ARIC Manuscript Proposal # 1734

PC Reviewed: 12/14/10  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T

b. Abbreviated Title (Length 26 characters): Biomarkers and highly sensitive cardiac troponin T

2. Writing Group:
   Writing group members:
   Vijay Nambi, MD
   Lloyd Chambless PhD
   Eric Boerwinkle, PhD
   Christie M. Ballantyne, MD
   Salim Virani MD
   Joe Coresh MD PhD
   A Richey Sharrett
   Aaron Folsom MD
   Gerardo Heiss MD
   Ron Hoogeveen PhD

   Others are welcome.

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]

First author: Vijay Nambi
Address: 6565 Fannin Street
         STE B 160/MS-A601
         Houston, TX 77030
         Phone: 713-798-7545    Fax: 713-798-4121
         E-mail: vnambi@bcm.tmc.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: Vijay Nambi
Address: 6565 Fannin Street
         STE B 160/MS-A601
         Houston, TX 77030
3. **Timeline**: Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the manuscript will be prepared within one year from approval of the analysis.

4. **Rationale**: Recent data from the ARIC study (MS # 1563) suggests that a novel high sensitivity cardiac troponin t (cTnT) is detectable in the majority of the ARIC participants at visit 4. Elevated levels of cTnT were also found to be associated with adverse prognosis with increased risk for incident coronary heart disease (CHD), all cause mortality and heart failure (HF). Although cTnT was significantly associated with all 3 adverse outcomes, the strongest associations were with mortality and HF.

**The determinants of cTnT are not known.** At visit 4, individuals with higher cTnT levels had significantly higher prevalence of several cardiovascular risk factors including age, hypertension, diabetes, BMI, HDL-cholesterol, left ventricular hypertrophy and renal function (eGFR). Total cholesterol was however lower in those with elevated cTnT as was current smoking. A significant difference in the level of in cTnT between men and women was also observed.

Given that elevated cTnT confers an adverse prognosis and given that mechanisms underlying the relationship between cTnT and the adverse prognosis are not known we propose to study factors associated with cTnT levels in ARIC.

Other manuscript proposals (either submitted or being written) are already looking at association of 1. Hemoglobin A1C and cTnT (MS#1596), 2. hypertension and cTnT (in preparation), 3. ECG predictors of cTnT (in preparation) and 4. sub-clinical atherosclerosis predictors of cTnT (in preparation). We will therefore evaluate the biomarker and anthropometric measures associated with cTnT in the ARIC study.

5. **Main Hypothesis/Study Questions:**
   a) To determine if there is a prospective association between biomarkers associated with hemostasis, lipids and clinical chemistry with cTnT
   b) To determine if changes in biomarker levels will be associated with cTnT levels
   c) To determine if there are associations between anthropometric measurements and cTnT levels
   d) If any associations between biomarkers and anthropometric measures are found, test if the associations persist after adjusting for the traditional risk factors known to be associated with cTnt based on MS 1563

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).

**Biomarkers and troponin**

**Inclusion criteria:** All individuals who participated in ARIC visit 4 and have available cTnT measurements will be eligible and included for the analysis

**Exclusion criteria:** Standard ARIC exclusions will apply
Individuals with missing cTnT and covariate data will be excluded

**Outcome variable** (dependent variable): 1. continuous cTnT levels
2. categories undetectable (<0.003 μg/L) versus detectable values

**Predictor variables** from visit 1 (independent variables):
1. Potassium
2. Magnesium
3. Sodium
4. Creatinine
5. Uric acid
6. Urea Nitrogen
7. Insulin
8. White blood cell count
9. Hemoglobin
10. Hematocrit
11. Factor VII
12. Factor VIII
13. Fibrinogen
14. Von Willebrand Factor
15. aPTT
16. Protein C
17. Antithrombin III
18. Lp(a)
19. Total cholesterol
20. HDL-cholesterol
21. LDL-cholesterol
22. Apo B

Linear regression analyses will be performed to identify univariate, and, multivariate predictors of cTnT after adjusting initially for age, gender and race and then for age, gender, race BP, diabetes, smoking status, eGFR (note: for the BUN, creatinine analyses we will not adjust for eGFR) and LVH (by ECG)
Logistic regression analyses will be performed for the categorical analysis (detectable versus non-detectable)
Similar analysis will be performed for biomarkers available at visit 3 as well (i.e. near term associations)

Finally, for biomarkers present in visit 1 and visit 4 (lipids, glucose, creatinine, insulin), the difference between the 2 visits will be estimated (delta) and the association of the difference (predictor variable) and cTnT (dependent variable) will be evaluated

Bonferroni correction will be performed for multiple testing (note that there are “groups” of biomarkers. For example, there are 5 cholesterol related variables, several coagulation related biomarkers, electrolytes; corrections for multiple testing will be done for each of these groups)

**Anthropometric measures and troponin:**

Inclusion, exclusion criteria and outcome variable will be as in the biomarker predictors of high sensitivity troponin

**Predictor variables:**

*Visit 1 ARIC*  
1. Body mass index  
2. Waist/hip ratio  
3. Calf circumference

*Visit 4 ARIC*  
1. Body mass index  
2. Waist/hip ratio

Visit 1 (prospective) and visit 4 (cross-sectional) anthropometric variables will be analyzed separately.  
Linear regression analyses will be performed to identify correlates of cTnT after adjusting initially for age, gender and race and then for age, gender, race BP, diabetes, glucose, smoking status, eGFR and LVH (by ECG). Logistic regression analyses will be done for the categorical (i.e. troponin detectable versus not) will also be performed

Changes in BMI and Waist/Hip ratio and the association of the differences (delta) with cTnT will also be evaluated

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?  
_x___ Yes ___ 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”?  
__x__ Yes _____ No

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  
__x__ 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)?

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  
____ 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/

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.