

ARIC Manuscript Proposal # 1405

PC Reviewed: 07/30/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Subclinical Measures GWA Collaboration: Carotid Intima-Media Thickness

b. Abbreviated Title (Length 26 characters): CHARGE CIMT

2. Writing Group: Kari North, Dan Arking, Kelly Volcik, Anna Kottgen, David Couper, Nora Franceschini, Christy Ballantyne, Tom Mosley, Gerardo Heiss

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __GH: Christy Ballantyne is unavailable and has not replied__ [**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: : Data analysis are underway following the analysis plan developed by the CHARGE working group on subclinical atherosclerosis - IMT. Meta-analyses are scheduled to begin by the end of July, conducted by the Framingham investigators who are members of this working group

4. Rationale:

GWA collaboration based on:

Initial in silico meta-analysis,

Reporting the evidence for association of each replicated SNP with other subclinical atherosclerotic measures (coronary, aortic, and peripheral arterial) with CIMT.

Replication in other cohorts with carotid IMT measures once results from meta-analysis are available.

5. Main Hypothesis/Study Questions:

Primary analysis: Intima Media Thickness of the Common Carotid Artery

Secondary analysis: Intima Media Thickness of the Internal Carotid Artery

Secondary analysis: presence of plaque ("yes"/"no" or 25% stenosis); the working group will consider a second clinically-defined dichotomous variable of CCA IMT mean-max ≥ 1.5 mm versus < 1.5 mm, after reviewing the numbers of subjects with this variable in the CHARGE cohorts.

5. 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).

Variables (phenotype): Baseline measurements of the far-wall common carotid and internal carotid intima media thickness, defined as the ln(mean of max).

Model: Linear regression for analysis of continuous variables, additive model. In FHS: linear mixed effects models to account for familial relations with adjustment for significant principal components, as needed. Analyses should be conducted either with covariates included in the model or by using unstandardized residuals. For analysis of dichotomous variables, we will use logistic regression analysis adjusted for covariates in the model.

Transform: Log transformed CIMT

Covariates: Basic model: age and sex adjusted

Multivariable -- in primary analyses, restrict to "top hits": age, sex, cigarette smoking (current, former, never), BMI, dichotomous hypertension (defined by SBP, DBP and treatment status), total cholesterol, HDL cholesterol, lipid lowering therapy, DM, triglycerides.

Subgroups: In secondary analyses, age specific (< 55 and > 55), sex-specific

Exclusions: Carotid endarterectomy/surgery prior to IMT measurement (not available in ARIC)

Control for multiple comparisons: 1 EFP; i.e., $p < 1/\#$ tests

Imputation: Imputation into HapMap 2.5 million SNPs

Meta-analysis: Meta-analysis centralized

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 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 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.csc.c.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)?

No overlapping manuscripts were identified

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* _2004,11)

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.c.unc.edu/atic/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.