ARIC Manuscript Proposal #2420

PC Reviewed: 9/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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]**

First author: **Elizabeth J. Bell**
Address: 1300 S. Second St., Ste 300
Minneapolis, MN 55454-1015

Phone: (612)626-0027 Fax: 612-624-0315
E-mail: ebell@umn.edu

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 ARIC data on diabetes and incident VTE will qualify as unpublished data.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)[25] 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 __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)?

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.cscc.unc.edu/aric/forms/

References:

1. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JCM, Hoekstra JBL. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost*. 2010;8(8):1663–9. doi:10.1111/j.1538-7836.2010.03910.x.

2. Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications*. 2001;15(1):44–54.

3. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002;162(10):1182–9.

4. Lutsey PL, Virnig BA, Durham SB, et al. Correlates and consequences of venous thromboembolism: The Iowa Women's Health Study. *Am J Public Health*. 2010;100(8):1506–13.

5. Petrauskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. *Diabetologia*. 2005;48(5):1017–21.

6. Movahed M, Hashemzadeh M, Jamal MM. The prevalence of pulmonary embolism and pulmonary hypertension in patients with type II diabetes mellitus. *Chest*. 2005;128(5):3568–71.

7. Stein PD, Goldman J, Matta F, Yaekoub AY. Diabetes mellitus and risk of venous thromboembolism. *Am J Med Sci*. 2009;337(4):259–64. doi:10.1097/MAJ.0b013e31818bbb8b.

8. Yegen HA, Lederer DJ, Barr RG, et al. Risk factors for venous thromboembolism after lung transplantation. *Chest*. 2007;132(2):547–53.

9. Hong C, Zhu F, Du D, Pilgram TK, Sicard GA, Bae KT. Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. *Atherosclerosis*. 2005;183(1):169–74. doi:10.1016/j.atherosclerosis.2005.03.047.

10. Lidegaard Ø, Edström B, Kreiner S. Oral contraceptives and venous thromboembolism: a five-year national case-control study. *Contraception*. 2002;65(3):187–196.

11. Wattanakit K, Lutsey PL, Bell EJ, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thromb Haemost*. 2012;108(3):1–8. doi:10.1160/TH11-10-0726.

12. Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA*. 1997;277(8):642–5.

13. Ageno W, Prandoni P, Romualdi E, et al. The metabolic syndrome and the risk of venous thrombosis: a case-control study. *J Thromb Haemost*. 2006;4(9):1914–8.

14. Heit JA, Leibson CL, Ashrani AA, Petterson TM, Bailey KR, Melton LJ. Is diabetes mellitus an independent risk factor for venous thromboembolism?: a population-based case-control study. *Arterioscler Thromb Vasc Biol*. 2009;29(9):1399–405.

15. Brækkan SK, Hald EM, Mathiesen EB, et al. Competing risk of atherosclerotic risk factors for arterial and venous thrombosis in a general population: the Tromso study. *Arterioscler Thromb Vasc Biol*. 2012;32(2):487–91.

16. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol*. 2005;162(10):975–82.

17. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation*. 2010;121(17):1896–903.

18. Mahmoodi BK, Gansevoort RT, Veeger NJGM, et al. Microalbuminuria and risk of venous thromboembolism. *JAMA*. 2009;301(17):1790–7.

19. Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL. Risk factors for clinically relevant pulmonary embolism and deep venous thrombosis in patients undergoing primary hip or knee arthroplasty. *Anesthesiology*. 2003;99(3):552–60; discussion 5A.

20. Quist-Paulsen P, Naess IA, Cannegieter SC, et al. Arterial cardiovascular risk factors and venous thrombosis: results from a population-based, prospective study (the HUNT 2). *Haematologica*. 2010;95(1):119–25. doi:10.3324/haematol.2009.011866.

21. Goldhaber SZ, Savage DD, Garrison RJ, et al. Risk factors for pulmonary embolism. The Framingham Study. *Am J Med*. 1983;74(6):1023–8.

22. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med*. 2000;132(9):689–96.

23. Wang S, Zhao Y. Diabetes Mellitus and the Incidence of Deep Vein Thrombosis after Total Knee Arthroplasty: A Retrospective Study. *J Arthroplasty*. 2012;(91):7–9. doi:10.1016/j.arth.2012.07.023.

24. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation*. 2008;117(1):93–102.

25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008–12.