Cardiometabolic risk factors and venous thrombosis

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Chapter 3

Lipid levels and risk of recurrent venous thrombosis: results from the MEGA follow-up study

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ABSTRACT

Background

Knowledge of risk factors for recurrent venous thrombosis may guide decisions on duration of anticoagulation. The association between lipid levels and first venous thrombosis has been studied extensively. However, data on the role of lipids in the risk of recurrence are scarce.

Objective

To assess the association between lipid levels and recurrent venous thrombosis.

Patients/Methods

Patients with a first venous thrombosis were included from the MEGA study. Follow-up started at the date of end of anticoagulant treatment. Percentile categories of total/low-density lipoprotein/high-density lipoprotein cholesterol, triglycerides, and apolipoproteins B and A1 were established (<10^{th}, 10^{th}-25^{th}, 25^{th}-75^{th} [reference], 75^{th}-90^{th}, >90^{th} percentile). Lipids were measured at least 3 months after discontinuing anticoagulation.

Results

Of 2106 patients followed for a median of 6.9 years, 326 developed recurrence (incidence rate 2.7/100 patient-years; 95% confidence interval [CI] 2.5-3.1). With hazard ratios ranging from 0.88 (95%CI 0.55-1.42) to 1.33 (95%CI 0.86-2.04) in the highest percentile category vs the reference, we found no association across percentile categories between recurrence and lipid levels in age- and sex-adjusted models, nor after further adjustments for body mass index, diabetes, estrogen- and statin-use, and duration of anticoagulation. Subgroup analyses stratified by unprovoked or provoked first events, location (deep vein thrombosis or pulmonary embolism), and sex neither revealed an association with any of the lipid levels studied.

Conclusions

Testing lipid levels did not identify patients at an increased risk of recurrent venous thrombosis in this study, including those with unprovoked first events, and these should not influence decisions on duration of anticoagulation.

INTRODUCTION

Venous thrombosis (VT) is a common disease [1] with a high 5-year cumulative incidence of recurrence that varies among studies from 12% to 30% [2,3]. Clinicians and patients often face a dilemma, in which discontinuing anticoagulant treatment may result in a new thrombotic event, while continuing oral anticoagulation is accompanied with an incidence of major bleeding of 1-3% per year [4,5]. In this respect, knowledge of risk factors for recurrent VT is crucial, as it may guide decisions on duration of anticoagulation after a first event of VT.

Several studies have suggested that lipid-lowering drugs (i.e., statins) are associated with a decreased risk of VT, including recurrence [6-8]. Such findings make lipids interesting candidates to be assessed in relation to the risk of VT. Indeed, there has been an increasing number of studies exploring the effect of lipid levels on the risk of a first event of VT in the past few years [9-16], which results have been controversial, particularly regarding the effect of apolipoproteins [10,11,14,15]. In contrast, data on the role of lipid levels in the risk of recurrent VT are scarce [17-19]. Hence, whether testing for lipids identifies patients at an increased risk of a recurrent event is as yet unclear.

Therefore, we aimed to investigate the association between lipid levels and risk of recurrent VT in a follow-up study, with particular attention to subgroup analyses, as patients with unprovoked first events and men are at an increased risk of recurrence [2,3]. For this purpose, we used data from the Multiple Environmental and Genetic Assessment of risk factors for VT (MEGA) follow-up study. We evaluated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and apolipoproteins A1 and B.

METHODS

Patients

Patients were recruited from the MEGA study, which details have been described elsewhere [20,21]. Briefly, between March 1999 and August 2004, 4956 patients aged 18-70 years with a first deep vein thrombosis (DVT) of the leg, pulmonary embolism (PE) or both were included. Of these, 225 did not consent for follow-up, leaving 4731 patients for the MEGA follow-up study. In the current analyses, 456 patients with active or previous history of malignancy within 5 years before first event were excluded. For logistic reasons, patients were asked to provide blood samples till June 2002 only. Among the 4275 patients eligible for follow-up, 2215 provided blood samples. Lastly, 109 patients were on anticoagulant treatment at the end of follow-up and were excluded, leaving 2106 patients with follow-up starting at the date of discontinuation of anticoagulation. Between 2007 and 2009, the vital status of all

patients was acquired from the central Dutch population register, and causes of death were obtained from the national register of death certificates at the Central Bureau of Statistics [21,22].This study was approved by the Ethics Committee of the Leiden University Medical Center, and all participants gave written informed consent.

Initial questionnaire (baseline characteristics) and blood sampling

Patients filled in a questionnaire on potential risk factors for VT within a few weeks after registration at the anticoagulation clinic [20]. Of interest for this analysis are body weight and height, estrogen- and statin-use, and self-reported diabetes. Body mass index (BMI) was calculated by dividing weight (in kg) by height squared (m^2). The index date was the date of diagnosis of the first thrombotic event. Unprovoked first VT was defined in the absence of trauma, surgery, immobilization (bedridden at home or hospitalization), plaster cast or pregnancy in the first 3 months before the index date, long-distance travel in the first 2 months before the index date, or estrogen use (oral contraceptive or hormonal replacement therapy) at the index date. Blood sampling was obtained at least 3 months after discontinuing anticoagulation, or 1 year after the index date in case of prolonged anticoagulation.

Assessment of recurrent VT

Short questionnaires concerning recurrence were sent to all consenting patients known to be alive between June 2008 and July 2009 [21]. Additional information was obtained from regional anticoagulation clinics and hospitals. Deaths owing to recurrent VT were considered fatal recurrent events. Based on hospital discharge letters, information from the anticoagulation clinics, questionnaires and causes of death, possible recurrences were classified into certain and uncertain events using a decision rule as previously described [21].

Laboratory measurements

Lipid levels were measured on stored (-80°C) and previously unthawed fasting serum samples. TC and triglycerides were measured by a colorimetric method on a Modular P analyser (Roche Diagnostics, Mannheim, Germany). HDL-C was measured by a direct method based on the Kyowa Medex reaction principle using polyethylene glycol (PEG)-modified enzymes (Roche Diagnostics, Mannheim, Germany). Apolipoproteins A1 and B were measured by immunoturbidimetry on a Cobas Integra analyzer (Roche Diagnostics, Mannheim, Germany). LDL-C levels were estimated using the Friedewald formula [23], and when triglycerides exceeded 4.52 mmol/L, LDL-C was not estimated.

Statistical analysis

Duration of follow-up was defined as the time from the date of discontinuation of anticoagulation to the end of follow-up, which was defined as the date of recurrence, death or emigration, or date of filling in the short questionnaire. If patients did not complete the questionnaire, they were censored at the last date we knew them to be recurrence-free [21] (date of death [n=17], date of emigration [n=1], or date when they were last seen by the anticoagulation clinic or for research purposes [n=246]). Analyses were limited to certain recurrences (n=326), and patients with uncertain recurrent events (n=77) were censored at that time.

Lipid categories were defined *a priori* according to the levels measured in controls from the MEGA study (<10th, 10th-25th, 25th-75th [reference category], 75th-90th, and >90th percentile) [24]. Crude incidence rates with 95% confidence intervals (CIs) of recurrent VT were estimated as the number of events over the accumulated follow-up time. Cox proportional hazard regression models were used to obtain hazard ratios (HRs) for recurrence with 95% CIs. HRs were adjusted for age and sex, estrogen use at blood sampling (dichotomous value), BMI (continuous values), statin use (dichotomous value), self-reported diabetes (dichotomous value), and duration of anticoagulant treatment (dichotomized as <6 months and ≥6 months). The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function.

Subgroup analyses involved stratification by VT type (unprovoked or provoked first events), VT initial location (DVT or PE), and sex. To quantify potential misclassification of outcomes, we performed several sensitivity analyses for overall recurrence: follow-up started at the date of first event or blood sampling, certain and uncertain recurrences were both taken into account, and patients lost to follow-up were considered to have developed recurrence at the end of the study (for which date of recurrence was set at the date on which vital status was checked). Statistical analyses were performed with SPSS for Windows, release 20.0 (SPSS Inc, Chicago, IL).

RESULTS AND DISCUSSION

Median duration of follow-up was 6.9 years (interquartile range [IQR] 2.9-8.0 years) among the 2106 patients with a first event of VT. Table 1 shows no substantial differences in the baseline characteristics of all patients compared with those who provided blood samples, indicating that the tested patients were representative of the whole cohort eligible for follow-up. Median age at discontinuation of anticoagulation was 49 years, 1161 (55%) patients were women, and most first events were provoked (70%) and DVTs (59%). Median time between first event and discontinuation of anticoagulation was 6 months (IQR 3.5-6.9 months).

Table 1. Baseline characteristics

	MEGA follow-up cohort*	Included for analyses
Total	4275 (100)	2106 (100)
Women	2351 (55)	1161 (55)
Age at discontinuation of anticoagulant therapy (years)	49 (38-59)	49 (38-58)
Classical venous thrombosis risk factors		
Provoked by†:	2876 (69)	1456 (70)
Trauma/surgery/immobilization	1661 (58)	824 (57)
Plaster cast	214 (7)	108 (7)
Estrogen use (women)	1322 (46)	696 (48)
Pregnancy/puerperium (women)	171 (6)	91 (6)
Travel > 4 h	689 (24)	364 (25)
Unprovoked	1301 (31)	621 (30)
Type of index event		
Deep vein thrombosis only	2497 (58)	1250 (59)
Pulmonary embolism ± deep vein thrombosis	1778 (42)	856 (41)

Continuous variables are shown as median (25th - 75th percentiles) and categorical variables as number (%).

Data were missing for some participants in some subgroups.

MEGA, Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis.

*Patients with active or previous history of malignancy 5 years before the first event were excluded from current analyses.

†As concomitance of provoked risk factors occurred frequently, patients could be counted twice or more.

During follow-up (11,900 patient-years), 326 patients developed recurrent VT, yielding an overall incidence rate of 2.7/100 patient-years (95% CI 2.5-3.1). Table 2 shows that TC, LDL-C, triglycerides, HDL-C, and apolipoproteins B and A1 levels were not associated with an increased risk of recurrence across percentile categories in age- and sex-adjusted models and after full adjustment. Likewise, sensitivity analyses revealed no association between lipid levels and risk of recurrence (data not shown).

As expected, rates of recurrence were higher in patients with unprovoked first events (4.5/100 patient-years, 95% CI 3.8-5.3) and men (4.1/100 patient-years, 95% CI 3.5-4.7) compared with those with provoked first events (2.1/100 patient-years, 95% CI 1.8-2.4) and women (1.8/100 patient-years, 95% CI 1.5-2.1). Subgroup analyses stratified by unprovoked or provoked first events, VT initial location (DVT or PE), and sex showed no consistent association across percentile categories between lipid levels and recurrence (Tables 3 and 4).

In this study, levels of TC, LDL-C, triglycerides, HDL-C and apolipoproteins B and apo A1 were not associated with an increased risk of recurrent VT, and none of these lipids appeared to influence the risk of recurrence in specific groups. Moreover, on the basis of our results, in the hypothesis that statins are causally associated with

Table 2. Lipid levels and risk of recurrent venous thrombosis

	PY	Events	IR	(95%CI)	HR*	(95%CI)	HR†	(95%CI)
TC (mmol L^{-1})								
< 10th (<4.28)	1133	29	2.56	(1.71-3.68)	1.03	(0.69-1.53)	1.07	(0.71-1.62)
10th - 25th (4.28-4.84)	1888	34	1.80	(1.25-2.52)	0.72	(0.49-1.04)	0.77	(0.53-1.12)
25th - 75th (4.84-6.30)	6089	174	2.86	(2.45-3.32)	1	reference	1	reference
75th - 90th (6.30-7.04)	1681	48	2.86	(2.11-3.79)	0.95	(0.69-1.31)	0.95	(0.68-1.33)
> 90th (>7.04)	1109	41	3.70	(2.65-5.02)	1.23	(0.87-1.72)	1.14	(0.79-1.64)
LDL-C (mmol L^{-1})								
< 10th (<2.38)	1119	27	2.41	(1.59-3.51)	1.07	(0.71-1.61)	1.12	(0.73-1.70)
10th - 25th (2.38-2.87)	1684	38	2.26	(1.60-3.09)	1.00	(0.70-1.44)	0.98	(0.68-1.42)
25th - 75th (2.87-4.17)	6075	158	2.60	(2.21-3.04)	1	reference	1	reference
75th - 90th (4.17-4.85)	1783	66	3.70	(2.86-4.71)	1.29	(0.97-1.73)	1.20	(0.88-1.62)
> 90th (>4.85)	1125	32	2.84	(1.95-4.02)	1.01	(0.69-1.48)	0.96	(0.65-1.44)
Triglycerides (mmol L^{-1})								
< 10th (<0.79)	1200	20	1.67	(1.02-2.57)	0.73	(0.46-1.18)	0.74	(0.46-1.21)
10th - 25th (0.79-1.00)	1812	33	1.82	(1.25-2.56)	0.76	(0.52-1.10)	0.75	(0.51-1.12)
25th - 75th (1.00-1.88)	6033	166	2.75	(2.35-3.20)	1	reference	1	reference
75th - 90th (1.88-2.58)	1736	69	3.97	(3.09-5.03)	1.29	(0.97-1.71)	1.23	(0.92-1.65)
> 90th (>2.58)	1119	38	3.40	(2.40-4.66)	1.02	(0.72-1.46)	1.01	(0.70-1.45)
Apo B (g L^{-1})								
< 10th (<0.68)	1666	29	1.74	(1.17-2.50)	0.76	(0.51-1.13)	0.82	(0.54-1.25)
10th - 25th (0.68-0.80)	1950	42	2.15	(1.55-2.91)	0.86	(0.61-1.21)	0.85	(0.59-1.21)
25th - 75th (0.80-1.15)	5815	170	2.92	(2.50-3.40)	1	reference	1	reference
75th - 90th (1.15-1.33)	1609	52	3.23	(2.41-4.24)	0.99	(0.72-1.35)	1.03	(0.74-1.41)
> 90th (>1.33)	860	33	3.83	(2.64-5.39)	1.19	(0.82-1.73)	1.16	(0.79-1.70)
HDL-C (mmol L^{-1})								
< 10th (<0.90)	1252	49	3.91	(2.90-5.17)	1.11	(0.80-1.54)	1.08	(0.77-1.53)
10th - 25th (0.90-1.07)	2050	56	2.73	(2.06-3.55)	0.84	(0.62-1.15)	0.82	(0.60-1.12)
25th - 75th (1.07-1.56)	5705	157	2.75	(2.34-3.22)	1	reference	1	reference
75th - 90th (1.56-1.86)	1868	44	2.36	(1.71-3.16)	1.01	(0.72-1.41)	1.06	(0.75-1.50)
> 90th (>1.86)	1025	20	1.95	(1.19-3.01)	0.88	(0.55-1.42)	0.70	(0.41-1.20)
Apo A1 (g L^{-1})								
< 10th (<1.09)	1603	51	3.18	(2.37-4.18)	1.04	(0.75-1.44)	1.02	(0.73-1.42)
10th - 25th (1.09-1.22)	1725	56	3.25	(2.45-4.21)	1.16	(0.85-1.57)	1.11	(0.81-1.53)
25th - 75th (1.22-1.59)	5996	153	2.55	(2.16-2.98)	1	reference	1	reference
75th - 90th (1.59-1.81)	1672	41	2.45	(1.76-3.33)	1.13	(0.80-1.61)	1.06	(0.73-1.54)
> 90th (>1.81)	904	25	2.76	(1.79-4.08)	1.33	(0.86-2.04)	1.16	(0.73-1.84)

Lipid categories were defined according to the levels measured in the control group from the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) Study [24].
Data were missing for some participants in some subgroups.
apo A1, apolipoprotein A1; apo B, apolipoprotein B; CI, confidence interval; HR, hazard ratio; HDL-C, high-density lipoprotein cholesterol; IR, incidence rate per 100 patient-years; LDL-C, low-density lipoprotein cholesterol; PY, patient-years; TC, total cholesterol.
*Adjusted for age and sex.
†Adjusted for age, sex, body mass index, estrogen use at blood sampling, statin use, self-reported diabetes, and duration of anticoagulant treatment.

Table 3. Lipid levels and risk of recurrent venous thrombosis by type and location of first event

	Unprovoked venous thrombosis n = 621				Provoked venous thrombosis n = 1456				Deep vein thrombosis n = 1250				Pulmonary embolism‡ n = 856			
	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)
TC (mmol L^{-1})																
< 10th (<4.28)	1.44	(0.80-2.61)	1.47	(0.81-2.67)	0.80	(0.47-1.38)	0.87	(0.49-1.54)	1.17	(0.71-1.93)	1.17	(0.70-1.97)	0.86	(0.44-1.68)	0.92	(0.46-1.85)
10th - 25th (4.28-4.84)	0.85	(0.49-1.46)	0.86	(0.50-1.50)	0.60	(0.36-1.00)	0.69	(0.41-1.15)	0.71	(0.44-1.15)	0.75	(0.46-1.21)	0.74	(0.41-1.33)	0.81	(0.45-1.47)
25th - 75th (4.84-6.30)	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference
75th - 90th (6.30-7.04)	1.15	(0.72-1.85)	1.05	(0.64-1.71)	0.85	(0.54-1.32)	0.90	(0.57-1.42)	0.99	(0.66-1.47)	1.04	(0.69-1.56)	0.88	(0.51-1.53)	0.81	(0.45-1.45)
> 90th (>7.04)	1.37	(0.86-2.17)	1.22	(0.74-2.00)	1.02	(0.61-1.71)	0.99	(0.58-1.68)	1.20	(0.79-1.83)	1.14	(0.74-1.77)	1.27	(0.71-2.26)	1.08	(0.56-2.05)
LDL-C (mmol L^{-1})																
< 10th (<2.38)	1.31	(0.69-2.48)	1.34	(0.70-2.59)	0.94	(0.55-1.62)	1.04	(0.60-1.80)	1.24	(0.76-2.04)	1.27	(0.77-2.10)	0.82	(0.39-1.74)	0.83	(0.38-1.80)
10th - 25th (2.38-2.87)	1.18	(0.68-2.04)	1.21	(0.69-2.10)	0.87	(0.54-1.40)	0.82	(0.50-1.36)	0.92	(0.59-1.46)	0.86	(0.54-1.38)	1.16	(0.65-2.07)	1.18	(0.65-2.16)
25th - 75th (2.87-4.17)	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference
75th - 90th (4.17-4.85)	1.85	(1.22-2.80)	1.71	(1.11-2.63)	1.02	(0.67-1.53)	0.93	(0.61-1.43)	1.21	(0.83-1.76)	1.13	(0.76-1.66)	1.45	(0.92-2.30)	1.33	(0.83-2.15)
> 90th (>4.85)	1.31	(0.80-2.15)	1.18	(0.70-2.00)	0.69	(0.37-1.29)	0.70	(0.37-1.31)	0.94	(0.59-1.49)	0.91	(0.57-1.47)	1.14	(0.58-2.25)	0.98	(0.46-2.08)

Table 3. (continued)

	Unprovoked venous thrombosis n = 621				Provoked venous thrombosis n = 1456				Deep vein thrombosis n = 1250				Pulmonary embolism‡ n = 856			
	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)
Triglycerides (mmol L^{-1})																
< 10th (<0.79)	0.97	(0.39-2.41)	0.94	(0.37-2.35)	0.67	(0.39-1.17)	0.71	(0.40-1.27)	0.74	(0.42-1.30)	0.77	(0.43-1.37)	0.70	(0.30-1.64)	0.65	(0.26-1.67)
10th - 25th (0.79-1.00)	0.83	(0.45-1.53)	0.80	(0.42-1.52)	0.68	(0.42-1.10)	0.73	(0.44-1.19)	0.84	(0.53-1.32)	0.81	(0.50-1.30)	0.62	(0.32-1.22)	0.63	(0.31-1.29)
25th - 75th (1.00-1.88)	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.88-2.58)	1.86	(1.26-2.73)	1.77	(1.19-2.64)	0.87	(0.56-1.35)	0.82	(0.52-1.28)	1.09	(0.75-1.57)	1.09	(0.74-1.58)	1.67	(1.07-2.60)	1.48	(0.92-2.38)
> 90th (>2.58)	1.15	(0.71-1.87)	1.22	(0.74-2.02)	0.89	(0.52-1.52)	0.81	(0.46-1.41)	1.08	(0.70-1.65)	1.12	(0.72-1.73)	0.89	(0.47-1.70)	0.79	(0.40-1.57)
Apo B (g L^{-1})																
< 10th (<0.68)	0.94	(0.50-1.77)	0.97	(0.51-1.87)	0.67	(0.40-1.13)	0.76	(0.44-1.32)	0.89	(0.54-1.49)	0.95	(0.57-1.57)	0.59	(0.29-1.20)	0.60	(0.28-1.30)
10th - 25th (0.68-0.80)	0.78	(0.44-1.38)	0.81	(0.45-1.46)	0.91	(0.59-1.40)	0.88	(0.55-1.39)	0.89	(0.57-1.37)	0.81	(0.50-1.29)	0.83	(0.48-1.44)	0.90	(0.51-1.59)
25th - 75th (0.80-1.15)	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.15-1.33)	1.13	(0.73-1.76)	1.13	(0.72-1.78)	0.92	(0.59-1.43)	0.93	(0.59-1.47)	0.89	(0.60-1.32)	0.93	(0.62-1.39)	1.17	(0.70-1.94)	1.18	(0.69-2.01)
> 90th (>1.33)	1.45	(0.89-2.36)	1.41	(0.85-2.35)	0.86	(0.47-1.58)	0.86	(0.47-1.58)	1.16	(0.73-1.84)	1.11	(0.69-1.78)	1.23	(0.65-2.33)	1.17	(0.59-2.31)

Table 3. (continued)

	Unprovoked venous thrombosis n = 621				Provoked venous thrombosis n = 1456				Deep vein thrombosis n = 1250				Pulmonary embolism‡ n = 856			
	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)	HR*	(95%CI)	HR†	(95%CI)
HDL-C (mmol L^{-1})																
< 10th (<0.90)	1.34	(0.86-2.08)	1.44	(0.90-2.30)	0.85	(0.51-1.41)	0.77	(0.45-1.32)	0.93	(0.61-1.41)	0.97	(0.62-1.49)	1.50	(0.89-2.53)	1.33	(0.76-2.33)
10th - 25th (0.90-1.07)	1.00	(0.66-1.52)	1.04	(0.68-1.61)	0.64	(0.40-1.03)	0.59	(0.36-0.96)	0.73	(0.49-1.10)	0.71	(0.47-1.07)	1.06	(0.65-1.72)	1.04	(0.63-1.71)
25th - 75th (1.07-1.56)	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.56-1.86)	0.74	(0.39-1.42)	0.77	(0.39-1.52)	1.14	(0.76-1.70)	1.23	(0.81-1.85)	1.11	(0.74-1.66)	1.17	(0.77-1.76)	0.80	(0.43-1.50)	0.84	(0.43-1.61)
> 90th (>1.86)	1.22	(0.60-2.48)	1.10	(0.52-2.37)	0.66	(0.34-1.28)	0.49	(0.22-1.06)	0.90	(0.51-1.58)	0.73	(0.39-1.38)	0.85	(0.36-2.00)	0.63	(0.22-1.78)
Apo A1 (g L^{-1})																
< 10th (<1.09)	1.20	(0.76-1.89)	1.25	(0.78-2.00)	0.90	(0.57-1.43)	0.85	(0.52-1.37)	0.81	(0.53-1.23)	0.83	(0.54-1.28)	1.59	(0.96-2.64)	1.48	(0.87-2.51)
10th - 25th (1.09-1.22)	1.58	(1.05-2.39)	1.65	(1.07-2.53)	0.75	(0.46-1.22)	0.72	(0.43-1.18)	0.90	(0.60-1.36)	0.86	(0.57-1.31)	1.75	(1.08-2.83)	1.78	(1.08-2.92)
25th - 75th (1.22-1.59)	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.59-1.81)	1.08	(0.60-1.93)	1.10	(0.60-2.01)	1.17	(0.75-1.84)	1.07	(0.67-1.72)	1.09	(0.71-1.67)	1.00	(0.63-1.58)	1.21	(0.65-2.25)	1.23	(0.64-2.36)
> 90th (>1.81)	1.37	(0.70-2.71)	1.18	(0.56-2.52)	1.25	(0.72-2.18)	1.08	(0.60-1.93)	1.16	(0.68-1.97)	1.01	(0.58-1.78)	1.75	(0.85-3.62)	1.53	(0.67-3.47)

Lipid categories were defined according to the levels measured in the control group from the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) Study [24]. Data were missing for some participants in some subgroups. apo A1, apolipoprotein A1; apo B, apolipoprotein B; CI, confidence interval; HR, hazard ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. *Adjusted for age and sex.†Adjusted for age, sex, body mass index, estrogen use at blood sampling, statin use, self-reported diabetes, and duration of anticoagulant treatment. ‡Pulmonary embolism with or without symptomatic deep vein thrombosis.

Table 4. Lipid levels and risk of recurrent venous thrombosis by sex

	Men n = 943				Women n = 1161			
	HR*	**(95%CI)**	**HR†**	**(95%CI)**	**HR***	**(95%CI)**	**HR†**	**(95%CI)**
TC (mmol L^{-1})								
< 10th (<4.28)	1.23	(0.73-2.05)	1.15	(0.67-1.99)	0.78	(0.41-1.47)	0.96	(0.50-1.83)
10th - 25th (4.28-4.84)	0.89	(0.56-1.43)	0.92	(0.58-1.48)	0.51	(0.28-0.93)	0.61	(0.33-1.13)
25th - 75th (4.84-6.30)	1	reference	1	reference	1	reference	1	reference
75th - 90th (6.30-7.04)	0.91	(0.60-1.37)	0.82	(0.53-1.26)	1.05	(0.62-1.78)	1.26	(0.74-2.15)
> 90th (>7.04)	1.28	(0.84-1.93)	1.18	(0.78-1.81)	1.19	(0.65-2.18)	1.04	(0.51-2.13)
LDL-C (mmol L^{-1})								
< 10th (<2.38)	1.27	(0.74-2.19)	1.23	(0.70-2.16)	0.84	(0.45-1.56)	0.94	(0.50-1.79)
10th - 25th (2.38-2.87)	1.41	(0.90-2.21)	1.38	(0.87-2.18)	0.63	(0.35-.1.13)	0.61	(0.33-1.12)
25th - 75th (2.87-4.17)	1	reference	1	reference	1	reference	1	reference
75th - 90th (4.17-4.85)	1.31	(0.92-1.88)	1.21	(0.84-1.75)	1.31	(0.80-2.15)	1.19	(0.70-2.02)
> 90th (>4.85)	1.16	(0.74-1.82)	1.06	(0.67-1.68)	0.77	(0.36-1.62)	0.74	(0.32-1.73)
Triglycerides (mmol L^{-1})								
< 10th (<0.79)	0.91	(0.46-1.80)	0.95	(0.47-1.89)	0.60	(0.31-1.15)	0.60	(0.30-1.18)
10th - 25th (0.79-1.00)	0.98	(0.60-1.61)	0.99	(0.59-1.64)	0.57	(0.31-0.99)	0.54	(0.29-1.02)
25th - 75th (1.00-1.88)	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.88-2.58)	1.33	(0.95-1.87)	1.31	(0.92-1.86)	1.24	(0.74-2.09)	1.09	(0.62-1.90)
> 90th (>2.58)	0.95	(0.63-1.45)	0.95	(0.62-1.47)	1.41	(0.72-2.75)	1.33	(0.65-2.72)
Apo B (g L^{-1})								
< 10th (<0.68)	0.98	(0.56-1.72)	0.99	(0.56-1.75)	0.60	(0.33-1.07)	0.69	(0.37-1.28)
10th - 25th (0.68-0.80)	0.88	(0.55-1.42)	0.93	(0.56-1.52)	0.81	(0.50-1.33)	0.80	(0.47-1.37)
25th - 75th (0.80-1.15)	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.15-1.33)	0.95	(0.66-1.38)	0.96	(0.66-1.40)	1.13	(0.63-2.02)	1.25	(0.68-2.31)
> 90th (>1.33)	1.21	(0.78-1.89)	1.15	(0.73-1.81)	1.18	(0.58-2.38)	1.18	(0.56-2.49)
HDL-C (mmol L^{-1})								
< 10th (<0.90)	1.07	(0.74-1.55)	1.10	(0.74-1.61)	1.40	(0.67-2.92)	1.16	(0.51-2.60)
10th - 25th (0.90-1.07)	0.83	(0.58-1.19)	0.85	(0.59-1.22)	0.92	(0.50-1.66)	0.79	(0.42-1.52)
25th - 75th (1.07-1.56)	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.56-1.86)	1.27	(0.80-2.02)	1.29	(0.81-2.06)	0.83	(0.51-1.34)	0.88	(0.53-1.46)
> 90th (>1.86)	0.75	(0.30-1.83)	0.61	(0.22-1.68)	0.94	(0.53-1.65)	0.74	(0.38-1.41)
Apo A1 (g L^{-1})								
< 10th (<1.09)	0.98	(0.67-1.41)	0.99	(0.68-1.45)	1.34	(0.70-2.57)	1.21	(0.61-2.42)
10th - 25th (1.09-1.22)	1.14	(0.79-1.64)	1.17	(0.81-1.69)	1.20	(0.68-2.13)	1.09	(0.59-2.01)
25th - 75th (1.22-1.59)	1	reference	1	reference	1	reference	1	reference
75th - 90th (1.59-1.81)	1.25	(0.76-2.05)	1.22	(0.73-2.05)	1.05	(0.64-1.73)	0.94	(0.55-1.61)
> 90th (>1.81)	1.20	(0.58-2.47)	1.25	(0.61-2.58)	1.42	(0.82-2.45)	1.13	(0.62-2.07)

Lipid categories were defined according to the levels measured in the control group from the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) Study [24]. Data were missing for some participants in some subgroups. apo A1, apolipoprotein A1; apo B, apolipoprotein B; CI, confidence interval; HR, hazard ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. *Adjusted for age. †Ajusted for age, body mass index, estrogen use at blood sampling (women), statin use, self-reported diabetes, and duration of anticoagulant treatment.

a decreased risk of recurrent VT, it is unlikely that this effect is due to statin lipid-lowering activities.

Only a few cohort studies have addressed the role of lipid levels in the risk of recurrent VT till date, and they were heterogeneous regarding the lipids studied [17-19]. In the Austrian Study on Recurrent Venous Thromboembolism [17], 772 patients with first unprovoked VT were followed for a median of 48 months. High apolipoprotein A1 levels were associated with a decreased risk of recurrence, whereas apolipoprotein B levels after adjustment for age and sex had no effect on the risk of recurrence. In contrast, we found no association between apolipoprotein A1 levels and recurrence, even among patients with unprovoked first events. The source and selection criteria of the study population, and the duration of follow-up might have accounted for the differences between the two cohorts. A Canadian study of 510 patients with first unprovoked VT [18], followed for a mean of 16.9 months, found no association between lipoprotein (a) levels and recurrence. Finally, a Swedish study of 443 patients with first unprovoked VT [19], followed for a mean of 36 months, found that low apolipoprotein M levels appeared to increase the risk of recurrence but in men only.

The strengths of this study include that this is the largest population-based cohort study that has been performed on this issue so far, in which levels of several lipids were measured after a first event of VT. Patients were followed for a long period of time for a recurrent event that was objectively confirmed [21]. Furthermore, several subgroup analyses were performed, enabling us to obtain detailed risk estimates. Some limitations of the study need to be addressed. First, weak associations between lipid levels and recurrence might have been missed due to inadequate statistical power in some subgroups, reflected in the wide CIs of the point estimates. However, weak associations, if present, will have little to no consequence regarding clinical decision-making [25]. Second, owing to the design of cohort studies, there was a time lag between the exposure (lipid assessment) and outcome (recurrence). Lipid levels might have changed over time in both groups, with and without recurrence, due to prescription of lipid-lowering drugs, changes in lifestyle (i.e., diet and physical activity), or simply aging, which could have resulted in an underestimation of the effect of lipid levels on the risk of recurrence. Third, patients were included in this study if they experienced their first event of VT up to 70 years old, and our results may therefore not be generalizable to an elderly population (i.e., >70 years old). Fourth, as blood was collected after the first event of VT, lipid levels might have been affected by acute-phase reactions at the time of the first event [26,27]. However, to avoid this problem blood was drawn with a median of 10 months (IQR 8.3-12.1 months) after the thrombotic event, by which time the effects of the acute-phase reaction would have worn off [28,29].

In conclusion, we have assessed the role of lipid levels in the risk of recurrent VT in a large longitudinal cohort of patients with a first VT, and found no evidence of an association, even among men or those with a first unprovoked event. Testing for lipid levels does not appear to be useful to identify patients at an increased risk of recurrence, and should not influence clinical decision-making regarding VT treatment.

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