The Natural Course of Hemodynamically Stable Pulmonary Embolism*

Clinical Outcome and Risk Factors in a Large Prospective Cohort Study

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Background: **Pulmonary embolism (PE) is a potentially fatal disease with risks of recurrent venous thrombotic events (venous thromboembolism [VTE]) and major bleeding from anticoagulant therapy. Identifying risk factors for recurrent VTE, bleeding, and mortality may guide clinical decision making.**

Objective: **To evaluate the incidence of recurrent VTE, hemorrhagic complications, and mortality in patients with PE, and to identify risk factors and the time course of these events.**

Design: **We evaluated consecutive patients with PE derived from a prospective management study, who were followed for 3 months, treated with anticoagulants, and underwent objective diagnostic testing for suspected recurrent VTE or bleeding.**

Results: **Of 673 patients with complete follow-up, 20 patients (3.0%; 95% confidence interval [CI], 1.8 to 4.6%) had recurrent VTE. Eleven of 14 patients with recurrent PE had a fatal PE (79%; 95% CI, 49 to 95%), occurring mostly in the first week after diagnosis of initial PE. In 23 patients (3.4%; 95% CI, 2.2 to 5.1%), a hemorrhagic complication occurred, 10 of which were major bleeds (1.5%; 95% CI, 0.7 to 2.7%), and 2 were fatal (0.3%; 95% CI, 0.04 to 1.1%). During the 3-month follow-up, 55 patients died (8.2%; 95% CI, 6.2 to 10.5%). Risk factors for recurrent VTE were immobilization for > 3 days and being an inpatient; having COPD or malignancies were risk factors for bleeding. Higher age, immobilization, malignancy, and being an inpatient were risk factors for mortality.**

Conclusions: **Recurrent VTE occurred in a small percentage of patients treated for an acute PE, and the majority of recurrent PEs were fatal. Immobilization, hospitalization, age, COPD, and malignancies were risk factors for recurrent VTE, bleeding, and mortality. Close monitoring may be indicated in these patients, precluding them from out-of-hospital start of treatment.**

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Key words: bleeding; complications; mortality; pulmonary embolism; recurrent venous thromboembolism

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; OR = odds ratio; PE = pulmonary embolism; VTE = venous thromboembolism

Pulmonary embolism (PE) is a potentially fatal disease with long-term sequelae such as recurrent thrombotic events and major bleeding from anticoagulant therapy. Few studies have investigated the clinical course of PE, and varying incidences of recurrent events, bleeding complications, and mortality have been reported.[1–4] During the first 3 months of anticoagulant treatment, the reported rate of recurrent venous thromboembolism (VTE) in patients with PE has ranged from 2 to 6%.[1–4] The rate of major bleeding during the first 3 months ranged from 2 to 4%.[1–4] An accurate estimate of both incidences of recurrent VTE and major bleeding is important, but moreover it is desirable to

identify risk factors indicating which patients are at increased risk for an adverse clinical outcome of PE. Previous studies[1–4] involved a relatively limited amount of patients with PE, precluding an accurate estimate of clinical outcomes. Further, in one study,[2] only risk factors for recurrent VTE were assessed while patients with PE as well as patients with deep vein thrombosis (DVT) were included, while it is known that patients with DVT may face a more favorable outcome than patients with PE.[2,5]

We evaluated the clinical outcome during 3 months in a large group of consecutive patients with PE. We aimed to assess the incidence of recurrent VTE, mortality, and hemorrhagic complications in patients with PE and treated with oral anticoagulants during this follow-up period. Second, we aimed to identify risk factors for recurrence, bleeding, and mortality, and to determine the time course of these events within 3 months of the start of treatment.

Materials and Methods

Study Design

Consecutive patients with PE confirmed by helical CT were included. They were derived from a large, prospective management study using a diagnostic algorithm that consisted of a clinical decision rule, a d-dimer test, and helical CT.[6] Outpatients as well as inpatients were eligible. Exclusion criteria of this management study were as follows: treatment with therapeutic doses of unfractionated or low-molecular-weight heparin for > 24 h; life expectancy < 3 months; pregnancy; geographic inaccessibility precluding follow-up; age < 18 years; allergy to IV contrast agents; or hemodynamic instability (defined as a systolic BP < 90 mm Hg or symptoms and signs of shock). The institutional review boards of all participating hospitals approved the study protocol, and written or oral informed consent were obtained from all participants, depending on the requirements of the local institutional review board.

Before any diagnostic test was performed, demographic data of all patients were recorded. An inpatient was defined as a patient hospitalized for some other health problem than PE who had symptoms possibly due to PE during hospitalization. Surgery was defined as major surgery within the past month, heart failure was defined as New York Heart Association functional class II-IV for which specific therapy was administered, and malignancy was defined as active malignancy with ongoing treatment or within the past 6 months or in the palliative stages. All patients were initially treated with body weight-adjusted therapeutic doses of low-molecular-weight heparin for at least 5 days or body weight-adjusted unfractionated heparin aiming at an activated partial thromboplastin time between 1.5 times and 2 times the baseline value, followed by vitamin K antagonists, aiming at an international normalized ratio of 2.0 to 3.0 for a period of 6 months.

Follow-up

Follow-up was vigorously pursued and consisted of a fixed hospital visit or telephone interview after 3 months. In addition, all patients received detailed instruction on signs and symptoms of recurrent PE and DVT, and they were instructed to contact the study center immediately in case of complaints suggestive of DVT, PE, or bleeding. At each visit, information was obtained on complaints suggestive for recurrent VTE and bleeding. In case of clinically suspected DVT, PE, or a hemorrhagic complication, appropriate objective tests were required to confirm or refute the diagnosis.

Outcome

The outcome of the study was the incidence of symptomatic recurrent VTE, as well as the incidence of hemorrhagic complications and mortality in patients with confirmed PE during the 3-month study period. Symptomatic recurrent VTE was considered to have occurred if recurrent PE or DVT were documented objectively, or if there was a death in which PE could not be confidently ruled out as a contributing cause. The objective criterion for the diagnosis of recurrent PE was a new intraluminal filling defect on spiral CT or pulmonary angiography; cut-off of contrast material in a vessel > 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75% of a segment, with corresponding normal ventilation (*ie*, a high probability lung scan); a new nondiagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy.[7,8] The objective criterion of a new DVT was a new, noncompressible venous segment or a substantial increase (≥ 4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.[9,10]

Mortality was defined as death due to recurrent PE (fatal PE), fatal bleeding, cancer, or another established diagnosis. Information about the cause of death was obtained from autopsy reports or from a clinical report. Hemorrhagic complications were the composite of major bleeding and clinically relevant bleeding. Major bleeding was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of ≥ 20 g/L (1.24 mmol/L), or leading to transfusion of ≥ 2 U of whole blood or red cells.[11]

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Bleeding was considered clinically relevant when the episode did not qualify as a major bleeding but included one of the following: epistaxis requiring intervention, or formation of a large hematoma visible on the skin or spontaneous macroscopic hematuria. All suspected outcome events were reviewed and classified by an independent adjudication committee. Deaths were classified by the committee as caused by PE if autopsy confirmed PE, in case of an objective test demonstrating PE prior to death, or if PE could not be confidently excluded as the cause of death. Other causes of death were classified based on autopsy findings or clinical reports.

Statistical Analysis

The univariate relation between baseline characteristics and outcome was examined by χ^2 statistics for categorical variables and *t* tests for continuous variables. Fisher exact test was used when the expected values were < 5. A level of significance of 0.05 (two tailed) was used in all tests. Multivariate stepwise logistic regression was used to identify independent predictors of recurrent VTE, bleeding, and mortality. Variables were included only in the final (multivariate) analysis based on their level of significance ($p < 0.10$), except for the variables age and sex, which were independent of significance included in the analysis. The odds ratio (OR) and corresponding 95% confidence interval (CI) were reported for each variable in the model. Analysis was performed using SPSS software (version 11; SPSS; Chicago, IL).

Results

Study Patients

Between November 2002 and September 2004, a total of 3,503 patients with clinically suspected PE were screened, of whom 197 patients (5.6%) were excluded because of predefined exclusion criteria or refused informed consent: > 24 h of low-molecular-weight heparin (n = 50), life expectancy < 3 months (n = 47), pregnancy (n = 26), geographic inaccessibility precluding follow-up (n = 20), and other reasons (n = 41). In addition, 13 patients refused informed consent.[6] In 674 patients (20%), PE was diagnosed. The baseline characteristics of these patients are described in Table 1. Three-month follow-up was completed in 673 of the 674 patients with PE (99.9%).

Table 1—*Baseline Characteristics of the 674 Patients With PE

Characteristics	Data
Age, yr†	58 (19–100)
Age < 55 yr	296 (44)
Age ≥ 55 to < 65 yr	117 (17)
Age ≥ 65 yr	261 (39)
Female gender	51
Duration of complaints, d‡	2 (0–90)
Localization of PE (highest branch)§	
Central	191 (30)
Segmental	332 (52)
Subsegmental	110 (17)
Outpatients	78
Risk factors for VTE	
Paralysis, paresis, or plaster cast lower limbs‖	6
Immobilization/bed rest > 3 d‖	17
Immobilization due to travel by car or air‖	7
Surgery‖	10
Previous DVT	9
Previous PE	10
Heart failure with therapy	6
COPD with therapy	9
Malignancy	19
Clinical findings	
Signs of DVT	15
Tachycardia (> 100 beats/min)	37
Hemoptysis	8

*Data are presented as No. (%) or % unless otherwise indicated.
†Data are presented as mean (range).
‡Data are presented as median (range).
§Missing data in 41 patients.
‖In female patients only.

Recurrent Symptomatic VTE

Of the 673 patients with PE and complete follow-up, 20 patients (3.0%; 95% CI, 1.8 to 4.6%) had an objectively confirmed recurrent VTE event during the 3-month follow-up period. Seventy percent of patients with a recurrent VTE (14 of 20 patients) had a recurrent PE (2.1% overall), and only 30% (6 of 20 patients) had DVT (0.9% overall). Recurrent PE was fatal in 11 of 14 patients (79%; 95% CI, 49 to 95%) with recurrent PE (1.6% overall), resulting in a case-fatality rate (number of fatal recurrences divided by total number of recurrences) of 55% (11 of 20 patients). Recurrent thrombotic events occurred predominantly within the first 3 weeks after the diagnosis (14 of 20 events; Fig 1). Recurrent fatal PE

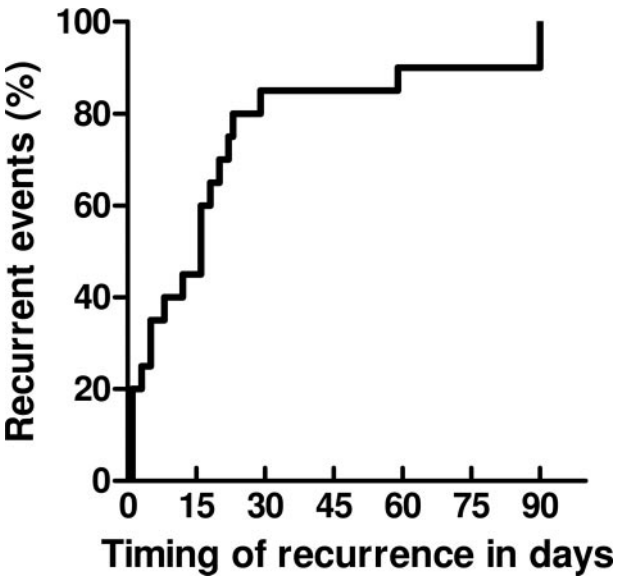

Figure 1. Timing of recurrent thrombotic events.

occurred mainly in the first week (6 of 11 events) and significantly earlier (median, 5 days; range, 1 to 58 days) than recurrent nonfatal PE (median, 29 days; range, 16 to 90 days; p = 0.04). All fatal recurrent PEs occurred during hospitalization, while one of three nonfatal recurrent PEs and two of six recurrent DVTs occurred in the hospital.

Predictors of Recurrent Thrombotic Events

Only one single variable, immobilization for > 3 days prior to the diagnosis of the initial PE, appeared as a significant predictor of a recurrent thrombotic event in univariate analysis (OR, 3.50; 95% CI, 1.40 to 8.77); therefore, multivariate analysis was not performed (Table 2). Patients with recurrences were older (mean age, 63 vs 57 years; OR, 1.02), but this risk factor did not reach significance. A separate analysis for risk factors of fatal recurrent PE was performed but did not show other results than for the whole group of recurrent events (immobilization as a risk factor for recurrent fatal PE: OR, 2.79; 95% CI, 1.43 to 5.45; other risk factors and ORs not shown).

Bleeding Rate in Patients With PE

A hemorrhagic complication of anticoagulant therapy occurred in 23 patients with PE (3.4%; 95% CI, 2.2 to 5.1%). Bleeding was major in 10 patients (1.5%; 95% CI, 0.7 to 2.7%), of which two were fatal (0.3%; 95% CI, 0.04 to 1.1%). Clinically relevant bleeding occurred in the remaining 13 patients (1.9%; 95% CI, 1.0 to 3.3%). The case fatality rate of bleeding was 9% (2 of 23 patients; 95% CI, 1 to 28%). Both fatal bleeding events occurred out of hospital, while 7 of the 8 nonfatal major bleedings occurred in the hospital and 7 of 13 clinically relevant bleedings occurred in the hospital.

Predictors of Bleeding

Table 3 shows the effect of clinical characteristics on the risk of clinically relevant or major bleeding using univariate and multivariate analysis. In multivariate analysis, being an inpatient (OR, 2.63; 95% CI, 1.02 to 6.77), having COPD (OR, 3.89; 95% CI, 1.22 to 12.4), or a malignancy (OR, 3.04; 95% CI, 1.16 to 7.97) remained independent risk factors for bleeding in patients with PE.

Mortality in Patients With PE

Of 673 patients with a diagnosis of PE and complete follow-up, 55 patients (8.2%; 95% CI, 6.2 to 10.5%) died during the 3-month follow-up period. Of these 55 patients, 11 patients died because of fatal recurrent PE (20%; 95% CI, 10 to 33%). None of these fatal recurrences underwent autopsy to confirm the cause of death. Two patients died because of fatal hemorrhage (4%; 95% CI, 0.4 to 13%). The cause of death in the remaining patients with PE was mainly malignancy (17 patients, 35%) or cardiovascular disease (9 patients, 16%). The time of death in patients with PE ranged from 1 to 90 days, with a median of 22 days (Fig 2).

Predictors of Mortality in Patients With PE

In multivariate analysis, four clinical characteristics were shown to be independent risk factors for

Table 2—*Risk Factors for Recurrent VTE in Patients With PE

Variables	Patients With PE and Recurrence	Patients With PE Without Recurrence	Univariate Analysis	
			p Value	OR (95% CI)
Patients, No.	20	653		
Age, yr†	63 (17)	57 (18)	0.15	1.02 (0.99–1.05)
Female gender	10 (50)	331 (51)	0.96	0.98 (0.40–2.38)
Inpatients	6 (30)	144 (22)	0.39	1.52 (0.58–4.04)
Paralysis/paresis	1 (5)	37 (6)	1.00	0.87 (0.11–6.67)
Immobilization > 3 d	8 (40)	105 (16)	0.005	3.50 (1.40–8.77)
Travel by air or car	2 (10)	44 (7)	0.64	1.55 (0.35–6.88)
Surgery	2 (10)	66 (10)	1.00	0.99 (0.23–4.36)
Previous VTE	3 (15)	126 (19)	0.78	0.74 (0.21–2.57)
Previous PE	2 (10)	64 (10)	1.00	1.02 (0.23–4.52)
Heart failure	0	40 (6)	0.63	0.94 (0.92–0.96)
COPD	2 (10)	60 (9)	0.71	1.09 (0.25–4.83)
Malignancy	4 (20)	126 (19)	1.00	1.05 (0.34–3.18)
Signs of DVT	5 (25)	95 (15)	0.20	1.96 (0.70–5.51)
Tachycardia	9 (45)	240 (37)	0.45	1.41 (0.58–3.46)

*Data are presented as No. (%) unless otherwise indicated.
†Data are presented as mean (SD).

Table 3—*Risk Factors for Bleeding in Patients With PE (Clinically Relevant and Major Bleeding)

Variables	With PE and Bleeding	With PE Without Bleeding	Univariate Analysis		Multivariate Analysis	
			p Value	OR (95% CI)	p Value	OR (95% CI)
Patients, No.	23	650				
Age, yr†	56 (17)	58 (18)	0.66	1.00 (0.97–1.02)		
Female gender	10 (44)	331 (51)	0.49	0.74 (0.32–1.72)		
Inpatients	11 (48)	139 (21)	0.003	3.39 (1.46–7.85)	0.05	2.63 (1.02–6.77)
Paralysis/paresis	1 (4)	37 (6)	1.0	0.75 (0.10–5.70)		
Immobilization > 3 d	4 (17)	109 (17)	1.0	1.05 (0.35–3.14)		
Travel by air or car	0	46 (7)	0.39	0.93 (0.91–0.95)		
Surgery	6 (26)	62 (10)	0.02	3.34 (1.27–8.79)	0.23	1.92 (0.66–5.59)
Previous VTE	4 (17)	125 (19)	1.0	0.89 (0.30–2.66)		
Previous PE	3 (13)	63 (10)	0.48	1.41 (0.41–4.86)		
Heart failure	1 (4)	39 (6)	1.0	0.71 (0.09–5.40)		
COPD	5 (22)	57 (9)	0.05	2.88 (1.03–8.05)	0.02	3.89 (1.22–12.4)
Malignancy	9 (39)	121 (19)	0.03	2.81 (1.19–6.64)	0.02	3.04 (1.16–7.97)
Hemoptysis	3 (13)	52 (8)	0.42	1.73 (0.50–6.01)		

*Data are presented as No. (%) unless otherwise indicated.
†Data are presented as mean (SD).

mortality in patients with PE (Table 4): (1) age (OR, 1.04; 95% CI, 1.02 to 1.07); (2) immobilization for > 3 days (OR, 2.07; 95% CI, 1.06 to 4.0); (3) malignancy (OR, 3.02; 95% CI, 1.65 to 5.52); and (4) being an inpatient (OR, 2.11; 95% CI, 1.15 to 3.88).

Discussion

We evaluated the clinical outcome of a large prospective cohort of patients with symptomatic, confirmed PE and aimed to assess an accurate incidence of recurrent VTE, mortality, and hemorrhagic complications during 3 months of anticoagulant treatment (Table 5). Moreover, we aimed to identify risk factors for these events and to determine the time course within 3 months of the start of treatment.

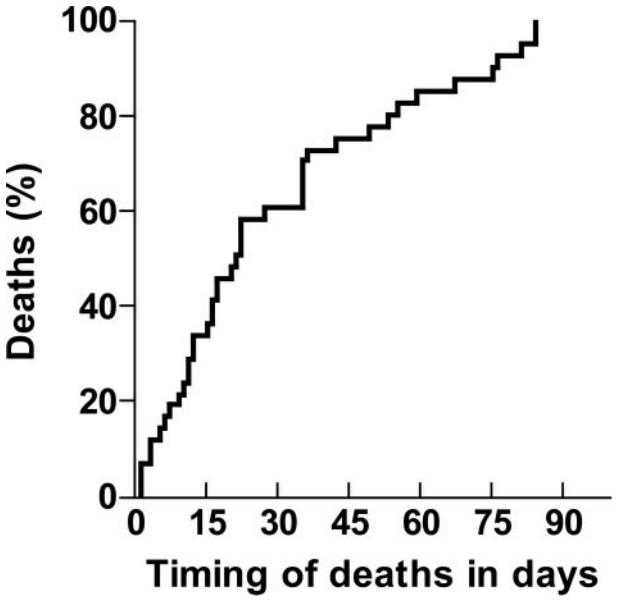

Figure 2. Timing of deaths.

There are two important conclusions to be drawn from our analysis. First, a recurrent thromboembolic event presenting as a recurrent PE occurred in 2.1% of patients with PE and was fatal in the majority (79%) of these patients, occurring mostly in the first week of follow-up. Second, risk factors for a complicated course of PE, *ie*, a recurrent VTE, bleeding, or death, were immobilization for > 3 days prior to diagnosis of PE, being an inpatient, higher age, and the presence of COPD or a malignancy.

The recurrence rate of 3% that we observed is comparable to three other cohort studies[1,3,4] in which incidences varied between 2.1% and 3.9%, but lower than the 6% (95% CI, 4.4 to 7.3%) recurrence rate in patients with PE in a study by Douketis et al.[2] The discrepancy with the last study might be due to a different comorbidity profile in that study, with a higher prevalence of cardiovascular disease (36% vs 6%) and older patients (mean, 62 ± 17 years vs 58 ± 18 years).[2] Our case fatality rate of recurrent VTE is consistent with the findings of another study,[12] in which a case-fatality rate of 45% was observed. Moreover, the observed clustering of recurrences in the first 3 weeks has been described previously,[2,12] but to our knowledge, the clustering of fatal events in the first week after diagnosis has not been described before.

Surprisingly, the only risk factor predicting a recurrent thrombotic event was immobilization for > 3 days. This finding seems to be in disagreement

Table 4—*Risk Factors for Mortality in Patients With PE

Variables	PE Patients Who Died	PE Patients Alive After 3 mo	Univariate Analysis		Multivariate Analysis	
			p Value	OR (95% CI)	p Value	OR (95% CI)
Patients, No.	55	618				
Age, yr†	69 (16)	57 (18)	< 0.001	1.05 (1.03–1.07)	< 0.001	1.04 (1.02–1.07)
Female gender	25 (46)	308 (50)	0.41	0.80 (0.46–1.38)		
Inpatients	25 (46)	125 (20)	< 0.001	3.31 (1.88–5.83)	0.02	2.11 (1.15–3.88)
Paralysis/paresis	2 (4)	36 (6)	0.49	0.60 (0.14–2.57)		
Immobilization > 3 d	17 (31)	95 (15)	0.004	2.41 (1.30–4.44)	0.03	2.07 (1.06–4.05)
Travel by air or car	0	45 (7)	0.03	0.93 (0.91–0.95)	0.69	0.003 (0–5 × 10^9)
Surgery	5 (9)	63 (10)	0.76	0.86 (0.33–2.24)		
Previous VTE	8 (15)	116 (19)	0.40	0.72 (0.33–1.56)		
Previous PE	6 (11)	60 (10)	0.77	1.14 (0.47–2.77)		
Heart failure	6 (11)	32 (5)	0.12	2.23 (0.89–5.59)		
COPD	10 (18)	48 (8)	0.02	2.62 (1.24–5.54)	0.17	1.77 (0.79–3.97)
Malignancy	24 (44)	104 (17)	< 0.001	3.72 (2.09–6.59)	< 0.001	3.02 (1.65–5.52)
Clinical signs of DVT	9 (16)	91 (15)	0.74	1.13 (0.54–2.39)		
Tachycardia	25 (46)	224 (36)	0.17	1.47 (0.84–2.56)		

*Data are presented as No. (%) unless otherwise indicated.
†Data are presented as mean (SD).

with an earlier study[2] in which the presence of cancer, chronic cardiovascular disease, chronic respiratory disease, and other clinically significant diseases were independent risk factors for recurrent VTE in patients with PE. Immobilization due to these chronic illnesses and subsequent venous stasis might explain the increased risk of recurrence but immobility might as well be a marker for more severe comorbid conditions and these patients are subjected to a higher risk for recurrence.[2–4,13]

The mortality rate of 8.2% during 3 months in patients with PE is consistent with the 7.7% found in a study by Perrier et al,[13] but lower than the 15% mortality rate in the study by van Strijen and colleagues.[4] In addition, the incidence of fatal PE was lower in our study population and in that of Perrier and colleagues[13] (1.6% and 2.3%), compared to the 5.6% in the study of van Strijen et al.[4] This latter study, however, had a relatively high percentage of inpatients (46%) compared to our study (22%) and the study of Perrier and colleagues (0%),[4] which may have led to a high-risk population.

Table 5—*Clinical Outcomes During 3 Months in Patients With PE (n = 673)*

Variables	No.	%	95% CI
Overall recurrence	20	3.0	1.8–4.6
Fatal recurrent PE	11	1.6	0.8–2.9
Nonfatal recurrent PE	3	0.5	0.09–1.3
Nonfatal recurrent DVT	6	0.9	0.3–1.9
Hemorrhagic complications	23	3.4	2.2–5.1
Fatal bleeding	2	0.3	0.04–1.1
Major bleeding	10	1.5	0.7–2.7
Clinically relevant bleeding	13	1.9	1.0–3.3
Overall mortality	55	8.2	6.2–10.5

There are some limitations of our study that should be addressed. First, the study population was derived from a diagnostic management study and excluded certain patients, including those who were treated with therapeutic doses of unfractionated or low-molecular-weight heparin for > 24 h, who had a life expectancy < 3 months, who were pregnant, or who were hemodynamically instable. Consequently, our findings may not apply to these patients.[14] However, only 5% of our screened population were excluded for abovementioned reasons; therefore, our findings are likely to be generalizable to most patients with PE who are hemodynamically stable. Second, we acknowledge that identifying risk factors for recurrence, bleeding, and mortality was not a primary goal of our study; hence, data concerning the adequacy of anticoagulation were not recorded. It is possible that some recurrent VTE episodes were related to inadequate initial anticoagulation; however, only four patients with recurrent VTE had been treated initially with IV unfractionated heparin, and it is unlikely to have affected our study results relating to risk factors for recurrent VTE. Third, our definition of fatal recurrent PE as "any death in which PE could not be confidently ruled out as a contributing cause" may have led to an overestimation of our fatality rate of recurrence. Fourth, a clear definition of a recurrent venous thromboembolic event occurring during treatment with anticoagulants is not available, and there is no expert opinion on the time limits for calling a venous thromboembolic event a complication of a first venous thromboembolic event or a recurrent event.

The clinical implications of our study are twofold. First, recurrent VTE occurs despite anticoagulant therapy and is most frequently encountered in the first 3 weeks after diagnosis of PE, while fatal recurrences occur predominantly in the first week after diagnosis. Since patients with nonmassive PE are increasingly treated with LMWH instead of IV unfractionated heparin,[15] early discharge or even home treatment is logistically feasible but the safety is unclear since large comparative studies are lacking. Although it has been recommended to extend current organization for outpatient management of DVT to stable patients with PE,[16] outpatient treatment of PE is not widely accepted because no explicit clinical criteria exist to accurately identify patients with PE at low risk of adverse outcomes. Our study was not designed to answer the question regarding the safety of home treatment. It remains to be studied whether the presence of the risk factors for an adverse outcome in patients with PE should guide decisions on hospital or home treatment and preclude early discharge from hospital in patients with these risk factors.

Second, based on our study results, patients in whom recurrent PE occurs face a substantial risk of mortality. We acknowledge that there is a potential for bias leading to overcall of this observation, since no autopsies were done to substantiate the clinical judgement of the adjudication committee. Whether awareness of this high risk and proper treatment of comorbidities might decrease this risk should be studied separately.

In summary, in patients with PE treated with anticoagulants, recurrent VTE is more likely to occur in patients who have been immobilized for > 3 days, while a major or clinically relevant bleeding is more likely to occur when patients are hospitalized or have COPD or a malignancy. Increasing age, immobilization for > 3 days, malignancy, and being an inpatient increases the risk of mortality in the first 3 months after the diagnosis. In patients with these characteristics, closer monitoring might be indicated, precluding these patients from early discharge from the hospital. Conformation of these variables as a risk factor for recurrence, death, and bleeding needs prospective validation.

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Appendix

Members of the writing group of the Christopher Study, in alphabetical order, are as follows: Arne van Belle, MD, Harry R. Büller, MD, Menno V. Huisman, MD, Peter M. Huisman, MD, Karin Kaasjager, MD, Pieter Willem Kamphuisen, MD, Mark Kramer, MD, Marieke J.H.A. Kruip, MD, Johanna M. Kwakkel-van Erp, MD, Frank W.G. Leebeek, MD, Mathilde Nijkeuter, MD, Martin H. Prins, MD, Maaike Söhne, MD, Lidwine W. Tick MD.

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