Smoking and Abdominal Obesity

Risk Factors for Venous Thromboembolism Among Middle-aged Men: “The Study of Men Born in 1913”

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Background: Risk factors for deep vein thrombosis and pulmonary embolism are mostly derived from case-control studies of hospitalized patients, and there are few long-term population-based studies.

Objective: To study the long-term risk factors for deep vein thrombosis and pulmonary embolism among middle-aged men.

Design: A prospective cohort study.

Setting: General community, “The Study of Men Born in 1913.”

Subjects: A random population sample of 855 men, all aged 50 years at baseline.

Main Outcome Measures: Eight-hundred fifty-five men participated in a screening examination in 1963 at the age of 50 years, and 792 of these men were reexamined in 1967 at the age of 54. All the men were followed up with periodic examinations until the age of 80. Objective methods were used to ascertain a diagnosis of deep vein thrombosis or pulmonary embolism.

Results: Waist circumference ($P = .004$) and smoking ($P = .02$) predicted a venous thromboembolic event in multivariate survival analysis. Men in the highest decile of waist circumference ($\geq 100$ cm) had an adjusted relative risk of 3.92 (95% confidence interval, 2.10-7.29; $P < .001$) compared with men with a waist circumference of less than 100 cm. For men who smoked 15 g of tobacco (15 cigarettes) a day or more, the adjusted relative risk was 2.82 (95% confidence interval, 1.30-6.13; $P = .009$) compared with nonsmokers.

Conclusions: Smoking and abdominal obesity were independent risk factors for venous thromboembolic events during follow-up. In addition to the prevention of smoking and obesity, a more aggressive strategy regarding the use of prophylactic agents among smokers and obese patients, in various risk situations, may be justified.

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VENOUS thromboembolic event (VTE) is a serious disorder, and, despite modern treatment, there is a high risk of recurrences. Surgical procedures, malignant neoplasms, immobilization, pregnancy, use of oral contraceptives, and inherited thrombophilia are known to increase the risk of a VTE.1 Most previous studies1 of the risk factors for VTE have been performed on selected hospitalized patient groups, often in relation to a postoperative phase, and there are few long-term population-based studies.

Obesity has been found to be a risk factor for VTEs in several hospital-based studies.2-6 Others7-9 have failed to show such an association. Only 2 studies10,11 have shown that obesity is a risk factor for pulmonary embolism (PE) in the general population, and this association was shown only among women. Heavy smoking and hypertension also increased the risk of PE among women in one study.11

The present study prospectively assessed the effect of obesity and other cardiovascular risk factors on the incidence of a VTE among middle-aged men, during a 30-year follow-up period.

RESULTS

Four men had a history of DVT or PE before the baseline examination in 1963. These men were excluded from further analyses. Accordingly, 851 men were at risk of developing a first VTE. During 30 years of follow-up, another 65 men had 1 or more VTEs. Twenty-nine men had a first episode of DVT, 14 had a first episode of a nonfatal PE, and 22 had a fatal PE. At the time of the first VTE, 12 (18%) of the 65 men had general surgery performed within the last 3 months. Seven of
METHODS AND STUDY POPULATION

The “Study of Men Born in 1913” is a longitudinal, prospective, population-based study of men born in 1913 and living in Go¨teborg, Sweden. The study population and sampling procedure have been described previously.12,13 In 1963, a random sample of one third of all 50-year-old men (n = 973) was invited to a health examination; of these men, 855 (87.9%) participated. All the men participating in 1963 were invited to a reexamination in 1967, at age 54 years. At that time, 792 (94.5% of those alive) of 838 men participated. The baseline characteristics in the present study derive from the 1963 and 1967 surveys.

FOLLOW-UP

All the men were invited to undergo new examinations in 1973, 1980, 1988, and 1993. Those who did not participate in the reexaminations were asked to answer questionnaires or participate in a telephone interview. Information about hospitalizations, medication, and morbidity since the last examination was obtained at each examination. Death certificates, autopsy reports, and medical records were studied for those who died. Information from the official Swedish Cancer Register was obtained. Finally, all hospitals in Sweden have a register based on the diagnoses at discharge from the hospital. These registers were also used to find nonparticipants who had been hospitalized in any of the 2 hospitals in Go¨teborg and treated for deep vein thrombosis (DVT) or PE.

By 1993, after 30 years of follow-up, 481 men (56.3%) had died. Death certificates and medical records could be found for those who died, except for 2 of the men.

Of those men still alive in 1993, 232 attended the examination. Of those men who did not participate, 67 were interviewed by telephone, 29 answered a questionnaire, and for another 32 medical records were studied. Six men had moved out of the country and were lost to follow-up. Among these 6 men, 1 had a PE at age 61 years and a DVT at age 75 years before he was lost to follow-up. Another 8 men were lost to end point registration as they moved out of the area and their medical records could not be found. Thus, the clinical follow-up rate during this 30-year follow-up period was 98%.

END POINT DEFINITIONS

Each screening examination included a medical history and a physical examination. All events of venous thromboembolism, myocardial infarction, stroke, diabetes mellitus, and cancer were registered. Medical records from hospital and outpatient clinics were reviewed by the same investigator (P.-O.H.). Deep vein thrombosis and PE were defined as a hospital discharge diagnosis of DVT or PE, or as a fatal PE found at autopsy. All men discharged alive from the hospital were treated with oral anticoagulation agents. The VTEs were objectively verified with phlebography (n = 23), ultrasonography (n = 1), plethysmography (n = 2), ventilation-perfusion lung scan (n = 15), and autopsy (n = 21); however, for 3 (4.6%) of the 65 men, the diagnosis of DVT was set by clinical grounds alone. Myocardial infarction was defined as a hospital discharge diagnosis according to standardized criteria,13 or as a fatal myocardial infarction found at autopsy. Stroke was defined as a sudden onset of focal neurologic signs of presumed vascular origin and hospitalization by the diagnosis of cerebral thrombosis, cerebral embolus, or cerebral hemorrhage. Subarachnoidal hemorrhages were not included. Diabetes mellitus was defined as a fasting blood glucose level of 6.7 mmol/L or more (≥120 mg/dL) or ongoing treatment for diabetes mellitus (pharmacological or dietary). Cancer was defined as a registration in the Swedish Cancer Register.

Death certificates were studied for those who died during follow-up according to the register of the National Bureau of Statistics, Stockholm, Sweden. All autopsy records were obtained. Only PE found at autopsy and considered as a primary or major contributing (secondary) cause of death was considered an end point. The autopsy rate was 89% from 1963 to 1973 and 63% from 1974 to 1983, but decreased to 33% from 1984 to 1993. The total autopsy rate in the present study was 51%.

BASELINE EXAMINATIONS

1963

Information on smoking habits was obtained by questionnaire. Smoking was categorized as follows: 1, never smoked; 2, ex-smoker for more than 1 month; 3, currently smoking tobacco (1-14 g/d); and 4, currently smoking tobacco (≥15 g/d). A cigarette was assumed to be the equivalent of 1 g of tobacco; a cheroot, 2 g; and a cigar, 5 g. Pipe smokers were classified according to their average daily consumption.

Body weight was measured using a balance scale to the nearest 0.1 kg, with the men wearing light indoor clothing. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was recorded in the right arm, with the participant seated after a 5-minute interval. A mercury sphygmomanometer with a cuff size of 12 × 23 cm was used. Hypertension was defined as a systolic blood pressure greater than 160 mm Hg, a diastolic blood pressure greater than 95 mm Hg, or the use of antihypertensive treatment. Absolute heart volume (in milliliters) was measured by chest x-ray according to Jonsell.10

1967

At this examination, waist circumference, hip circumference, and plasma fibrinogen level were measured. Waist circumference was measured to the nearest centimeter at the level of the umbilicus, with the subject standing and breathing normally. Hip circumference was measured to the nearest centimeter at the level of the iliac crest. The waist-hip ratio was calculated as waist circumference divided by hip circumference.

STATISTICAL ANALYSIS

All analyses were performed using computer software (SAS; SAS Institute Inc, Cary, NC). The Wilcoxon rank sum test was used to analyze differences between groups. Linear trends in proportions were analyzed using the χ² test. The hazard ratio for a VTE was calculated using a stepwise Cox proportional hazards model. In the time-dependent Cox proportional hazards model, data from the 1967, 1973, 1980, 1988, and 1993 examinations were used. Kaplan-Meier estimates were used for the visual assessment of VTE-free survival in Figure 1 and Figure 2.
these postoperative VTEs were after cancer surgery. Another 14 men (22%) had a diagnosed cancer disease at the time of the VTE but were not in a postoperative phase, and 2 men (3%) had no diagnosed cancer at the time of VTE, but developed a cancer during follow-up. Seventeen men (26%) were immobilized from other causes than surgery for at least 1 week before the diagnosis of a VTE, while 20 VTEs (31%) were considered idiopathic.

Five men experienced a VTE between 1963 and 1967. These men were excluded when baseline data from the examination in 1967 were included in the analyses. Another 4 men who developed a VTE during follow-up declined participation in the 1967 examination. So, 56 men experienced a VTE during 26 years of follow-up from baseline at age 54 years.

In Table 1, the baseline characteristics are shown for men with and without a VTE during follow-up. Body weight, heart volume, waist circumference, and hip circumference were all significantly higher in men who developed a VTE compared with those who did not.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men Without a VTE</th>
<th>Men With a VTE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>782 75.6</td>
<td>65 78.8</td>
<td>.03</td>
</tr>
<tr>
<td>Height, cm</td>
<td>782 175</td>
<td>65 176</td>
<td>&gt;.20</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>782 24.7</td>
<td>65 25.5</td>
<td>.12</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Systolic</td>
<td>786 138</td>
<td>65 140</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>786 91.5</td>
<td>65 92.8</td>
</tr>
<tr>
<td>Heart volume, mL</td>
<td>772 747</td>
<td>64 794</td>
<td>.01</td>
</tr>
<tr>
<td>Cholesterol, mmol/L (mg/dL)</td>
<td>786 6.45 (248)</td>
<td>65 6.12 (235)</td>
<td>.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (mg/dL)</td>
<td>786 1.27 (112)</td>
<td>65 1.21 (107)</td>
<td>&gt;.20</td>
</tr>
<tr>
<td>Glucose, mmol/L (mg/dL)</td>
<td>786 4.59 (83)</td>
<td>65 4.61 (83)</td>
<td>&gt;.20</td>
</tr>
<tr>
<td>Waist circumference, cm*</td>
<td>724 86.7</td>
<td>56 89.8</td>
<td>.05</td>
</tr>
<tr>
<td>Hip circumference, cm*</td>
<td>721 93.5</td>
<td>56 95.9</td>
<td>.03</td>
</tr>
<tr>
<td>Waist-hip ratio*</td>
<td>721 0.93</td>
<td>56 0.94</td>
<td>&gt;.20</td>
</tr>
<tr>
<td>Fibrinogen, g/L*</td>
<td>724 3.34</td>
<td>56 3.32</td>
<td>&gt;.20</td>
</tr>
<tr>
<td>Smoking habits†</td>
<td>195 (24.8)</td>
<td>12 (18)</td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>155 (19.7)</td>
<td>13 (20)</td>
<td></td>
</tr>
<tr>
<td>Ex-smokers (≥1 mo)</td>
<td>275 (35.0)</td>
<td>20 (31)</td>
<td></td>
</tr>
<tr>
<td>Smoking tobacco, g/d</td>
<td>≥15</td>
<td>161 (20.5)</td>
<td>20 (31)</td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>214 (27.2)</td>
<td>20 (31)</td>
<td></td>
</tr>
</tbody>
</table>

*Measured in 1967 at age 54 years.
†Data are given as number (percentage) of the total; n = 786 for men without a VTE, and n = 65 for men with a VTE.
‡Hypertension is indicated by a systolic blood pressure higher than 160 mm Hg, a diastolic blood pressure higher than 95 mm Hg, or ongoing antihypertensive treatment.
who experienced a VTE had lower mean cholesterol levels compared with men without a VTE.

In a multivariate survival analysis (Cox regression), including body weight, body mass index, heart volume, waist circumference, hip circumference, serum cholesterol level, smoking status, hypertension, and serum fibrinogen level, only waist circumference (P = .004) and smoking status (P = .02) were independent predictors of a VTE.

Table 2 shows the univariate and adjusted relative risk and 95% confidence intervals for VTE in relation to quintiles of waist circumference. For men in the highest quintile of waist circumference (>95 cm), the risk of a VTE was significantly higher compared with those in the lowest quintile. Table 2 also shows the relative risk for smoking habits, with nonsmokers as the reference group. Men who smoked 15 g of tobacco a day or more ran a significantly higher risk of developing a VTE compared with nonsmokers.

Figure 1 shows probability curves comparing men in the highest decile of waist circumference with the rest of the men for VTE-free survival during 26 years of follow-up. The cumulative incidence of VTE was 26.7% for men with a waist circumference of 100 cm or more and 7.9% for men with a waist circumference of less than 100 cm (P < .001, log-rank test). Figure 2 shows probability curves comparing men smoking tobacco, 15 g/d or more, with those who never smoked. The cumulative incidence of a VTE was 16.3% for heavy smokers compared with 6.5% for never smokers (P = .008, log-rank test). In this analysis, ex-smokers and men smoking less than 15 g of tobacco per day were excluded.

To test whether changes in waist circumference or smoking habits during follow-up would alter the risk of a VTE, we used waist circumferences registered in the 1973, 1980, and 1993 examinations and smoking habits registered in the 1973, 1980, and 1988, and 1993 examinations as time-dependent covariates in a Cox proportional hazards model. In this analysis, smoking (P = .006) and waist circumference (P = .001) were still related to an increased risk of venous thromboembolism during follow-up.

In a further analysis, comorbidity factors such as cancer, myocardial infarction, stroke, and diabetes mellitus during follow-up were included in a Cox proportional hazards model in addition to smoking habits and waist circumference at baseline. In that analysis, smoking (P = .05), waist circumference (P = .006), and cancer (P = .02) were independently related to an increased risk of a VTE during follow-up.

The present study is the first prospective study including both DVT and PE as end points during a long-term follow-up of middle-aged men. Waist circumference and smoking status were independently related to the incidence of VTEs. In several reports, obesity has been found to be a risk factor for venous thromboembolic event; Cl, confidence interval; and ellipses, data not applicable. *Total number of years until death or lost to follow-up for all study participants. ‡Reference group.

Table 2. Relative Risk of Venous Thromboembolism by Quintiles and 10th Decile of Waist Circumference (Univariate and Adjusted for Smoking Habits) and by Smoking Habits (Univariate and Adjusted for Quintiles of Waist Circumference)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Men</th>
<th>No. of VTEs</th>
<th>Observation Years†</th>
<th>Univariate Relative Risk (95% CI)</th>
<th>P</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, cm Quintile 1 (&lt; 78)‡</td>
<td>146</td>
<td>8</td>
<td>3101</td>
<td>1.00 (1.00)</td>
<td>...</td>
<td>1.00 (1.00)</td>
<td>...</td>
</tr>
<tr>
<td>2 (79-83)</td>
<td>154</td>
<td>11</td>
<td>3370</td>
<td>1.26 (0.51-3.14)</td>
<td>&gt; .20</td>
<td>1.30 (0.52-3.22)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>3 (84-88)</td>
<td>153</td>
<td>9</td>
<td>3225</td>
<td>1.08 (0.42-2.81)</td>
<td>&gt; .20</td>
<td>1.11 (0.43-2.89)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>4 (89-94)</td>
<td>176</td>
<td>10</td>
<td>3813</td>
<td>1.02 (0.40-2.57)</td>
<td>&gt; .20</td>
<td>1.05 (0.42-2.67)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>5 (95+)</td>
<td>151</td>
<td>18</td>
<td>2998</td>
<td>2.39 (1.04-5.50)</td>
<td>.04</td>
<td>2.62 (1.14-6.04)</td>
<td>.02</td>
</tr>
<tr>
<td>Decile 1-9 (&lt; 100)‡</td>
<td>711</td>
<td>43</td>
<td>15268</td>
<td>1.00 (1.00)</td>
<td>...</td>
<td>1.00 (1.00)</td>
<td>...</td>
</tr>
<tr>
<td>10 (100+)</td>
<td>69</td>
<td>13</td>
<td>1239</td>
<td>3.93 (2.11-7.32)</td>
<td>&lt; .001</td>
<td>3.92 (2.10-7.29)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers‡</td>
<td>193</td>
<td>10</td>
<td>4343</td>
<td>1.00 (1.00)</td>
<td>...</td>
<td>1.00 (1.00)</td>
<td>...</td>
</tr>
<tr>
<td>Ex-smokers (1-5 mo)</td>
<td>161</td>
<td>12</td>
<td>3628</td>
<td>1.43 (0.62-3.31)</td>
<td>&gt; .20</td>
<td>1.39 (0.60-3.22)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>Smoking tobacco, g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-14</td>
<td>268</td>
<td>16</td>
<td>5532</td>
<td>1.29 (0.59-2.85)</td>
<td>&gt; .20</td>
<td>1.38 (0.63-3.06)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>≥ 15</td>
<td>158</td>
<td>18</td>
<td>3004</td>
<td>2.76 (1.27-6.00)</td>
<td>.01</td>
<td>2.82 (1.30-6.13)</td>
<td>.009</td>
</tr>
</tbody>
</table>

*Baseline examination in 1963 for smoking and in 1967 for waist circumference. Follow-up from January 1, 1968, to December 31, 1993. VTE indicates venous thromboembolic event; CI, confidence interval; and ellipses, data not applicable. †Total number of years until death or lost to follow-up for all study participants. ‡Reference group.

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differ between men and women. Blood pressure levels were somewhat higher among men with a VTE compared with men without a VTE, although not statistically significant (Table 1). The sample size with comparatively few end points is a limit of the present study, and there might have been a difference in VTE incidence between hypertensive and normotensive men, too small to be detected in our study. In the multivariate regression analysis, there were only 56 events. However, the same age of all men eliminated the problem of age adjustments in the analysis.

Another limitation in this kind of study is that the end point often occurs many years after the baseline examination and many confounding diseases and events may have occurred during follow-up. Other studies conducted on hospital inpatients have shown that various cardiovascular diseases, malignant neoplasms, surgical procedures, or other forms of immobilization are important risk factors for VTEs. The association with smoking in our study might be caused by a higher morbidity among smokers, leading to a secondary VTE. We tried to minimize this bias by including comorbidity during follow-up in a multivariate survival analysis. In this analysis, we still found smoking and abdominal obesity to be independent risk factors for venous thromboembolism, also when the incidence of cancer, myocardial infarction, stroke, and diabetes mellitus were taken into account.

Central obesity may increase the risk of a VTE as a result of changes in hemostasis. Such changes in hemostasis have been reported in the presence of abdominal obesity.18 With hypertension, glucose intolerance, and elevated lipid levels as parts of a metabolic syndrome, a link to disturbances in the fibrinolytic system has also been described.19

The higher risk for a VTE among smokers is hard to interpret. Smoking may affect hemostasis by increasing the level of fibrinogen.20 However, this is probably not an important reason for a higher risk of VTE among smokers in the present study since the fibrinogen levels were the same for men with and without a VTE during follow-up (Table 1).

The cause of a VTE is often multifactorial, and many risk factors may interact. Smoking and obesity might thus be amplifiers of other possible risk factors and could be contributory factors to the development of a VTE in various risk situations (eg, surgery). Obesity is a growing public health problem in the industrialized part of the world. The fact that widespread use of prophylactic therapy does not seem to decrease the incidence of venous thromboembolism in the population may partly be explained by a higher exposure to this risk factor.

In conclusion, abdominal obesity and smoking habits appear to be important risk factors for a VTE. Consequently, these risk factors might be used to identify those patients who should receive prolonged prophylactic agents after surgery or after a verified thromboembolic event. Reducing obesity and smoking in the population may have a major preventive effect also from a socioeconomic point of view.

REFERENCES


