High-density lipoprotein cholesterol and venous thromboembolism in the Longitudinal Investigation of Thromboembolism Etiology (LITE)

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We determined prospectively the risk of venous thromboembolism (VTE) in relation to baseline high-density lipoprotein cholesterol (HDL-c) in 19 049 participants of the Longitudinal Investigation of Thromboembolism Etiology (LITE), which was composed of 14 490 participants of the Atherosclerosis Risk in Communities (ARIC) study and 4559 participants of the Cardiovascular Health Study (CHS). In addition, we determined the risk of VTE in relation to baseline subfractions of HDL (HDL_2 and HDL_3) and apolipoprotein A-I (apoA-I) in 14 488 participants of the ARIC study. Age-adjusted incidence rates of VTE by HDL-c quartile ranged from 1.64 to 1.91 per 1000 person-years in men and 1.40 to 1.94 per 1000 person-years in women; however, there was no apparent trend of VTE incidence across HDL-c quartiles for either sex. The multivariate adjusted hazard ratios of VTE by HDL-c quartiles (with quartile 4 as the reference) were nonsignificant for both sexes and ranged between 0.91 and 0.99 for men and 0.78 and 1.22 for women. Results did not differ in separate evaluations of idiopathic and secondary VTE. In the ARIC study, there was no trend of VTE hazard ratios across quartiles of HDL_2, HDL_3, or apoA-I. Low HDL-c does not appear to be an important VTE risk factor. (Blood. 2008; 112:2675-2680)

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 1 per 1000 individuals annually.[1-3] Risk factors for VTE include greater age and body mass, malignancy, surgery, trauma, immobilization, hereditary predisposition, pregnancy, oral contraceptive use, and hormone replacement therapy.[2-4]

Most atherosclerosis risk factors, such as elevated cholesterol, hypertension, and cigarette smoking, do not increase risk of VTE.[5,6] Nevertheless, a recent meta-analysis pooling data from 4 case-control studies and 1 cohort study found a significant inverse association between high-density lipoprotein cholesterol (HDL-c) and VTE.[7]

HDL-c may reduce the risk of atherosclerotic lesions via reverse cholesterol transport, anti-inflammatory and antioxidant effects, and attenuation of endothelial dysfunction,[8] but the relevance of these mechanisms to VTE is unclear. We therefore determined the risk of future VTE in relation to baseline HDL-c levels, as well as subfractions of HDL (HDL_2 and HDL_3) and apolipoprotein A-I (apoA-I) level, in the Longitudinal Investigation of Thromboembolism Etiology (LITE).

Methods

Study population

The LITE is a combination of the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS). The design and recruitment for the ARIC[9] study and the CHS[10,11] have been previously described. Briefly, the ARIC study is a prospective cohort of adults aged 45 to 64 years gathered from 4 communities in the United States: Forsyth County, NC; Jackson, MS; the suburbs of Minneapolis, MN; and Washington County, MD. Sampling differed by recruitment area, and only African Americans were recruited from Jackson, MS. A total of 15 792 participants were enrolled by probability sampling from 1987 to 1989, and completed a home interview and clinic visit.

The CHS is a population-based longitudinal study of adults 65 years of age and older sampled from Medicare eligibility lists from 4 communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. A total of 5201 men and women were recruited between 1989 and 1990 and an additional 687 African Americans were recruited between 1992 and 1993.

Written informed consent was obtained from all participants according to the Declaration of Helsinki. The ARIC was approved by the institutional review boards at Johns Hopkins University (Baltimore, MD), University of Mississippi Medical Center (Jackson, MS), University of Minnesota (Minneapolis, MN), and Wake Forest University (Winston-Salem, NC). The CHS was approved by the institutional review boards at University of California, Davis (Davis, CA), University of Pittsburgh (Pittsburgh, PA), Wake Forest University and Johns Hopkins University.

VTE case ascertainment

The ARIC participants had clinic visits every 3 years through 1998 and were contacted annually by telephone. Participant report and surveillance of local hospital discharge lists were used to identify hospitalizations. The CHS participants had alternating clinic visits and telephone contacts every 6 months through 1999 and telephone contacts at 6-month intervals since 1999. Participant or proxy report and Health Care Financing Administration record searches identified hospitalizations.

The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge codes were obtained for every hospitalization of ARIC or CHS participants. Cases of VTE were identified using the following ICD-9-CM codes: 415.1x, 451, 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, as well as

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procedure code 38.7. After identification through ICD-9-CM code, hospital records including additional hospitalizations within the previous 3 months, physician and consultant reports, discharge summaries, and vascular and radiologic studies were copied. Two physicians then assigned VTE classification for all identified cases, and inconsistencies in classification were resolved by discussion.[12]

Among VTE cases, physician statements were recorded on history of prior thrombosis and associated cancer, and recent trauma, surgery, and immobility. Secondary VTE was defined as events that were associated with cancer or chemotherapy or that occurred within 90 days of major trauma, surgery, or marked immobility. Idiopathic VTE events were not associated with any of the previous conditions.

HDL cholesterol determination

Blood collection and processing techniques for the CHS were modeled after the ARIC study as previously described.[13,14] HDL cholesterol was measured enzymatically after dextran sulfate-Mg^{2+} precipitation of other lipoproteins.[15] In ARIC, HDL_3 was determined by reprecipitation of the total HDL-c supernatant, HDL_2 was calculated by subtracting HDL_3 from HDL-c, and apoA-I was measured by radioimmunoassay.[16]

Accuracy of HDL-c measurements in the ARIC study and the CHS was assessed using standards from the Centers for Disease Control and Prevention (CDC). Repeatability of cholesterol measurements was tested by duplicate blood samples in approximately 5% of ARIC and 3% of CHS study participants shipped to the laboratory 1 week after the original sample. The coefficient of variation of blind duplicate samples for HDL-c was 5% in both the ARIC study and the CHS.[14,17] The reliability coefficient of 3 intraindividual measurements at 1- to 2-week intervals in ARIC was 0.94 for HDL-c, 0.70 for HDL_3, 0.77 for HDL_2, and 0.60 for apoA-I.[17]

Additional baseline measurements

Factor VIIIc was measured by a coagulation assay by determining the ability of the sample to correct the clotting time of human factor VIII–deficient plasma obtained from George King Bio-Medical (Overland Park, KS). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Diabetes status was determined by fasting blood glucose and self-report of physician diagnosis or current medication use for diabetes. A participant was categorized as diabetic if fasting glucose was 126 mg/dL or higher (or, if a fasting sample was not available, nonfasting glucose of 200 mg/dL or higher) or if the participant reported a physician diagnosis of diabetes or was currently taking medication for diabetes. If fasting glucose was between 110 mg/dL and 126 mg/dL and there was no self-report of physician diagnosis or use of diabetes medication, the participant was categorized as having impaired fasting glucose. Smoking and alcohol consumption were determined by self-report. Responses to number of cigarettes smoked per day and duration of smoking were used to calculate pack-years of smoking. The weekly number of glasses of wine, bottles or cans of beer, and shots of liquor were used to determine average alcohol intake in grams per week. Participants were asked to bring all medications with them to clinic visits. A prescription or self-report was used to determine cholesterol medication use and estrogen and/or progestin hormone replacement therapy (HRT) use in women at baseline.

ABO blood type, factor V Leiden, α-fibrinogen Thr312Ala, prothrombin 20210A, and fibrinogen 455G/A were measured in a case-control subset in LITE (n = 1489; 441 cases and 1048 controls). The case-control sample included all VTE cases and randomly selected controls frequency matched in a 2:1 ratio to cases on sex, race, age (in 5-year increments), study, and follow-up time.

Statistical analysis

All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC). Of the 21 680 participants in LITE, we excluded those who were not of white or African American race (n = 38 Asian/Pacific Islanders, n = 29 American Indian/Alaska Natives, and n = 20 other/unknown), or who self-reported a history of VTE or were taking warfarin at baseline (n = 765), resulting in 20 828 participants in our dataset. Sex-specific participant baseline characteristics by quartile of HDL-c were compared using a χ^2 for categorical measures and analysis of variance for continuous measures.

Incident VTE was defined as the first occurrence of validated deep vein thrombosis or pulmonary embolism from baseline through December 31, 2001. Age-adjusted incidence rates of VTE were calculated using Poisson regression models. Sex-specific hazard ratios for incident VTE by baseline quartile of HDL-c (using the highest quartile as the reference) were estimated using Cox regression after adjustment for the following covariates at baseline: age (years), study (ARIC, CHS), race (white, African American), BMI (< 25, 25 to < 30, ≥ 30 kg/m^2), diabetes status (normal, impaired fasting glucose, diabetic), factor VIIIc (percentage), smoking amount (pack-years), and current HRT use in women (no, yes). Covariates included in the fully adjusted model were well-known risk factors for VTE and variables that confounded the association between HDL-c and VTE by changing the fully adjusted betas for HDL-c quartile by at least 10% compared with a model without the confounding variable. We also examined potential confounding by thrombophilic polymorphisms in the case-control subset within LITE.

Hazard ratios were also estimated separately for idiopathic and secondary VTE, as well as hazard ratios with both sexes pooled together. We also modeled HDL-c as a continuous variable and determined hazard ratios for VTE per 1 standard deviation increment in HDL-c. Finally, we tested interactions of HDL-c with low-density lipoprotein cholesterol (LDL-c) and triglycerides (TGs) by examining the χ^2 statistic for the cross product terms to determine whether any association of HDL-c with VTE was modified by other lipids.

In ARIC, we also examined hazard ratios of incident VTE by quartiles of HDL_2, HDL_3, and apoA-I using the highest quartile as the referent group. Hazard ratios were reported separately for men and women and were adjusted for the same covariates as the HDL-c model.

Results

After excluding participants who were not of white or African American race, who had prevalent VTE at baseline, or who were taking warfarin at baseline, a total of 20 828 participants were at risk for VTE. Because of missing values for covariates in our full model, the multivariate models were based on a sample size of 19 049 participants (8656 men and 10 393 women), which pooled 14 490 participants from ARIC and 4559 participants from CHS. The largest contributors of missing values were factor VIIIc (n = 981) and pack-years of smoking (n = 450). Table 1 describes baseline characteristics of study participants by HDL-c quartile in men and women. In general, lower HDL-c levels were correlated with greater BMI, diabetes and impaired fasting glucose, higher factor VIIIc, greater use of lipid-lowering medication, greater frequency of smoking, and less consumption of alcohol. In men, increasing age was associated positively with HDL-c, and HRT use was associated with higher HDL-c in women.

A sensitivity analysis was conducted excluding participants with a history of cancer at baseline, and no difference was found in hazard ratios between participants who were free of cancer at baseline and all participants (data not shown). Therefore, we included in our dataset participants who had a history of cancer at baseline. We also tested interactions of HDL-c quartile by sex and study on hazard ratios of VTE and both interactions were statistically nonsignificant. However, we chose to report the results stratified by sex for interest's sake.

Crude VTE incidence rates were 1.43 and 3.26 per 1000 in the ARIC and CHS studies, and 1.88 and 1.76 per 1000 in men and women, respectively. Age-adjusted incidence rates and multivariate-adjusted hazard ratios by HDL-c quartiles are shown in Table 2.

Table 1. Baseline participant characteristics by HDL-c quartile, LITE

	HDL-c quartile, mg/dL, men				
Characteristic	**9.6 to <35.6**	**35.6 to <43.0**	**43.0 to <52.0**	**52.0 to 156**	***P***
Age, y	57.6 ± 0.2	58.8 ± 0.2	60.0 ± 0.2	60.6 ± 0.2	<.001
Race					
White	1855 (88.2)	1969 (83.9)	1875 (79.6)	1608 (68.4)	<.001
African American	248 (11.8)	378 (16.1)	482 (20.4)	742 (31.6)	
Study					
ARIC	1754 (83.4)	1816 (77.4)	1644 (69.7)	1637 (69.7)	<.001
CHS	349 (16.6)	531 (22.6)	713 (30.3)	713 (30.3)	
BMI, kg/m^2					
Less than 25	356 (16.9)	583 (24.9)	757 (32.2)	1042 (44.4)	<.001
25 to less than 30	1070 (50.9)	1227 (52.3)	1150 (48.8)	1012 (43.2)	
30 or greater	676 (32.2)	534 (22.8)	448 (19.0)	290 (12.4)	
Diabetes					
Yes	432 (20.6)	335 (14.3)	262 (11.1)	220 (9.4)	<.001
IFG	346 (16.5)	376 (16.1)	299 (12.7)	296 (12.6)	
No	1317 (62.9)	1628 (69.6)	1790 (76.2)	1829 (78.0)	
Factor VIIIc, %	127.5 ± 0.8	124.9 ± 0.8	123.0 ± 0.8	125.8 ± 0.8	.001
Alcohol, g/wk	36.6 ± 2.6	50.7 ± 2.6	66.0 ± 2.5	106.7 ± 2.6	<.001
Smoking, pack-years	25.8 ± 0.6	24.3 ± 0.6	22.1 ± 0.6	22.7 ± 0.6	<.001
Lipid medication	101 (4.8)	88 (3.8)	73 (3.1)	50 (2.2)	<.001
	HDL-c quartile, mg/dL, women				
Characteristic	**11.6 to <46.2**	**46.2 to <55.9**	**55.9 to <67.4**	**67.4 to 163**	***P***
Age, y	58.2 ± 0.2	58.9 ± 0.2	59.3 ± 0.2	58.9 ± 0.2	<.001
Race					
White	2131 (75.0)	2071 (73.8)	2053 (73.6)	2187 (74.4)	.627
African American	709 (25.0)	734 (26.2)	735 (26.4)	753 (25.6)	
Study					
ARIC	2179 (76.7)	2030 (72.4)	1968 (70.6)	2124 (72.2)	<.001
CHS	661 (23.3)	775 (27.6)	820 (29.4)	816 (27.8)	
BMI, kg/m^2					
Less than 25	684 (24.1)	877 (31.3)	1195 (42.9)	1656 (56.4)	<.001
25 to less than 30	964 (34.0)	971 (34.7)	943 (33.9)	867 (29.5)	
30 or greater	1189 (41.9)	950 (34.0)	647 (23.2)	413 (14.1)	
Diabetes					
Yes	623 (22.0)	378 (13.5)	232 (8.3)	142 (4.8)	<.001
IFG	382 (13.5)	297 (10.6)	231 (8.3)	186 (6.4)	
No	1826 (64.5)	2126 (75.9)	2319 (83.4)	2603 (88.8)	
Factor VIIIc, %	138.6 ± 0.8	132.8 ± 0.8	129.6 ± 0.8	126.2 ± 0.8	<.001
Alcohol, g/wk	10.7 ± 2.0	15.8 ± 2.0	21.9 ± 2.0	39.9 ± 1.9	<.001
Smoking, pack-years	13.5 ± 0.3	10.6 ± 0.3	9.7 ± 0.3	9.7 ± 0.3	<.001
Lipid medication	147 (5.2)	97 (3.5)	83 (3.0)	84 (2.9)	<.001
HRT use	243 (8.8)	332 (12.1)	457 (16.9)	869 (30.3)	<.001

Values are n (%) for categorical variables and mean plus or minus SEM for continuous variables.
BMI indicates body mass index; IFG, impaired fasting glucose; ARIC, Atherosclerosis Risk in Communities study; and CHS, Cardiovascular Health Study.

Age-adjusted incidence rates of VTE by HDL-c quartile ranged from 1.64 to 1.91 per 1000 person-years in men and 1.40 to 1.94 per 1000 person-years in women. There was no apparent trend of VTE incidence rates across quartiles of HDL-c for either men or women or both sexes pooled together. The multivariate adjusted hazard ratios of VTE by HDL-c quartiles (with quartile 4 as the referent group) were nonsignificant for both sexes and ranged between 0.91 and 0.99 for men and 0.78 and 1.22 for women. Sex-specific hazard ratios for idiopathic and secondary VTE in men and women were also close to 1.0, as were the adjusted hazard ratios for idiopathic and secondary VTE in both sexes together. Finally, the null association of HDL-c with incident VTE was not modified by LDL-c or TGs (data not shown).

In the case-control subset, the odds ratios of VTE for HDL-c quartiles did not appreciably change when additionally adjusted for ABO blood type, factor V Leiden, α-fibrinogen Thr312Ala, prothrombin 20210A, and fibrinogen −455G/A. The odds ratios for VTE (with 95% confidence intervals) for HDL-c quartiles 1, 2, 3, and 4 were 1.29 (0.87-1.93), 1.49 (1.03-2.18), 1.20 (0.84-1.71), and 1.00 (reference), respectively, when adjusted for all covariates in our full Cox regression model. After additional adjustment for all thrombophilic polymorphisms, the odds ratios were 1.18 (0.78-1.81), 1.46 (0.98-2.17), 1.19 (0.82-1.71), and 1.00, respectively. Thus, there still was no association of HDL-c with VTE after adjusting for several markers of inherited thrombophilia.

In addition, there was no association between HDL-c and VTE for ARIC and CHS analyzed separately (data not shown) or when we conducted a time-dependent sensitivity analysis adding HDL-c values from later study examinations (years 3, 6, and 9 in ARIC and year 5 in CHS; data not shown). When HDL-c was modeled as a continuous variable, hazard ratios for VTE per 1 standard deviation increment in HDL-c were very close to 1.0 with confidence intervals that overlapped 1.0 (data not shown).

Table 2. Venous thromboembolism incidence rates and hazard ratios by HDL-c quartile, LITE

	HDL-c quartile, mg/dL			
Men	**9.6 to <35.6**	**35.6 to <43.0**	**43.0 to <52.0**	**52.0 to 156**
Number of events	44	49	49	55
Person-years	24 120	27 343	27 252	26 270
Incidence rate*	1.91	1.75	1.64	1.85
Hazard ratio†	0.94	0.99	0.91	1.00
95% CI	(0.60-1.47)	(0.65-1.51)	(0.60-1.39)	Ref.
Idiopathic VTE				
Number of events	12	20	21	22
Person-years	23 912	27 085	27 032	26 009
Hazard ratio†	0.74	1.09	1.08	1.00
95% CI	(0.34-1.62)	(0.55-2.17)	(0.54-2.13)	Ref.
Secondary VTE				
Number of events	32	29	28	33
Person-years	24 040	27 206	27 085	26 110
Hazard ratio†	1.05	0.93	0.82	1.00
95% CI	(0.60-1.81)	(0.55-1.59)	(0.48-1.42)	Ref.

	HDL-c quartile, mg/dL			
Women	**11.6 to <46.2**	**46.2 to <55.9**	**55.9 to <67.4**	**67.4 to 163**
Number of events	52	62	71	53
Person-years	33 414	33 568	33 559	35 461
Incidence rate*	1.52	1.74	1.94	1.40
Hazard ratio†	0.78	0.99	1.22	1.00
95% CI	(0.50-1.20)	(0.66-1.49)	(0.83-1.80)	Ref.
Idiopathic VTE				
Number of events	21	22	32	27
Person-years	33 107	33 211	33 205	35 270
Hazard ratio†	0.54	0.70	1.08	1.00
95% CI	(0.27-1.05)	(0.38-1.30)	(0.62-1.88)	Ref.
Secondary VTE				
Number of events	31	40	39	26
Person-years	33 256	33 358	33 309	35 238
Hazard ratio†	1.03	1.29	1.38	1.00
95% CI	(0.57-1.85)	(0.74-2.25)	(0.80-2.37)	Ref.

	HDL-c quartile, mg/dL			
Men and women	**9.6 to <40.0**	**40.0 to <49.1**	**49.1 to <61.6**	**61.6 to 163.0**
Number of events	108	97	119	111
Person-years	56 994	58 885	62 908	62 236
Incidence rate*	1.94	1.51	1.74	1.65
Hazard ratio‡	0.92	0.77	0.94	1.00
95% CI	(0.67-1.28)	(0.56-1.05)	(0.71-1.26)	Ref.
Idiopathic VTE				
Number of events	38	39	48	52
Person-years	56 452	58 344	62 255	61 780
Hazard ratio‡	0.73	0.67	0.88	1.00
95% CI	(0.43-1.22)	(0.41-1.10)	(0.57-1.36)	Ref.
Secondary VTE				
Number of events	70	58	71	59
Person-years	56 727	58 563	62 487	61 825
Hazard ratio‡	1.07	0.84	0.99	1.00
95% CI	(0.70-1.64)	(0.56-1.27)	(0.67-1.45)	Ref.

Ref. indicates reference.

*Age-adjusted incidence rate per 1000 person-years.

†Multivariable model adjusted for the following covariates at baseline: age, race, study, BMI, diabetes, factor VIIIc, pack-years of smoking, and HRT use in women.

‡Multivariable model adjusted for the following covariates at baseline: sex, age, race, study, BMI, diabetes, factor VIIIc, pack-years of smoking, and HRT use in women.

In the ARIC study, 14 488 participants (6681 men and 7807 women) were at risk for VTE after exclusions. There was no trend of VTE hazard ratios across quartiles of HDL_2, HDL_3, or apoA-I (Table 3). Likewise, hazard ratios of VTE across quartiles of apolipoprotein B/apolipoprotein A-I ratio were very close to 1.0 (data not shown).

Table 3. Venous thromboembolism hazard ratios by HDL_2, HDL_3, and ApoA-I quartiles, ARIC

	HDL_2 quartile			
	1	2	3	4
Men				
HDL_2, mg/dL	0 to <6.74	6.74 to <9.63	9.63 to <13.5	13.5 to 95.3
Number of events	28	27	37	29
Hazard ratio*	1.19	0.97	1.29	1.00
95% CI	(0.69-2.03)	(0.57-1.67)	(0.78-2.13)	Ref.
Women				
HDL_2, mg/dL	0 to <10.6	10.6 to <15.4	15.4 to <21.2	21.2 to 92.5
Number of events	43	43	32	29
Hazard ratio*	1.17	1.14	1.07	1.00
95% CI	(0.70-1.98)	(0.69-1.90)	(0.63-1.82)	Ref.
	HDL_3 quartile			
	1	2	3	4
Men				
HDL_3, mg/dL	1.93 to <27.0	27.0 to <32.7	32.7 to <39.5	39.5 to 86.7
Number of events	30	28	24	39
Hazard ratio*	0.72	0.76	0.65	1.00
95% CI	(0.44-1.19)	(0.46-1.25)	(0.39-1.09)	Ref.
Women				
HDL_3, mg/dL	2.00 to <33.0	33.0 to <40.5	40.5 to <47.2	47.2 to 99.0
Number of events	33	49	28	37
Hazard ratio*	0.78	1.24	0.78	1.00
95% CI	(0.46-1.32)	(0.78-1.97)	(0.46-1.31)	Ref.
	ApoA-I quartile			
	1	2	3	4
Men				
ApoA-I, mg/L	380 to <1030	1030 to <1190	1190 to <1360	1360 to 3040
Number of events	30	26	27	38
Hazard ratio*	0.88	0.67	0.77	1.00
95% CI	(0.53-1.44)	(0.40-1.12)	(0.47-1.25)	Ref.
Women				
ApoA-I, mg/L	200 to <1210	1210 to <1400	1400 to <1610	1610 to 3040
Number of events	40	38	34	35
Hazard ratio*	1.01	0.98	0.89	1.00
95% CI	(0.61-1.68)	(0.60-1.61)	(0.54-1.47)	Ref.

*Multivariable model adjusted for the following covariates at baseline: age, race, BMI, diabetes, factor VIIIc, pack-years of smoking, and HRT use in women.

Discussion

In this population-based prospective study, there was no association of baseline HDL-c, HDL_2, HDL_3, or apoA-I with incident VTE. Our results are consistent with a previous analysis of this cohort with shorter follow-up and approximately half as many events, which reported nonsignificant hazard ratios of VTE for tertiles of HDL-c.[6] The current results conflict with a meta-analysis that reported that HDL-c levels were, on average, 2.86 mg/dL lower in patients with VTE compared with controls.[7] However, residual confounding was responsible for the association of HDL-c with VTE in 2 of these studies,[18,19] and a third study reported only unadjusted estimates.[20] Furthermore, the prior analysis within the LITE study, which reported no association between HDL-c and VTE, was not included in this meta-analysis.[6]

The meta-analysis by Ageno et al[7] included mostly case-control studies.[18,19,21,22] The association between HDL-c and VTE was strongest in a 1:1 matched case-control study of 49 male VTE patients less than 55 years of age (adjusted OR for first quartile vs second to fourth quartiles = 4.4; 95% CI, 1.2-16).[21] A second case-control study found only extremely low HDL-c levels (lowest 10%) to be inversely related to VTE in males but not in females.[22] Quartile-based adjusted odds ratios of VTE were not significant in a case-control study of postmenopausal women, although a significant inverse relation was found when dichotomizing HDL-c at the cut point of the fourth quartile.[19] The remaining case-control study found no association of HDL-c with VTE after adjustment for BMI.[18] The only cohort study included in this meta-analysis reported that those who developed VTE had 0.1 mM lower crude HDL-c at baseline than those free of VTE after 23 years of follow-up.[20] Our longitudinal cohort study did not find an association between HDL-c, HDL subfractions, or apoA-I with VTE and did not demonstrate differences between men and women.

There are a few limitations in this study. First, our study was large enough that moderate to large associations between HDL-c and VTE would have been detected, but weak associations may have been missed due to inadequate statistical power. In men, we had 80% power at a 2-sided .05 significance level to detect a hazard ratio of VTE of 1.66 for quartile 1 versus quartile 4. For women, we had 80% power to detect a hazard ratio of 1.63 for quartile 1 versus quartile 4. However, since our observed hazard ratios are nonsignificant, HDL-c may not be a risk factor for VTE. Second, as with most studies of VTE, some nonhospitalized and undetected VTE events

were missed; however, it is unlikely that these losses would have been related to HDL-c in a way that would mask any association between HDL-c and VTE. Since the late 1990s, outpatient care for VTE has grown, but our estimate is that few nonhospitalized VTE events would have been missed by our study over the entire 1987 to 2001 follow-up period. Finally, it seems unlikely that our finding of no association between HDL-c and VTE is due to uncontrolled confounding. We measured most major correlates of HDL-c and results were null, whether adjusted or not.

Our study examined the relationship of incident VTE with HDL-c, HDL_2, HDL_3, and apoA-I in a large sample of 19 049 participants followed for up to 14 years. In our large prospective sample, we found no association of these HDL measures with future VTE. Thus, low HDL-c does not appear to be an important VTE risk factor.

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Authorship

Contribution: A.M.C. and A.R.F. designed the study, conducted analyses, and wrote the paper; and A.M.C., A.R.F., S.R.H., W.D.R., and M.C. made substantial conceptual contributions and revisions.

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