

ARIC Manuscript Proposal # 1200

PC Reviewed: 11/21/06

Status: A

Priority: 2

SC Reviewed: 12/07/06

Status: A

Priority: 2

1.a. Full Title: Factor VII level and genotype and venous thromboembolism

b. Abbreviated Title (Length 26 characters): Factor VII and VTE

2. Writing Group:

Writing group members:

A. Folsom, M. Cushman, L. Rasmussen-Torvik, T. Ohira, S. Heckbert, M. Tsai

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

First author: Aaron R. Folsom, MD

Address:

Division of Epidemiology & Community Health
School of Public Health
University of Minnesota
1300 South 2nd Street, Suite 300
Minneapolis, MN 55454-1015

Phone: 612-626-8862

Fax: 612-624-0315

E-mail: folsom@epi.umn.edu

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

Address:

Phone:

Fax:

E-mail:

3. Timeline: Finished paper in 3 months.

4. Rationale:

Abnormalities in the coagulation-anticoagulation process, for example, elevated plasma factor VIII level or activated protein C resistance, increase the risk of venous thrombosis and pulmonary embolism (venous thromboembolism, VTE) [1]. An elevated factor VII however has not been associated with VTE risk in most prior studies [2,3]. The exception is our Longitudinal Investigation of Venous Thromboembolism Etiology

(LITE), which reported a VTE rate ratio of 2.4 (95% confidence interval 1.2-4.8) for a factor VII coagulant activity (factor VII_c) level above the 95th percentile compared with the lowest factor VII_c quartile [4].

Variations in the level or activity of factor VII have been linked to polymorphisms in the factor VII gene. A -670A→C polymorphism is in tight linkage disequilibrium with a -402G→A polymorphism, and both are associated with higher levels of factor VII_c than are their corresponding wild genotypes [5-7]. Based on gene expression studies, -670C contributes to this effect, and not -402A [7]. Some studies suggest that the -670C and -402A alleles increase the risk of coronary heart disease [7-9]. To our knowledge, no study has examined risk of VTE in relation these factor VII gene polymorphisms.

The purposes of this investigation are to determine (1) whether the short term association observed in LITE between factor VII_c and risk of VTE [4] persisted with extended follow-up and more than twice as many VTE events and (2) whether VTE risk was increased in those with the -670C or -402A polymorphisms.

5. Main Hypothesis/Study Questions:

Factor VII_c and Factor VII genotype is associated with 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).

VTE events are from LITE (ARIC and CHS). For the analysis of factor VII_c with VTE, we exclude participants who were not white or black or were scarcely represented in some field centers (n = 103), and then participants who had a history of cancer at baseline (n = 1,711), were taking warfarin (n = 181), or were missing factor VII_c data (n = 602). For the nested case-control analysis, we exclude those without consent to use DNA (n = 48), who were taking warfarin at baseline (n = 20), who were not white or black (n = 6), or who were missing factor VII genotypes (n = 7).

Factor VII_c and VTE will be analyzed by longitudinal methods and factor VII genotypes by nested case-control methods. Risk factors for VTE previously identified by LITE will be considered for potential confounding.

We will calculate rate ratios of factor VII_c with VTE using Cox proportional hazards models. The associations of factor VII polymorphisms with several risk factors for VTE will be assessed using ANOVA. Unconditional logistic regression will be used to calculate odds ratios and 95% CIs of VTE in relation to factor VII polymorphisms.

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? 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)?

None.

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* 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.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.

References:

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

2. Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briet E, Vandenbroucke JP. Factor VII and fibrinogen levels as risk factors for venous thrombosis. A case-control study of plasma levels and DNA polymorphisms--the Leiden Thrombophilia Study (LETS). *Thromb Haemost* 1994;71:719-722.
3. Lowe G, Woodward M, Vessey M, Rumley A, Gough P, Daly E. Thrombotic variables and risk of idiopathic venous thromboembolism in women aged 45-64 years. Relationships to hormone replacement therapy. *Thromb Haemost* 2000;83:530-535.
4. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy R, Aleksic N, Folsom AR. Coagulation factors, inflammation markers, and venous thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Med* 2002;113:636-642.
5. van't Hooft FM, Silveira A, Tornvall P, Iliadou A, Ehrenborg E, Eriksson P, Hamsten A. Two common functional polymorphisms in the promoter region of the coagulation factor VII gene determining plasma factor VII activity and mass concentration. *Blood* 1999;93:3432-3441.
6. Lindman AS, Pedersen JI, Hjerkin EM, Veierød MB, Kavlie A, Arnesen H, Seljeflot I. The influence of the -401G/T and -402G/A polymorphisms of the coagulation FVII promoter on plasma levels of FVII. *Thromb Res* 2005;116:313-320.
7. Carew JA, Basso F, Miller GJ, Hawe E, Jackson AA, Humphries SE, Bauer KA. A functional haplotype in the 5' flanking region of the factor VII gene is associated with an increased risk of coronary heart disease. *J Thromb Haemost* 2003;1:2179-2185.
8. Lindman AS. Association between the factor VII haplotype containing the -402A allele and myocardial infarction in a population of elderly men at high risk for coronary heart disease [Letter]. *Thromb Haemost* 2005;94:226-227.
9. Bozzini C, Girelli D, Bernardi F, Ferraresi P, Olivieri O, Pinotti M, Martinelli N, Manzato F, Friso S, Villa G, Pizzolo F, Beltrame F, Corrocher R. Influence of polymorphisms in the factor VII gene promoter on activated factor VII levels and on the risk of myocardial infarction in advanced coronary atherosclerosis. *Thromb Haemost* 2004;92:541-549.