

## ARIC Manuscript Proposal #1936

PC Reviewed: 4/17/12  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Determination of the normal reference range for the hs-cTnT assay: results from 3 population-based cohorts

**b. Abbreviated Title (Length 26 characters):** Normal reference range for hs-cTnT assay

### 2. Writing Group:

**Writing group members:** James de Lemos, MD, Christopher deFilippe, MD, Christie Ballantyne, MD, Vijay Nambi, MD Steven Seliger, MD, Anand Rohatgi, MD, Darren McGuire

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

**First author: James de Lemos, MD**

Address: UT Southwestern Medical Center  
5909 Harry Hines Blvd, HA 9.133  
Dallas, TX 75390-9047

Phone: 214-645-76528

Fax: 214-645-7501

E-mail: james.delemos@utsouthwestern.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: Christie Ballantyne, MD

Address: Baylor College of Medicine, 6565 Fannin, M.S. A-601, Houston, TX 77030

Phone: 713-798-5034

Fax: 713-798-3057

E-mail: cmb@bcm.tmc.edu

### 3. Timeline:

Data analysis May 15-June 30. Paper preparation July 1-August 15. Review by study groups Aug 15-Sept 15. Submit Oct 1.

**4. Rationale:** The newly developed highly sensitive assay for cardiac troponin T (hs-cTnT) is now used in many parts of the world for diagnosing myocardial infarction but is not yet available for use in the United States. By convention, the 99<sup>th</sup> percentile troponin value from a healthy reference population is the cutpoint used to diagnose myocardial infarction.<sup>1</sup> Studies to date have accepted and used a cutoff value of 14 pg/mL for the hs-cTnT assay, selected as the value representing the 99<sup>th</sup> percentile of a healthy control population. These normal reference range data were generated from two small studies. One of these was performed by the manufacturer in “533 healthy volunteers,” and is included in the product label, with no details of the cohort provided. The second study combined “healthy volunteers” and blood donors, aged 20-71 years<sup>2</sup> with no phenotypic characterization provided of the study populations. Although little attention is paid to the normal reference range studies used to generate cutpoints for biomarker assays, a highly accurate determination of the 99<sup>th</sup> percentile value is critical, given the central role specific troponin values play in MI diagnosis.

Comparisons of the hs-cTnT assay with conventional troponin assays have reported improved sensitivity but lower specificity for the hs-cTnT assay.<sup>3,4</sup> Since the conventional and hs-cTn assays are highly correlated, and both detect values at or below the 99<sup>th</sup> percentile, it is not clear why sensitivity should be so notably increased with the hs-cTnT assay. We propose that these findings are not valid due to poor characterization of the 99<sup>th</sup> percentile value for the hs-cTnT assay.

We recently published analyses from three large population-based cohorts in which cTnT was measured with the hs-cTnT assay: ARIC,<sup>5</sup> the Dallas Heart Study (DHS),<sup>6</sup> and the Cardiovascular Health Study (CHS).<sup>7</sup> Although these studies were not performed to determine the normal reference range for hs-cTnT, in each of the studies, it was noted that a much larger than anticipated proportion of generally healthy individuals had cTnT levels above the prespecified 99<sup>th</sup> percentile value of 14 pg/mL. These three studies are much larger, and have much more careful phenotype characterization, than the normal reference range studies performed previously. These preliminary observations suggest that the 99<sup>th</sup> percentile value is in fact considerably higher than suggested by the manufacturer.

A more accurate determination of the 99<sup>th</sup> percentile value in well characterized population cohorts would have immediate, and important, implications for MI diagnosis throughout the world.

**5. Main Hypothesis/Study Questions:** Our hypothesis is that the currently recommended 99<sup>th</sup> percentile value for the hs-cTnT value is incorrect, leading to MI misclassification. We speculate that the value currently used as the 99<sup>th</sup> percentile is likely closer to the 95<sup>th</sup> percentile value. Misclassification of “MI” rather than intrinsic assay properties, may largely explain differences in test performance between highly sensitive and conventional troponin assays.

We propose a simple paper in which we will perform parallel analyses from ARIC, DHS, and CHS, creating 3 independent validation cohorts to define the true 99<sup>th</sup> percentile values for the hs-cTnT assay. We will also assess whether the 99<sup>th</sup> percentile values vary based on sex, age, and race.

Finally, we will assess the implications of various restrictions on the “normal population” on the 99<sup>th</sup> percentile cTnT value selected.

**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).**

The study design is a simple descriptive analysis of the distribution of cTnT values in a series of subgroups of ARIC. Parallel analyses will be performed in the DHS and CHS and the findings will be reported together in a single manuscript, with data reported individually for each study. In the DHS, additional sensitivity analyses will exclude individuals with subclinical atherosclerosis defined by the presence of coronary artery calcium.

We will define the following subcohorts from ARIC

1. Free from recent hospitalization (6 months), clinical CVD (CHD, CHF, atrial fibrillation, prior stroke) or stage III or greater CKD. This cohort will exclude all individuals with previously diagnosed cardiovascular disease and those with an estimated GFR < 60 cc/min.
2. Free from recent hospitalization, clinical **and subclinical CVD** or stage III or greater CKD. This cohort will further exclude individuals with LVH or LVEF < 55% by echo, LVH by ECG and those with an NT-proBNP  $\geq$  450 pg/mL. NT-proBNP is now commonly used as a screening test to exclude occult CVD in normal reference range studies.
3. “Healthy normal cohort.” This group will further exclude individuals with hypertension, and diabetes.
4. “Hypernormal cohort” This will further exclude individuals with GFR < 90 cc/min.

Analyses:

1. Distribution, box and whisker plots, 99<sup>th</sup> percentile values for each subcohort
2. Stratified analyses based on sex, race, and age deciles.
3. Sensitivity analyses varying LVEF, NT-proBNP, and renal function thresholds for exclusion. Will also do sensitivity analyses restricting to participants with self-reported general health as good, very good, or excellent. In addition to assessing the influence of these parameters on the 99<sup>th</sup> percentile value, we will also determine the influence of more restrictive exclusions on sample size, in order to inform design of future reference range studies.

7.a. Will the data be used for non-CVD analysis in this manuscript?  Yes  
 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  
 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.csc.unc.edu/ARIC/search.php>  
 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)?

This proposal is related to a published paper<sup>5</sup> and approved ancillary study

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

2008.10 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\*  
2009.10)

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.csc.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.csc.unc.edu/arie/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References

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3. Reichlin T, Hochholzer W, Bassetti S, et al. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. *N Engl J Med*. August 27, 2009 2009;361(9):858-867.
4. Keller T, Zeller T, Peetz D, et al. Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction. *N Engl J Med*. August 27, 2009 2009;361(9):868-877.
5. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation*. Apr 5 2011;123(13):1367-1376.
6. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. Dec 8 2010;304(22):2503-2512.
7. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA*. Dec 8 2010;304(22):2494-2502.