1.a. Full Title: Elastase and venous thromboembolism

b. Abbreviated Title (Length 26 characters):

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

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4. Rationale:

   Although many cases of venous thromboembolism (VTE) can be attributed to known risk factors that include the inherited thrombophilias (such as factor V Leiden mutation and the prothrombin 20210A gene), acquired prothrombotic states (surgery, immobility, pregnancy), or vascular trauma, many venous thrombotic events develop in the absence of any known risk factor. In the investigation of additional entities that may promote clot formation, the role of inflammation has been targeted. In particular, neutrophil elastase may be a plausible component of the inflammatory process to focus on due to its relationship with hemostasis.

   Neutrophil elastase is a serine protease produced by the azurophilic granules of activated neutrophils in the vasculature during acute inflammation. Elastase, along with collagenase, aids penetration of cells through the extracellular matrix during local vessel microbicidal activity (1). This antimicrobial protein has been shown to influence coagulation by activating platelets and promoting factor XIIa dependent fibrin formation (2,3). It also cleaves the zymogen factor V causing its activation, and may be involved in activating other coagulation factors (4).

   We hypothesize that higher circulating elastase concentration might represent a novel risk marker for venous thrombosis, providing further evidence of a link between inflammation and coagulation activation. No previous study has assessed this association.

References

5. **Main Hypothesis/Study Questions:**
   1. To determine if elevated elastase levels are associated with an increased incidence of VTE.

6. **Data (variables, time window, source, inclusions/exclusions):**
   **Inclusion/exclusion:** the LITE nested case-control study group

   **Analysis:** Analysis of the cross-sectional associations of elastase levels with venous thrombosis risk factors will be undertaken using t-tests, ANOVA, or correlation coefficients, as appropriate. The primary measure of association will be the odds ratio for VTE in relation to categorized elastase. Logistic regression will be used. Covariates include other VTE risk factors: age, race, sex, BMI, diabetes, factor V Leiden mutation, prothrombin 20210A gene mutation, D-dimer, factor VIII. Subgroup analysis will be done for incident/recurrent and idiopathic/secondary VTE. We will determine whether higher elastase further increases the risk of thrombosis in the presence of factor V Leiden, elevated factor VIII or elevated D-dimer.

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/cscc/ARIC/stdy/studymem.html](http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html)
  ____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)?
   None

11. 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.