ARIC Manuscript Proposal # 764

PC Reviewed: 01/16/01	**Status: A**	**Priority: 1**
SC Reviewed: 01/30/01	**Status: A**	**Priority: 1**

1.a. Title: Hemostatic factors and venous thromboembolism incidence: The Longitudinal Investigation of Thromboembolism Etiology (LITE) Study

CHS/ARIC Manuscript Proposal: **Ancillary Study Manuscript**
CHS Ancillary Study C5, ARIC Ancillary Study, "Epidemiology of Venous Thrombosis and Pulmonary Embolism in the ARIC and CHS Cohorts"

b. Short Title: Hemostatic factors and venous thromboembolism

Timeline: Analysis: June 2000; Draft MS: August 2000; Submission: October 2000

2. Writing Group (list individual with lead responsibility first):
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Key Words: deep vein thrombosis / pulmonary embolism / venous thromboembolism/ hemostatic factors/ epidemiology

NOTE: The analysis in this study is part of the LITE ancillary study, and will be conducted by Albert Tsai, funded by the LITE study.

Background
Venous thromboembolism (VTE) is defined as either validated definite or probable deep venous thrombosis or validated definite pulmonary embolism. A number of risk factors for VTE have been established, including immobilization, surgery, cancer, and exogenous female hormones.

Pathophysiologically, three major contributing components may be important in the development and propagation of a thrombus: a hypercoagulable state, endothelial vessel injury, and stasis of the blood. Any factor associated with these three components is likely to affect the risk of thrombosis. Hemostatic factors may thus play an important role in venous thrombogenesis, as

enhanced coagulation and impaired fibrinolysis or anticoagulation theoretically should increase risk of clotting in the deep veins of the thigh. Some of the suspected hemostatic factors which have been studied with regard to deep vein thrombosis (DVT) include fibrinogen, factors VII and VIII, protein C, platelet count, antithrombin III, and von Willebrand factor. The evidence that abnormal levels of hemostatic factors are associated with VTE, however, is either lacking or conflicting for most of these.

A high fibrinogen level is associated with increased risk, as found in case-control studies (1-3). Koster et al. found an almost four-fold increase of thrombosis risk in those with plasma fibrinogen greater than 5g/l (3). However, factor VII was not found to be related to DVT in this same study (3). Factor VIII may be involved in the etiology of VTE, as those with elevated factor VIII concentrations (>1500 IU/L vs <1000 IU/L) were found to have an adjusted odds ratio of 4.8 (95% CI 2.3-10.0) in the Leiden Thrombophilia Study (LETS) (4). This study also reported a positive association between von Willebrand factor and DVT, but this association was explained by factor VIII concentration in the multivariate analysis (4).

Deficiencies in or abnormalities of coagulation inhibitors such as antithrombin III or regulatory system factors such as protein C and protein S account for less than 10% (5-7) of thromboembolic disease. These conditions are relatively rare in the population, however, and thus their contribution to the risk in the population is small. Protein C deficiency affects 0.2-0.4% of the population and antithrombin deficiency affects only 0.2% of the population (8). However, the risk of VTE for those who have it has been estimated to be approximately ten-times that of normal individuals (9). The relative risk for thrombosis was estimated to be 6.5 (95% CI, 1.8 to 24) for protein C deficiency alone in the LETS study (10). While clinical data have shown increases in risk for those with abnormalities in their hemostatic system, many of these factors have not been firmly established to increase risk of venous thromboembolism in epidemiologic studies. nowledge is also lacking concerning the increased risk of VTE with abnormal levels of inflammatory factors such as C-reactive protein and white blood cell count.

The LITE study combines the wealth of information from two prospective cohort studies, the Cardiovascular Health Study and the Atherosclerosis Risk In Communities Study. The strength of this study is the ability to address questions concerning hemostatic factors and their relationship to incidence of venous thromboembolism using a prospective epidemiologic study design.

5. Research questions/hypothesis:

1. Do the following hemostatic factors at the baseline examination predict increased risk for venous thromboembolism: fibrinogen, factor VIIc, factor VIII, platelets, von Willebrand factor, antithrombin III, Protein C, C-reactive protein, white blood cell count.
2. Do the associations differ by age, race and gender groups?
3. Are the associations different by BMI or diabetes mellitus status?

Methods

Subjects

This is a cohort study combining the CHS and ARIC cohorts. Cases of possible VTE were identified primarily by hospital discharge codes. Details of case ascertainment and validation are found elsewhere (11).

Data to be Used

We will be using a merged dataset, combining CHS and ARIC datasets which have already been validated by the respective coordinating centers. We will use baseline data from the ARIC and CHS cohorts. Baseline disease status variables will be used (prevalent cardiovascular disease, diabetes status, hypertension status, history of cancer). Follow up ARIC and CHS variables pertaining to cancer diagnoses will be used.

Analysis

Dependent variable: venous thromboembolism (VTE) status through June 30, 1997 in CHS, December31,1996 in ARIC.

Independent variables: fibrinogen, factor VIIc, factor VIII, platelet count, von Willebrand factor, antithrombin III, Protein C, C-reactive protein, white blood cell count, hematocrit, hemoglobin. Analyses including Protein C and Antithrombin will be restricted to ARIC, and analyses including C-reactive protein will be restricted to CHS.

Exclusions will be made on prevalent VTE at baseline, prevalent anticoagulant medication use, and history of cancer.

Univariate statistics (means and proportions) for potential covariates, overall, and by gender and race groups, will be calculated. Bivariate associations will also be computed using chi-squared tests for categorical data and Student's t-tests for continuous data.

Cox proportional hazards regression models will be used to predict hazard rate ratios of VTE. Independence of variables will be determined by statistical significance of the Wald Chi-square values for main effect terms after adding covariates into the models.

Tests for interaction will precede tests for confounding and independence. Potential interaction terms include age, race and sex. If these interaction terms are found to be statistically significant, we will then stratify analyses to the different levels of these variables.

Potential confounders include, but are not restricted to, the following variables:
Age, gender, ethnicity (white/non-white), field center, education level attained, body mass index, diabetes mellitus, prevalent hypertension, and pack-years of smoking.

Expected Results

We hypothesize that increased levels of fibrinogen, factor VII, factor VIII, von Willebrand factor, C-reactive protein and platelet count will be positively associated with risk of VTE. We also

hypothesize that low levels of antithrombin III, protein C will be positively associated with risk of VTE.

Conclusions

This will be the first prospective US study to report associations of hemostatic factors with validated venous thrombosis in a cohort study representing wide age, race, and geographical ranges of the general population. Results will provide information that might be helpful to other researchers for considering risk factors which may be important to consider for prevention of VTE as well as their potential role in confounding other associations.

References

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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 _X_ 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