ARIC Manuscript Proposal #2468

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

1.a. Full Title: Low level troponin T and cardiovascular events: a collaborative analysis between ARIC, CHS and Dallas Heart Study

b. Abbreviated Title (Length 26 characters): **Low troponin T levels and outcomes**

2. Writing Group:

Writing group members:

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

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3. Timeline: Analysis to begin upon approval of the proposal. Anticipate communicating results within 3-9 months

4. Rationale: The high-sensitivity (hs) troponin assays have improved risk stratification in patients with chronic cardiovascular diseases and the general population compared to conventional troponin assays because of a 10-100-fold lower level of detection. Currently, controversy surrounds the reporting of hs cardiac troponin T (hs-cTnT) results to as low as the limit of blank (LOB, 3 ng/L) or the limit of detection (LOD, 5 ng/L). This has often resulted in conflicting requests from reviewers, confusion for editors and investigators and challenges in prospectively planning studies to prognostically use this test. The LOB is defined as the highest apparent concentration of cTnT in an analyte-free sample. The LOD is defined as the lowest actual concentration of cTnT that can be reliably quantified in a given sample. This is particularly relevant to application of the test to asymptomatic populations where a sizable minority of subjects can have values that fall between the LOB and LOD. Several large-scale epidemiological community cohort studies using previously frozen blood samples have evaluated the prognostic significance hs-cTnT. Three of these studies, including the Dallas Heart Study (DHS), Cardiovascular Health Study (CHS), and Atherosclerosis Risk in Communities (ARIC) Study, reported hs-cTnT values down to the LOB and suggested an increased prevalence of cardiovascular risk factors, increased evidence of structural cardiac abnormalities with cardiac imaging and a poorer prognosis with hs-cTnT levels between the LOB and the LOD versus those with values less than the LOB (<3 ng/L). For this proposal we will reanalyze data from these cohorts to determine if there is a significantly higher rate of cardiovascular events (including cardiovascular death and incident heart failure) and higher prevalence of cardiac pathology in participants with hs-cTnT levels between the LOB and LOD of the assay compared to subjects with levels below the LOB (< 3 ng/mL).

5. Main Hypothesis/Study Questions:
Hypothesis: Cardiac troponin T levels between limit of blank and limit of detection are associated with incident cardiovascular events.
Question to be answered: Are troponin T levels between 3-4.99 ng/L associated with increased heart failure and mortality

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).
Participants from ARIC, CHS and Dallas Heart Study without a prior diagnosis (prevalent) heart failure and with either a baseline hs-cTnT value < 3.0 ng/L (group 1) or between the LOB and LOD (3-5 ng/L) (group 2) will be analyzed on a cohort-specific level. The CHS group included 1427 subjects in group 1 and 579 in group 2. Similarly,

DHS included 957 subjects in group 1 and group 2 is to be determined. The ARIC study will include 3258 subjects in group 1 and 2500 subjects in group 2.

Data from DHS will be reanalyzed based on the two subgroups (hs-cTnT < 3.0 ng/L versus 3-5 ng/L) with respect to cross sectional MRI information for left ventricular structure and CT scan information for coronary calcium. The ARIC and CHS cohorts will provide differentiated long-term cardiovascular outcomes for cardiovascular death and new-onset (incident) heart failure hospitalization. Providing information on three different cohorts will make our results more generalizable.

Statistical Analysis

Groups 1 and 2 of the CHS population will be compared using an unpaired T-test for normally distributed variables and Mann-Whitney U test for the non-normally distributed continuous variables and χ^2 test for the binary variables. Cumulative incidence of heart failure and cardiovascular death in each category will be presented. Multivariate analyses will be performed by using Cox proportional hazard regression models. Outcomes will be first adjusted for demographics including age, sex, race (black vs. other). We then will compare the risk of incident heart failure and cardiovascular death between the two groups using previously validated models specific for heart failure and cardiovascular death. Formal and graphical methods will be used to confirm the assumption of proportional hazards. Subgroup analysis will be performed to determine effect of gender on overall results.

The methodology for cross sectional associations between groups 1 and 2 in DHS have been previously described in detail and are similar in approach as the cross sectional analysis in CHS. The outcomes for the ARIC study for groups 1 and 2 will also be reported as incidence rates, unadjusted, and adjusted Cox models. Multivariate analysis of the ARIC cohort included a model adjusting for demographics as well as a model adjusting for the traditional cardiovascular risk factors (diabetes, systolic blood pressure, smoking history, total cholesterol, HDL-c).

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)?

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.

References

1. 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 2010;304:2503-12.
2. Latini R, Masson S, Anand IS et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242-9.
3. Omland T, de Lemos JA, Sabatine MS et al. A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. The New England journal of medicine 2009;361:2538-2547.
4. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clinical chemistry 2010;56:254-61.
5. Saenger AK, Beyrau R, Braun S et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. Clin Chim Acta 2011;412:748-54.
6. Eggers KM, Venge P, Lindahl B, Lind L. Cardiac troponin I levels measured with a high-sensitive assay increase over time and are strong predictors of mortality in an elderly population. Journal of the American College of Cardiology 2013;61:1906-13.
7. 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 2011;123:1367-76.

8. 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 2010;304:2494-502.
9. Kalogeropoulos A, Psaty BM, Vasan RS et al. Validation of the health ABC heart failure model for incident heart failure risk prediction: the Cardiovascular Health Study. Circulation Heart failure 2010;3:495-502.
10. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 2009;119:3078-84.