ARIC Manuscript Proposal # 1383r

PC Reviewed: 07/08/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: CHARGE GWAS for hemostatic factors

b. Abbreviated Title (Length 26 characters): Hemostasis GWAS

2. Writing Group: CHARGE hemostatic factor working group

ARIC writing group members: Aaron Folsom, Weihong Tang, Saonli Basu, Jim Pankow, David Couper, Eric Boerwinkle, Jing-Fei Dong. Other authors from additional CHARGE cohorts. The plan is to maintain symmetry across cohort.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AF ___ **[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: summer 2008

4. Rationale: Hemostatic factors contribute to venous and arterial thromboembolic diseases. Evidence suggests that key coagulation factors, such as fibrinogen, factor VII, factor VIII, and von Willebrand factor are heritable. Some variants in genes for these factors have been identified that determine plasma levels, but additional genes likely

contribute. There have been no genome wide association studies (GWAS) of hemostatic factors.

CHARGE (ARIC, CHS, Rotterdam, Framingham, and selected other cohorts) is doing a meta analysis of GWAS findings related to hemostatic factors. The group is chaired by Jacqueline Witteman from Rotterdam. The analysis is focusing on a) fibrinogen and b) factors VII, VIII and von Willebrand. Given the related nature we pursue one ARIC manuscript proposal and if there are indeed sufficiently promising results we will have write more than one paper and notify the committee.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with levels of hemostatic factors: a) fibrinogen and b) factors VII, VIII, and von Willebrand factor.

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).

Design: meta analysis of GWAS studies

Participating groups:

Framingham Study
Rotterdam Study
ARIC
CHS (2400)
MONICA/KORA
British birth cohort

Phenotypes: a) Fibrinogen, b)VWF, factor VII, factor VIII

1. Model: Linear regression for cross-sectional analysis

Main analysis will include only whites. Blacks will be run for ARIC /CHS as a secondary analysis. CARE policies for the African-American GWAS data will be followed.

Genetic model: additive. For top hits, further testing of genetic model to test deviations from an additive model.

2. Transform: no transform, no scaling.

3. Covariates:

1. Age and sex adjusted (+ cohort/center where appropriate)

2. Multivariate adjusted: Age (continuous), smoker (current, former, never), BMI (continuous), diabetes (y,n), CVD (y,n), TG (continuous), HDL-C (continuous), total cholesterol, alcohol (continuous, with 0 for nondrinker), SBP, htnrx, HRT.

3. Subgroups / Interactions: Age specific (< 55 and > 55), Sex specific, BMI (< 25 and > 25 kg/m2), Smoking.

4. Exclusions: use of anti-coagulation therapy

5. Control for multiple comparisons: Bonferroni adjustment

6. Imputation
Imputation to Hapmap 2.1 M using data provided by the ARIC central GWAS imputation group.

7. Meta-analysis:
Meta-analysis based on 2.1 M observed and imputed SNPs

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)?

None

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
___ A. primarily the result of an ancillary study (list number* _____)
_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03, 2007.02

*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.