ARIC Manuscript Proposal # 1200

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:

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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]

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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 VIIc) level above the 95th percentile compared with the lowest factor VIIc 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 VIIc 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 VIIc 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 VIIc 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 VIIc 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 VIIc 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 VIIc 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 VIIc 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   ___ 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)?

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  

___ 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:


