Risk Factors for Deep Vein Thrombosis and Pulmonary Embolism

A Population-Based Case-Control Study

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Background: Reported risk factors for venous thromboembolism (VTE) vary widely, and the magnitude and independence of each are uncertain.

Objectives: To identify independent risk factors for deep vein thrombosis and pulmonary embolism and to estimate the magnitude of risk for each.

Patients and Methods: We performed a population-based, nested, case-control study of 625 Olmsted County, Minnesota, patients with a first lifetime VTE diagnosed during the 15-year period from January 1, 1976, through December 31, 1990, and 625 Olmsted County patients without VTE. The 2 groups were matched on age, sex, calendar year, and medical record number.

Results: Independent risk factors for VTE included surgery (odds ratio [OR], 21.7; 95% confidence interval [CI], 9.4-49.9), trauma (OR, 12.7; 95% CI, 4.1-39.7), hospital or nursing home confinement (OR, 8.0; 95% CI, 4.5-14.2), malignant neoplasm with (OR, 6.5; 95% CI, 2.1-20.2) or without (OR, 4.1; 95% CI, 1.9-8.5) chemotherapy, central venous catheter or pacemaker (OR, 5.6; 95% CI, 1.6-19.6), superficial vein thrombosis (OR, 4.3; 95% CI, 1.8-10.6), and neurological disease with extremity paresis (OR, 3.0; 95% CI, 1.3-7.4). The risk associated with varicose veins diminished with age (for age 45 years: OR, 4.2; 95% CI, 1.6-11.3; for age 60 years: OR, 1.9; 95% CI, 1.0-3.6; for age 75 years: OR, 0.9; 95% CI, 0.6-1.4), while patients with liver disease had a reduced risk (OR, 0.1; 95% CI, 0.0-0.7).

Conclusion: Hospital or nursing home confinement, surgery, trauma, malignant neoplasm, chemotherapy, neurologic disease with paresis, central venous catheter or pacemaker, varicose veins, and superficial vein thrombosis are independent and important risk factors for VTE.

Arch Intern Med. 2000;160:809-815

Enous thromboembolism (VTE) is a major national health problem, with at least 201,000 first lifetime cases reported each year in the United States. Of these, about 25% die within 7 days of VTE onset; for about 22% of all patients with VTE, death is so rapid, there is insufficient time for intervention. Thus, to improve survival, patients at risk must be identified and given appropriate prophylaxis in order to reduce the incidence of VTE. Despite improved prophylaxis regimens, however, the annual incidence of VTE has been relatively constant, at about 1 event per 1000 person-years since 1979. The failure to reduce this rate may be a result of uncertainty regarding risk factors for VTE and the associated difficulty in recognizing individuals at risk.

Reported risk factors vary widely, and the independence and magnitude of each are uncertain. Several study design issues may account for this variability. For example, studies that identified cases solely by autopsy or only included patients who were enrolled in clinical trials or of one sex may not have identified important risk factors, since the full clinical spectrum of disease was not represented. Moreover, previous prospective cohort studies were limited by the relatively low incidence of VTE and the correspondingly small sample sizes. Because these cohort studies were not designed to determine risk factors for VTE, the baseline characteristics available for analysis did not include all potential characteristics thought to place patients at risk. Finally, previous case-control studies either included an inappropriate control group or only addressed the risk among women receiving oral contraceptives or hormone replacement therapy.

See also page 761

We have identified the inception cohort of Olmsted County, Minnesota, resi-
PATIENTS AND METHODS

STUDY SETTING AND DESIGN

Using the data resources of the Rochester Epidemiology Project,® we identified the inception cohort of Olmsted County residents with a first lifetime DVT or PE during the 25-year period from 1966 through 1990 as previously described.1 We then performed a case-control study nested within the Olmsted County population. All Olmsted County residents with a first lifetime definite DVT or PE diagnosed during the 15-year period from January 1, 1976, through December 31, 1990, were included in the present study. The Rochester Epidemiology Project also provides an enumeration of the population from which controls can be sampled, as described elsewhere.10 Using this system, the Olmsted County resident matched for age (±1 year), calendar year (±1 year), and sex whose medical record number was closest to the medical record number of each patient with DVT or PE was selected as a control. The study was approved by the Mayo Clinic Institutional Review Board.

DEFINITION OF DVT AND PE

A DVT was categorized as definite when confirmed by venogram, computed tomographic scan, magnetic resonance image, or pathologic examination of thrombus removed at surgery or autopsy. A PE was categorized as definite when confirmed by pulmonary angiogram, computed tomographic scan, magnetic resonance image, or pathologic examination of thrombus removed at surgery or autopsy.

Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of persons who died within Olmsted County during the study period. Autopsy-discovered PE events were classified as a cause of death only if the pathologist labeled them as such in the autopsy report or if the death certificate listed PE as an immediate or underlying cause of death or included PE on part I of the death certificate. Autopsy-discovered PE events were classified as a “contributory cause of death” if PE was listed as a contributing cause or other significant

condition on part II of the death certificate. Pulmonary embolism events that were first identified on autopsy examination but not specifically labeled as a cause of death in the autopsy report or listed on the death certificate were categorized as “noncausal for death.”

BASELINE CHARACTERISTICS

A large number of baseline characteristics were tested as risk factors for VTE. Data were obtained by review of all medical records (inpatient and outpatient) in the community for each subject; consequently, it was not possible to blind the nurse abstractors to case or control status. The overall mean duration of prior medical record documentation was 34.7 years (34.7 years for patients with DVT or PE and 34.7 years for controls). The characteristics assessed included type of incident event (PE, DVT, or both); age at incident event; sex; year of incident event; patient location at incident event onset (community, community but hospitalized in the previous 90 days, hospital, or nursing home); body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters: weight [kg]/[height (m)]²); chronic heart disease (congestive heart failure vs other heart disease [ie, congenital heart disease, cardiomyopathy, ischemic heart disease, or valvular heart disease]); active malignant neoplasm (excluding nonmelanoma skin cancer) with or without chemotherapy (cytotoxic or immunosuppressive therapy for malignant neoplasm, excluding tamoxifen); serious neurologic disease (stroke or other disease affecting the nervous system with associated extremity paresis, or acute stroke with extremity paresis requiring hospitalization within the previous 3 months); surgery requiring anesthesia (general, orthopedic, neurologic, or gynecologic surgery); trauma requiring hospital admission (major fracture or severe soft-tissue injury); chronic lung disease (chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchiectasis, interstitial lung disease, pulmonary hypertension [asthma was included only if there was documented evidence of fixed airflow obstruction]); serious liver disease (including active hepatitis within the previous 3 months);
chronic renal disease (physician’s diagnosis and either creatinine level >175 μmol/L [2 mg/dL] for at least 3 months or nephrotic syndrome; arteriovenous fistula thrombosis excluded); inflammatory bowel disease; previous superficial vein thrombosis; varicose veins (varicose veins or treated varicose veins [injection sclerotherapy or stripping]); central venous catheter or transvenous pacemaker placement; anticoagulation therapy or prophylaxis immediately preceding or at the time of the incident event; smoking status (none, former, or current [cigarettes only]); and (for women only) pregnancy or postpartum at the time of the incident event, oral contraceptive use, hormone therapy (estrogen or progestrone), gynecologic surgery, and tamoxifen therapy. It was necessary that active malignant neoplasm, chemotherapy, serious neurologic disease (acute stroke or temporary lower-extremity paresis), all surgery variables, anesthesi a, trauma, serious liver disease (active or chronic hepatitis only), hormone therapy, central vein catheterization, oral contraceptive use, and tamoxifen therapy be documented in the 3 months prior to the incident event. Congestive heart failure and other heart disease, serious neurologic disease (with unresolved lower-extremity paresis), chronic lung disease, serious liver disease (cirrhosis only), chronic renal disease, nephrotic syndrome, inflammatory bowel disease, previous superficial vein thrombosis, varicose veins, and permanent transvenous pacemaker placement could be documented any time prior to the incident event. Body mass index was based on the most recent height and weight measurements prior to the incident event.

Body mass index could not be calculated for 16 cases and 176 controls, mainly because of missing height measurements. For these cases and controls, we imputed BMI values by assigning to each the respective average height or weight of the same sex and 10-year age group of cases or controls. For the one child younger than 15 years with a missing measurement for height, we used the 50th height percentile from the 1976 National Center for Health Statistics growth chart. Because smoking status was missing in 88 case-control pairs, this variable was evaluated only after determination of the otherwise final model, including interactions, since only a subset of the cases could be used. In the subset of cases with complete smoking information, we verified that the final multivariate model variables did not have odds ratios differing from those computed using all cases. We then categorized those patients with missing smoking status as nonsmokers, reasoning that this would be the most conservative approach. Because pregnancy and the postpartum period, oral contraceptive use, hormone replacement therapy, tamoxifen therapy, and gynecologic surgery could only be evaluated in women, these variables were assessed after determining the otherwise final model, including interactions. In the univariate analyses, the surgery variables were important risk factors. In the multivariate modeling, however, the surgery variables were nonsignificant after adjusting for patient location at VTE onset, and it was not possible to address interactions of surgery and hospitalization. Therefore, we created a new variable with the following categories: community onset with no recent (within 90 days) institutionalization (confinement in hospital or nursing home), onset while institutionalized but without recent (within 90 days) surgery, and onset while institutionalized with recent surgery.

ANALYSIS

Baseline characteristics were assessed as potential risk factors for VTE using conditional logistic regression. We used stepwise and backwards conditional logistic regression to identify a “final model.” P<.05 was required to enter the model. The variables selected were validated using a bootstrap method in which 500 random samples of the case-control pairs were selected with replacement. A stepwise regression was run for each sample. Variables were considered validated and retained in the final model only if they entered more than 70% of the 500 logistic regression models. When the list of main effect variables was finalized, all 2-way interactions of the main variables in the model were validated using the bootstrap technique. Discrete variables with multiple components could not be assessed using the usual stepwise technique. Such variables were validated separately, as were all interactions.

This population-based case-control study identified a number of independent risk factors for VTE. Our study is the first to identify hospital, nursing home, or other chronic care facility confinement as an independent risk factor for VTE. It is likely that the increased risk associated with hospital confinement reflects relative immobilization and the acuity and severity of illness. However, it is less clear...
that the risk associated with nursing home or chronic care facility confinement represents immobilization, since many such residents remain mobile. Further studies of the risk associated with these residents are warranted, since prophylaxis is seldom provided.

The VTE risk was highest among patients who were hospitalized with previous surgery, with nearly a 22-fold increased risk. This risk is much higher than previously reported, likely a result of differences in study design. Clinical trial data support the high risk of VTE associated with surgery. Recent trauma was the next most potent risk for VTE in our study, with nearly a 13-fold increase in risk. Both autopsy and cohort studies support an increased risk of VTE with trauma.

We found a 4-fold increased risk of VTE among patients with malignant neoplasm alone, which is similar

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Case-Control Pairs, No.</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>138 124 108 169</td>
<td>1.38 (1.09-1.74)</td>
</tr>
<tr>
<td>Body mass index, kg/m²†</td>
<td></td>
<td>0.98 (0.96-1.00)</td>
</tr>
<tr>
<td>Smoking (ever)‡</td>
<td>138 124 108 169</td>
<td>1.15 (0.89-1.49)</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td>1.30 (0.91-1.85)</td>
</tr>
<tr>
<td>Former</td>
<td></td>
<td>1.07 (0.79-1.44)</td>
</tr>
<tr>
<td>Institutionalization within previous 90 days</td>
<td>73 332 18 203</td>
<td>18.44 (11.48-29.84)</td>
</tr>
<tr>
<td>Community acquired</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Community acquired/hospitalized within 90 days</td>
<td></td>
<td>10.03 (5.78-17.42)</td>
</tr>
<tr>
<td>Nursing home acquired</td>
<td></td>
<td>10.64 (5.55-20.38)</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td></td>
<td>464.95 (62.68-3448.83)</td>
</tr>
<tr>
<td>Previous superficial vein thrombosis</td>
<td>4 40 16 565</td>
<td>2.50 (1.40-4.46)</td>
</tr>
<tr>
<td>Previous central venous catheter or pacemaker</td>
<td>0 71 6 548</td>
<td>11.83 (5.14-27.23)</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>23 117 84 401</td>
<td>1.39 (1.05-1.84)</td>
</tr>
<tr>
<td>All cardiac diseases</td>
<td>65 124 79 357</td>
<td>1.57 (1.18-2.08)</td>
</tr>
<tr>
<td>No cardiac disease</td>
<td></td>
<td>2.78 (1.85-4.17)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td>0.99 (0.69-1.41)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>15 81 66 463</td>
<td>1.23 (0.89-1.70)</td>
</tr>
<tr>
<td>Serious liver disease</td>
<td>0 5 6 614</td>
<td>0.83 (0.25-2.73)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>0 4 5 616</td>
<td>0.80 (0.21-2.98)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>0 18 6 601</td>
<td>3.00 (1.19-7.56)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>0 3 1 621</td>
<td>3.00 (0.31-28.84)</td>
</tr>
<tr>
<td>Myeloproliferative disease</td>
<td>0 8 2 615</td>
<td>4.00 (0.85-18.94)</td>
</tr>
<tr>
<td>Coagulation disorders</td>
<td>0 2 1 622</td>
<td>2.00 (0.18-22.06)</td>
</tr>
<tr>
<td>Neurologic disease with extremity paresis</td>
<td>2 62 12 549</td>
<td>5.17 (2.79-9.59)</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>4 138 18 465</td>
<td>7.67 (4.69-12.53)</td>
</tr>
</tbody>
</table>

*+/+ indicates that both the case and the control had the characteristic, +/-, that the case had the characteristic while the control did not, -/+, that the case did not have the characteristic while the control did, and --/−, that neither the case nor the control had the characteristic.
†Missing height, weight, and body mass index values were imputed.
‡Data on smoking status were missing among 88 case-control pairs.
§Methods were adapted from Fleiss to estimate the odds ratio and 95% CI.
||Women only.
to the increase in PE prevalence among patients with cancer who underwent autopsy.\textsuperscript{4,5,23} Moreover, malignant neoplasm has been reported as an independent risk factor for outpatient-acquired DVT.\textsuperscript{8} Patients with cancer receiving immunosuppressive or cytotoxic chemotherapy were at an even higher risk for VTE. Previous studies have shown an increased risk of VTE among patients with breast cancer who were receiving chemotherapy.\textsuperscript{24,25}

Patients with neurologic disease and extremity paresis or plegia had a 3-fold increased risk for VTE that was independent of hospital confinement. Consistent with this finding, the prevalence of PE is increased among patients with paraplegia or quadriplegia who underwent autopsy,\textsuperscript{3} and the risk of DVT among patients with neurologic disease and paralyzed legs\textsuperscript{26-28} and among nonambulatory patients who had strokes is increased.\textsuperscript{20}

Our study is the first to document the magnitude of risk for PE or upper-extremity DVT among patients with a current or recent central venous catheter or a transvenous pacemaker, as well as the first to identify superficial vein thrombosis and varicose veins as independent risk factors for VTE. Although the risk associated with central venous catheterization may reflect risk from comorbid conditions, we controlled for most conditions in which such catheters likely would be used. We found that the risk associated with varicose veins varied by patient age. For example, 45-year-old patients with varicose veins had a 4-fold increased risk of VTE compared with a 2-fold increased risk for 60-year-old patients and no increased risk for 75-year-old patients. In contrast, varicose veins were not an independent predictor of major PE discovered at autopsy in the Framingham Study.\textsuperscript{6} Similarly, varicose veins were not an independent risk factor for DVT among outpatients with no recent trauma, surgery, or immobilization.\textsuperscript{8} Aside from differences in study population and design, we have no explanation for this discrepancy. It is likely that varicose veins among the young are caused by an inherited connective-tissue defect.\textsuperscript{30}

Interestingly, serious liver disease was associated with a 90% decrease in risk for VTE in our population. This finding is biologically plausible. Patients with serious liver disease often have prolonged clotting times, reduced clearance of fibrin degradation products, and thrombocytopenia. Together, these impairments of normal hemostasis may act to protect patients from VTE.

Congestive heart failure was a risk factor for postmortem VTE that was not a cause of death, but not for VTE that was either manifest before death or categorized as a cause of death. Other cardiac disease was also not an independent risk factor for VTE. Our findings contrast with autopsy studies that demonstrate an increased prevalence of PE among patients who are dying from cardiac disease, especially cardiac disease causing congestive heart failure.\textsuperscript{4,5} In addition, Cogo et al\textsuperscript{8} found heart failure to be an independent risk factor for DVT among outpatients with no recent trauma, surgery, or immobilization. We cannot exclude the possibility of de-
tion bias and misclassification of cause of death among patients with congestive heart failure whose PE was discovered on autopsy. In our study, patients who were dying of congestive heart failure may have been more likely to undergo autopsy and thus have an autopsy-discovered PE. However, the attending pathologist may have attributed the cause of death to congestive heart failure rather than PE. Alternatively, congestive heart failure or other cardiac disease may not be a risk factor for VTE independent of hospital confinement.

Neither BMI nor current or past tobacco smoking was an independent risk factor for VTE. While previous studies reported increased risk caused by obesity and smoking, most of these earlier studies failed to control for hospital confinement or other risk factors. Although our ability to identify an above-normal BMI as a risk factor may have been limited because of missing weight or height data among controls, we do not believe our results are biased since most of the missing data were body height measurements. Moreover, additional analyses of weight as a potential risk factor did not change our conclusions. We also confirmed that chronic obstructive pulmonary disease and renal failure were not independent risk factors for VTE. A previous study found that the risk of VTE among patients who underwent surgery was less with regional (spinal or epidural) anesthesia compared with general anesthesia. In our univariate analyses, regional anesthesia was associated with an 11.5-fold increased risk, while general anesthesia was associated with a 19-fold increased risk. However, in the multivariate analysis, type of anesthesia was not an independent risk factor for VTE after controlling for surgery.

Among women, pregnancy, postpartum period, oral contraceptive use, hormone therapy, and tamoxifen therapy were not independent risk factors for VTE. While several cohort studies showed no significant increase in VTE incidence among pregnant women compared with the general population, the incidence during the postpartum period was increased about 2-fold. In addition, the vast majority of evidence suggests that both oral contraceptive use and hormone replacement therapy are significant risk factors for VTE. Since only 24 patients who had definite VTE events were pregnant (n = 3), postpartum (n = 9), or taking oral contraceptives (n = 12) at baseline, it is likely that the power was insufficient to identify these variables as independent risk factors.

We believe our results are valid because we avoided the potential distortions associated with referral bias by performing a population-based study with both cases and controls selected from residents in the community. Moreover, all cases met strict criteria for VTE; the diagnosis was confirmed by either venogram, pulmonary angiogram, or postmortem examination. We separated VTE events that were detected on postmortem examination into clinically important VTE events that were the immediate, underlying, or a contributory cause of death and incidentally noted VTE events (essentially all PE events) that were discovered on postmortem examination but not judged by the pathologist as sufficiently important to be listed in either part I or part II of the death certificate. Our modeling strategy required that risk factors included in our final model be present in 70% or more of separate bootstrap validations, thus reducing the chance of a type I error. Finally, we evaluated a large number of baseline characteristics as potential risk factors for VTE, including all interactions.

It is also important to address potential limitations of our study. We were unable to evaluate age or sex as independent risk factors for VTE because of our matching strategy. Several studies have either shown an increased incidence of VTE with increased age or identified increased age as an independent risk factor for DVT. The risk associated with sex remains uncertain; previous studies have reported either no difference in autopsy-discovered PE by sex, or an increase in the risk for PE and DVT among men. Because of concern regarding diagnostic suspicion bias, we did not analyze the potential risk associated with immobilization independent of hospital or nursing home confinement (eg, immobilization during prolonged travel). We required that all risk factors be documented in the medical record prior to the onset of the VTE event, and data on such immobilization could not be reliably ascertained from the medical record for controls.

It is likely that our study had insufficient power to exclude hormone therapy, tamoxifen therapy, inflammatory bowel disease, systemic lupus erythematosus, or myeloproliferative diseases as risk factors for VTE. Although we collected all available data on coagulation disorders, most cases and controls were not tested for these disorders. Moreover, the most common coagulation disorder (eg, activated protein C resistance) had not been described at the inception of our study.

In summary, we have described independent baseline characteristics that identify a population at risk for VTE and estimated the magnitude of risk associated with each characteristic. For many of these risk factors, available prophylaxis has clear benefit, and all affected individuals should receive appropriate prophylaxis. Additional data regarding genetic and acquired disorders as VTE risk factors are needed in order to better assess risk in the individual and to target prophylaxis.

Accepted for publication July 14, 1999.

This study was funded in part by grants HL46974 and AR30583 from the National Institutes of Health, Bethesda, Md; and by the Mayo Foundation, Rochester, Minn.

We thank C. Mary Beard, RN, for assistance in managing the study; Janet Ebersold, RN, Kay Traverse, RN, Mary Lou Notermann, RN, and Susan Stotz, RN, for their untiring medical record review; Randall Stick, BS, for programming; Diana Rademacher, BS, and Christine Lohse, BS, for assistance with data analysis; and Stephanie Wellick for secretarial support.

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