

## CHS/ARIC Manuscript Proposal #708

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

b. **Abbreviated title:** Cardiovascular Risk Factors and Venous Thromboembolism

### 2. **Timeline:**

9/99-12/99: Analysis

12/99: Begin writing draft

3/00: Submit first draft for editing by co-authors

### 3. **Proposed Authors:**

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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.

**Key Words:** deep vein thrombosis / pulmonary embolism / venous thromboembolism/  
cardiovascular risk factors/ epidemiology

### 4. **Background and Rationale:**

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. This paper focuses on non-hemostatic atherosclerotic disease risk factors and VTE.

Cigarette smoking has been shown to be associated with higher levels of plasma fibrinogen. In addition, smoking may activate the intrinsic pathway through intimal wall damage or anoxia. Because smoking is associated with these changes, it is plausible that it might increase risk of venous thrombosis. High blood pressure may also play a role in vascular wall damage, and thus may elevate risk of VTE. Lipids, particularly via the Lp(a) system, may be associated with factors in the coagulation cascade and thus may increase risk of VTE. Physical activity, (lower) obesity and diabetes are all associated with enhanced coagulation, both through increased procoagulation and reduced fibrinolytic potential. Alcohol use is also associated with enhanced fibrinolysis and reduced fibrinogen and procoagulation. Still, the precise mechanisms by which physical activity, alcohol intake, diabetes, and obesity may increase risk are not yet clear.

Evidence that demonstrated lifestyle-related risk factors for arterial thrombotic disease are associated with VTE in the population is either lacking or conflicting. Goldhaber and colleagues (1) found that obesity, heavy cigarette smoking and hypertension were independent predictors (relative risks (95% confidence intervals) of 2.9 (1.5-5.4), 3.3 (1.7-6.5) and 1.9 (1.2-2.8), respectively) of PE in 112,822 women in the Nurses' Health Study. Yet others (2) state that the risk factors for venous thrombosis differ from those for arterial disease, including smoking, hypertension, and hyperlipidemia. Pollack and Evans (3) reported that incidence rates of DVT in a series of 166 patients undergoing surgery were actually lower in cigarette smokers than in non-smokers. Others also found that cigarette smoking did not increase risk of VTE (4).

In the Framingham Study, Goldhaber found no association between traditional cardiovascular risk factors and risk of death from PE over 26 years of follow-up. Data on age, systolic blood pressure, cholesterol level, cigarette use, glucose level, Metropolitan relative weight, and varicose veins were collected. Only relative weight in women remained statistically significantly associated with major PE in multivariate analysis ( $\beta = .69$ ,  $p < .0001$ ), with cigarette use marginally significant ( $\beta = .25$ ,  $p = .07$ ) (5). Diabetes was not found to be related to primary PE (RR = 0.7 (95% CI 0.3-1.9)) in the Nurses' Health Study (1). The data on diabetes and increased risk of VTE are equivocal, but because of the amount of vascular damage that diabetics incur, it is plausible that there is a positive association. To our knowledge, other risk factors have not yet been examined, including triglycerides, alcohol consumption, and physical inactivity. Triglycerides will be especially important because higher triglycerides is associated with higher Factor VII.

Few prospective epidemiologic studies have assessed these and other risk factors for VTE in general populations. The LITE study combines the wealth of information from two prospective cohort studies, the Cardiovascular Health Study and Atherosclerosis Risk In Communities Study. The strength of this study is the ability to address questions concerning traditional, non-hemostatic atherosclerotic disease risk factors using a prospective epidemiologic study design.

## 5. Research questions/hypothesis:

1. Do the following risk factors at the baseline examination predict increased risk for venous thromboembolism: current cigarette smoking; pack-years of cigarette smoking; body mass index and waist-to-hip ratio; elevated total cholesterol, LDL-C, triglycerides and lipoprotein(a) and decreased HDL-C; diabetes; hypertension; no or elevated alcohol consumption; physical inactivity.
2. Do the associations differ by age, race and gender groups?

## 6. 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.(6)

### *Data to be Used*

We will use baseline data from the ARIC and CHS datasets. The variables to be used include field center, age, sex, race, and medication use (anticoagulants, hormone therapy). Other variables to describe the risk factors will include education level. We will be using a merged dataset, combining CHS and ARIC datasets have already been validated by the respective coordinating centers. A separate dataset we have created containing variables generated from LITE case adjudication will also be used.

### *Analysis*

Dependent variable: validated venous thromboembolism, through 1997.

Independent variables:

Cigarette smoking (status and pack-years)

Obesity: body mass index; waist-to-hip ratio

Lipids: total cholesterol, LDL-C, HDL-C, triglycerides, Lp(a)

Diabetes: ADA diabetic status

Blood pressure: systolic blood pressure, diastolic blood pressure

Medication use: antihypertensive meds, hormone therapy

Alcohol: usual weekly intake

Physical activity at baseline: ARIC-Baecke questionnaire; CHS: LTPA score

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:

Age, gender, ethnicity (black/non-black), field center, education level attained, hormone replacement therapy.

Exclusions will be made on prevalent VTE at baseline, prevalent anticoagulant medication, and active cancer at baseline.

## **7. Conclusions**

This will be the first prospective US study to report associations of traditional cardiovascular risk 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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