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

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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)\textsuperscript{1,2} or highly selective populations such as dialysis dependent and kidney transplant patients.\textsuperscript{3,4} 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.\textsuperscript{3} 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\textsuperscript{2} 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\textsuperscript{2}.\textsuperscript{4}

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 \textgreater{} 90, 60-89, 30-59, and 15-29 ml/min/1.73m\textsuperscript{2})\textsuperscript{5} 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\textsuperscript{2} 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.cscc.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)?


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
___x___ 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.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


