ARIC Manuscript Proposal # 1255

PC Reviewed: __5_/8__/07	**Status: _A___**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Thrombin generation test and Venous Thromboembolism (VTE) in LITE

b. Abbreviated Title (Length 26 characters): Thrombin generation and VTE

2. Writing Group:
Writing group members: Aaron Folsom, Mary Cushman, Susan Heckbert

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __x___ **[please confirm with your initials electronically or in writing]**

F**irst author**: Aaron Folsom
Address: Divison of Epidemiology and Community Health
University of Minnesota
1300 S 2nd St. #300
Minneapolis, MN 55454
Phone: 612-626-8862 Fax: 612-624-0315
E-mail: folsom@epi.umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address:

Phone: Fax:
E-mail:

3. Timeline: begin summer 2007

4. Rationale: In a recent JAMA article (1), a new Thrombin Generation Test was studied in relation to recurrent VTE. Compared to patients who had high thrombin generation (>400 nM), the RR of recurrence was 0.42 (95% CI 0.26-0.67) in patients with values of 300-400 nM, and the RR was 0.37 (0.21-0.66) for values<300 nM. These RRs were independent of age, sex, BMI, duration of anticoagulant therapy, fV leiden, and factor II G20210A. Thrombin generation was associated positively with fVIII

(borderline) and fIX. This study did not measure D-dimer, which might be highly correlated with thrombin generation. No study to our knowledge has determined whether thrombin generation is elevated before first VTE or whether any association with VTE is independent of D-dimer.

The LITE study is investigating VTE in the ARIC and CHS cohorts. As part of the nested case-control analyses, we have measured thrombin generation on VTE cases and controls in ARIC. We will examine its association with VTE in LITE.

(1) Hron G, Kollars M, Binder KR, Eichinger S, Kyrle PA. Identification of patients at low risk for recurrent venous thromboembolism by measuring thrombin generation. Hana 2996l296:397-402.

5. Main Hypothesis/Study Questions:
Thrombin generation is associated positively with risk of VTE independent of other non-coagulation VTE risk factors, but will be highly correlated with D-dimer and not independent of this marker of thrombosis.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Inclusions: LITE nested VTE cases and controls

Exclusions: Warfarin use, missing lab variables

Dependent variable: case/control status. Also subdivided by ARIC/CHS, idiopathic/secondary.

Independent variable: thrombin generation measured in the UVT lab

Covariates: Age, race, sex, BMI, diabetes, fV Leiden, and other non-coagulation factor analytes measured on the nested case-control sample. Coagulation factors and D-dimer are likely intermediaries and will be examined in explanatory models.

Analysis:
Odds ratios and 95% CIs of VTE will be calculated for thrombin generation using the cutpoints of the JAMA article, with adjustment for age and other confounders using logistic regression. Subgroup analyses will be conducted via stratification and interactions tested using cross product terms. Explanatory variables will be examined in a separate model.

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? __x__ 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"?
__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://www.cscc.unc.edu/ARIC/search.php

___x___ 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)?

Other LITE papers.

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

11.b. If yes, is the proposal
__x_ A. primarily the result of an ancillary study (list number* __1998.03_)
___ 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.