ARIC Manuscript Proposal # 3110

PC Reviewed: 2/13/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: High molecular weight kininogen (HMWK) or prekallikrein and Venous Thromboembolism (VTE)

b. Abbreviated Title (Length 26 characters): HMWK, prekallikrein and VTE

2. Writing Group:

Writing group members: Aaron Folsom, Weihong Tang, Saonli Basu, Susan Heckbert, Mary Cushman

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

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3. Timeline: Summer-Fall 2018

4. Rationale:

Coagulation pathways are clearly involved in the etiology of VTE, with higher levels of plasma factor VIII, XI, von Willebrand factor, and D-dimer being predictive of VTE in the Longitudinal Investigation of Thromboembolism (LITE) study, which comprises ARIC and CHS. In addition, many of the common and low-frequency variants consistently associated with VTE risk in GWAS (*ABO, F11, F2, F5, FGG, GP6, KNG1, PROCR, SLC44A2, STXBP5, TSPAN15* and *VWF*)[193] are involved in coagulation pathways.

In addition, high molecular weight kininogen (HMWK) or prekallikrein may also identify VTE risk but this hypothesis has been rarely examined. HMWK is part of the contact pathway of coagulation, which also includes the proteins factor XI, factor XII, and prekallikrein, the precursor of HMWK. Activation of the contact system leads to procoagulant and proinflammatory reactions. The contact system is essential for surface-initiated coagulation, as

exemplified by the aPTT, but whether the contact system has any role in initiating physiologic in vivo coagulation is disputed. Over the last few years, there has been renewed interest, especially because of experimental evidence suggesting that the contact system contributes to thrombosis.[167] Knockout mice deficient in one of the contact proteins were protected against artificially induced thrombosis. Furthermore, inhibiting agents such as monoclonal antibodies, antisense oligonucleotides, and small molecules were found to prevent thrombosis in rodents and primates in both venous and arterial vascular beds. Factor XI is a strong VTE risk factor,[75] and anti-factor XI prevented VTE in orthopedic patients.[168] HMWK helps to optimally position prekallikrein and factor XI next to factor XII; it also inhibits the thrombin- and plasmin-induced aggregation of platelets. Although HMWK and prekallikrein have been associated with arterial CVD in limited studies,[92,95] to our knowledge, only one retrospective study has examined the association of VTE with plasma HMWK, which was higher in VTE patients than in controls, whereas prekallikrein did not differ.[170] However, those VTE patients were on vitamin K antagonists, which might have influenced results.

The LITE study recently updated VTE occurrence in ARIC through 2015. LITE is currently measuring HMWK and prekallikrein in ARIC), using a case-cohort design (600 VTE events and a cohort random sample of 4200). We therefore can test the hypothesis outlined below.

[Note: Reference numbers are from the LITE renewal and are available upon request.]

5. Main Hypothesis/Study Questions:

Higher plasma HMWK or prekallikrein is associated with increased VTE incidence.

Depending on the findings, this proposal may yield two manuscripts rather than one.

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).

Hypothesis: Measure HMWK and prekallikrein and determine their associations with VTE.

We exclude people with pre-baseline VTE or those with anticoagulant use. We will examine correlates of HMWK and prekallikrein to assess potential confounders. We will use a cubic spline analysis to examine the shape of the associations with VTE. The associations of VTE with HMWK or prekallikrein will be performed in 600 VTE events and a cohort random sample of 4,200 using proportional hazards models and employing Barlow's method for variance estimation of the case-cohort design.[179] We will use quartiles or continuous representations of the biomarkers and use the model to adjust for potential confounders (age, race, sex, BMI, CKD, other coagulation factors), race, or VTE genetic risk score.

In our grant proposal, we used a slightly higher sample size to estimate minimal detectable HRs. We used the ccsize[180] function in the R package `gap' to estimate the power of detection of a binary exposure variable for a cohort of 16,800 individuals and a case-cohort design with 850 VTE cases and a cohort random sample of 4,150 individuals. At α=0.05 we should have 80%

power to detect a HR of 1.24 for the highest vs. lowest three quartiles of HMWK or prekallikrein; detectable HRs are 1.30 in whites and 1.46 in African Americans alone.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _xx___ 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? _xx__ 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __xx__ 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

___xx___ 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)?

None

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _xx___ Yes ____ No

11.b. If yes, is the proposal

_xx__ A. primarily the result of an ancillary study (list number* ___2001.16 LITE__)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)