ARIC Manuscript Proposal # 1126

PC Reviewed: _01/24/06 **Status: _____** **Priority: ____**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

The association of Fibrinogen alpha Thr312Ala polymorphism and Venous Thromboembolism in the LITE study

b. Abbreviated Title (Length 26 characters):

Fibrinogen α Thr312Ala and VTE

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___LJR-T__ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data analysis completed 1/1/06
Abstract submitted by 2/3/06
Paper draft to coauthors by 4/1/06
Paper draft to manuscript committee 6/1/06

4. Rationale:

Venous Thromboembolism (VTE) is a common, life-threatening disease in the United States. The Longitudinal Investigation of Thromboembolism Etiology (LITE) study found an incidence of 1.92 per 1000 person years for VTE in a population cohort of middle and older aged subjects.[1] In this study, those subjects experiencing a first incidence of VTE had 11% 28 day case fatality rate[1]. Despite the frequency and severity of VTE, there is limited knowledge about risk factors for the disease. The LITE study found that age, race, sex, BMI, and diabetes were associated with VTE, but other common cardiovascular risk factors such as smoking, dyslipidemia, physical inactivity and alcohol consumption were not associated with VTE in this cohort[2].

Some groups have investigated plasma levels of coagulation factors as risk factors for VTE. In the Leiden Thrombophilia Study (LETS) increasing plasma fibrinogen levels were associated with increased risk of deep vein thrombosis[3], but in the LITE study levels of plasma fibrinogen were not associated with VTE[4]. Other studies have examined polymorphisms in the proteins encoding coagulation factors. One polymorphism of interest is the Thr312Ala polymorphism. This polymorphism has been shown to impact clot structure and properties by increased factor XIII cross-linking and formation of thicker fibrin fibers[5]. It is also a fairly common polymorphism with a minor Allele frequency of 23% in a UK sample[6]. This polymorphism was shown to be associated with venous thromboembolism in a case control study using patients from the UK., although the association did not remain significant after adjustment for age, sex, malignancy, FV leiden, and factor 8 Val134Leu polymorphism[6].

We wish to use the LITE dataset to try to replicate the significant association of alpha fibrinogen Thr312Ala with VTE. Additionally, the large number of cases in the dataset will allow us to examine this association with several subsets of VTE (such as incident or recurrent VTE, non-cancer related VTE, and DVT [Deep vein thrombosis] vs. PE [pulmonary embolism] vs. both).

5. Main Hypothesis/Study Questions:

The Fibrinogen alpha Thr312Ala polymorphism will be associated with VTE. Specifically, having 1 or 2 copies of the Ala312 variant will increase the odds of incident VTE in the study population.

6. Data (variables, time window, source, inclusions/exclusions):

We will use the LITE case-control data set that has already been assembled; the data set contains 993 controls and 646 cases. This sample is frequency matched on age, sex, race, study (CHS and ARIC), and follow-up time. Controls were selected at a ratio of 2.1 per case.

Dependent variable -- The dependent variable in this analysis will be case or control status. Classification of cases and controls has already occurred.

Independent variable -- The primary independent variable in the analysis will be Fibrinogen alpha Thr312Ala genotype. This variable will be represented as a two degree of freedom class variable in all analyses with the T/A SNP having values TT, TA, or AA.

Covariates -- The following covariates may be used in the analysis: age, race, sex, study (CHS or ARIC), BMI, diabetes

Subgroups – Analyses may be done with the following subgroups: incident VTE, recurrent VTE, non-cancer related VTE, DVT only, PE only.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __XX__ 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? __XX__ 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"?
__XX__ 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

___XX___ 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)?

Proposal 810: Investigation of the protective effects of a Factor XIII Val34Leu polymorphism and a fibrinogen Hae III polymorphism in venous thromboembolism(VTE)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __XX__ Yes ____ No

11.b. If yes, is the proposal

_XX_ A. primarily the result of an ancillary study (list number* ____25___)

___ 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.

13. References

1. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med.* 2004;117:19-25.

2. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med.* 2002;162:1182-1189.

3. 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.

4. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, 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. Standeven KF, Grant PJ, Carter AM, Scheiner T, Weisel JW, Ariens RA. Functional analysis of the fibrinogen Aalpha Thr312Ala polymorphism: effects on fibrin structure and function. *Circulation.* 2003;107:2326-2330.

6. Carter AM, Catto AJ, Kohler HP, Ariens RA, Stickland MH, Grant PJ. alpha-fibrinogen Thr312Ala polymorphism and venous thromboembolism. *Blood.* 2000;96:1177-1179.