ARIC Manuscript Proposal # 821

PC Reviewed: 08/23/01	**Status: __A__**	**Priority: __1__**
SC Reviewed: 09/06/01	**Status: __A__**	**Priority: __1__**

1.a. Full Title: Protein Z, protein Z-dependent protease inhibitor (ZPI) and arterial thrombosis

b. Abbreviated Title (Length 26 characters): PZ, ZPI and thrombosis

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

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3. Timeline: 12 weeks- Protein Z and ZPI assays of plasma samples

4-6 weeks- Data analysis and manuscript preparation

4. Rationale

Protein Z (PZ) is a vitamin K-dependant protein highly homologous to coagulation factors VII, IX and X, and protein C, PS and prothrombin. It is not the precursor of a serine protease, its plasma concentration spans a very broad range in normal individuals and its plasma concentration is greatly reduced during oral anticoagulation with coumarin derivatives. Although human PZ was isolated in 1984, the physiological function of PZ remained uncertain. Recently, it has been demonstrated that PZ limits the coagulation response (1000 fold), acting as a cofactor for the inhibition of activated factor X by newly described PZ-dependent protease inhibitor (1). Investigators have shown that the disruption of PZ gene in mice leads to a prothrombotic phenotype (2). The risk of thrombosis associated with PZ deficiency in human beings has not been established. A preliminary report (3) suggests that in people with factor V Leiden and concomitant PZ deficiency, thrombotic episodes occur earlier in life and more often than in individuals with factor V Leiden alone. A recent Lancet paper (4) suggests PZ deficiency may be associated with stroke in young patients. Clearly its results must be confirmed and more work done to better define the roles of both protein Z

and ZPI in thrombotic disease in man. The ARIC study provides an excellent opportunity for this.

1. Han X, Fiehler R, Broze GJ Jr. Characterization of protein Z-dependent protease inhibitor. Blood 2000; 96: 3049-3055.

2. Yin Z-F, Huang Z-F, Cui J, Fiehler R, Lasky N, Ginsburg D, Broze GJ Jr. Prothrombotic phenotype of protein Z deficiency. Proc. Nat. Acad. Sci. 2000; 97: 6734-6738 .

3. Kemkes-Matthes B, Matzdorff AC, Matthes KJ. Protein Z influences prothrombotic phenotype of factor V Leiden in humans. Blood 2000; 96 (suppl. 1): 534a. Abstract.

4. Vasse M, Guegan-Massardier E, Borg J-Y, Woimant F, Soria C. High frequency of protein Z deficiency in patients with ischemic stroke. Lancet 2000; 357: 933-934..

5. **Main Hypothesis/Study Questions: Is** there an association between levels of protein Z and ZPI and arterial thrombosis?

6. **Data (variables, time window, source, inclusions/exclusions):** Immunoassays will be used to determine levels of protein Z and ZPI in the ARIC Visit 2 plasma samples (50 uL) from incident CHD cases and a cohort random sample. Protein Z levels in individuals on oral anticoagulant therapy will be censored from analysis.

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? ____ Yes __X__ 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

___X___ Yes _____ No