

ARIC Manuscript Proposal # 1425

PC Reviewed: 09/09/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The clinical utility of carotid intimal medial thickness (CIMT) and a single nucleotide polymorphism on chromosome 9p21 in reclassifying risk for incident CHD and stroke in the ARIC study

b. Abbreviated Title (Length 26 characters): IMT, 9p21, reclassifying risk

2. Writing Group:

Writing group members:

Vijay Nambi MD

Christie M Ballantyne MD

Eric Boerwinkle PhD

Aaron Folsom MD

Lloyd Chambless MD

Ariel Brautbar MD

Salim Virani MD

Kim Lawson PhD

Others are welcome

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**]

First author: Vijay Nambi

Address: 6565 Fannin Street

STE B 160/MS-A601

Houston, TX 77030

Phone: 713-798-7545

Fax: 713-798-7885

E-mail: vnambi@bcm.tmc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

Address:

Phone:
E-mail:

Fax:

3. **Timeline:** Analysis to start as soon as approval obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the analysis and manuscript preparation will take place within one year from approval of the proposal.
4. **Rationale:** We have shown that carotid intima media thickness (CIMT) improves incident coronary heart disease (CHD) risk prediction and can reclassify an individuals predicted risk when added to traditional risk factors (TRF) in the ARIC study (MS 611, 1213). Similarly we have also shown that the addition of the 9p21 allele to the TRF in whites in the ARIC study improves CHD risk prediction in the ARIC study as well (MS1291). Given that another recent report suggested that the risk allele for the 9p21 SNP is not associated with C-IMT we propose that the addition of C-IMT and 9p21 will be additive and further improve CHD risk prediction in Whites in the ARIC study.

5. Main Hypothesis/Study Questions:

Hypothesis: CIMT and the risk allele of the SNP in chromosome 9p21 when added to traditional risk scores such as the ARIC risk score (ARS) will improve classification of patients in the various risk groups

Questions to be addressed in a step wise manner:

- a. Does the addition of 9p21 and C-IMT improve CHD risk prediction in Whites in the ARIC study?
- b. Does the addition of 9p21 and C-IMT improve stroke risk prediction in Whites in the ARIC study?
- c. Does the addition of 9p21 and C-IMT improve CVD (cardiovascular disease: CHD + stroke) risk prediction in Whites in the ARIC study?
- d. Does the addition of 9p21, C-IMT and carotid artery plaque improve CHD, stroke, CVD risk prediction in Whites in the ARIC study?

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).

The analysis design would be similar to the prior manuscripts which evaluated if adding 9p21 and IMT improves CHD risk classification in ARIC

After excluding patients with CHD at baseline, all the other White individuals in the ARIC study on whom an ARIC coronary risk score can be calculated and have available

C-IMTs and genotyping data (9p21) available will be eligible for the CHD analysis. Similarly for stroke prediction, those on whom an ARIC stroke risk score can be calculated and who don't have stroke at the baseline ARIC visit (prevalent stroke) and have CIMT, 9p21 data will be eligible.

All the C-IMT analyses presented will be done using C-IMT as both a continuous variable, possibly non-linear, and as C-IMT stratified as CIMT >75th percentile, 25th to 75th percentile and <25th percentile. The CIMT will be age, sex and race specific.

We would:

1. Define the ARIC coronary risk score at baseline and classify as low (10 year CHD risk less than or equal to 5%), low-intermediate (10 year CHD risk 5-10%) and intermediate-high (10 year CHD risk >10-20%) and high risk (10 year CHD risk >20%).
2. To determine predictivity of the models, describe the AUC for CHD risk prediction using traditional risk factors (TRF) alone, then adding 9p21 and CIMT individually and finally adding both 9p21 and CIMT together. Perform bootstrap analysis to correct for over optimism
3. Using a Cox proportional hazards model, the 10-year predicted CHD risk of the study participants will be calculated using a model with TRF alone and then by adding C-IMT and 9p21 to the TRF. Participants will be categorized into the various risk groups (<5%, 5-10%, 10-20% and >20% 10 year CHD risk) and the number of individuals reclassified by the addition of CIMT and 9p21 described.
4. Describe the actual observed incident CHD events in the different categories of by ACRS alone and then in the various categories after the addition of 9p21 and C-IMT
5. Classify individuals based on their C-IMT and presence or absence of plaque into various risk groups and then add along with 9p21 to see if this further improves CHD risk predictivity and reclassification as described above (points 1-4)
6. Determine if reclassification with the addition of CIMT ± plaque and 9p21 is superior to that by TRF alone by evaluating comparing the observed and expected events by goodness of fit tests such as the Grønnesby-Borgan statistic.
7. Determine the number of individuals who would have therapy changed based on the risk reclassification and baseline LDL-c levels
8. Repeat the above steps for stroke risk prediction
9. Repeat the above steps for CVD (CHD + stroke) risk prediction

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 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
 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.csc.unc.edu/ARIC/search.php>

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 1213 and MS 1291

Lead authors from both these studies are included in this proposal

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.csc.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.