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Hemostatic factors, inflammatory markers and risk of incident venous thromboembolism: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: Several hemostatic factors and inflammatory markers are associated with the risk of incident venous thromboembolism (VTE), however most existing data are from case-control studies in Caucasian populations.

Objectives: We aimed to prospectively confirm previous findings, and explore less studied biomarkers in relation to VTE risk in a multi-racial/ethnic cohort.

Methods: Circulating levels of factor VIII, fibrinogen, D-dimer, plasmin-antiplasmin complex (PAP), C-reactive protein (CRP) and interleukin-6 (IL-6) were measured at baseline (2000–02) in 6,706 participants of the Multi-Ethnic Study of Atherosclerosis (MESA). Incident VTE was identified using hospitalization discharge codes from baseline to December 31, 2015. Hazard ratios (HRs) of VTE were estimated in Cox regression models.

Results: There were 227 events during a median of 14 years of follow-up. Compared with participants in the lowest quartile, the HRs for those above the 95th percentile and p for trend across categories were 3.50 (95% CI 1.98–6.19; p<0.001) for D-dimer, 1.49 (95% CI 0.84–2.63;

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Conflicts of interest

The authors report no conflicts of interest.

Addendum

L. H. Evensen analyzed and interpreted the data and drafted the manuscript, A. Folsom, J. S. Pankow, J. B. Hansen, M. A. Allison and M. Cushman interpreted the data and revised the manuscript. P. L. Lutsey designed the study, interpreted the data and revised the manuscript.

p=0.02) for factor VIII, 1.32 (95% CI 0.76–2.28; *p*=0.99) for fibrinogen, 1.92 (95%CI 1.08–3.42; *p*=0.15) for PAP, 1.68 (95% CI 0.81–3.48; *p*=0.08) for CRP and 2.55 (95% CI 1.15–5.66; *p*=0.07) for IL-6, after adjustment for demographics and body mass index. For CRP and IL-6, follow-up was restricted to ten years due to violations of the proportional hazards assumption. No significant interactions by race/ethnicity were observed.

Conclusions: We demonstrated a fairly novel association between PAP and risk of incident VTE, and contributed further prospective confirmation regarding the associations of D-dimer, factor VIII, and IL-6 with VTE.

Keywords

Blood Coagulation; Fibrinolysis; Inflammation; Risk Factors; Venous Thromboembolism

Introduction

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in 1–4 per 1000 adults annually and imposes a significant health burden worldwide [1–4]. Although a multifactorial disease, an imbalance between pro- and anticoagulant activity is at the core of VTE pathophysiology [5, 6]. Thus, biomarkers reflecting such processes may be tools for risk stratification and targets for intervention to prevent VTE.

Several studies have reported associations between circulating levels of coagulation factors, as well as markers of coagulation activation and fibrinolysis, and VTE risk. As coagulation and inflammation are closely linked, inflammatory markers are also relevant in this context. [7] For some biomarkers, such as coagulation factor VIII [8–11] and D-dimer [12–14], the available evidence consistently supports that those with elevated levels have a higher risk of VTE. For others, such as fibrinogen [8, 10, 15], plasmin-antiplasmin complex (PAP) [9, 16], C-reactive protein (CRP) [17–20] and interleukin-6 (IL-6) [21, 22], the data are not definitive. That is, a large amount of the evidence originated from case-control studies, of which some may be biased due to blood collection shortly after the VTE event, exclusion of fatal cases, or flawed control group selection. Thus, there is a need to replicate previous findings in independent populations, and for more data from prospective studies.

Towards this end, we used data from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study to test the associations between baseline levels of hemostatic, fibrinolytic and inflammatory markers and risk of incident VTE. We hypothesized that individuals with elevated levels of these biomarkers would be at higher risk. Additionally, because levels of these biomarkers and VTE rates vary across racial/ethnic groups [23–25], we leveraged the multiethnic composition of MESA to explore potential interactions by race/ethnicity on the association between biomarkers and risk of VTE.

Methods

Study Population

MESA, initiated in 2000, is a prospective cohort of 6,814 men and women recruited from six field centers across the United States: St. Paul, MN, Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; and New York, NY.[26] Participants were aged 45–84 years at inclusion and self-identified as Caucasian, African American, Hispanic or Chinese American. At baseline, all were free from cardiovascular disease, active cancer, and other serious medical conditions that participants felt would prevent long-term participation in the study (based on self-report). For the present analyses, we excluded individuals who reported previous VTE (n=5), who were under anticoagulant treatment at baseline (n=24), with missing information on all main exposure variables (n=31) or confounders (n=21), or with no follow-up data (n=27). For the present analysis participants were followed through December 31, 2015 for incident events. Consequently, the analytical sample consisted of 6,706 individuals. The study was approved by the Institutional Review Boards of the six field centers, and all participants provided written informed consent prior to inclusion.

Baseline Assessments

Baseline information was collected by centrally trained study personnel. Height and weight were measured by standardized procedures, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Participants were classified as normal weight (BMI < 25.0 kg/m^2), overweight (BMI 25–29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) according to World Health Organization criteria [27]. Information on educational attainment was obtained through questionnaire. Fasting blood samples were collected and handled according to standardized protocols [28].

Laboratory Methods

All biomarkers were analyzed at the Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington, VT, USA. Factor VIII coagulant activity was determined utilizing the Sta-R analyzer (STA-Deficient VIII; Diagnostica Stago, Parsippany, NJ, USA; inter-assay coefficient of variation [CV]: 8.8% to 14.6%), and D-dimer by immunoturbidometry on the Sta-R analyzer (Liatest D-DI; Diagnostica Stago, Parsippany, NJ, USA; inter-assay CV: 5.8% to 18.6%). Fibrinogen and CRP were measured using the BN™II nephelometer (N Antiserum to Human Fibrinogen and N High Sensitivity CRP, Dade Behring Inc., Deerfield, IL, USA). The inter-assay CVs were 2.6% and 2.1% to 5.7%, respectively. PAP was measured by a two-site enzyme-linked immunosorbent assay (ELISA) that utilizes two monoclonal antibodies [29] (inter-assay CV: 6.7% to 11.1%), and IL-6 by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN, USA; inter-assay CV: 6.3%). Creatinine was measured using colorimetry with the Johnson & Johnson Vitros 950 Analyzer (Johnson & Johnson Clinical Diagnostics Inc., Rochester, NY, USA), and estimated glomerular filtration rate (eGFR) was obtained from the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [30]. The presence of diabetes was defined as fasting glucose ≥6.99 mmol/L (126 mg/dL) or self-reported use of insulin or oral hypoglycemic agents.

Outcome Identification

MESA participants are called every 9 to 12 months, and asked about any interim hospital admissions and deaths. Copies of medical records are obtained for participants who reported being hospitalized for cardiovascular disease. For participants who died of cardiovascular causes outside the hospital, MESA conduct interviews with next of kin and request copies of death certificates, as well as information on recent hospitalizations so that those records can be obtained as well. Hospitalization International Classification of Diseases (ICD) discharge codes are recorded. VTE was defined by presence, in any position, of the following International Classification of Diseases (ICD)-9 revision codes: 415, 415.x (except 415.0), 451, 451.1x, 451.2, 451.81, 451.9, 453.1, 453.2, 453.4x, 453.5x, 453.8, 453.82, and 453.9 or the following ICD-10 revision codes: I26, I26.0, I26.0x, I26.9, I26.90, I26.92, I26.99, I80.1, I80.1x, I80.2, I80.20, I80.20x, I80.21, I80.21x, I80.22, I80.22x, I80.23, I80.23x, I80.29, I80.29x, I80.3, I80.8, I80.9, I82.1, I82.22, I82.220, I82.221, I82.4, I82.40, I82.40x, I82.41, I82.41x, I82.42, I82.42x, I82.43, I82.43x, I82.44, 82.44x, I82.49, I82.49x, I82.4Y, I82.4Yx, I82.4Z, I82.4Zx, I82.5, I82.50, I82.50x, I82.51, I82.51x, I82.52, 82.52x, I82.53, I82.53x, I82.54, I82.54x, I82.59, I82.59x, I82.5Y, I82.5Yx, I82.5Z, I82.5Zx, I82.9, I82.90 and I82.91. MESA did not capture outpatient VTEs, nor did it review medical records to validate hospital VTE discharge codes.

Statistical Analyses

For each participant, person-time accrued from the date of enrollment (2000–02) to the date of incident VTE, death or the most recent follow-up call (no later than December 31, 2015), whichever occurred first. The biomarkers were modeled as categories according to percentiles (<25, 26–50, 51–75, 76–95 and >95). Crude incidence rates (IRs) with 95% confidence intervals (CIs) were calculated and expressed as the number of events per 1000 person-years. Adjusted hazard ratios (HRs) with 95% CIs were estimated in Cox proportional hazards regression models with time on study as the timescale. Model 1 adjusted for age, sex, race/ethnicity, education and MESA field center, model 2 further adjusted for BMI (continuous) and model 3 additionally adjusted for diabetes (yes/no) and eGFR (continuous). Linear trends were tested by entering the categories as ordinal variables in the Cox model. Multiplicative interactions between each biomarker and race/ethnicity, sex and age (continuous) were tested by including the cross-product terms one by one in the fully adjusted Cox model. We also explored non-linear associations between biomarkers (as continuous variables) and the risk of VTE using restricted cubic splines with model 3 adjustments. The median value was used as reference, with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th} and 95^{th} percentiles. In order to address potential regression dilution bias, we conducted sensitivity analyses with follow-up restricted to maximum 8 years from baseline. The proportional hazards (PH) assumption was evaluated on the basis of Schoenfeld residuals. All statistical analyses were performed using STATA version 14.2 (Stata Corp., College Station, TX, USA).

Results

The mean age at baseline was 62 ± 10 years and 53% were women. The racial/ethnic composition was 39% Caucasian, 28% African American, 22% Hispanic and 12% Chinese

American. Baseline characteristics according to race/ethnicity, incident VTE over follow-up and biomarker categories are shown in Tables 1–3 and Tables S1–5. The prevalences of obesity and diabetes were highest in African Americans and Hispanics, whereas the Caucasians were most likely to have decreased kidney function (eGFR < 60 mL/min/1.73m^2). The concentrations of hemostatic and inflammatory markers were generally higher in African Americans and Hispanics than in Caucasians and Chinese American (Table 1). Participants who developed VTE during follow-up were older, had a higher prevalence of obesity and were more likely to have decreased kidney function compared with those who remained free from VTE (Table 2). Participants with higher D-dimer levels were more likely to be older, female, African American, have higher BMI and higher prevalence of diabetes, but had lower eGFR and education levels (Table 3). Similar trends were also observed across categories of the remaining biomarkers, however there was no gradient of diabetes prevalence and BMI across categories of PAP, and no gradient of age and eGFR across categories of CRP (Tables S1–5)

There were 227 VTE events during a median follow-up of 14.0 years (maximum 15.1 years), and the overall IR was 2.75 (95% CI 2.42–3.13) per 1000 person-years. Slightly more than half of all events (55%) occurred in women, and DVT without coded PE was the most common clinical presentation (53%), while the remaining (47%) were PEs with or without DVT.

In the minimally adjusted model, the highest level (>95th percentile) of all biomarkers tended to be associated with an elevated hazard of VTE compared with the lowest quartile, and the *p* for trend was significant (<0.05) for all but fibrinogen and PAP (Table 4). The HRs for those above the 95th percentile were 4.18 (95% CI 2.38–7.35) for D-dimer, 1.72 (95% CI 0.98–3.03) for factor VIII, 2.06 (95% CI 1.22–3.47) for fibrinogen, 1.71 (95% CI 0.96–3.05) for PAP, 1.88 (95% CI 1.03–3.43) for CRP and 1.96 (95% CI 1.04–3.68) for IL-6. With the exception of PAP and D-dimer, for which VTE risk remained significantly elevated above the 95th percentile, HRs were attenuated after adjustment for BMI, and only D-dimer and factor VIII showed significant linear associations with VTE risk. In this model, the HRs for those above the 95th percentile were 3.50 (95% CI 1.98–6.19) for D-dimer, 1.92 (95% CI 1.08–3.42) for PAP and 1.49 (95% CI 0.84–2.63) for factor VIII. Further adjustment for diabetes and eGFR did not alter the results. Likewise, additional adjustment for statin use and weekly amount of moderate- and vigorous physical activity yielded similar results (data not shown). There were no significant interactions between any of the biomarkers and age, race/ethnicity or gender (Table S6).

Due to violations of the PH assumption for CRP and IL-6, we analyzed the data with follow-up restricted to ten years (n VTE events: 152), whereupon the assumption was met. In these analyses, the effect sizes tended to be larger, most notably for IL-6. The model 2 HRs were 2.20 (95% CI 1.19–4.05), 1.53 (95% CI 0.81–2.91), 2.12 (95% CI 1.11–4.05) and 2.55 (95% CI 1.15–5.66) across categories of increasing IL-6 (p=0.07). For the remaining factors, the model 2 HRs for those above the 95th percentile and *p* for linear trends were 3.94 (95% CI 1.95–7.98; p<0.001) for D-dimer, 1.51 (95% CI 0.78–2.91; p=0.03) for factor VIII, 1.84 (95% CI 0.99–3.42; p=0.43) for fibrinogen, 2.13 (95% CI 1.06–4.28; p=0.08) for PAP and 1.68 (95% CI 0.81–3.48; p=0.08) for CRP.

In sensitivity analyses with follow-up restricted to maximum 8 years, the associations were generally similar as in the main analyses, however most effect estimates were modestly higher, and the CIs were wider (Table S7). These analyses were based on only 130 VTE events and must be interpreted with caution due to low statistical power.

We also modelled the association between biomarkers and VTE risk as a restricted cubic spline with model 3 adjustments (Figure S1–6). For FVIII, the association appeared to be dose-depended, with progressively increasing risk at levels above the median (93%) (Figure S1). D-dimer showed a strong dose-dependent association with VTE risk up to approximately 1 μg/mL, which levelled off, but increased steadily with increasing levels (Figure S2). For PAP, the association appeared to be weakly dose-dependent, although the risk decreased slightly at levels just above the median (4.40 nM) before continuing to increase (Figure S3). However, CIs were wide and never reached statistical significance. For fibrinogen, the association appeared to be U-shaped, but CIs were wide and did not reach statistical significance. Finally, CRP (Figure S5) and IL-6 (Figure S6) appeared to be dose-dependently associated with VTE at low levels before leveling off, however CIs were wide.

Discussion

In the multiethnic and prospective MESA cohort, we demonstrated that elevated levels of several coagulation and fibrinolytic factors were independently associated with a higher risk of incident VTE. The association of higher D-dimer was most prominent, with levels above the median associated with a 2–3.5-fold higher risk. Particularly noteworthy is the association between high PAP and increased risk of VTE, and the confirmation of the associations of D-dimer, IL-6 and coagulation factor VIII with VTE. Despite the racial/ethnic differences in biomarker levels and VTE rates, there was no evidence of interaction by race/ethnicity.

Elevated PAP was associated with higher risk of VTE, but only in those with PAP >95th percentile (≥8.40 nM) after model 2 adjustments. There was weak evidence of dose response. Few studies have explored this association; however, our findings are in line with one previous report. In a prospective nested case-control study from Women's Health Initiative (WHI) clinical trials, baseline PAP >90th percentile (>7.5nM) was associated with a 2.4-fold (95% CI 1.5–3.8) higher risk of VTE.[9] A larger 1-year increase in PAP was also modestly associated with VTE risk [9]. On the contrary, in a prospective nested case-control study based on the Longitudinal Investigation of Thromboembolism Etiology (LITE), no association between PAP and VTE risk was observed [16]. The discrepant findings from three studies utilizing the same assay performed in the same laboratory may be explained by different categorization of the biomarker. While we and the WHI study found associations with VTE only at the top of the distribution (>90th and >95th percentiles), the highest category in LITE was the upper 20th percentile.[16] In another study, there was no association between preoperative PAP, also measured with ELISA (Enzygnost-PAP), and the risk of DVT (symptomatic and asymptomatic) 8–14 days after elective hip replacement [31]. Likely, other risk factors, such as comorbidities, infections etc., are more important in surgery-related VTE than basal levels of hemostatic factors [32]. The PAP complex

is formed from the extremely potent plasmin inhibition by α_2-antiplasmin, and signifies a fibrinolytic response to fibrin formation [33]. Thus, it is likely that the association between elevated PAP and VTE is explained by an overall hypercoagulable state with higher coagulant and reactive fibrinolytic activity. This is supported by studies demonstrating positive associations between PAP and other prothrombotic indicators, such age, factor VIII, prothrombin fragment 1+2 and D-dimer [34, 35].

We confirmed the previously reported strong association of elevated D-dimer with increased risk of incident VTE [9, 12, 14]. In contrast, an earlier MESA publication failed to reproduce the known association between D-dimer and the risk of arterial thrombotic disease [34]. The unexpected finding may relate to short duration of follow-up and limited power, as well as the rigorous exclusion of individuals with clinical disease at baseline in MESA. Although somewhat replicative, the present MESA analysis demonstrating a strong association between D-dimer and risk of incident VTE adds important prospective evidence, and extends previous findings to a more racially/ethnically diverse study population. In the present study and the Atherosclerosis Risk in Communities Study (ARIC) [12], VTE risk was elevated at much lower D-dimer levels (~0.20 μg/mL) than used to rule out VTE in clinical practice (<0.5 μg/mL) [36]. D-dimer is a degradation product that is formed when cross-linked fibrin is cleaved by plasmin, and reflects ongoing coagulation and fibrinolysis [36]. As discussed in previous reports, it is unlikely that D-dimer is a causal risk factor for VTE; like PAP, it may be a marker of other inherited or acquired causes of hypercoagulability [12, 14], though the contribution of genetic factors seems small.

Although an association between factor VIII and risk of incident VTE is widely accepted, the majority of the evidence is from case-control studies [10, 11, 37]. Among the prospective studies, only LITE has reported a strong positive association in multivariable-adjusted models [8]. In the previously mentioned WHI hormone trial, the association was significant only when factor VIII was modeled continuously, but not when dichotomized at 150% [9]. Potentially, as both we and LITE observed an increased VTE risk even below this value, a cut-off at 150% may be too high to reveal an association. In the cohort of elective hip surgery-patients, the association was not significant in the multivariable-adjusted model, but the precision was poor [31]. We also noted considerable attenuation of the risk estimates after adjustment for BMI, a correlate of factor VIII. Plasma level of factor VIII is determined by both inherited and acquired factors. Among the former are genes that code for ABO blood type and von Willebrand Factor (the factor VIII carrier protein), and among the latter: age, sex, pregnancy, surgery, acute phase responses, obesity, diabetes etc. [6, 37]. Interestingly, a recent multiethnic genome-wide association study identified novel loci regulating plasma levels of factor VIII, and a Mendelian Randomization analysis suggested a causal effect of factor VIII on the risk of VTE [38]. Mechanistically, it is speculated that elevated factor VIII exerts a thrombotic effect through enhanced thrombin generation [37].

The associations for fibrinogen, IL-6 and CRP disappeared after 2 model adjustments. However, in analyses with restricted follow-up done because of violation of the PH assumption for IL-6 and CRP, those with IL-6 above the 25th percentile (≥0.77 pg/mL) were at greater risk of VTE, although precision was poor. Previous prospective studies, based on the Cardiovascular Health Study (CHS) and the Nord-Trøndelag Health (HUNT) Study did

not find an association between IL-6 and VTE risk[21, 39], including when assessed as a continuous variable [39]. However, in the HUNT Study the lower detectable limit of the assay was 2.5 pg/mL and the lack of an IL-6 gradient may have influenced the results [21], while in CHS there was not a large number of cases [39]. For CRP, our results are in line with some other prospective studies [20, 40–42], but in contrast to others [9, 17, 19]. Studies with shorter duration of follow-up or with updated measurements were able to demonstrate a relationship [19, 43, 44]. We also observed stronger, but not significant, associations in time-restricted analyses. CRP synthesis is mainly under control by IL-6, and both are highly variable and reflect a systemic inflammatory response [45, 46]. Taken together, it can be speculated that acute inflammation may constitute a triggering factor for VTE, rather than being a long-term risk factor. However, the lack of a long-term association, and the fact that longitudinal increases and genetically elevated CRP are not related to VTE risk, are arguments against a causal association [18, 47, 48].

Main strengths of the present study include a prospective design and a well-characterized, multiethnic study population that was enrolled concurrently with the obesity epidemic in the United States. Some limitations merit consideration. First, case identification was based on self-report of hospitalizations and the accuracy of discharge ICD codes; diagnoses were not verified by thorough medical record review. Validation studies have demonstrated a moderately high validity of VTE based on ICD codes, with a positive predictive value of approximately 80% [49–52]. Additionally, detection of expected associations of risk factors with VTE provides some reassurance of accuracy. VTEs treated in the outpatient setting would be missed, but it seems unlikely that this should have greatly biased hazard ratios examining biomarkers and VTE. However, incidence rates may be underestimated and generalization of results to VTE treated outside the hospital setting must be done with caution. Some VTEs were likely missed in participants lost to follow-up, but the rarity of VTE mitigates issues of bias. Potential misclassification of cases would be non-differential and generally lead to underestimates of the true association. Further, the analyses were based on single baseline measurements only; these may have changed during the long follow-up (median 14 years) and introduced regression dilution bias [53]. We also acknowledge that the power to detect interaction by race/ethnicity was limited. Additionally, the inclusion of relatively healthy individuals may impact the generalizability of our findings. Finally, due to the observational nature of the study, we cannot rule out residual confounding.

In summary, elevated factor VIII, D-dimer and PAP, but not fibrinogen and CRP, were associated with higher risk of incident VTE during 14 years of follow-up in a multiethnic cohort. There was also some evidence that IL-6 may be implicated in VTE risk. There was no evidence of interaction by race/ethnicity on the association between biomarkers and risk of VTE. The study adds important prospective evidence and strengthens the case for these biomarkers, D-dimer in particular, as predictors of incident VTE in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Essentials

- Data on hemostatic factors in relation to venous thromboembolism (VTE) are scarce.
- This association a was investigated in a multi-ethnic prospective cohort.
- We demonstrated a fairly novel association between plasmin-antiplasmin complex and VTE risk.
- We added prospective confirmation on the associations of D-dimer, factor VIII, and interleukin-6.

Table 1

Baseline characteristics by race/ethnicity. The Multi-Ethnic Study of Atherosclerosis, 2000–2002

	Caucasian	Chinese American	African American	Hispanic
N	2583	800	1843	1480
Demographics				
Age, years (mean ± SD)	62.5 ± 10.3	62.4 ± 10.3	62.2 ± 10.1	61.2 ± 10.3
Female, n (%)	1347 (52.2)	412 (51.5)	1017 (55.2)	767 (51.8)
Education, n (%)				
< High school	125 (4.8)	196 (24.5)	224 (12.2)	660 (44.6)
High school	435 (16.8)	130 (16.3)	350 (19.0)	303 (20.5)
Some college	735 (28.5)	162 (20.3)	640 (34.7)	369 (24.9)
Bachelor's degree	577 (22.3)	182 (22.8)	321 (17.4)	83 (5.6)
Graduate/professional degree	711 (27.5)	130 (16.3)	308 (16.7)	65 (4.4)
BMI, kg/m^2 (mean ± SD)	27.7 ± 5.0	24.0 ± 3.3	30.2 ± 5.8	29.4 ± 5.1
BMI categories, n (%)				
Normal [*]	837 (32.4)	519 (64.9)	321 (17.4)	247 (16.7)
Overweight 1[†]	1040 (40.3)	246 (30.8)	686 (37.2)	662 (44.7)
Obese3[‡]	706 (27.3)	35 (4.4)	836 (45.4)	571 (38.6)
eGFR, mL/min/1.73m^2 (mean ± SD)	73.9 ± 14.2	79.6 ± 15.6	80.3 ± 18.0	80.3 ± 16.2
eGFR category, n (%)				
>90 mL/min/1.73m^2	343 (13.3)	227 (28.5)	535 (29.1)	444 (30.0)
60–90 mL/min/1.73m^2	1825 (70.7)	471 (59.0)	1089 (59.2)	884 (59.8)
<60 mL/min/1.73m^2	412 (16.0)	100 (12.5)	216 (11.7)	151 (10.2)
Diabetes, n (%)	153 (5.9)	103 (12.9)	325 (17.7)	259 (17.5)
Hemostatic and inflammatory markers, median (IQR)				
Factor VIII, %	90 (70–114)	93 (73–116)	100 (77–131)	91 (74–117)
Fibrinogen, mg/dL	327 (287–365)	323 (287–365)	353 (304–406)	351 (307–401)
D-dimer, µg/mL	0.20 (0.13–0.35)	0.18 (0.10–0.30)	0.25 (0.15.0.44)	0.23 (0.13–0.42)
PAP, nM	4.41 (3.43–5.58)	3.85 (3.11–4.86)	4.76 (3.77–6.18)	4.26 (3.39–5.43)
CRP, pg/mL	1.74 (0.77–3.98)	0.87 (0.47–1.78)	2.53 (1.08–5.64)	2.45 (1.15–4.90)
IL-6, pg/mL	1.12 (0.73–1.74)	0.86 (0.60–1.31)	1.34 (0.89–2.11)	1.38 (0.91–2.12)

BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; IQR, interquartile range; PAP, plasmin-antiplasmin complex; SD, standard deviation

[*] BMI <25.0 kg/m^2

[†] BMI 25.0–29.9 kg/m^2

[‡] BMI ≥30.0 kg/m^2

Table 2

Baseline characteristics by whether participants developed incident venous thromboembolism during follow-up. The Multi-Ethnic Study of Atherosclerosis, 2000–2015

	No VTE	VTE
N	6479	227
Demographics		
Age, years (mean ± SD)	62.0 ± 10.2	66.5 ± 9.5
Female, n (%)	3418 (52.8)	125 (55.1)
Race/ethnicity, n (%)		
Caucasian,	2486 (38.4)	97 (42.7)
Chinese American	792 (12.2)	8 (3.5)
African American	1756 (27.1)	87 (38.3)
Hispanic	1445 (22.3)	35 (15.4)
Education, n (%)		
< High school	1168 (18.0)	37 (16.3)
High school	1176 (18.2)	42 (18.5)
Some college	1838 (28.4)	68 (30.0)
Bachelor's degree	1118 (17.3)	45 (19.8)
Graduate/professional degree	1179 (18.2)	35 (15.4)
BMI, kg/m^2 (mean ± SD)	28.2 ± 5.4	30.3 ± 6.1
BMI categories, n (%)		
Normal *	1878 (29.0)	46 (20.3)
Overweight †	2554 (39.4)	80 (35.2)
Obese ‡	2047 (31.6)	101 (44.5)
eGFR, mL/min/1.73m^2 (mean ± SD)	77.9 ± 16.1	74.0 ± 17.9
eGFR category, n (%)		
>90 mL/min/1.73m^2	1507 (23.3)	42 (18.5)
60–90 mL/min/1.73m^2	4131 (63.9)	138 (60.8)
<60 mL/min/1.73m^2	832 (12.9)	47 (20.7)
Diabetes, n (%)	804 (12.4)	36 (15.9)
Hemostatic and inflammatory markers, median (IQR)		
Factor VIII, %	92 (73–119)	101 (79–134)
Fibrinogen, mg/dL	338 (296–388)	344 (303–406)
D-dimer, μg/mL	0.20 (0.13–0.37)	0.34 (0.20–0.59)
PAP, nM	4.39 (3.43–5.61)	4.56 (3.78–5.96)
CRP, pg/mL	1.90 (0.83–4.22)	2.37 (1.15–4.46)
IL-6, pg/mL	1.20 (0.77–1.87)	1.37 (0.89–2.53)

BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; IQR, interquartile range; PAP, plasmin-antiplasmin complex; SD, standard deviation; VTE, venous thromboembolism

* BMI <25.0 kg/m^2

† BMI 25.0–29.9 kg/m^2

[≠] BMI ≥30.0 kg/m^2

Table 3

Baseline characteristics by D-dimer categories. The Multi-Ethnic Study of Atherosclerosis, 2000-2002

D-dimer percentile	1–25	26–50	51–75	76–95	96–100
N	1899	1449	1708	1303	334
D-dimer, μg/mL, median (range)	0.10 (0.01–0.13)	0.18 (0.15–0.2)	0.28 (0.23–0.37)	0.55 (0.38–1.09)	1.63 (1.1–20)
Demographics					
Age, years (mean ± SD)	57 ± 9	61 ± 9	64 ± 10	67 ± 10	68 ± 10
Female, n (%)	837 (44.1)	770 (53.1)	987 (57.8)	747 (57.3)	192 (57.5)
Race/ethnicity, n (%)					
Caucasian	774 (40.8)	611 (42.2)	652 (38.2)	430 (33.0)	110 (32.9)
Chinese American	318 (16.8)	173 (11.9)	179 (10.5)	107 (8.2)	23 (6.9)
African American	407 (21.4)	361 (24.9)	510 (29.9)	433 (33.2)	127 (38.0)
Hispanic	400 (21.1)	304 (21.0)	367 (21.5)	333 (25.6)	74 (22.2)
Education, n (%)					
< High school	275 (15.5)	217 (15.0)	344 (20.1)	297 (22.3)	70 (21.0)
High school	277 (14.6)	261 (18.0)	346 (20.3)	270 (20.7)	62 (18.6)
Some college	535 (28.2)	437 (30.2)	469 (27.5)	360 (27.6)	100 (29.9)
Bachelor's degree	375 (19.8)	264 (18.2)	286 (16.7)	191 (14.7)	44 (13.2)
Graduate/professional degree	437 (23.0)	270 (18.6)	263 (15.4)	185 (14.2)	58 (17.4)
BMI, kg/m^2 (mean ± SD)	27.2 ± 4.9	28.4 ± 5.4	28.7 ± 5.6	29.2 ± 5.6	29.1 ± 6.2
BMI categories, n (%)					
Normal *	669 (35.2)	417 (28.8)	457 (26.8)	295 (22.6)	85 (25.5)
Overweight †	768 (40.4)	545 (37.6)	666 (39.0)	526 (40.4)	124 (37.1)
Obese ‡	462 (24.3)	487 (33.6)	585 (34.3)	482 (37.0)	125 (37.4)
eGFR, mL/min/1.73m^2 (mean ± SD)	82.8 ± 14.6	78.5 ± 15.0	76.2 ± 16.1	73.1 ± 16.8	72.0 ± 19.5
eGFR category, n (%)					
>90 mL/min/1.73m^2	620 (32.7)	330 (22.8)	342 (20.1)	191 (14.7)	64 (19.2)
60–90 mL/min/1.73m^2	1169 (61.6)	969 (67.0)	1095 (64.2)	837 (64.3)	193 (57.8)
<60 mL/min/1.73m^2	108 (5.7)	147 (10.2)	269 (15.8)	274 (21.0)	77 (23.1)
Diabetes, n (%)	187 (9.9)	173 (12.0)	229 (13.4)	197 (15.1)	53 (15.9)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation

* BMI <25.0 kg/m^2

† BMI 25.0–29.9 kg/m^2

‡ BMI ≥30.0 kg/m^2

Table 4

Incidence rates and hazard ratios of venous thromboembolism by categories of hemostatic and inflammatory markers: The Multi-Ethnic Study of Atherosclerosis, 2000–2015

Percentiles	1–25	26–50	51–75	76–95	96–100	p for trend
Factor VIII (%)						
Median (range)	61 (18–73)	83 (74–93)	105 (94–119)	136 (120–168)	188 (169–288)	
N total	1739	1644	1634	1353	319	
N events	45	46	51	66	17	
IR (95% CI)	2.02 (1.51–2.70)	2.24 (1.68–2.99)	2.57 (1.96–3.39)	4.11 (3.23–5.24)	4.69 (2.91–7.55)	
HR (95% CI)						
Model 1*	ref.	1.02 (0.68–1.55)	1.08 (0.68–1.54)	**1.63 (1.11–2.40)**	1.72 (0.98–3.03)	**0.004**
Model 2†	ref.	0.98 (0.65–1.47)	1.03 (0.69–1.55)	**1.47 (1.00–2.16)**	1.49 (0.84–2.63)	**0.025**
Model 3‡	ref.	0.97 (0.65–1.47)	1.03 (0.69–1.54)	1.46 (0.99–2.15)	1.47 (0.83–2.61)	**0.028**
Fibrinogen (mg/dL)						
Median (range)	269 (114–295)	317 (296–338)	362 (339–389)	420 (390–477)	517 (478–945)	
N total	1697	1665	1683	1313	333	
N events	48	56	52	49	22	
IR (95% CI)	2.24 (1.69–2.97)	2.69 (2.07–3.50)	2.51 (1.91–3.30)	3.12 (2.36–4.12)	6.01 (3.95–9.12)	
HR (95% CI)						
Model 1*	ref.	1.09 (0.74–1.61)	0.95 (0.64–1.42)	1.13 (0.75–1.71)	**2.06 (1.22–3.47)**	0.096
Model 2†	ref.	1.00 (0.68–1.47)	0.83 (0.56–1.24)	0.89 (0.58–1.35)	1.32 (0.76–2.28)	0.99
Model 3‡	ref.	1.00 (0.68–1.48)	0.83 (0.56–1.24)	0.88 (0.58–1.34)	1.30 (0.75–2.26)	0.96
D-dimer (μg/mL)						
Median (range)	0.10 (0.01–0.13)	0.18 (0.14–0.20)	0.28 (0.21–0.37)	0.55 (0.38–1.09)	1.63 (1.10–20)	
N total	1899	1449	1708	1303	334	
N events	28	39	63	73	24	
IR (95% CI)	1.12 (0.77–1.61)	2.12 (1.55–2.90)	3.06 (2.39–3.91)	4.99 (3.97–6.28)	6.60 (4.42–9.84)	
HR (95% CI)						
Model 1*	ref.	**1.64 (1.01–2.68)**	**2.13 (1.35–3.37)**	**3.17 (2.00–5.01)**	**4.18 (2.38–7.35)**	**<0.001**
Model 2†	ref.	1.49 (0.91–2.43)	**1.86 (1.18–2.96)**	**2.67 (1.68–4.25)**	**3.50 (1.98–6.19)**	**<0.001**
Model 3‡	ref.	1.49 (0.91–2.44)	**1.87 (1.18–2.97)**	**2.68 (1.68–4.26)**	**3.50 (1.98–6.19)**	**<0.001**
PAP (nM)						
Median (range)	2.90 (0.22–3.43)	3.91 (3.43–4.40)	4.92 (4.40–5.63)	6.52 (5.63–8.40)	9.57 (8.40–54.16)	
N total	1639	1638	1638	1311	327	
N events	39	56	52	48	19	
IR (95% CI)	1.83 (1.34–2.50)	2.76 (2.12–3.58)	2.59 (1.98–3.40)	3.12 (2.35–4.14)	5.47 (3.49–8.57)	
HR (95% CI)						

Percentiles	**1–25**	**26–50**	**51–75**	**76–95**	**96–100**	**p for trend**
Model 1*	ref.	1.25 (0.83–1.89)	1.04 (0.68–1.60)	1.07 (0.69–1.68)	1.71 (0.96–3.05)	0.427
Model 2†	ref.	1.32 (0.87–1.99)	1.17 (0.76–1.79)	1.23 (0.79–1.93)	**1.92 (1.08–3.42)**	0.148
Model 3‡	ref.	1.32 (0.88–2.00)	1.18 (0.77–1.81)	1.25 (0.80–1.95)	**1.96 (1.10–3.50)**	0.133
CRP (mg/L)						
Median (range)	0.50 (0.15–0.84)	1.28 (0.85–1.91)	2.87 (1.92–4.23)	6.53 (4.24–13.1)	19.00 (13.2–97.4)	
N total	1694	1656	1664	1340	331	
N events	41	54	64	51	15	
IR (95% CI)	1.93 (1.42–2.62)	2.61 (2.00–3.41)	3.18 (2.49–4.06)	3.13 (2.38–4.12)	3.88 (2.34–6.44)	
HR (95% CI)						
Model 1*	ref.	1.22 (0.82–1.84)	**1.49 (1.00–2.21)**	**1.59 (1.04–2.43)**	**1.88 (1.03–3.43)**	**0.007**
Model 2†	ref.	1.11 (0.74–1.67)	1.18 (0.76–1.76)	1.09 (0.70–1.71)	1.18 (0.63–2.21)	0.616
Model 3‡	ref.	1.11 (0.74–1.67)	1.18 (0.78–1.76)	1.09 (0.70–1.70)	1.19 (0.63–2.22)	0.613
IL-6 (pg/mL)						
Median (range)	0.58 (0.13–0.77)	0.97 (0.77–1.20)	1.49 (1.20–1.88)	2.47 (1.89–3.93)	5.07 (3.93–13.0)	
N total	1637	1636	1636	1309	327	
N events	33	52	58	58	14	
IR (95% CI)	1.53 (1.09–2.15)	2.52 (1.92–3.30)	2.93 (2.27–3.79)	3.86 (2.99–5.00)	3.83 (2.27–6.47)	
HR (95% CI)						
Model 1*	ref.	1.38 (0.89–2.14)	1.49 (0.96–2.30)	**1.99 (1.29–3.09)**	**1.96 (1.04–3.68)**	**0.001**
Model 2†	ref.	1.17 (0.75–1.82)	1.12 (0.71–1.75)	1.28 (0.80–2.05)	1.22 (0.63–2.35)	0.396
Model 3‡	ref.	1.17 (0.75–1.82)	1.11 (0.71–1.75)	1.28 (0.80–2.05)	1.20 (0.62–2.34)	0.409

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IL-6, interleukin-6; IR, incidence rate; PAP, plasmin-antiplasmin complex

*adjusted for age, sex, race/ethnicity, education and field center

†model 1 + body mass index

‡model 2 + diabetes and eGFR