1.a. Full Title: HbA1c and incident VTE: The ARIC cohort study

b. Abbreviated Title (Length 26 characters): HbA1c 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.\textsuperscript{1} Prevention strategies for VTE are based on exposure to one of its known risk factors,\textsuperscript{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\textsuperscript{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\textsuperscript{5–12} and half found none\textsuperscript{13–25}. To add to the controversy, more than half\textsuperscript{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\textsuperscript{20,26,27} and may explain the association between diabetes and VTE. A meta-analysis was conducted\textsuperscript{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\textsuperscript{7,23,24} studies have looked at diabetes/hyperglycemia dichotomously: yes/no. Dichotomizing when not appropriate can lead to problems\textsuperscript{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\textsuperscript{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\textsubscript{1c} (HbA\textsubscript{1c}) level, a marker of long-term glycemic control. HbA\textsubscript{1c} estimates the average level of glucose in the blood over the previous 2-3 months and tracks well in individuals over time\textsuperscript{30}. No other study has looked at the relation of HbA\textsubscript{1c} and subsequent VTE. Because of prior conflicting evidence on the topic, we sought to assess whether glycemia, as measured by HbA\textsubscript{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 exists: Is 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\textsubscript{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\textsubscript{1c} was
measured), which will be considered baseline for this study.

Exclusions
- Participants with missing data for HbA1c 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
- HbA1c, measured from whole-blood samples from ARIC visit 2.

Outcome
- Incident VTE after visit 2.

Other variables
- VTE risk factors20,26,27, 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

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 HbA1c. Analysis will first test for interactions by age10 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 HbA1c and VTE will first be explored with restricted cubic
splines. Then, HbA1c will be split into the diagnostic categories31 for diabetes: ≤5.7, 5.7-
6.5, and ≥ 6.5%. If there are not enough events per category, we will use tertiles instead.
If there is evidence of a linear relationship between HbA1c and VTE, HbA1c will be
modeled as a continuous variable. If, after looking at the spline and categories, there is
evidence of a quadratic relation, a quadratic HbA1c 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 HbA1c level.

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 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  ___ 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.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)?

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?  ___ Yes   ___ No

11.b. If yes, is the proposal  ___ Yes   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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.
References


