ARIC Manuscript Proposal # 1171

PC Reviewed: _06/_20_/06	**Status: _A__**	**Priority: _2__**
SC Reviewed: __06/23/06__	**Status: _A___**	**Priority: _2__**

1.a. Full Title: Protein Z Related Genotypes and Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): Protein Z and VTE

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

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

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Address:

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3. Timeline: Complete by 12/2006.

4. Rationale: Protein Z is a circulating vitamin K-dependent glycoprotein that interacts with Protein Z dependent protease inhibitor (PZI) to inhibit coagulation factor Xa (1,2). PZI can also inactivate factors IXa and XIa.

Deficiencies of Protein Z or PZI have been hypothesized to increase thrombosis risk. A few small, clinical studies have suggested levels of Protein Z may relate inversely to stroke risk (3,4). Some animal and scanty human data suggest possible inverse associations with VTE (5,6), but there was no association between plasma Protein Z or ZPI and VTE in the best-designed studies (7, 10).

A few investigations have suggested ZPI genetic variants may affect VTE risk (8,9). We measured three ZPI polymorphisms in LITE to test this hypothesis.

5. Main Hypothesis/Study Questions:

Protein Z Dependent Protease Inhibitor genetic variants are associated with VTE incidence.

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).

Design: LITE nested case-control study: ARIC and CHS cases through 2002; 2:1 controls to cases.

Exclusions: Warfarin use at baseline, no DNA use.

Outcome: VTE

Exposures: R67X, W303X, Gln363Arg polymorphisms of ZPI

Analysis: Standard, unconditional logistic regression. Main covariates are age, race, sex, study, BMI, diabetes, factor V Leiden, prothrombin G20210A, D-dimer, factor VIII. Analyses are also done by study (ARIC, CHS); primary or secondary VTE; incident or recurrent VTE; and subgroups based on other covariates.

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)?

None.

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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2. Koren-Michowitz M, Rahimi-Levene N, Volcheck Y, et al. Protein Z and its role in venous and arterial thrombosis. *IMAJ* 2006;8:53-55.

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8. Kemkes-Matthes B, Matthes KJ, Souri M, et al. R255H amino acid substitution of protein Z identified in patients with factor V Leiden mutation. *Br J Haematol* 2005;128:248-252.

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10. Martinelli I, Razzari C, Biguzzi E, et al. Low levels of protein Z and the risk of venous thromboembolism [Letter]. *J Thromb Haemost* 2005;3:2817-2819.