ARIC Manuscript Proposal # 1159

PC Reviewed: _05_/_23_/06 Status: __A__ Priority: __2__
SC Reviewed: _05/24/06____ Status: __A__ Priority: __2__

1.a. Full Title: Activated Partial Thromboplastin Time and Risk of Incident Venous Thrombo-embolism

b. Abbreviated Title (Length 26 characters): aPTT and risk of VTE

2. Writing Group:
Writing group members:

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3. Timeline: from approval: analysis and first draft, 3 months. Penultimate draft 3 more months

4. Rationale:

A shortened activated partial thromboplastin (aPTT) time has been associated with venous thromboembolism (VTE)[1, 2]. This may relate to increased activity of coagulation factors in the intrinsic or common pathways of coagulation or to activated protein C (APC) resistance[1-3]. Prior studies had a retrospective design[2] or only evaluated hospitalized patients[1]. There are no prospective studies available assessing the aPTT and VTE risk in the general population.

The ARIC study, by way of information gathered for the Longitudinal Investigation in Thrombosis Etiology (LITE) ancillary study provides an opportunity to study the relationship between the aPTT and VTE, examining the confounding effects of traditional VTE risk factors, coagulation factor levels that are correlated with the aPTT and APC resistance[4].

5. Main Hypothesis/Study Questions:

1) A shortened aPTT will be associated with future VTE in univariate analysis

2) Adjustment for coagulation factor levels and APC resistance will attenuate and perhaps eliminate the association of a short aPTT with VTE.

3) Associations will be larger for idiopathic than secondary VTE.

6. Data (variables, time window, source, inclusions/exclusions):

Variables: From ARIC: age, gender, race (white, non-white), body mass index, factor VIII, fibrinogen, aPTT, von Willebrand factor antigen, protein C
From LITE: factor IX, factor XI, D-dimer, factor V Leiden gene mutation, prothrombin gene mutation, blood group.

Time Window: Enrollment to 31 December 1996 (VTE events ascertained)

Exclusions: 1) No baseline aPTT measured
2) Baseline VTE
3) Baseline Cancer
4) Baseline warfarin use

Outcome variable: Incident VTE (n = need updated number)

Analysis Plan:

We will assess baseline aPTT in relation to VTE risk by evaluating the standard deviation increment and by quantile to assess linearity. We will look at incidence rates of VTE by categories of aPTT. Cox-proportional hazards models will be used to estimate the relative risk of overall VTE first in an unadjusted analysis, then with adjustment for VTE risk factors (age, sex, race, BMI). We will then adjust further for coagulation factors in the intrinsic and common pathway (Factors VIII, IX, XI and fibrinogen, which are evaluated clinically using the aPTT) as well as for von-Willebrand antigen and blood group, which are correlated with the aPTT and are risk factors for VTE. We will then run separate age, sex, race and BMI-adjusted models adjusting individually for factor V Leiden, APC resistance, the prothrombin 20210A gene mutation, D-dimer and protein C level to assess any role of these factors on the association of aPTT with VTE. As factor V Leiden, APC ratio, prothrombin 20210A, blood group, and factors IX, XI and D-dimer were only measured in a nested case-control sample, this analysis will not include the entire cohort[4, 5]. If the nested case-control analysis for the other analyses yields the same information as the unrestricted analysis, we will report only the case-control analyses. We will run both analyses with and without women on hormone replacement therapy to assess for confounding. We will also repeat analyses with idiopathic VTE events as an outcome.

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)?
No proposals on PTT and VTE

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: LITE, 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.

References

1. Aboud MR, Ma DD. Increased incidence of venous thrombosis in patients with shortened activated partial thromboplastin times and low ratios for activated protein C resistance. *Clinical & Laboratory Haematology* 2001;23:411-6.
2. Tripodi A, Chantarangkul V, Martinelli I, Bucciarelli P, Mannucci PM. A shortened activated partial thromboplastin time is associated with the risk of venous thromboembolism. *Blood* 2004;104:3631-4.
3. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. *N Engl J Med* 1994;330:517-522.
4. Cushman M, Tsai AW, White RH et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the Longitudinal Investigation of Thromboembolism Etiology. *American Journal of Medicine* 2004;117:19-25.
5. Tsai AW, Cushman M, Rosamond WD et al. Coagulation factors, inflammation markers, and venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE).[see comment]. *American Journal of Medicine* 2002;113:636-42.