ARIC Manuscript Proposal # 1668

PC Reviewed: 7/13/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome wide association study (GWAS) for Novel highly sensitive cardiac Troponin-T (hs-cTnT) levels in the ARIC Study

b. Abbreviated Title (Length 26 characters): GWAS for hs-cTnT levels.

2. Writing Group:

Writing group members:
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Others are welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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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 well established markers that are used in clinical practice to identify patients with acute coronary syndromes (ACS) (Alpert et al. 2000). In recent analysis in the ARIC population using highly sensitive cardiac Troponin-T (hs-cTnT) a strong association was observed between hs-cTnT levels and incident cardiovascular events (MS #1563). We propose to identify SNP's associated with hs-cTnT using two approaches: first we will perform an association test using candidate SNP's that were previously shown to be associated with CHD. We will then apply genome wide association analysis (GWAS) to identify novel genetic variants that are associated with hs-cTnT and in particular examine weather SNPs identified via the GWAS would be directly associated with cardiovascular outcomes (mendelian randomization). The advantage of using the candidate SNP approach would be that a P value corrected for the number of SNP's tested would be acceptable.

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

1. Gene variants associated with hs-cTnT levels can be identified performing genome-wide association analysis of hs-cTnT levels
2. Gene variants identified by GWAS analysis are associated with hs-cTnT levels in ARIC are associated with CVD events.
3. Gene variants previously associated with CHD or heart failure may be associated with hs-cTnT levels.

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. Analysis will be performed for blacks and whites separately.
2. Subjects from visit 4 will be included.

3. For the candidate SNP approach previously identified SNP's that were directly associated with CHD or heart failure will be used using the NHGRI database. The threshold for statistical significance will be less demanding than that for GWAS since these candidate SNPs are already known to have a role in CHD. The threshold will be determined by bonferoni correction for the number of independent SNPs examined.
4. The following analysis will be performed separately for the candidate gene and GWAS approach for the following subjects and models:
    a. All subjects with hs-cTnT measurements with the following covariates: age and sex.
    b. All subjects with hs-cTnT measurements with the following covariates: age, sex, prevalent CHD
    c. All subjects with hs-cTnT measurements with the following covariates: Age, sex, Prevalent CHD, smoking, diabetes mellitus, Systolic Blood pressure, Renal function (estimated Glomerular Filtration Rate), and total cholesterol and HDL-c, BMI, hs-CRP, and NT-proBNP
5. GWAS Significant SNPs associated with hs-cTnT will be tested for association with CHD, stroke, fatal CHD, total CV events, heart failure prevalence at visit 4 as well as incidence from baseline.
6. Replication of any positive findings will be sought in an additional population study (CHS as first option).

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? ___ X _ Yes ___ 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"? __ X __ 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?

__ X __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 #1563 – (Saunders et al. 2008)

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.

References

Alpert, J., K. Thygesen, E. Antman & J. Bassand (2000) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol,* 36**,** 959-69.