ARIC Manuscript Proposal # 1082

PC Reviewed: __05/13/05   Status: _A__   Priority: __2_
SC Reviewed: ___05/13/05   Status: _A___   Priority: _2__

1.a. Full Title: Interrelations of Obesity with Hemostatic and other Risk Factors for Venous Thrombosis: the LITE study

  b. Abbreviated Title (Length 26 characters): *Obesity, biomarker, and thrombosis risk*

2.   Writing Group:
     Writing group members: **Aaron Folsom (folsom@epi.umn.edu), Susan Heckbert (Heckbert@u.washington.edu), Neil Zakai (neil_zakai@yahoo.com), Ellen O'Meara (analyst;** eomeara@u.washington.edu**), Wayne Rosamond**

     F**irst author**:   Mary Cushman, MD, MSc
     Address: Dept of Medicine, University of Vermont, 208 South Park Dr., Suite 2, Colchester, VT 05446

                    Phone: 802-656-8959   Fax: 802-656-8965
                    E-mail: Mary.Cushman@uvm.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: summer 2005

4. Rationale: Other than age, obesity is the major cardiovascular risk factor associated with risk of venous thrombosis (VT). VT is a multicausal disease, with interactions of genetic and environmental factors playing a key role [1]. For example, among young women the risk of VT with factor V Leiden, a common gene variant, is about 7-fold increased. The relative risk of VT with oral contraceptives is about 3. However the combination of these two risk factors is associated with a 34-fold increase in risk [2]. There are several risk factors that have additive (or supra-additive) interaction as well (eg. obesity and postmenopausal hormones [3]).

As for mechanisms explaining an association of obesity with VT, it is possible the relationship is due to hypercoagulability, large body size with impaired venous return, increased inflammation, or differences in the venous vessel wall. Abdollahi et al reported that adjustment for levels of some coagulation and inflammation factors that are correlated with obesity (factors VIII and IX, D-dimer, fibrinogen, C-reactive protein) did not attenuate the association of obesity with thrombosis, suggesting that hypercoagulability may not explain the association of obesity with thrombosis [4]. Interactions of obesity and hemostasis factors were not evaluated that study. Considering body size in relation to VT, we are aware of no studies evaluating waist or hip circumference or waist-hip ratio as a risk factor.

There has been little work on the influence of combinations of other VT risk factors with obesity in determining VT risk. Higher levels of several hemostatic factors are associated with increased risk of VT. Whether or not these factors add to the risk associated with obesity is not known. Inflammatory factors are not associated with VT risk, however they are associated with obesity, and whether inflammation factors predict VT among obese subjects is not known. This information would be clinically useful to further refine risk, especially given the increasing use of hemostasis testing in asymptomatic family members of those with VT. Conversely, most obese patients will not develop VT even though they are at increased risk. An ability to identify obese subjects with even higher VT risk might be useful from the clinical perspective.

The LITE ancillary study is examining VT risk factors in the ARIC and CHS cohorts. We reported the association of obesity assessed as BMI with VTE risk [5]. We have just updated VT events and now have 210 CHS participants and 339 ARIC participants with validated VT. Now that we have more VT events we wish to evaluate the interrelations of obesity, hemostasis and inflammation with VT.

5. **Main Hypothesis/Study Questions**:

    1. Higher waist and hip circumference, waist-to-hip ratio, height, weight and BMI will be associated with increased risk of VTE.
    2. Percent body fat will not be related to VT risk, but leg size (eg. calf circumference) will.
    3. Levels of hemostatic or inflammatory risk factors will not confound the associations of body size measures with VT.
    4. Other VTE risk factors and hemostasis and inflammation factors (eg. age, black race, diabetes, CRP, IL-6, factor VIIIc) will be more than additive to the association of body size with VT.

    5. **Data (variables, time window, source, inclusions/exclusions)**:

We will use the existing LITE data set. We will exclude subjects with prior history of VTE, warfarin use, and missing lab variables. Obesity will be categorized using the body-mass index (BMI) into 4 categories, <25, 25-30, 30-40, and 40+. Elevated waist will be defined as >88 cm in women and >102 cm in men and we will analyze waist, hip, and WHR as continuous variables or quartiles. Fat-free mass by impedence (CHS only) and calf circumference (ARIC only) will be analyzed as continuous variables or quartiles. Race will be categorized as black and non-black, as blacks are at higher VT risk than other ethnic groups. Diabetes status will be defined by the ADA criteria. The biomarkers to be assessed were measured at enrollment on all subjects in both cohorts (factor VIIc, factor VIIIc, fibrinogen, WBC), on all in CHS (C-reactive protein, interleukin-6), or all in ARIC (von Willebrand factor, aPTT, protein C).

Brief analysis plan and methods:
Incidence rates of VT will be computed by categories of baseline risk factors (obesity status, waist, elevated factor VIIIc and other biomarkers, to update prior LITE analyses with new cases). Proportional hazards models will be run for univariable and multivariable determination of hazard ratios of VT. Stratification will be done for some analyses by whether the VT was idiopathic or secondary. We will determine whether BMI and WHR both add important information as risk factors using cross classification. We will explore associations of different components of body size with VT (body fat as weight minus fat-free mass (CHS) and calf circumference (ARIC). Risk factor adjustment will include, (a) age, race, sex, diabetes; and (b) factor VII, von Willebrand factor, factor VIII, WBC, CRP, IL-6, aPTT, and/or protein C. The association of obesity together with other VTE risk factors will be assessed through cross-classification, assessing for supra-additive associations.

Summary/conclusion: We expect to show that the combination of obesity and other VT risk factors enhance the risk of VT in more than additive fashion. Results will provide information useful in assessing risk of VTE in the general population.

References:

1. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;353:1167-73.
2. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet*. 1994;344:1453-57.
3. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR. Estrogen plus progestin and risk of venous thrombosis. *Jama*. 2004;292:1573-80.
4. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thromb Haemost*. 2003;89:493-8.
5. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the Longitudinal Investigation of Thromboembolism Etiology. *Arch Intern Med*. 2002;162:1182-9.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __xx__ 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? _xx___ 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"?
        _xx___ 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

   ___xx___ 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? _xx__ Yes ____ No

11.b. If yes, is the proposal
     __xx_ A. primarily the result of an ancillary study (list number* __23_____)
     ___ B. primiarly 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.