Arterial cardiovascular risk factors and venous thrombosis: results from a population-based, prospective study (the HUNT 2)

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ABSTRACT

Background

An explanation for the increased risk of myocardial infarction and stroke in patients with venous thrombosis is lacking. The objective of this study was to investigate whether risk factors for arterial cardiovascular disease also increase the risk of venous thrombosis.

Design and Methods

Cases who had a first venous thrombosis (n=515) and matched controls (n=1,505) were identified from a population-based, nested, case-cohort study (the HUNT 2 study) comprising 71% (n=66,140) of the adult residents of Nord-Trøndelag County in Norway.

Results

The age- and sex-adjusted odds ratio of venous thrombosis for subjects with concentrations of C-reactive protein in the highest quintile was 1.6 (95% confidence interval: 1.2-2.2) compared to subjects with C-reactive protein in the lowest quintile. This association was strongest in subjects who experienced venous thrombosis within a year after blood sampling with a three-fold increased risk of participants in the highest *versus* the lowest quintile. Having first degree relatives who had a myocardial infarction before the age of 60 years was positively associated with venous thrombosis compared to not having a positive family history [odds ratio 1.3 (95% confidence interval: 1.1-1.6)]. Subjects with blood pressure in the highest quintile had half the risk of developing venous thrombosis compared to subjects whose blood pressure was in the lowest quintile. There were no associations between the risk of venous thrombosis and total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, glucose or smoking. We confirmed the positive association between obesity and venous thrombosis.

Conclusions

C-reactive protein and a family history of myocardial infarction were positively associated with subsequent venous thrombosis. Blood pressure was inversely correlated to venous thrombosis. These findings should be confirmed by further investigations.

Key words: deep vein thrombosis, pulmonary embolism, risk factors, cardiovascular, C-reactive protein.

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Introduction

Venous and arterial thromboses have been regarded as separate diseases with different causes.[1,2] However, during the last years it has been shown that patients with venous thrombosis have an increased risk of myocardial infarction and stroke.[3-7] Although arterial and venous thromboses share some risk factors, such as age, obesity and the use of estrogens,[8,9] there is an ongoing debate about explanations for this association.[9] The inherited thrombophilias, such as factor V Leiden mutation and prothrombin gene mutation, are only weakly associated with arterial thrombosis.[8] Case-control investigations have indicated an association between venous thrombosis and dyslipidemia, and smoking,[10,11] but cohort studies have not confirmed these findings.[12-15] It is still uncertain whether hypertension and diabetes are significant risk factors for venous thrombosis.[9,12,16,17] There is only one published study investigating the role of a positive family history for arterial thrombosis.[13] This study showed a slightly elevated risk of venous thrombosis in subjects with first degree relatives who had had a myocardial infarction before the age of 60 years.

Low grade inflammation is associated with the metabolic syndrome and atherosclerosis.[18] Inflammation may also trigger coagulation, both in the arterial and venous circulation.[19,20] C-reactive protein (CRP) is regarded as a marker of inflammation,[21] and has been shown to be associated with myocardial infarction and stroke in prospective studies.[22,23] Some studies found elevated levels of inflammatory cytokines in patients with venous thrombosis,[20,24,25] but it was unclear whether the elevated levels were the cause or the result of the venous thrombosis. Two prospective cohort studies addressed this issue without finding an association between CRP and subsequent venous thrombosis.[22,26] However, both investigations were small, including 101 and 159 cases of venous thrombosis.

In a nested, case-cohort study we aimed to assess whether the classical risk factors for atherosclerosis are associated with venous thrombosis, and whether inflammation, as assessed by CRP levels, predisposes to venous thrombosis.

Design and Methods

The study population

This study is based on the second Nord-Trøndelag Health Study (HUNT 2), which is a population-based survey in Nord-Trøndelag County in Norway. All residents aged 20 years and older (n=94,194) were invited to attend between August 1995 and June 1997. Overall, 66,140 (71.2%) eligible adults participated. The HUNT 2 study includes a comprehensive questionnaire containing questions on medication, history of diabetes, hypertension, cardiovascular and cerebrovascular diseases, and a history of myocardial infarction before the age of 60 years and cerebrovascular disease in first degree relatives. Subjects were defined as smokers if they answered yes to the question *Do you smoke cigarettes, cigars, or a pipe daily?* Standardized measurements of blood pressure, height, and weight were performed. A non-fasting serum sample and a clot or EDTA-blood was obtained from 98.7% of the participants. Further details regarding the HUNT 2 survey are provided elsewhere.[27]

Each participant signed written consent to participation in the HUNT 2 study, which was approved by the National Data Inspectorate and the Regional Committee for Medical Research Ethics of Central Norway.

Cases

Two hospitals in Nord-Trøndelag County (Levanger and Namsos hospitals) treat all cases of venous thrombosis. Cases registered from 1 January, 1995 to 31 December, 2001 with ICD-9 and ICD-10 diagnostic codes for deep vein thrombosis and pulmonary embolism were identified from the electronic discharge registries of the hospitals. Cases were also identified by assessing positive diagnostic procedure codes from the registries of the radiology departments for venography, duplex ultrasound and Doppler ultrasound. Finally, we identified cases of venous thrombosis in the HUNT 2 cohort from the electronic discharge registry from the tertiary care hospital in the region, the University Hospital in Trondheim, St Olavs Hospital. This case-finding procedure led to the identification of 2,136 subjects. To validate the diagnosis and to assess the clinical circumstances of the venous thrombotic events, the medical records of these patients were reviewed by two physicians.

Deep vein thrombosis was defined by an intraluminal filling defect or no venous filling on ascending contrast venography in the leg or arm, non-compressible venous segment or no venous flow in popliteal, femoral or axillary veins on duplex ultrasound, a positive computed tomography scan or a positive autopsy. Pulmonary embolism was defined by a ventilation-perfusion scan with one or more segmental or subsegmental perfusion defects with normal ventilation, a contrast defect on pulmonary computed tomography scanning or a positive autopsy. Secondary events were defined as those occurring in association with: (i) trauma, surgery or immobilization (specified as paresis, paralysis, prolonged bed rest because of an acute medical illness, or > 8 h travel) within the preceding 3 months; (ii) pregnancy or puerperium; (iii) oral contraceptive use at the event or within the preceding 30 days; (iv) tumor obstruction, central vein catheter, and vessel anomalies; and (v) active malignancy registered at the event or within 6 months after. When none of the precipitating factors for secondary VT was registered in the patient's history the event was classified as idiopathic. The use of hormone replacement therapy was not registered in the case-finding procedure.

After having reviewed the records, we had 1,271 eligible patients who had had a venous thrombotic event. Of these, 798 were identified within the HUNT 2 cohort. After exclusion of all cases with a history of venous thrombosis before entry into the HUNT 2 survey, and those with an eye vein thrombosis (n= 283), we were left with 515 cases which were included in the present investigation. The mean follow-up period from registration in HUNT 2 until the event was 33 months. Blood samples taken on entry into the HUNT 2 study were available for 508 of these 515 patients.

Controls

From the HUNT 2 cohort 1,505 controls were randomly selected apart from frequency matching to the cases by sex and age in 5-year bands. Twenty-nine subjects were excluded because they had had a venous thrombotic event before entering the HUNT 2 cohort. Blood samples were not available for seven controls.

Due to the case-cohort design in which every person in the cohort, including the cases, has the same probability of being selected to the control group, 29 controls were also cases. These 29 subjects were included both as cases and as controls.[28]

Laboratory analyses

Blood pressure was measured three times at intervals of 1 min by trained personnel using an automatic oscillometric method (Dina map 845 XT, Criticon, Tampa, FL, USA) after participants had rested in a sitting position for a minimum of 2 min. The mean of the second and third readings was used in this study. Height and weight were recorded with participants wearing light clothes and no shoes; height was measured to the nearest 1 cm and weight to the nearest 0.5 kg. Body mass index was calculated as *weight (kg)/height (m)*^{2}.[27]

Serum was separated from the blood by centrifugation within 2 h at the screening site and placed in a refrigerator at 4°C. The samples were sent to the Central Laboratory at Levanger Hospital in a cooler the same day (samples drawn on Friday were sent the following Monday). Measurements of total cholesterol, high density lipoprotein-cholesterol, triglycerides, and glucose were analyzed subsequent to sampling,[27] while CRP was analyzed on serum stored in the HUNT biobank at –70°C.[27] A Hitachi 911 Auto-analyzer (Mito, Japan) was used to analyze serum lipid levels, with reagents from Boehringer Mannheim (Mannheim, Germany). Triglyceride levels were measured with an enzymatic calorimetric method, and total cholesterol and high density lipoprotein-cholesterol after precipitation with phosphor tungsten and magnesium ions. Glucose was measured by using an enzymatic hexokinase method. Day-to-day coefficients of variation were 1.3%-1.9% for total cholesterol, 2.4% for high density lipoprotein-cholesterol, 0.7% - 1.3% for triglyceride, and 1.3% - 2.0% for glucose. To calculate the low density lipoprotein-cholesterol concentration, the Friedewald formula was used: *low density lipoprotein cholesterol = total cholesterol – high density lipoprotein-cholesterol – 0.45 x triglyceride concentration*.[29] An ultrasensitive assay (Tina-quant®, Roche, Basel, Switzerland) was used to analyze CRP on the Hitachi 911, using particle-enhanced immunological agglutination. The degree of particle agglutination was measured turbidimetrically; the measurement range was 0.1 - 20 mg/L, and the lowest detectable value that could be separated from zero was 0.03 mg/L.

Statistical methods

Logistic regression analysis was used to calculate odds ratios and their 95% confidence intervals (95% CI) as a measure of the relative risk for each cardiovascular risk factor registered at baseline in HUNT 2 on the development of venous thrombosis. Apart from age, continuous variables were investigated as quintiles determined by the distribution in the control subjects. The lowest quintile was set as the reference, and each quintile of the predictor variable was compared to the reference quintile, and a *P* value for trend was calculated from the logistic regression analysis. Age and sex were included in the crude logistic regression analysis. In the adjusted logistic regression analyses, age, sex, body mass index, systolic and diastolic blood pressures, and smoking were all included in addition to the predictor variable. Further adjustments and stratifications are described in the results section. Cases with missing data were not included in analyses. The data were analyzed using SPSS version 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Of the 515 cases of venous thrombosis, 267 (52%) were regarded as idiopathic (Table 1). Most of the secondary thromboses were due to cancer (n=92), surgery (n=94) or trauma/immobilization (n=115). The mean age of both cases and controls was approximately 66 years, with slightly more women than men in both groups (Table 2). Some information on baseline characteristics was missing: the highest number of missing values (10%) was for a family history of myocardial infarction and stroke (Table 3).

Having a CRP concentration at baseline above the lowest quintile was positively associated with the subsequent risk of venous thrombosis. The risk of venous thrombosis increased slightly with increasing levels of CPR, such that there was a 1.6 (95% CI 1.2-2.2) increased risk of thrombosis in subjects with CRP in the highest quintile as compared to the risk in subjects with CRP in the lowest quintile (Table 3). Table 4 shows that this association only seemed to be present in a short time frame, i.e. in patients suffering venous thrombosis within 1 year of blood sampling. The association was strongest in the group with

Table 1. Characteristics of the venous thrombotic events (n=515).

	n (%)
Deep vein thrombosis (DVT)	326 (63)
Pulmonary embolism (PE)	155 (30)
Both DVT and PE	34 (8)
Idiopathic venous thrombosis	267 (52)
Secondary venous thrombosis	248 (48)
Cancer	92 (18)
Surgery	94 (18)
Trauma	65 (13)
Immobilization	50 (10)
Pregnancy or puerperium	7 (1)
Oral contraceptives	5 (1)
Other trigger factors[1]	13 (2)

[1]*Tumor obstruction, central vein catheter, and vessel anomalies.*

Table 2. Characteristics of cases with venous thrombosis and controls.

	Cases (n=515)	Controls (n=1476)
Mean age in years (SD)	65.9 (15.1)	66.3 (14.6)
Number of females (%)	287 (55.7)	800 (54.2)
Mean systolic blood pressure in mmHg (SD)[1]	146 (24)	150 (25)
Mean diastolic blood pressure in mmHg (SD)[1]	82 (12)	85 (13)
Mean cholesterol in mmol/L (SD)	6.3 (1.3)	6.3 (1.2)
Mean triglycerides in mmol/L (SD)	1.9 (1.1)	1.9 (1.1)
Mean HDL cholesterol in mmol/L (SD)	1.4 (0.4)	1.4 (0.4)
Mean LDL cholesterol in mmol/L (SD)[2]	4.1(1.2)	4.1 (1.1)
Mean glucose in mmol/L (SD)	5.8 (1.8)	5.9 (1.9)
Mean height in cm (SD)	167.6 (9.6)	167.1 (9.5)
Mean weight in kg (SD)	78.4 (15.1)	75.5 (13.8)
Mean body mass index in kg/m^2 (SD)	27.9 (4.7)	27.0 (4.2)
Median C-reactive protein in mg/L (range)	2.2 (0-84)	1.9 (0-197)

[1]*The mean of the last two of a total of three measurements are presented.* [2]*Calculated using the Friedewald formula.*

Table 3. Age- and sex-adjusted odds ratios (OR) with 95% confidence intervals (CI) for venous thrombosis by baseline characteristics.

	Cases, n (%)	Controls, n (%)	OR (95% CI)	p for trend
Family history of myocardial infarction before 60 years of age				
No	194 (41.5)	647 (48.0)	1.0 (reference)	
Yes	274 (58.5)	701 (53.7)	1.3 (1.1-1.6)	
Family history of stroke before 60 years of age				
No	189 (40.4)	608 (45.1)	1.0 (reference)	
Yes	279 (59.6)	740 (54.9)	1.2 (1.0-1.5)	
Systolic blood pressure (mmHg)				
<126	102 (20.1)	264 (18.3)	1.0 (reference)	0.01
126-141	136 (26.8)	322 (22.3)	1.1 (0.8-1.5)	
142-156	116 (22.8)	305 (21.1)	0.9 (0.7-1.3)	
157-171	80 (15.7)	266 (18.4)	0.7 (0.5-1.1)	
>171	74 (14.6)	288 (19.6)	0.6 (0.4-0.9)	
Diastolic blood pressure (mmHg)				
<75	145 (28.5)	323 (22.4)	1.0 (reference)	0.04
75-80	96 (18.9)	270 (18.7)	0.8 (0.6-1.1)	
81-87	110 (21.7)	309 (21.4)	0.8 (0.6-1.1)	
88-95	94 (18.5)	266 (18.4)	0.8 (0.6-1.1)	
>95	63 (12.4)	277 (19.2)	0.5 (0.4-0.7)	
Low density lipoprotein cholesterol (mmol/L)				
<3.3	104 (20.2)	295 (20.0)	1.0 (reference)	0.9
3.3-3.8	100 (19.4)	298 (20.2)	1.0 (0.7-1.3)	
3.9-4.3	95 (18.4)	300 (20.3)	0.9 (0.7-1.3)	
4.4-5.0	110 (21.4)	290 (19.6)	1.1 (0.8-1.5)	
>5.0	104 (20.2)	293 (19.9)	1.1 (0.7-1.4)	
Glucose (mmol/L)				
<5.0	145 (28.3)	359 (24.3)	1.0 (reference)	0.3
5.0-5.2	84 (16.4)	240 (16.3)	0.9 (0.6-1.2)	
5.3-5.7	123 (24.0)	336 (22.8)	0.9 (0.7-1.2)	
5.8-6.5	78 (15.2)	250 (16.9)	0.8 (0.6-1.1)	
>6.5	83 (16.2)	291 (19.7)	0.7 (0.5-1.0)	
Self-reported diabetes mellitus				
No	477 (94.1)	1354 (93.8)	1.0 (reference)	
Yes	30 (5.9)	89 (6.2)	1.0 (0.7-1.6)	
Daily smoking				
No	374 (77.4)	1025 (75.3)	1.0 (reference)	
Yes	109 (22.6)	337 (24.7)	0.9 (0.7-1.1)	
Body mass index				
<23.5	68 (13.7)	285 (20.0)	1.0 (reference)	0.02
23.5-25.6	98 (19.2)	285 (20.0)	1.4 (1.0-2.0)	
25.6-27.6	108 (21.8)	284 (19.9)	1.6 (1.1-2.3)	
27.6-30.3	108 (21.8)	285 (20.0)	1.6 (1.1-2.3)	
>30.3	117 (23.6)	285 (20.0)	1.7 (1.2-2.4)	
C-reactive protein in mg/L				
<0.8	89 (17.5)	351 (24.0)	1.0 (reference)	0.03
0.8-1.4	86(16.9)	250 (17.1)	1.4 (1.0-1.9)	
1.5-2.5	106 (20.9)	291 (19.9)	1.5 (1.1-2.0)	
2.6-5.0	113 (22.2)	287 (19.6)	1.6 (1.2-2.2)	
>5.0	114 (22.4)	285 (19.5)	1.6 (1.2-2.2)	

idiopathic thrombosis, and not significant in the secondary cases (Table 4). The odds ratios regarding CRP were not significantly altered in the adjusted analysis.

Having first degree relatives who had had a myocardial infarction before the age of 60 years was associated with a slightly increased risk of venous thrombosis (age- and sex-adjusted odds ratio 1.3, 95% CI 1.1-1.6; Table 3). An association with a family history of stroke was less clear (Table 3). The association between a positive family history and venous thrombosis only seemed to be present in the group with idiopathic thrombosis (Table 5).

Both systolic and diastolic blood pressures were associated with venous thrombosis. Table 3 shows a decreasing risk of venous thrombosis with increasing levels of systolic and diastolic blood pressures. Subjects with blood pressure levels in the highest quintile had approximately half the risk of venous thrombosis compared to subjects with blood pressures in the lowest quintile (Tables 3 and 5). Additional adjustments for the use of blood pressure medication, the use of any medication daily or almost daily during the last 12 months, and a history of cardiovascular or cerebrovascular disease did not alter the result. The associations also remained unchanged after exclusion of subjects with secondary thrombosis.

We found no associations between venous thrombosis and cholesterol, high density lipoprotein-cholesterol, triglycerides, low density lipoprotein-cholesterol, glucose, self-reported diabetes or smoking (Table 3).

The risk of venous thrombosis was increased about 1.5 to 2-fold for overweight and obese individuals, with a weak dose-response effect (Table 3).

Discussion

In this population-based study we found that CRP was a positive predictor of venous thrombosis and that myocardial infarction in first degree relatives was associated with an increased risk of venous thrombosis.

Elevated levels of CRP in atherosclerosis are believed to reflect inflammation in atherosclerotic plaques,[30] and have been found to predict myocardial infarction and ischemic stroke many years in the future.[22] In contrast, CRP only seemed to predict venous thrombosis in a short time frame in our study, with a 3-fold increased risk of developing venous thrombosis within a year in subjects whose CRP concentration was in the highest quintile compared to those whose CRP was in the lowest quintile. This finding may support the hypothesis of direct stimulation of the coagulation system by a temporary inflammatory process as the mechanism, as suggested from experimental studies.[19] An alternative explanation is that individuals with elevated CRP were ill and that illness affects both CRP and the risk of venous thrombosis. However, the association between CRP and venous thrombosis was strongest for the idiopathic thrombotic events, which may serve as an argument against this hypothesis. Interestingly, Sørensen *et al.* found that the excess risk of subsequent myocardial infarction and stroke in patients suffering from venous thrombosis was most pronounced during the first year after the thrombotic event.[3] Previous prospective investigations assessing whether CRP is associated with venous thrombosis had a long follow-up period of approximately 8 years, and only 101 and 159 cases with venous thrombosis.[22,26] Thus, few patients developed venous thrombosis within a year from blood sampling in these studies, which may explain their negative results. In a previous study of the same subjects as in our investigation we found no associations between venous thrombosis and the inflammatory cytokines interleukin (IL)1β, IL-6, IL-8, IL-12p70, and tumor necrosis factor-α, even in a short time perspective.[31] The reason for this might be that single cytokines are less sensitive parameters than CRP for demonstrating subclinical inflammation, or that the level of sensitivity of the methods used to analyze cytokines and CRP differs. We found no statistically significant correlation between CRP and these cytokines.

Earlier studies showed that coronary artery disease in first degree relatives is strongly associated with arterial thrombosis, with the risk of myocardial infarction being approximately double in subjects with a positive family history compared to that in subjects with a negative family history.[32-34] We found that subjects who had first degree relatives who had had a myocardial infarction also had a slightly increased risk of venous thrombosis, with an odds ratio of 1.3 (95% CI 1.1-1.6) compared to subjects with first degree relatives without a history of myocardial infarction. The same odds ratio was found in the Tromsø

Table 4. Sex- and age-adjusted odds ratios with 95% confidence intervals for venous thrombosis (VT) according to quintiles of C-reactive protein concentration at baseline.

	All cases (n=508)	Secondary VT (n=242)	Idiopathic VT (n=266)	<1 year between blood sampling and VT (n=89)	1-3 years between blood sampling and VT (n=190)	≥3 years between blood sampling and VT (n=229)
C-reactive protein in mg/L						
<0.8	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.8-1.4	1.4 (1.0-1.9)	1.3 (0.8-2.0)	1.4 (0.9-2.3)	1.8 (0.8-3.9)	1.4 (0.8-2.4)	1.3 (0.8-2.0)
1.5-2.5	1.5 (1.1-2.0)	1.6 (1.0-2.4)	1.4 (0.9-2.1)	2.0 (0.9-4.4)	1.7 (1.0-2.7)	1.2 (0.8-1.9)
2.6-5.0	1.6 (1.2-2.2)	1.6 (1.0-2.5)	1.6 (1.1-2.4)	1.6 (0.7-3.5)	1.9 (1.1-3.0)	1.4 (0.9-2.1)
>5.0	1.6 (1.2-2.2)	1.3 (0.9-2.1)	1.9 (1.3-2.9)	3.3 (1.6-6.7)	1.6 (0.9-2.7)	1.2 (0.8-1.8)
P for trend	0.03	0.2	0.05	0.01	0.1	0.6

Table 5. Adjusted odds ratios with 95% confidence intervals for secondary and idiopathic venous thrombosis (VT) according to myocardial infarction and stroke in first degree relatives, and quintiles of blood pressure.[1]

	All cases (n=471)	Secondary VT (n=221)	Idiopathic VT (n=250)
Family history of myocardial infarction before 60 years of age (yes/no)	1.3 (1.1-1.7)	1.0 (0.7-1.3)	1.6 (1.2-2.1)
Family history of stroke before 60 years of age (yes/no)	1.3 (1.0-1.6)	1.0 (0.8-1.4)	1.5 (1.1-2.1)
Systolic blood pressure (mmHg)			
<126	1.0 (reference)	1.0 (reference)	1.0 (reference)
126-141	1.1 (0.8-1.5)	0.9 (0.6-1.4)	1.3 (0.9-2.0)
142-156	0.9 (0.6-1.2)	0.8 (0.5-1.3)	1.0 (0.6-1.6)
157-171	0.7 (0.5-1.0)	0.6 (0.3-0.9)	0.8 (0.5-1.4)
>171	0.6 (0.4-0.9)	0.5 (0.3-0.8)	0.7 (0.4-1.2)
P for trend	0.003	0.3	0.08
Diastolic blood pressure (mmHg)			
<75	1.0 (reference)	1.0 (reference)	1.0 (reference)
75-80	0.8 (0.5-1.0)	0.7 (0.5-1.1)	0.8 (0.5-1.2)
81-87	0.7 (0.5-1.0)	0.7 (0.5-1.1)	0.7 (0.5-1.1)
88-95	0.7 (0.5-1.0)	0.8 (0.5-1.2)	0.6 (0.4-0.9)
>95	0.5 (0.3-0.7)	0.4 (0.2-0.7)	0.5 (0.3-0.8)
P for trend	0.001	0.01	0.03

[1]*The odds ratios were adjusted for age, sex, body mass index, systolic and diastolic blood pressures, and smoking.*

Study, the only other investigation so far on this topic.[13] The cause of this association is unclear. When adjusting for other risk factors that could be family-related, i.e. body mass index, blood pressure, and smoking, the association remained unchanged. Prospective, large cohort studies have not found that patients with atherosclerosis have an increased risk of developing venous thrombosis.[35,36] The link between a positive family history and venous thrombosis may be related to mechanisms other than atherosclerosis, such as inflammatory mediators, procoagulant factors, or environmental or socioeconomic factors.

We found a decreased risk of venous thrombosis in subjects with elevated blood pressure. This is in contrast to other investigations which found either no association,[12-14] or a positive association with venous thrombosis.[17] A meta-analysis showed an odds ratio of 1.5 (95% CI: 1.2-1.9) for venous thrombosis in participants with hypertension, but this result may have been flawed by the inclusion of studies with suboptimal selection of controls.[16] It is difficult to explain our finding. The increased risk of venous thrombosis in subjects with obesity would lead to an effect in the opposite direction, as being overweight tends to increase blood pressure. Patients with cancer-related thrombosis or other secondary venous thrombotic events may have low blood pressures, but the association was also present in the group with idiopathic thrombosis. There were slightly increased numbers of subjects using medication for high blood pressure (20.0% *versus* 18.6%, respectively) as well as using any medication (50.5% *versus* 46.3%, respectively) among the cases compared to the controls. However, even after exclusion of these participants, the protective effect of high blood pressure persisted.

Lack of statistical power was probably not the explanation for the neutral findings regarding hyperlipidemia and smoking. We should have been able to discover a difference of 0.2 mmol/L in mean total cholesterol in cases *versus* controls with a 5% significance level and a power of 80%. A reduced risk of venous thrombosis has been shown in subjects using statins,[37,38] but it is unknown whether this effect is due to lowering of the low density lipoprotein-cholesterol concentration or other mechanisms. Unfortunately, we have no specific information on the use of statins, but controlling for the use of heart medication or any medication did not alter the results regarding hyperlipidemia.

In a recent meta-analysis, Ageno *et al.* reported a relative risk of venous thrombosis of 2.3 (95% CI: 1.7-3.2) for obesity,[16] a finding similar to that of our study. As type II diabetes mellitus is linked to obesity and the metabolic syndrome, it is somewhat surprising that we did not find an association between diabetes and venous thrombosis. In this case, a lack of power might be implicated, as there were only 30 venous thrombosis cases with diabetes. The LITE Study demonstrated a risk of 1.5 (95% CI: 1.0-2.1) for venous thrombosis in subjects with diabetes, although this association was only present in the group with secondary venous thrombosis, and no association was found between fasting glucose concentrations and venous thrombosis.[12] No association was found between venous thrombosis and diabetes in the Nurses' Health Study, the Physicians Health Study, and the Tromsø Study, which were all well-designed, prospective surveys.[13,14,17]

It is unlikely that our results were biased by the selection of the control group, as the selection – apart from frequency matching by age and sex – was random and based on a population survey representing over 70% of the residents in the county. It is possible that the exposure status of the participants changed before the venous thrombotic event occurred, but compared to other studies our study had a relatively short follow-up period with a median of 33 months, which should minimize this problem. In addition, our study was limited by its reliance on self-reported information on cardiovascular risk factors. However, except from smoking, we cannot see that this should pose relevant problems in the interpretation of the results as a high specificity has been found for self-reported data.[39]

In conclusion, we found that elevated levels of CRP are a predictor of subsequent venous thrombosis, and that a family history of myocardial infarction is associated with venous thrombosis. These findings should be confirmed by further investigations. Other classical risk factors for atherosclerosis, *i.e.* smoking, diabetes, hypertension and dyslipidemia, do not seem to increase the risk of venous thrombosis. Our findings may explain some of the associations between venous and arterial thromboses, but further studies are needed to explore alternative mechanisms.

Authorship and Disclosures

IAN, SCC, PRR, SCC, FRR and JH designed the study and obtained data. PQP, IAN and PR analyzed data. PQP wrote the paper. All the authors were involved in the interpretation of the results, read, gave comments, and approved the final version of the manuscript. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors reported no potential conflicts of interest.

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