HHS Public Access

Author manuscript

Thromb Res. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Thromb Res. 2015 October ; 136(4): 781–785. doi:10.1016/j.thromres.2015.08.013.

Prospective study of plasma D-dimer and incident venous thromboembolism: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Introduction—Plasma D-dimer is a useful clinical test for acute venous thromboembolism (VTE), and concentrations remain higher in VTE patients after treatment than in controls. Yet, evidence is limited on whether higher basal D-dimer concentrations in the general population are associated with greater risk of first VTE.

Objective—To assess the prospective association between D-dimer and incident VTE over a long follow-up.

Methods—We measured plasma D-dimer in 12,097 participants, initially free of VTE, in the Atherosclerosis Risk in Communities Study. Over a median follow-up of 17 years, we identified 521 VTEs. We calculated hazard ratios of VTE using proportional hazards regression.

Results—The age, race, and sex adjusted hazard ratios of VTE across quintiles of D-dimer were 1, 1.5, 1.8, 2.1, and 3.2 (p for trend <0.0001). For the first 10 years of follow-up, the hazard ratio

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Conflict of Interest Statement

None.

Addendum

All authors contributed to critical revision of the manuscript and approved the final version. In addition, A. R. Folsom contributed to concept and design, classified VTE cases, and drafted the manuscript; A. Alonso helped obtain funding; K. M. George analyzed the data; N. S. Roetker analyzed the data; W. Tang contributed to concept and design; and M. Cushman contributed to concept and design, and classified VTE cases.

for the highest versus lowest quintile was 3.5, and was 2.9 after 10 years. In both whites and African Americans, VTE risk remained strongly associated with D-dimer after further adjustment for diabetes, body mass index, kidney function, and several thrombophilia genetic markers. D-dimer was associated with both unprovoked and provoked VTE, but more strongly with unprovoked.

Conclusions—A higher basal level of plasma D-dimer in the general population, presumably reflecting a predisposition to thrombosis, is a strong, long-term risk factor for a first VTE.

Keywords

Deep vein thrombosis; D-dimer; Prospective studies; Pulmonary embolism; risk factors

Introduction

The plasma concentration of D-dimer, a fibrin degradation product, is an important clinical marker of acute venous thromboembolism (VTE)—i.e., venous thrombosis (DVT) or pulmonary embolism (PE). Basal D-dimer concentrations vary widely in the general population, and higher levels are strongly associated with increased incidence of atherothrombotic conditions, such as coronary heart disease and stroke [1].

To our knowledge, only one prospective population-based study has linked higher basal plasma D-dimer in the general population to increased risk of future VTE: In a small nested case-control study (n=307 incident VTEs and 616 controls), our Longitudinal Investigation of Thromboembolism Etiology (LITE) found that VTE occurrence during follow-up was four-fold higher in the fifth versus first quintile of baseline plasma D-dimer concentrations [2]. The Leiden Thrombophilia Study reported that a D-dimer above the 70th percentile, measured ≥ 6 months after VTE and compared with controls, was associated with a 2.2 fold increased odds of VTE [3]. Another VTE case-control study in women as well as a prospective study of VTE after hip replacement reported that D-dimer was positively associated with VTE occurrence [4, 5]. Clinical studies have shown that higher D-dimer after VTE recovery is also associated with increased risk of recurrent VTE [6-10].

We recently expanded plasma D-dimer measurement to nearly the entire Atherosclerosis Risk in Communities (ARIC) portion of LITE. Therefore, we now update the prospective associations between D-dimer and incident VTE in ARIC with a larger sample size and longer follow-up than our previous report [2]. The larger sample size allowed us to explore race-specific associations and the possible contribution of several genetic variants to the D-dimer findings.

Methods

Study population

We reported the ARIC study design, methods, and VTE incidence rates in detail elsewhere [11, 12]. 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 between examinations. The institutional review committees at each study center approved the methods and staff obtained informed participant consent.

Plasma D-dimer measurements

ARIC had exhausted most baseline citrate plasma samples previously. Therefore, we measured D-dimer concentrations on fasting citrate plasma collected at ARIC visit 3 (in 1993-95) and stored unthawed at −70°C until analysis in 2014. The Laboratory for Clinical Biochemistry Research at the University of Vermont used an immuno-turbidimetric assay (Liatest D-DI; Diagnostica Stago, Parsippany, NJ) on the Evolution analyzer (Diagnostica Stago, Parsippany, NJ). The analytical coefficient of variation for this assay is 4 - 16%. Blind analysis of 73 pairs of ARIC samples split at the time of blood draw and stored until 2014 yielded an intra-class reliability coefficient of 0.92. The normal reference range is 0.22 - 4.0 μg/mL, with expected normal values <0.4 μg/mL. The laboratory recorded 222 values below the limit of detection (<0.01 μg/mL) and 28 values above the detection limit. For analysis, we assigned these groups respective values of 0.01 and 20 μg/mL (the latter being the maximum in our sample); doing so yielded virtually identical results to dropping them altogether.

Measurement of risk factors

We analyzed risk factors measured at ARIC visit 3, in which D-dimer was measured. We calculated body mass index as measured weight (kg)/height $(m)^2$. 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 physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. We estimated the glomerular filtration rate (eGFR) from cystatin C at ARIC visit 2 in 1990-92. ARIC also measured several genetic variants (SNPs) associated with VTE: *F5* Leiden rs6025, *F2* rs1799963, *ABO* rs8176719 (O vs. non-O groups), *FGG* rs2066865, *F11* rs2036914, and in African Americans, hemoglobin S (rs334) [13-16].

VTE occurrence

Staff contacted ARIC participants annually by phone and asked about all hospitalizations in the previous year. In addition, ARIC conducted surveillance of hospital discharge lists from local hospitals. Staff obtained all International Classification of Diseases (ICD) discharge codes. For ICD codes harboring possible VTE events [12], staff obtained copies of the hospital records. To validate VTE events, two physicians reviewed the records using standardized criteria [12], requiring positive imaging tests for diagnosis of DVT and PE. We restricted DVTs for this analysis to those occurring through 2011 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 provoked (associated with cancer, major trauma, surgery, marked immobility) or unprovoked (all others).

Statistical analysis

Of the 12,887 ARIC participants who attended visit 3, we excluded those without D-dimer measurement (n=340), those with a VTE prior to biomarker assessment (n=293), those taking warfarin (n=119), those who were not white or African American (n=36), and those

with no VTE follow-up (n=2). This left a maximum of 12,097 participants for the present analyses of incident VTE. Time at risk 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. We used version 9.3 of SAS (SAS Institute, Cary, NC) for analyses.

We analyzed D-dimer as quintiles and as a log-transformed continuous variable. We first described, by D-dimer quintile, participants' characteristics and frequencies of genetic variants for VTE. The genetic variants were coded as any risk allele versus no risk allele. Our main hypothesis was that D-dimer concentration would be associated positively with VTE incidence. We plotted Kaplan-Meier curves and used Poisson regression to compute incidence rates. We graphically modeled the natural logarithm of D-dimer using restricted cubic splines and then performed Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals of incident VTE by D-dimer quintile. We performed a test for trend in VTE occurrence across D-dimer quintiles in the Cox models using an ordinal variable representing the D-dimer median for each quintile. We confirmed the proportional hazards assumption of the Cox models by testing a D-dimer quintiles by log follow-up time interaction term. Because there was no evidence of a multiplicative D-dimer by race interaction ($p>0.05$), we pooled whites and African Americans for most analyses. Model 1 analyzed D-dimer with VTE adjusted for age (continuous), sex, and race; Model 2 additionally adjusted for characteristics previously associated with VTE in this cohort: diabetes status (yes or no), body mass index and eGFR (both continuous).

To determine whether D-dimer associations differ according to the presence or absence of each genetic marker of VTE risk, we tested for multiplicative interactions of log-transformed D-dimer and each genetic variant by including cross-product terms in Model 2, by race. Finally, to examine the degree to which the genetic variants for VTE might explain the race-specific D-dimer associations with VTE, we added (in Model 3) the genetic variants individually to Model 2. In the African American analysis, we initially included 10 principal components of ancestry to control for possible population stratification, but results without adjustment were the same.

Results

Among the 12,097 participants initially free of VTE, the proportions of African Americans, women, and diabetic participants and the mean age and BMI were higher across D-dimer quintiles, whereas the mean eGFR was lower across D-dimer quintiles (Table 1). D-dimer was also associated positively with having one or more risk alleles for VTE in *F5* Leiden, *F2* rs179963, non-O blood group, and hemoglobin S.

Over a median of 17 years of follow-up, we identified 521 DVTs of the lower extremity or PE. The cumulative incidence of VTE was greater across baseline D-dimer quintiles (Figure 1), with the age, race, and sex adjusted incidence rates of VTE across quintiles being 1.7, 2.4, 3.0, 3.4, and 5.2 per 1,000 person years (Table 2). Thus, the age, race, and sex adjusted hazard ratio of VTE (Model 1) was 3.2 [95% CI 2.3, 4.4] for participants in the highest versus lowest quintile of D-dimer (Table 2). This hazard ratio was 2.7 [95% CI 1.8, 4.2] for

men and 4.0 [95% CI 2.4, 6.6] for women. D-dimer was associated with both unprovoked and provoked VTE, but stronger for unprovoked (Table 2). Further adjustment for diabetes, BMI, and eGFR (Model 2) had little impact on hazard ratios (Table 2).

D-dimer was associated positively with incident VTE rates both ≤ 10 years and >10 years of follow-up, although somewhat weaker for later follow-up. For example, the age, race and sex adjusted hazard ratios of total VTE across quintiles (Model 1) were 1, 1.6, 1.8, 2.3, and 3.5 (p-trend < 0.0001) in the first 10 years and 1, 1.4, 1.8, 2.0, and 2.9 (p-trend <0.0001) for >10 years.

The continuous relation between D-dimer and VTE is shown in Figure 2. Adjusted for age, race, and sex, the hazard of VTE was 33% greater (95% CI 21%, 46%) per standard deviation increment of continuous log D-dimer.

Race-specific associations of D-dimer with VTE were similar by genotype (p for multiplicative interaction ≥0.05, testing all of the individual SNPs depicted in Table 1; data shown for factor V Leiden and non-O type blood type in Table 3). That is, there was no evidence on the multiplicative scale that D-dimer was more strongly associated with VTE in the presence or absence of risk alleles for any of the VTE SNPs. Likewise, the SNPs were not more strongly associated with VTE at higher versus lower D-dimer levels.

Finally, we tested, in whites and African Americans separately, the degree to which the genetic variants for VTE may explain the D-dimer associations with VTE (Table 4). For whites, the 3.0-fold gradient in VTE incidence across D-dimer quintiles fell to 2.9-fold with adjustment for the five main variants. For African Americans, the gradient in VTE remained 2.3-fold with or without adjustment for the five variants plus the hemoglobin S variant (Table 4).

Discussion

This large population-based prospective study documented that a higher basal plasma concentration of D-dimer was associated moderately strongly with greater risk of VTE over a median of 17 years of follow-up. The association proved stronger for unprovoked (or spontaneous) VTE than for VTE provoked by triggers such as cancer, major trauma, or surgery. The association also was somewhat stronger for the first 10 years of follow-up, but remained significant even after 10 years, suggesting that elevated D-dimer is a marker of increased risk of VTE over the long-term. Multiplicative interaction testing showed that key SNPs did not modify the association of D-dimer with VTE. However, adjustment for the genetic variants slightly weakened the D-dimer associations with VTE. Notably, the D-dimer levels associated with increased risk of VTE were well below clinical D-dimer cutpoints for acute VTE diagnosis.

Our previous publication from LITE included D-dimer measured in ARIC by a research assay on samples from 1987-89 and 169 incident VTEs occurring from 1987 through 1998 [2]. In contrast, the present ARIC study included a D-dimer measured using a commercial assay on samples from 1993-95 and 521 incident VTEs from 1993 through 2011. The VTEs mostly did not overlap, and the hazard ratios here were quite similar to those reported

previously for ARIC [2]. Case-control and clinical epidemiological studies also have corroborated strong, positive associations between D-dimer and VTE occurrence [3-10].

The most likely explanation for higher basal D-dimer concentrations being associated with long-term VTE risk in the general population is that elevated D-dimer is a marker of genetic and environmental contributors to thrombosis. Indeed, this study and others [17-19] found D-dimer associated with environmental risk factors for VTE (i.e., BMI, diabetes, and eGFR), ethnicity (higher in African Americans than whites) and several genetic variants. Most genetic variants associated with D-dimer are located in hemostatic factor genes (e.g., *F5*, *F3*, *FGA*, and *FGG*) [18]. We confirmed that D-dimer was higher in participants with risk alleles for *F5* Leiden, *F2*, and in African Americans, *FGG* and hemoglobin S, but not with ABO or *F11*. Genome-wide association studies have consistently reported the SNPs we studied to be associated with VTE [13-16]. These variants explained part of the D-dimer association with VTE. Yet, even after adjustment for age, sex, genetic variants, and environmental factors, D-dimer remained independently associated with VTE. In addition, the waning of the association between D-dimer and VTE with longer follow-up suggests that D-dimer is not reflecting only genetic risk of VTE.

Some potential limitations of our study warrant consideration. Firstly, we measured D-dimer on plasma samples that had been stored for approximately 20 years at −70°C. Yet, previous evidence suggests D-dimer is stable in samples frozen for up to 6 years [20]. Any sample deterioration, if uniform across the D-dimer distribution, should not have biased our results. However, it is possible that sample deterioration had a non-uniform distribution. Secondly, D-dimer concentrations may have fluctuated during the long follow-up, and such fluctuations would tend to weaken the observed association with VTE. Thirdly, we identified VTEs via participant recall of hospitalizations and via local hospital surveillance. The few hospitalizations missed should be random with respect to D-dimer, and thus not significantly bias results. We also would have missed sudden fatal VTEs or outpatient-treated VTEs. However, ARIC pilot data suggest the vast majority of patients with first VTEs in ARIC during 1999 through 2011 were hospitalized.

In conclusion, a higher basal level of D-dimer in the general population is a strong risk factor for VTE over at least two decades in African Americans, as well as whites. We clearly need a better understanding of why some ostensibly healthy people have elevated basal D-dimer levels, as well as further clarification of genetic and preventable environmental and lifestyle contributors to thrombosis. In this regard, “maintenance of ideal cardiovascular health” is associated with lower D-dimer [19] and reduced VTE incidence [21, 22], and may be one strategy to reduce the large public health burden of VTE. Use of statins also can lower D-dimer [23] but whether they reduce VTE remains controversial [24].

Acknowledgements

The authors thank the staff and participants of the ARIC Study for their important contributions, and Elaine Cornell for supervising D-dimer measurements.

Sources of Funding

The National Heart, Lung, and Blood Institute (NHLBI) supported the D-dimer measurements via U01 HL096902, LITE via R01-HL0597367, and ARIC via contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C.

Abbreviations

ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
DVT	venous thrombosis
eGFR	estimate glomerular filtration rate
HR	hazard ratio
LITE	Longitudinal Investigation of Thromboembolism Etiology
PE	pulmonary embolism
SNP	single nucleotide polymorphisms
VTE	venous thromboembolism.

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Highlights

- We measured D-dimer in 12,097 participants free of venous thromboembolism (VTE).
- Over a median of 17 years, 521 developed VTEs.
- VTE risk was strongly, independently, and positively associated with D-dimer.
- This was true in both whites and African Americans.

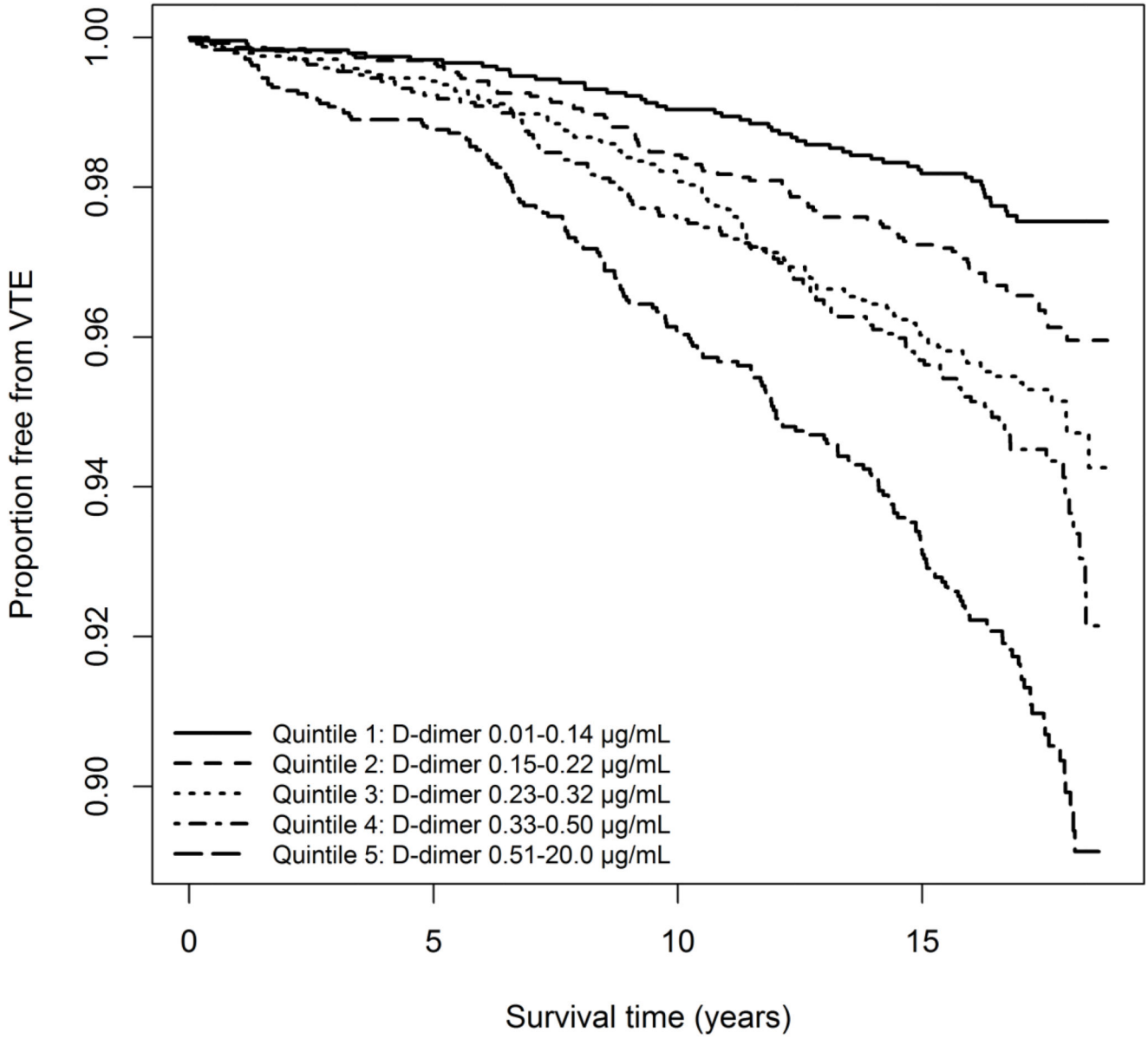

Figure 1.
Survival free of venous thromboembolism (VTE) in relation to quintiles of plasma D-dimer, ARIC, 1993-2011

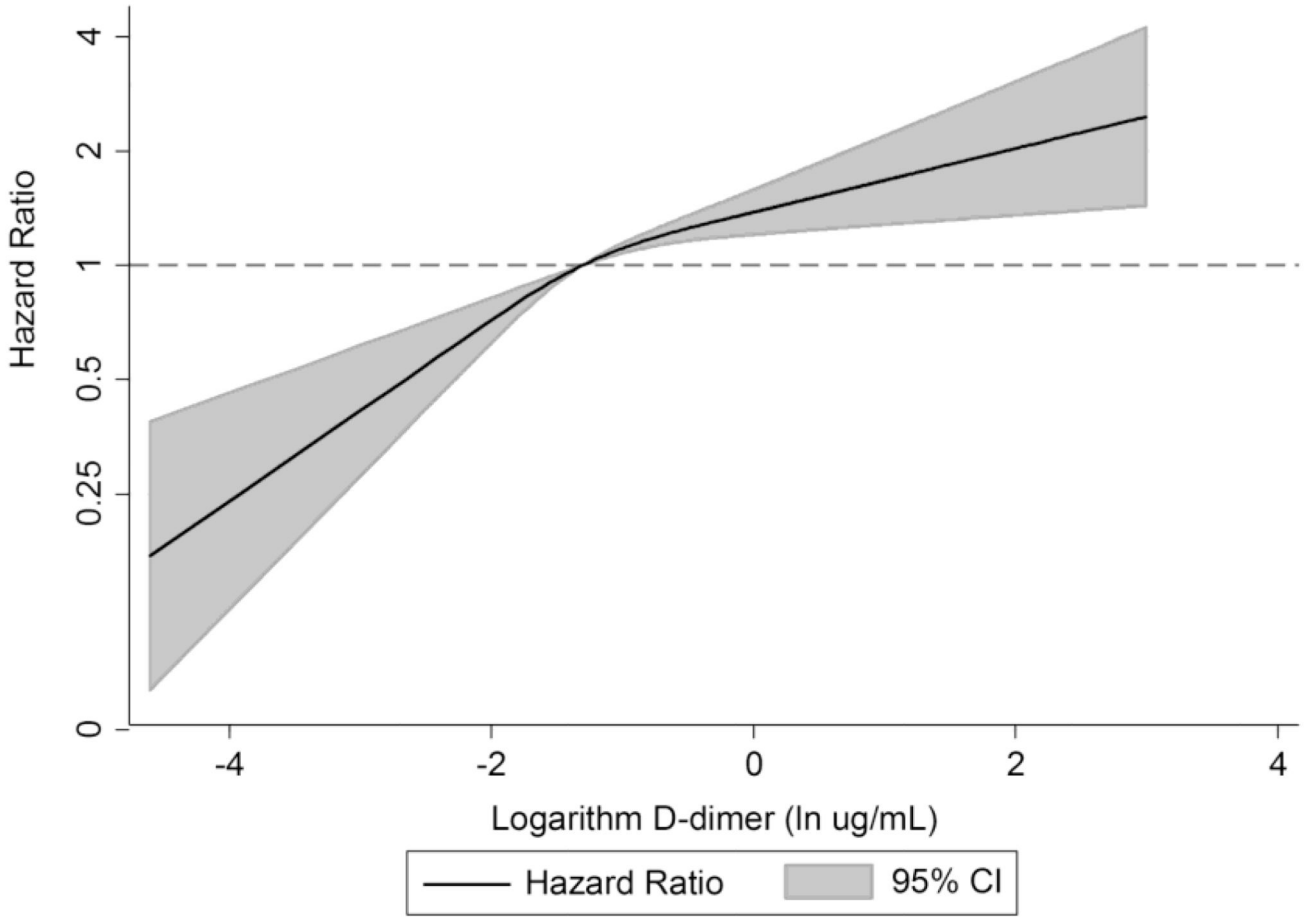

Figure 2.

Age, race, sex-adjusted hazard ratio of venous thromboembolism in relation to logarithm-transformed D-dimer*, ARIC, 1993-2011

* Analyzed using restricted cubic splines with knots at the fifth, fiftieth, and ninety-fifth percentiles of the log D-dimer distribution.

Table 1

Participant Characteristics [Mean ± SD or %] in Relation to Quintiles of D-dimer, ARIC Visit 3, 1993-1995.

	Quintile of D-dimer (μg/mL)				
Characteristic	**0.01-0.14**	**0.15-0.22**	**0.23-0.32**	**0.33-0.50**	**0.51-20.0**
n	2,370	2,622	2,429	2,242	2,434
Age, y	58.4 ± 5.4	59.3 ± 5.5	60.0 ± 5.6	60.5 ± 5.8	61.5 ± 5.7
BMI, kg/m^2	27.1 ± 4.7	27.9 ± 4.9	28.8 ± 5.3	29.5 ± 6.1	29.1 ± 6.1
eGFR, ml/min/1.73 m^2 †	98.3 ± 14.0	97.5 ± 14.7	95.8 ± 15.9	95.7 ± 16.8	92.6 ± 18.6
African American	11%	15%	25%	33%	34%
Women	49%	51%	58%	59%	61%
Diabetes	11%	14%	15%	18%	18%
Whites					
F5 Leiden rs6025*	2.7%	3.8%	6.1%	8.4%	8.1%
F2 rs1799963*	1.6%	2.5%	2.8%	3.3%	4.6%
ABO non-O group	59%	58%	58%	61%	63%
FGG rs2066865*	45%	46%	46%	45%	45%
F11 rs2036914*	79%	77%	79%	77%	79%
African Americans					
F5 Leiden rs6025*	--	0.3%	0.9%	1.3%	1.4%
F2 rs1799963*	0.9%	--	0.4%	0.6%	1.1%
ABO non-O group	50%	50%	51%	50%	47%
FGG rs2066865*	50%	51%	52%	54%	56%
F11 rs2036914*	85%	86%	88%	87%	87%
Hemoglobin S (rs334)*	2.0%	3.4%	4.6%	7.5%	9.7%

* Prevalence of any risk allele for VTE.

† From 1990-92 visit.

Table 2

Incidence Rates and Hazard Ratios (HRs) of Venous Thromboembolism in Relation to Quintiles of D-dimer, ARIC, 1993-2011.

	Quintile of D-dimer (μg/mL)					
	0.01-0.14	**0.15-0.22**	**0.23-0.32**	**0.33-0.50**	**0.51-20.0**	**p-trend**
Total VTE						
N of VTEs	51	84	102	110	174	
Incidence rate (per 10^3 py)*	1.7	2.4	3.0	3.4	5.2	
[95% CI]	[1.3, 2.2]	[1.9, 3.0]	[2.5, 3.7]	[2.8, 4.1]	[4.4, 6.0]	
Model 1 HR*	1	1.5	1.8	2.1	3.2	<0.0001
[95% CI]	--	[1.0, 2.1]	[1.3, 2.6]	[1.5, 2.9]	[2.3, 4.4]	
Model 2 HR†	1	1.4	1.7	1.8	2.8	<0.0001
[95% CI]	--	[1.0, 1.9]	[1.2, 2.4]	[1.3, 2.5]	[2.0, 3.9]	
Men						
N of VTEs	32	46	39	46	71	
Model 1 HR*	1	1.3	1.3	1.7	2.7	<0.0001
[95% CI]	--	[0.8, 2.0]	[0.8, 2.0]	[1.0, 2.6]	[1.8, 4.2]	
Women						
N of VTEs	19	38	63	64	103	
Model 1 HR*	1	1.7	2.6	2.8	4.0	<0.0001
[95% CI]	--	[1.0, 3.0]	[1.6, 4.4]	[1.6, 4.6]	[2.4, 6.6]	
Unprovoked VTE						
N of VTEs	13	25	41	45	76	
Model 1 HR*	1	1.7	3.0	3.6	6.0	<0.0001
[95% CI]	--	[0.9, 3.4]	[1.6, 5.7]	[1.9, 6.7]	[3.3, 11.0]	
Provoked VTEs						
N of VTEs	38	59	61	65	98	
Model 1 HR*	1	1.4	1.4	1.6	2.3	<0.0001
[95% CI]	--	[0.9, 2.0]	[1.0, 2.2]	[1.1, 2.4]	[1.6, 3.4]	

*Adjusted for age, race, and sex, except where sex-stratified,

†Adjusted for age, race, sex, diabetes, BMI, and eGFR.

Table 3

Hazard Ratios (HRs) and 95% CI of Venous Thromboembolism (VTE) in Relation to Dichotomized D-dimer and Thrombophilia SNPs, ARIC, 1993-2011.

	Factor V Leiden, No		Factor V Leiden, Yes	
	Low D-dimer*	**High D-dimer***	**Low D-dimer***	**High D-dimer***
HR† of VTE	1	1.8	2.0	4.3
[95% CI]	--	[1.5, 2.1]	[1.2, 3.5]	[2.9, 6.2]
n VTEs	*212*	*245*	*14*	*30*
	O-Blood Type		**Non-O Blood Type**	
	Low D-dimer*	**High D-dimer***	**Low D-dimer***	**High D-dimer***
HR† of VTE	1	1.7	1.4	2.6
[95% CI]	--	[1.3, 2.4]	[1.1, 1.9]	[2.6, 3.4]
n VTEs	*79*	*93*	*146*	*175*

*Low D-dimer is lowest three quintiles (≤ 0.32 μg/mL) and high D-dimer is highest two quintiles (>0.32 μg/mL).

†HR adjusted for sex, race, and age.

Table 4

Race-Specific Hazard Ratios (HRs) of Total Venous Thromboembolism in Relation to Quintiles of D-dimer, ARIC, 1993-2011.

	Quintile of D-dimer (μg/mL)					
	0.01-0.14	**0.15-0.22**	**0.23-0.32**	**0.33-0.50**	**0.51-20.0**	**p-trend**
Whites						
N of VTEs	42	67	71	61	101	
Model 2 HR*	1	1.4	1.8	1.7	3.0	<0.0001
[95% CI]	--	[0.9, 2.0]	[1.2, 2.6]	[1.2, 2.6]	[2.1, 4.3]	
Model 3 HR†	1	1.2	1.8	1.6	2.9	<0.0001
[95% CI]	--	[0.8, 1.9]	[1.2, 2.7]	[1.1, 2.5]	[1.9, 4.3]	
African Americans						
N of VTEs	9	17	31	49	73	
Model 2 HR*	1	1.3	1.3	1.7	2.3	0.002
[95% CI]	--	[0.6, 2.9]	[0.6, 2.7]	[0.8, 3.4]	[1.1, 4.7]	
Model 3 HR‡	1	1.2	1.1	1.4	2.1	0.008
[95% CI]	--	[0.5, 3.0]	[0.5, 2.6]	[0.6, 3.1]	[0.9, 4.7]	

*Adjusted for age, sex, diabetes, BMI, and eGFR.

†Adjusted for age, sex, diabetes, BMI, eGFR, and presence of ≥1 risk allele for five SNPs adjusted individually (*F5* Leiden rs6025, *F2* rs1799963, *ABO* non-O group rs8176719, *FGG* rs2066865, *F11* rs2036914).

‡Adjusted for age, sex, diabetes, BMI, eGFR, and presence of ≥1 risk allele for six SNPs adjusted individually (*F5* Leiden rs6025, *F2* rs1799963, *ABO* non-O group rs8176719, *FGG* rs2066865, *F11* rs2036914, hemoglobin S rs334).