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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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 drugs[11] or placement of vena cava filters[12] 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.

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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.[20,21] 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 from each patient 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/m^2), 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 multivariable stepwise logistic regression analysis. Highly correlated predictors were considered in the multivariable model instead of rather than in addition to the previous one. Only those variables associated with a α value $\leq$0.05 were retained in the final model.

The accuracy of the model was assessed by data splitting. A training model was performed on a cohort obtained by randomly dividing the dataset into two thirds. To develop a model that can be used in clinical practice, the training model was simplified, retaining the variables with the most predictive information. The simplified model was then applied to the remaining sample to obtain the validation model. The c statistic methodology, derived from the receiver operating characteristic curve, was used to assess the quality of the fit of these models for predicting death from PE at 3 months.[23] A stepwise variable selection method was used to produce a parsimonious model. All analyses were adjusted to the duration of anticoagulant treatment categorized as "less than," "equal to," or "longer than" 3 months. Because some predictor variables were measured in only part of the study population, we could not develop a "single best" multivariable model and >1 model-building strategy was needed to display all clinically relevant findings.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 1. Patient Characteristics (N=15 520)

Men, n (%)	7720 (49.7)
Age, mean±SD, y	66.3±16.9
Age >75 years, n (%)	5800 (37.4)
Body-mass index >30 kg/m^2, n (%)*	2739 (27.2)
History of venous thromboembolism, n (%)	2471 (15.9)
Varicose veins, n (%)†	2304 (20.2)
Cancer, n (%)	3172 (20.4)
Cardiac or respiratory disease, n (%)	2611 (16.8)
Recent surgery, n (%)	2006 (12.9)
Immobilisation >4 days for neurological disease, n (%)	567 (3.6)
Type of index venous thromboembolism, n (%)	
Symptomatic distal deep-vein thrombosis	2109 (13.6)
Symptomatic proximal deep-vein thrombosis	6899 (44.4)
Symptomatic non-massive pulmonary embolism	6264 (40.4)
Symptomatic massive pulmonary embolism‡	248 (1.6)

*5444 missing values; †456 missing values.

‡Massive pulmonary embolism was defined as pulmonary embolism with systolic blood pressure <90 mm Hg.

Results

Between March 2001 and July 2006, 15 520 consecutive patients with acute deep-vein thrombosis, PE, or both were included in the study. The age of the study population (mean±SD) was 66.3±16.9 years (Table 1). Men and women were equal in number. Cancer was reported in 20.4% of patients and cardiac or respiratory disease in 16.8%. Symptomatic deep-vein thrombosis without PE was observed in 58.0% of patients, symptomatic nonmassive PE in 40.4%, and symptomatic massive PE in 1.6%. At inclusion, 15 423 patients (99.4%) had received heparin (unfractionated heparin or low–molecular-weight heparin) or vitamin K antagonists. A vena cava filter was inserted in 323 patients (2.1%), and fibrinolytic therapy was used in 206 patients (1.2%).

Incidence of Fatal Pulmonary Embolism

At 3 months, 1342 patients had died, resulting in a cumulative rate of overall mortality of 8.65%. Death was considered to be

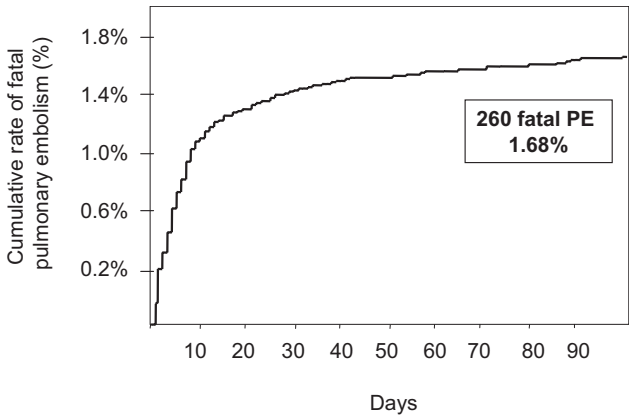

Figure. Cumulative rate of fatal PE.

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)*

	Alive or Death Not Related to Pulmonary Embolism (n=15 260), %	Fatal PE (n=260), %	Odds Ratio	95% Confidence Interval
Index venous thromboembolism				
Distal/proximal deep-vein thrombosis without symptomatic pulmonary embolism†	58.7	19.2	1	...
Symptomatic nonmassive pulmonary embolism	39.8	71.9	5.62	4.11–7.70
Symptomatic massive pulmonary embolism	1.5	8.9	18.6	11.2–31.1
Immobilisation >4 days for neurological disease	3.5	10.8	3.30	2.21–4.92
Age ≥75 years	36.9	65.0	3.18	2.46–4.11
Cardiac or respiratory disease	16.8	29.2	2.07	1.58–2.72
Cancer‡	20.2	34.2	2.06	1.59–2.66
Men	49.9	41.9	0.72	0.57–0.93
Varicose veins	20.6	14.1	0.63	0.44–0.91
History of venous thromboembolism	16.0	10.8	0.63	0.43–0.94
Recent surgery	13.0	8.1	0.59	0.37–0.92
Body-mass index ≥30 kg/m^2	27.3	15.8	0.50	0.32–0.79

*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.

Table 3. Clinical Predictors for Fatal Pulmonary Embolism Within 3 Months (Multivariable Analysis, Training and Validation Models)*

	Training Model (n=10 346)			Validation Model (n=5174)		
	Odds Ratio	95% Confidence Interval	P	Odds Ratio	95% Confidence Interval	P
Index venous thromboembolism						
Distal/proximal deep-vein thrombosis	1	...		1	...	
Symptomatic nonmassive pulmonary embolism	5.66	3.79–8.44	<0.0001	5.42	3.19–9.20	<0.0001
Symptomatic massive pulmonary embolism	16.3	8.50–31.4		17.5	7.45–41.2	
Immobilisation >4 days for neurological disease	2.80	1.61–4.86	0.0001	4.90	2.71–8.84	<0.0001
Age >75 years	2.31	1.67–3.21	<0.0001	2.54	1.58–3.81	<0.0001
Cancer	2.40	1.72–3.26	<0.0001	2.04	1.29–3.21	0.0022
Cardiac or respiratory disease†	1.89	1.35–2.65	0.0001	1.34	0.84–2.16	0.22
Recent surgery†	0.53	0.29–0.96	0.034	0.54	0.23–1.25	0.15

*The analysis was adjusted for treatment duration (< or >3 months).

†Not considered in the simplified model because of its low predictive value in the validation model.

tality[3,20,24] or recurrence of PE[13,15–17]) but not specifically fatal PE. Nevertheless, the main results of all these studies, in terms of the characterization of high-risk patients, are consistent, with apparently the same predictors for fatal PE and overall mortality. This is not surprising, because, in our study, 1 death in 5 resulted from PE. In the International Cooperative Pulmonary Embolism Registry (ICOPER) study, risk factors for death also included advanced age, cancer, systolic arterial hypotension, and underlying cardiovascular disease.[3] In the Heit cohort study, factors for death within 7 days of a venous thromboembolic event also included neurological disease, chronic lung or congestive heart failure, and cancer.[24] Finally, in our study, above all, the kind of thromboembolic event and severity of the venous thromboembolic event at presentation also appear to have had a major impact on the risk of death: symptomatic nonmassive PE and massive PE on presentation were associated respectively with a 6-fold and 16-fold higher risk of subsequent fatal PE than distal/proximal deep-vein thrombosis without symptomatic PE. Similarly, in an overview of 26 studies with a total of 5523 patients, the rate of fatal PE among patients presenting with deep-vein thrombosis was 0.4% (95% CI 0.2 to 0.6), whereas it was 1.5% (95% CI 0.9 to 2.2) among patients presenting with PE.[14] Furthermore, the type of venous thromboembolism at presentation was also found to be a significant predictor of PE recurrence.[13–17]

Table 4. Risk of Fatal Pulmonary Embolism Within 3 Months in Patients With a Treatment Duration of at Least 3 Months

Case Report	Risk of Fatal Pulmonary Embolism (N=15 520), %
Patient <75 years, deep-vein thrombosis	0.23
Patient <75 years, nonmassive symptomatic pulmonary embolism	1.24
Patient >75 years, nonmassive symptomatic pulmonary embolism	3.42
Patient >75 years, nonmassive symptomatic pulmonary embolism, immobilisation >4 days for neurological disease	9.81
Patient >75 years, massive pulmonary embolism, immobilisation >4 days for neurological disease	24.7

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 registry[1] and 7% in the ICOPER registry[3]). Likewise, overall mortality was similarly lower in the RIETE registry (8.65%) than in the previous registries (12% to 18%).[1,3] 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 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 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[4] 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.[27–29] Likewise, the quality of treatment with vitamin K antagonists was not taken into account. Although biological variables, such as troponin levels,[4,30] 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.[9,10] 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.[31] 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.[32,33] This hypothesis need to be confirmed in randomized clinical trials.

Appendix

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Disclosures

None.

References

1. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med*. 1991;151:933–938.
2. The Columbus Investigators. Low–molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med*. 1997;337:657–662.
3. Goldhaber SZ, Visani L, De Rosa M, for ICOPER. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386–1389.
4. Douketis JD. Prognosis in pulmonary embolism. *Curr Opin Pulm Med*. 2001;7:354–359.
5. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, van den Berg-Segers AE, Cariou R, Leeuwenkamp O, Lensing AW; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695–702.
6. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, Segers AE, Cariou R, Leeuwenkamp O, Lensing AW; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140:867–873.
7. Prandoni P, Carnovali M, Marchiori A; Galilei Investigators. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low–molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med*. 2004;164:1077–1083.
8. Wells PS, Anderson DR, Rodger MA, Forgie MA, Florack P, Touchie D, Morrow B, Gray L, O'Rourke K, Wells G, Kovacs J, Kovacs MJ. A randomized trial comparing 2 low–molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. *Arch Intern Med*. 2005;165:733–738.
9. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl):401S–428S.
10. Goldhaber SZ. Pulmonary embolism. *Lancet*. 2004;363:1295–1305.
11. Wan S, Quinlan D, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110:744–749.
12. Hann CL, Streiff MB. The role of vena caval filters in the management of venous thromboembolism. *Blood Rev*. 2005;19:179–202.
13. Monreal M, Lafoz E, Ruiz J, Callejas JM, Arias A. Recurrent pulmonary embolism in patients treated because of acute venous thromboembolism: a prospective study. *Eur J Vasc Surg*. 1994;8:584–589.
14. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA*. 1998;279:458–462.
15. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med*. 2000;160:761–768.
16. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. *Arch Intern Med*. 2000;160:3431–3436.

17. Eichinger S, Weltermann A, Minar E, Stain M, Schönauer V, Schneider B, Kyrle PA. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. *Arch Intern Med*. 2004;164:92–96.
18. Monreal M, Kakkar AK, Caprini JA, Barba R, Uresandi F, Valle R, Suarez C, Otero R; RIETE Investigators. The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients: findings from the RIETE registry. *J Thromb Haemost*. 2004;2: 1892–1898.
19. Nieto JA, De Tuesta AD, Marchena PJ, Tiberio G, Todoli JA, Samperiz AL, Monreal M; Riete Investigators. Clinical outcome of patients with venous thromboembolism and recent major bleeding: findings from a prospective registry (RIETE). *J Thromb Haemost*. 2005;3:703–709.
20. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED). *JAMA*. 1990;263:2753–2759.
21. Perrier A, Roy PM, Sanchez O, Le Gal G, Meyer G, Gourdier AL, Furber A, Revel MP, Howarth N, Davido A, Bounameaux H. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med*. 2005;352:1760–1768.
22. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation*. 2006;113:577–582.
23. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
24. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 1999;159: 445–453.
25. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Study Group. *N Engl J Med*. 1995;332:1661–1665.
26. Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. *J Clin Pathol*. 2004;57: 1254–127.
27. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, Conti A, Agnelli G, Berni G. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation*. 2000;101:2817–2822.
28. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality. *Am Heart J*. 1997;134:479–487.
29. Kasper W, Konstantinides S, Geibel A, Tiede N, Krause T, Just H. Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. *Heart*. 1997;77:346–349.
30. Scridon T, Scridon C, Skali H, Alvarez A, Goldhaber SZ, Solomon SD. Prognostic significance of troponin elevation and right ventricular enlargement in acute pulmonary embolism. *Am J Cardiol*. 2005;96: 303–305.
31. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. A prediction rule to identify low-risk patients with pulmonary embolism. *Arch Intern Med*. 2006;166:169–175.
32. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, Laporte S, Faivre R, Charbonnier B, Barral FG, Huet Y, Simonneau G, for the PREPIC study group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med*. 1998;338:409–415.
33. The PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism. The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation*. 2005;112:416–422.

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 TromboEmbolica 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.