High-sensitivity C-reactive protein is not a risk factor for venous thromboembolism: the Tromsø study

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Funding: Erin Mathiesen Hald receives a research grant from the Northern Norway Regional Health Authority.

Manuscript received on October 6, 2010. Revised version arrived on April 13, 2011. Manuscript accepted on April 15, 2011.

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ABSTRACT

Background

High-sensitivity C-reactive protein is associated with risk of arterial cardiovascular disease but conflicting results have been reported on its role in venous thromboembolic disease. The objective of our study was to investigate the association between high-sensitivity C-reactive protein levels and risk of future venous thromboembolism in a prospective cohort recruited from a general population.

Design and Methods

High-sensitivity C-reactive protein was measured in serum samples from 6,426 men and women, aged 25-84 years, recruited from the Tromsø Study in the period 1994-1995. Incident venous thromboembolism events (n=209) were registered during a median of 12.5 years of follow up. Cox's proportional hazards regression models were used to estimate age- and gender- and multivariable-adjusted hazard ratios with 95% confidence intervals for total venous thromboembolism, and for provoked and unprovoked venous thromboembolism by increasing levels of high-sensitivity C-reactive protein.

Results

There was no increased risk of venous thromboembolism *per* 1 standard deviation increase in high-sensitivity C-reactive protein (hazard ratio 1.08; 95% confidence interval 0.95-1.23) or across quartiles of high-sensitivity C-reactive protein (*P* for trend 0.6) in analyses adjusted for age and gender. Further adjustment for body mass index, smoking and diabetes did not alter the risk estimates. Moreover, high-sensitivity C-reactive protein was not associated with venous thromboembolism in either gender specific analysis or in separate analyses of provoked and unprovoked venous thromboembolism events.

Conclusions

In this prospective study, serum levels of high-sensitivity C-reactive protein were not associated with future development of venous thromboembolism. Our findings do not suggest a causal role for C-reactive protein in the pathogenesis of venous thromboembolism.

Key words: venous thromboembolism, C-reactive protein, risk factors, prospective study, cardiovascular disease.

Citation: Hald EM, Brækkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Brox J and Hansen J-B. High-sensitivity C-reactive protein is not a risk factor for venous thromboembolism: the Tromsø study. Haematologica 2011;96(8):1189-1194. doi:10.3324/haematol.2010.034991

Introduction

The concept of arterial cardiovascular disease (CVD) and venous thromboembolism (VTE) as separate disease entities has recently been challenged, as several epidemiological studies have reported an association between VTE and CVD.[1-3] The two conditions share risk factors such as age and obesity;[4] however, there is still controversy over the extent and nature of common pathophysiological mechanisms.

Inflammation is well established as a key factor in the development of arterial atherothrombosis.[5] C-reactive protein, a highly sensitive, non-specific systemic marker of inflammation,[6] is independently associated with incident cardiovascular disease[7-10] and may be of value in the identification and stratification of individuals at risk for cardiovascular events.[5,11]

In contrast, the role of CRP in VTE is unclear. Serum CRP increases with established risk factors for VTE[12,13] such as advancing age, obesity, pregnancy and malignancy.[14-17] Furthermore, CRP can induce tissue factor synthesis and expression in human peripheral blood monocytes.[18] In 2009, Luxembourg *et al.* reported higher levels of high-sensitivity CRP (hs-CRP) in patients with unprovoked compared to provoked VTE and controls,[19] and CRP was associated with total VTE in multivariable analyses in the Atherosclerosis Risk in Communities (ARIC) cohort.[20] These findings were supported by a recent population-based, nested case-cohort study reporting a 1.6-fold increased risk of VTE among subjects in the highest quintile *versus* the lowest quintile of CRP.[21] Two large prospective studies contradict these findings, showing no association between serum CRP levels and subsequent risk of VTE.[8,22] Accordingly, genetic polymorphisms that increase CRP levels have not been associated with increased VTE risk.[23-25]

The objective of our study was to assess whether low-grade systemic inflammation, measured by serum hs-CRP, was associated with risk of future VTE in a prospective, population-based cohort study.

Design and Methods

Study population

Participants were recruited from the fourth survey of the Tromsø Study, a single-center, prospective, population-based health study, with repeated health surveys of inhabitants in Tromsø, Norway. The fourth survey was carried out in the period 1994-1995 and consisted of two screening visits with an interval of 4-12 weeks. All inhabitants born before 1970 were invited to the first visit. All participants born in the period 1920-1944 (1920-1939 in men) and 5-10% samples in the other 5-year birth cohorts (1909-1919 and 1940-1969) were invited for a more extensive second visit. A total of 7,965 subjects attended both visits, with a response rate of 77% in women and 74% in men. Among the subjects who attended both visits, 1,055 were women participating in a sub-study with limited evaluation data; these were excluded from our study. Subjects who did not give their consent to participate in medical research (n=48), subjects with prior VTE (n=23) or lacking information about prior VTE (n=1), subjects not officially registered as inhabitants of the municipality of Tromsø at the date of examination (n=13), and subjects for whom hs-CRP evaluation data were not available (n=122) were excluded. To avoid possible acute phase reactions, participants with hs-CRP levels over 10 mg/L (n=277) were excluded from further analysis. In total, 6,426 subjects were included in the study and followed from the date of enrolment to 1st September 2007. The median follow-up time was 12.5 years (range 0.06-13.0 years) and incident VTE events were recorded. The study was approved by the Regional Committee for Medical and Health Research Ethics.

Baseline measurements

Baseline information was collected by physical examination, non-fasting blood samples and self-administered questionnaires. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846; Critikon Inc., Tampa, FL, USA) by trained personnel. Participants rested for 2 min in a sitting position and then three readings were taken on the upper right arm at 2-min intervals. The average of the two last readings was used in the analysis. Non-fasting blood samples were collected from an antecubital vein. Serum was prepared by centrifugation after one hour respite at room temperature and analyzed at the Department of Clinical Biochemistry, University Hospital of North Norway. Hs-CRP was measured by a particle-enhanced immunoturbidimetric assay on a Modular P autoanalyzer (Roche/Hitachi) using reagents from Roche Diagnostics GmbH, Mannheim, Germany. The lower detection limit of the hs-CRP assay was 0.03 mg/L and measurements of hs-CRP lower than 0.03 mg/L were, therefore, set at this value. Daily changes in precision of the assay for hs-CRP levels between 0.1 and 20 mg/L was less than 4%. Serum total cholesterol was analyzed by an enzymatic colorimetric method using a commercially available kit (CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Information on diabetes, current smoking and use of hormone therapy was collected from a self-administered questionnaire. The self-reported diabetes data were supplemented with data on confirmed diabetes from the diabetes registry of the Tromsø Study. Information on cancer was obtained from the Cancer Registry of Norway where all new cancer cases in Norway are registered according to date of diagnosis.

Outcome assessment

All first lifetime VTE events during follow up were identified by searching the discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway, as previously described.[1] Based on the presence of provoking factors at the time of diagnosis, the VTE event was further classified as unprovoked (no provoking factors) or provoked (≥ one provoking factor(s)). Major surgery, trauma or an acute medical condition (acute MI, ischemic stroke or major infectious disease) within eight weeks prior to the event, active cancer at the time of the event, marked immobilization (bed rest ≥ 3 days, wheelchair, long distance travel ≥ 4 h within 14 days prior to the event), or other potential provoking factors described by a physician in the medical record (e.g. intravascular catheter) were considered provoking factors.

Statistical analyses

Person years of follow up were accrued for each participant from the date of enrolment in the Tromsø Study (1994-1995) to the date on which a VTE event was first diagnosed, the date the participant died or officially moved from the municipality of Tromsø, or to the end of the study period (1st September 2007). Subjects who moved from the municipality of Tromsø (n=467) and subjects who died during the study period (n=1,239) were censored.

Statistical analysis was carried out using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Power was estimated using PASS (Number Cruncher Statistical Systems, Kaysville, UT, USA). Differences in age-adjusted baseline characteristics across quartiles of hs-CRP were estimated using multivariable linear or logistic regression models. Cox's proportional hazards regression models were used to estimate age- and gender- and multivariable-adjusted hazard ratios (HR) with 95% confidence intervals (CI) for total VTE, and for provoked and unprovoked VTE by increasing levels of hs-CRP. A two-sided *P* value below 0.05 was considered statistically significant. Hs-CRP was categorized into quartiles (<0.60, 0.60-1.14, 1.15-2.28 and > 2.28 mg/L), as well as into low-risk (<1.0 mg/L), intermediate-risk (1.0-3.0 mg/L) or high-risk (>3.0 mg/L) groups according to the American Heart Association and Centers for Disease Control and Prevention (AHA/CDC) guidelines for cardiovascular risk.[11] In the Cox's models, the lowest categories were used as reference groups. Potential two-way interactions were tested by including cross-product terms in the proportional hazards models for all risk factors with age and gender. The proportional hazards assumption was verified by evaluating the parallelism between the curves of the log-log survivor function in levels of the independent variables. The discriminating power of a cohort study lies in the population size, number of events during follow up and the incidence of the exposure variable in the population. In our population, the power was greater than 95% to detect a hazard ratio of total VTE of 1.15 per 1 unit change in hs-CRP levels at the 0.05 significance level. In general, the statistical power of subgroup analyses will be significantly reduced.

Results

There were 209 incident VTE events during 70,572 person years of follow up (median 12.5 years). Time from hs-CRP measurement to VTE event ranged from 0.3 to 12.8 years. The mean and median time to event was 7.0 and 7.1 years, respectively. The overall crude incidence rate (IR) of VTE was 3.0 *per* 1,000 person years. There was no difference in incidence rates of VTE between men and women (IR 3.1 *per* 1,000 person years and 2.9 *per* 1,000 person years, respectively; *P*=0.6).

Age-adjusted baseline characteristics across quartiles of hs-CRP are shown in Table 1. As expected, age, BMI, systolic blood pressure, and the proportion of diabetics and smokers increased across quartiles of hs-CRP, whereas HDL-levels decreased significantly (all *P* values for trend <0.001). There was no significant difference in the number of women on hormone therapy across quartiles of hs-CRP; however, information on hormone therapy was not available for 1,473 (45%) subjects (Table 1). Among the VTE patients, 62.7% had deep venous thrombosis (DVT) and 37.3% had pulmonary embolism (PE), with or without concurrent DVT (Table 2). A total of 82 VTE events (39.2%) were unprovoked. Cancer was the most common provoking factor and 26.8% of the VTE patients had a cancer-related VTE event (Table 2).

There was no significant increase in incidence rate of total VTE across quartiles of hs-CRP (Table 3). Subjects in the upper quartile of hs-CRP (> 2.28 mg/L) had an age- and gender-adjusted HR of 1.08 (95%CI 0.73-1.58) for total VTE compared to subjects in the lower quartile and there was no linear trend across quartiles of hs-CRP (*P* for trend 0.6) (Table 3). In the multivariable model, the HR for total VTE was 0.91 (95%CI 0.61-1.36) for subjects in the upper quartile *versus* the lower quartile of hs-CRP. When analyzing hs-CRP as a continuous variable, there was no increase in risk of VTE *per* 1 standard deviation (SD) increase in hs-CRP in either age- and gender-adjusted analysis (HR 1.08; 95%CI 0.95-1.23) or in multivariable analysis (HR 1.04; 95%CI 0.90-1.19) (Table 3). In an analysis excluding subjects with a cancer diagnosis either prior to inclusion date or during follow up (n=1,230), the multivariable HR for VTE per 1 SD increase in hs-CRP remained virtually unchanged (HR 1.07, 95%CI 0.90-1.26) (*data not shown*).

In subgroup analyses, hs-CRP levels showed no association with either unprovoked (multivariable HR per 1 SD 1.08, 95%CI 0.87-1.33) or provoked VTE (multivariable HR per 1 SD 1.01, 95%CI 0.85-1.21) (Table 3). Gender-specific analyses confirmed that there was no increase in risk of VTE across quartiles of hs-CRP in either men (*P* for trend 0.5) or women (*P* for trend 0.8) (*data not shown*). Multivariate analysis restricting to events that occurred within the first year after blood sampling (n=8) yielded a Hazard ratio for VTE by 1 SD increase in hs-CRP of 0.64 (95%CI 0.25 – 1.61). Moreover, in time-dependent Cox's regression analysis, there was no significant change in the risk of VTE by hs-CRP over time (*P*=0.3) (*data not shown*).

When classified according to the AHA/CDC guidelines for cardiovascular risk, subjects with hs-CRP levels in the high-risk group (>3.0 mg/L), had no increased risk of total VTE compared to subjects in the low-risk group (hs-CRP < 1 mg/L) (HR 1.06; 95%CI 0.71-1.58) in the multivariable model, and there was no linear trend across groups (*P*=0.7) (Table 4). When the 277 subjects with hs-CRP levels greater than 10 mg/L were included in multivariate analysis of hs-CRP levels greater than 3 mg/L *versus* less than 1

Table 1. Age-adjusted baseline characteristics of study participants by quartiles of hs-CRP: the Tromsø Study 1994-2007.[1]

	Q1	Q2	Q3	Q4	*P* for trend
Quartile range hs-CRP (mg/L)	<0.60	0.60-1.14	1.15-2.28	>2.28	
Age (yrs)	57.4±11.4	59.9±10.0	61.4±8.9	61.7±9.5	*P*<0.001
BMI (kg/m^2)	24.5±3.8	25.7±3.8	26.6±3.6	27.0±3.8	*P*<0.001
Systolic blood pressure (mmHg)	141±21	145±21	146±21	148±21	*P*<0.001
Smoking (%)	414 (25.6)	433 (26.4)	579 (36.1)	638 (39.9)	*P*<0.001
Diabetes (%)	20 (1.2)	38 (2.4)	45 (2.8)	67 (4.2)	*P*<0.001
Total cholesterol (mmol/L)	6.65±1.25	6.71±1.23	6.83±1.24	6.80±1.24	*P*<0.001
HDL cholesterol (mmol/L)	1.65±0.44	1.56±0.44	1.49±0.44	1.46±0.44	*P*<0.001
Hormone therapy (%)[2]	68 (12.0)	51 (12.1)	64 (15.0)	55 (14.4)	*P*=0.16

[1]Values are means +/- SD or numbers with percentages in brackets. [2]Women only. Information on hormone therapy was missing for 1,473 (45%) subjects.

mg/L, similar results were observed (HR 1.01; 95%CI 0.71-1.55). Moreover, there was no association between high hs-CRP levels and risk of VTE. HR for hs-CRP levels 10 mg/L or over (277 subjects, 9 VTE events) *versus* less than 1 mg/L was 1.06 (95%CI 0.73-1.54) (*data not shown*).

Discussion

In our population-based cohort study we found that hs-CRP was not associated with risk of future VTE. These findings were consistent in both age- and gender-adjusted analyses and in multivariable analyses. Furthermore, hs-CRP showed no association with either unprovoked or provoked VTE in subgroup analyses. When using a categorized approach, neither quartiles of hs-CRP nor hs-CRP levels classified according to the AHA/CDC guidelines for cardiovascular risk were associated with risk of VTE.

To date, the number of studies on the association between CRP and VTE is limited and the results are conflicting. A recent review found weak evidence for a causal role of CRP in VTE etiology.[26] Our findings are consistent with reports from previous prospective cohort studies; in both the Physicians' Health Study[8] and the Longitudinal Investigation of Thromboembolism Etiology Study,[22] CRP levels were not predictive of future VTE. In agreement with our study, hs-CRP levels in the AHA/CDC high-risk category were not associated with a first VTE event in the Prevention of Renal and Vascular End-stage Disease Study.[27]

In the Leiden Thrombophilia Study, mean and median CRP levels were higher in VTE patients than in controls. When the analysis was restricted to patients with CRP levels below the 95th percentile of control values (9.75 mg/L), the statistical significance disappeared.[28] In our cohort, analysis was restricted to subjects with hs-CRP levels 10 mg/L or under in order to exclude subjects with a concurrent acute inflammatory disease at the time of blood sampling. Nevertheless, when the 277 subjects with hs-CRP levels greater than 10 mg/L were included in multivariate analysis of hs-CRP levels greater than 3 mg/L *versus* less

Table 2. Characteristics of venous thromboembolism (VTE) patients at the time of VTE diagnosis: the Tromsø Study 1994-2007.[1]

	Total n=209 n (%)
Deep vein thrombosis	131 (62.7)
Pulmonary embolism	78 (37.3)
Unprovoked	82 (39.2)
Clinical risk factors	
Estrogens (HRT, oral contraceptives)	-
Heredity[1]	4 (1.9)
Pregnancy	-
Other medical conditions[2]	47 (22.5)
Provoking factors	
Surgery	46 (22.0)
Trauma	11 (5.3)
Acute medical conditions	31 (14.8)
Cancer	56 (26.8)
Immobilization (bed rest>3 days, wheelchair)	19 (9.1)
Other[3]	8 (3.8)

[1]Family history of VTE (in first degree relative before 60 years of age). [2]Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders). [3]Other provoking factors described by a physician in the medical record (e.g. intravascular catheter).

Table 3. Crude incidence rates (IR), age- and gender-adjusted and multivariable-adjusted hazard ratios (HR) for total venous thromboembolism (VTE), unprovoked and provoked VTE by quartiles of hs-CRP: the Tromsø Study 1994-2007.[1]

	Person-years	Events	Crude IR (95% CI)	Age- and gender-adjusted HR (95% CI)	Multivariable[1] HR (95% CI)
Total VTE					
Q1	18467	49	2.65 (2.01-3.51)	1.00	1.00
Q2	17870	48	2.69 (2.02-3.56)	0.89 (0.59-1.32)	0.83 (0.55-1.24)
Q3	17702	55	3.11 (2.39-4.05)	0.98 (0.66-1.43)	0.86 (0.58-1.28)
Q4	16533	57	3.45 (2.66-4.47)	1.08 (0.73-1.58)	0.91 (0.61-1.36)
P for trend	-	-	*0.5*	*0.6*	*0.8*
HR per 1 SD increase in hs-CRP	-	-	-	1.08 (0.95-1.23)	1.04 (0.90-1.19)
Unprovoked					
Q1	18259	19	1.04 (0.66-1.63)	1.00	1.00
Q2	17658	18	1.02 (0.65-1.62)	0.85 (0.44-1.61)	0.81 (0.42-1.55)
Q3	17459	20	1.15 (0.74-1.78)	0.90 (0.48-1.69)	0.87 (0.46-1.66)
Q4	16324	25	1.53 (1.03-2.27)	1.19 (0.65-2.18)	1.15 (0.62-2.15)
P for trend	-	-	*0.5*	*0.5*	*0.6*
HR per 1 SD increase in hs-CRP	-	-	-	1.08 (0.88-1.32)	1.08 (0.87-1.33)
Provoked					
Q1	18326	30	1.65 (1.14-2.34)	1.00	1.00
Q2	17721	30	1.69 (1.18-2.42)	0.91 (0.55-1.51)	0.84 (0.50-1.40)
Q3	17565	35	1.99 (1.43-2.78)	1.02 (0.63-1.67)	0.84 (0.51-1.40)
Q4	16379	32	1.95 (1.38-2.76)	1.00 (0.60-1.65)	0.77 (0.46-1.31)
P for trend	-	-	*0.8*	*0.9*	*0.4*
HR per 1 SD increase in hs-CRP	-	-	-	1.08 (0.92-1.28)	1.01 (0.85-1.21)

[1]Multivariable model adjusted for the following covariates at baseline; age, sex, body mass index (BMI), diabetes and smoking.

Table 4. Crude incidence rates (IR), age- and gender-adjusted and multivariable-adjusted hazard ratios (HR) for total venous thromboembolism (VTE) by the AHA/CDC classification for cardiovascular risk: the Tromsø Study 1994-2007.[1]

Hs-CRP (mg/L)	Person-years	Events	Crude IR (95% CI)	Age- and gender-adjusted HR (95% CI)	Multivariable[1] HR (95% CI)
Total VTE					
Low-risk (<1.0 mg/L)	32530	81	2.49 (2.01-3.10)	1.0	1.0
Intermediate-risk (1-3 mg/L)	27190	90	3.31 (2.69-4.07)	1.17 (0.87-1.58)	1.07 (0.79-1.46)
High-risk (> 3.0 mg/L)	10920	38	3.48 (2.53-4.78)	1.22 (0.83-1.79)	1.06 (0.71-1.58)
P for trend	-	-	-	0.3	0.7

[1]Multivariable model adjusted for the following covariates at baseline; age, sex, body mass index (BMI), diabetes and smoking.

than 1 mg/L, no significant difference in results was observed. A recent study examining thrombosis risk and survival in cancer patients found no independent association between elevated CRP and VTE.[29]

Some studies have found a positive association between CRP and VTE. A prospective study from the ARIC cohort found that subjects with CRP in the upper quintile had a multivariable HR of 1.74 for VTE compared to subjects in the lowest quintile of CRP.[20] However, there was no apparent increase in risk across quintiles when excluding the upper quintile (subjects with CRP levels above 5.95 mg/L). In contrast, Quist-Paulsen *et al.* reported a positive association between CRP and subsequent VTE in the second Nord-Trøndelag Health Study,[21] but the significant trend across quintiles of CRP was driven solely by a low risk of VTE in the lowest quintile of CRP. Furthermore, CRP predicted VTE only within the first year between blood sampling and VTE.[21] This finding differs from the observed effect of CRP on arterial cardiovascular disease, where CRP levels have been found to predict myocardial infarction and ischemic stroke many years prior to the event.[8,11]

In subgroup analyses of provoked and unprovoked VTE, we found no association between CRP and VTE for either group. This contradicts the findings from Luxembourg and co-workers[19] who reported elevated levels of hs-CRP in patients with unprovoked compared to provoked VTE; however, this study was limited by its small sample size.[19] In a case-control study by Vormittag *et al.*, increased basal CRP was not an independent risk factor for unprovoked VTE in multivariable analyses.[30]

Examining the role of inflammation in VTE, case-control studies have shown higher levels of both hs-CRP[31] and IL-6,[32,33] the main stimulus for CRP synthesis, in VTE patients compared to controls. However, these studies were not designed to answer the question as to whether inflammation is a cause or a consequence of the thrombotic event. Recently, hs-CRP remained associated with risk of VTE after multivariable adjustments in the large cross-sectional Copenhagen General Population Study, whereas the significant prediction of hs-CRP for VTE was lost after multivariable adjustments in The Copenhagen City Heart Study, a large prospective cohort study.[23] Furthermore, CRP genotypes associated with increased serum levels of CRP were not associated with VTE risk in either study.[23] Using a nested case-cohort design, Christiansen and co-workers found no evidence that levels of several pro-inflammatory markers, including IL-6, were increased in individuals who later developed VTE.[34] Thus, it is likely that an inflammatory reaction may be a consequence of VTE rather than a risk factor predicting future disease.

Statin treatment is known to decrease CRP levels independent of reduction in LDL-cholesterol, suggesting an anti-inflammatory drug effect.[35,36] The benefit of statin treatment in the prevention of cardiovascular disease and mortality is well documented.[35,37] Some studies have reported a reduced VTE risk in statin users as well.[38,39] In the JUPITER study, rosuvastatin treatment was associated with a significant reduction in VTE events compared to placebo among subjects with normal LDL cholesterol (<130 mg/dL or 3.4 mmol/L) and elevated hs-CRP levels (≥2.0 mg/L) at inclusion.[40] As LDL-cholesterol does not appear to be associated with VTE risk,[21,41] it has been hypothesized that the observed effect of statin treatment in VTE might be due to an anti-inflammatory drug effect.[42] However, the antithrombotic properties of statins may also explain these findings. Statins hamper thrombogenicity by increasing thrombomodulin expression in endothelial cells, dampen platelet reactivity, inhibit tissue factor and plasminogen activator inhibitor (PAI-1) expression, and increase tissue plasminogen activator (tPA).[43]

Recently, an association between CVD and VTE has been demonstrated in several studies,[2,3,44] but the mechanisms underlying these observations have not been fully clarified. It is plausible that the two conditions share risk factors, etiological pathways, or both. Common pathophysiological substrates have been suggested in the literature: atherosclerosis is associated with activation of platelets and blood coagulation, and an increased fibrin turnover, thus promoting a procoagulant state that may increase VTE risk.[3,45] Furthermore, low-grade inflammation has been suggested to be a trigger for both CVD and VTE.[42] In our study, however, hs-CRP was not associated with VTE. As this inflammation marker is independently associated with future cardiovascular events,[8,9] our findings indicate that hs-CRP is not a shared risk factor for CVD and VTE.

The main strengths of our study are the large number of participants and validated VTE events, the prospective, population-based design and long-term follow up. The thorough validation of VTE events in our cohort also allowed for separate examination of clinically important patient subgroups (provoked and unprovoked VTE).

The potential limitations of our data also merit consideration. Our analyses are based on a single baseline measurement of hs-CRP that may not accurately reflect inflammatory status over time. A modifiable risk factor represents a potential limitation of cohort studies, especially when a long period of time elapses between exposure and disease manifestation. As our CRP levels were measured in serum samples months to years prior to a VTE event, a subsequent rise in CRP as a potential trigger for VTE cannot be ruled out. However, as the self-correlation coefficient of basal CRP measurements repeated years apart is about 0.5, comparable to that of cholesterol, and there is no significant seasonal variation in basal CRP,[6] this seems unlikely. Indeed, Vormittag *et al.* found virtually identical individual hs-CRP values (median difference 0.15 mg/L) in a sample of 22 VTE patients with two hs-CRP measurements three months apart; the first blood collection a median 255 days after the thrombotic event.[30] Our time-dependent Cox's regression analysis revealed no significant change in the risk of VTE by hs-CRP over time.

In conclusion, serum levels of hs-CRP were not associated with future development of VTE in our prospective, population-based cohort study. Despite a definitive role in cardiovascular disease, our findings suggest that low-grade inflammation may not play a causal role in the pathogenesis of VTE.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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