Relative Impact of Risk Factors for Deep Vein Thrombosis and Pulmonary Embolism

A Population-Based Study

John A. Heit, MD; W. Michael O’Fallon, PhD; Tanya M. Petterson, MS; Christine M. Lohse, BS; Marc D. Silverstein, MD; David N. Mohr, MD; L. Joseph Melton III, MD

Objective: To assess the potential impact of controlling risk factors on the incidence of venous thromboembolism by estimating the population attributable risk (defined as the percentage of all cases of a disease in a population that can be “attributed” to a risk factor) for deep vein thrombosis and pulmonary embolism associated with venous thromboembolism risk factors.

Methods: Using data from a population-based, nested, case-control study of the 625 Olmsted County, Minnesota, residents with a definite first lifetime deep vein thrombosis or pulmonary embolism diagnosed during the 15-year period 1976 to 1990 and 625 unaffected Olmsted County residents matched for age and sex, we developed a conditional logistic regression model appropriate to the matched case-control study design and then estimated attributable risk for the risk factors individually and collectively.

Results: Fifty-nine percent of the cases of venous thromboembolism in the community could be attributed to institutionalization (current or recent hospitalization or nursing home residence). Hospitalization for surgery (24%) and for medical illness (22%) accounted for a similar proportion of the cases, while nursing home residence accounted for 13%. The individual attributable risk estimates for malignant neoplasm, trauma, congestive heart failure, central venous catheter or pacemaker placement, neurological disease with extremity paresis, and superficial vein thrombosis were 18%, 12%, 10%, 9%, 7%, and 5%, respectively. Together, the 8 risk factors accounted for 74% of disease occurrence.

Conclusions: Factors associated with institutionalization independently account for more than 50% of all cases of venous thromboembolism in the community. Greater emphasis should be placed on prophylaxis for hospitalized medical patients. Other recognized risk factors account for about 25% of all cases of venous thromboembolism, while the remaining 25% of cases are idiopathic.

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PATIENTS AND METHODS

STUDY SETTING AND DESIGN

Using the data resources of the Rochester Epidemiology Project,12 we identified the inception cohort of Olmsted County, Minnesota, residents with a first lifetime definite deep vein thrombosis or pulmonary embolism during a 25-year period (1966-1990), as previously described.3 We then performed a case-control study nested within the Olmsted County population, also as previously described.6 All 625 Olmsted County residents with a first lifetime definite deep vein thrombosis or pulmonary embolism diagnosed during the 15-year period 1976 to 1990 were included as cases. The Rochester Epidemiology Project also provides an enumeration of the population from which controls can be sampled as described elsewhere.13 Using this system, the age (±5 years)-, sex-, and event year (±1 year)-matched Olmsted County resident whose medical record number was closest to each case’s medical record number was selected as a control. Data were obtained by review of all medical records (inpatient and outpatient) in the community for each subject.13 The overall mean duration of prior medical record documentation was 34.7 years (34.7 years for cases and 34.7 years for controls). Our sample size provided us with at least 80% power to detect a 2-fold increase in risk for risk factors occurring in more than 5% of the population or a 50% increase in risk for factors occurring in more than 20% of the population. The study was approved by the institutional review board of the Mayo Clinic, Rochester.

DEFINITION OF TERMS

The definitions of definite deep vein thrombosis and of definite pulmonary embolism have been previously described.1 Briefly, a deep vein thrombosis was categorized as definite when confirmed by venography, computed tomographic scan, magnetic resonance imaging scan, or the findings of pathologic examination of a thrombus that had been removed at surgery or autopsy. A pulmonary embolism was categorized as definite when confirmed by pulmonary angiography, computed tomographic scan, magnetic resonance imaging scan, or the findings of pathologic examination of a thrombus that had been removed at surgery or autopsy. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of the persons who died within Olmsted County during the study period.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

A large number of baseline characteristics were tested as potential risk factors for deep vein thrombosis and pulmonary embolism in a multivariate conditional logistic regression model, as previously reported.6 Independent risk factors for venous thromboembolism included age at incident venous thromboembolism event; male sex; calendar year; institutionalized at onset (eg, hospitalized or in a nursing home or hospitalized within the previous 90 days [with and without surgery]); active malignant neoplasm (with and without chemotherapy); congestive heart failure; serious neurological disease resulting in lower extremity paresis; major fracture or severe soft tissue injury; central vein catheterization or transvenous pacemaker placement; prior superficial vein thrombosis; varicose veins; and serious liver disease.

ANALYSIS

The development of the final multivariate logistic regression model referred to above has been described in detail.6 As outlined by Bruzzi et al14 and Benichou and Gail15 and discussed in detail by Kahn et al,16 such a logistic model can be used to estimate attributable risk for individual risk factors, or for several risk factors collectively, while adjusting for appropriate covariates.

As described by Kahn et al,16 this generalized attributable risk estimate, \( \hat{\text{AR}} \), takes on the following form:

\[
\hat{\text{AR}} = 1 - \frac{1}{n} \sum_{i=1}^{n} \exp \left\{ - \hat{\beta} \Delta_i \right\},
\]

where \( n \) is the number of cases in the case-control study, \( \hat{\beta} \) is the estimated parameter vector from the logistic model, and \( \Delta_i \) is the difference between the observed and target vectors for the \( i \)th case. Thus, after fitting the logistic model, the calculation of \( \hat{\text{AR}} \) involves only the cases. Bootstrap methodology was used to obtain 95% CI estimates of \( \hat{\text{AR}} \) as described by Kahn and coworkers.

RESULTS

The attributable risk estimates associated with the independent risk factors for venous thromboembolism are shown in the Table. After adjusting for only the matching variables, we estimated that 61% (95% confidence interval [CI], 57%-66%) of all cases of definite venous thromboembolism could be attributed to institutionalization (current hospital or nursing home confinement or such confinement within the preceding 3 months). After adjusting for all variables in the final model,16 59% of incident venous thromboembolism cases could be attributed to institutionalization. This estimate can be partitioned into the proportions attributable to hospitalization with surgery (24%), other hospitalizations (22%), and nursing home residence (13%).

Eighteen percent of incident venous thromboembolism cases were attributable to active malignant neoplasm, with or without chemotherapy (Table). Malignant neoplasm without chemotherapy was responsible for a larger percentage of the risk of venous thromboembolism (12%) than was malignancy with chemotherapy (6%). Trauma, congestive heart failure, and prior central venous catheter or pacemaker placement were responsible for 12%, 10%, and 9% of the venous thromboembolism cases, respectively (Table). Seven percent of venous thromboembolism cases were attributable to neurological disease and 5% to prior superficial vein thrombosis. We initially estimated that 6% of the cases of venous thromboembolism were attributable to varicose veins or vein stripping. However, after adjusting for the other risk factors, none (95% CI, 0%-10%) of the incident venous
thromboembolism cases could be attributed to varicose veins or vein stripping.

The percentages of incident venous thromboembolism cases attributed to combinations of individual risk factors (after adjusting for the final model) are illustrated in the Figure. For example, institutionalization and malignant neoplasm jointly accounted for 65% (95% CI, 60%-69%) of the incident venous thromboembolism cases. Thus, malignant neoplasm can be thought of as having contributed an additional 6% to venous thromboembolism once we accounted for hospitalization or nursing home residency (which accounted for 59% alone) or, conversely, that hospitalization or nursing home residency can be thought of as having contributed an additional 47% of the cases once we accounted for malignant neoplasm. Institutionalization plus trauma accounted for 62% of incident venous thromboembolism cases, while institutionalization plus congestive heart failure accounted for 61% of cases and institutionalization plus prior central venous catheter or pacemaker accounted for 60% of cases. All 8 risk factors together accounted for 74% (95% CI, 70%-79%) of all venous thromboembolism cases observed. Thus, if all 8 risk factors could be eliminated, just over 25% of the venous thromboembolism cases in the community would still be unexplained.

### COMMENT

Proper interpretation of population attributable risk, defined as the percentage of all cases of a disease in a population that can be attributed to a risk factor, requires the establishment of causality between the risk factor and the disease. However, causality is a complex concept and raises many questions that are not easily resolved. It is not easy to establish that a factor “causes” a disease, and, after centuries of debate, there is little consensus regarding the definitions of causality or how to establish it. This fact notwithstanding, we believe that the elucidation of attributable risk estimators, even when causality remains uncertain, is extremely useful in focusing further research. Thus, it is logical that further research or even intervention be planned around factors that alone or collectively are associated with large attributable risk estimators rather than around those factors associated with minimal attributable risk estimators.

Our analysis indicates that the incidence of venous thromboembolism might be reduced by about 75% if prophylaxis were universally prescribed and effective, and if other currently recognized risk factors could be modified or avoided. Thus, hospitalization and nursing home residence (current or recent) together accounted for almost 60% of all cases of venous thromboembolism disease in the community. Of note, hospitalization for medical illness and hospitalization for surgery accounted for almost equal proportions of venous thromboembolism (22% and 24%, respectively), emphasizing the need to

### Table: Adjusted Population Attributable Risk (AR) Associated With Independent Risk Factors for First Lifetime Definite Venous Thromboembolism Among Olmsted County, Minnesota, Residents (1976-1990)*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AR</th>
<th>95% CI</th>
<th>AR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization or nursing home</td>
<td>61.2</td>
<td>56.9-65.6</td>
<td>58.8</td>
<td>53.4-64.2</td>
</tr>
<tr>
<td>Hospitalization with surgery</td>
<td>24.2</td>
<td>20.8-27.6</td>
<td>23.8</td>
<td>20.3-27.3</td>
</tr>
<tr>
<td>Hospitalization without surgery</td>
<td>22.5</td>
<td>19.0-26.0</td>
<td>21.5</td>
<td>17.3-25.6</td>
</tr>
<tr>
<td>Nursing home</td>
<td>14.4</td>
<td>11.3-17.4</td>
<td>13.3</td>
<td>9.9-16.8</td>
</tr>
<tr>
<td>Active malignant neoplasm</td>
<td>19.8</td>
<td>16.2-23.3</td>
<td>18.0</td>
<td>13.4-22.6</td>
</tr>
<tr>
<td>Malignant neoplasm with chemotherapy</td>
<td>6.8</td>
<td>4.7-8.9</td>
<td>6.4</td>
<td>3.9-9.0</td>
</tr>
<tr>
<td>Malignant neoplasm without chemotherapy</td>
<td>13.0</td>
<td>9.9-16.0</td>
<td>11.6</td>
<td>7.6-15.5</td>
</tr>
<tr>
<td>Trauma</td>
<td>12.5</td>
<td>9.8-15.2</td>
<td>12.0</td>
<td>9.0-14.9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11.8</td>
<td>8.0-15.7</td>
<td>9.5</td>
<td>3.3-15.8</td>
</tr>
<tr>
<td>Prior central venous catheter or pacemaker</td>
<td>10.5</td>
<td>7.9-13.0</td>
<td>9.1</td>
<td>5.7-12.6</td>
</tr>
<tr>
<td>Neurological disease with extremity paresis</td>
<td>8.2</td>
<td>5.5-10.8</td>
<td>6.9</td>
<td>3.5-10.2</td>
</tr>
<tr>
<td>Prior superficial vein thrombosis</td>
<td>4.3</td>
<td>1.9-6.7</td>
<td>5.4</td>
<td>3.0-7.7</td>
</tr>
<tr>
<td>Varicose veins/vein stripping</td>
<td>6.0</td>
<td>0.7-11.2</td>
<td>0.0</td>
<td>0.0-10.2</td>
</tr>
</tbody>
</table>

*All values are given as percentages. CI indicates confidence interval.
provide prophylaxis for both of these risk groups. Only 9% of our hospitalized patients were receiving anticoagulants at the time of venous thromboembolism onset, including 10% of patients hospitalized with surgery and 7% of patients hospitalized for medical illness.

Nursing home residence independently accounted for more than one tenth of all cases of venous thromboembolism disease in the community. Nursing home residents usually have not been considered for venous thromboembolism prophylaxis. Moreover, these patients often have other conditions that place them at high risk for anticoagulant-related complications, particularly bleeding. Consequently, universal prophylaxis for such patients is unlikely to be cost-effective. Additional studies are needed to identify risk factors for venous thromboembolism among nursing home residents (independent of cancer, congestive heart failure, or neurological disease with extremity paresis) such that prophylaxis can be targeted to those patients at highest risk when appropriate.

Malignant neoplasm accounted for almost one fifth of all cases of venous thromboembolism disease in the community. Among patients with cancer, malignant neoplasms not requiring cytotoxic or immunosuppressive chemotherapy accounted for almost twice the incidence of venous thromboembolism compared with cancers requiring chemotherapy. Although we did not collect data on cancer type, breast and prostate cancer commonly are treated with therapies other than cytotoxic or immunosuppressive chemotherapy and may account for a substantial proportion of venous thromboembolism due to malignant neoplasm. Additional studies are needed to identify risk factors for venous thromboembolism among patients with cancer.

Trauma, congestive heart failure, and placement of a central venous catheter or transvenous pacemaker accounted for similar proportions of venous thromboembolism in the community. The burden of disease accounted for by central venous catheters (9%) is particularly noteworthy as a relatively recent risk factor and emphasizes the need for additional studies addressing the safety and efficacy of anticoagulant-based prophylaxis in this patient group. The proportion of disease accounted for by neurological disease with extremity paresis and prior superficial vein thrombosis also was similar.

About 25% of all cases of venous thromboembolism in the community could not be accounted for by these risk factors. Only a small portion of this disease could be attributed to other potential risk factors not identified in our case-control study. For example, only 91 of our 1244 female patients with incident venous thromboembolism had pregnancy or the puerperium as a baseline characteristic, and only 173 were receiving oral contraceptives (n=103), hormone replacement therapy (n=68), or both (n=2). Although we collected all available clinical data on coagulation disorders, most patients and controls did not undergo laboratory testing for these disorders. Moreover, the most common coagulation disorder (eg, activated protein C resistance) had not been described at the inception of our study.

A major strength of our study is that it is population-based. Therefore, our study is completely representative of persons within Olmsted County who met our criteria for a definite deep vein thrombosis or a definite pulmonary embolism over the 15-year period 1976-1990. Over this study period, the population of Olmsted County was approximately 98% white and of non-Hispanic ancestry. Consequently, our results can only be generalized to similar populations.

In summary, currently recognized clinical risk factors account for about 75% of venous thromboembolism cases in the community, while about 25% remain idiopathic. Appropriate prophylaxis should be provided for all patients at risk, and, where possible, exposure to risk factors should be avoided or minimized. However, of the patients with one or more of these risk factors, most do not develop venous thromboembolism. Additional studies are needed to identify characteristics that can stratify risk among these patient subsets and allow prophylaxis to be tailored accordingly.

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Corresponding author: John A. Heit, MD, Hematology Research, Stable 660, Mayo Clinic, 200 First St SW, Rochester, MN 55905.