ARIC Manuscript Proposal #1992

PC Reviewed: 9/11/12	**Status:** <u>A</u>	**Priority:** <u>2</u>
SC Reviewed: _____	**Status:** _____	**Priority:** ____

1.a. Full Title: HbA$_{1c}$ and incident VTE: The ARIC cohort study

  b. Abbreviated Title (Length 26 characters): HbA$_{1c}$ and VTE

2. Writing Group:
        Writing group members: Elizabeth J. Bell, Pamela L. Lutsey, Vijay Nambi, Mary Cushman, Elizabeth Selvin, Aaron R. Folsom

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

   First author: Elizabeth Bell
   Address:
            1300 S. Second Street, Suite 300
            Minneapolis, MN 55454-1015

            Phone: 612-626-0027   Fax: 612-624-0315
            E-mail: ebell@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: 1300 S. Second Street, Suite 300
              Minneapolis, MN 55454-1015

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

3. Timeline: Finish by spring 2013

4. Rationale:
Pulmonary embolism (PE) and deep vein thrombosis (DVT) are collectively referred to as "venous thromboembolism" (VTE). In the United States, it affects about 1 in 1000 for the first time, per year.[1] Mortality within a month of diagnosis occurs in about 6% of DVT cases and 12% of PE cases. Despite the huge public health burden of VTE, much

remains unknown about its etiology: In 25-50% of patients with incident VTE, it is unprovoked, meaning there is no readily identifiable risk factor.[1] Prevention strategies for VTE are based on exposure to one of its known risk factors,[2] so further illumination of modifiable risk factors would have clinical utility.

One proposed risk factor for VTE is diabetes, with the postulated mechanism being coagulation activation and hypofibrinolysis, resulting in a procoagulant state[3,4]. However, the evidence on whether or not diabetes and VTE are associated is mixed. About half of the research found a positive association[5–12] and half found none[13–25]. To add to the controversy, more than half[5,8,9,11,13,15–19,22,23,25] of the research did not adjust for body mass index (BMI), which is a strong risk factor for VTE[20,26,27] and may explain the association between diabetes and VTE. A meta-analysis was conducted[28], but it did not adjust for any potential confounders, making its results hard to interpret.

One way to address this controversy is to look at diabetes a different way. All except three[7,23,24] studies have looked at diabetes/hyperglycemia dichotomously: yes/no. Dichotomizing when not appropriate can lead to problems[29]: statistical power to detect an association is reduced, meaningful variability within each group is lost, and a non-linear relationship would be concealed. Glucose levels play an important role in the development of the procoagulant state that is associated with diabetes[3] and it may be that it is glucose, modeled continuously, that is an independent risk factor for VTE.

The Atherosclerosis Risk in Communities Study (ARIC) - a large, prospective epidemiologic study being conducted in four U.S. communities - measured hemoglobin A_{1c} (HbA$_{1c}$) level, a marker of long-term glycemic control. HbA$_{1c}$ estimates the average level of glucose in the blood over the previous 2-3 months and tracks well in individuals over time[30]. No other study has looked at the relation of HbA$_{1c}$ and subsequent VTE. Because of prior conflicting evidence on the topic, we sought to assess whether glycemia, as measured by HbA$_{1c}$, is related to incident VTE after adjustment for known VTE risk factors, including BMI. A second aim of the study was characterize the association if it does exist: Is it there evidence of linearity, curvilinearity, or a threshold effect? We also hypothesize that adjusting for hemostatic factors - aPTT, factor VIII, and eGFR – will attenuate any association toward the null, which would lend evidence towards the proposed mechanism of coagulation activation and hypofibrinolysis.

5.   Main Hypothesis/Study Questions:

HbA$_{1c}$ is positively associated with VTE incidence.

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 cohort analysis of participants who attended ARIC visit 2 (when HbA$_{1c}$ was

measured), which will be considered baseline for this study.

Exclusions
-Participants with missing data for HbA_{1c} or covariates of interest; participants who report a race other than Caucasian or African American (due to small numbers); participants with VTE and/or anticoagulant use prior to visit 2; participants who reported anticoagulant use during follow-up visits were censored at the visit prior to this reported use; African-Americans from Washington County and Minneapolis suburbs (due to small numbers); participants who fasted less than 8 hours prior to the visit or who were missing information on fasting status.

Exposure
-$HbA_{1c,}$ measured from whole-blood samples from ARIC visit 2.

Outcome
-Incident VTE after visit 2.

Other variables
-VTE risk factors[20,26,27], measured at visit 2 unless otherwise specified, including age, race, sex, hormone use, BMI, possibly waist-to-hip ratio, cigarette smoking, antihypertensive medication use, eGFR, insulin (visit 1), aPTT (visit 1), factor VIII (visit 1).

Statistical analysis

Because HbA1c may not track as well among diagnosed diabetics (it could be confounded by factors that have a substantial impact on glucose levels, such as treatment for hyperglycemia), analyses will be stratified by diagnosed diabetes at visit 2 (self-report or on diabetes medication) and everyone else.

Cox proportional hazards regression will be used to estimate the adjusted hazard ratios of incident VTE by HbA_{1c}. Analysis will first test for interactions by age[10] and race; stratified results will be presented if there is interaction. If effect modification is absent:
Model 1: age, sex and race in this minimally adjusted model
Model 2: Model 1 + behavioral risk factors (hormone use, cigarette smoking)
Model 3: Model 2 + BMI (and WHR if it is associated with HbA1c above and beyond BMI)
Model 4 (an overadjusted model with hemostatic factors): Model 3 + aPTT, factor VIII, eGFR

The relationship between HbA_{1c} and VTE will first be explored with restricted cubic splines. Then, HbA_{1c} will be split into the diagnostic categories[31] for diabetes: <5.7, 5.7-6.5, and $\geq 6.5\%$. If there are not enough events per category, we will use tertiles instead. If there is evidence of a linear relationship between HbA_{1c} and VTE, HbA_{1c} will be modeled as a continuous variable. If, after looking at the spline and categories, there is evidence of a quadratic relation, a quadratic HbA_{1c} term will be fit.

In addition to total VTE, we will also analyze provoked and unprovoked VTE as separate outcomes. Incidence rates of total VTE will be calculated, stratified by HbA_{1c} level.

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)?**

708: Cardiovascular risk factors and venous thromboembolism incidence: the Longitudinal Investigation of Thromboembolism Etiology

1617: A Time-Dependent Analysis of the Association between Cardiovascular Disease Risk Factors and the Risk of 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* #2003.5)

       ___   **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.

References

1.   White, R.H. The epidemiology of venous thromboembolism. *Circulation* **107**, I4-8 (2003).

2.   Geerts, W.H. *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* **133**, 381S-453S (2008).

3.   Lemkes, B. a *et al.* Hyperglycemia: a prothrombotic factor? *Journal of thrombosis and haemostasis : JTH* **8**, 1663-9 (2010).

4.   Carr, M.E. Diabetes mellitus: a hypercoagulable state. *Journal of diabetes and its complications* **15**, 44-54 (2001).

5.   Tsai, A.W. *et al.* Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Archives of internal medicine* **162**, 1182-9 (2002).

6.   Lutsey, P.L. *et al.* Correlates and consequences of venous thromboembolism: The Iowa Women's Health Study. *American journal of public health* **100**, 1506-13 (2010).

7.   Mraovic, B. *et al.* Preadmission hyperglycemia is an independent risk factor for in-hospital symptomatic pulmonary embolism after major orthopedic surgery. *The Journal of arthroplasty* **25**, 64-70 (2010).

8.   Petrauskiene, V., Falk, M., Waernbaum, I., Norberg, M. & Eriksson, J.W. The risk of venous thromboembolism is markedly elevated in patients with diabetes. *Diabetologia* **48**, 1017-21 (2005).

9.   Movahed, M.-R., Hashemzadeh, M. & Jamal, M.M. The prevalence of pulmonary embolism and pulmonary hypertension in patients with type II diabetes mellitus. *Chest* **128**, 3568-71 (2005).

10.   Stein, P.D., Goldman, J., Matta, F. & Yaekoub, A.Y. Diabetes mellitus and risk of venous thromboembolism. *The American journal of the medical sciences* **337**, 259-64 (2009).

11.   Yegen, H.A. *et al.* Risk factors for venous thromboembolism after lung transplantation. *Chest* **132**, 547-53 (2007).

12.   Hong, C. *et al.* Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. *Atherosclerosis* **183**, 169-74 (2005).

13. Lidegaard, Ø., Edström, B. & Kreiner, S. Oral contraceptives and venous thromboembolism: a five-year national case-control study☆. *Contraception* **65**, 187-196 (2002).

14. Wattanakit, K. *et al.* Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thrombosis and haemostasis* **108**, 1-8 (2012).

15. Goldhaber, S.Z. *et al.* A prospective study of risk factors for pulmonary embolism in women. *JAMA : the journal of the American Medical Association* **277**, 642-5 (1997).

16. Ageno, W. *et al.* The metabolic syndrome and the risk of venous thrombosis: a case-control study. *Journal of thrombosis and haemostasis : JTH* **4**, 1914-8 (2006).

17. Heit, J.A. *et al.* Is diabetes mellitus an independent risk factor for venous thromboembolism?: a population-based case-control study. *Arteriosclerosis, thrombosis, and vascular biology* **29**, 1399-405 (2009).

18. Brækkan, S.K. *et al.* Competing risk of atherosclerotic risk factors for arterial and venous thrombosis in a general population: the Tromso study. *Arteriosclerosis, thrombosis, and vascular biology* **32**, 487-91 (2012).

19. Glynn, R.J. & Rosner, B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *American journal of epidemiology* **162**, 975-82 (2005).

20. Holst, A.G., Jensen, G. & Prescott, E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation* **121**, 1896-903 (2010).

21. Mahmoodi, B.K. *et al.* Microalbuminuria and risk of venous thromboembolism. *JAMA : the journal of the American Medical Association* **301**, 1790-7 (2009).

22. Mantilla, C.B., Horlocker, T.T., Schroeder, D.R., Berry, D.J. & Brown, D.L. Risk factors for clinically relevant pulmonary embolism and deep venous thrombosis in patients undergoing primary hip or knee arthroplasty. *Anesthesiology* **99**, 552-60; discussion 5A (2003).

23. Quist-Paulsen, P. *et al.* Arterial cardiovascular risk factors and venous thrombosis: results from a population-based, prospective study (the HUNT 2). *Haematologica* **95**, 119-25 (2010).

24. Goldhaber, S.Z. *et al.* Risk factors for pulmonary embolism. The Framingham Study. *The American journal of medicine* **74**, 1023-8 (1983).

25.   Grady, D. *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Annals of internal medicine* **132**, 689-96 (2000).

26.   Goldhaber, S.Z. & Bounameaux, H. Pulmonary embolism and deep vein thrombosis. *Lancet* **379**, 1835-46 (2012).

27.   Kroegel, C. & Reissig, A. Principle mechanisms underlying venous thromboembolism: epidemiology, risk factors, pathophysiology and pathogenesis. *Respiration; international review of thoracic diseases* **70**, 7-30 (2003).

28.   Ageno, W., Becattini, C., Brighton, T., Selby, R. & Kamphuisen, P.W. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation* **117**, 93-102 (2008).

29.   Altman, D.G. & Royston, P. The cost of dichotomising continuous variables. *BMJ (Clinical research ed.)* **332**, 1080 (2006).

30.   Meigs, J.B., Nathan, D.M., Cupples, L. a, Wilson, P.W. & Singer, D.E. Tracking of glycated hemoglobin in the original cohort of the Framingham Heart Study. *Journal of clinical epidemiology* **49**, 411-7 (1996).

31.   American Diabetes Association Standards of medical care in diabetes--2012. *Diabetes care* **35 Suppl 1**, S11-63 (2012).