs-cTnT) and incident CVD, we have shown that troponin T improves prediction of heart failure (HF) risk when added to models used in the prediction of HF risk such as the ARIC HF risk score (*Nambi V, Clin Chem 2013; 59: 1802-10*).

Metabolic syndrome has been shown in several studies to be associated with all the above mentioned CVD (Gami AS J Am Coll Cardiol, 49 (2007), pp. 403–414). Given that the presence of metabolic syndrome is associated with a high incidence of incident HF, the American College of Cardiology and American Heart Association have categorized those with metabolic syndrome to be in "Stage A" heart failure i.e. individuals at increased risk of incident clinical HF (*Hunt SA Circulation 2005; 112; e154-235*).

Recently we have generated data that shows (MS 2116) that troponin T measured with a high sensitivity assay can help identify higher risk subjects across blood pressure categories (systolic, diastolic, and pulse pressure). Blood pressure, similar to metabolic syndrome is another factor that would classify an individual as Stage A heart failure. When stratified by systolic, diastolic, and PP blood pressure of higher troponin T levels were associated with an increased hazards for incident CVD (including HF) when compared to those with undetectable troponin T. In additional analyses, we found that those with a systolic blood pressure between 150-159 mmHg and undetectable troponin T had lesser incidence of HF than those with a systolic blood pressure of 120-129 mmHg and a troponin T >5 ng/L. We now propose to evaluate whether troponin T can help identify subjects with metabolic syndrome at higher risk for incident CHD, heart failure, and stroke much like it does for hypertension. If troponin T does identify subjects with metabolic syndrome at higher risk of CVD, it may help

us identify subjects who may benefit from intensive treatment of risk factors and identify higher risk subjects to include in clinical trials. These of course will first need to be tested.

5. Main Hypothesis/Study Questions:

Hypothesis:

Cardiac troponin T will identify subjects at higher and lower risk of cardiovascular events among individuals with metabolic syndrome.

Study questions:

1. Describe if troponin T (classified by categories) can identify subjects with metabolic syndrome who are at higher and lower risk for incident adverse cardiovascular events (CHD, stroke, heart failure assessed together as a composite and individually) and death
2. Describe the association between troponin T and incident CVD stratified by the number of metabolic syndrome 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 methodological limitations or challenges if present).

We will exclude individuals whose race is neither black nor white, and, black participants from the Washington County or Minneapolis field centers.

All other individuals with available troponin T and information about the variables that constitute metabolic syndrome will be eligible for analysis. Metabolic syndrome will be defined according to Adult Treatment Panel III (ATP III). Briefly, individuals will be classified as having metabolic syndrome if they have three or more of the following components: elevated blood pressure (systolic blood pressure >130 mmHg or diastolic blood pressure >85 mm Hg and/or use of anti-hypertensive medications [yes/no]); elevated triglycerides (≥150 mg/dL); low HDL-C (men [M] <40 mg/dL, women [W] <50 mg/dL); impaired fasting glucose (>100 mg/dL); and large waist circumference (M >102 cm [>40 inches], W >88 cm [>35 inches]).
For each outcome of interest, those with prevalent disease will be excluded (example for incident heart failure, those with prevalent heart failure will be excluded). ARIC visit 4 will form the baseline for this analysis.

We will first describe the number of subjects with metabolic syndrome in the ARIC study and describe the troponin T levels among those with and without metabolic syndrome.

Then, using those with metabolic syndrome and troponin T < 5ng/L as the referent group, we will evaluate if subjects with metabolic syndrome and a troponin T >5 ng/L have higher hazard ratios for incident cardiovascular disease

including MI, heart failure, stroke and death. In further analysis, troponin T >5 ng/L will be additionally categorized as 5-8, 9-13 and ≥13 ng/L. The analysis will initially be adjusted for age, gender, race and center. In subsequent models we will adjust for renal function (estimated glomerular filtration rate as measured using the CKD-EPI equation), total cholesterol, current cigarette smoking, C-reactive protein, and NT-proBNP.

Then we will categorize the individuals by the number of metabolic syndrome risk factors (range 0-5) to see if higher levels of troponin T are associated with an increased risk of CVD at each level (i.e. in an individual with 0 factors that constitute metabolic syndrome to all 5 factors). We expect that with more risk factors for metabolic syndrome, the strength of association between elevated troponin T and outcomes will be of greater magnitude (i.e. there will be a multiplicative interaction).

Finally, additional analyses will be performed to evaluate which metabolic syndrome component will be most strongly associated with elevated hs-cTnT (with controlling for other metabolic syndrome components)

Limitations: The concept of "metabolic syndrome" has been controversial (i.e. whether it deserves the status of a syndrome etc.). However, for our analysis we are primarily evaluating if someone with metabolic syndrome as defined by ATP III recommendations, who by definition have Stage A HF, is at higher risk for future CVD. The lack of echocardiographic data is a limitation when evaluating HF 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 ICTDER 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)?
MS 1808, 1757, 1759, 1564, 2116

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* __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/

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.