ARIC Manuscript Proposal # 1617

PC Reviewed: 3/9/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: _**

1.a. Full Title: A Time-Dependent Analysis of the Association between Cardiovascular Disease Risk Factors and the Risk of Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): Time dependent CVD risk factors and VTE risk

2. Writing Group: Keattiyoat Wattanakit, MD, MPH, Pamela Lutsey, PhD, Heather Gornik, MD, MSc, Wayne Rosamond, MD, Susan Heckbert, MD, Mary Cushman, MD, MSc, Aaron Folsom, MD, MPH (Order to be determined)

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3. Timeline: Analysis will be performed at the University of Minnesota following approval of proposal. A manuscript is expected to be completed in June 2010.

4. Rationale:

It is still controversial whether there is an association between atherosclerotic cardiovascular disease (CVD) and venous thromboembolism (VTE). One study reported that patients with idiopathic VTE were more likely to have a higher prevalence of subclinical atherosclerotic plaque in the carotid artery and coronary artery calcification than a non-VTE control group.[1] In addition, these patients were more likely to have symptomatic CVD events compared to those with secondary VTE.[2, 3] In contrast, the two large population-based studies, the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Heart Study (CHS), reported that subclinical atherosclerosis,

defined by increased carotid intima-media thickness, were not predictive of increased risk for VTE.[4, 5]

If an association between CVD and VTE exists, the mechanism is presumed to relate to the sharing of common risk factors between the two diseases. To date, including the Longitudinal Investigation of Thromboembolism Etiology (LITE) study, only obesity is consistently associated with VTE risk,[6] whereas the roles of other CVD risk factors such as diabetes, hypertension, smoking, total cholesterol, HDL-cholesterol, triglycerides, alcohol nonuse, and physical inactivity are less clear.[7] One reason is that these CVD risk factors, which are known to fluctuate over time, were measured only once at baseline in existing cohort studies, or once after VTE cases were identified in case-control studies. This makes it difficult to demonstrate associations with risk factors when, in cohort studies, VTE events occur years after their baseline measurement. To date, there is no study that has analyzed the association between CVD risk factors and VTE events in a time-dependent manner.

In the ARIC study, participants had CVD risk factors measured at the initial and subsequent visits, and VTE events were ascertained over a long period of follow-up time. We propose to use the data to further characterize the association of time dependent CVD risk factors and VTE risk.

5. Hypothesis: We hypothesize that CVD risk factors, when analyze as time-dependent exposure variables, are associated with increased VTE risk.

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

Outcome variable: First VTE events (sub-analysis for idiopathic VTE events only)

Time dependent exposure variables: body mass index, hypertension, smoking, LDL cholesterol, HDL cholesterol, triglycerides, diabetes, alcohol, physical activity. All of these were measured at each ARIC exam, except physical activity, which was measured twice.

Time dependent covariates: age, hormone replacement therapy (HRT), cancer occurrence during follow-up, use of statins, aspirin, and warfarin.

Covariates measured once: sex, race, ARIC field center, ABO blood type, baseline factor VIII, von Willebrand factor, and aPPT.

Inclusions/exclusions:
Inclusion: all participants with baseline measurements.
Exclusion: participants with baseline anticoagulant use, history of VTE or cancer.

Statistical Analysis:

The primary sample of this analysis includes all participants who had CVD risk factors measured at the baseline. We will compare incidence rates of VTE according to CVD risk factor levels. Incident VTE will be analyzed through the year 2005. Follow-up time will be calculated as the time elapsed between the baseline measurement and the first VTE event. For non-cases, the follow up time will end on the date of death, the date of last known contact, or on December 31, 2005. Modeling will be performed using Cox proportional hazards methods.

Because the risk factors are known to change over time, we will perform a Cox analysis using exposure variables as time-dependent variables from the visit 1 to visit 4. Continuous risk factors will be analyzed as continuous variables or divided in quartiles. Hazard ratios and 95% confidence interval will be calculated from the Cox proportional hazards model.

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)?

Reich LM, Folsom AR, Key NS, Boland LL, Heckbert SR, Rosamond WD, Cushman M. Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism. *J Thromb Haemost.* 2006;4(9):1909-1913.

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(10):1182-1189.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

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. Hong C, Zhu F, Du D, Pilgram TK, Sicard GA, Bae KT. Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. *Atherosclerosis.* 2005;183(1):169-174.

2. Prandoni P, Ghirarduzzi A, Prins MH, Pengo V, Davidson BL, Sorensen H, Pesavento R, Iotti M, Casiglia E, Iliceto S, Pagnan A, Lensing AW. Venous thromboembolism and the risk of subsequent symptomatic atherosclerosis. *J Thromb Haemost.* 2006;4(9):1891-1896.

3. Sorensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet.* 2007;370(9601):1773-1779.

4. Reich LM, Folsom AR, Key NS, Boland LL, Heckbert SR, Rosamond WD, Cushman M. Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism. *J Thromb Haemost.* 2006;4(9):1909-1913.

5. van der Hagen PB, Folsom AR, Jenny NS, Heckbert SR, O'Meara ES, Reich LM, Rosendaal FR, Cushman M. Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study. *J Thromb Haemost.* 2006;4(9):1903-1908.

6. 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(10):1182-1189.

7. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation.* 2008;117(1):93-102.