ARIC MANUSCRIPT PROPOSAL # 800

PC Reviewed: 06/05/01	**Status: A**	**Priority: N/A**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1. a. Full Title: Fibrinolytic Factors and Venous Thromboembolism (VTE)
   b. Abbreviated Title (Length 26): Fibrinolysis and VTE

2. Writing Group (list individual with lead responsibility first):

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3. Timeline: Paper to be finished mid-summer.

4. Rationale:
Fibrinolysis is the process of thrombus degradation. Tissue plasminogen activator, which is inhibited by plasminogen activator inhibitor-1 (PAI-1), converts plasminogen to plasmin. Plasmin degrades fibrin of the thrombus. Plasmin is deactivated by antiplasmin.

There is equivocal evidence that plasma levels of fibrinolytic factors are associated with VTE (1). Most studies have been case-control studies. The few prospective studies of VTE recurrence and fibrinolysis are equivocal (2-4). Only two prospective incidence studies have been done, in Physicians (5) and surgery patients (6); both showed no association between fibrinolytic factors and VTE.

As part of the LITE ancillary study of ARIC and CHS, we performed a nested case-control study of VTE. We measured PAI-1, tPA/PAI-1 complex, and plasmin-antiplasmin (PAP). High levels of these indicate decreased fibrinolytic capacity.

This analysis will associate these fibrinolytic factors with VTE occurrence.

5. Main Hypothesis/Study Questions:

   1. Elevated PAI-1, tPA/PAI-1, and PAP will be risk factors for VTE. (Note: The three are likely to be correlated, so the may represent a single phenomenon.)

   2. These associations will be independent of other common VTE risk factors in LITE (age, race, sex, factor VIIIc, BMI, factor V Leiden).

   3. Interactions with age, factor VIIIc and factor V Leiden will exist.

6. Data (variables, time window, source, inclusions/exclusions):
   Inclusions: LITE nested VTE cases and controls

   Dependent variable: Case/control

   Independent variables: PAI/1, tPA/PAI-1, and PAP

   Covariates: Age, race, sex, factor VIIIc, BMI, factor V Leiden

   Analysis: (1) Examine bivariate associations of covariates with independent variables via ANOVA

   (2) Logistic regression using quartiles of independent variables.

   (a) Age-adjusted
   (b) Adjustment for all covariates

   (c) Interactions examined via joint risk factor stratified models.

7. a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

If Yes, is the author aware that the file ICTDER01 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

a. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

__x__ Yes ___ No

References

1. Prins MH, Hirsh J. A critical review of the evidence supporting a relationship between impaired fibrinolytic activity and venous thromboembolism. *Arch Intern Med* 1991;151(9):1721-31.

2. Korninger C, Lechner K, Niessner H, et al. Impaired fibrinolytic capacity predisposes for recurrence of venous thrombosis. *Thromb Haemost* 1984;52:127-30.

3. Crowther MA, Roberts J, Roberts R, et al. Fibrinolytic variables in patients with recurrent venous thrombosis: a prospective cohort study. *Thromb Haemost* 2001;85:390-4.

4. Schulman S, Wiman B. The significance of hypofibrinolysis for the risk of recurrence of venous thromboembolism. Duration of Anticoagulation (DURAC) Trial Study Group. *Thromb Haemost* 1996;75(4):607-11.

5. Ridker PM, Vaughan DE, Stampfer MJ, et al: Baseline fibrinolytic state and the risk of future venous thrombosis. A prospective study of endogenous tissue-type plasminogen activator and plasminogen activator inhibitor. *Circulation* 1992;85:1822-7.

6. Lowe GD, Haverkate F, Thompson SG, et al. Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: the ECAT DVT Study. *Thromb Haemost* 1999;81:879-86.