

# Cardiovascular Risk Factors and Venous Thromboembolism Incidence

## *The Longitudinal Investigation of Thromboembolism Etiology*

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**Background:** The association between traditional cardiovascular risk factors and risk of venous thromboembolism (VTE) has not been extensively examined in prospective studies.

**Methods:** To determine whether atherosclerotic risk factors are also associated with increased incidence of VTE, we conducted a prospective study of 19 293 men and women without previous VTE in 6 US communities between 1987 and 1998.

**Results:** There were 215 validated VTE events (1.45 per 1000 person-years) during a median of 8 years of follow-up. The age-adjusted hazard ratio was 1.4 (95% confidence interval [CI], 1.1-1.9) for men vs women, 1.6 (95% CI, 1.2-2.2) for blacks vs whites, and 1.7 (95% CI, 1.5-2.0) per decade of age. Cigarette smoking, hypertension, dyslipidemia, physical inactivity, and alcohol consumption

were not associated with risk of VTE. Age-, race-, and sex-adjusted hazard ratios for body mass index categories (calculated as the weight in kilograms divided by the height in meters squared) of less than 25, 25 to less than 30, 30 to less than 35, 35 to less than 40, and 40 or more were 1.0, 1.5, 2.2, 1.5, and 2.7, respectively ( $P < .001$  for the trend). Diabetes was also associated with an increased risk of VTE (adjusted hazard ratio, 1.5 [95% CI, 1.0-2.1]).

**Conclusions:** Our data showing no relationship of some arterial risk factors with VTE corroborate the view that the etiology of VTE differs from atherosclerotic cardiovascular disease. In addition, the findings suggest a hypothesis that avoidance of obesity and diabetes or vigilance in prophylaxis in patients with those conditions may prevent some venous thromboses.

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**D**EEP VEIN thrombosis (DVT) and pulmonary embolus (PE), collectively referred to as venous thromboembolism (VTE), are major sources of morbidity and mortality. Several risk factors for VTE are well established, including hereditary predisposition, immobilization, surgery, and cancer.<sup>1</sup> However, it remains unclear whether arterial disease risk factors are also important to VTE because few population-based prospective epidemiologic studies of VTE have been done.<sup>2-4</sup> None has examined whether physical inactivity or abstaining from alcohol may increase risk of VTE.

Risk factors might contribute to the development and propagation of a venous thrombus by enhancing coagulability, endothelial injury, or venous stasis. For example, cigarette smoking is associated with elevated levels of plasma fibrinogen and may activate the intrinsic coagulation pathway through endothelial wall damage or anoxia.<sup>5,6</sup> Physical inactivity, obesity, and diabetes are associated with enhanced coagulation and reduced fibrinolytic potential and may contribute to ve-

nous stasis.<sup>6</sup> Lipids, particularly elevated lipoprotein(a) ([Lp(a)]) or triglycerides, interact with the coagulation and fibrinolytic cascades.<sup>6</sup> In contrast, alcohol use is associated with enhanced fibrinolysis and reduced fibrinogen levels.<sup>5,6</sup>

The Longitudinal Investigation of Thromboembolism Etiology combines information from 2 prospective cohort studies, the Atherosclerosis Risk In Communities (ARIC) study<sup>7</sup> and the Cardiovascular Health Study (CHS),<sup>8,9</sup> to investigate multiple risk factors for VTE. This analysis explores the associations between arterial disease risk factors and incidence of VTE.

## RESULTS

The mean age of the 19 293 participants at baseline was 59 years, with 55% of the sample being women, 26% black, and 92% having a high school education or less. After exclusions, there were 215 validated incident VTE events (93 idiopathic, 122 secondary) during 148 054 person-years of follow-up (median, 7.8 years) for an overall crude incidence rate of VTE of 1.45 per 1000 person-years (95% CI, 1.27-1.66). Of

## SUBJECTS AND METHODS

### STUDY POPULATION

The ARIC study is a prospective epidemiologic study that investigates the etiology of atherosclerosis and its clinical sequelae in 4 US communities.<sup>7</sup> These communities include Forsyth County, North Carolina; Jackson, Miss; suburbs of Minneapolis, Minn; and Washington County, Maryland. The study population consisted of 15 792 men and women, aged 45 to 64 years at recruitment in 1987 through 1989. Three samples represent the ethnic mix of their communities; the Jackson sample is composed exclusively of black subjects. A home interview, which included items on cardiovascular risk factors, socioeconomic factors, and family medical history, was administered to each cohort member. A subsequent clinic visit included physical measures, including sitting blood pressure, anthropometry, venipuncture, and medical history. Participants underwent reexamination in 1990 through 1992 (93% return rate), 1993 through 1995 (86%), and 1996 through 1998 (80%). A telephone questionnaire was administered annually to update information on cardiovascular events and hospitalizations.

The CHS is a population-based longitudinal study of coronary heart disease and stroke in adults 65 years and older.<sup>8,9</sup> A total of 5201 men and women sampled from Medicare eligibility lists were recruited from 4 communities in 1989 through 1990. These communities were Forsyth County, North Carolina; Sacramento County, Calif; Washington County, Maryland; and Pittsburgh, Pa. An additional 687 black subjects were recruited in 1992 and 1993. Extensive physical and laboratory evaluations were performed to identify the presence and severity of cardiovascular disease risk factors. Follow-up included semianual contacts, alternating between telephone calls and surveillance clinic visits through 1999. The participation rate (for clinic, phone, or proxy contact) in 1998-1999 was 95%. Both studies were approved by institutional review committees, and the subjects gave written informed consent at the baseline interviews.

### RISK FACTOR MEASUREMENTS

The 2 studies had very similar protocols for many baseline risk factor measurements, allowing us to pool data to increase statistical power. In both studies, weight in pounds, standing height, and waist and hip circumference in centimeters were measured at the clinic examination by standard protocols. Level of overweight was measured by body mass index (BMI). Both studies asked questions on number of cigarettes smoked per day and duration of smoking; responses to these questions provided the foundation for the definitions of smoking status and pack-years of smoking. Average alcohol intake (grams per week) was calculated in both studies based on the weekly number of glasses of wine,

number of bottles and/or cans of beer, and number of drinks of liquor.

Blood pressure was measured in both studies using the same protocol. Three measurements were taken with a random-zero sphygmomanometer, and the mean of the last 2 of 3 measurements was used. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher or current treatment with blood pressure medications.

Pooling of some variables was not possible between the ARIC and CHS studies. The ARIC study used the Baecke questionnaire<sup>10</sup> for physical activity, expressed as a sport index or a leisure-time index ranging from 0 (low) to 5 (high). In the CHS, a modified Health Interview Survey questionnaire<sup>11</sup> was administered, yielding an estimate of total kilocalories expended per week, including total leisure activity and household kilocalories.

### LABORATORY METHODS

Blood collection, sample preparation, and laboratory quality assurance methods in the CHS were patterned after the ARIC study.<sup>12-15</sup> Diabetes mellitus was defined at baseline as fasting glucose levels of 126 mg/dL (7 mmol/L) or higher,<sup>16</sup> nonfasting glucose levels of 200 mg/dL (11.1 mmol/L) or higher, or a history of or treatment for diabetes. Impaired fasting glucose level was defined as 110 mg/dL (6.1 mmol/L) or higher but lower than 126 mg/dL (7 mmol/L). Plasma total cholesterol (milligrams per deciliter) and triglyceride levels (milligrams per deciliter) were measured by enzymatic methods in both studies using Centers for Disease Control and Prevention-standardized laboratories, and low-density lipoprotein (LDL) cholesterol (milligrams per deciliter) was calculated indirectly using the Friedewald equation.<sup>17</sup> High-density lipoprotein (HDL) cholesterol was measured after precipitation of the other lipoprotein fractions by dextran sulfate.<sup>18</sup> In the ARIC study, Lp(a) (milligrams per deciliter) was measured as its total apolipoprotein by using a double-antibody enzyme-linked immunosorbent assay technique for apolipoprotein(a) detection.<sup>19</sup> In the CHS, Lp(a) was measured as its total apolipoprotein using a double-antibody enzyme-linked immunosorbent assay that detects the various isoforms of Lp(a) using in-house reagents, with monoclonal antibodies and calibrator provided by Wei Lee Wong, PhD, at Genentech Inc, South San Francisco, Calif.<sup>20</sup>

### CASE ASCERTAINMENT

The ARIC study cohort was contacted annually by telephone and seen at a clinic visit every 3 years through 1998. Hospitalizations were identified by participant report and surveillance of local hospital discharge lists for cohort members. For each hospitalization identified, *International Classification of Diseases, Ninth Revision, Clinical Modification*

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the 215 events, 130 occurred within the ARIC study sample while 85 occurred in the CHS (**Table 1**). The crude incidence rate was higher in the older CHS cohort (2.80 per 1000 person-years) than in the ARIC study cohort (1.10 per 1000 person-years). The event rate was higher in men (1.70 per 1000 person-years) than in women (1.24 per 1000

person-years). In addition, the rate in blacks was higher than in whites (1.68 vs 1.38 per 1000 person-years).

**Table 2** summarizes age-adjusted incidence rates of VTE and HRS adjusted for age, race, and sex by various levels of cardiovascular risk factors under consideration. Compared with subjects younger than 55 years at

(ICD-9-CM) discharge codes were recorded. In the CHS, follow-up involved alternating telephone calls and clinic visits every 6 months. Hospitalizations were identified primarily by self-report of the participant or proxy, and additionally by search of Health Care Financing Administration records. For every hospitalization, hospital discharge summaries and ICD-9-CM discharge codes were obtained. From each study's discharge code database, cases of possible VTE were identified by each study's coordinating center using the following ICD-9-CM codes: 415.1x, 451.1x, 451.2, 451.8x, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7x, 997.2, and 999.2, and procedure code 38.7.

Hospital records were obtained at each field center and photocopies made of discharge summaries, physician and consultant reports, vascular and radiological studies, and records of hospitalizations within 3 months of the index hospitalization. Information retrieved from the hospital records was assigned a VTE classification separately by 2 physicians (M.C. and A.R.F.). Differences between the 2 physicians were adjudicated by discussion.

### CASE CLASSIFICATION

Deep vein thrombosis was classified as definite, probable, or absent. Definite DVT was defined by a positive duplex ultrasound or venogram finding or occasionally by other means such as computed tomography. Probable DVT required a positive Doppler ultrasound or impedance plethysmography finding. A clinical diagnosis in the absence of objective tests was not considered to be a DVT. Deep vein thrombosis was further categorized as right or left lower extremity, upper extremity, or other site, and if in the lower extremity, as proximal, distal, or unknown. Pulmonary embolus was classified as definite or absent based on high-probability lung scintigraphy findings classified according to the PLOPED criteria,<sup>21</sup> angiogram results, or autopsy findings. Classification as definite PE required ventilation perfusion scanning that showed multiple segmental or subsegmental mismatched perfusion defects, a positive pulmonary angiogram, or occasionally another positive test finding (eg, computed tomography). Indeterminate scans without angiograms, positive findings of perfusion scans in the absence of ventilation scans, and clinical diagnosis in the absence of objective testing were considered nondiagnostic.

At the time of adjudication, each event was classified as an idiopathic or secondary VTE. All events that occurred within 12 months of a cancer diagnosis or within 90 days of acute medical conditions (eg, major trauma, surgery, or marked immobility) were classified as secondary.

### SUBJECTS

Participants with self-reported prevalent VTE at baseline (n=630), those taking anticoagulant medication (n=185),

and those having a history of cancer at baseline (n=1714) were excluded from the analysis. Prevalent VTE was defined in the CHS by participants' positive response to either of the following baseline questions: "Has a doctor ever told you that you had deep vein thrombosis or blood clots in your legs?" or "Has a doctor ever told you that you had pulmonary embolus or blood clots in your lungs?" In the ARIC study, prevalent VTE at baseline was determined retrospectively at the visit-4 examination by participants' positive response to either of the following questions: "Has a doctor ever told you that you had a blood clot in the leg (deep vein thrombosis)?" or "Has a doctor ever told you that you had a blood clot in your lungs (pulmonary embolus)?" In the ARIC study, prevalent VTE information was missing on participants who did not attend the visit-4 exam; these people and those who reported their VTE history as unknown (total, 4269) were included as at risk for incident VTE. Participants with a history of cancer were excluded.

### STATISTICAL ANALYSIS

The dependent variable was occurrence of first validated VTE (definite or probable DVT or definite PE) from baseline (1989-1990) through June 30, 1997, in the CHS and baseline (1987-1990) through December 31, 1996, in the ARIC study. All independent variables were measured at the baseline examination.

Incidence rates and 95% confidence intervals (CIs) were calculated using Poisson regression models. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) of VTE by level of each risk factor. A test for interaction of each risk factor with time showed that the proportional hazards assumption was not violated. Independence of variables was determined by statistical significance of the Wald  $\chi^2$  values for main effect terms after adding covariates to the models. Potential interactions of all risk factors with age, race, or sex were tested by using cross-product terms in the proportional hazards models. Trends in HRs were examined by fitting a linear model to the median values within increasing categories of each risk factor. We explored the possibility that those at the extreme values of some of these risk factors might be at increased risk of VTE by computing the HRs in the upper decile compared with the lowest tertile of LDL cholesterol, HDL cholesterol, total cholesterol, triglyceride, and Lp(a) levels, and the lowest decile of alcohol consumption and physical activity vs the highest tertile. Etiologic fractions (EF) were calculated using a standard formula:  $EF = p(RR - 1) / (1 + p(RR - 1))$ , where p is the proportion of population exposed to the risk factor, and RR is the estimate for relative risk (HR) for the disease for those above vs below a standard cutoff point of that risk factor.

baseline, the incidence of VTE was 2 to 7 times higher in older age groups. Incidence increased 74% (95% CI, 53%-98%) per decade of age when modeled as a continuous variable. Men were at substantially increased risk compared with women (HR, 1.44; 95% CI, 1.10-1.89), as were blacks compared with whites (HR, 1.64; 95% CI, 1.21-2.22). We found no association between education level and the incidence of VTE.

Many of the traditional atherosclerotic risk factors, including cigarette smoking (status and pack-years), hypertension, low alcohol consumption, physical inactivity, and dyslipidemia were not associated with elevated risk of VTE (Table 2). Tests for trends in HRs were not statistically significant for any of those risk factors. Those in the extreme categories of each of these risk factors were not at significantly higher risk of VTE. The ARIC study, but not the CHS,

had data on number of cigarettes smoked currently; current heavy smokers ( $\geq 25$  cigarettes per day) were at non-significantly higher risk than never smokers (HR, 1.68; 95% CI, 0.91-3.1). Nonsteroidal anti-inflammatory medication use was associated with a 1.44-fold increase in risk (95% CI, 1.03-2.02), but this association became null after further adjustment for BMI and diabetes. Other variables, including aspirin use, elevated hematocrit, elevated hemoglobin level, and elevated platelet count were also not associated with increased risk of VTE (Table 2).

In contrast, obesity and diabetes were each associated with significantly increased risks of VTE in the age-, race-, and sex-adjusted models (Table 2). The incidence of VTE in the upper tertile of BMI (calculated as the weight in kilograms divided by height in meters squared) was 2.42 times that in those in the lowest BMI tertile. The incidence of VTE in obese individuals (BMI  $\geq 30$ ) was 2.01 (95% CI, 1.60-2.52) per 1000 person-years, compared with 0.83 (95% CI, 0.62-1.11) in those with BMI lower than 25. Those with diabetes at baseline had a 1.70-fold greater risk (95% CI, 1.20-2.40) than those with normal fasting glucose levels, although those with impaired fasting glucose levels were not at increased risk.

**Table 3** shows the multivariate-adjusted HRs for VTE. Increasing age conveyed greater risk of VTE, with those 85 years or older having a 15-fold higher risk than those aged 45 to 54 years. The age association was greater for secondary than for idiopathic VTE (**Figure**). The HR for any VTE was 1.40 (95% CI, 1.02-1.93) for blacks vs whites, slightly larger for secondary than for idiopathic (Figure). Men were at higher risk than women, and this HR was only significant for secondary VTE (HR, 1.65; 95% CI, 1.14-2.40) (Figure).

In the multivariate model, BMI (5 categories) remained positively associated with VTE incidence ( $P < .001$  for the trend), although the HRs did not increase in a monotonic manner (Table 3). Those subjects in the highest category of BMI ( $\geq 40$ ) were at nearly 3 times greater risk of VTE than those with BMIs lower than 25. In a separate model (not shown) with BMI as a dichotomous variable (cutoff BMI, 30), the etiologic fraction of VTE due to obesity was calculated to be 15%, based on a prevalence of 26% of the sample with a BMI of 30 or higher and an HR of 1.71 (1.27-2.29) for a BMI of 30 or higher vs lower than 30. The association of BMI and VTE was greater for idiopathic VTE than secondary VTE, as shown in the Figure. After adjustment for BMI, the HR for VTE for diabetes vs no diabetes was attenuated to 1.46 (95% CI, 1.03-2.05). Compared with those subjects with no diabetes, those with diabetes had a greater risk for secondary VTE (HR, 1.62; 95% CI, 1.03-2.54) than for idiopathic VTE (HR, 1.27; 95% CI, 0.75-2.16).

There was a statistically significant age-by-race interaction ( $P = .02$ ), with older blacks at highest risk of VTE. However, a stratified analysis suggested that the HR differences between the race groups with increasing age were minimal, and there were relatively few VTE events among blacks. In the absence of a main effect, an age-by-hypertension interaction was statistically significant ( $P = .02$ ), with those of older age with hypertension at highest risk. No other interactions between any of the remaining risk factors and age, race, or sex were observed.

**Table 1. Number of Incident Venous Thrombosis or Pulmonary Embolic (VTE) Events and Crude VTE Incidence Rates\***

Characteristic	No. of Events	No. of Subjects	Person-Years	Incidence Rate† (95% CI)
Study				
ARIC	130	14 594	117 736	1.10 (0.93-1.31)
CHS	85	4699	30 318	2.80 (2.27-3.47)
Sex				
Female	102	10 633	82 332	1.24 (1.02-1.50)
Male	113	8660	65 722	1.70 (1.43-2.07)
Race				
White	154	14 356	111 816	1.38 (1.18-1.61)
Black	61	4937	36 238	1.68 (1.31-2.16)
Overall	215	19 293	148 054	1.45 (1.27-1.66)

\*Subjects with self-reported history of VTE at baseline, self-reported use of warfarin at baseline, or history of cancer at baseline were excluded. ARIC indicates Atherosclerosis Risk in Communities study<sup>7</sup>; CHS, Cardiovascular Health Study<sup>8,9</sup>; and CI, confidence interval.

†Per 1000 person-years.

## COMMENT

We found that VTE incidence was associated with older age, male sex, black ethnicity, BMI, and diabetes. Venous thromboembolism was not associated with educational attainment, smoking, alcohol consumption, physical inactivity, hypertension, or lipid or Lp(a) levels.

There are few epidemiologic reports on the association between coronary heart disease risk factors and VTE. To our knowledge, no data have been reported on the association of VTE with alcohol consumption or physical activity. While we hypothesized that low consumption of alcohol might increase risk of venous thrombosis, we found no such association. Similarly, very low physical activity might be associated with venous stasis, but there was no increase in risk of VTE with low physical activity levels, as measured at baseline.

Results vary across studies of the association of VTE incidence and dyslipidemia, cigarette smoking, and hypertension. In the Framingham Study,<sup>2</sup> higher total serum cholesterol levels in women (but not men) predicted increased PE death. A Japanese case-control study showed that hyperlipidemia was more prevalent in patients with DVT than in controls.<sup>22</sup> However, a study of Swedish men found no association between serum cholesterol or triglyceride levels and VTE.<sup>23</sup> Likewise, the Nurses' Health Study<sup>3</sup> found no association between high serum cholesterol levels and primary PE. In a study of children, no difference in plasma levels of cholesterol, triglycerides, HDL cholesterol, or LDL cholesterol was found between those with venous thrombosis and controls, but an increased Lp(a) level ( $> 30$  mg/dL) was a risk factor (odds ratio, 7.2; 95% CI, 3.7-14.5).<sup>24</sup> Elevated Lp(a) levels, as a potential antifibrinolytic factor, may also increase risk of VTE. In a case-control study, von Depka et al<sup>25</sup> found that VTE was associated with elevated Lp(a) levels. We found no association, however, between lipid levels and risk of VTE. The only suggested association was between Lp(a) levels and VTE in blacks, but this was hampered by a limited sample size.



**Table 2. Age-Adjusted Incidence Rates of Venous Thrombosis or Pulmonary Embolic (VTE) Events per 1000 Person-Years by Risk Factor Status and Age-, Race-, and Sex-Adjusted Hazard Ratios of VTE\***

Characteristic	Person-Years	Incidence Rate (95% CI)	Hazard Ratio (95% CI)
Age, y			
45 to <55	70 080	0.72 (0.54-0.95)	1.00
55 to <65	46 900	1.58 (1.27-1.95)	2.25 (1.57-3.23)
65 to <75	21 873	2.47 (1.89-3.22)	4.09 (2.73-6.12)
75 to <85	8339	3.12 (2.12-4.58)	5.37 (3.28-8.77)
≥85	862	6.96 (3.12-15.5)	12.6 (5.35-29.7)
Sex			
Female	82 332	1.14 (0.93-1.39)	1.00
Male	65 722	1.58 (1.30-1.91)	1.44 (1.10-1.89)
Race			
White	111 816	1.20 (1.01-1.42)	1.00
Black	36 238	1.78 (1.39-2.29)	1.64 (1.21-2.22)
Education			
>High school	10 435	1.28 (0.84-1.95)	1.00
High school	56 567	1.25 (0.99-1.58)	1.00 (0.63-1.58)
<High school	80 716	1.41 (1.16-1.70)	1.10 (0.67-1.81)
Cigarette smoking			
Never	64 155	1.26 (1.01-1.56)	1.00
Former	50 185	1.40 (1.11-1.76)	1.02 (0.75-1.40)
Current	33 563	1.40 (1.03-1.88)	1.03 (0.71-1.49)
Pack-years of smoking			
Never smokers	64 750	1.26 (1.01-1.56)	1.00
>0 to <25	40 410	1.30 (0.99-1.70)	0.95 (0.67-1.33)
≥25	39 861	1.46 (1.13-1.88)	1.05 (0.74-1.47)
Alcohol consumption, g/wk			
>60.4	29 717	1.38 (1.01-1.87)	1.00
>0-60.4	31 083	1.34 (1.00-1.78)	1.04 (0.69-1.59)
0	86 070	1.28 (1.06-1.54)	0.98 (0.68-1.42)
ARIC physical activity sport score			
≥3.00	33 000	1.45 (1.04-2.00)	1.00
2.25 to <3.00	35 483	1.40 (1.01-1.93)	0.99 (0.63-1.55)
1.75 to <2.25	29 902	1.35 (0.95-1.92)	0.94 (0.58-1.52)
1.50 to <1.75	11 849	1.76 (1.07-2.90)	1.25 (0.69-2.27)
1.00 to <1.50	7022	0.96 (0.40-2.33)	0.68 (0.27-1.75)
ARIC physical activity leisure time score			
≥2.75	37 166	1.33 (0.96-1.84)	1.00
2.25 to <2.75	39 510	1.07 (0.75-1.52)	0.79 (0.50-1.25)
2.00 to <2.25	17 573	1.79 (1.20-2.66)	1.36 (0.88-2.12)
1.50 to <2.00	19 210	2.04 (1.43-2.93)	1.45 (0.75-2.83)
1.00 to <1.50	3995	0.64 (0.16-2.56)	0.46 (0.11-1.94)
CHS physical activity, kcal/wk			
≥2317	8113	1.82 (0.95-3.48)	1.00
1080 to <2317	7804	1.76 (0.89-3.48)	0.94 (0.53-1.68)
390 to <1080	7407	1.74 (0.86-3.52)	0.88 (0.49-1.58)
135 to <390	2781	1.24 (0.46-3.35)	0.62 (0.26-1.45)
<135	4117	1.35 (0.56-3.25)	0.63 (0.29-1.40)
Hypertension status			
Normal	88 068	1.21 (0.99-1.47)	1.00
Hypertensive	59 382	1.51 (1.21-1.85)	1.20 (0.90-1.60)
Systolic BP, mm Hg			
<114	48 338	1.35 (1.04-1.75)	1.00
114 to <130	52 078	1.51 (1.21-1.89)	1.06 (0.75-1.49)
≥130	47 479	1.14 (0.88-1.47)	0.81 (0.55-1.16)
Diastolic BP, mm Hg			
<69	45 839	1.34 (1.05-1.71)	1.00
69 to <76	49 057	1.37 (1.08-1.74)	0.95 (0.69-1.33)
≥76	52 966	1.30 (1.02-1.64)	0.81 (0.57-1.14)

*Continued*

Despite a reasonable biological basis for hypothesizing a relationship between smoking and VTE, we found no association. A number of case-control studies<sup>26-28</sup> and 1 prospective study<sup>29</sup> also found no association between

cigarette smoking and risk of VTE. The Framingham Study<sup>2</sup> reported a borderline association of PE death with cigarette use in men but not in women. However, the Nurses' Health Study found that heavy cigarette smoking pre-

**Table 2. Age-Adjusted Incidence Rates of Venous Thrombosis or Pulmonary Embolic (VTE) Events per 1000 Person-Years by Risk Factor Status and Age-, Race-, and Sex-Adjusted Hazard Ratios of VTE\* (cont)**

Characteristic	Person-Years	Incidence Rate (95% CI)	Hazard Ratio (95% CI)
ADA diabetes status			
Normal	112 359	1.19 (1.00-1.41)	1.00
IFG	16 974	1.44 (0.99-2.10)	1.16 (0.77-1.75)
Diabetes	17 411	2.12 (1.56-2.87)	1.70 (1.20-2.40)
BMI†			
<25	50 503	0.83 (0.62-1.11)	1.00
25 to <30	59 286	1.35 (1.09-1.67)	1.51 (1.06-2.14)
≥30	37 953	2.01 (1.60-2.52)	2.27 (1.57-3.28)
LDL cholesterol, mg/dL (mmol/L)			
<130 (<3.37)	65 982	1.41 (1.15-1.72)	1.00
130 to <160 (3.37 to <4.14)	42 670	1.28 (0.99-1.66)	0.93 (0.67-1.28)
≥160 (≥4.14)	35 414	1.26 (0.94-1.68)	0.89 (0.63-1.27)
HDL cholesterol, mg/dL (mmol/L)			
≥57 (≥1.48)	48 174	1.41 (1.12-1.78)	1.00
43 to <57 (1.11 to <1.48)	52 066	1.14 (0.89-1.46)	0.76 (0.54-1.06)
<43 (<1.11)	45 807	1.46 (1.15-1.85)	0.91 (0.64-1.30)
Total cholesterol, mg/dL (mmol/L)			
<200 (<5.18)	55 258	1.34 (1.07-1.68)	1.00
200 to <240 (5.18 to <6.22)	55 207	1.37 (1.09-1.71)	1.05 (0.77-1.43)
≥240 (≥6.22)	35 602	1.26 (0.95-1.67)	1.03 (0.71-1.48)
Triglycerides, mg/dL (mmol/L)			
<91 (<1.03)	48 302	1.03 (0.78-1.37)	1.00
91 to <140 (1.03 to <1.58)	49 556	1.59 (1.28-1.98)	1.60 (1.12-2.27)
140 to <222 (1.58 to <2.51)	33 704	1.36 (1.03-1.79)	1.39 (0.93-2.06)
≥222 (≥2.51)	14 527	1.31 (0.85-2.02)	1.34 (0.80-2.25)
Lp(a), mg/dL			
Whites			
<9	36 595	1.22 (0.90-1.64)	1.00
9 to <34	38 538	1.41 (1.09-1.84)	1.17 (0.79-1.74)
≥34	34 938	1.09 (0.80-1.48)	0.92 (0.60-1.41)
Blacks			
<27	10 588	1.07 (0.56-2.06)	1.00
27 to <57	10 813	1.49 (0.86-2.57)	1.38 (0.59-3.24)
≥57	10 214	2.16 (1.40-3.33)	2.07 (0.93-4.61)
Aspirin use			
No	74 406	1.38 (1.14-1.67)	1.00
Yes	72 546	1.31 (1.07-1.60)	0.98 (0.75-1.28)
NSAID use			
No	123 597	1.26 (1.07-1.48)	1.00
Yes	24 457	1.72 (1.27-2.33)	1.44 (1.03-2.02)
Hematocrit, %			
<40	47 843	1.25 (0.98-1.61)	1.00
40 to <43.5	49 894	1.24 (0.97-1.58)	0.94 (0.66-1.34)
≥43.5	48 269	1.49 (1.18-1.87)	1.03 (0.69-1.53)
Hemoglobin, g/dL			
<13.3	47 303	1.21 (0.93-1.56)	1.00
13.3 to <14.5	47 444	1.40 (1.11-1.78)	1.11 (0.77-1.58)
≥14.5	51 259	1.36 (1.08-1.72)	0.97 (0.64-1.46)
Platelet count, ×10 <sup>3</sup> /μL			
<223	45 127	1.51 (1.20-1.90)	1.00
223 to <275	48 392	1.26 (0.98-1.62)	0.89 (0.64-1.23)
≥275	47 999	1.20 (0.93-1.56)	0.89 (0.63-1.26)

\*Subjects with self-reported history of VTE at baseline, self-reported use of warfarin at baseline, or history of cancer at baseline were excluded. CI indicates confidence interval; ARIC, Atherosclerosis Risk in Communities study<sup>7</sup>; CHS, Cardiovascular Health Study<sup>8,9</sup>; BP, blood pressure; ADA, American Diabetes Association; IFG, impaired fasting glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein(a); and NSAID, nonsteroidal anti-inflammatory drug.

†BMI indicates body mass index, which is calculated as the weight in kilograms divided by the height in meters squared.

dicted PE (HR, 3.3; 95% CI, 1.7-6.5),<sup>3</sup> and a study of Swedish men found that smoking 15 cigarettes per day or more carried an HR of 2.82 (95% CI, 1.30-6.13).<sup>23</sup>

There is conflicting evidence from past studies about the association of hypertension with VTE. The Nurses'

Health Study found that self-reported hypertension was associated with PE incidence (HR, 1.9; 95% CI, 1.2-2.8). However, no association was found between blood pressure and risk of death from PE in the Framingham cohort<sup>2</sup> or incidence of VTE in Swedish men.<sup>23</sup> There was no evidence

for an association of hypertension with VTE in the Longitudinal Investigation of Thromboembolism Etiology.

We found that VTE incidence increases with age, consistent with previous studies.<sup>4,30</sup> Age is a very significant risk factor for VTE, since the HRs are dramatically increased in the later decades of life. Men were at higher risk for VTE than women in this study, which agrees with other reports of middle-aged to older subjects.<sup>1,30-32</sup> In contrast,

studies of younger subjects have reported VTE incidence higher in women than in men.<sup>31</sup> Blacks had a higher incidence of VTE than whites. Other researchers have reported higher mortality<sup>33,34</sup> and incidence<sup>35</sup> of VTE in blacks.

Obesity is another important cardiovascular risk factor whose role in venous disease has not been extensively studied. Our findings of a significant positive and independent association between BMI and risk of VTE are consistent with several previous studies.<sup>2,3,23,27,36,37</sup> In addition, higher BMI was associated with a somewhat greater risk of idiopathic than secondary VTE. Obesity is associated with venous stasis and with higher levels of prothrombotic factors such as fibrinogen, plasminogen activator inhibitor 1, and factor VII,<sup>38,39</sup> which may partly explain the relationship. On the other hand, it is possible that obese individuals were more likely to be hospitalized (and thus subject to precipitating factors such as surgery and immobilization) during the follow-up period. In any case, we found that a considerable amount of VTE (etiologic fraction, 15%) might be due to obesity in the population.

There is little information about the association of diabetes mellitus with the risk of VTE. Diabetes was not related to idiopathic PE (HR, 0.7; 95% CI, 0.3-1.9) in the Nurses' Health Study.<sup>3</sup> In addition, neither the Framingham Study<sup>2</sup> nor the study of Swedish men<sup>23</sup> found any relationship between glucose level and VTE end points. In contrast, our results suggest that diabetes is associated with a 60% increase in the risk of VTE. Diabetes is associated with a hypercoagulable state and vascular damage,<sup>40</sup> which may play a causal role in VTE. Because the association was attenuated after accounting for BMI, it is likely that some of the association with diabetes mellitus is related to a higher prevalence of obesity among people with diabetes.

Since few established arterial disease risk factors are associated with the risk of VTE, it is reasonable to conclude that venous disease has a different etiology from arterial disease. Although thrombosis following athero-

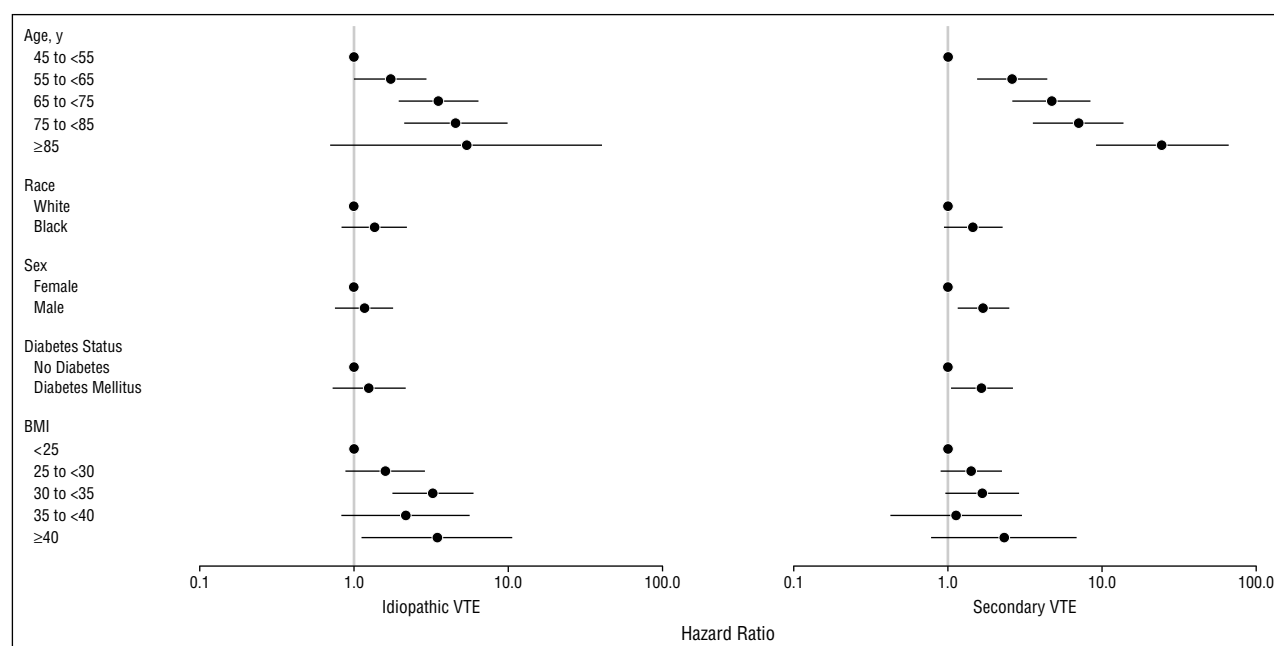
**Table 3. Multivariate Hazard Ratios for Venous Thrombosis or Pulmonary Embolic (VTE) Events by Risk Factor Level\***

Characteristic	Hazard Ratio (95% CI)
Age, y	
45 to <55	1.00
55 to <65	2.12 (1.48-3.06)
65 to <75	3.99 (2.66-6.01)
75 to <85	5.66 (3.44-9.30)
≥85	14.8 (6.26-35.1)
Race	
White	1.00
Black	1.40 (1.02-1.93)
Sex	
Female	1.00
Male	1.43 (1.09-1.89)
ADA diabetes status	
No diabetes	1.00
Diabetes mellitus	1.46 (1.03-2.05)
BMI†	
<25	1.00
25 to <30	1.47 (1.04-2.10)
30 to <35	2.23 (1.50-3.11)
35 to <40	1.52 (0.78-2.96)
≥40	2.71 (1.26-5.84)

\*Subjects with self-reported history of VTE at baseline, self-reported use of warfarin at baseline, or history of cancer at baseline were excluded.

CI indicates confidence interval; ADA, American Diabetes Association.

†BMI indicates body mass index, which is calculated as the weight in kilograms divided by the height in meters squared.



Multivariate hazard ratios with confidence intervals for idiopathic and secondary venous thrombosis or pulmonary embolic (VTE) events by risk factor level. Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared.

sclerotic plaque rupture is important, risk factors such as cigarette smoking and hypertension may contribute more to atherosclerosis, endothelial dysfunction, and plaque instability than to thrombosis per se. Levels of prothrombotic or fibrinolytic factors may play a larger role in venous disease than do atherosclerosis risk factors.

The present study has many strengths. It is one of the largest epidemiologic studies to investigate risk factors for VTE. The cohorts studied are typical of general US adult populations, including a wide age range. Validation of VTE events was standardized and thorough, and risk factors were accurately measured. The main limitation was that the ARIC and CHS studies had somewhat different methods for measuring a few risk factors, but the fact that there were no important interactions with age suggests that pooling the results probably did not create a biased result. Another limitation was that statistical power was insufficient for detailed analysis of VTE risk factors by race or sex.

In summary, among traditional risk factors for atherosclerotic cardiovascular disease, only age, male sex, black ethnicity, obesity, and diabetes were independently associated with VTE incidence in these pooled cohorts. The fact that smoking, high blood pressure, and dyslipidemia were not associated with VTE corroborates that venous disease likely has a different etiology from that of atherosclerotic cardiovascular disease. However, our data suggest a hypothesis that avoidance of obesity and diabetes, or vigilance in prophylaxis of patients with these conditions, might be able to prevent some venous thromboses.

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