ARIC Manuscript Proposal #2616

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum Uric Acid, Gout and Venous Thromboembolism: the ARIC Study.

b. Abbreviated Title (Length 26 characters): Uric acid, gout and VTE

2. Writing Group:

Writing group members: Yasuhiko Kubota, Mara McAdams DeMarco, Aaron Folsom

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

F**irst author**: **Yasuhiko Kubota**
Address: Division of Epidemiology and Community Health
University of Minnesota

Phone: 612-625-1016 Fax: 612-624-0315
E-mail: kubot007@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 R. Folsom
Address: Division of Epidemiology and Community Health
University of Minnesota

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

3. Timeline:

Data analysis: 1-2 months from manuscript approval date.
First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:

Venous thromboembolism (VTE), usually manifested by deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common medical problem with an estimated incidence of 1-2 per 1000 person-years (1, 2). Patients who develop VTE have high mortality rates of 11-30% (1-3). Therefore, VTE is important public health concern, and is very important to prevent.

While there are several traditional risk factors for VTE such as immobilization, surgery, and malignancy (4), recent studies have shown positive associations between some rheumatologic diseases, including rheumatoid arthritis and systemic lupus erythematosus, and VTE (5-7). Chronic inflammation in these rheumatologic diseases is considered to increase the risk of VTE by up-regulating procoagulants, down-regulating anti-coagulants, suppressing fibrinolysis and endothelial dysfunction (5-7).

Gout, which is caused by hyperuricemia, another rheumatologic disease, is primarily characterized by acute and chronic arthritis through monosodium urate crystals deposition in the joints (8). Monosodium urate crystals are pro-inflammatory stimuli that can initiate, amplify, and sustain an intense inflammatory response, and thus gout is the most common inflammatory disease (9). In addition, hyperuricemia itself has proinflammatory effects on vascular cells (10).

Therefore, hyperuricemia and gout are expected to be positively associated with VTE, but, to the best of our knowledge, so far there has been no study investigating these associations.

5. Main Hypothesis/Study Questions:
To investigate whether the level of serum uric acid and/or a history of gout are independently and positively associated with the risks of VTE, as well as VTE subcategories: provoked VTE (associated with cancer, major trauma, surgery, or marked immobility), unprovoked VTE (no obvious cause), DVT and PE.

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).

Design
Time to event analysis using ARIC visit 1 as baseline.

Inclusion/exclusion criteria
Inclusion: participants whose serum uric acid was measured at visit 1 (to investigate the association between serum uric acid and VTE). Those who provided information on a history of gout at visit 4 or later annual follow-up (to investigate the association between gout and VTE).

Exclusion: those who at visit 1 were taking anticoagulants or had a history of VTE, coronary heart disease (CHD), stroke, or heart failure. In addition, for those with uric acid at visit 2 (which will be averaged with visit 1 when available), we will exclude those who met the same exclusion criteria at visit 2.

Outcome and other variables of interest

Main exposure: (1) Mean value of serum uric acid at visit 1 and 2 if serum uric acid at visit 2 is available and the participant did not have a VTE between visit 1 and 2 (otherwise, value of serum uric acid at visit 1 only). (2) Gout history (yes vs. no) at visit 1. Participants with a history of gout at visit 1 are defined as those with a history of gout which occurred at a younger age than the participants' age at the ARIC baseline assessment (1987–89).

Covariates: age (continuous), sex, race, ARIC field center, body mass index (BMI, continuous), diabetes, cigarette smoking (current/former/never), eGFR (continuous), von Willebrand factor (continuous), and factor Ⅷ (continuous) at visit 1.

Outcome: VTE (also its subtypes) through 2011.

Statistical analysis

Covariates first will be examined by level of uric acid or gout, to identify possible confounding variables. Hazard ratios and their 95% confidence intervals for each outcome will be calculated using Cox proportional hazard models in relation to continuous and categorical (normal; serum uric acid<7.0 mg/dl/abnormal; >7.0 mg/dl, but if necessary, other cutpoints will be explored) serum uric acid concentration and gout status. Restricted cubic splines also will be created to study the shape of the uric acid relation. We will also explore whether there are interactions with sex, race, or treatment for gout.

- Model 1: adjustment for age, sex, race, and ARIC study site.
- Model 2: Model 1 + adjustment for BMI, diabetes, cigarette smoking.
- Model 3: Model 2 + adjustment for eGFR, von Willebrand factor, and factor Ⅷ.

Limitations

Our definition of gout is based on self-report, rather than observation of monosodium urate crystals in joint fluid or ACR criteria for gout (11). Ascertainment of gout is conditional on survival to and participation in visit 4 when gout status was assessed.

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)?

No previous manuscript proposals in ARIC have specifically examined the association between serum uric acid or gout status and VTE. Other ARIC manuscripts have explored the association between serum uric acid and other outcomes.

#759: Serum uric acid and stroke
#1473: BMI and gout in women
#525: Serum uric acid and CHD
#1077: Serum uric acid and hypertension

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* 2006.16)
___ 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 ____ No.

References:

1. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117:19-25.
2. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5:692-9.
3. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med. 1999;159:445-53.
4. Ungprasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2014;33:297-304.
5. Holmqvist ME, Neovius M, Eriksson J, Mantel Ä, Wållberg-Jonsson S, Jacobsson LT, Askling J. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA. 2012;308:1350-6.
6. Choi HK, Rho YH, Zhu Y, Cea-Soriano L, Aviña-Zubieta JA, Zhang Y. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. Ann Rheum Dis. 2013;72:1182-7.
7. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis. 2009;68:238-41.
8. Selmi C, Generali E, Massarotti M, Bianchi G, Sciré CA. New treatments for inflammatory rheumatic disease. Immunol Res. 2014;60:277-88.
9. Richette P, Bardin T. Gout. Lancet. 2010;375:318-28.
10. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359:1811-21.
11. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977; 20(3):895–900.