ARIC Manuscript Proposal #2338

PC Reviewed: 4/8/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Association of traditional cardiovascular risk factors with venous thromboembolism: meta-analysis of community-based prospective cohorts

b. Abbreviated Title (Length 26 characters):

CVD risk factors and VTE

2. Writing Group:

Writing group members:

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

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3. Timeline:
April-July 2014: data retrieval and analysis of individual studies.
August-September 2014: drafting the meta-analysis
October 2014: submission to a journal

4. Rationale:

Venous thromboembolism (VTE) is a substantial public health concern. Data from the United States shows that annually 60.000-100.000 individuals die from VTE, and that among VTE-survivors 50% have long-term complications.[1] Only about 50% of the VTE cases occur in individuals with established risk factors.[2] Established acquired risk factors for VTE include immobilization, surgery, major trauma, pregnancy, puerperium, malignancy, hormonal replacement therapy or oral contraceptives and long distance travel (i.e., >4 hours).[3] VTE that occurs within 3 months from the mentioned acquired risk factors is considered provoked or secondary VTE. In absence of these risk factors VTE is considered unprovoked. In contrast, it is widely acknowledged that arterial thromboembolism (ATE), comprising coronary heart disease, stroke or transient cerebral ischaemic attack, and peripheral artery disease is secondary to atherosclerosis, which is caused by various traditional cardiovascular risk factors, such as hypertension, hyperlipidemia, diabetes, smoking, and obesity.[4]

Thromboembolic diseases of venous and arterial systems have been viewed as two different diseases with distinct risk factors.[5] This notion was challenged in the last decade since an increased incidence of ATE had been observed in subjects with VTE, especially in subjects with unprovoked VTE.[5] Moreover, various studies reported an association of classic atherosclerosis risk factors (i.e., hypertension, hyperlipidemia, diabetes, obesity, and smoking) with VTE, though results are inconsistent. In 2008 a meta-analysis showed positive associations for hypertension, diabetes, hyperlipidemia and smoking with VTE incidence.[6] However, most of the studies included in that meta-analysis were case-control studies, and in the cohort studies no age adjustment was performed. Hence, the results of this meta-analysis may be unreliable.[6] Compared to cohort studies, case-control studies are more prone to bias and miss temporal dimensions. In cohort studies exposure is identified before the outcome, therefore the temporal framework allows better potential to assess causality, so may provide stronger scientific evidence. In current proposal we are planning a meta-analysis of community-based prospective cohort studies in which traditional cardiovascular risk factors and VTE events are ascertained and adjudicated.

5. Main Hypothesis/Study Questions:

Except gender, older age and obesity, which are well-established risk factors for VTE, other traditional cardiovascular risk factors (i.e., hypertension, hyperlipidemia, smoking, and diabetes) do not predispose to VTE.

6. Design and analysis:

Data:

A total of 7 community-based cohorts from the United States and Europe will be included. Brief information on the sample-size, number of events, baseline year(s) and region is provided in the Table below. As shown in the last column, all of these studies have already published on the association of the traditional cardiovascular risk factors with VTE with some inconsistencies across studies.

Cohort*	Region	Baseline Year	Number of participants	Number of VTEs	Reference
ARIC	USA	1987-89	15,792	516	[7, 8]
CCHS	Denmark	1976	18,954	969	[9]
CHS	USA	1989	5,888	210	[7]
HUNT2	Norway	1995-1997	64,793	509	[10]
PREVEND	Netherlands	1997-98	8,592	129	[11]
REGARDS	USA	2003-07	29,556	268	[12]
Tromsø	Norway	1994-95	29,974	540	[13]
Total			**173,549**	**3,141**	

ARIC denotes the Atherosclerosis Risk in Communities Study Study; CCHS, the Copenhagen City Heart study; CHS, the Cardiovascular Health Study; HUNT2, the second Nord-Trøndelag Health Study; PREVEND, the Prevention of REnal and Vascular ENd-stage Disease; REGARDS, the Reasons for Geographic and Racial Differences in Stroke; Tromsø, the Tromsø study.

*Depending on the missing data, the final numbers from each study may deviate slightly.

Outcome Variable: VTE (provoked and unprovoked), deep-vein thrombosis, and pulmonary embolism. The classifications of provoked versus unprovoked VTE are largely similar across studies with only minor inconsistencies. When possible the same definitions of provoked and unprovoked VTE will be used across all studies.

Baseline variables of interest:

Age, gender, race, hypertension status (systolic and diastolic blood pressure); hyperlipidemia status (total cholesterol, LDL, HDL and triglycerides levels, and statin use); diabetes status (fasting glucose levels); obesity (waist circumference, body mass index [length, weight]), smoking status (current, former) and history of cardiovascular disease at baseline (i.e., peripheral artery disease, myocardial infarction/revascularization or stroke).

Brief analysis plan and methods:

a. Since not all studies will be providing individual participant level data (IPD), each study will be first analyzed separately using a centrally developed STATA code. Studies that provide IPD to the writing chair (Dr. Mahmoodi), which will include the ARIC study, this part of the analysis will be performed by the writing chair. For other studies such as the REGARDS and CCHS studies the representing co-authors of these studies will be running the same code and will be sharing only the obtained estimates with the writing chair. Definitions and cut-off values will be harmonized across all studies. Associations of each cardiovascular risk factor with VTE will be explored univariately, adjusted for age, race and sex, and fully adjusted (including all traditional cardiovascular risk factors in the same model). Estimates will be presented for overall VTE and separately for pulmonary embolism, deep-vein thrombosis, unprovoked and provoked VTE. Cox proportional hazard models will be used to calculate hazard ratios and 95% confidence intervals, and for continuous variable the associations will also be graphically depicted by using restricted cubic splines.
b. The obtained estimates from each cohort will then be meta-analyzed using random-effect meta-analysis to obtain the overall pooled estimates of the seven studies. Previously, this approach of aggregated meta-analysis using the same definitions with centrally developed code showed similar properties as compared to pooled analysis of individual participant level data.[14] The main difference was somewhat wider confidence intervals with the aggregated two-stage method.

Summary/conclusion:

Meta-analysis of the proposed well-designed prospective cohort studies may provide conclusive evidence on the association of traditional cardiovascular risk factors with VTE. Depending on the results of the meta-analysis, findings may inform the design of clinical trials or result in re-allocation of research resources to other more promising areas of VTE research.

References:

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010; **38**: S495-501.
2. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003; **107**: I4-8.

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4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013.
5. Prandoni P. Venous thromboembolism and atherosclerosis: is there a link? *Journal of thrombosis and haemostasis : JTH*. 2007; **5 Suppl 1**: 270-5.
6. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation*. 2008; **117**: 93-102.
7. 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**: 508-15.
8. 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**: 1182-9.
9. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation*. 2010; **121**: 1896-903.
10. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007; **5**: 692-9.
11. Mahmoodi BK, Gansevoort RT, Veeger NJ, et al. Microalbuminuria and risk of venous thromboembolism. *JAMA*. 2009; **301**: 1790-7.
12. Zakai NA, McClure LA, Judd SE, et al. Racial and Regional Differences in Venous Thromboembolism in the United States in Three Cohorts. *Circulation*. 2014.
13. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromso study. *JTH*. 2008; **6**: 1851-7.
14. Sang Y, Matsushita K, Mahmoodi BK, Astor BC, Coresh J, Woodward M. Abstract P343: Comparison of Two-stage and One-stage Meta-analyses: An Example of eGFR-Cardiovascular Mortality Association (for CKD-PC collaborators). *Circulation*. 2012; **125**: AP343.

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)?

a. 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: 508-15.
b. 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: 1182-9.

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 [LITE])

___ 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.