1.a. Full Title: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study

b. Abbreviated Title (Length 26 characters): hs-cTnT predicts MACE

2. Writing Group:
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Others are welcome.

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

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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**: Cardiac troponins are widely used in practice to identify patients with acute coronary syndromes (ACS) (Alpert et al. 2000), and elevated levels are predictive of poor outcomes in non-ACS patients with chronic kidney disease (CKD) and congestive heart failure (CHF) (Freda et al. 2002, Sato et al. 2001). Assays for cardiac Troponin-T (cTnT) are sufficiently sensitive to diagnose ACS at a serum concentration of 0.01μg/L; however, screening the general population of at risk individuals requires a much more sensitive assay (Katus et al. 1991, Wu and Jaffe 2008). Using the current commercially available 4th generation assay, cTnT is elevated in only 0.7% of the general population, but when elevated is associated with the presence of cardiovascular disease or high risk phenotypes (Wallace et al. 2006). Newer highly sensitive cardiac Troponin-T (hs-cTnT) assays have a detectable range 10 fold lower than fourth generation cTnT assays (Tate 2008) and have higher sensitivity identifying patients at risk for adverse cardiac events. This novel assay has never been applied to a population-based sample.

   A novel hs-cTnT assay using (Roche Diagnostics, on platform - Roche Cobas e411) detects low level elevations in 90% of patients 6 months post myocardial infarction, is elevated in patients with CHF, and provided incremental prognostic value in the presence of serum BNP levels (Neizel et al. 2009, Latini et al. 2007). The recent study by Reichlin et al. highlighted the improved performance of this assay in diagnosis of an MI (Reichlin et al. 2009). This precommercial hs-cTnT assay will be measured in plasma samples from 11,336 individuals who completed the ARIC visit 4. We propose a primary analysis to determine if a correlation between hs-cTnT and all cause mortality exists. We also will perform secondary analyses to evaluate the association of hs-cTnT with adverse cardiovascular events both as composite and individual outcome measures.

5. **Main Hypothesis/Study Questions**:

   a. Detectable levels of hs-cTnT are significantly associated with total mortality in the ARIC study regardless of prevalent CVD
   b. Detectable levels of hs-cTnT will be significantly associated with adverse cardiovascular events both as composite and individual measures
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).

1. After standard ARIC exclusions, subjects from ARIC visit 4 will be eligible
   a. For the primary endpoint of all cause mortality, we will perform separate analysis for patients with and without prevalent CVD
   b. For secondary endpoints we will perform separate analysis for patients with and without prevalent CVD. We will examine secondary endpoints as individual and composite outcomes of adverse cardiovascular events
      i. CV death
      ii. Hospitalization for CHF
      iii. Hospitalized MI or fatal CHD or coronary revascularization procedure
      iv. Hospitalized CVA or fatal stroke
      v. Hospitalization unstable angina (ICD-9 411.1)

2. Highly sensitive cardiac Troponin-T will be modeled as both a continuous variable and as a categorical variable

3. Association of hs-cTnT quartiles and the above listed clinical endpoints will be evaluated using Kaplan Meier survival analysis

4. The association between hs-cTnT and clinical endpoints will tested using Cox-proportional hazards models adjusted for:
   a. Demographic variables - age, gender, and study center.
   b. BMI and abdominal circumference
   c. Traditional CV risk factors (TRF) - Smoking, Diabetes mellitus, Hypertension, Systolic Blood pressure, ECG evidence of LVH, Family history of premature CAD, Renal function (estimated Glomerular Filtration Rate), and plasma lipid parameters
   d. TRF + lipid parameters + hs-CRP
   e. TRF + lipid parameters + hs-CRP + NT-proBNP

5. If Cox-proportional hazards models show significant association with clinical endpoints, we will estimate the effect of hs-cTnT on the area under the receiver operating curve (C-statistic) for patients without CVD in a model including other risk factors (age, gender, total cholesterol, HDL-c, systolic blood pressure, smoking status, and diabetes)
   a. We will test the discriminative ability of hs-cTnT using two methods
i. Net Reclassification Improvement (NRI) with categories of risk of adverse cardiovascular event of \( \leq 5\%\), \( >5 \) to \( \leq 20\%\), \( >20\%\) (Zethelius et al. 2008)

ii. Integrated Discrimination Improvement

6. We will perform exploratory analyses to assess for interactions within different subgroups for the primary and secondary outcomes. We will assess whether the association between hs-cTnT and outcomes differs by levels of eGFR, by race, by gender, or by BMI

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? ____ 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

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? ____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 #6 - (Sharrett et al. 1994)

   MS #606 - (Folsom et al. 2002)

   MS #889 - (Ballantyne et al. 2004)

   MS #934 - (Folsom et al. 2006)
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?   

   Yes   No

11.b. If yes, is the proposal
   A. primarily the result of an ancillary study (list number* __________)
   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.

References


