1. **Full Title:** Concentration of thrombin activatable fibrinolysis inhibitor (TAFI), a polymorphism of the TAFI gene, and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology

2. **Abbreviated Title (Length 26 characters):** TAFI and Venous Thrombosis

3. **Type:** Ancillary study (LITE), using CHS/ARIC longitudinal data, with analysis in MN

4. **Writing Group (list individual with lead responsibility first):**
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5. **Timeline:** Winter 2000: analysis and first draft

6. **Rationale:**
   The LITE Study is examining venous thromboembolism (VTE) in the combined ARIC and CHS cohorts. Over the past 10 years, the etiology of VTE has become increasingly understood as an oligogenic disorder. Among those with idiopathic VTE genetic disorders can be identified in up to 60% of patients. Presence of multiple genetic defects, for example the combination of factor V Leiden and protein C deficiency, increases the risk of thrombosis. It is currently hypothesized that unknown genetic disorders exist which might further explain occurrence of VTE.

   Thrombin Activatable Fibrinolysis Inhibitor (TAFI) is a member of the carboxypeptidase family, found in plasma. Activated TAFI (TAFla) is formed subsequent to thrombin’s complexing with thrombomodulin on the endothelial cell surface. Activated TAFI inhibits fibrinolysis by removal of carboxy-terminal Arg and Lys residues from partially degraded fibrin. Thus, higher levels of TAFI would be expected to be associated with risk of thrombosis. In a CHS substudy higher TAFI was associated with higher levels of factor VIIc, protein C, D-dimer, and PAI-1 (Crainich
et al, CHS manuscript in preparation). Levels were not associated with demographic factors, cardiac risk factors, or subclinical atherosclerosis.

One case control study reported that higher TAFI levels were associated with deep vein thrombosis (DVT): OR 1.7 (95%CI 1.1-2.5) \(^4\). In that study TAFI was associated with age, fibrinogen, protein C, antithrombin and prothrombin levels. In the joint presence of elevated TAFI levels (>90\(^{th}\) percentile) and the factor V Leiden mutation, the risk for thrombosis was not higher than that related to the individual risks. However, the combination of elevated factor VIII and elevated TAFI levels appeared to increase thrombotic risk supra-additively.

The promoter region of TAFI was recently screened for polymorphisms. A G→A polymorphism at position –438 was strongly associated with TAFI levels in a CHS analysis (Crainich et al, CHS manuscript # ). The approximate allele frequencies are G/G – 60%, G/A – 36% and A/A – 4%. TAFI levels corresponding to these genotypes were 5.77, 4.07, and 2.33 mg/L. The general lack of association of TAFI levels with risk factors, as noted above, suggests that TAFI levels are largely under genetic control, consistent with our findings on the association of genotype with level.

This manuscript will analyze the associations of TAFI levels and the –438 polymorphism in the LITE. In other LITE analyses, factor V Leiden and higher factor VIIIc were both associated with risk of VTE, with larger associations for idiopathic VTE. Associations were similar comparing incident and recurrent VTE. Given the prior report of a TAFI interaction with factor VIIIc, it is important to assess this interaction prospectively in LITE.

5. Main Hypothesis/Study Questions:
   a. Higher baseline TAFI concentration is a risk factor for venous thrombosis
   b. The association of TAFI with VTE will be higher in participants with idiopathic compared to secondary VTE.
   c. Higher TAFI will be associated with both incident and recurrent VTE.
   d. The TAFI –453A allele will be protective for VTE.
   e. Joint presence of higher TAFI and Factor V Leiden or high factor VIIIc will confer a larger risk than the presence of either factor alone
   f. TAFI –453A will remain protective of VTE among participants with factor V Leiden or high factor VIIIc.

6. Data (variables, time window, source, inclusions/exclusions):
   Sample: Existing LITE nested case-control sample of 323 incident VTE cases and 688 frequency matched controls.

   Data: Baseline risk factors measured in ARIC and CHS, including coagulation factors and genotypes measured only on this sample.

   Analysis:  (1) examine inter-relations among factors using cross-tabs and correlations
              (2) logistic regression to test study hypotheses
Expected Results:

We anticipate that higher TAFI will be associated with risk of VTE. This will be independent of other VTE risk factors, such as age, sex, race, and obesity. The joint presence of factor V Leiden or high factor VIIIc and higher TAFI levels will increase the risk to a greater than additive degree. The TAFI –453A polymorphism will be protective for VTE.

Conclusions:

This will be the first prospective study to report associations of TAFI with VTE. No prior study has assessed TAFI and pulmonary embolus. It will be the first study of the TAFI –453A polymorphism and VTE. Results will improve our understanding of risk factors and their interrelations in the occurrence of VTE.

Key words: venous thrombosis, risk factors, TAFI, prospective study

Will the data be used for non-CVD analysis in this manuscript? No

Will the DNA data be used in this manuscript? Yes

If yes, is the author aware that either DNA distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA=”No use/storage DNA”? Yes.

References