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## Prospective study of circulating factor XI and incident venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE)

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### Abstract

Elevated plasma concentrations of coagulation factor XI may increase risk of venous thromboembolism (VTE), but prospective data are limited. We studied prospectively the associations of plasma factor XI and a key *F11* genetic variant with incident VTE in whites and African Americans. We measured factor XI in 16,299 participants, initially free of VTE, in two prospective population cohorts. We also measured the *F11* single nucleotide polymorphism rs4241824, which a genome-wide association study had linked to factor XI concentration. During follow-up, we identified 606 VTEs. The age, race, sex, and study-adjusted hazard ratio of VTE increased across factor XI quintiles ( $p < 0.001$  for trend), and the hazard ratio was 1.51 (95% CI 1.16, 1.97) for the highest versus lowest quintile overall, and was 1.42 (95% CI 1.03, 1.95) in whites and 1.72 (95% CI 1.08, 2.73) in African Americans. In whites, the *F11* variant was associated with both factor XI concentration and VTE incidence (1.15-fold greater incidence of VTE per risk allele). In African Americans, these associations were absent. In conclusion, this cohort study documented that an elevated plasma factor XI concentration is a risk factor for VTE over extended follow-up, not only in whites but also in African Americans. In whites, the association of the *F11* genetic variant with VTE suggests a causal relation, but we did not observe this genetic relation in African Americans.

### Keywords

deep vein thrombosis; factor XI; prospective study; pulmonary embolism

## Introduction

The balance between the endogenous procoagulant and anticoagulant systems contributes to the etiologies of venous thromboembolism (VTE), that is, venous thrombosis (DVT) and pulmonary embolism (PE). On the procoagulant side, a few studies have reported that elevated circulating intrinsic coagulation factor XI concentrations may increase VTE risk [1, 2], but prospective data are limited. In a small prospective nested-case control study in the Longitudinal Investigation of Thromboembolism Etiology (LITE), we reported that the incidence of VTE was 1.8 fold higher (95% CI, 1.3–2.7) for participants in the fifth compared with the first quintile of factor XI [3]. Another study reported that patients with severe factor XI deficiency have reduced incidence of VTE [4]. Moreover, a clinical trial showed that inhibition of factor XI prevents post-surgical VTEs [5].

Supporting a potential etiologic role for factor XI, two [6, 7] of four [6–9] genome-wide association studies (GWAS) in whites and some candidate-gene studies [10–13] have linked SNPs in the structural *F11* gene to VTE risk in whites or blacks [12]. Our GWAS for VTE found the top SNP was rs4253399 [6], which is in high linkage disequilibrium (LD) with other *F11* variants linked to VTE, namely, rs3756008, rs2036914, and rs2289252. These latter three SNPs have been associated with factor XI concentrations, and adjustment for factor XI concentrations attenuated the SNP associations with VTE [10, 13]. A separate GWAS of plasma factor XI levels in individuals of European ancestry recently identified and replicated two SNPs significantly associated with factor XI: rs710446 in the *kininogen 1* (*KNG1*) gene and rs4241824 in *F11* [14]. According to 1000 Genomes, phase 1 data, *F11* rs4241824 and rs4253399 are moderately correlated in individuals of European ancestry (CEU,  $r^2 = 0.60$ ) but virtually uncorrelated in Americans of African ancestry (ASW,  $r^2 = 0.09$ ). In summary, prior research suggests an underlying *F11* or *KNG1* locus might increase risk of VTE by elevating factor XI.

Because *F11* was important in our VTE GWAS, we recently expanded factor XI measurement to the entire LITE study population in order to examine the associations between factor XI concentration and VTE occurrence. We also explored whether VTE is associated with the top *F11* SNP (rs4241824) related to factor XI concentration [14].

## Methods

### Study population

The Longitudinal Investigation of Thromboembolism Etiology (LITE) study is a prospective study of VTE occurrence in 2 pooled, multi-center, longitudinal population-based cohort studies: the Atherosclerosis Risk in Communities (ARIC) Study [15] and the Cardiovascular Health Study (CHS) [16]. We reported the LITE study design, methods, and VTE incidence rates in detail elsewhere [17, 18]. In brief, 15,792 men and women aged 45 to 64 years enrolled in the ARIC study in 1987–1989, and had subsequent examinations in 1990–92, 1993–95, 1996–98, and 2011–13, with annual telephone contact in between. In CHS, 5,201 men and women aged 65 years enrolled in 1989–1990. CHS recruited an additional 687 African Americans using similar methods in 1992–1993. CHS contacted participants every six months for follow-up, alternating between a telephone interview and clinic visit for the

first 10 years and by telephone interview only after that. The institutional review committees at each study center approved the methods and staff obtained informed participant consent.

### **Factor XI plasma measurements and F11 genotyping**

ARIC and CHS exhausted most baseline citrated plasma previously; therefore we measured Factor XI concentrations on fasting citrate plasma that had been collected at ARIC in 1993–95 (6 years after baseline) and CHS in 1992–93 (3 years after baseline for the original cohort and at baseline for the African American cohort) and stored unfrozen at  $-70^{\circ}\text{C}$  until analysis in 2014. The Laboratory for Clinical Biochemistry Research at the University of Vermont assayed factor XI by sandwich ELISA with affinity-purified polyclonal antibodies from Affinity Biologicals (Ancaster, Ontario, CAN). The coefficient of variation for control samples during this study averaged 9.6%. Blind analysis of 74 pairs of ARIC samples split at the time of blood draw and stored until 2014 yielded a coefficient of variation of 10.8% and an intra-class reliability coefficient of 0.81.

Each study performed genotyping using the IBC genotyping array [19], from which we obtained information on *F11* SNP rs4241824, the *F11* SNP most strongly associated with FXI concentration in whites [14]. The rs4241824 call rate was 98% in both whites and African Americans, and it was in Hardy-Weinberg equilibrium for both groups. Blind analysis of 196 pairs of ARIC samples split and genotyped separately yielded >99% agreement on rs4241824. In order to control for population stratification in African Americans, we used exome chip data [20] to derive ten principal components of ancestry using EIGENSTRAT [21].

### **Measurement of risk factors**

We analyzed risk factors measured at the ARIC or CHS visits in which factor XI was measured. We calculated body mass index as weight (kg)/height (m)<sup>2</sup>. We defined diabetes as a fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks.

### **VTE occurrence**

Staff contacted ARIC and CHS participants annually or semi-annually by phone and asked about all hospitalizations in the previous year. They retrieved hospital records for possible VTE events through 2011 in ARIC and through 2001 in CHS. To validate VTE events, two physicians reviewed the records using standardized criteria [17], requiring positive imaging tests for diagnosis of DVT and PE. We restricted DVTs for this analysis to those in the lower extremity or vena cava, because upper extremity DVTs were relatively few and almost always the result of venous catheters. The reviewers sub-classified VTEs as unprovoked (no obvious cause) or provoked (associated with cancer, major trauma, surgery, marked immobility).

### **Statistical analysis**

Of the 12,887 ARIC and 5,265 CHS participants who attended the relevant exam, we excluded those not white or African American ( $n = 38$  ARIC, 34 CHS), those with a VTE

prior to the blood draw (n = 302 ARIC, 323 CHS), those taking anticoagulants (n = 124 ARIC, 107 CHS), those without citrate plasma specimens or factor XI measurements (n = 299 ARIC, 624 CHS), and those with no further follow-up (n = 2 ARIC). This left a maximum of 16,299 participants (12,122 in ARIC and 4,177 in CHS) for the present analyses. Time at risk for VTE was computed from the date of biomarker measurement to the earliest of the following: date of hospital admission for incident VTE, date of death, date of last follow-up contact, or end of follow-up.

Our main hypothesis was that factor XI concentration is associated positively with VTE incidence. We used Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence intervals of incident VTE. For analyses, factor XI was analyzed as quintiles of the entire sample or a continuous variable. We ran analyses separately for ARIC and CHS and pooled them only after verifying associations appeared similar for both studies. We performed a test for trend in VTE occurrence across factor XI quintiles using the median factor XI value to represent each quintile. We verified the proportional hazards assumption of the Cox models by testing an interaction of factor XI with log follow-up time. Model 1 associating factor XI with VTE included adjustment for age (continuous), sex, race, and study (ARIC, CHS); Model 2 adjusted additionally for characteristics previously associated with VTE in this cohort: diabetes status (yes or no) and body mass index.

In ARIC, we also examined the race-specific associations of the *F11* SNP rs4241824 with VTE. Of the ARIC sample (n = 12,122), 11,411 gave permission for DNA use and had rs4241824 data. For each participant, we coded the SNP as having 0, 1, or 2 risk alleles and used an additive genetic model. For the analysis in African Americans, we also adjusted for ten principal components of ancestry.

## Results

Among the 16,299 participants initially free of VTE, the distribution of plasma factor XI concentration was normal and similar for the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS). As shown in Table I, the proportions who were African American, women, or had diabetes increased across quintiles of factor XI, as did mean body mass index.

Over a median of 17 years of follow-up in ARIC and 9 years in CHS, we identified 606 (n = 523 ARIC, 83 CHS) DVTs of the lower extremity or PE. The incidence rates of VTE per 1,000 person-years rose similarly across factor XI quintiles in ARIC (2.5, 2.5, 2.8, 3.0, and 3.4) and CHS (1.7, 2.7, 2.2, 2.8, and 3.5). The hazard ratios of VTE increased steadily across factor XI concentration in both studies, without evidence that VTE risk was limited to the highest concentrations (Figure 1). We pooled ARIC and CHS for the remaining analyses.

Overall, the age, race, sex, and study-adjusted hazard ratios of VTE (Model 1) increased across factor XI quintiles (p<0.001 for trend), and the hazard ratio was 1.51 (95% CI 1.16, 1.97) for the highest versus lowest quintile (Table II). Additional adjustment for diabetes and BMI weakened the association (p = 0.007 for trend). The association between factor XI and VTE appeared somewhat stronger for unprovoked than provoked VTE, for PE than

DVT, and in African Americans than whites, although the race by factor XI interaction was nonsignificant ( $p = 0.31$ ).

To further verify the role of factor XI in VTE, we examined the association with the *F11* SNP rs4241824 in ARIC. The frequencies of having 0, 1, or 2 copies of the A risk allele were 25%, 50%, and 25% in whites and 15%, 46%, and 39% in African Americans. For 0, 1, or 2 copies, the mean factor XI values were 106%, 112%, and 119% in whites ( $p$  for difference  $<0.0001$ ), and the variant explained a small amount of factor XI variation ( $r^2 = 0.036$ ). For 0, 1, or 2 copies, in African Americans, factor XI values varied little: means were 115%, 116%, and 118% ( $p$  for difference = 0.20, and  $r^2 = 0.001$ ). Table III shows that participants with AA status had 1.33-fold higher VTE risk than GG, among whites, but there was no relation to VTE in African Americans.

In Model 2 for VTE incidence, each risk allele copy for this SNP was associated with a 1.15-fold (95% CI 0.99, 1.34) greater hazard of VTE in ARIC whites, but this estimate was 0.87 (95% CI 0.70, 1.09) in African Americans. These hazard ratios changed very little when adjusted for continuous plasma factor XI concentration: 1.14 (95% CI 0.98, 1.34) in whites and 0.87 (95% CI 0.69, 1.09) in African Americans. In contrast, adjusted for rs4241824, the Model 2 hazard ratios for VTE per SD of factor XI concentration in ARIC were 1.03 (95% CI 0.91, 1.16) in whites and 1.09 (95% CI 0.95, 1.26) in African Americans, which are considerably attenuated from the race-specific hazard ratios of 1.07 for whites and 1.15 for African Americans in Table II.

## Discussion

This large prospective study involving two cohorts showed that a higher plasma concentration of factor XI was associated with modestly increased risk of VTE. The association was stronger for unprovoked than provoked VTE, for PE than DVT, and for African Americans than whites. In ARIC whites, risk alleles for *F11* SNP rs4241824 were also associated with greater factor XI concentration and greater VTE incidence; yet, plasma factor XI concentration explained little of the SNP association with VTE. In ARIC African Americans, this *F11* SNP was associated weakly with plasma factor XI and not associated with VTE risk.

Our previous publication from LITE included factor XI measured on plasma samples from 1987–89 in ARIC and from 1989–90 in CHS (with a few from 1992–93). It included 462 VTEs occurring from 1987 through 2002 in ARIC and 1989 through 2002 in CHS and 1047 participants who remained free of VTE [3]. In contrast, the present study measured plasma factor XI from 1993–95 in ARIC and from 1992–93 in CHS and had 606 incident VTEs, most of which overlapped with those analyzed previously for CHS but few overlapped for ARIC, as ARIC follow-up now went through 2011. The hazard ratios were similar to those we reported previously [3]. With more VTE events, we now were able to confirm that plasma factor XI is a VTE risk factor in African Americans. Previous case-control studies are consistent with plasma factor XI being a VTE risk factor in whites [1, 2] and African Americans [12]. Factor XI has an important role in propagation and stabilization of thrombi [22], and humans with severe factor XI deficiency have reduced incidence of VTE [4].

To support a potential causal association between higher factor XI and VTE, studies in whites have shown that several correlated *F11* SNPs are associated with plasma factor XI and VTE in a parallel fashion [6–14]. A recent GWAS found *F11* rs4241824 and a *KNG1* SNP to be the top SNPs associated with factor XI concentration and they were also associated with activated partial thromboplastin time [14]. We chose to study *F11* rs4241824 as our instrumental variable for factor XI because of concerns that *KNG1* may affect thrombosis by other pathways besides factor XI. *F11* rs4241824 proved to be associated with VTE in ARIC whites. Yet, somewhat surprisingly, in statistical models plasma factor XI did not at all explain the SNP association with VTE in whites. Conversely, the SNP statistically explained a moderate degree of the association between plasma factor XI and VTE. We have no clear explanation for these observations from statistical modeling, but perhaps the SNP may act in ways other than increasing factor XI antigen, such as influencing factor XI activity or by interacting with other coagulation factors. While rs4241824 is located in an intron of *F11*, it seems to have a role in altering regulatory motifs of other genes according to HaploReg v2 [23], an online annotation of functional non-coding sequences. Additionally, this SNP is in high LD ( $r^2 = 0.9$ ) with another *F11* SNP rs3822057 that may influence promoter histone marks, regulatory motifs, and regulatory protein binding. Regardless, both factor XI concentration and *F11* were associated with VTE in whites.

In ARIC African Americans, despite the positive association between factor XI concentration and VTE, *F11* rs4241824 was unassociated with both factor XI and VTE. Thus, rs4241824 may be a poor instrumental variable for factor XI in African Americans or nongenetic factors may explain their association of factor XI with VTE. A previous case-control study found a different *F11* SNP, rs2036914, associated with VTE but not factor XI concentration in African Americans [12]. In a supplemental analysis (not shown), we found the race-specific associations of rs2036914 with factor XI concentrations and VTE to mirror almost identically those for rs4241824. This is not surprising given rs2036914 was highly correlated with rs4241824 in both African Americans ( $r^2 = 0.60$ ) and whites ( $r^2 = 0.88$ ). Yet, our finding is not in accord with the only previous study of African Americans [12], and so the degree to which *F11* variation determines factor XI levels and VTE in African Americans remains uncertain.

Some potential limitations of our study warrant consideration. Firstly, we measured factor XI on plasma samples that had been stored for approximately 20 years at  $-70^{\circ}\text{C}$ . Previous evidence suggests that factor XI is stable in samples frozen for up to 18 months [24]. Any sample deterioration likely would have weakened the estimated association between factor XI and VTE. Secondly, factor XI was studied at only one ARIC visit. Factor XI concentrations may have fluctuated during the long follow-up, and such fluctuations would tend to weaken the observed association with VTE. Thirdly, we could not determine whether factor XI was associated with VTE independently from other hemostatic factors, since they were measured at different study visits. Fourthly, we identified hospitalized VTE patients only, but pilot data suggest the vast majority of patients with first VTEs in ARIC and CHS were hospitalized.

We used a factor XI antigen assay. It is likely correlated with factor XI activity assays typically used to detect factor XI deficiency in clinical practice, but we do not know the actual correlation. We hesitate to translate our measurements to those in clinical practice or to suggest that there are current implications of our analysis to clinical practice.

In conclusion, this cohort study documented that a higher plasma factor XI concentration is a risk factor for VTE over extended follow-up, not only in whites but also in African Americans. In whites, an association of a *F11* genetic variant with VTE suggests a causal relation, but we did not observe this genetic relation in African Americans. Clinical trial evidence that inhibition of factor XI can prevent VTE further supports its role in VTE etiology [5].

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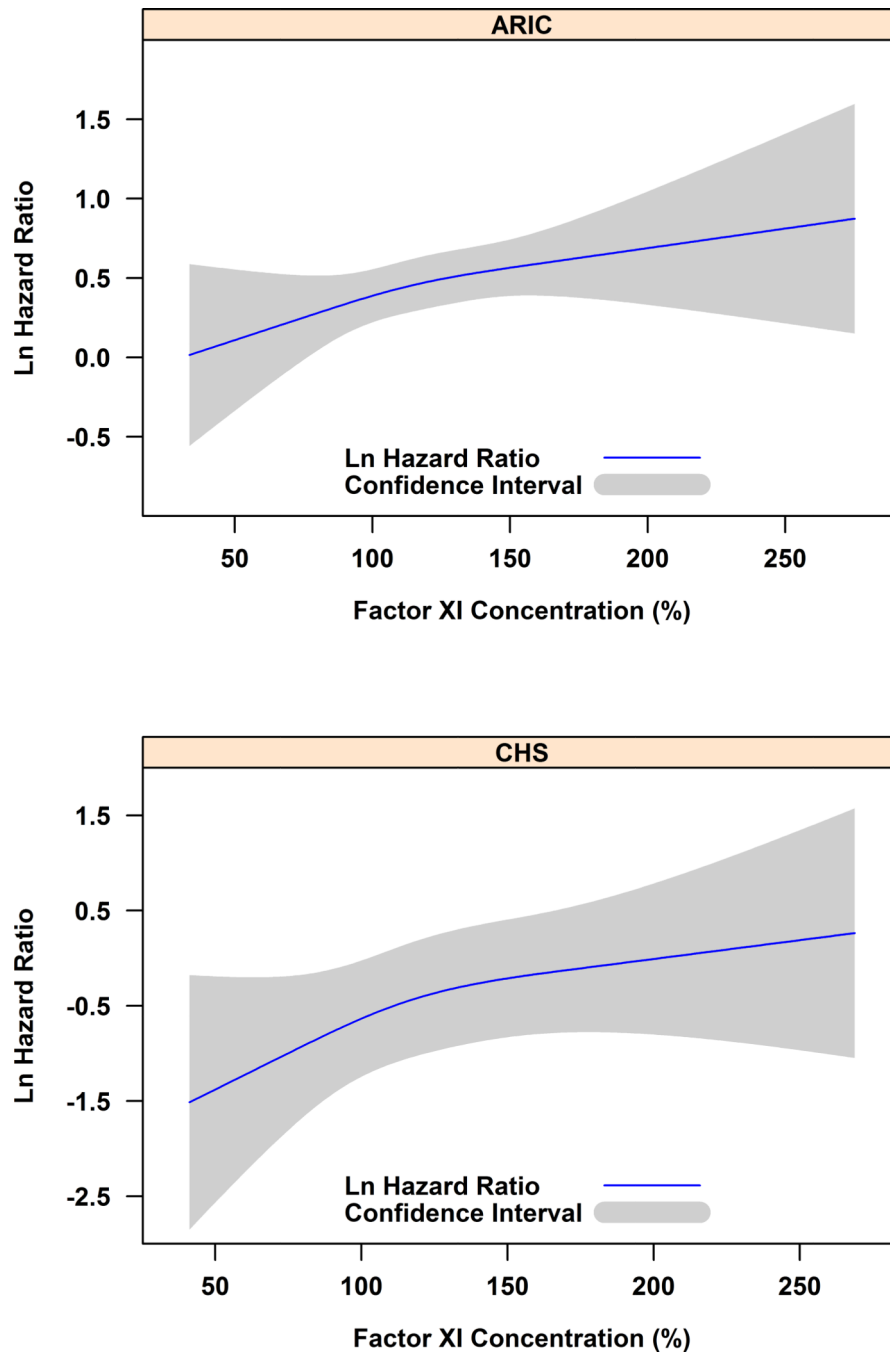
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**Figure 1.** Logarithm hazard ratio of venous thromboembolism in relation to factor XI concentration\*, ARIC and CHS.

\* Analyzed by restricted cubic splines with knots at the fifth, fiftieth, and ninety-fifth percentiles of the study-specific factor XI distribution.

Table 1

Participant Characteristics [Mean  $\pm$  SD or %] in Relation to Quintiles of Factor XI, ARIC, 1993–1995; CHS, 1992–1993

Characteristic	Quintile of Factor XI (%)				
	8.0–92.2	92.2–105.1	105.1–117.3	117.3–133.4	133.4–400.0
Pooled					
N	3,259	3,260	3,260	3,261	3,259
Age, years	64.4 (8.7)	63.1 (8.3)	63.2 (8.2)	63.1 (8.1)	64.0 (8.2)
African American	19%	20%	21%	23%	25%
Women	39%	49%	56%	64%	72%
Diabetes	11%	12%	14%	16%	24%
BMI, kg/m <sup>2</sup>	27.2 (5.0)	27.6 (4.9)	28.1 (5.6)	28.3 (5.4)	28.9 (5.6)
ARIC					
N	2,390	2,526	2,484	2,461	2,261
Age, years	60.4 (5.9)	59.8 (5.7)	59.8 (5.7)	59.7 (5.6)	59.9 (5.6)
African American	21%	21%	22%	25%	28%
Women	39%	48%	55%	64%	72%
Diabetes	10%	12%	13%	17%	25%
BMI, kg/m <sup>2</sup>	27.6 (5.2)	27.9 (5.0)	28.5 (5.8)	28.8 (5.5)	29.6 (5.8)
CHS					
N	869	734	776	800	998
Age, years	75.3 (5.4)	74.2 (5.4)	74.1 (5.0)	73.7 (4.9)	73.3 (5.0)
African American	14%	16%	16%	19%	18%
Women	38%	52%	57%	66%	74%
Diabetes	14%	11%	16%	16%	19%
BMI, kg/m <sup>2</sup>	26.1 (4.3)	26.6 (4.7)	26.9 (4.7)	27.0 (4.6)	27.2 (4.9)

**Table II**

Incidence Rates and Hazard Ratios (HRs) of Venous Thromboembolism in Relation to Factor XI, ARIC, 1993–2011, CHS 1992–2001

	Quintile of Factor XI (Ag %)					p-trend	Per 1-SD increment in FXI*	p-value
	8.0–92.2	92.2–105.1	105.1–117.3	117.3–133.4	133.4–400.0			
Pooled								
Total VTE								
N of VTEs	101	113	121	129	142			
Person years	42,040	44,224	44,127	43,713	41,656			
Incidence rate (per 10 <sup>3</sup> py)	2.4	2.6	2.7	3.0	3.4			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.09 (0.83, 1.43)	1.19 (0.91, 1.55)	1.31 (1.00, 1.70)	1.51 (1.16, 1.97)	<0.001		
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.09 (0.83, 1.43)	1.13 (0.86, 1.47)	1.24 (0.95, 1.62)	1.40 (1.07, 1.82)	0.007	1.10 (1.02, 1.19)	0.02
Unprovoked VTE								
N of VTEs	40	45	42	45	57			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.11 (0.73, 1.71)	1.06 (0.69, 1.64)	1.19 (0.77, 1.83)	1.60 (1.05–2.42)	0.02		
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.11 (0.72, 1.70)	0.99 (0.64, 1.54)	1.10 (0.71, 1.70)	1.49 (0.98, 2.26)	0.06	1.15 (1.01, 1.30)	0.03
Provoked VTE								
N of VTEs	61	68	79	84	85			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.08 (0.77, 1.53)	1.27 (0.91, 1.78)	1.39 (0.99, 1.94)	1.48 (1.05, 2.07)	0.009		
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.08 (0.76, 1.53)	1.21 (0.87, 1.70)	1.33 (0.95, 1.86)	1.35 (0.96, 1.90)	0.05	1.07 (0.97, 1.19)	0.19
PE								
N of PEs	43	48	64	73	72			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.07 (0.71, 1.61)	1.42 (0.96, 2.10)	1.66 (1.13, 2.43)	1.72 (1.17, 2.53)	<0.001		
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.06 (0.70, 1.61)	1.32 (0.90, 1.96)	1.54 (1.05, 2.27)	1.58 (1.07, 2.33)	0.006	1.17 (1.05, 1.30)	0.003
DVT								
N of DVTs	58	65	57	56	70			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.12 (0.79, 1.60)	1.01 (0.70, 1.46)	1.05 (0.72, 1.52)	1.38 (0.96, 1.97)	0.11		
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.12 (0.78, 1.60)	0.97 (0.67, 1.40)	1.00 (0.69, 1.46)	1.27 (0.88, 1.82)	0.28	1.03 (0.91, 1.16)	0.65
Total VTE, African Americans								
N of VTEs	29	37	29	41	54			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.15 (0.71, 1.88)	0.91 (0.54, 1.53)	1.27 (0.79, 2.06)	1.72 (1.08, 2.73)	0.01		

	Quintile of Factor XI (Ag %)					p-trend	Per 1-SD increment in FXI*	p-value
	8.0–92.2	92.2–105.1	105.1–117.3	117.3–133.4	133.4–400.0			
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.13 (0.70, 1.84)	0.81 (0.48, 1.36)	1.18 (0.73, 1.91)	1.51 (0.94, 2.42)	0.05	1.15 (1.01, 1.29)	0.03
Total VTE, Whites								
N of VTEs	72	76	92	88	88			
Model 1 HR (95% CI) <sup>†</sup>	1 (Ref.)	1.07 (0.77, 1.47)	1.32 (0.97, 1.80)	1.33 (0.97, 1.82)	1.42 (1.03, 1.95)	0.01		
Model 2 HR (95% CI) <sup>‡</sup>	1 (Ref.)	1.07 (0.77, 1.47)	1.27 (0.93, 1.73)	1.26 (0.92, 1.73)	1.32 (0.96, 1.82)	0.06	1.07 (0.97, 1.19)	0.17

\* FXI standard deviation = 28.2.

<sup>†</sup> Age, race, sex, and study adjusted, except race omitted when stratified.

<sup>‡</sup> Adjusted further for diabetes and BMI.

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**Table III**

Race-Specific Incidence Rate and Hazard Ratio (HR) of Venous Thromboembolism in Relation to *F11* Genotype, ARIC, 1993–2011, CHS, 1992–2001

	rs4241824 Genotype		
	GG	GA	AA
Whites			
N of VTEs	70	152	95
Person years	33,738	67,362	34,343
Adjusted VTE rate*	2.0	2.2	2.7
Adjusted HR (95% CI)	1 (Ref.)	1.09 (0.82, 1.44)	1.33 (0.98, 1.82)
African Americans			
N of VTEs	31	71	59
Person years	5,724	17,754	14,677
Adjusted VTE rate*	5.4	3.8	4.0
Adjusted HR (95% CI)	1 (Ref.)	0.71 (0.46, 1.08)	0.74 (0.48, 1.15)

\* Incidence rate per 10<sup>3</sup> person years, adjusted for age and sex and, in African Americans, for 10 principal components of ancestry.

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