1.a. Full Title: Metabolic syndrome and risk of venous thromboembolism

b. Abbreviated Title (Length 26 characters): MetSyn and VTE

2. Writing Group:

Writing group members: Lyn M. Steffen, Jim Peacock, Mary Cushman, Susan Heckbert, David R. Jacobs, Wayne D. Rosamond, Aaron R. Folsom

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

First author: Lyn M. Steffen, PhD, MPH
Address: University of Minnesota School of Public Health
         Division of Epidemiology and Community Health
         1300 South Second St, Suite 300
         Minneapolis, MN 55454

         Phone: (612)625-9307  Fax: (612) 624-0315
         E-mail: steffen@epi.umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address:
         Phone:  Fax:
         E-mail:

3. Timeline:
   Data analysis: 4 months
   Writing the first draft, revisions: 6 months
   Coauthor review: 2 months
   Revision, approval by coauthors, ARIC, NHLBI: 3 months
   Total manuscript preparation time: 12-15 months

4. Rationale:
   Several studies have suggested a link between venous thromboembolism (VTE) and atherosclerosis via common risk factors, including central adiposity (1,2), obesity (3,4), smoking (1,3), hypertension (3), low HDL-cholesterol (5), high LDL-cholesterol (5), high levels of lipoprotein(a) (6), and diabetes (4). However, results are inconsistent among studies and in the
LITE study, there was no association of VTE with atherosclerosis and the only risk factors associated with VTE were obesity and diabetes (4). Several of these risk factors are components of the metabolic syndrome, known to be associated with cardiovascular disease risk (7). The mechanism by which metabolic syndrome is associated with VTE may be through endothelial dysfunction and alterations in hemostasis, including increased levels of factor VII and vonWillebrand factor (8). Factors VII and VIII and vonWillebrand factor were independent risk factor for VTE in LITE (9). Fibrinogen levels are also increased in the metabolic syndrome promoted by increased levels of PAI-1 as a result of abdominal obesity (10), although fibrinogen was not related to VTE as previously reported in LITE (9).

According to national surveys (11), about 23% of the US adult population has been identified with the metabolic syndrome (defined as 3 or more of the following risk factors, including central adiposity, high systolic blood pressure, high levels of triglycerides, high glucose levels or diagnosed with diabetes, and/or low levels of HDL-cholesterol). In a recent case-control study, over 50% of idiopathic deep vein thrombosis (DVT) cases had the metabolic syndrome compared to 35% of controls. Prevalence of the metabolic syndrome was almost 2 times more likely in DVT cases than controls, after adjusting for age, sex, body mass index, and smoking (OR 1.93; 95% C.I. 1.05, 3.56) (12). To date, there are no published prospective studies investigating the relation between metabolic syndrome and risk of incident venous thromboembolism in middle-aged and elderly, Caucasian and African American men and women. We will test this hypothesis in the LITE study of pooled VTE in ARIC and CHS.

References

5. **Main Hypothesis/Study Questions:**
   Incidence of venous thromboembolism is higher among adults with the metabolic syndrome compared to those without, independent of age, sex, BMI, and factor VIIIc. In addition, associations will be larger for idiopathic than secondary VTE.

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:** prospective study using the LITE database

**Exclusion criteria:**
1. Race other than white or black
2. Prevalent VTE at baseline
3. Use of warfarin at baseline
4. Incident cancer-related VTE

**Exposure variable:** metabolic syndrome: 3 or more risk factors as defined by the ATP3 recommendations, including
- Abdominal obesity: waist circumference for men ≥ 102 cm, ≥ 88 cm for women;
- High triglyceride levels ≥ 150 mg/dl;
- High glucose levels ≥ 100 or on drug treatment for elevated glucose;
- Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on antihypertensive therapy;
- Low HDL-cholesterol levels for men < 40 mg/dl; for women < 50 mg/dl.

**Outcome:** Incident VTE

**Confounding factors:** age, gender, race, field center, vitamin supplement use, BMI, factor VIII. If important, in our nested case-control subset, we can also adjust for additional factors that may confound.

**Analysis plan:**
Follow-up time will be calculated as time from baseline to incident VTE, death, last follow-up contact, or through 2001 for CHS and 2002 for ARIC, whichever occurred first. Means or proportions will be computed to describe baseline characteristics of participants. Cox proportional hazards regression analyses will be used to assess the relationship of the metabolic syndrome, as well as each of the metabolic syndrome components, with risk of VTE, adjusting for potential confounders. We will further assess the same relations for idiopathic cases only. Finally, each component of the metabolic syndrome will be evaluated for its relation with VTE. Possible effect modification by study, and other VTE risk factors, including factor V
Leiden, will be explored. In sensitivity analysis, we will assess whether lipid medication use as one of the criteria for metabolic syndrome affects study findings.

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 ICTDER02 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 ICTDER02 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? _x_ 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 ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _x_ 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)? Done

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/

12. 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.