

## ARIC Manuscript Proposal # 1109

PC Reviewed: \_10/18/05  
SC Reviewed: \_\_10/19/05

Status: \_A\_\_\_\_  
Status: \_A\_\_\_\_

Priority: \_2\_\_\_\_  
Priority: \_\_2\_\_

1.a. Full Title:

Chronic Kidney Disease and Risk of Venous Thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE).

b. Abbreviated Title (Length 26 characters): CKD and VTE Risk

2. Writing Group:

Writing group members: Keattiyoat Wattanakit, Shauna Runchey, Aaron Folsom, Mary Cushman, Catherine Stehman-Breen, and Susan Heckbert

First author: Keattiyoat Wattanakit, MD, MPH  
Address: Division of Epidemiology and Community Health, School of Public Health, University of Minnesota  
1300 S Second St, Suite 300,  
Minneapolis, MN 55454  
Phone: (612) 672-8873  
E-mail: wattanakit@epi.umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

Aaron R. Folsom, MD, MPH  
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota,  
1300 S Second St, Suite 300, Minneapolis, MN 55454  
Phone: (612) 626-8872  
Email: folsom@epi.umn.edu

3. Timeline: Analysis will begin following approval; a manuscript is expected to be completed in December 2005.

4. Rationale:

It is well established that chronic kidney disease (CKD) increases the risk of cardiovascular morbidity and mortality. Whether CKD also increases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred as venous thromboembolism (VTE), is largely unknown. Studies that examined this relationship have reported results from data derived from either autopsy series of VTE in patients with

end stage renal disease (ESRD)<sup>1,2</sup> or highly selective populations such as dialysis dependent and kidney transplant patients.<sup>3,4</sup> For example, combining data from the US Renal Data System record in 1996 and the National Center for Health Statistics, Tveit et al reported that the incidence of PE after 1 year follow-up was about 149.9 per 100,000 dialysis dependent ESRD patients compared with an expected rate of 24.6 per 100,000 persons in the US population, with an age adjusted incidence ratio of 2.34.<sup>3</sup> Similarly, Abbott et al published a study of 28,924 Medicare kidney transplant patients in which those with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m<sup>2</sup> was associated with a two fold higher risk for VTE at one year after kidney transplantation compared to those with eGFR > 30 ml/min/1.73 m<sup>2</sup>.<sup>4</sup>

While there is some evidence that suggest an increased risk for VTE in patients with ESRD and kidney transplant, and some evidence to support that this risk is associated with the level of kidney function, there have been no studies evaluating VTE risk in non-transplant, non-dialysis dependent CKD patients. Hence, data from the general population is needed to evaluate CKD as an independent risk factor for VTE. If an association is found, reduced renal function should be considered for further study as an etiologic factor in thrombotic events.

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

Main Hypothesis: This proposed study aims to test the hypothesis that risk of VTE is inversely related to eGFR.

Other study questions: We would evaluate the association of CKD and VTE stratified by cause of VTE (idiopathic vs secondary), study (ARIC vs CHS), sex, race, and obesity. We would also like to use cystatin C (available in CHS only), which is a novel measure of kidney function, as an exposure variable.

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

Exposure variables: eGFR, calculated by using the equation from the Modification of Diet in Renal Disease (MDRD) Study (eGFR ≥ 90, 60-89, 30-59, and 15-29 ml/min/1.73m<sup>2</sup>)<sup>5</sup> or abnormal cystatin C (> 1mg/L).

Outcome variable: First VTE events

Covariates (available in LITE): age, sex, race, study, diabetes, body mass index, factor VII, factor VIII, fibrinogen, lipoprotein(a).

Covariates (available in only CHS): albuminuria, CRP, and IL-6.

Inclusions/exclusions:

Inclusions: participants with baseline serum creatinine

Exclusions: participants with eGFR < 15 ml/min/1.73m<sup>2</sup> or history of renal dialysis.

Statistical Analysis

LITE data, a CHS -ARIC merged database, with comparable baseline data.

- 1) Crude incident VTE rate using person-time methods. Start time is baseline of the study. End time is event, loss-to-follow up, Dec 31, 2001, or censoring.
- 2) Kaplan-Meier curves describe probability of remaining free of VTE over follow-up time.
- 3) Cox regression analyses to calculate relative risks and 95% confidence intervals for VTE event.
- 4) Spline regression to describe predicted log hazard ratios as a function of eGFR.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☒ Yes  
☐ 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  
☒ 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.csc.unc.edu/ARIC/search.php>

☒ 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)?

Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Am J Med. 2004; 117:19-25.

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

11.b. If yes, is the proposal

☒ A. primarily the result of an ancillary study

LITE, 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.csc.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. Wiesholzer M, Kitzwogerer M, Harm F, et al. Prevalence of preterminal pulmonary thromboembolism among patients on maintenance hemodialysis treatment before and after introduction of recombinant erythropoietin. *Am J Kidney Dis.* Apr 1999;33(4):702-708.
2. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest.* Oct 1995;108(4):978-981.
3. Tveit DP, Hypolite IO, Hsieh P, et al. Chronic dialysis patients have high risk for pulmonary embolism. *Am J Kidney Dis.* May 2002;39(5):1011-1017.
4. Abbott KC, Cruess DF, Agodoa LY, et al. Early renal insufficiency and late venous thromboembolism after renal transplantation in the United States. *Am J Kidney Dis.* Jan 2004;43(1):120-130.
5. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* Mar 16 1999;130(6):461-470.