

**ARIC Manuscript Proposal # 1404**

**PC Reviewed:** 07/30/08  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** GWAS of the Ankle-brachial index

**b. Abbreviated Title (Length 26 characters):** CHARGE ABI

4. **2. Writing Group:** Vijay Nambi, Aaron Folsom, Xia Li, Lynne Wagenknecht, Elizabeth Selvin, David Couper, Gerardo Heiss, Eric Boerwinkle

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. GH [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 - ABI. 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:**

To conduct a meta-analysis of genome-wide association study data in relation to ankle-brachial index and clinical measures of peripheral arterial disease among participants in multiple prospective cohort studies of cardiovascular disease. The collaboration is 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. Study Questions

Conduct a genome-wide association analysis for ABI and clinical measures of peripheral arterial disease using the set of genotyped and imputed SNPs.

Primary analysis: Ankle brachial index

Secondary analysis: Peripheral arterial disease, define as ABI <0.90

## 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).

Variables (phenotype): Baseline measurements of the ankle-brachial index

**Model:** Linear regression for analysis of continuous variables, additive model. Analyses will 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 ABI

**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:** ABI  $\geq$  1.4

**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 \_\_\_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?**  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.cscce.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.cscce.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.**