1.a. Full Title: High molecular weight kininogen (HK), prekallikrein (PK) and incident CHD or stroke

   b. Abbreviated Title (Length 26 characters): HK, prekallikrein and CVD

2. Writing Group:
   Writing group members: Jeff Misialek, Aaron Folsom, Romil Parikh, Wayne Rosamond, Weihong Tang, 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: draft manuscript by Spring 2019

4. Rationale:

The contact activation system (CAS) and the kallikrein/kinin system (KKS) play important roles in regulation of hemostasis, thrombosis and inflammation. High molecular weight kininogen (HK) acts as a co-factor in facilitating activation of Factor XII, which is the first step in the intrinsic/contact-activation pathway of the coagulation cascade. Factor XIIa facilitates conversion of protein prekallikrein (PK) to plasma kallikrein, which in turn activates FXII, thereby forming a cyclical auto-activation chain-reaction. Activation of the contact system leads to procoagulant and proinflammatory reactions potentially contributing to cardiovascular diseases (CVD) such as CHD and stroke.\(^1\) However, HK & PK participate in the KKS as well, yielding bradykinin which has cardioprotective properties.\(^2\) Positive association of HK and PK with CVD have been demonstrated in animal studies\(^1\), however their association is disputed in limited number of human studies.\(^3,^4\)
We wish to investigate this association in a large cohort in the US. The LITE ancillary study of ARIC measured plasma HK and PK at ARIC visit 3 in venous thromboembolism cases and a cohort random sample. We propose to study these biomarkers and risk of incident CHD and stroke in the cohort sample. A detailed understanding of the association of HK and PK with CVD outcomes may aid in understanding etiology, risk prediction, identifying preventive measures, as well as identifying potential target molecules for developing new therapeutic interventions.


5. **Main Hypothesis/Study Questions:**

Higher plasma HK and prekallikrein are associated with increased CVD incidence.

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).**

Study design: prospective cohort, using visit 3 random sample with biomarkers measured (N~3800 without CVD at baseline)

Exclusions: pre-visit 3 CHD or stroke, use of anticoagulants, missing key covariates

Exposure: HK and PK at visit 3

Outcome: incident CHD (definite/probable MI or definite fatal CHD) and definite/probable ischemic stroke based on ARIC criteria. Analyses will be done using first CVD event and then repeated separately for CHD and ischemic stroke.

Confounding variables (taken from visit 3): age, race, sex, BMI, total and HDL cholesterol, TG, hormone replacement therapy, diabetes, CKD, atrial fibrillation, alcohol, smoking, SBP and antihypertensive medications, and inflammatory biomarkers (eg CRP). Further, as a
supplemental analysis, models for each outcome will be adjusted for competing risk of the other outcome.

We will examine correlates of HK and PK to assess potential confounders. We will use a cubic spline analysis to examine the shape of the associations with CVD. The associations of CVD with HK and PK will be assessed in the cohort random sample of N~4000. The approximate number of incident CHD and stroke cases expected are 500 and 350, respectively. We will use quartiles or continuous representations of the biomarkers and use Cox proportional hazards regression to adjust for potential confounders.

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)?

3110. High molecular weight kininogen (HK) or prekallikrein and venous thromboembolism (VTE)—Folsom et al.

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
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)* __________ __________ __________)