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: Division 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?  ____ 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://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


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. 
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]