Published in final edited form as:

Thromb Haemost. 2010 August 2; 104(2): 207–212. doi:10.1160/TH09-10-0693.

Total Tissue Factor Pathway Inhibitor and Venous Thrombosis: The Longitudinal Investigation of Thromboembolism Etiology

Neil A. Zakai, MD, MSc¹, Pamela L. Lutsey, PhD, MPH², Aaron R. Folsom, MD, MPH², Susan R. Heckbert, MD, PhD³, and Mary Cushman, MD, MSc¹

¹Departments of Medicine and Pathology, University of Vermont College of Medicine, Burlington, VT

²School of Public Health, Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN

³Department of Epidemiology, University of Washington, Seattle, WA

Abstract

Tissue factor pathway inhibitor (TFPI) inhibits tissue factor, a potent coagulation initiator. Limited evidence suggests that low TFPI levels are associated with increased risk of venous thrombosis (VTE). We measured total TFPI in a nested case-control study in the Longitudinal Investigation of Thromboembolism Etiology. Control subjects were frequency matched 2:1 to cases on age, sex, race, and cohort. Odds ratio for VTE by TFPI levels were computed using logistic regression models adjusting for age, race, sex, coagulation factors (factors VII, VIII, IX, XI, D-dimer), and body mass index. To evaluate for greater than additive interactions, we calculated the percent relative excess risk due to interaction between TFPI and other VTE risk factors. 534 cases of VTE occurred and matched to 1091 controls. Mean baseline TFPI in ng/mL (standard deviation) in those who developed VTE and controls was 36.4 (12.8) and 35.0 (11.1), respectively. Higher TFPI was associated with male sex, age, body mass index, factors VII, VIII, IX, XI, and D-dimer. TFPI level did not differ by ethnicity, factor V Leiden, or prothrombin G20210A. Compared with those in the upper 95%, the bottom 5% of TFPI had an age-, sex-, race-, and study-adjusted odds ratio (95% CI) of 1.35 (0.86, 2.12) for VTE. Adjusting for factors VII, VIII, IX, and XI the odds ratio was 1.93 (1.05, 3.53). Further addition of D-dimer and BMI to this model the odds ratio was 1.70 (0.98, 2.93). Low TFPI did not demonstrate greater than additive interaction with other VTE risk factors.

Keywords

Venous Thrombosis; Tissue Factor Pathway Inhibitor; Epidemiologic Studies

Introduction

Tissue factor pathway inhibitor (TFPI) is a potent inhibitor of coagulation(1). When tissue factor (TF) is exposed with damage to the vessel wall, it initiates coagulation via factor VII. TFPI reversibly binds and inactivates factor Xa and the TFPI-Xa complex inhibits factor VIIa-TF complexes(1). Despite animal models suggesting a critical role for TFPI in regulating thrombosis and that exogenous TFPI exerts an anticoagulant effect, data are limited in humans on whether TFPI levels affect thrombosis risk(2).

Corresponding Author: Neil A. Zakai, MD, MSc University of Vermont College of Medicine Departments of Medicine and Pathology Colchester Research Facility 102 South Park Drive Colchester, VT 05446 (802) 656-3154 (phone) (802) 656-8965 (fax) neil.zakai@uvm.edu.

TFPI antigen circulates both unbound (free TFPI) as well as bound to factor Xa. In humans, lower total and free TFPI antigen levels and TFPI activity were associated with greater venous thromboembolism (VTE) risk in the Leiden Thrombophilia Study (LETS)(3). Lower free TFPI levels were associated with risk of recurrent VTE in the Austrian Study of Recurrent Venous Thromboembolism (AUREC)(4). While informative, these studies are limited in that they did not examine pre-VTE blood samples, studied only VTE recurrence, or did not include other coagulation biomarkers in modeling. There are no prospective data about the impact of pre-VTE TFPI levels on VTE occurrence. The Longitudinal Investigation of Thromboembolism Etiology (LITE) is a population-based cohort study, allowing use of pre-event blood samples to assess the association of risk factors with VTE. We hypothesized that low levels of total TFPI would be associated with increased incidence of VTE in LITE, and that there would be greater than additive interactions of TFPI with other established VTE risk factors.

Materials and Methods

Study Population

LITE(5) combines data from two studies: the Atherosclerosis Risk in Communities(6) (ARIC) cohort and the Cardiovascular Health Study(7) (CHS), which are prospective cohort studies on risk factors for and consequences of cardiovascular diseases. ARIC enrolled 15,792 participants aged 45 to 64 years-old between 1987 and 1989. CHS enrolled 5201 men and women 65 years or older between 1989 and 1990 with an additional cohort of 687 black men and women recruited in 1992 and 1993, giving CHS a total cohort of 5888. Baseline examinations at six field sites included extensive risk factor collection, including self-reported race, measured body mass index, and phlebotomy. Each cohort maintained a baseline blood sample repository. Written informed consent was obtained within each cohort upon participant enrollment and each study was approved by relevant institutional review boards.

Within LITE, a nested case-control study sample consisted of participants with incident VTE diagnosed through December 1, 2001 in CHS and through December 31, 2002 in ARIC, and controls who were frequency matched to cases by age (within 5 years), sex, race (white, non-white), and follow-up time (case event date within 2 years of an assigned date for controls).

Event Ascertainment

In ARIC, participants were contacted annually by telephone and seen every 3 years through 1998, with phone contact annually thereafter. In CHS, participants were contacted biannually alternating between phone calls and in-person exams through 1999, with phone calls every 6 months thereafter. Hospitalizations were identified by participant or proxy reports, or by reviews of local hospital discharge lists(8). Medical records from participants with hospital discharge codes for VTE were reviewed and deep venous thrombosis (DVT) and pulmonary embolism (PE) were defined using standardized criteria that required positive imaging(8). VTE was defined as secondary if preceded within 90 days by major trauma, surgery, or marked immobility, or associated with active cancer or chemotherapy(5).

Laboratory Analysis

In each study, blood was drawn at entry after an 8-hour fast and plasma stored at -70°C . TFPI was measured by enzyme-linked sandwich immunosorbent assay (ELISA) from stored plasma using a polyclonal anti-TFPI antibody as the capture antibody (Imubind Total TFPI ELISA Kit, American Diagnostica, Inc.; Stamford, CT). TFPI is detected using a biotinylated monoclonal antibody specific for the Kunitz domain 1 of TFPI. Binding of streptavidin conjugated horse radish peroxidase to the TFPI-antibody complex and the addition of substrate provide a colorimetric determination of the amount of TFPI in the sample. This assay was performed at the Laboratory for Clinical Biochemistry Research (University of Vermont,

Burlington, VT). Intra-assay and inter-assay CVs range from 6.2–7.1% and 5.5–7.3%, respectively. Factor VIII coagulant activity (VIIIc) was measured during enrollment in the central laboratory of each study in all participants by measuring the clotting time after adding factor VIII deficient plasma(8–10). In the nested case-control study, Factors IX and XI were measured by ELISA (Enzyme Research Laboratories, South Bend, ID) and D-dimer by automated immunoturbidometric assay (STA-R instrument, Liatest D-Di, Stagnostica Stago, Parsippany, NJ). Factor V Leiden and prothrombin 20210A were detected using standard techniques among 98.3% of participants in the case-control subset who consented to genetic testing(11).

Statistical Analysis

Twenty participants on warfarin at baseline were excluded. For analysis, TFPI was divided into quartiles (based on the distribution in controls) or dichotomized at the 5th or 10th percentile of values based on the distribution in controls(12). Mean values or prevalences of thrombosis risk factors at baseline according to TFPI quartiles were compared using analysis of variance for continuous variables and χ^2 analysis for dichotomous variables. P-values for trend were calculated as the linear trend across the TFPI quartiles. Unconditional logistic regression models were used to study the association of TFPI and VTE. The reference quartile was quartile 4 (highest TFPI values). Model 1 was adjusted for age, sex, race, and study. Model 2 (co-morbid conditions model) adjusted for variables in Model 1 and for baseline diabetes mellitus (fasting plasma blood glucose ≥ 126 mg/dL, physician diagnosis of diabetes, or taking medications for diabetes), obesity (body mass index $> 30\text{kg/m}^2$), and coronary heart disease (CHD). Model 3 (coagulation factor-adjusted model) included variables in Model 1 and factors VII, VIII, IX, and XI as continuous variables. An additional model (Model 4) added obesity and D-dimer (a marker of coagulation activation) to model 3 to study if any association of TFPI with VTE was dependent on coagulation activation.

We evaluated for greater than additive interactions of VTE risk factors using age, sex, and race-adjusted models by cross-classifying participants on the basis of TFPI above or below the 5th percentile and elevated factor VII (top 5%)(13), factor VIII (top 25%)(14), factor IX (top 10%)(15), factor XI (top 10%)(16) and D-dimer ($>\text{median}$)(17), factor V Leiden (present or absent), prothrombin 20210A (present or absent), and obesity ($\text{BMI} > 30\text{kg/m}^2$) using established cut-off values from other investigations. For each risk factor, the relative excess risk proportion over what would be seen in an additive model of two risk factors alone was calculated(18).

Sensitivity analyses were run excluding participants with prebaseline VTE, using exogenous estrogens at the time of phlebotomy, and by VTE type (idiopathic versus provoked).

Given 534 events with a case-to-control ratio of 1:2 and a α of 0.05, we had 80% power to detect an OR of 1.81 for the most extreme 5% of TFPI values (versus the remaining 95%) or an OR of 1.39 for the most extreme quartile (versus the remaining 75%).

Results

During a maximum of 16 years of follow-up in ARIC (median = 11.5 years) and a maximum of 14 years in CHS (median = 9.0), there were 534 VTEs validated, 457 of which had TFPI values available (missing values were due to unavailability of suitable blood samples in the biorepository and exclusion of warfarin users). 194 VTE were idiopathic, 311 were deep venous thrombosis (DVT) only, and 146 were DVT and/or pulmonary embolism (PE). Mean (standard deviation) TFPI levels were 36.4 (12.8) ng/mL for people who developed VTE and 35.0 (11.1) ng/mL for controls, with no evidence of a skewed distribution (Figure 1). Increasing age, male sex, BMI, diabetes mellitus, coronary heart disease and higher levels of factors VII,

VIII, IX, XI, D-dimer were associated with higher TFPI levels (Table 1). TFPI levels did not differ by race, factor V Leiden, or prothrombin 20210A.

The association of quartiles of TFPI and the lowest 5% and 10% of TFPI values with VTE were evaluated in a series of sequentially adjusted logistic regression models (Table 2). The odds of VTE did not differ from 1.0 for the lowest quartile (<27.4 ng/mL) versus the highest quartile (>42.0 ng/mL) or lowest decile (<22.2 ng/mL) versus all higher values in any model. Compared with the upper 95%, the lowest 5% (<18.8 ng/mL) had increased odds of VTE in demographic (Model 1) and co-morbid-condition (Model 2) adjusted models, with ORs of 1.35 (95% CI 0.86, 2.12) and 1.45 (0.91, 2.31) respectively. After adjusting for coagulation factors VII, VIII, IX, and XI (Model 3), the bottom 5% of TFPI was associated with increased VTE risk (OR 1.93, 95% CI 1.05, 3.53). After further adjustment for BMI and D-dimer (Model 4), the magnitude of the association of TFPI with VTE weakened slightly (OR 1.70; 95% CI 0.98, 2.93).

In models adjusted for age, sex, race, and study, no additive interactions were observed between TFPI in the bottom 5% and elevated factors VII, VIII, IX XI or D-dimer, factor V Leiden, or prothrombin 20210A (all $p > 0.05$).

Sensitivity analyses were conducted excluding individuals who self-reported a pre-baseline history of VTE (57 cases, 30 controls), women taking postmenopausal estrogen at baseline (32 cases, 86 controls), and stratifying by median time to VTE (≤ 8 years and > 8 years). Results of these analyses were similar to those above (data not shown).

Discussion

Total TFPI levels were greater with higher values of many VTE risk factors (age, BMI, factors VII, VIII, IX, XI, and D-dimer). In this prospective population-based study, very low levels of total TFPI were associated with increased risk of VTE. There was no evidence of greater than additive interactions of low ($<5\%$ normal) total TFPI with factors VII, VIII, IX, XI, obesity, or genetic VTE risk factors.

A key finding here was the positive association of TFPI levels with levels of procoagulant factors (factors VII, VIII, IX, and XI) and D-dimer. This is similar to results from LETS where there was a positive correlation between total TFPI and coagulation factors II, V, VIII, IX, X, and XI(12). The positive association between TFPI and many procoagulant factors seen here and in the LETS could suggest a physiologic feedback loop where high levels of procoagulants are countered in vivo by high levels of coagulation inhibitors. Alternatively, there could be common regulation of transcription of multiple coagulation factors including TFPI.

Prior investigations reported that low free TFPI antigen is a risk factor for recurrent VTE(4), that low total TFPI is a risk factor for VTE in children(19), and that low total and free TFPI antigen are risk factors for VTE in adults(12,20). In contrast to other studies, our data are the first where TFPI levels were measured before VTE occurrence and where multivariable models explored the impact of adjustment for other coagulation factors and D-dimer(21).

Our results differed from the results published in LETS(12), in that we saw no association between low TFPI and VTE in our demographic-adjusted models. Further, the magnitude of the association was less than that observed in LETS; in LITE the demographic-adjusted VTE OR for the bottom 5% versus upper 95% of TFPI levels was 1.35 and this was 2.1 (95% CI 1.1 – 4.1) in LETS(12). There are several possible explanations for differences between the findings of our study and LETS. First, LETS had a large number of women with thrombosis associated with oral estrogens (127 of 473 VTE events) with fewer in the control group. Estrogen (both oral contraception and hormone replacement therapy) substantially lowers total

TFPI antigen levels(12,22). Women with low-normal levels of TFPI may be at greater risk of estrogen-induced VTE thus enhancing the association seen between TFPI and VTE in LETS. In addition, it is possible that treatment for VTE or the sequelae of VTE may increase TFPI levels, explaining the stronger association seen in LETS.

Several issues must be addressed to put our results in context. First, though LITE is a large, multicenter prospective cohort study which followed 21,680 individuals over 12 years, VTE was relatively rare with only 534 documented events. As presented in the methods section, our power to detect modest effects was limited for some analyses (such as when the risk factor is rare, i.e. the bottom 5% of the distribution). Second, there are several TFPI assays (activity, free (unbound) TFPI, and total TFPI), and we measured total TFPI. Based on LETS, (3,12) which measured total TFPI, free TFPI, and TFPI activity we do not expect our results would differ by measuring free TFPI or TFPI activity. Third, as we only saw associations at very low levels of TFPI (<5%), we had insufficient power for subgroup analyses based on type of VTE (PE versus DVT), race, or for provoked versus unprovoked VTE. Another limitation is that, although uniform for most studies, TFPI was measured only once and often years prior to the VTE event and so we cannot account for either short-term or long-term variability in TFPI levels over time. Short-term and long-term variability in TFPI levels, however, would bias our results towards the null.

In summary, total TFPI was higher in those with higher procoagulant factor levels and with increasing age. Individuals with TFPI levels below the 5th percentile (<18.8ng/mL) were at moderately increased risk of VTE after adjusting for procoagulant factor levels. These results suggest that while measuring total TFPI in patients at risk for VTE does not seem warranted, further investigation of the epidemiology of low TFPI (both inherited and acquired) as a risk factor for VTE is needed.

Acknowledgments

We are grateful to the investigators, staff and participants of the Atherosclerosis Risk in Communities Study (<http://www.csc.unc.edu/aric>) and the Cardiovascular Health Study (<http://www.chs-nhlbi.org>). ARIC is supported by contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC 55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, with additional support from R01-HL-59367, all from the National Heart, Lung, and Blood Institute, Bethesda, MD. CHS is supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129 and N01-HC-15103 and research project grant R01HL054711 from the National Heart, Lung, and Blood Institute, Bethesda, MD. LITE is supported by a grant from the National Heart, Lung, and Blood Institute (R01 HL59367).

Grant Support: ARIC is supported by contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC 55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, with additional support from R01-HL-59367, all from the National Heart, Lung, and Blood Institute, Bethesda, MD. CHS is supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129 and N01-HC-15103 and research project grant R01HL054711 from the National Heart, Lung, and Blood Institute, Bethesda, MD. LITE is supported by a grant from the National Heart, Lung, and Blood Institute (R01 HL59367).

References

1. Lindahl AK. Tissue factor pathway inhibitor: a potent inhibitor of in-vitro coagulation and in-vivo thrombus formation. *Curr Opin Lipidol* Dec;1994 5(6):434–9. [PubMed: 7712048]
2. Holst J, Lindblad B, Bergqvist D, et al. Antithrombotic effect of recombinant truncated tissue factor pathway inhibitor (TFPI1-161) in experimental venous thrombosis--a comparison with low molecular weight heparin. *Thromb Haemost* Feb;1994 71(2):214–9. [PubMed: 8191401]
3. Dahm A, Rosendaal FR, Andersen TO, et al. Tissue factor pathway inhibitor anticoagulant activity: risk for venous thrombosis and effect of hormonal state. *Br J Haematol* Feb;2006 132(3):333–8. [PubMed: 16409298]
4. Hoke M, Kyrle PA, Minar E, et al. Tissue factor pathway inhibitor and the risk of recurrent venous thromboembolism. *Thromb Haemost* Oct;2005 94(4):787–90. [PubMed: 16270631]

5. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the Longitudinal Investigation of Thromboembolism Etiology. *Am J Med* Jul 1;2004 117(1):19–25. [PubMed: 15210384]
6. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives; The ARIC investigators. *Am J Epidemiol* Apr;1989 129(4):687–702. [PubMed: 2646917]
7. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* Feb;1991 1(3):263–76. [PubMed: 1669507]
8. Tsai AW, Cushman M, Rosamond WD, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Med* Dec 1;2002 113(8):636–42. see comment. [PubMed: 12505113]
9. Chambless LE, McMahon R, Wu K, et al. Short-term intraindividual variability in hemostasis factors. The ARIC Study. Atherosclerosis Risk in Communities Intraindividual Variability Study. *Ann Epidemiol* Sep;1992 2(5):723–33. [PubMed: 1342324]
10. Folsom AR, Wu KK, Rosamond WD, et al. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* Aug 19;1997 96(4):1102–8. [PubMed: 9286936]
11. Cushman M, Folsom AR, Wang L, et al. Fibrin fragment D-dimer and the risk of future venous thrombosis. *Blood* Feb 15;2003 101(4):1243–8. see comment. [PubMed: 12393393]
12. Dahm A, Van Hylckama Vlieg A, Bendz B, et al. Low levels of tissue factor pathway inhibitor (TFPI) increase the risk of venous thrombosis. *Blood* Jun 1;2003 101(11):4387–92. [PubMed: 12560220]
13. Koster T, Rosendaal FR, Reitsma PH, et al. Factor VII and fibrinogen levels as risk factors for venous thrombosis. A case-control study of plasma levels and DNA polymorphisms--the Leiden Thrombophilia Study (LETS). *Thromb Haemost* Jun;1994 71(6):719–22. [PubMed: 7974338]
14. Koster T, Blann AD, Briet E, et al. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* Jan 21;1995 345(8943):152–5. [PubMed: 7823669]
15. van Hylckama Vlieg A, van der Linden IK, Bertina RM, et al. High levels of factor IX increase the risk of venous thrombosis. *Blood* Jun 15;2000 95(12):3678–82. [PubMed: 10845896]
16. Meijers JC, Tekelenburg WL, Bouma BN, et al. High levels of coagulation factor XI as a risk factor for venous thrombosis. *The New England journal of medicine* Mar 9;2000 342(10):696–701. [PubMed: 10706899]
17. Zakai NA, Ohira T, White R, et al. Activated partial thromboplastin time and risk of future venous thromboembolism. *The American journal of medicine* Mar;2008 121(3):231–8. [PubMed: 18328308]
18. Knol MJ, van der Tweel I, Grobbee DE, et al. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International journal of epidemiology* Oct; 2007 36(5):1111–8. [PubMed: 17726040]
19. Duering C, Kosch A, Langer C, et al. Total tissue factor pathway inhibitor is an independent risk factor for symptomatic paediatric venous thromboembolism and stroke. *Thromb Haemost* Oct;2004 92(4):707–12. [PubMed: 15467899]
20. Amini-Nekoo A, Futers TS, Moia M, et al. Analysis of the tissue factor pathway inhibitor gene and antigen levels in relation to venous thrombosis. *Br J Haematol* May;2001 113(2):537–43. [PubMed: 11380428]
21. Andreescu AC, Cushman M, Rosendaal FR. D-dimer as a risk factor for deep vein thrombosis: the Leiden Thrombophilia Study. *Thromb Haemost* Jan;2002 87(1):47–51. [PubMed: 11858188]
22. Hoibraaten E, Qvigstad E, Andersen TO, et al. The effects of hormone replacement therapy (HRT) on hemostatic variables in women with previous venous thromboembolism--results from a randomized, double-blind, clinical trial. *Thromb Haemost* May;2001 85(5):775–81. [PubMed: 11372667]

Figure 1.
Histogram of Total Tissue Factor Pathway Inhibitor Values (ng/mL) by Subsequent Case or Control Status, LITE

Table 1

VTE Risk Factor Levels by Total TFPI Quartiles, LITE

	Quartiles (Controls Only)				p for trend
	1	2	3	4	
N	262	271	265	237	
TFPI (ng/mL, range)	22.3 (7.1, 27.4)	30.9 (27.5, 34.0)	37.5 (34.1, 41.9)	51 (42.0, 91.5)	
Demographics					
Age (years, SD)	59.9 (9.9)	62.2 (10.1)	63.6 (9.8)	64.0 (9.9)	<0.001
Black Race (n, %)*	94 (25)	110 (29)	96 (26)	100 (27)	0.56
Female Sex (n, %)*	246 (66)	200 (54)	198 (53)	197 (53)	0.003
Physiologic Characteristics					
BMI (SD)	27.3 (4.9)	28.0 (4.9)	28.6 (6.0)	27.9 (5.1)	0.05
Diabetes (n, %)*	30 (8)	43 (12)	63 (17)	60 (16)	0.01
Coronary Heart Disease (n, %)	16 (4)	42 (11)	37 (10)	33 (9)	0.004
Genetic Risk Factors					
Factor V Leiden (n, %)*	21 (6)	17 (5)	20 (6)	15 (4)	0.71
Prothrombin 20210A (n, %)*	8 (2)	9 (2)	7 (2)	10 (3)	0.89
Biomarkers					
Factor VII (% , SD)	120 (30)	116 (27)	123 (29)	125 (28)	<0.001
Factor VIII (% , SD)	124 (36)	131 (38)	135 (43)	138 (47)	<0.001
Factor IX (% , SD)	136 (31)	141 (30)	147 (31)	155 (31)	<0.001
Factor XI (% SD)	126 (32)	128 (33)	135 (35)	144 (34)	<0.001
D-dimer (ug/mL, SD)	0.51 (0.53)	0.51 (0.43)	0.61 (0.53)	0.65 (0.58)	<0.001

* p-value for χ^2 test, other p-values from ANOVA

Table 2

Adjusted Odds Ratios of VTE by Total TFPI Quartiles, LITE*

	TFPI Quartiles (OR 95% CI)				P for trend	Lowest 5% TFPI < 18.8 ng/mL	Lowest 10% TFPI < 22.2 ng/mL
	1	2	3	4			
Cases (n)	111	102	108	136		32	48
Controls (n)	262	271	265	237		56	115
Model 1	0.75 (0.55, 1.03)	0.66 (0.48, 0.90)	0.71 (0.52, 0.97)	1.00 (Ref)	0.06	1.35 (0.86, 2.12)	0.96 (0.67, 1.38)
Model 2	0.82 (0.59, 1.13)	0.67 (0.49, 0.92)	0.67 (0.49, 0.92)	1.00 (Ref)	0.20	1.45 (0.91, 2.31)	1.02 (0.70, 1.48)
Model 3	1.00 (0.71, 1.41)	0.81 (0.58, 1.14)	0.79 (0.57, 1.11)	1.00 (Ref)	0.21	1.93 (1.05, 3.53)	1.15 (0.72, 1.86)
Model 4	0.96 (0.66, 1.38)	0.79 (0.55, 1.13)	0.74 (0.52, 1.06)	1.00 (Ref)	0.87	1.70 (0.98, 2.93)	1.16 (0.76, 1.78)

Model 1: age, sex, race (CHS, ARIC)

Model 2: Model 1, obesity (BMI>30kg/m²), diabetes mellitus (yes, no), coronary heart disease (yes, no)

Model 3: Model 1, factors VII, VIII, IX, and XI (continuous)

Model 4: Model 1, obesity (BMI>30kg/m²), factors VII, VIII, IX, XI, D-dimer (continuous)

Table 3

Clinical Summary

Clinical Summary	
What is known in this topic:	
■	Low TFPI levels are a risk factor for recurrent VTE
■	Low TFPI levels measured after VTE are a risk factor for VTE
What this paper adds:	
■	Accounting for other VTE risks, low TFPI levels are a prospective risk factor for VTE
■	There is no synergy with TFPI and other common genetic risk factors