1.a. Full Title: The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD

b. Abbreviated Title (Length 26 characters): high sensitivity troponin and prevalent CHD

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

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3. **Timeline**: Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. **Rationale**: Troponin is the recommended biomarker for use in the diagnosis of acute myocardial injury. Troponin has been noted to be elevated in several other clinical conditions as well. Additionally, troponin has been detected in both a general population and in those with cardiac disease (prevalent coronary heart disease and CHF) and has prognostic implications (N Engl J Med. 2009 Dec 24;361(26):2538-47, Circulation. 2007 Sep 11;116(11):1242-9).

A new high sensitivity troponin which can detect troponin at 10-fold lower concentrations is now available.

Using this assay, we have shown that cardiac troponin T improves the prediction of coronary heart disease (CHD), heart failure (HF) and mortality in the ARIC population (in press, Circulation). Similar findings have been reported in the Dallas Heart Study and CHS (JAMA. 2010 Dec 8;304(22):2503-12, JAMA. 2010 Dec 8;304(22):2494-502).

The PEACE investigators (a randomized controlled trial of ACE inhibitors in patients with prevalent heart disease) (N Engl J Med. 2009 Dec 24;361(26):2538-47) also showed that high sensitivity cardiac troponin T had predictive value in individuals with prevalent CHD. However, this was in a setting of a randomized controlled trial and included predominantly Whites and men. It will therefore be of importance to evaluate the value of high sensitivity troponin T in individuals with prevalent CHD in ARIC.

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

   **Hypothesis**: High sensitivity troponin T will be associated with incident mortality, heart failure hospitalization and recurrent coronary heart disease events in individuals with prevalent CHD at visit 4 in the ARIC study.

   **Questions to be addressed in a stepwise manner**:
   1. Is high sensitivity cTnT associated with heart failure hospitalization and mortality in the ARIC study?
   2. Is high sensitivity cTnT associated with recurrent CHD events in the ARIC study?
   3. Will the strength of association between troponin and events vary by the type of prevalent CHD event (i.e. revascularization versus MI)?
   4. Is high sensitivity cTnT associated with recurrent CHD events, HF hospitalization and mortality in individuals with prevalent CVD (defined as prevalent CHD, HF or stroke)?
   5. How does troponin compare to NT-pro BNP and hs-CRP with respect to association with adverse events and prediction of events?

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).

I. Definition of prevalent CHD: Two definitions will be used
   a. MI or revascularization before visit 4
   b. MI before visit 4

(Note: Prevalent CHD at baseline was based on self report of MI/ revascularization or definite ECG evidence of MI)

Analysis will be done for both definitions (definition 1 will be soft CHD while definition 2 will be hard CHD)

In a secondary analysis we should examine troponin in the setting of prevalent cardiovascular disease defined as prevalent CHD or prevalent HF or prevalent stroke

II. Inclusions: Include those with prevalent CHD at visit 4 and with follow up. For the secondary analysis those with prevalent HF or stroke will also be included

Exclusions: Missing troponin information, missing covariate information

III. Analysis plan: (to be done for both primary and secondary aims)

1. Describe the distribution of high sensitivity TnT (cTnT) (overall and by sex and by race). Note if the distribution is similar to what we observed in those without prevalent CHD/ CVD
2. Describe the 99th percentile in this population and describe how many would have had troponin detectable by conventional, currently used clinical assay (this corresponds to 0.03 in the high sensitivity assay
3. Describe the distribution of high sensitivity troponin in those who had MI as the qualification for prevalent CHD as opposed to revascularization and similarly those who had prevalent HF/ stroke
4. Describe associations between cTnT and a composite of HF + mortality and then a composite of recurrent CHD event, heart failure hospitalization and death (?stroke). Separate analysis by outcome will then (i.e. CHD, HF hospitalization and mortality) be required. Both hard (i.e. CHD death +MI) and all CHD (i.e. hard CHD + revascularization) will need to be examined.
5. Troponin will be modeled both as categories (as done for the first cTnT paper, MS 1566) and as a continuous variable
6. We will need to assess for confounding by CV meds. We will need to look at ASA use, statin/ lipid lowering therapy use and then perhaps anti-hypertensives. We will need to examine if there are differences in troponin levels between those on and not on these medications and for those in which there is a significant difference consider adding to the models
7. Cox proportional hazards model with minimal adjustments (age, gender, race, and field center) and then full adjustment (age, gender, race, center, body mass
index, waist girth, hypertension, systolic blood pressure, total cholesterol, HDL-cholesterol, smoking, diabetes, eGFR, LVH, hs-CRP and NT-proBNP)

8. An additional model to be considered for CHD risk prediction could be based on paper by Wattanakit K et al AHJ 2005; 149: 606-12 where determinants of recurrent events in ARIC was described. We will not have all the variables used in the model as this was based on visit 1 data. Factors associated with recurrent events included traditional risk factors as above (but excluding BNP, CRP and serum creatinine instead of eGFR) and in addition low albumin, physical inactivity and IMT

9. For HF prediction we could now use the ARIC HF prediction model. For mortality we can also use the ARIC HF model as in our previous paper

10. We may need to do sex/ race stratified analysis

11. Proportional hazard assumption will be tested and whether cTnT is more associated with early rather than late events will need to be looked at

12. K-M curves will be generated by cTnT categories

13. AUC, NRI, clinical NRI, IDI and goodness of fit test (i.e. usual risk prediction testing) will need to be done comparing the base model to the expanded model

14. We will need the following expanded models: a. add cTnT alone to the basic model  b. add BNP alone to the basic model c. add TnT and BNP to the basic model (Basic model will be the one described in #8)

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 ICTDER02 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 ICTDER02 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 ICTDER02 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/

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.