ARIC Manuscript Proposal # 1199

PC Reviewed: _11/_21/06__ **Status: _A__** **Priority: _2__**
SC Reviewed: _12/07/06 **Status: __A__** **Priority: _2__**

1.a. Full Title: Coagulation factors and VTE

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members:

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

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3. Timeline: 6 months.

4. Rationale:

Venous thromboembolism (VTE) is a common cardiovascular disease that is intimately tied to the coagulation-anticoagulation system.

As reviewed by Lowe [1], most epidemiologic information on levels of coagulation factors and VTE risk has come from the Leiden Thrombophilia Study (LETS), a case–control study. LETS has reported increased risk of VTE in persons in the upper parts of the population distributions of factor IX [2,3]; factor X [4] and factor XI [5]; but not factor XII [6]. An inverse association of VTE with factor XIII (activity and the Val 34 Leu polymorphism) has been reported [7]. As expected from the associations of intrinsic system factors, such as factors VIII and IX, with VTE, and with the APTT in population studies [8], a shortened APTT has also been associated with risk of VTE [9]. The ECAT-DVT study of postoperative asymptomatic DVT showed associations with APTT and factor VIII, but not with fibrinogen or factors VII, IX or VWF [10].

It is important to confirm these results in prospective studies. The Vermont lab recently measured factors IX through XIII in LITE study nested case control sample. We will be the first prospective study to thoroughly address these associations.

5. Main Hypothesis/Study Questions:

Coagulation factors IX, X, XI, and XII are associated positively and factor XIII negatively with risk of VTE.

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).

Independent variables: factors IX through XIII.
Dependent variable: VTE case status.
Covariates: Matching variables (age, race, sex, study), other VTE risk factors (factor VIII, BMI, diabetes, D-dimer, factor V Leiden).

We will first examine in the controls the correlation among the independent variables and between the independent variables and the covariates. We will group factor levels into quintiles and perform unconditional logistic regression to calculate odds ratios. Associations at extreme values will also be assessed. Models will examine each factor separately, adding covariates in successive models based on hypothesized causal paths. The independence of each coagulation factor in a single model also will be considered, as will the number of elevated factors. In our typical fashion, we will repeat analyses for VTE case group subsets (ARIC vs CHS, idiopathic vs secondary, incident vs recurrent). We also will explore potential effect modification with covariates, primarily by stratification, and in particular for obesity and elevated D-dimer.

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 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? _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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__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)?

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* 1998.03)
___ 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:

1. Lowe GD. Can haematological tests predict cardiovascular risk? The 2005 Kettle Lecture. *Br J Haematol* 2006;133:232-250.

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3. Van Hylckama Vlieg A, van der Linden I, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000;95:3678-3682.

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5. Meijers JCM, Tekelenburg WLH, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000;342:696-701.

6. Koster T, Rosendaal FR, Briët E, Vandenbroucke JP. John Hageman's factor and deep-vein thrombosis: Leiden Thrombophilia Study. *Br J Haematol* 1994;87:422-424.

7. Van Hylckama Vlieg A, Komanasin N, Ariens RAS, Poort SR, Grant PJ, Bertina RM, Rosendaal FR. Factor XIII Val34Leu polymorphism, factor XIII antigen levels and activity and the risk of deep venous thrombosis. *Br J Haematol* 2002;119:169-175.

8. Lowe GDO, Rumley A, Woodward M, Reid E, Rumley J. Activated protein C resistance and the FV: R506Q mutation in a random population sample: associations with cardiovascular risk factors and coagulation variables. *Thromb Haemost* 1999;81:918-924.

9. Tripodi A, Chantarangkul V, Martinelli I, Bucciarelli P, Mannucci PM. A shortened activated partial thromboplastin time is associated with the risk of venous thromboembolism. *Blood* 2004;104:3631-3640.

10. Lowe GDO, Haverkate F, Thompson SG, Turner RM, Bertina RM, Turpie AGG, Mannucci, PM, on behalf of the ECAT DVT Study Group. Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: the ECAT DVT Study. *Thromb Haemost* 1999;81:879-886.