ARIC Manuscript Proposal # 823

PC Reviewed: 08/23/01	**Status: __A__**	**Priority: _____**
SC Reviewed: 09/06/01	**Status: __A__**	**Priority: _____**

CHS Manuscript Proposal Form

1.a. Full Title: D-dimer as a Risk Factor for Future Venous Thrombosis

b. Abbreviated Title (Length 26 characters):

2. Type of study: _____ Main _____ Substudy ___X_ Ancillary (see below)

(Ancillary Study title and name of PI): LITE Study, Cushman, Folsom

3. Type of data: __X___ Events _____ Longitudinal __ ___ Cross-sectional

4. Genetic Information:
Genetic information is defined as any data from a participant's DNA. Please be advised that the Penultimate Draft of your paper must describe the IRB approval and informed consent process at each site. The number of cases removed from the data set due to a lack of specific consent for the analyses performed must also be stated in the Methods section.

a. Does your proposal contain the use of any genetic data? (please check one)

___ No (go to question 5) __x_ Yes (see question 4b)

b. Is genetic information used to address a primary aim or secondary aim of the Cardiovascular Health Study? (please check one or both)

_x__ Primary aim (heart and vascular disease) ___ Secondary aim (other health conditions)

5. Location of analysis: _____ Central __x__ Local (Site)

6. Name, address, phone number, and email address of investigator:
Mary Cushman, MD

7. Name, address, phone number, and email address of CHS sponsor, if applicable:

8. Names, justification for inclusion as co-authors, addresses, phone numbers, and email addresses of co-authors, if this paper will not be centrally analyzed:
Aaron Folsom, Nena Aleksic, Wayne Rosamond, Russ Tracy, Susan Heckbert, N David Yanez
All are LITE investigators.

9. Key words:
Deep vein thrombosis, pulmonary embolus, risk factor, D-dimer, blood coagulation

10. Introduction/background:

D-dimer is elevated during acute venous thrombosis because it is a marker of fibrin formation and reactive fibrinolysis. In this setting, as a clinical test, a low D-dimer concentration may be used as a screening test for exclusion of thrombosis. However, among healthy individuals, there is significant between-person variability of D-dimer, and there are no prospective studies relating D-dimer concentration to the incidence of future venous thrombosis. Higher D-dimer is known to be associated with the risk of future myocardial infarction in the ARIC and CHS studies, as well as others [1-3]. In this context, D-dimer may represent the summation of procoagulant balance, the extent of subclinical atherosclerosis, the stability of subclinical atherosclerosis, or the presence of underlying unknown coagulation disorders that predispose to coronary thrombosis.

Our understanding of the genetic basis for venous thrombosis has expanded rapidly over the past ten years [4]. However, among those with venous thrombosis and a positive family history, about 40% have undefined disorders. Further, among asymptomatic persons with known genetic traits that predispose to venous thrombosis, such as factor V Leiden, the absolute risk of thrombosis is relatively low, and the ability to select those at higher risk is limited. As a marker of ongoing fibrin formation, D-dimer may be a potential marker both for the presence of unknown genetic traits, or as a modifier of the risk of thrombosis among those with known genetic traits, such as factor V Leiden.

Using a seminal retrospective case control study, the Leiden Thrombophilia Study [5], we recently discovered a potentially important relationship between elevated D-dimer and the risk of venous thrombosis [6]. In this study, including 474 cases of deep vein thrombosis and 474 controls, D-dimer above the 70th percentile of the population distribution was associated with a 2.5-fold increased risk of thrombosis. This was independent of other risk factors for thrombosis, including the genetic factors, factor V Leiden and prothrombin 20210A, as well as the presumed genetic traits of elevated factor VIII or factor IX. Moreover, the joint presence of factor V Leiden or prothrombin 20210A with D-dimer above the 70th percentile conferred supra-additive risks of thrombosis, suggesting the possibility that D-dimer may have clinical utility in these two populations, in particular. Because the Leiden study is a retrospective study, these data require urgent confirmation. The LITE study is the largest population-derived prospective study of risk factors for venous thrombosis, and offers the optimal setting in which to address this finding further.

The aim of this paper is to study the prospective association of elevated D-dimer with incidence of venous thrombosis in the LITE ancillary study.

11. Hypotheses:

1. Elevated D-dimer will be a risk factor for venous thrombosis (deep vein thrombosis or pulmonary embolus) in the LITE ancillary study.

2. This association will be independent of other risk factors for venous thrombosis (age, sex, ethnic group, obesity).
3. This association will be present among those with and without hemostatic risk factors for thrombosis (factor V Leiden, prothrombin 20210A, elevated factor VIIIc). The relationship of the joint presence of elevated D-dimer and any of these factors with venous thrombosis will be supra-additive.

12. Analysis plan and methods:

Subjects

LITE nested case control study participants. Assessment of incident VTE.

Variables to be used:

LITE database; variables above.

Statistical analysis

The association of D-dimer with demographic factors and venous thrombosis risk factors will be analyzed among controls using ANOVA, t-tests, or linear regression, as appropriate. Logistic regression will be used to analyze the association of D-dimer with venous thrombosis, assessing D-dimer both as a continuous term and in quintiles of the population distribution. Adjustment will be made for age, sex, ethnic group (black, white), then for body mass index. Further adjustment will be made for the hemostatic risk factors (factor V Leiden, prothrombin 20210A, and elevated factor VIII). Stratified models will be run based on presence or absence (individually and together) of these hemostatic factors, as well as based on presence of DVT vs PE, cohort membership (CHS or ARIC), ethnic group, and idiopathic thrombosis vs venous thrombosis associated with either temporary risk factors or cancer.

13. Summary/conclusion:

This study aims to establish the association between elevated D-dimer and venous thrombosis in a prospective study.

14. References:

1. Lowe GDO, Yarnell JWG, Sweetnam PM, Rumley A, Thomas HF, Elwood PC. Fibrin D-dimer, tissue plasminogen activator, plasminogen activator inhibitor, and the risk of major ischemic heart disease in the Caerphilly Study. Thromb Haemost 1998; 79:129-33.
2. Cushman M, Lemaitre RN, Kuller LH, et al. Fibrinolytic activation markers predict myocardial infarction in the elderly: the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 1999; 19:493-98.
3. Folsom AR, Aleksic N, Park E, Salomaa V, Juneja H, Wu KK. A prospective study of fibrinolytic factors and incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb Vasc Biol in press.
4. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353:1167-73.

5. Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993; 342:1503-1506.
6. Cushman M, Andreescu ACM, Rosendaal FR. D-dimer and risk of venous thrombosis: the Leiden Thrombophilia Study [abstract]. Blood 2000; 96:650a.

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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

_____ Yes _____ No