ARIC Manuscript Proposal # 1874

PC Reviewed: 12/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between the metabolic syndrome and unprovoked venous thromboembolism: results of a patient-level meta-analysis

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

2. Writing Group:

Writing group members: Walter Ageno, Francesco Dentali, Alessandro Squizzato, Lyn M. Steffen, Mary Cushman

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

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3. Timeline: November 2011-January 2012

4. Rationale: A number of studies have suggested that the metabolic syndrome may contribute to the pathogenesis of venous thromboembolism, but this association remains

uncertain. In particular, prospective cohort studies have suggested that abdominal obesity, a major component of the metabolic syndrome, but not the syndrome itself, is independently associated with venous thromboembolism. Furthermore, a gender specific effect was hypothesized

5. Main Hypothesis/Study Questions: By separately combining the data of case control studies and of prospective cohort studies in a patient-level meta-analysis, we aim to assess whether this association is attributable to the metabolic syndrome or to abdominal obesity alone, with no additional contribution by the other components, and whether this association is gender specific.

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).

We aim to perform a patient-level meta-analysis of case-control studies and of prospective cohort studies that evaluated the role of the metabolic syndrome in patients with unprovoked VTE.
Using data from LITE (ARIC + CHS) and another prospective study about VTE, we will conduct a meta-analysis of metabolic syndrome and VTE.

Study population: LITE study population includes 5,888 CHS adults and 15,792 ARIC adults.

Exclusion criteria: Of the 15,792 ARIC participants and 5,888 CHS participants, we excluded from the analyses those with a history of VTE before baseline (n=477), who used warfarin at baseline (n=185), or who developed cancer-related VTE during follow-up (n=125). We further excluded 933 individuals with non-fasting blood specimens and other missing data. Seventy-two individuals were excluded because they were not white or African American, leaving 20,374, including 11,429 women and 8,945 men.

Request the following variables:

1. Age (at baseline)
2. Sex
3. Ethnicity (Caucasian/African American)
4. Blood pressure at baseline
5. diagnosis of hypertension (1/0); anti-hypertensive treatment (1/0) [at baseline]
6. BMI (baseline)
7. Waist circumference (baseline)
8. Glycemic levels: baseline fasting glucose levels;
9. drug therapy for diabetes (1/0)
10. Diabetes status (yes/no)
11. Total cholesterol,
12. HDL cholesterol,
13. LDL cholesterol,
14. triglycerides levels;

15. drug therapy with statins or fibrates (1/0) at baseline
16. Active smoking (1/0) (current, former, never at baseline)
17. Hormonal therapy, women (1/0) (yes, no at baseline)
18. Risk factors at the time of VTE if available: recent surgery (1/0), trauma (1/0), hospitalization (1/0)
19. Antiplatelet therapy at the time of VTE (1/0)
20. Anticoagulant therapy at the time of VTE (1/0)
21. Site of VTE (PE-DVT)
22. Death (1/0)
23. Date of death
24. Major arterial events prior to VTE (CVD, CHD, CABG, PTCA, stroke)
25. VTE – secondary, idiopathic
26. VTE – cancer/non-cancer events
27. Previous VTE (yes/no)
28. Follow-up Time to VTE event

After the completion of the individual patient level meta-analysis of the four identified case-control studies (methods available upon request), we propose to conduct an individual patient level meta-analysis of the two identified prospective studies (LITE, Norwegian cohort). The analysis plan is the following: we will use Kaplan-Meier analysis to calculate the cumulative incidence of venous thromboembolism, with associated 95% confidence intervals. Follow-up will be calculated as time from baseline to time when one of the following events occurred: the patient developed a venous thromboembolism, the patient died from another cause, or last follow up of the study occurred. We will calculate hazard ratios and 95% confidence intervals for venous thromboembolism in patients with compared with patients without metabolic syndrome by using multivariable Cox regression. We will allow for across study heterogeneity by initially running a Cox model with random effect ("shared frailty" γ distributed) for the study variable. If we will find no significant variance of γ distribution, we will use a study stratified Cox model under the fixed effect assumption. Other variables a priori defined in the regression model were age, BMI, sex, as potential confounding variables. We will handle patient's age as a continuous variable. Obesity will be categorized as a dichotomous variable using the ethnic specific definitions previously reported. We will retain all variables if P was less than 0.10 or if they significantly affected the regression coefficients of other variables. We will assess the proportional hazards assumption by analysis of Schoenfeld residuals. The analysis will be subsequently performed including all previous variables and the individual components of the metabolic syndrome in the place of the metabolic syndrome.
Hazard regression models will be used to investigate the impact of increasing number of individual components of the metabolic syndrome on the risk of VTE, and to explore the influence of abdominal obesity on this relationship. Subjects with no components of the metabolic syndrome will used as a reference population, and the analyses will be carried out in three different models of the metabolic syndrome: (i) HRs by increasing number of individual components for our original definition of the syndrome; (ii) HRs by increasing number of components in a modified model including abdominal obesity as a mandatory criterion of the metabolic syndrome; and (iii) HRs by increasing number of components in a modified model excluding abdominal obesity as a criterion for the metabolic syndrome.

All the analyses were performed using Minitab and SPSS 18 (SPSS Inc., Chicago, IL, USA).

Summary/conclusion: The results of two patient-level meta-analyses, one of case-control studies and one of prospective cohort studies, will allow use to better explore the role of the metabolic syndrome as an independent risk factor for VTE and to assess this potential association between the metabolic syndrome and, in particular, unprovoked VTE in different patients subgroups. Furthermore, the central role of increased waist circumference will be separately evaluated in the two meta-analyses. We expect to have additional evidences on the role of cardiovascular risk factors on the risk of VTE, on their additive effects, and, last but not least, on the role of waist circumference as a risk factor for VTE in comparison to obesity defined by the body mass index.

References:

1. Ageno W, Prandoni P, Romualdi E, Ghirarduzzi A, Dentali F, Pesavento R, Crowther M, Venco A. The metabolic syndrome and the risk of venous thrombosis. A case control study. J Thromb Haemost 2006;4:1914–1918.
2. Ay C, Tengler T, Vormittag R, Simanek R, Dorda W, Vukovich T, Pabinger I. Venous thromboembolism – a manifestation of the metabolic syndrome. Haematologica 2007;92:373-379.
3. Jang MJ, Choi W, Bang SM, Lee T, Kim YK, Ageno W, Oh D. Metabolic Syndrome Is Associated With Venous Thromboembolism in the Korean Population. Atheroscl Thromb Vasc Biol 2009;29:311-315.
4. Di Minno MND, Tufano A, Guida A, Di Capua M, De Gregorio AM, Cerbone AM, Tarantino G, Di Minno G. Abnormally high prevalence of major components of the metabolic syndrome in subjects with early-onset idiopathic venous thromboembolism. Thromb Res 2011 Jan 12; Epub ahead of print
5. Borch K, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Abdominal obesity is essential for the risk of venous thromboembolism in the metabolic syndrome – The Tromso Study. J Thromb Haemost 2009;7:739-745
6. Steffen LM, Cushman M, Peacock JM, Heckbert SR, Jacobs DR, Rosamond WD, Folsom AR. Metabolic syndrome and risk of venous thromboembolism: Longitudinal Investigation of Thromboembolism Etiology (LITE). J Thromb Haemost 2009;7:746-751

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)?

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* LITE study)

___ 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.