Published in final edited form as:
J Thromb Haemost. 2009 April ; 7(4): 588–596. doi:10.1111/j.1538-7836.2009.03302.x.

Lipid biomarkers, hormone therapy, and the risk of venous thromboembolism in women

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Abstract

Background—Published reports of a relationship between lipids and incident venous thromboembolism (VTE) are conflicting.

Objectives—To clarify the relationship between lipids and VTE risk in healthy women, including potential effect modification by hormone therapy (HT).

Patients/Methods—Among 27,081 initially healthy women followed prospectively for incident VTE, we measured a full panel of lipid biomarkers, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and apolipoproteins A–I (apo A–I) and B_{100}.

Results—VTE occurred in 355 women during a median follow up of 11.4 years. We observed no relationship between any of the lipids and VTE risk. However, when unprovoked VTE was considered separately (N=161), both HDL-C and apo A–I were positively associated with risk. Fully adjusted hazard ratios (HR) and (95% CI) for extreme tertiles of HDL-C and apo A–I were 1.75 (1.13–2.73) and 1.70 (1.10–2.62), respectively. After stratifying by HT use, this relationship was present only among HT users; the HRs for unprovoked VTE for extreme tertiles of HDL-C and apo A–I were 3.58 (1.69–7.58) and 2.88 (1.29–6.42) among users, but only 0.79 (0.39–1.62) and 0.89 (0.50–1.57) among non-users. The interactions were statistically significant (each $P_{interaction}$ <0.05).

Conclusions—We observed little evidence that lipid levels predict risk of incident VTE among non-users of HT. High levels of HDL-C and apo A–I associate with unprovoked VTE risk among HT users. This observation likely reflects prothrombotic effects of hormone therapy that are concomitant with HDL-C and apo A–I levels, rather than direct effects of those lipids.

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Keywords

lipids; lipoproteins; thrombosis; venous thromboembolism; women

Introduction

Established risk factors for VTE include age, a prior event, surgery, trauma, immobilization, prothrombotic mutations, obesity, and hormone therapy.[1–7] There are conflicting reports, however, as to whether lipid biomarkers such as triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein (apo) A–I alter VTE risk.[2,8–12] Lipids may alter hemostasis by modulating the expression or activity of important hemostatic proteins, such as activated factors V, VII, and X and plasminogen activator inhibitor-1.[13,14] While a recent meta-analysis reported that triglycerides were slightly higher and HDL-C levels slightly lower among patients with VTE when compared to those without VTE, [15] careful epidemiological investigations of the relationship between lipid levels and the risk of VTE have yielded conflicting results. While some investigators have reported a relationship between triglyceride levels and the risk of VTE, [9,16,17] others have failed to show that same relationship after controlling for obesity.[18] Other work has associated high HDL-C levels with reduced risk for VTE, both in postmenopausal women, [9] and among men and women with recurrent VTE.[11]

However, many of these studies were unable to consider important confounders or effect modifiers of the relationship between lipid levels and incident VTE, such as body mass index (BMI) and hormone therapy use (HT).[11] HT use, in particular, is associated with VTE risk [4–6,19] and is well known to alter lipid levels[20] and measures of hemostasis.[21,22]

To address these issues, we analyzed a full panel of traditional and novel lipid biomarkers in a large prospective cohort of women at risk for future VTE. Our specific aim was to evaluate the risk of future provoked and unprovoked VTE for each of the measured biomarkers, and to address whether any observed risk was modified by hormone therapy use.

Methods

The Women's Health Study (WHS) is an ongoing prospective cohort study, which includes a randomized double-blind placebo-controlled 2 × 2 factorial design trial of aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among women aged 45 years and older. Eligible subjects were free of cardiovascular disease and cancer at baseline and were enrolled between November 1992 and July 1995 and were followed prospectively for all cardiovascular events. Incident venous thromboembolism was a prospectively evaluated secondary endpoint.[23,24] The randomized trial portion of the study was complete in March 2004. All participants in the WHS provided written informed consent, and the study protocol was approved by the institutional review board of the Brigham and Women's Hospital (Boston, Massachusetts).

Among WHS participants, 28,345 provided blood samples and information regarding hormone therapy use at baseline. These samples were stored inliquid nitrogen until they underwent lipid analysis in a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization program. Levels of total cholesterol and HDL-C were measured enzymatically on a Hitachi 911 autoanalyzer (Roche Diagnostics, Basel, Switzerland), and low-density lipoprotein cholesterol (LDL-C) was determined directly (Genzyme, Cambridge, Massachusetts). Triglycerides were measured enzymatically with correction for endogenous glycerol[25] using a Hitachi 917 analyzer and reagents and

calibrators from Roche Diagnostics. Levels of apolipoproteins B_{100} and A–I were measured by an immunoturbidometric technique on the Hitachi 911 analyzer.[26]

End Point Definition

Venous thromboembolism was ascertained by self-report at randomization, 6 months, 12 months, and then every 12 months until the end of study. On each follow-up questionnaire, women were asked separately about the new occurrence of deep vein thrombosis and pulmonary embolism. Those reporting events, including next-of-kin of decedents, were asked for permission to obtain medical records. An end points committee of physicians reviewed records in a blinded fashion. Diagnosis of deep vein thrombosis was confirmed by a positive report of venous ultrasound or venography, and diagnosis of pulmonary embolism was considered confirmed in the presence of a positive angiogram or computed tomography scan of the chest or a ventilation-perfusion scan with ≥2 mismatched defects. Deaths due to pulmonary embolism were confirmed when autopsy reports, symptoms, circumstances of death, and medical history were consistent with this diagnosis. Only events confirmed by the end points committee were included.

Unprovoked deep vein thrombosis or pulmonary embolism was defined as occurring in the absence of known malignancy (diagnosed either before or up to 3 months after the VTE), trauma, hospitalization (lasting ≥3 days), or surgery within 3 months before the VTE. Provoked VTE included events that occurred in patients with cancer or during or shortly after trauma or surgery.

Statistical Analysis

The study sample is comprised of 27,081 participants without prevalent VTE at baseline, who reported use or non-use of hormone therapy, and who underwent successful evaluation for standard lipid measures (total cholesterol, LDL-C, HDL-C, and triglycerides). Of these, apolipoprotein A–I and B_{100} measures were successful in 26906 (99.4 percent) and 26902 (99.2 percent) participants, respectively. Population distributions for each of the lipid biomarkers were computed and were divided into increasing tertiles. Differences between baseline characteristics of participants within each HDL-C category were analyzed using the chi-square test for proportions and analysis of variance for continuous measures. Unadjusted incidence rates were calculated for each lipid biomarker tertile. Trend analysis for incidence rates across tertiles used a score variable equal to the median value within increasing categories of each risk factor in unadjusted Poisson regression models. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for future VTE for the second and third tertiles for each of the lipid biomarkers as compared with the first (lowest) tertile of that biomarker. Analyses were adjusted for age, body mass index (kg/m^2), current smoking, randomized treatment assignment, and hormone therapy use at the time of blood collection. Secondary analyses limited to the first 5 years of follow up were also performed. Trend analysis for HRs across tertiles used the tertile score variable described above in fully-adjusted Cox models.

Because of the well-established impact of hormone therapy on both lipid levels and the risk of VTE, [5,20] analyses were also stratified by hormone therapy use and by VTE classification (provoked or unprovoked) on an *a priori* basis. The hypothesis that the risk of provoked as compared with unprovoked VTE would vary with increasing lipid levels was by tested by examining the equality of trends across lipid tertiles in a competing risks model adjusted for age, body mass index, current smoking, randomized treatment assignment, and hormone therapy use.[27] The hypothesis that the risk of VTE associated with lipid biomarkers would vary according to hormone therapy use was tested by means of a Cox regression model that included a term for the interaction between hormone therapy use and the tertile score variable

(described above) in addition to the main effect variables. A two-tailed P-value of <0.05 was required for either comparison to be considered statistically significant.

Results

The mean (SD) age of the study population was 54.2 (7.1) years, and the mean (SD) body mass index (BMI) was 25.9 (4.9) kg/m^2. Of the 27,801 women, 11,797 (43.6%) were users of hormone therapy at baseline. Overall, there were 355 VTE events, of which 194were provoked and 161 were unprovoked, during 298,261 person-years of follow up (median, 11.4 years, IQR 10.8, 11.8 years). The overall VTE incidence rate was 1.19 per 1,000 person-years of follow up. The incidence rates of provoked and unprovoked VTE were 0.65 and 0.54 per 1,000 person-years of follow up, respectively.

The baseline characteristics of the study population divided according to baseline HDL-C tertile are presented in Table 1. Increasing levels of HDL-C were associated with age, body mass index, and the prevalence of prevalence of hormone therapy use and current smoking.

Table 2 depicts the unadjusted incidence rates of VTE in our cohort according to baseline tertile of each of the lipid biomarkers. As shown, there is a statistically significant increase in the incidence of all VTE events with increasing levels of total cholesterol, apo B_{100}, and triglycerides. We then divided VTE events into the clinical categories of provoked and unprovoked VTE. The incidence of provoked VTE increased with increasing levels of total cholesterol, apo B_{100} and triglycerides, while the incidence of unprovoked VTE increased with apo A–I and triglyceride levels.

Table 3 depicts the hazard ratios (HR) and 95% confidence intervals (CI) of future VTE, according to baseline tertile of each of the lipid biomarkers, adjusted for age, body mass index (BMI), current smoking, hormone therapy use, and randomized treatment assignment. As shown, no statistically significant associations were observed between total VTE and any lipid biomarker. However, when VTE events were divided into provoked and unprovoked VTE, increasing levels of HDL-C and apo A–I were associated with increased risk of unprovoked VTE, but not an increased risk of provoked VTE. Specifically, the risk of future unprovoked VTE for those in the highest as compared with lowest tertiles of HDL-C and apo A–I were 1.75 (95% CI, 1.13–2.73) and 1.70 (95% CI, 1.10–2.62), respectively, while the risks for provoked VTE were 1.06 (95% CI, 0.73–1.54) and 0.94 (95% CI, 0.63–1.40) for extreme tertiles of HDL-C and apo A–I, respectively. The observed differences in the trend of association between lipid levels and provoked as compared with unprovoked events was statistically significant for apo A–I (P for equality of trends = 0.05), but not for any of the other lipid biomarkers.

After stratifying by hormone therapy use and adjusting for age, BMI, current smoking, and randomized treatment assignment, the increased risk of unprovoked VTE observed with increasing levels of HDL-C and apo A–I was apparent only among users of hormone therapy (Table 3). For example, the risk of future unprovoked VTE for those in the highest as compared to the lowest tertile of HDL-C was 3.58 (95% CI, 1.69–7.58) for users and 0.79 (95% CI, 0.39–1.62) for non-users of hormone therapy (P for interaction = 0.003). Similar results were observed for apo A–I (P for interaction = 0.03).

Stratification by hormone therapy use also revealed that among users of hormone therapy, high levels of apo B_{100} were associated with a reduced risk of unprovoked VTE (adjusted HR for extreme tertiles, 0.55, 95% CI, 0.31–0.97). By contrast, among non-users of HT, we observed the opposite trend, with an association of borderline statistical significance (P=0.06) between higher levels of apo B_{100} and increased unprovoked VTE risk (P for interaction = 0.008). We observed no statistically significant association between plasma levels of total cholesterol,

LDL-C, or triglycerides and future unprovoked VTE risk among either users or non-users of HT (Table 4). We did not observe any association between the lipid biomarkers and provoked VTE (Table 5) in either HT users or non-users.

Because HT is well-known to alter lipid levels, [20] we repeated this stratified analysis for HDL-C and apo A–I with tertile cutpoints derived from the distribution of those variables within each stratum of users and non-users of HT. Using this approach, the cutpoints separating the first from the second tertile and second from the third tertiles among HT users, respectively, were 49.7 mg/dL and 62.4 mg/dL for HDL-C and 150.9 mg/dL and 173.4 for apo A–I. For HT users, the magnitude of the risk for unprovoked VTE appeared to be somewhat smaller using these new cutpoints for HDL-C and apo A–I, but was similar in direction and statistically significant. Specifically, the adjusted HRs (95% CI) for future unprovoked VTE for the 2nd and 3rd tertiles were 1.95 (1.08–3.55) and 2.34 (1.27–4.33) (P-trend = 0.008) for HDL-C and 1.79 (0.98–3.27) and 2.21(1.22–4.03) (P-trend = 0.01) for apo A–I. Among HT non-users, adjusted HRs (95% CI) for future unprovoked VTE for the 2nd and 3rd tertiles were 1.68 (1.00–2.81) and 0.87 (0.45–1.68) (P-trend = 0.71) for HDL-C and 1.49 (0.85–2.59) and 1.45 (0.81–2.61) (P-trend = 0.23) for apo A–I. Risk estimates for the other lipid biomarkers did not change substantially after altering the tertile cutpoints.

In order to determine whether lipid levels might be associated with VTE risk soon after lipid sampling, we repeated our initial, fully-adjusted analysis and included only the first 5 years of follow up. During that time period, there were 126 VTE events (60 provoked and 66 unprovoked). Women in the highest tertile of HDL-C were at increased risk of unprovoked VTE (HR 2.59; 95% CI, 1.32–5.08; P-trend<0.01) during the first 5 years of follow-up. The risk of unprovoked VTE for women in the highest tertile of apo A–I in this analysis was similar to that in the analysis using the complete follow-up time, but was not statistically significant (HR for extreme tertiles, 1.80, 95% CI 0.94–3.45; P-trend = 0.07). We observed no association between total cholesterol, LDL-C, apo B_{100}, or triglycerides and any of the VTE endpoints (data not shown).

Discussion

In this prospective cohort of initially healthy women, we evaluated total cholesterol, LDL-C, HDL-C, triglycerides, and the apolipoproteins A–I and B_{100} as risk determinants of future VTE, stratifying our study sample according to hormone therapy use. Overall, after adjustment for important confounders and effect modifiers, there was no clear relationship between lipid levels and increased risk of VTE. Among users of HT we observed an independent, statistically significant relationship between increasing HDL-C, apo A–I, and apo B_{100} levels and the risk of unprovoked VTE. By contrast, among non-users of HT, we saw no significant relationship between any of the lipid biomarkers and the risk of unprovoked VTE.

We observed an increase in the unadjusted incidence of total VTE with increasing levels of total cholesterol, apo B_{100}, and triglycerides. These data are consistent with prior reports of altered lipid levels in subjects with VTE.[10,11,18] However, in Cox proportional hazards models accounting for important confounders and effect modifiers of the relationship between VTE risk and lipid levels, such as BMI and hormone therapy, this relationship was no longer apparent.

Our finding of no association between total cholesterol and incident VTE risk is consistent with data from 2 prospective cohorts and one case-control study.[2,9,28] The relationship between LDL-C and the risk of VTE is less well characterized, with some authors reporting lower LDL-C levels in VTE cases[16] and others increased odds of VTE among those with high levels of LDL-C.[10,17] The absence of a clear association between either total cholesterol

or LDL-C and VTE risk in the literature and in any of our predefined subgroups suggests that neither lipid measure is strongly related to VTE risk, an observation that differs markedly from the established relationship between total and LDL cholesterol and incident coronary heart disease.[29]

We also did not observe an association between triglyceride levels and either provoked or unprovoked VTE, even after stratifying by hormone therapy use. These data are consistent with those from the ARIC and CHS cohorts, [2] and another case-control study.[18] However, our data conflict with those of Doggen and colleagues, who reported a strong association between VTE and triglycerides (OR 1.9, 95% CI 1.1–3.3 for extreme quartiles) after controlling for weight, height, hospitalization, malignancy, and hormone therapy in their analysis of a large health maintenance organization's database.[9]

HDL-C and apo A–I levels did not associate with provoked VTE risk in our cohort. However, an unanticipated observation in our study was that high levels of HDL-C and apo A–I were positively associated with increased risk of unprovoked VTE among women who were using HT at the time of blood collection. While our results agree with some published reports, [2,8, 12] they may appear to contradict others.[10,11] However, our study differs from those reporting an association between HDL-C or apo A–I and VTE risk in that our cohort is composed entirely of women and the mean age of our population is somewhat higher, and we were also able to adjust for other important confounders of the association between lipids and VTE, such as body mass index. While it is possible that HDL-C and apo A–I are acting directly to increase VTE risk, a number of other possibilities seem more likely. One possible explanation is that the observed relationship may reflect concomitant prothrombotic effects of hormone therapy. The alterations in haemostatic balance seen with hormone therapy are well documented, and include increased levels of factor VII, factor VIII, and prothrombin fragments 1 and 2; decreased levels of protein C and antithrombin III; increased resistance to activated protein C, and an excess of VTE events.[19,22,30–32] Hormone therapy users with the largest alterations in their HDL-C, apo A–I, and apo B_{100} levels may be those with the most significant alterations in their hemostatic balance. Alternatively, hormone therapy preferentially increases levels of large HDL-C particles, [33] which could have a different relationship with VTE risk. However, large HDL-C particles have been reported to associate with reduced VTE risk.[10, 11] Lastly, even though we have a large sample size and note significant P-values for the main effect and for the interaction between HT and HDL-C and apo A–I levels, our observation may be due to chance.

We also observed a trend of borderline statistical significance towards an increased risk of unprovoked VTE among women with increased apo B_{100} levels who were not using HT. While there are no reports of an association between apo B_{100} and VTE risk in women of which we are aware, our observation is consistent with the association seen in men between the apo B_{100} to apoA–I ratio and VTE risk.[10]

Despite our large sample size, 11 year prospective follow up, careful ascertainment of lipids and inherited VTE risk factors and other epidemiologic covariates in over 27,000 women, limitations of our study should be considered. Participants in our study were part of a randomized, controlled trial and may be healthier than the general population. We measured lipids once, and both simple intra–individual variability and a long period of follow-up might increase the chances of misclassification. Neither of these limitations has proved a problem in prior studies using this cohort, [34] and our analysis of only the first 5 years of follow-up data demonstrates similar results to the analysis of the complete follow-up period. Lastly, hormone users and non-users were defined at the time of blood sampling, and many women may have stopped or started therapy during the years of follow-up. However, this kind of misclassification would be likely to bias us towards the null.

In conclusion, we observed little evidence that lipid levels predict incident provoked or unprovoked VTE among non-users of hormone therapy. However, hormone therapy appears to modify the effect of lipids on VTE risk, such that among users of hormone therapy, apo A–I and HDL-C are associated with an increased risk of unprovoked VTE. While it is possible that this association represents a direct thrombotic effect of high levels of apo A–I and HDL-C among hormone therapy users, it more likely reflects concomitant but unmeasured changes in haemostatic balance.

Acknowledgments

We are indebted to the participants and staff of the Women's Health Study for their dedicated and conscientious collaboration.

Sources of Funding: The Women's Health Study is supported by grants HL-43851 and CA-47988 from the National Heart, Lung, and Blood Institute and the National Cancer Institute. This work was also supported by grants from the Donald W. Reynolds Foundation and the National Institute of Aging (AG-031061). Dr. Everett is supported by the American Heart Association (0835304N).

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Table 1

Baseline characteristics of the participants.

Characteristic	Tertile of HDL-C (mg/dL)			P-value*
	1 (<46.2)	2 (46.2–58.4)	3 (>58.4)	
Number of participants	9084	8987	9010	
Mean age (SD), years	54.0 (7.3)	53.9 (7.0)	54.5 (6.9)	<0.0001
Mean body mass index (SD), kg/m2	28.1 (5.5)	25.6 (4.5)	23.9 (3.8)	<0.0001
Hormone therapy use, %	31.9	42.6	56.2	<0.0001
Aspirin use, %	49.6	50.1	50.3	0.61
Vitamin E use, %	49.8	50.3	49.8	0.72
Current smokers, %	15.5	10.7	8.5	<0.0001
White race, %	95.0	95.3	95.4	0.44

*P-values were calculated using analysis of variance for continuous variables and chi-square tests for categorical variables.

Abbreviations: HDL-C, high-density lipoprotein cholesterol

Table 2

Unadjusted incidence rates for venous thromboembolism according to baseline levels of lipid biomarkers

	Lipid Tertile			
Lipid Biomarker	**1**	**2**	**3**	**P-trend**
Total cholesterol (range, mg/dl)	<194	194–225	>225	
Incidence rate (per 1,000 person-years)				
All	1.0	1.1	1.4	0.02
Provoked	0.56	0.59	0.81	0.03
Unprovoked	0.49	0.55	0.58	0.36
Low-density lipoprotein cholesterol (range, mg/dl)	<107.9	107.9–135.6	>135.6	
Incidence rate (per 1,000 person-years)				
All	1.1	1.1	1.4	0.06
Provoked	0.59	0.58	0.77	0.10
Unprovoked	0.48	0.55	0.58	0.33
High-density lipoprotein cholesterol (range, mg/dl)	<46.2	46.2–58.4	>58.4	
Incidence rate (per 1,000 person-years)				
All	1.1	1.3	1.1	0.92
Provoked	0.70	0.65	0.60	0.41
Unprovoked	0.42	0.66	0.54	0.29
Apolipoprotein A–I (range, mg/dl)	<138.1	138.1–160.8	>160.8	
Incidence rate (per 1,000 person-years)				
All	1.1	1.2	1.3	0.25
Provoked	0.66	0.68	0.60	0.61
Unprovoked	0.44	0.52	0.67	0.02
Apolipoprotein B_{100} (range, mg/dl)	<89.6	89.6–114.1	>114.1	
Incidence rate (per 1,000 person-years)				
All	0.96	1.2	1.4	0.007
Provoked	0.50	0.66	0.78	0.02
Unprovoked	0.46	0.55	0.62	0.14
Triglycerides (range, mg/dl)	<95.0	95.0–153.0	>153.0	
Incidence rate (per 1,000 person-years)				
All	0.97	1.1	1.5	0.001
Provoked	0.58	0.58	0.80	0.04
Unprovoked	0.40	0.55	0.67	0.01

Table 3

Fully adjusted* hazard ratios and 95% confidence intervals for future venous thromboembolism according to baseline levels of lipid biomarkers

	Lipid Tertile			
Lipid Biomarker	**1**	**2**	**3**	**P-trend**
Total cholesterol (range, mg/dl)	**<194**	**194–225**	**>225**	
All, N	107	110	138	
Hazard ratio (95% CI)	1.0	0.93 (0.71–1.22)	1.04 (0.80–1.34)	0.72
Provoked, N	57	57	80	
Hazard ratio (95% CI)	1.0	0.90 (0.62–1.30)	1.09 (0.77–1.55)	0.53
Unprovoked, N	50	53	58	
Hazard ratio (95% CI)	1.0	0.96 (0.65–1.42)	0.97 (0.66–1.43)	0.88
Equality of trends†				0.60
Low-density lipoprotein cholesterol (range, mg/dl)	**<107.9**	**107.9–135.6**	**>135.6**	
All, N	107	113	135	
Hazard ratio (95% CI)	1.0	0.90 (0.69–1.18)	1.02 (0.78–1.32)	0.83
Provoked, N	59	58	77	
Hazard ratio (95% CI)	1.0	0.83 (0.58–1.20)	1.00 (0.71–1.42)	0.88
Unprovoked, N	48	55	58	
Hazard ratio (95% CI)	1.0	0.99 (0.67–1.46)	1.03 (0.70–1.52)	0.87
Equality of trends				0.99
High-density lipoprotein cholesterol (range, mg/dl)	**<46.2**	**46.2–58.4**	**>58.4**	
All, N	112	129	114	
Hazard ratio (95% CI)	1.0	1.39 (1.07–1.81)	1.31 (0.98–1.74)	0.08
Provoked, N	70	64	60	
Hazard ratio (95% CI)	1.0	1.07 (0.75–1.52)	1.06 (0.73–1.54)	0.78
Unprovoked, N	42	65	54	
Hazard ratio (95% CI)	1.0	1.97 (1.31–2.95)	1.75 (1.13–2.73)	0.02
Equality of trends				0.99
Apolipoprotein A–I (range, mg/dl)	**<138.1**	**138.1–160.8**	**>160.8**	
All, N	108	119	125	
Hazard ratio (95% CI)	1.0	1.17 (0.90–1.54)	1.24 (0.92–1.65)	0.16
Provoked, N	65	67	59	
Hazard ratio (95% CI)	1.0	1.09 (0.77–1.55)	0.94 (0.63–1.40)	0.75
Unprovoked, N	43	52	66	
Hazard ratio (95% CI)	1.0	1.30 (0.85–1.97)	1.70 (1.10–2.62)	0.02
Equality of trends				0.05
Apolipoprotein B_{100} (range, mg/dl)	**<89.6**	**89.6–114.1**	**>114.1**	

	Lipid Tertile			
Lipid Biomarker	**1**	**2**	**3**	**P-trend**
All, N	96	119	137	
Hazard ratio (95% CI)	1.0	0.97 (0.74–1.28)	1.00 (0.76–1.31)	0.99
Provoked, N	50	65	76	
Hazard ratio (95% CI)	1.0	1.01 (0.70–1.48)	1.04 (0.72–1.51)	0.82
Unprovoked, N	46	54	61	
Hazard ratio (95% CI)	1.0	0.92 (0.62–1.38)	0.94 (0.63–1.41)	0.82
Equality of trends				0.74
Triglycerides (range, mg/dl)	**<95.0**	**95.0–153.0**	**>153.0**	
All, N	98	113	144	
Hazard ratio (95% CI)	1.0	0.92 (0.70–1.22)	1.03 (0.78–1.35)	0.67
Provoked, N	58	58	78	
Hazard ratio (95% CI)	1.0	0.81 (0.56–1.17)	0.96 (0.67–1.38)	0.91
Unprovoked, N	40	55	66	
Hazard ratio (95% CI)	1.0	1.09 (0.72–1.65)	1.13 (0.74–1.71)	0.61
Equality of trends				0.77

[*] All hazard ratios and 95% confidence intervals are adjusted for age, body mass index (kg/m^2), current smoking, hormone therapy use and randomized treatment assignment.

[†] Test for equality of trends across lipid tertiles comparing provoked versus unprovoked venous thromboembolic events in a model adjusted for the covariables described above.

Abbreviations: CI, confidence interval.

Table 4

Fully adjusted* hazard ratios and 95% confidence intervals for future unprovoked venous thromboembolism according to baseline levels of lipid biomarkers, stratified according to hormone therapy use.

	Fully-Adjusted Hazard Ratio (95% CI)*			
Lipid Biomarker Tertile	**1**	**2**	**3**	**P-value**
Total cholesterol (range, mg/dl)	**<194**	**194–225**	**>225**	
Users				
Unprovoked, N	25	33	24	
Hazard ratio (95% CI)	1.0	1.12 (0.66–1.88)	0.75 (0.43–1.33)	0.29
Non-users				
Unprovoked, N	25	20	34	
Hazard ratio (95% CI)	1.0	0.78 (0.43–1.43)	1.23 (0.72–2.11)	0.36
Test for interaction				0.17
Low-density lipoprotein cholesterol (range, mg/dl)	**<107.9**	**107.9–135.6**	**>135.6**	
Users				
Unprovoked, N	30	32	20	
Hazard ratio (95% CI)	1.0	0.99 (0.59–1.64)	0.74 (0.42–1.31)	0.31
Non-users				
Unprovoked, N	18	23	38	
Hazard ratio (95% CI)	1.0	1.02 (0.55–1.91)	1.41 (0.79–2.51)	0.19
Test for interaction				0.11
High-density lipoprotein cholesterol (range, mg/dl)	**<46.2**	**46.2–58.4**	**>58.4**	
Users				
Unprovoked, N	10	29	43	
Hazard ratio (95% CI)	1.0	2.82 (1.33–6.00)	3.58 (1.69–7.58)	0.0013
Non-users				
Unprovoked, N	32	36	11	
Hazard ratio (95% CI)	1.0	1.77 (1.08–2.91)	0.79 (0.39–1.62)	0.84
Test for interaction				0.003
Apolipoprotein A–I (range, mg/dl)	**<138.1**	**138.1–160.8**	**>160.8**	
Users				
Unprovoked, N	7	21	54	
Hazard ratio (95% CI)	1.0	1.71 (0.72–4.05)	2.88 (1.29–6.42)	0.0028
Non-users				
Unprovoked, N	36	31	12	
Hazard ratio (95% CI)	1.0	1.27 (0.78–2.08)	1.00 (0.51–1.95)	0.81
Test for interaction				0.03
Apolipoprotein B_{100} (range, mg/dl)	**<89.6**	**89.6–114.1**	**>114.1**	

	Fully-Adjusted Hazard Ratio (95% CI)*			
Lipid Biomarker Tertile	**1**	**2**	**3**	**P-value**
Users				
Unprovoked, N	30	29	23	
Hazard ratio (95% CI)	1.0	0.76 (0.45–1.27)	0.55 (0.31–0.97)	0.04
Non-users				
Unprovoked, N	16	25	38	
Hazard ratio (95% CI)	1.0	1.27 (0.67–2.42)	1.73 (0.94–3.20)	0.06
Test for interaction				0.008
Triglycerides (range, mg/dl)	<95.0	95.0–153.0	>153.0	
Users				
Unprovoked, N	20	31	31	
Hazard ratio (95% CI)	1.0	0.98 (0.55–1.73)	0.78 (0.44–1.41)	0.35
Non-users				
Unprovoked, N	20	24	35	
Hazard ratio (95% CI)	1.0	1.17 (0.64–2.14)	1.59 (0.89–2.85)	0.10
Test for interaction				0.08

*All hazard ratios and 95% confidence intervals are adjusted for age, body mass index (kg/m^2), current smoking, and randomized treatment assignment.

Table 5

Fully adjusted* hazard ratios and 95% confidence intervals for future provoked venous thromboembolism according to baseline levels of lipid biomarkers, stratified according to hormone therapy use.

	Fully-Adjusted Hazard Ratio (95% CI)*			
Lipid Biomarker Tertile	**1**	**2**	**3**	**P-value**
Total cholesterol (range, mg/dl)	**<194**	**194–225**	**>225**	
Users				
Provoked, N	25	24	36	
Hazard ratio (95% CI)	1.0	0.82 (0.47–1.43)	1.11 (0.67–1.86)	0.57
Non-users				
Provoked, N	32	33	44	
Hazard ratio (95% CI)	1.0	0.98(0.60–01.61)	1.08 (0.67–1.73)	0.74
Test for interaction				0.76
Low-density lipoprotein cholesterol (range, mg/dl)	**<107.9**	**107.9–135.6**	**>135.6**	
Users				
Provoked, N	22	37	26	
Hazard ratio (95% CI)	1.0	1.61 (0.95–2.73)	1.25 (0.71–2.22)	0.51
Non-users				
Provoked, N	37	21	51	
Hazard ratio (95% CI)	1.0	0.41 (0.23–0.71)	0.81 (0.52–1.26)	0.68
Test for interaction				0.32
High-density lipoprotein cholesterol (range, mg/dl)	**<46.2**	**46.2–58.4**	**>58.4**	
Users				
Provoked, N	22	33	30	
Hazard ratio (95% CI)	1.0	1.31 (0.76–2.26)	1.02 (0.57–1.83)	0.92
Non-users				
Provoked, N	48	31	30	
Hazard ratio (95% CI)	1.0	0.88 (0.55–1.40)	1.16 (0.71–1.90)	0.59
Test for interaction				0.33
Apolipoprotein A–I (range, mg/dl)	**<138.1**	**138.1–160.8**	**>160.8**	
Users				
Provoked, N	16	27	41	
Hazard ratio (95% CI)	1.0	1.05 (0.56–1.95)	0.99 (0.54–1.79)	0.91
Non-users				
Provoked, N	49	40	18	
Hazard ratio (95% CI)	1.0	1.11 (0.72–1.70)	0.89 (0.50–1.57)	0.80
Test for interaction				0.96
Apolipoproteins B_{100} (range, mg/dl)	**<89.6**	**89.6–114.1**	**>114.1**	

	Fully-Adjusted Hazard Ratio (95% CI)*			
Lipid Biomarker Tertile	**1**	**2**	**3**	**P-value**
Users				
Provoked, N	18	32	34	
Hazard ratio (95% CI)	1.0	1.39 (0.78–2.49)	1.35 (0.75–2.41)	0.40
Non-users				
Provoked, N	32	33	42	
Hazard ratio (95% CI)	1.0	0.79 (0.48–1.31)	0.87 (0.53–1.41)	0.66
Test for interaction				0.20
Triglycerides (range, mg/dl)	<95.0	95.0–153.0	>153.0	
Users				
Provoked, N	24	26	35	
Hazard ratio (95% CI)	1.0	0.67 (0.38–1.17)	0.70 (0.41–1.19)	0.34
Non-users				
Provoked, N	34	32	43	
Hazard ratio (95% CI)	1.0	0.94 (0.57–1.55)	1.25 (0.77–2.02)	0.28
Test for interaction				0.32

*All hazard ratios and 95% confidence intervals are adjusted for age, body mass index (kg/m^2), current smoking, and randomized treatment assignment.