ARIC Manuscript Proposal # 1254

PC Reviewed: _5__/8__/07	**Status: __A__**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Tissue Factor Pathway Inhibitor (TFPI) and Venous Thromboembolism (VTE) in LITE

b. Abbreviated Title (Length 26 characters): TFPI and VTE in LITE

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]**

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3. Timeline: start summer 2007

4. Rationale: Tissue factor is an initiator of thrombosis and is inhibited by TFPI (1). Animal models suggest TFPI reduces thrombosis risk. In humans, there is limited evidence that greater TFPI is associated with reduced risk of VTE. The Leiden Study, for example, found that low levels of TFPI antigen, free-antigen, and activity, were related to increased odds of VTE (2,3): the OR for the lowest

5%ile vs higher levels of TFPI antigen was 2.1 (95% CI 1.1-4.1). Other studies support these findings (4-7).

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

5. Main Hypothesis/Study Questions: Low levels of TFPI are associated independently with increased risk of VTE in LITE. The association also will be seen in various subgroups typically analyzed in LITE.

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: TFPI measured in the UVT lab

Covariates: Age, race, sex, BMI, diabetes, fVIII, fV Leiden, D-dimer, and other analytes measured in the nested case-control sample

Analysis:
Odds ratios and 95% CIs of VTE for low TFPI (e.g., <10%ile) relative to higher TFPI will be calculated with adjustment for age and other covariates using logistic regression. Cubic spline graphs will be considered to further explore the shape of the association. Subgroup analyses will be conducted via stratification and interactions tested using cross product terms.

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)?

The most related proposals are from LITE. There are no overlapping manuscripts.

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.

References

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Tissue factor pathway inhibitor: a potent inhibitor of in-vitro coagulation and in-vivo thrombus formation.
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2: Duering C, Kosch A, Langer C, Thedieck S, Nowak-Gottl U.
Total tissue factor pathway inhibitor is an independent risk factor for symptomatic paediatric venous thromboembolism and stroke.
Thromb Haemost. 2004 Oct;92(4):707-12.
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5: Tardy-Poncet B, Tardy B, Laporte S, Mismetti P, Amiral J, Piot M, Reynaud J, Campos L, Decousus H.
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6: Ameziane N, Seguin C, Borgel D, Fumeron F, Moatti D, Alhenc-Gelas M, Grandchamp B, Aiach M, Emmerich J, de Prost D.
The -33T-->C polymorphism in intron 7 of the TFPI gene influences the risk of venous thromboembolism, independently of the factor V Leiden and prothrombin mutations.
Thromb Haemost. 2002 Aug;88(2):195-9.
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7: Amini-Nekoo A, Futers TS, Moia M, Mannucci PM, Grant PJ, Ariens RA.
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