Clinical Predictors for Fatal Pulmonary Embolism in 15 520 Patients With Venous Thromboembolism

Findings From the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry

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Background—Clinical predictors for fatal pulmonary embolism (PE) in patients with venous thromboembolism have never been studied.

Methods and Results—Using data from the international prospective Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry about patients with objectively confirmed symptomatic acute venous thromboembolism, we determined independent predictive factors for fatal PE. Between March 2001 and July 2006, 15 520 consecutive patients (mean age ± SD, 66.3 ± 16.9 years; 49.7% men) with acute venous thromboembolism were included. Symptomatic deep-vein thrombosis without symptomatic PE was observed in 58.0% (n = 9008) of patients, symptomatic nonmassive PE in 40.4% (n = 6264), and symptomatic massive PE in 1.6% (n = 248). At 3 months, the cumulative rates of overall mortality and fatal PE were 8.65% and 1.68%, respectively. On multivariable analysis, patients with symptomatic nonmassive PE at presentation exhibited a 5.42-fold higher risk of fatal PE compared with patients with deep-vein thrombosis without symptomatic PE (P = 0.001). The risk of fatal PE was multiplied by 17.5 in patients presenting with a symptomatic massive PE. Other clinical factors independently associated with an increased risk of fatal PE were immobilization for neurological disease, age >75 years, and cancer.

Conclusion—PE remains a potentially fatal disease. The clinical predictors identified in the present study should be included in any clinical risk stratification scheme to optimally adapt the treatment of PE to the risk of the fatal outcome. (Circulation. 2008;117:1711-1716.)

Key Words: death, sudden | prognosis | pulmonary embolism | thrombosis

Pulmonary embolism (PE) is known to be a major cause of death in patients with venous thromboembolism. Yet in cohort studies, randomized clinical trials, and general reviews on this topic, the incidence of fatal PE varied from <1% to 7%.1-8 This variability, mainly related to the type of patients studied, highlights that venous thromboembolism is a heterogeneous disease with various presentations and prognoses. The key to appropriate therapy is therefore risk stratification to identify patients at high risk of death who should receive specific therapeutic management.9,10 This step is all the more important in that the use of generally recommended treatments, such as administration of fibrinolytic drugs11 or placement of vena cava filters12 in high-risk patients may be complicated by severe adverse events. However, to date, the clinical variables indicating a high risk of fatal PE in patients with venous thromboembolism remain largely unknown. Available studies in this setting are few, generally small or retrospective, or do not analyze this specific outcome.3,13-17

Clinical Perspective p 1716

The Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry is an international, multicenter, observational, prospective registry of consecutive patients with objectively confirmed symptomatic acute venous thromboembolism.18,19 We analyzed the data of this registry to determine independent clinical predictors for fatal PE in patients treated in daily practice for acute venous thromboembolism.
Patients and Methods

Registry Design and Data Collection

The RIETE registry is an ongoing, international, multicenter, prospective cohort of consecutive patients presenting with symptomatic venous thromboembolism (deep-vein thrombosis, PE, or both) confirmed by objective tests. Patients are managed according to the clinical practice of each participating hospital center. The only 2 exclusion criteria are a planned follow-up < 3 months and participation in another study. The following information was collected: demographic data, symptoms on presentation, type of symptomatic venous thromboembolism, types and results of diagnosis methods, risk factors for venous thromboembolism, and therapeutic management for both the acute phase and the subsequent 3 months. At each participating center, a registry coordinator controlled the quality of data collection (eg, internal validity and coherence) and recorded the data on a computer-based case report form. Coordinators ensured that all consecutive patients with confirmed venous thromboembolism were included in the registry. In addition, the database of each analysis was controlled. The information was then transferred online via a secure Web site to the Study Coordinating Centre responsible for data management. Data quality was also monitored by members of contract research organizations who compared the data on medical records with the data transferred online during periodic visits to participating hospitals. All patients provided oral or written consent to their participation in the registry, in accordance with the requirements of the ethics committee of each country.

Study Outcome

In the present study, fatal PE was the outcome that was analyzed during a 3-month follow-up period. In patients with acute respiratory symptoms suggesting PE, symptomatic PE was confirmed if it was documented objectively (positive helical computed tomography scan, high-probability ventilation-perfusion lung scintigraphy, positive pulmonary angiography, visualization of thrombus on echocardiogram, or indeterminate-probability ventilation-perfusion lung scintigraphy associated with deep-vein thrombosis in the lower limbs confirmed by compression ultrasonography or contrast venography). In the event of death, death was considered to be due to PE if this diagnosis was documented at autopsy or if the patient died shortly after objectively confirmed symptomatic PE and in the absence of any alternative diagnosis. These events were reviewed by a central adjudication committee.

Data Analysis

The cumulative rates of overall death and fatal PE were estimated using the Kaplan-Meier method. The selection of candidate clinical predictors for fatal PE was based on the results of published models and on expert clinical opinion. The following variables were analyzed to determine their value in predicting the risk for fatal PE: age, gender, body weight, obesity (defined as a body mass index $\geq 30$ kg/m²), a history of venous thromboembolism, cardiac or respiratory disease (eg, ischemic heart disease, heart failure, or chronic lung disease), cancer, immobilization > 4 days for neurological disease (ie, stroke or other neurological disease associated with leg paralysis), infection, recent surgery (ie, any surgical intervention in the past 2 months), recent trauma (ie, any trauma requiring immobilization in the past 2 months), recent travel (ie, travel lasting > 6 hours in the previous 3 weeks), and, for women only, estrogen intake in the previous 2 months and pregnancy. The predictive value of the type of venous thromboembolism at presentation was also analyzed. Venous thromboembolism was classified as distal or proximal deep-vein thrombosis without symptomatic PE, symptomatic nonmassive PE, or symptomatic massive PE. Pulmonary embolism was defined as massive if systolic blood pressure was < 90 mm Hg.22 A single logistic regression model was used to examine the individual relationship between each potential prognosis factor and the risk for fatal PE. Odds ratios and 95% confidence intervals (CIs) were used to quantify the association. Second, all variables that achieved a significance level of 0.15 were eligible for inclusion in the multivari-
due to PE in 260 patients (19.4% of deaths), giving an estimated cumulative rate of fatal PE at 3 months of 1.68% (Figure). The cumulative rate of fatal PE was estimated to be 0.55% in patients with symptomatic deep-vein thrombosis without PE, 2.99% in patients with symptomatic nonmassive PE, and 9.27% in patients with symptomatic massive PE. Fifty percent of fatal PEs occurred within 5 days of venous thromboembolism and 75% within 12 days of inclusion.

Predictors of Fatal Pulmonary Embolism
Several potential predictors for fatal PE were identified on single predictor analyses (Table 2). On multiple regression analysis, the training model, performed on 10 346 patients, showed that patients with symptomatic nonmassive PE at presentation exhibited a 5.66-fold [95% CI 3.79; 8.44] higher risk of fatal PE than patients with deep-vein thrombosis without symptomatic PE (Table 3). The risk of fatal PE was multiplied by 16.3 [95% CI 8.50 to 31.4] in patients initially presenting symptomatic massive PE. The risk was 2- to 3-fold higher in patients immobilized for a neurological disease, those with cancer, those >75 years of age and those with cardiac or respiratory disease. In contrast, recent surgery was significantly associated with a lower risk of fatal PE. The c statistic for the training model was 0.80, indicating an excellent discriminating value between patients with and without fatal PE.

Because the validation model performed on the remaining sample of 5174 patients did not confirm the predictive value of recent surgery and of cardiac or respiratory disease, these variables were excluded from the simplified model. The c statistics of the simplified and validation models were similar (ie, 0.79 and 0.79, respectively). Finally, Table 4 shows the risk of fatal PE estimated for patients presenting a combination of the prognostic factors.

Discussion
To the best of our knowledge, the present study is the first with sufficient statistical power to examine the predictors of PE. After adjustment for anticoagulant treatment duration, clinical predictors of fatal PE are the presence of PE or massive PE compared with deep-vein thrombosis alone, an immobilization >4 days for neurological disease, cancer, and advanced age.

Prior studies in this setting examined variables capable of predicting more frequent events (ie, either the overall mor-

Table 2. Clinical Predictors for Fatal Pulmonary Embolism Within 3 Months (Single Predictor)*

<table>
<thead>
<tr>
<th></th>
<th>Alive or Death Not Related to Pulmonary Embolism</th>
<th>Fatal PE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index venous thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal/proximal deep-vein thrombosis</td>
<td>58.7</td>
<td>19.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>without symptomatic pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic nonmassive pulmonary</td>
<td>39.8</td>
<td>71.9</td>
<td>5.62</td>
<td>4.11–7.70</td>
</tr>
<tr>
<td>embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic massive pulmonary</td>
<td>1.5</td>
<td>8.9</td>
<td>18.6</td>
<td>11.2–31.1</td>
</tr>
<tr>
<td>embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobilisation &gt;4 days for neurological disease</td>
<td>3.5</td>
<td>10.8</td>
<td>3.30</td>
<td>2.21–4.92</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>36.9</td>
<td>65.0</td>
<td>3.18</td>
<td>2.46–4.11</td>
</tr>
<tr>
<td>Cardiac or respiratory disease</td>
<td>16.8</td>
<td>29.2</td>
<td>2.07</td>
<td>1.58–2.72</td>
</tr>
<tr>
<td>Cancer†</td>
<td>20.2</td>
<td>34.2</td>
<td>2.06</td>
<td>1.59–2.66</td>
</tr>
<tr>
<td>Men</td>
<td>49.9</td>
<td>41.9</td>
<td>0.72</td>
<td>0.57–0.93</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>20.6</td>
<td>14.1</td>
<td>0.63</td>
<td>0.44–0.91</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>16.0</td>
<td>10.8</td>
<td>0.63</td>
<td>0.43–0.94</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>13.0</td>
<td>8.1</td>
<td>0.59</td>
<td>0.37–0.92</td>
</tr>
<tr>
<td>Body-mass index ≥30 kg/m²</td>
<td>27.3</td>
<td>15.8</td>
<td>0.50</td>
<td>0.32–0.79</td>
</tr>
</tbody>
</table>

*Only data with P<0.15 are shown; the analyses were adjusted for treatment duration (< or ≥3 months).
†Distal and proximal deep-vein thromboses were pooled in the same category of events in view of the lack of any significant difference between proximal deep-vein thrombosis and distal deep-vein thrombosis: Odds ratio (95% confidence interval) = 1.9 (0.85–4.19).
‡The predictive value of cancer was the same irrespective of whether or not patients received any chemotherapy.
Arterial hypotension, and underlying cardiovascular disease.3

In the International Cooperative Pulmonary Embolism Registry (ICOPER) study, risk factors for death also included advanced age, cancer, systolic blood pressure at least 110 mm Hg, or immobility for more than 4 days. In our study, factors significantly associated with death in 1 of every 5 patients included advanced age, cancer, immobilisation, recent surgery, or respiratory insufficiency. The type of venous thromboembolism (ie, proximal vs distal) may be due to a lack of power. Interestingly, recent surgery was a negative prognostic factor for fatal PE. Although this result may have been due to chance, because it was not confirmed on the validation dataset, its predictive value as a parameter was previously reported for venous thromboembolic recurrence.25 This result also supports necropsy data showing that fatal PE was more frequent in nonsurgical than in surgical patients.26 The fact that our study did not confirm the predictive value of cardiac or respiratory insufficiency may be due to a lack of power.

In this large observational study, the cumulative rate of fatal PE 3 months after venous thromboembolism was 1.68% (ie, substantially lower than those reported in the 2 most recent comparable registries, 5% in the Worcester DVT registry1 and 7% in the ICOPER registry3). Likewise, overall mortality was similarly lower in the RIETE registry (8.65%) than in the previous registries (12% to 18%). First, this result may reflect differences in study populations. Whereas the ICOPER registry included only patients with acute PE, most of whom having been hospitalized in emergency departments,3 the RIETE registry recruited patients with all types of venous thromboembolism, most of whom having been hospitalized in units specializing in the management of this disease. Second, the result may reflect a progressive improvement in the routine management of patients with venous thromboembolism: The Worcester DVT study was conducted in the 1980s,1 the ICOPER study in the 1990s,3 and the RIETE study in the 2000s. The 1.68% cumulative incidence of fatal PE in clinical practice is very close to that observed in one of the most recent clinical trials on the treatment of venous thromboembolism, in which 3-month rates of fatal PE varied between 0% and 1.5%.2,5–8

We believe that our results are valid and may apply to patients treated in daily practice. All data were collected prospectively and all venous thromboembolic events were objectively confirmed. Unlike in clinical trials, no exclusion criteria were used. The type of venous thromboembolism (ie, proximal vs distal) may be due to a lack of power. Interestingly, recent surgery was a negative prognostic factor for fatal PE. Although this result may have been due to chance, because it was not confirmed on the validation dataset, its predictive value as a parameter was previously reported for venous thromboembolic recurrence.25 This result also supports necropsy data showing that fatal PE was more frequent in nonsurgical than in surgical patients.26 The fact that our study did not confirm the predictive value of cardiac or respiratory insufficiency may be due to a lack of power.
criteria were applied and patients were managed according to the current practices prevalent in the various participating countries. As in all similar studies, patients with sudden death due to PE before hospitalization could not be taken into account. A 90-day follow-up, standard in this type of study, was chosen because, beyond this period, the cumulative mortality rate tends to plateau and the treatment duration was not standardized. The size of the registry population allowed us to specifically analyze clinical predictors for fatal PE rather than overall mortality, a focus that may be more valuable with respect to determining the factors appropriate for inclusion in a risk stratification scheme designed to optimize the therapeutic management of patients with PE. Only clinical variables were analyzed in the present study. The prognostic value of asymptomatic PE and echocardiographic right ventricular dysfunction was not examined, because these variables were not systematically investigated. Likewise, the quality of treatment with vitamin K antagonists was not taken into account. Although biological variables, such as troponin levels, may be of great prognostic value, data on such variables have only been collected in the RIETE registry since 2004 and were therefore not included in the present analysis.

In conclusion, PE remains a substantial cause of death in patients with venous thromboembolism (19.4% in our study). Identifying patients at increased risk of fatal PE is therefore important for optimally adapting treatment to the level of risk. The 4 clinical factors predicting a fatal PE identified in this study (namely type of venous thromboembolism at presentation, advanced age, cancer, and immobilization for neurological disease) can be routinely identified and could therefore easily be included in a risk stratification scheme in daily practice. In addition, the identification of high-risk patients should allow determination of the survival benefit of “aggressive” therapeutic strategies, especially vena cava filter insertion in high-risk populations. This hypothesis need to be confirmed in randomized clinical trials.

Appendix

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Disclosures

None.

References

CLINICAL PERSPECTIVE

Pulmonary embolism (PE) remains a potentially fatal disease in patients with venous thromboembolism. Its incidence varies widely in the literature, from <1% to 7%. Identifying patients at increased risk of fatal PE is therefore important for optimally adapting treatment to the level of risk. This is all the more important because the use of generally recommended treatments in high-risk patients, such as administration of fibrinolytic drugs or placement of vena cava filters, may be complicated by severe adverse events. Using data from the international prospective Registro Informatizado de la Enfermedad Tromboembólica venosa (RIETE) registry about 15,520 patients with objectively confirmed symptomatic acute venous thromboembolism, we determined independent predictive factors for fatal PE. Symptomatic nonmassive PE was observed in 40.4%, and massive PE in 1.6%. At 3 months, the cumulative rate of fatal PE was 1.68%. On multivariable analysis, compared to patients with deep-vein thrombosis at presentation, the risk of fatal PE was multiplied by 5.42 in patients with symptomatic nonmassive PE and by 17.5 in patients presenting a symptomatic massive PE. Other clinical factors independently associated with an increased risk of fatal PE were immobilisation for neurological disease (4.90-fold higher), age >75 years (2.54-fold higher), and cancer (2.04-fold higher). The clinical factors predicting a fatal PE identified in this study can be routinely identified and could therefore easily be included in a risk stratification scheme for daily practice. These results may help to improve the management of patients with PE and therefore increase survival rates.
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