ARIC Manuscript Proposal # 1253

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

1.a. Full Title: Endothelial protein C receptor (EPCR) and polymorphism and Venous Thromboembolism (VTE) in LITE

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

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

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]**

First 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:

The protein C system is an important anticoagulation system that operates to inactivate factors Va and VIIIa to reduce thrombin formation. Recently, an endothelial cell

activated protein C receptor in large arteries was described that interacts with the protein C system. It also exists in a soluble form and this molecule inhibits activated Protein C.

Saposnik et al. (1) described a haplotype (A3) in the EPCR gene that is related to higher soluble EPCR (sEPCR) levels and increased risk of VTE (OR=1.8), presumably due to decreased efficiency of the protein C system in carriers of A3. Other studies confirmed that the A3 haplotype increases VTE risk (2). A Ser219Gly polymorphism seems to explain the A3 haplotype (3,4). Other polymorphism and haplotypes have been described that affect sEPCR levels and further suggest a positive association between sEPCR and VTE (5-7). Recently, autoantibodies to EPCR also have been associated positively with VTE risk (8).

The LITE study is investigating VTE in the ARIC and CHS cohorts. As part of the nested case-control analyses, we have measured sEPCR and the A3 haplotype on VTE cases and controls in LITE. We will examine their association with VTE in LITE, the first prospective study on this topic.

5. Main Hypothesis/Study Questions:

Levels of sEPCR and the A3 haplotype are associated positively with VTE in LITE. The associations 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: sEPCR level measured in the UVM lab and haplotype measured in the UMN 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 EPCR level will be calculated across quintiles with adjustment for age and other covariates using logistic regression. The A3 haplotype will be similarly studied. 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)?

None. The only close papers are from LITE.

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

1: Saposnik B, Reny JL, Gaussem P, Emmerich J, Aiach M, Gandrille S.
A haplotype of the EPCR gene is associated with increased plasma levels of sEPCR and is a candidate risk factor for thrombosis.
Blood. 2004 Feb 15;103(4):1311-8.
PMID: 14576048 [PubMed - indexed for MEDLINE]

2: Simioni P, Morboeuf O, Tognin G, Gavasso S, Tormene D, Woodhams B, Pagnan A.
Soluble endothelial protein C receptor (sEPCR) levels and venous thromboembolism in carriers of two dysfunctional protein C variants.
Thromb Res. 2006;117(5):523-8.
PMID: 15921724 [PubMed - indexed for MEDLINE]

3: Medina P, Navarro S, Estelles A, Vaya A, Woodhams B, Mira Y, Villa P, Migaud-Fressart M, Ferrando F, Aznar J, Bertina RM, Espana F.
Contribution of polymorphisms in the endothelial protein C receptor gene to soluble endothelial protein C receptor and circulating activated protein C levels, and thrombotic risk.
Thromb Haemost. 2004 May;91(5):905-11.
PMID: 15116250 [PubMed - indexed for MEDLINE]

4: Qu D, Wang Y, Song Y, Esmon NL, Esmon CT.
The Ser219-->Gly dimorphism of the endothelial protein C receptor contributes to the higher soluble protein levels observed in individuals with the A3 haplotype.
J Thromb Haemost. 2006 Jan;4(1):229-35.
PMID: 16409473 [PubMed - indexed for MEDLINE]

5: Uitte de Willige S, Van Marion V, Rosendaal FR, Vos HL, de Visser MC, Bertina RM.
Haplotypes of the EPCR gene, plasma sEPCR levels and the risk of deep venous thrombosis.
J Thromb Haemost. 2004 Aug;2(8):1305-10.
PMID: 15304035 [PubMed - indexed for MEDLINE]

6: Medina P, Navarro S, Estelles A, Vaya A, Bertina RM, Espana F.
Influence of the 4600A/G and 4678G/C polymorphisms in the endothelial protein C receptor (EPCR) gene on the risk of venous thromboembolism in carriers of factor V Leiden.
Thromb Haemost. 2005 Aug;94(2):389-94.
PMID: 16113830 [PubMed - indexed for MEDLINE]

7: Poort SR, Vos HL, Rosendaal FR, Bertina RM.
The endothelial protein C receptor (EPCR) 23 bp insert mutation and the risk of venous thrombosis.
Thromb Haemost. 2002 Jul;88(1):160-2. No abstract available.
PMID: 12152660 [PubMed - indexed for MEDLINE]

8: van Hylckama Vlieg A, Montes R, Rosendaal FR, Hermida J.
Auto-antibodies against EPCR and the risk of a first deep venous thrombosis.
J Thromb Haemost. 2007 Apr 16; [Epub ahead of print]
PMID: 17439632 [PubMed - as supplied by publisher]