1.a. Full Title: Activated factor XI and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology

b. Abbreviated Title (Length 26 characters): Factor XI and Venous Thrombosis

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

   March 2002 – analysis and first draft
   May 2002 – penultimate draft
   June 2002 – manuscript submission

4. Rationale:
   Factor XI plays a pivotal role in coagulation by amplifying thrombin generation. Before the revision of the cascade or waterfall hypothesis of hemostasis (1,2) the contact system (including factor XII, high molecular weight kininogen and prekallikrein) was thought to play a major role in the activation of factor XI. The lack of bleeding with factor XII deficiency suggested an alternative mechanism of such activation. We know now that factor XI is not essential for in vivo activation of the cascade, but is required to sustain hemostasis after primary thrombin generation has been assured through exposure of plasma to subendothelial tissue factor at the site of injury. The formation of thrombin and its feedback activation of factor XI result in additional formation of thrombin (secondary thrombin generation) that protects fibrin clots from fibrinolysis (3). Recent studies (4) showed a positive effect of factor Xla on the activation of TAFI (Thrombin Activatable Fibrinolysis Inhibitor), implying that activation of Factor XI stabilizes the clot by making it more resistant to fibrinolysis.
The activation of Factor XI to its active form (factor XIa) is detectable in plasma using an ELISA assay (5) that measures the coagulation factor – inhibitor complex, FXIa-α1-antitrypsin (FXIa-α1-AT). Measurement of this complex detects early stages of hypercoagulability in patients with disseminated intravascular coagulation (6). The role of factor XI in thrombosis in humans is unclear. One case control study reported higher factor XI coagulant activity with previous deep vein thrombosis (7). However, there are no prospective data confirming this finding.

5. Main Hypothesis/Study Questions:

1) Higher baseline factor XI concentration is a risk factor for venous thrombosis independently of other known risk factors
2) The association of factor XI concentration with VTE will be larger in participants with idiopathic compared to secondary VTE.
3) Simultaneous presence of higher factor XI and Factor V Leiden will confer a larger risk than the presence of either factor alone

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

Existing LITE database. Factor XIa-α1-AT was measured using an enzyme-linked immunosorbent assay method described previously in the literature (8)

Table one – Baseline characteristics by thrombosis status (variables) will include: age, sex, race, BMI, DM, and factor V Leiden (FVL). They will be studied univariately by calculating prevalence or mean values in cases and controls.

Table two – Determinants of factor XIa-α1-AT levels in controls.

a) continuous variables – using linear regression or correlation coefficients
b) categorical variables – FVL (positive/negative), race (white/non-white) and diabetes (NL, IFG, DM) – using either t-tests or analysis of variance.

Table three – Using first quintile as the reference group we will examine the contribution of each higher quintile of factor XIa-α1-AT to the risk of venous thrombosis by calculating odds ratios (with 95% confidence intervals), as estimates of the relative risk. Unconditional logistic regression will be used for that purpose. Adjustment will be made for age in all models; and race, sex, BMI, DM and FVL in additional models.

Table four – We will test the hypothesis of increased risk of thrombosis with simultaneous presence of FVL and higher factor XI concentration (using >90%).

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://bios.unc.edu/units/csc/ARIC/stdy/studymem.html](http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html)  

  ___X___ Yes  _______ No