Competing Risk of Atherosclerotic Risk Factors for Arterial and Venous Thrombosis in a General Population: The Tromsø Study


Objective—To investigate and compare the impact of traditional atherosclerotic risk factors for the risk of arterial and venous thrombosis, taking into account competing risks.

Methods and Results—In 1994–1995, 26,185 subjects were screened in the Tromsø study. Information on traditional atherosclerotic risk factors was obtained by physical examination, blood samples, and questionnaires. Subjects were followed to the first incident event of myocardial infarction (MI) or venous thromboembolism (VTE), or December 31, 2005. During a median of 10.8 years of follow-up, there were 1279 cases of incident MI and 341 VTE events. Advancing age and high body mass index were both associated with MI and VTE. Hazard ratio per decade of age was 2.34 (95% CI: 2.25–2.43) for MI and 1.87 (1.74–2.01) for VTE, and 3 kg/m² increase in body mass index was associated with 1.16 (1.11–1.21) and 1.20 (1.12–1.29) increased risk of MI and VTE, respectively. Blood pressure, high levels of triglycerides and total cholesterol, low HDL cholesterol, self-reported diabetes, and smoking were all associated with increased risk of MI but not associated with VTE.

Conclusion—Our findings imply that traditional atherosclerotic risk factors, such as smoking, hypertension, dyslipidemia, and diabetes mellitus are not shared by arterial and venous thrombosis. (Arterioscler Thromb Vasc Biol. 2012;32:487-491.)

Key Words: arterial thrombosis risk factors venous thrombosis

Conventionally, arterial thrombotic diseases (eg, myocardial infarction [MI] or ischemic stroke) and venous thromboembolism (VTE) have been considered as separate disease entities with different underlying pathology and treatment. However, during the recent years, growing evidence has supported a potential link between arterial and venous thrombosis. Studies have shown that the long-term incidence of arterial cardiovascular events is substantially increased in subjects with VTE compared to population controls, and it has also been suggested that a first arterial event is associated with subsequent development of VTE. Furthermore, patients with unprovoked VTE were shown to have a higher frequency of carotid plaques than hospitalized controls, whereas later prospective studies of general populations failed to confirm an association between subclinical atherosclerosis and VTE. It is uncertain whether the association between arterial and venous thrombosis exist only for clinically manifest disease or may be explained by shared common risk factors. However, controversies exist on the impact of traditional atherosclerotic risk factors, such as hypertension, dyslipidemia, smoking, and diabetes on the risk of VTE.

Competing risk methods can be used to analyze whether people at high risk of one type of event are at risk of other events. In the competing risk approach, failure time is calculated to the first event, thereby eliminating the opportunity that one failure alters the risk of another, and that apparent common risk factors are confounders by acting as a proxy for cause. Most previous prospective studies have not investigated the effect of atherosclerotic risk factors on VTE in the absence of development of arterial thrombosis. Moreover, a comparison of the risk for arterial and venous thrombosis by atherosclerotic risk factors within a general population may be useful to clarify uncertainties about potential common risk factors.

The aim of the present prospective cohort study was to assess and compare the risk estimates of traditional atherosclerotic risk factors of myocardial infarction and venous thrombosis in a general adult population by a competing risk model.
Methods

Study Population
Participants were recruited from the fourth survey of the Tromsø study (conducted in 1994–1995), a single-center prospective population-based study with repeated health surveys of inhabitants in Tromsø, Norway. All inhabitants aged ≥25 years were invited, and 27,158 (77% of the eligible population) participated. The study was approved by the regional committee for research ethics, and all participants gave informed consent to participate. Subjects who did not consent to medical research (n=201), subjects not officially registered inhabitants of the municipality of Tromsø at baseline (n=43), and subjects with a history of MI (n=681) or known history of VTE (n=48) were excluded from the study. In total, 26,185 subjects were included in the study, and followed from the date of enrollment in 1994 to 1995 through the end of the study period, December 31, 2005.

Cardiovascular Risk Factors
Baseline information was collected by physical examinations, blood samples, and self-administered questionnaires. Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor) by specially trained personnel. Participants rested for 2 minutes in a sitting position, and then 3 readings were taken on the upper right arm, separated by 2-minute intervals. The average of the 2 last readings was used in the analysis. Height and weight were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms, divided by the square of height in meters (kg/m²). Nonfasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after 1 hour respite at room temperature, and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by enzymatic, colorimetric methods and commercially available kits (CHOD-PAP for cholesterol, and GPO-PAP for triglycerides; Boeringer Mannheim). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Information on self-reported diabetes (“do you have or have you had diabetes?” yes/no) and current smoking (“do you smoke cigarettes, cigar or pipe daily?” yes/no) was collected from a self-administered questionnaire. Overweight (BMI=25–29.9 kg/m²) and obesity (BMI ≥30 kg/m²) was classified according to the World Health Organization definition,14 and high triglyceride levels (≥1.7 mmol/L) and low HDL-cholesterol levels (≥1.03 mmol/L in men or ≥1.30 mmol/L in women) according to the National Cholesterol Education Program-Adult Treatment Panel III guidelines.15 Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or current treatment with antihypertensives.

Outcome Assessment of Myocardial Infarction
Adjudication of hospitalized and out-of-hospital events was performed by an independent endpoint committee and based on data from hospital and out-of-hospital journals, autopsy records, and death certificates. The national 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of incident myocardial infarction were identified by linkage to the hospital discharge diagnosis registry at the University Hospital of North Norway with search for the International Classification of Diseases, Ninth Revision codes 410 to 414, and 430 to 438 in the period 1994 to 98 and thereafter for the International Classification of Diseases, Tenth Revision codes I20-I25, and I60-I69. The hospital medical records were retrieved for case validation. Slightly modified World Health Organization MONICA/MORGAM16 criteria for myocardial infarction were used and included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers and autopsy reports when applicable. Further, linkage to the National Causes of Death Registry at Statistics Norway allowed identification of fatal incident cases of myocardial infarction that occurred as out-of-hospital deaths, including deaths that occurred outside of Tromsø, as well as information on all-cause mortality. Information from the death certificates was used to collect relevant information of the event from additional sources such as autopsy reports and records from nursing homes, ambulance services, and general practitioners.

Outcome Assessment of Venous Thromboembolism
All first lifetime events of VTE during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway from date of enrollment (1994–1995) to December 31, 2005, as previously described.17 The medical records for each potential VTE-case were reviewed by trained personnel. For subjects derived from the hospital discharge diagnosis registry and the radiology procedure registry, an episode of VTE was recorded when all 4 of the following criteria were met: (1) objectively confirmed by diagnostic procedures including compression ultrasonography, venography, spiral computed tomography (spiral CT), perfusion-ventilation scan (high or moderate probability for pulmonary embolism), pulmonary angiography, or autopsy; (2) the medical record indicated that a physician had made a diagnosis of deep vein thrombosis or pulmonary embolism (PE); (3) signs and symptoms consistent with deep vein thrombosis or pulmonary embolism were present; and (4) treatment with anticoagulants (heparin, warfarin), thrombolytic therapy, or vascular surgery was required. For patients derived from the autopsy registry, a VTE-event was recorded when the autopsy record indicated VTE as cause of death or as a significant condition contributing to death.

Statistical Analyses
Statistical analysis was carried out using SPSS version 17.0 (SPSS, Chicago, IL). The significance level was 0.05. Failure time (years) was calculated from baseline enrollment to the first event of MI or VTE. All subjects had at most 1 of the 2 outcomes on the date of first occurrence. Subjects who did not experience an event during follow-up were censored from the date of death or migration or at the end of the study period (December 31, 2005).

The data were prepared by duplication of the dataset, giving each subject a separate observation for each outcome as described by Lunn and McNeil.18 Cox proportional hazard regression models, stratified by event type, were used to assess the association between risk factors and outcomes adjusted for age and sex. In order to assess differences in hazard ratios (HRs) for each outcome, an interaction term between each risk factor and event type were included in the model. We also estimated HRs for MI and VTE by predefined cut-offs for atherosclerotic risk factors using the lowest category as reference group. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for different categories of the variables.

Results
The mean baseline age was 46 (range=25–97, SD=5 years) and 47% (n=12,245) were men. During a median follow-up of 10.8 years there were 1279 incident MIs and 341 incident VTEs. Forty-four subjects developed both MI and VTE during follow-up. The overall crude incidence rates were 5.2 (95% CI: 4.9–5.4) per 1000 person-years for MI, and 1.4 (95% CI: 1.2–1.5) per 1000 person-years for VTE. Table 1 shows the baseline distribution of atherosclerotic risk factors in those who did not develop any event during follow-up, and those who developed MI and VTE, respectively.

Comparison of atherosclerotic risk factors for the competing risk of MI and VTE are shown in Table 2. Advancing age was associated with both MI (HR per decade: 2.34, 95% CI: 2.25–2.43) and VTE (HR per decade: 1.87, 95% CI: 1.74–2.01) (Table 2). Moreover, BMI was associated with a similar 1.2-fold increased risk of both MI (HR per 3 kg/m²: 1.16, 95% CI: 1.11–1.21) and VTE (HR per 3 kg/m²: 1.20, 95% CI: 1.12–1.29). Male gender was associated with a 2.5-fold
increased risk of MI (HR: 2.49 95% CI: 2.22–2.79) and a 1.2-fold increased risk of VTE (HR: 1.19, 95% CI: 0.96–1.47). Subjects with self-reported diabetes had a 2.5-fold increased risk of MI (HR: 2.51, 95% CI: 2.03–3.09) and nonsignificant 1.4-fold increased risk of VTE (HR: 1.37, 95% CI: 0.78–2.40). Higher levels of systolic blood pressure, diastolic blood pressure, triglycerides and total cholesterol, and lower levels of HDL-cholesterol, were associated with increased risk of MI but not with VTE. Current daily smoking was associated with an 80% increased risk of MI (HR: 1.82, 95% CI: 1.59–2.08), and a 1.2-fold increased risk of VTE (95% CI: 1.15–1.47) (Table 2).

Table 3 shows HRs with 95% CI for MI and VTE by predefined cut-offs of the atherosclerotic risk factors. Advancing age was more strongly associated with MI than with VTE.

Table 2. Age- and Sex-Adjusted Hazard Ratios (HR) With 95% Confidence Interval (CI) for Myocardial Infarction (MI) and Venous Thromboembolism (VTE) by Traditional Atherosclerotic Risk Factors: The Tromsø Study, 1994–2005

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No Event (n=24 565)</th>
<th>MI (n=1279)</th>
<th>VTE (n=341)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45±14</td>
<td>64±13</td>
<td>60±14</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>46</td>
<td>62</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1±3.8</td>
<td>26.6±4.1</td>
<td>26.9±4.5</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>133±20</td>
<td>155±24</td>
<td>144±24</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78±12</td>
<td>88±14</td>
<td>82±14</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.52±1.03</td>
<td>1.97±1.15</td>
<td>1.64±0.91</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.98±1.29</td>
<td>6.99±1.30</td>
<td>6.58±1.27</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.51±0.41</td>
<td>1.40±0.41</td>
<td>1.55±0.43</td>
<td></td>
</tr>
<tr>
<td>Self-reported diabetes (%)</td>
<td>1.3</td>
<td>7.7</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>36.9</td>
<td>41.4</td>
<td>37.2</td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure.

Discussion

In the present study, advancing age and obesity were identified as common risk factors for arterial and venous thrombosis. Traditional atherosclerotic risk factors, such as male sex, hypertension, dyslipidemia, self-reported diabetes, and current daily smoking were clearly associated with increased risk of arterial thrombosis but not with venous thrombosis.

To our knowledge, the Physicians’ Health Study, a prospective cohort of 18 622 male physicians, is the only previous study using a competing risk approach to assess the
impact of cardiovascular risk factors on arterial and venous thrombosis. In agreement with our findings in a general population, they showed that advancing age and higher BMI was significantly associated with risk of both coronary heart disease and VTE, whereas hypertension, elevated cholesterol, diabetes, smoking, and physical activity (inverse) was significantly associated with coronary heart disease but not with VTE.

Our findings confirm that traditional risk factors for atherosclerosis are associated with risk of MI\(^{19-21}\) but were not associated with VTE in the same population. The discriminatory impact of atherosclerotic risk factors, except for age and obesity, on MI and VTE suggest that these risk factors do not play an important role in the etiology of VTE. Previous reports on the association between atherosclerotic risk factors and VTE have been inconsistent.\(^{7-10,12}\) Obesity has consistently been identified as a common risk factor for both arterial and venous thrombosis,\(^{22}\) and the Physicians’ Health Study,\(^{8}\) in contrast to our findings, implied that obesity was a stronger risk factor for VTE than MI. Abdominal obesity is associated with raised intra-abdominal pressure and reduced venous blood flow velocity, which may render blood more susceptible to thrombosis.\(^{23,24}\) Moreover, visceral adipose tissue is highly metabolic active, releasing proinflammatory, proatherogenic, and prothrombotic substances which may also contribute to thrombosis risk.\(^{25,26}\) Although several case-control studies have demonstrated an association between serum lipids, such as triglycerides, HDL-cholesterol, and lipoprotein (a) with VTE,\(^{6,7,11,13}\) large prospective studies have failed to confirm these observations, supporting no role of serum lipids in the pathogenesis of VTE.\(^{5,8,12}\) Hypertension was a risk factor for pulmonary embolism in the Nurses’ Health Study,\(^{9}\) but most of the other prospective cohorts found no association between blood pressure and VTE.\(^{8,10,12}\) Daily smoking, regardless of duration and amount, was not a risk factor in the LITE study,\(^{12}\) and in the Physicians’ Health Study.\(^{10}\) However, heavy cigarette smoking has been identified as a risk factor for VTE in several studies.\(^{9,10,27-29}\) Because smoking was assessed as a dichotomous variable in our study, the possible effects of amount and duration of smoking were not considered. Nevertheless, smoking status per se was associated with an 81% increased risk of MI in our study, whereas no association was shown with VTE.

The competing risk approach has several advantages in assessing potential shared risk factors for interrelated diseases. First, the direct impact of the risk factors on each outcome is assessed, because the possibility is eliminated that the 2 outcomes influence the risk of one another in the model. Second, comparison within the same population ensures that the degree of both known and unknown confounding is similar for the 2 outcomes. The risk estimates for MI by atherosclerotic risk factors was similar to and consistent with that of other cohorts,\(^{21,30}\) indicating that the observed nonassociative nature of atherosclerotic risk factors and VTE is not explained by unrecognized confounding.

A meta-analysis from 2007, mainly based on case-control studies and selected prospective studies with verified endpoints, concluded that cardiovascular risk factors such as hypertension, diabetes, low HDL-cholesterol, and high serum triglycerides were significantly associated with VTE.\(^{31}\) The results of the present study, along with other recently published prospective studies on this topic,\(^{32-34}\) emphasize the need of an updated systematic review.

Besides being a large prospective cohort generated from a general population with a high attendance rate, the study has several strengths. The municipality of Tromsø is served by a single hospital, and supplemental use of the National Causes of Death Registry and the National population registry facilitate a thorough outcome ascertainment of both MI and VTE. The competing risk approach provides an opportunity to compare the magnitude of associations on arterial and venous thrombosis within the same population and allows for formal evaluation of differences in associations. The only previous study using this approach was restricted to males,\(^{8}\) whereas our study included men and women within a wide age range. Nondifferential misclassification, which leads to bias toward the null, is often pointed out as a potential limitation of cohort studies when exposure is self-reported or modifiable over time. When comparing the impact of atherosclerotic factors on risk of MI and VTE within the same population, it is likely that the degree of random misclassification of exposure was similar with regard to both outcomes, and thereby did not influence the comparison between the 2.

In conclusion, our findings imply that traditional atherosclerotic risk factors are not shared by arterial and venous thrombosis. If the link between arterial and venous thrombosis is mediated through common risk factors, our findings suggest that potential common determinants for arterial and venous thrombosis are probably related to mechanisms of coagulation and thrombus formation, rather than atherosclerosis. Alternatively, the observed link may be restricted to clinically manifest disease.

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Disclosures
None.

References


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