ARIC Manuscript Proposal # 1808

PC Reviewed: 6/14/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The utility high sensitivity cardiac troponin t in the prediction of heart failure risk

b. Abbreviated Title (Length 26 characters): **high sensitivity troponin and heart failure risk prediction**

2. Writing Group:

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

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3. Timeline: Analysis to start as soon as approval is obtained. We request co-ordinating center to perform the statistical analyses. 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: A new high sensitivity troponin assay which can detect troponin T at 10-fold lower concentrations is now available and has been used to measure the cardiac troponin T (cTnT) concentrations in samples collected at ARIC Study visit 4 and stored at – 70 °C. *(ancillary study 2008.10)*

Although troponin is a known marker of myocardial injury, there are other causes for elevated troponin including heart failure *(Jeremais A Annals of Internal Medicine 2005 May 3;142(9):786-91)*. Troponin, measured using the high sensitivity assay, has recently been shown to have prognostic implications even in a general population (including ARIC) (de Lemos JA JAMA. 2010 Dec 8;304(22):2503-12., deFillipi CR JAMA. 2010 Dec 8;304(22):2494-502, Saunders JT Circulation. 2011 Apr 5;123(13):1367-76). Indeed about 2/3rd of community based ARIC cohort had detectable levels of cTNT at visit 4.Interestingly, the association between troponin and heart failure (HF), and, troponin and mortality was stronger than the association between troponin and coronary heart disease. Furthermore, the troponin levels measured using the highly sensitive assay was reported to be associated with adverse cardiovascular outcomes in patients with prevalent HF in the VaLHefT study (Latini R *Circulation.* 2007;116:1242–1249).

Recently, Agarwal and colleagues described a heart failure risk prediction score in the ARIC study (MS # 1376). This HF risk prediction score does not include troponin T. In preliminary analysis done for our first troponin related analysis (MS # 1563) (published in Circulation), troponin did improve heart failure risk prediction over a base model that included many but not all the variables used in the heart failure risk prediction model that has now been developed in ARIC.

The heart failure prediction model used in our troponin analysis included age, gender, race, systolic blood pressure, antihypertensive medication use, smoking status, presence of diabetes mellitus (fasting blood glucose >126 mg/dL or antidiabetic medication use) body mass index, total cholesterol, high-density lipoprotein cholesterol, left ventricular hypertrophy, and creatinine while that used in the ARIC heart failure analysis includes age, gender, race, systolic blood pressure, antihypertensive medication use, smoking status, diabetes mellitus, body mass index, CHD and heart rate i.e. our model - that was improved by addition of troponin - included cholesterol variables, left ventricular hypertrophy, and creatinine while the ARIC heart failure model included prevalent CHD and heart rate.

In further analysis in the development of the ARIC heart failure model, Agarwal and colleagues found that of various biomarkers tested including hs-CRP, cystatin and NT-proBNP, only NT-proBNP added significantly to the HF risk prediction model

In our previous analysis of troponin, although, we did not have NT-proBNP in our risk prediction models, the hazards ratio for the association of troponin T with HF remained significant even when adjusted for NT-proBNP. Therefore we believe that troponin T will add to the prediction of heart failure risk in the ARIC study

5. Main Hypothesis/Study Questions:

Hypotheses:

1. Troponin T (measured with the high sensitivity troponin T assay) will improve HF risk prediction in the ARIC study
2. Age, gender, race, high sensitivity troponin T and NT-proBNP will perform as well as the ARIC HF model in HF risk prediction in the ARIC study

Questions to be addressed in a stepwise manner;:

1. Does high sensitivity cTnT add to the ARIC incident heart failure hospitalization risk score in the ARIC study?
2. Does age, gender, race, high sensitivity troponin and NT-proBNP do as well as the ARIC HF model?
3. Identify troponin T and NT-proBNP cut points that can be used to identify risk of heart failure

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).

a. Since troponin was measured in ARIC visit 4, this will form the baseline visit for our analyses
b. Inclusions and exclusions for our analysis will be similar to that in MS #1376 (Agarwal et al) which described the ARIC HF risk score. Briefly this proposal excluded individuals with prevalent HF at ARIC visit 1(defined as "current intake of HF medication, n=83, evidence of manifest HF based on Gotheburg criteria stage 3 (n=669) i.e. total n=752). In addition for our analysis we will also exclude those with heart failure hospitalization between visit 1 and visit 4 (ICD 9 code 428) (since troponin was measured only in visit 4). Finally, we will also exclude those with missing troponin information, missing NT-proBNP and missing covariate information
c. Follow up for incident HF will be until December 31st 2007 (or the latest available incident hospitalization data)

In a secondary analysis we will examine troponin after excluding prevalent CHD in order to determine the impact of troponin to predict incident HF in a population free of overt ischemic heart disease - a well recognized high risk group where risk prediction may not add much to their risk stratification or care.

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).
2. Troponin will be modeled both as categories (as done for the first cTnT paper, MS 1566) and as a continuous variable. We will also look at the AUC curves to determine if the cut-points in MS 1566 are appropriate for the HF risk prediction analyses as well.

3. Cox proportional hazards model will be used to describe the association of troponin T with HF after minimal adjustments (age, gender and race) followed by adjustments for the ARIC HF model (age, gender, race, systolic blood pressure, antihypertensive medication use, smoking status, diabetes mellitus, body mass index, prevalent CHD and heart rate). In further analysis the association of troponin with heart failure will be evaluated after adding NT-proBNP to the ARIC HF model.
4. Proportional hazard assumption will be tested
5. K-M curves will be generated by troponin T categories
6. AUC, NRI, clinical NRI, IDI and goodness of fit test (i.e. testing metrics of a marker in risk prediction) will be performed comparing the base model (ARIC HF model) to the expanded model (ARIC HF model + troponin T). Risk categories used in the ARIC HF model description paper (namely 0-5%, 5-10%, 10-20% and >20% 10-year HF risk) will be used for this analysis as well. As always bootstrapping will be required to adjust for optimism
7. The following additional expanded models will also be evaluated:
    a. a. add cTnT to a basic model that consists of ARIC HF score +NT-proBNP
    b. b. add troponin T and NT-proBNP to the ARIC HF model and compare with the ARIC HF model
8. Then compare a model that includes age, gender, race, NT-proBNP and troponin T with the ARIC HF model to evaluate which of the two models better predict HF by comparing the AUC's of the 2 models
9. Finally, in order to find the optimal troponin T and NT-proBNP cut-points we will first examine the association between the biomarkers (each will be examined individually) and incident heart failure. Based on our initial analyses although there were knots, the association between troponin and HF was graded (i.e. no clear threshold). If this is the case, in general, using the biomarker as a continuous variable in risk estimation may be the preferred scientific/ statistical approach. However, in clinical practice cut points will be helpful. Therefore, we will look for points of inflection in the risk curve, when the risk begins to rise significantly and thereby try identifying cut-points/ thresholds. We will also describe the Youdens index (i.e. Y= sensitivity + specificity-1) to estimate the "optimal cut-point". In evaluating the "optimal cut-point" we will describe the cut-points when "ruling in" and "ruling out" the risk of heart failure is the goal (i.e. maximizing specificity and sensitivity respectively)

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.