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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 (VT) is lacking. The objective in this study was to investigate whether risk factors for arterial cardiovascular disease also increase the risk of VT.

Design and Methods
Cases who had their first VT (n=515) and matched controls (n=1505) were identified from a population based nested case cohort study comprising 71% (n=66 140) of the adult residents (the HUNT 2 study).

Results
The age- and sex-adjusted odds ratio of VT for subjects with concentrations of C-reactive protein (CRP) in the highest quintile was 1.6 (95% CI 1.2-2.2) compared to subjects with CRP in the lowest quintile. This association was strongest in subjects who experienced VT within a year from blood sampling with a three-fold increased risk of participants in the highest versus the lowest quintile. Having first degree relatives with myocardial infarction before the age of 60 years was positively associated with VT compared to participants not having a positive family history (odds ratio 1.3 (95% CI 1.1-1.6). Subjects in the highest quintile of blood pressures had half the risk of developing VT compared to subjects in the lowest quintile. There were no associations between the risk of VT and total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose or smoking. We confirmed the positive association between obesity and VT.

Conclusions
CRP and a family history of myocardial infarction were positively associated with subsequent VT. Blood pressure was inversely correlated to VT. 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 thrombosis have been regarded as separate diseases with different causes. However, during the last years it has been shown that patients with venous thrombosis (VT) have an increased risk of myocardial infarction and stroke. Although arterial and venous thrombosis share some risk factors, such as age, obesity and the use of estrogens, there is a debate going on about explanations for this association. The inherited thrombophilias, such as factor V Leiden mutation and prothrombin gene mutation, are only weakly associated with arterial thrombosis. Control investigations have indicated an association between VT and dyslipidemia, and smoking, but cohort studies have not confirmed these findings. It is still uncertain whether hypertension and diabetes are significant risk factors for VT. There is only one previous publication investigating a positive family history for arterial thrombosis. This study showed a slightly elevated risk of VT in subjects having first degree relatives with myocardial infarction before the age of 60 years.

Low grade inflammation is associated with the metabolic syndrome and atherosclerosis. Inflammation may also trigger coagulation, both in the arterial and venous circulation. C-reactive protein (CRP) is regarded as a marker of inflammation, and has been shown to be associated with myocardial infarction and stroke in prospective studies. Regarding VT, some studies have shown elevated inflammatory cytokines in patients with VT, but it is unclear whether the elevated levels were the cause or the result of the VT. Two prospective cohort studies have addressed this without finding an association between CRP and subsequent VT. However, both investigations were small with 101 and 159 VT cases, respectively.

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

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%) of eligible adults participated. The HUNT 2 study includes a comprehensive questionnaire containing queries on medication, history of diabetes, hypertension, cardiovascular and cerebrovascular diseases, and 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 on 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 have been described elsewhere.

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

Cases

In Nord-Trøndelag County there are two hospitals (Levanger and Namsos hospitals) treating all VT cases. 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 VT cases belonging to 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 2136 subjects. To validate the diagnosis and to assess the clinical circumstances regarding the VT 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, noncompressible venous segment or no venous flow in popliteal, femoral or axillary veins on duplex ultrasound, a positive CT scanning 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 CT scanning or a positive autopsy. Secondary events were defined by (1) trauma, surgery or immobilization (specified as paresis, paralysis, prolonged bed rest because of an acute medical illness, or > 8 h travel) within the last 8 months, (2) pregnancy or puerperium, (3) oral contraceptive use at the event or within the last 30 days, (4) tumor obstruction, central vein catheter, and vessel anomalies, and (5) 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 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 1271 eligible patients with a VT event. Of these, 798 were identified within the HUNT 2 cohort. After exclusion of all cases with a history of VT before entry in 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 in the HUNT 2 study were available in 508 of these 515 patients.
Controls

From the HUNT 2 cohort 1505 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 VT event before entering the HUNT 2 cohort. Blood samples were missing in 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 controls.

Laboratory analyses

Blood pressure was measured three times at intervals of one minute by trained personnel using an automatic oscillometric method (Dina map 845 XT, Criticon, Tampa, FL) after participants had rested in the sitting position for a minimum of two minutes. The mean of the second and third reading 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.

Serum was separated from the blood by centrifugation within two hours at the screening site and placed in a refrigerator (4°C). The samples were sent to the Central Laboratory at Leverang 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, while CRP was analyzed on serum stored in the HUNT bio bank at minus 70°C. 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 (LDL cholesterol), the Friedewald formula was used: LDL cholesterol = total cholesterol - high density lipoprotein cholesterol - 0.45 x triglyceride concentration. An ultra-sensitive 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 measuring 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 as a measure of the relative risk for each cardiovascular risk factor registered at baseline in HUNT 2 on development of VT. 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 pressure, and smoking were all included in addition to the predictor variable. Further adjustments and stratifications are described in the results section.

Results

Among the 515 VT cases, 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). Among the baseline characteristics, the family history of myocardial infarction and stroke had the highest number of missing values (i.e. 10%, Table 3). Having a CRP concentration at baseline above the lowest quintile was positively associated with the subsequent risk of VT. The risk of VT increased slightly with increasing levels, displaying 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 lowest (Table 3). Table 4 shows that this association only seemed to be present in a short time frame, i.e. in patients suffering VT within a year from blood sampling. The association was strongest in the group with 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 with myocardial infarction before the age of 60 years was associated with a slightly increased risk of VT (age and sex adjusted odds ratio 1.3, 95% CI 1.1-1.6, Table 3). Regarding a family history of stroke, the association was less clear (Table 3). The association between a positive family history and VT only seemed to be present in the group with idiopathic thrombosis (Table 5).

Both systolic and diastolic blood pressures were associated with VT. Table 3 shows a decreasing risk of VT with increasing levels of systolic and diastolic blood pressures. Subjects with blood pressure levels in the highest quintile had approximately half the risk of VT compared to subjects 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 remained unchanged also after exclusion of subjects with secondary thrombosis.
We found no associations between VT and cholesterol, high density lipoprotein cholesterol, triglycerides, low density lipoprotein cholesterol, glucose, self-reported diabetes or smoking (Table 3).

The risk of VT 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 VT and that myocardial infarction in first degree relatives was associated with an increased risk of VT.

Elevated CRP in atherosclerosis is believed to reflect inflammation in atherosclerotic plaques, and it has been found to predict myocardial infarction and ischemic stroke many years ahead. In contrast, CRP only seemed to predict VT in a short time frame in our study, with a three-fold increased risk of developing VT within a year in subjects with CRP in the highest quintile compared to the lowest. This finding may support the hypothesis of a direct stimulation of the coagulation system by a temporary inflammatory process as the mechanism, as suggested from experimental studies.

An alternative explanation is that individuals with elevated CRP were ill and that illness affects both CRP and the risk of VT. However, the association between CRP and VT was strongest for the idiopathic VT’s, 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 VT was most pronounced during the first year after the VT. The previous prospective investigations assessing whether CRP is associated with VT had a long follow-up period of approximately eight years, and only 101 and 159 cases with VT. Thus, few patients developed VT 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 VT and the inflammatory cytokines interleukin (IL) 1β, IL-6, IL-8, IL-12p70, and TNF-α, even in a short time perspective. The reason for this might be that single cytokines are less sensitive parameters than CRP in detecting subclinical inflammation, or that the sensitivity level differs between the methods used to analyze cytokines and CRP. We found no statistically significant correlation between CRP and these cytokines.

Earlier studies have shown that coronary artery disease in first degree relatives is strongly associated with arterial thrombosis, with approximately a doubling of the risk of myocardial infarction compared to subjects with a negative family history. We found that subjects with myocardial infarction in first degree relatives also had a slightly increased risk of VT, with an odds ratio of 1.3 (95% CI 1.1-1.6) compared to subjects without myocardial infarction in first degree relatives. The same odds ratio was found in the Tromsø Study, the only other investigation so far on this topic. The cause of this association is unclear. When adjusting for other risk factors that possibly 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 VT. The link between a positive family history and VT may be related to other mechanisms than atherosclerosis, such as inflammatory mediators, procoagulant factors, or environmental or socioeconomic factors.

We found a decreased risk of VT in subjects with elevated blood pressure. This is in contrast to other investigations which either found no association, or a positive association with VT. A meta-analysis found an odds ratio of 1.5 (95% CI 1.2-1.9) of VT in participants with hypertension, but this result may have been flawed by the inclusion of studies with suboptimal selection of controls. It is difficult to explain our finding. The increased risk of VT in subjects with obesity would lead to an effect in the opposite direction, as overweight tend to increase the blood pressure. Patients

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Cases (n=515)</th>
<th>Controls (n=1476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>326 (63)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism (PE)</td>
<td>155 (30)</td>
<td></td>
</tr>
<tr>
<td>Both DVT and PE</td>
<td>34 (8)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic venous thrombosis (VT)</td>
<td>267 (52)</td>
<td></td>
</tr>
<tr>
<td>Secondary VT</td>
<td>248 (48)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>92 (18)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>94 (18)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>65 (13)</td>
<td></td>
</tr>
<tr>
<td>Immobilization</td>
<td>50 (10)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy or puerperal period</td>
<td>7 (1)</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>5 (1)</td>
<td></td>
</tr>
<tr>
<td>Other trigger factors</td>
<td>13 (2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trigger factors</th>
<th>Cases (n=515)</th>
<th>Controls (n=1476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor obstruction, central vein catheter, and vessel anomalies.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=515)</th>
<th>Controls (n=1476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>65.9 (15.1)</td>
<td>66.3 (14.6)</td>
</tr>
<tr>
<td>Number of females (%)</td>
<td>287 (55.7)</td>
<td>800 (54.2)</td>
</tr>
<tr>
<td>Mean systolic blood pressure in mmHg (SD)</td>
<td>146 (24)</td>
<td>150 (25)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure in mmHg (SD)</td>
<td>82 (12)</td>
<td>85 (13)</td>
</tr>
<tr>
<td>Mean cholesterol in mmol/L (SD)</td>
<td>6.3 (1.3)</td>
<td>6.3 (1.2)</td>
</tr>
<tr>
<td>Mean triglycerides in mmol/L (SD)</td>
<td>1.9 (1.1)</td>
<td>1.9 (1.1)</td>
</tr>
<tr>
<td>Mean HDL cholesterol in mmol/L (SD)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Mean LDL cholesterol in mmol/L (SD)</td>
<td>4.1 (1.2)</td>
<td>4.1 (1.1)</td>
</tr>
<tr>
<td>Mean glucose in mmol/L (SD)</td>
<td>5.8 (1.8)</td>
<td>5.9 (1.9)</td>
</tr>
<tr>
<td>Mean height in cm (SD)</td>
<td>167.6 (9.6)</td>
<td>167.1 (9.5)</td>
</tr>
<tr>
<td>Mean weight in kg (SD)</td>
<td>78.4 (15.1)</td>
<td>75.5 (13.8)</td>
</tr>
<tr>
<td>Mean body mass index in kg/m² (SD)</td>
<td>27.9 (4.7)</td>
<td>27.0 (4.2)</td>
</tr>
<tr>
<td>Median C-reactive protein in mg/L (range)</td>
<td>2.2 (0.94)</td>
<td>1.9 (0.97)</td>
</tr>
</tbody>
</table>

1The mean of the last two of a total of three measurements are presented.

2Calculated from the Friedewald formula.
with cancer or other secondary VTs 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. But even after exclusion of these participants, the protective effect of high blood pressure persisted.

Lack of statistical power was probably not the reason for the indifferent findings regarding hyperlipidemia and smoking. We should be 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 VT has been shown in subjects using statins, but it is unknown whether this effect is

<table>
<thead>
<tr>
<th>Table 3. Age and sex adjusted odds ratios (OR) with 95% confidence intervals (CI) for venous thrombosis by baseline characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, n (%)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Family history of myocardial infarction before 60 years of age</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>Family history of stroke before 60 years of age</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
</tr>
<tr>
<td>&lt;126</td>
</tr>
<tr>
<td>126-141</td>
</tr>
<tr>
<td>142-156</td>
</tr>
<tr>
<td>157-171</td>
</tr>
<tr>
<td>&gt;171</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
</tr>
<tr>
<td>&lt;75</td>
</tr>
<tr>
<td>75-80</td>
</tr>
<tr>
<td>81-87</td>
</tr>
<tr>
<td>88-95</td>
</tr>
<tr>
<td>&gt;95</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/L)</strong></td>
</tr>
<tr>
<td>&lt;3.3</td>
</tr>
<tr>
<td>3.3-3.8</td>
</tr>
<tr>
<td>3.9-4.3</td>
</tr>
<tr>
<td>4.4-5.0</td>
</tr>
<tr>
<td>&gt;5.0</td>
</tr>
<tr>
<td><strong>Glucose (mmol/L)</strong></td>
</tr>
<tr>
<td>&lt;5.0</td>
</tr>
<tr>
<td>5.0-5.2</td>
</tr>
<tr>
<td>5.3-5.7</td>
</tr>
<tr>
<td>5.8-6.5</td>
</tr>
<tr>
<td>&gt;6.5</td>
</tr>
<tr>
<td><strong>Self-reported diabetes mellitus</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>Daily smoking</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
</tr>
<tr>
<td>&lt;23.5</td>
</tr>
<tr>
<td>23.5-25.6</td>
</tr>
<tr>
<td>25.6-27.6</td>
</tr>
<tr>
<td>27.6-30.3</td>
</tr>
<tr>
<td>&gt;30.3</td>
</tr>
<tr>
<td><strong>C-reactive protein in mg/L</strong></td>
</tr>
<tr>
<td>&lt;0.8</td>
</tr>
<tr>
<td>0.8-1.4</td>
</tr>
<tr>
<td>1.5-2.5</td>
</tr>
<tr>
<td>2.6-5.0</td>
</tr>
<tr>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>
Table 4. Sex and age adjusted odds ratios with 95% confidence intervals for venous thrombosis (VT) according to quintiles of C-reactive protein at baseline.

<table>
<thead>
<tr>
<th>C-reactive protein in mg/L</th>
<th>All cases (n=508)</th>
<th>Secondary VT (n=242)</th>
<th>Idiopathic VT (n=266)</th>
<th>&lt;1 year between blood sampling and VT (n=89)</th>
<th>1.3 years between blood sampling and VT (n=190)</th>
<th>≥3 years between blood sampling and VT (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.8</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>0.8-1.4</td>
<td>1.4 (1.0-1.9)</td>
<td>1.3 (0.8-2.0)</td>
<td>1.4 (0.9-2.3)</td>
<td>1.8 (0.8-3.9)</td>
<td>1.4 (0.8-2.4)</td>
<td>1.3 (0.8-2.0)</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>1.5 (1.1-2.0)</td>
<td>1.6 (1.0-2.4)</td>
<td>1.4 (0.9-2.1)</td>
<td>2.0 (0.9-4.4)</td>
<td>1.7 (1.0-2.7)</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td>2.6-5.0</td>
<td>1.6 (1.2-2.2)</td>
<td>1.6 (1.0-2.5)</td>
<td>1.6 (1.1-2.4)</td>
<td>1.6 (0.7-3.5)</td>
<td>1.9 (1.1-3.0)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>≥5.0</td>
<td>1.6 (1.2-2.2)</td>
<td>1.3 (0.9-2.1)</td>
<td>1.9 (1.3-2.9)</td>
<td>3.3 (1.6-6.7)</td>
<td>1.6 (0.9-2.7)</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.03</td>
<td>0.2</td>
<td>0.05</td>
<td>0.01</td>
<td>0.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 5. Adjusted odds ratios with 95% confidence intervals for secondary and idiopathic venous thrombosis (VT) according to quintiles of blood pressure.

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>All cases (n=471)</th>
<th>Secondary VT (n=221)</th>
<th>Idiopathic VT (n=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of myocardial infarction before 60 years of age (yes _ no)</td>
<td>1.3 (1.1-1.7)</td>
<td>1.0 (0.7-1.3)</td>
<td>1.6 (1.2-2.1)</td>
</tr>
<tr>
<td>Family history of stroke before 60 years of age (yes _ no)</td>
<td>1.3 (1.0-1.6)</td>
<td>1.0 (0.5-1.4)</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;126</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>126-141</td>
<td>1.1 (0.8-1.5)</td>
<td>0.9 (0.6-1.4)</td>
<td>1.3 (0.9-2.0)</td>
</tr>
<tr>
<td>142-156</td>
<td>0.9 (0.6-1.2)</td>
<td>0.8 (0.5-1.3)</td>
<td>1.0 (0.6-1.6)</td>
</tr>
<tr>
<td>157-171</td>
<td>0.7 (0.5-1.0)</td>
<td>0.6 (0.3-0.9)</td>
<td>0.8 (0.5-1.4)</td>
</tr>
<tr>
<td>&gt;171</td>
<td>0.6 (0.4-0.9)</td>
<td>0.5 (0.3-0.8)</td>
<td>0.7 (0.4-1.2)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.003</td>
<td>0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>75-90</td>
<td>0.8 (0.5-1.0)</td>
<td>0.7 (0.5-1.1)</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>81-87</td>
<td>0.7 (0.5-1.0)</td>
<td>0.7 (0.5-1.1)</td>
<td>0.7 (0.5-1.1)</td>
</tr>
<tr>
<td>88-95</td>
<td>0.7 (0.5-1.0)</td>
<td>0.8 (0.5-1.2)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>≥95</td>
<td>0.5 (0.3-0.7)</td>
<td>0.4 (0.2-0.7)</td>
<td>0.5 (0.3-0.8)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.001</td>
<td>0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*The odds ratios were adjusted for age, sex, body mass index, systolic and diastolic blood pressure, and smoking.

due to the lowering of the LDL-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 VT of 2.8 (95% CI 1.7-3.2) for obesity, a finding similar to 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 VT. This might be due to a lack of power as we only had 30 VT cases with diabetes. The LITE Study demonstrated a risk of 1.5 (95% CI 1.0-2.1) for VT in subjects with diabetes, but this association was only present in the group with secondary VT, and they found no association between the fasting glucose concentration and VT. The Nurses’ Health Study, the Physicians Health Study, and the Tromsø Study, which were all well designed prospective surveys, found no association between VT and diabetes.

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 VT occurred, but compared to other studies we 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 can not see that this should pose relevant problems in the interpretation of the results as a high specificity has been found for self reported data.

In conclusion, we found that elevated levels of CRP are a predictor of subsequent VT, and that a family history of myocardial infarction is associated with VT. These findings should be confirmed by further investigations. The other classical risk factors of atherosclerosis; smoking, diabetes, hypertension and dyslipidemia, do not seem to increase the risk of VT. Our findings may explain some of the associations between venous and arterial thrombosis, 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.
HUNT 2 population-based prospective study

References