ARIC Manuscript Proposal # 1640

PC Reviewed: 4/13/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Interrelations of albuminuria and eGFR in the risk of incident venous thromboembolism: A pooled analysis of the PREVEND and ARIC cohorts.

b. Abbreviated Title (Length 26 characters): **eGFR/albuminuria and VTE**

2. Writing Group: Bakhtawar K. Mahmoodi, Pamela L Lutsey, Hanneke C. Kluin-Nelemans, Brad Astor, Nic J.G.M. Veeger, Aaron R. Folsom, Ron T. Gansevoort, Mary Cushman

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

First author: Bakhtawar K. Mahmoodi
Address: Dep Hematology, University Medical Center Groningen,
Hanzeplein 1, 9713 GZ, Groningen, The Netherlands

Phone: 0031 503612791 Fax: 0031 503611790
E-mail: b.k.mahmoodi@int.umcg.nl

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 R. Folsom

Address: University of Minnesota
Division of Epidemiology and Community Health

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

3. Timeline: Between April and September 2010

4. Rationale:
ARIC and PREVEND are two of the very few, if not the only two, population based cohorts in the world with information on albuminuria and venous thromboembolism (VTE).[1,2] We believe that both eGFR and albuminuria are risk factors for VTE.

In PREVEND hazard ratios of VTE by eGFR level have been described that are comparable to those found in ARIC, but these did not reach statistical significance, perhaps due to limited power.[2] For albuminuria, PREVEND is better powered due to the enrichment of the cohort with albuminuric subjects. ARIC on the other hand, is probably better powered for subjects with lower eGFR, but under-powered for albuminuria.[1] The weaker HR conferred by albuminuria in ARIC as compared to PREVEND, may be due to the fact that subjects with albuminuria >30mg/d in ARIC are mainly diabetics, while in PREVEND these are non-diabetics(unpublished data). This may have influenced the risk estimates, as diabetic subjects are usually on statin therapy and these subjects are more frequently treated for their cardiovascular morbidity with anti-platelet medication. The JUPITER trial indeed suggested an effect of statin therapy on the VTE risk.[3]

By pooling of ARIC and PREVEND data we hope to obtain sufficient power to address the risk VTE with a low eGFR, as estimated by various estimation equations, and the influence of increased levels of albuminuria on incidence of VTE in general, as well as in diabetic and non-diabetic subjects separately.

5. Main Hypothesis/Study Questions:

eGFR and microalbuminuria are independent risk factors for venous thromboembolism.

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

The PREVEND and ARIC datasets will be pooled on the individual subject level. The analysis will be prospective, as incident venous thromboembolism is the outcome of interest.

Inclusion/Exclusion Criteria

Participants taking warfarin at baseline will be excluded.

Exposure Variables

Albuminuria and eGFR. Both continuous and categorical representations will be explored. eGFR will be assessed by various estimation equations (i.e., creatinine based (MDRD, CKD-EPI) and cystatin C based). Since the 4th visit of ARIC (between 1996-1998) correspond to the baseline of PREVEND (1997-1998), the 4th visit measurement of ARIC and baseline measurements of PREVEND will serve as the overall baseline. Albuminuria will be expressed as urinary albumin/creatinine ratio (ACR).

Confounding/Interacting Variables

- Age, sex, race
- Established CV risk factors: cholesterol, glucose (in combination with fasting status), smoking, BMI, cardiovascular disease history, systolic blood pressure and diastolic blood pressure. To avoid potential co-linearity problems, highly

associated variables such as systolic and diastolic blood pressure will not be included in the same model.

- Interfering medication (BP, cholesterol, glucose lowering medication, as well as antiplatelet / antithrombotic agents).
- Study (ARIC versus PREVEND being entered as categorical variables)

Outcome Variables
Incident venous thromboembolism. In secondary analyses, we will also stratify by whether the event was idiopathic or secondary.

Data Analysis
Distributions of pertinent variables will be reported, stratified by cohort (PREVEND, ARIC). The primary analysis will use Cox regression.

A. First, we will use an assumption free categorical analysis, with CKD being defined according to the K/DOQI guidelines:

- No chronic kidney disease (CKD) and eGFR ≥90 (reference category)
- No CKD and eGFR 60-89
- CKD stage 1 (i.e., albuminuria ≥30mg/d and eGFR ≥90)
- CKD stage 2 (i.e., albuminuria ≥30mg/d and eGFR 60-89)
- CKD stage 3 without albuminuria (i.e., eGFR 30-59 and albuminuria <30mg/d)
- CKD stage 3 with albuminuria (i.e., eGFR 30-59 and albuminuria >30mg/d)

For stage 4 there are probably very few subjects for separate analysis (e.g.: in PREVEND only 8 subjects have CKD stage 4) and will be therefore exclude from analysis.

B. Second, in another Cox regression analysis eGFR and albuminuria will be expressed as continuous variables.

- We will check whether there is an interaction between albuminuria and eGFR in predicting incident VTE.
- In case there is an interaction, the risk of GFR for VTE will be assessed in various albuminuria strata.
- In case there is no interaction, both variables will be implemented in the same model.

Adjustment
For analyses A and B the following models will be run:

- Crude
- Adjustment for age, race and gender
- Adjustment for age, race, gender, established CV risk factors and interfering medication.

Additional Analyses

Analyses will be performed for the overall number of VTE events, as well as separately for provoked and idiopathic VTE.

We will also evaluate whether diabetes status is an effect modifier of these associations. Regardless, given inherent scientific interest, we intend to report results stratified by diabetes status.

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 ICTDER03 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)?

#1109 (Keattiyoat Wattanakit): Chronic kidney disease and risk of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology

#1480 (Aaron Folsom): Cystatin C and venous thromboembolism

#1480B (Aaron Folsom): Serum albumin and venous thromboembolism

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/

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. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism.J Am Soc Nephrol. 2008;19:135-40.
2. Mahmoodi BK, Gansevoort RT, Veeger NJ, Matthews AG, Navis G, Hillege HL, van der Meer J. Microalbuminuria and risk of venous thromboembolism. JAMA. 2009;301:1790-7.
3. Glynn RJ, Danielson E, Fonseca FA,et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360:1851-61.