ARIC Manuscript Proposal #2663

PC Reviewed: 11/10/15   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title:
Hospitalization with Infection and Incident Venous Thromboembolism: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Infection and VTE: ARIC

2.   Writing Group:
Writing group members: Logan Cowan, Pamela Lutsey, James Pankow, Aaron Folsom

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __LC__ **[please confirm with your initials electronically or in writing]**

First author: Logan Cowan
Address: Div. Epidemiology & Community Health
                1300 S. 2nd Street, Suite 300
                Minneapolis MN 55454 United States

                Phone: 612-624-5238   Fax: 612-624-0315
                E-mail: cowan046@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

                Name: Aaron Folsom
                Address: Div. Epidemiology & Community Health
                1300 S. 2nd Street, Suite 300
                Minneapolis MN 55454 United States

                Phone: 612-626-8862   Fax: 612-624-0315
                E-mail: folso001@umn.edu

3.   Timeline:
Obtain data set: Fall 2015
Complete statistical analysis: Winter 2015/2016
Complete manuscript: Spring 2016

4. Rationale:

Venous Thromboembolism (VTE) is a common, life-threatening disease in the United States with over 500,000 hospitalized VTE cases annually.[1] The Longitudinal Investigation of Thromboembolism Etiology (LITE) study found an incidence rate of 1.92 per 1000 person years for VTE in a community-based cohort of middle and older aged individuales[2]. Study participants experiencing a first incidence of VTE had a 28-day case fatality rate of 11%.[2] Despite the frequency and severity of VTE, better understanding of VTE triggers is needed.

Several studies have identified and described potential VTE triggers including surgery, trauma, prolonged immobility and paralysis, malignancy and chemotherapy, and pregnancy and puerperium[3,4]. Multiple case-control studies have identified infection as a potential VTE trigger.[4-8] Rogers et al. used a case-crossover design to measure infection as a potential VTE trigger.[4] They found that infection occurred 2.9 times more often before a VTE hospitalization than in the comparison periods.[4] It has been proposed that infection triggers VTE through activating inflammatory, coagulation, and fibrinolysis processes associated with thrombosis, although immobility could also contribute.[9]

While recognition of infection as a trigger of VTE is growing, previous studies were often small, failed to account for the seasonality of infection, and failed to properly account for potential confounding factors. We propose to use the data collected in the long-running, prospective Atherosclerosis Risk in Communities (ARIC) cohort to study the association further. If infection is found to be a VTE trigger, an improved understanding of post-infection VTE risk could help patients with recent infections and their clinicians take steps to reduce their otherwise elevated VTE risk.

5. Main Hypothesis/Study Questions:

We hypothesize that there is an association between hospitalization with infection and subsequent short-term VTE risk that exceeds the known association between hospitalization and VTE among participants in the ARIC study.

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).

Study Design:

A case-crossover study design will be used in which all ARIC participants with pulmonary embolism (PE) or deep vein thrombosis (DVT) in the leg (n=755) during follow-up will serve as their own control. The case-crossover design affords the ability to isolate exposures that vary over time within persons and better control for potential confounding that might occur between persons. Since hospitalization is a known VTE trigger, we will isolate the impact of infection by comparing the occurrence of hospitalization without infection and hospitalization with infection at intervals of 14, 30, 42, and 90 days prior to the VTE with two preceding control periods (1 year and 2 years prior to the VTE).

Inclusion/Exclusion:
All ARIC participants with pulmonary embolism (PE) or deep vein thrombosis (DVT) in the leg (n=755) during follow-up will be included. Cases whose control periods occurred prior to ARIC study enrollment will be excluded.

Exposure/Outcome:
The exposure of interest is hospitalization with and without infection 14, 30, 42, and 90 days prior to VTE diagnosis for the case period. Exposure will be classified as no hospitalization (referent), hospitalization without infection, and hospitalization with infection to isolate any potential added risk associated with infection. For the control periods we will use equivalent length periods exactly 1 and 2 years before VTE diagnosis, to account for the seasonality of infection rates. Hospitalization with infection will be assessed using hospital discharge ICD-9 codes. The following ICD-9 codes adapted from methodology used by Rogers et al.[4] for infections will be included:

0xx.xx, 11x.xx, 245.0x, 254.1x, 320.xx, 321.xx, 322.xx, 323.xx, 324.xx,
 357.0x, 360.0x, 370.55, 373.13, 376.01, 379.09, 380.1x, 382.0x, 382.1x, 382.2x,
382.3x, 382.4x, 383.0x, 386.33, 391.xx, 420.90, 420.99, 421.xx, 422.92, 429.89,
46x.xx, 475.xx, 478.22, 478.24, 478.29, 48x.xx, 491.1x, 510.xx, 511.1x, 513.xx,
519.01, 519.2x, 522.5x, 522.7x, 523.3x, 527.3x, 528.3x, 536.41, 540.xx, 566.xx,
567.0x, 567.1x, 567.2x, 567.30x, 569.5x, 569.61, 572.0x, 575.0x, 575.12, 577.0x,
590.xx, 595.0x, 597.0x, 599.0x, 601.2x, 604.0x, 607.1x, 607.2x, 608.0x, 608.4x,
616.10, 616.3x, 616.4x, 68x.xx, 711.xx, 727.89, 728.0x, 728.86, 730.xx, 785.4x,
785.52, 790.7x, 995.91, 995.92, 996.6x, 997.62, 998.5x, 999.3x, V09.xx

Codes in any position will be counted. The hospital discharge date for infection will be considered the infection date and the infection date must precede the VTE diagnosis date. The outcome of interest is VTE as defined for ARIC (n = 755). The hospital admission date abstracted from the patient medical record will be considered the VTE date.

Analysis:
Conditional logistic regression will be used to estimate the prevalence of exposure 14, 30, 42, and 90-days prior to VTE compared to the corresponding time periods exactly 1 and 2 years prior to VTE. Analysis will be conducted using a definition which includes all PE's but restricts DVTs to those occurring in the leg (n=755). We will control for the annual number of hospitalizations for each case or control period year to account for potential decline in overall health status due to age and immobility associated with hospitalization.

Limitations:
Confounding by age is possible because as participants age their VTE and hospitalization with infection risk increase. To reduce potential confounding, only time periods proximal to VTE (1 and 2 years previous) will be included. Some potential confounders that vary over the exposure and control periods assessed are not measured. We are only including infections in a hospital setting and thus we are under-ascertaining infection. There are infections that did not require hospitalization.

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 ICTDER03 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 ICTDER 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 ICTDER03 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)?

#1295 - Association of Chronic Obstructive Pulmonary Disease with Venous Thromboembolism in the Atherosclerosis Risk in Communities (ARIC) Study

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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References:

1. Centers for Disease, C., & Prevention. (2012). Venous thromboembolism in adult hospitalizations - United States, 2007-2009. *MMWR Morb Mortal Wkly Rep, 61*(22), 401-404.

2. Cushman, M., Tsai, A. W., White, R. H., Heckbert, S. R., Rosamond, W. D., Enright, P., & Folsom, A. R. (2004). Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med, 117*(1), 19-25

3. Lippi, G., Franchini, M., & Favaloro, E. J. (2009). Unsuspected triggers of venous thromboembolism--trivial or not so trivial? *Semin Thromb Hemost, 35*(7), 597-604.

4. Rogers, M. A., Levine, D. A., Blumberg, N., Flanders, S. A., Chopra, V., & Langa, K. M. (2012). Triggers of hospitalization for venous thromboembolism. *Circulation*, 125(17), 2092-2099

5. Schmidt, M., Horvath-Puho, E., Thomsen, R. W., Smeeth, L., & Sorensen, H. T. (2012). Acute infections and venous thromboembolism. *J Intern Med*, 271(6), 608-618

6. Clayton, T. C., Gaskin, M., & Meade, T. W. (2011). Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. Int J Epidemiol, 40(3), 819-827.

7. Chen, Y. G., Lin, T. Y., Huang, W. Y., Lin, C. L., Dai, M. S., & Kao, C. H. (2015). Association between pneumococcal pneumonia and venous thromboembolism in hospitalized patients: A nationwide population-based study. *Respirology*, 20(5), 799-804

8. Smeeth, L., Cook, C., Thomas, S., Hall, A. J., Hubbard, R., & Vallance, P. (2006). Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet*, 367(9516), 1075-1079

9. Epaulard, O., Foote, A., & Bosson, J. L. (2015). Chronic Infection and Venous Thromboembolic Disease. *Semin Thromb Hemost.*