1.a. Full Title: Venous thromboembolism in relation to subclinical and clinical arterial vascular disease (CHS/ARIC ancillary study manuscript proposal; ancillary study: Longitudinal Investigation of Thromboembolism Etiology (LITE))

1.b. Abbreviated Title (Length 26 characters): VTE and arterial disease

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Location of analysis: Ancillary study personnel, Seattle, WA

3. Timeline

9/00 Analysis
11/00 Begin writing draft
1/01 Submit first draft for editing by co-authors

Key Words: deep vein thrombosis; pulmonary embolism; venous thromboembolism; arterial disease; epidemiology; subclinical disease; atherosclerosis; myocardial infarction; stroke; angina; coronary artery disease

4. Background and Rationale

A number of traditional cardiovascular risk factors have been identified as independent risk factors for venous thromboembolism (deep venous thrombosis or pulmonary embolism), including advanced age, male gender, non-white race/ethnicity, elevated body mass index, and diabetes mellitus, in several settings (1, 2) including the combined ARIC and CHS cohorts (3). Other cardiovascular risk factors, including cigarette smoking, hypertension, dyslipidemia, physical inactivity, and alcohol use have been less consistently associated with increased risk of
Venous thromboembolism (4), and were not identified as independent risk factors in the combined ARIC and CHS cohorts (3).

Although venous thromboembolism shares a number of risk factors with subclinical and clinical atherosclerosis, little information is available about whether the presence of atherosclerosis, at either a subclinical or a clinical level, is associated with increased risk of venous thromboembolism. The purpose of this paper is to examine the association of subclinical or clinical arterial vascular disease with the risk of venous thromboembolism.

Atherosclerosis is associated with higher levels of inflammatory markers including plasma fibrinogen, Factor VIII and C-reactive protein, but it is not clear whether these markers cause or are the result of atherosclerosis (5, 6). In preliminary analyses in the combined ARIC/CHS cohort, the risk of incident venous thromboembolism during 8 years of follow-up was associated with higher baseline levels of Factor VIII but was not associated with baseline levels of fibrinogen or Factor VII (7).

If there is an association of arterial disease with VTE risk, it would be of interest to determine whether the association is seen only in those with both arterial disease and shared risk factors/inflammatory markers, or whether an association is also present in those with arterial disease but no shared risk factors/inflammatory markers. To begin to address this question, we will examine both the overall association of subclinical and clinical arterial disease with risk of VTE, and the risk in subgroups defined by risk factors measured at baseline, and by baseline levels of inflammatory markers and coagulation factors.

5. **Hypotheses**

(1) Subclinical and clinical arterial disease at baseline are associated with increased risk of incident venous thromboembolism.

(2) The associations are stronger in participants with shared risk factors for both arterial disease and venous thromboembolism.

(3) The associations are stronger in participants with elevated levels of inflammatory markers or coagulation factors.

6. **Analysis Plan and Methods**

**Subjects**

The Longitudinal Investigation of Thromboembolism Etiology (LITE) Study is an ancillary study to both the ARIC Study and the CHS. This cohort study combines the CHS and ARIC cohorts, and investigates risk factors for VTE. Details of case ascertainment and validation are found elsewhere (8). For this analysis, participants with prevalent VTE at baseline, prevalent use of anticoagulant medication at baseline, and active cancer at baseline will be excluded.
Data to be Used

We will use baseline data from the ARIC and CHS datasets. The variables to be used include field center, smoking, hypertension, dyslipidemia, physical activity, alcohol use, aspirin use, anticoagulant use, postmenopausal hormone use in women, and the variables listed below. As noted, some of the baseline measures listed are not available on the ARIC cohort.

Subclinical arterial disease will be defined as any one or more of the following at baseline (9):
- ankle-arm index $\leq 0.9$
- internal carotid artery wall thickness (IMT) $> 80^{th}$ percentile (mean IMT in ARIC; maximum IMT in CHS)
- common carotid artery IMT $> 80^{th}$ percentile (mean IMT in ARIC; maximum IMT in CHS)
- carotid stenosis $> 25$
- major ECG abnormalities (10)
- abnormal ejection fraction on echocardiogram (CHS only)
- abnormal wall motion on echocardiogram (CHS only)
- Rose questionnaire claudication positive
- Rose questionnaire angina positive

Clinical arterial disease will be defined as any one or more of the following at baseline:
- atrial fibrillation or pacemaker
- history of claudication or peripheral vascular surgery
- history of congestive Heart failure
- history of coronary artery bypass graft surgery or angioplasty
- history of angina or use of nitroglycerin
- history of myocardial infarction
- history of stroke

Shared risk factors for arterial disease and VTE:
- advanced age
- male gender
- non-white race/ethnicity
- elevated body mass index
- diabetes mellitus

Inflammatory markers/ coagulation factors:
- C-reactive protein (CHS only)
- fibrinogen
- factor VII

The LITE study has created a separate dataset containing variables generated from VTE event adjudication, and these variables will be used.
Analysis

The significance of bivariate associations of arterial disease with subject characteristics will be assessed using the chi-square test for categorical data and the t-test for continuous data. The association of subclinical and clinical arterial disease with the risk of incident VTE will be assessed using Cox regression. Because some of the baseline measures of subclinical disease are not available on the ARIC cohort are defined differently, some analyses will need to be conducted separately in CHS and ARIC. The associations in subgroups defined by traditional cardiovascular risk factors and levels of inflammatory markers or coagulation parameters will be assessed by adding interaction terms for subgroup by arterial disease to the Cox regression model. Again, some of these analyses will need to be conducted separately due to differences in available data between CHS and ARIC. Potential confounding factors may include field center, hormone replacement therapy in women, and aspirin use.

Summary/Conclusion

We expect to find that the risk of VTE is elevated in participants with subclinical or clinical arterial disease, particularly in those who also have traditional CVD risk factors or elevated inflammatory or coagulation parameters.

ARIC Questions 7 & 8:
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 ICTDER01 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 ICTDER01 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  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

References


