ARIC Manuscript Proposal #2128

PC Reviewed: 5/14/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Six-year change in high sensitivity cardiac troponin T and risk of cardiovascular events

b. Abbreviated Title (Length 26 characters): Change in hs-cTnT and CVD risk

2. Writing Group:

Writing group members: Elizabeth Selvin; Andreea Rawlings; Mariana Lazo; Chiadi Ndumele; Michael Steffes; Ron C. Hoogeveen; Vijay Nambi; Christie M. Ballantyne; Josef Coresh; others welcome

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

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3. Timeline: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

Cardiac troponins are elevated in the setting of myocardial damage and are the standard measures used for the diagnosis of myocardial infarction. There have been several generations of increasingly sensitive tests that reliably detect lower and lower concentrations of troponin in the blood. Recently, ultra high-sensitivity assays have been developed that can detect concentrations of troponin 10-fold lower than conventional assays (1, 2). For example, a novel high-sensitivity assay for cardiac troponin T (hs-cTnT) recently developed by Roche Diagnostics allows for measurement of troponin T concentrations far below the conventional limit of detection (1). Using this high sensitivity Roche assay, it has been shown that over 60% of adults with no history of cardiovascular disease in the ARIC Study at visit 4 had detectable concentrations of troponin in their blood (3). Recent studies in ARIC and other cohorts have also shown that minutely elevated troponin concentrations strongly predict risk of future cardiovascular events and mortality even after adjustment for traditional cardiovascular risk factors (3-8). Nonetheless, the full clinical ramifications of minor elevations in troponin detected by these next generation assays are unknown. Furthermore, most prior studies have relied on single measurements; thus, the prognostic implications of changes in hs-cTnT in in persons with no history of cardiovascular disease are largely uncharacterized.

The biggest impact of high sensitivity cardiac troponin assays is likely to be on primary (or perhaps secondary) care; physicians may eventually use hs-cTnT to monitor risk in asymptomatic individuals. Changes in hs-cTnT may also be used as surrogate endpoints in clinical trials. But it is unclear what types of changes in hs-cTnT are clinically relevant. The goal of the proposed study is to characterize long-term changes in hs-cTnT and the risk implications of such changes in the population.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize the associations of traditional cardiovascular risk factors with six-year change in hs-cTnT in the community-based ARIC population.

Aim 2: To characterize the association of six-year change in hs-cTnT with risk of subsequent cardiovascular events and death in the community-based ARIC population before and after adjustment for traditional cardiovascular 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 methodologic limitations or challenges if present).

Study design: Prospective cohort analysis examining risk factors for change in hs-cTnT from visit 2 (1990-1992) to visit 4 (1996-1998) and the association of six-year change in hs-cTnT (visit 2 to visit 4) with risk of cardiovascular events occurring after visit 4.

Hs-cTnT: Cardiac troponin T was measured at two time points using the same high sensitivity (pre-commercial) Roche assay.

Visit 2: cardiac troponin T concentrations were measured from stored (visit 2) serum samples using a sandwich immunoassay method (Roche Diagnostics) implemented on a Roche Elecys 2010 Analyzer in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study (#2009.16).

Visit 4: cardiac troponin T concentrations were measured from stored (visit 4) plasma samples using the same sandwich immunoassay method implemented on a Cobas e411 analyzer in 2010 at the Baylor College of Medicine as part of Dr. Ballantyne's ancillary study (#2008.10).

Calibration of visit 2 and 4 measurements: A calibration study is currently underway to test the comparability of different laboratory assays between different ARIC visits (V1-V5), including the Roche hs-cTnT assay at visit 2 (serum, Roche Elecsys2010 at UMN) and visit 4 (plasma, Cobas e411 at Baylor). Anticipated completion date of the calibration study is ~May 2013. If systematic differences are observed between hs-cTnT values obtained using the method at UMN in serum compared to the method used at Baylor in plasma, we will use a statistical calibration to align the measurements and correct for the bias ("drift").

Cardiovascular outcomes: The proposed study will focus on determinants of change in hs-cTnT and the associations of change in hs-cTnT with incident coronary heart disease, heart failure hospitalizations, and all-cause mortality. ARIC participants are contacted annually by telephone and reported hospitalizations and deaths are identified. ARIC investigators also survey lists of discharges from local hospitals and death certificates from state vital statistics offices for potential events. Hospital records are abstracted and potential coronary heart disease, ischemic stroke, and heart failure events (after 2004 only) are adjudicated by an end points committee.

Coronary heart disease: We will define incident coronary heart disease cases using the composite definition incorporating definite or probable myocardial infarction, cardiac procedures, and deaths from coronary heart disease identified during active surveillance for all hospitalizations and deaths among ARIC participants.

Heart failure: We will identify incident hospitalizations and deaths related to heart failure using discharge codes (ICD-9 code 428 for hospitalizations and ICD-10 code I50 for deaths). Additionally, an expert panel has additionally adjudicated those heart failure events occurring after 2004.

Mortality: Death from any cause identified during active surveillance of all participants in the ARIC study.

Exclusions: Persons who did not attend visits 2 and 4, were missing information on exposures or covariates of interest, who had a history of cardiovascular disease (coronary heart disease, stroke, or heart failure) or chronic kidney disease at visit 2, persons whose race was reported to be other than white or black, and blacks in the Minneapolis and Washington County cohorts.

Aim 1 - Statistical analyses: We will conduct analyses of risk factors for 6-year change in hs-cTnT (from visit 2 to visit 4) using linear and logistic regression models. We will characterize the associations of traditional cardiovascular risk factors (assessed at visit 2) with change in hs-cTnT from visit 2 to visit 4. Among persons with no detectable levels of hs-cTnT at visit 2, we will examine risk factors for incident detectable hs-cTnT at visit 4 (binary variable). We will consider the following core models:

Model 1: age, sex, race-center.
Model 2: age, sex, race-center, total cholesterol, body mass index, hypertension status, diabetes status, smoking status, and C-reactive protein.
Model 3: all variables in Model 2 + estimated GFR
Model 4: Framingham Risk Score (clinical categories)

Aim 2 – Statistical analyses: We will categorize individuals as having undetectable and detectable concentrations of hs-cTnT at visit 2 and visit 4. Among persons with detectable concentrations of hs-cTnT, we split the population into approximate thirds as per previous analyses of hs-cTnT in ARIC (3). We will characterize change across these categories (i.e., movement from undetectable at visit 2 to detectable at visit 4 and, among persons with detectable concentrations of hs-cTnT at visit 2, movement across thirds of hs-cTnT from visit 2 to visit 4).

We will conduct analyses with and without adjustment for baseline (visit 2) concentrations. In secondary analyses we will conduct analyses of past change– to answer the question of whether past concentrations and changes from visit 2 to visit 4 add prognostic value to current (visit 4) concentrations (9). It is possible that adjustment for baseline (visit 2) hs-cTnT concentrations may be biased due to regression to the mean. In contrast, adjustment for follow-up (visit 4) hs-cTnT may also be problematic since adjustment for baseline in the presence of measurement error can inflate regression the coefficients (10). Thus, we will also look at percent change without adjustment for hs-cTnT at either visit.

For comparability to previous epidemiologic studies with serial measurements of hs-cTnT, we will compare the risk of cardiovascular events and mortality among persons with and without detectable hs-cTnT concentrations at follow-up before and after adjustment for confounding factors. Among participants with detectable hs-cTnT at visit 2, we will categorize the population by categories of relative change in hs-cTnT level, i.e. greater than 50% increase, greater than 50% decrease, and change of 50% or less (reference group). We will compare risk of cardiovascular events and death across these categories. The 50% change cut-point was previously used in an analysis of hs-cTnT and cardiovascular events and death in the Cardiovascular Health Study (6). Due to limitations of the above–described (but previously used) approach we will also conduct analyses with three categories at each visit (undetectable, detectable, elevated). We will cross-classify these categories at the two visits to create a 3x3 grid (9 groups) and compare risk across these groups. If there is sufficient sample size (precision within cells), we will also examine tertiles within the detectable groups at visit 2 and visit 4 and

generate a 4x4 grid (undetectable, detectable tertile 1, detectable tertile 2, detectable tertile 3) and compare risk across these 16 groups.

We will generate Bland-Altman plots of hs-cTnT to compare the variability of hs-cTnT at the two visits. We will generate Bland-Altman plots on (difference against the mean) on the absolute and log scales to evaluate whether the variance is stabilized by the log transformation.

We will generate a Kaplan-Meier plot to visually show the survival functions for the different outcomes by categories of 6-year change in hs-cTnT. We will estimate hazard ratios and their 95% confidence intervals using Cox proportional hazards models with adjustment for covariates. The proportional hazards assumption will be examined using log-(-log) plots and by testing risk factor-by-time interactions; if the assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly. We will consider the following core models:

Model 1: age, sex, race-center.
Model 2: age, sex, race-center, total and high-density cholesterol levels, body mass index, systolic blood pressure, hypertension medication use, diabetes status, smoking status, and C-reactive protein.
Model 3: all variables in Model 2 + estimated GFR
Model 4: all variables in Model 3 + left ventricular hypertrophy (calculated by ECG Cornell criteria)

To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs for the quartiles and we will also implement restricted cubic splines to obtain a smoother fit to the data. We will formally test for interactions by race and sex and present stratified analyses if there is evidence for interaction.

Sensitivity analyses: We will conduct sensitivity analyses excluding persons with events between visits 2 and 4, excluding persons with low estimated GFR at visit 2, and analyses examining whether physical activity is an important confounding factor that should be included in our main analyses.

Limitations:

- Measurements of hs-cTnT at only two time points, 6 years apart.
- The measurements of hs-cTnT were conducted by different laboratories at different time points. We will conduct a rigorous direct calibration study to assess comparability of these measurements and attempt statistical correction but it is possible that systematic differences due to laboratory methods, Roche reagents, etc may remain.
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

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)?

Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, Huxley RR, Ballantyne CM. Troponin T, N-Terminal Pro-B-Type Natriuretic Peptide, and Incidence of Stroke: The Atherosclerosis Risk in Communities Study.
Stroke. 2013 Mar 7. [Epub ahead of print] PMID: 23471272

Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E.
Chronic hyperglycemia and subclinical myocardial injury. J Am Coll Cardiol. 2012 Jan 31;59(5):484-9. doi: 10.1016/j.jacc.2011.10.875. PMID: 22281251

Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. 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 Apr 5;123(13):1367-76.

Agarwal SK, Avery CL, Ballantyne CM, Catellier D, Nambi V, Saunders J, Sharrett AR, Coresh J, Heiss G, Hoogeveen RC. Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study.

Clin Chem. 2011 Jun;57(6):891-7. doi: 10.1373/clinchem.2010.159350. Epub 2011 Apr 25. PMID: 21519038

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* 2009.16 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/

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

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2. Kavsak PA, MacRae AR, Yerna MJ, Jaffe AS. Analytic and clinical utility of a next-generation, highly sensitive cardiac troponin I assay for early detection of myocardial injury. Clin Chem. 2009;55(3):573-7. PMID: 19168557
3. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, 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(13):1367-76. PMCID: PMC3072024. PMID: 21422391
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