1.a. Full Title: Diabetes Mellitus and Venous Thromboembolism: A Systematic Review and Meta-analysis

b. Abbreviated Title (Length 26 characters): DM & VTE review

2. Writing Group:
   Writing group members: Aaron R. Folsom, Pamela L. Lutsey, Elizabeth Selvin, Alvaro Alonso, Neil Zakai, Mary Cushman

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]

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3. Timeline: Hope to finish by summer 2015.

4. Rationale:

Diabetes has been proposed as a risk factor for VTE, the theoretical mechanism being that hyperglycemia contributes to elevated coagulation factors and impaired fibrinolysis.\(^1,2\) Indeed, laboratory evidence suggests that high glucose levels 1) increase oxidative stress, which in turn increases gene transcription of coagulation factors; 2) degrade the glycocalyx layer of the endothelial wall, which releases coagulation factors; and 3) increase glycation of proteins involved in coagulation and fibrinolysis, shifting their activity towards a procoagulant state.\(^1\) However, reported associations of diabetes with VTE are inconsistent,\(^3-23\) and more than half of prior investigations did not adjust for adiposity - an important confounding variable - hampering interpretation. A previous systematic review and meta-analysis\(^24\) estimated a 40% increased risk of VTE for persons with diabetes compared to persons without diabetes. However, the meta-analysis was based on crude results; therefore, the reported association is likely confounded by age,
adiposity, and other confounders. Our systematic review and meta-analysis will attempt to clarify the diabetes-VTE association by obtaining adequately adjusted point estimates and including recent literature.

5. **Main Hypothesis/Study Questions:**

Perform a literature-based systematic review and meta-analysis, including ARIC data, to characterize the risk relation between diabetes mellitus and VTE. ARIC data on diabetes and incident VTE will qualify as unpublished data.

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 group: ARIC baseline. Exclude those with prior VTE history or on anticoagulation.

Events: Incident VTEs after baseline.

Exposure: Diabetes assessed at visit 1.

Variables to be used: diabetes status at baseline, baseline venous thromboembolism status, anticoagulant use at baseline, incident venous thromboembolism, time to venous thromboembolism, age, and BMI status of participants. We will also use variables indicating race, sex, hormone therapy use, and smoking status.

Exclusions: We will exclude individuals from analyses if they had a history of VTE or anticoagulant use at baseline, or had missing data on any variable included in the analysis.

Brief analysis plan and methods: We will follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting of systematic reviews. ARIC data on the diabetes-VTE association would be considered unpublished data for the manuscript.

Using Cox regression, we would like to obtain a hazard ratio (95% confidence interval) for the association of diabetes with VTE in the ARIC study, adjusted for (at a minimum) age and BMI. We may want an estimate adjusted for age, BMI, race, sex, hormone therapy use, and smoking status as well.

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 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.csc.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)?

   Manuscript proposals 1992, 2338, and 1617. Of note, the diabetes-VTE association has
   been published previously, making this a non-controversial topic. However, now that
   follow-up for incident VTE is available through 2011, unpublished data exists.

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.csc.unc.edu/aric/forms/
References:


