Pulmonary embolism: outpatient treatment and risk stratification

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Chapter 8

Patient outcomes after acute pulmonary embolism: a pooled survival analysis of different adverse events

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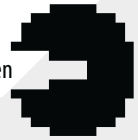


Am J Respir Crit Care Med. 2010 Mar 1; 181(5): 501-6

Abstract

Background

The aim of this study was to assess the long term risk for adverse events after acute pulmonary embolism (PE).

Methods

Consecutive patients diagnosed with PE between January 2001 and July 2007, and patients in whom PE was ruled out from a previous study were followed until July 2008 for the occurrence of adverse clinical events: mortality, symptomatic recurrent venous thromboembolism (VTE), cancer, arterial cardiovascular events and chronic thromboembolic pulmonary hypertension (CTEPH). Hazard ratios (HR) for all endpoints and a combined endpoint were calculated and adjusted for potential confounders.

Results

308 patients with unprovoked, 558 with provoked and 334 without PE were studied with a median follow-up period of 3.3 years. Patients with unprovoked PE had lower overall risk for mortality than patients with provoked PE (HR 0.59, 95% CI 0.43-0.82), but higher risk for non-malignancy related mortality (HR 1.8, 95% CI 1.3-2.5), recurrent VTE (HR 2.1, 95% CI 1.3-3.1), cancer (HR 4.4, 95% CI 2.0-10), cardiovascular events (HR 2.6, 1.5-3.8) and CTEPH (1.5% vs. 0%). The risk for the combined endpoint did not differ between both groups (HR 0.98, 95% CI 0.82-1.1). Patients without PE had similar risks for malignancy and cardiovascular events than patients with provoked PE, but lower risks for the remaining outcomes. The fraction of both patients with provoked and unprovoked PE without events after 1 year was only 70%, and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients.

Conclusion

The clinical course of acute PE is complicated by high rates of serious adverse events, which occur in half of the patients within 4 years.

Introduction

Acute pulmonary embolism (PE) is a common and potentially serious medical condition.[1] The interaction of an extensive pulmonary artery obstruction rate and presence of cardiopulmonary comorbidity may lead to right ventricular dysfunction, which is associated with hemodynamic instability and, in severe cases, with death.[2] This PE attributable mortality occurs in approximately 2-6% of patients with hemodynamically stable PE and in 30% or more of patients with PE presenting with hemodynamic instability or in shock.[2-4] Of note, 25% of the patients do not survive the first year after diagnosis, although the majority of deaths during this time are related to underlying conditions, such as cancer or chronic heart disease, rather than to PE itself.[3,4] Even after surviving the acute episode, the clinical course of acute PE can be complicated by several thrombotic and non-thrombotic adverse events. Bleeding complications and recurrent episodes of venous thromboembolism (VTE) are common and chronic obstruction of the pulmonary vessels with organized blood clots may lead to chronic thromboembolic pulmonary hypertension (CTEPH).[3,5-8] This latter disease is further characterized by pulmonary arteriopathy and progressive right heart failure.[6] Furthermore, it has been well established that patients with acute PE are at higher risk of being subsequently diagnosed with cancer as well as with arterial cardiovascular events than population controls.[9,10] The prognosis of patients diagnosed with unprovoked PE, i.e. PE occurring in the absence of established risk factors or predisposing illnesses, might be less favourable than that of patients suffering from provoked PE. Several studies have shown that patients with unprovoked PE are at particular risk for recurrent PE, CTEPH, arterial cardiovascular events and the detection of cancer.[9,11-18]

Although all individual complications of PE have been studied extensively, the combined risk for all adverse clinical events has not been reported yet. Knowledge of this short and long term prognosis after acute PE is of great importance since this should guide clinical decision making regarding treatment regimes, specific preventive screening programs and follow-up duration. Accordingly, we have performed a prospective cohort study evaluating the overall occurrence of complications in the clinical follow-up of patients diagnosed with acute PE. We contrasted the studied complication rate in patients with unprovoked PE to patients with provoked PE and to a control group of patients in whom PE was suspected but ruled out.

Methods

Patients

The original admission charts of all consecutive in- and outpatients diagnosed with acute PE between January 1st 2001 and July 1st 2007 in an academic (LUMC, Leiden, the Netherlands) and affiliated teaching hospital (Medical Center Haaglanden, The Hague, the Netherlands)

were systematically reviewed using predefined criteria for the diagnosis of acute PE, i.e. intraluminal filling defects on pulmonary angiography or computed tomography pulmonary angiography (CTPA), high probability ventilation perfusion scintigraphy (V/Q-scan) or intermediate probability V/Q-scan in combination with objectively diagnosed deep vein thrombosis (DVT).[14,19] All patients fulfilling these criteria were included in this analysis. Patients were initially treated with at least 5 days of either unfractionated heparin or weight based therapeutic doses of low molecular weight heparin, followed by vitamin K antagonists for a period of at least 6 months with a target international normalized ratio (INR) of 2.0 to 3.0.[20] In patients with severe acute PE presenting with hemodynamic instability, anticoagulant treatment was preceded by administration of thrombolytic drugs, thrombosuction or surgical embolectomy according to the judgment of the attending clinician. The control cohort consisted of patients in whom PE was clinically suspected but ruled out by either an unlikely probability (Wells rule ≤4 points) in combination with a normal high sensitive D-dimer test or a CT scan without signs of PE. These patients were recruited for participation in a previous outcome study between November 2002 and September 2004.[21]

Procedures

Detailed information regarding diagnostic management, cause, treatment and documented clinical course of the index PE were extracted from the medical charts of the included patients with and without PE. When a patient had died, the pathology report was scrutinized to establish the cause of death. In case autopsy was not performed, the likely cause of death was verified with the treating physician or general practitioner. All surviving patients were contacted by mail or phone and were asked to complete our data with the latest information regarding their medical history and clinical condition. Patients living abroad or for whom up-to-date contact specifications were not available were excluded. This study was approved by the Institutional Review Board of both participating hospitals and all patients provided informed consent.

Outcome

Unprovoked PE was defined as PE occurring in the absence of the following risk factors: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peri-partum period and use of oral contraception or hormone replacement therapy.[1] All-cause mortality, symptomatic recurrent VTE, i.e. acute PE as well as deep vein thrombosis, CTEPH, arterial cardiovascular events or detection of a previously unknown malignancy were considered to be adverse events in the clinical course of acute PE. Only information on anticoagulant related fatal bleeding was available. Recurrent PE was defined as 1) a new filling defect revealed by pulmonary angiography or spiral CTPA or 2) a new high probability perfusion defect revealed by VQ-scan or 3) any new defects after earlier normalizing of the scan.[5,7] Criteria for the diagnosis of CTEPH were mean pulmonary

artery pressures assessed by right heart catheterization exceeding 25 mmHg respectively and normal pulmonary capillary wedge pressure in combination with an abnormal perfusion scintigram and signs for CTEPH on pulmonary angiography.[6] Arterial cardiovascular events were defined as clinically adjudicated acute myocardial infarction, stroke or transient ischemic attack, claudication, unstable angina, carotid endarterectomy, coronary artery bypass graft, peripheral arterial bypass or angioplasty.[13,22] Apart from standard clinical work-up for expected acute PE, the included patients were not systematically screened for occult cancer in neither of the two participating hospitals. Thus, the patients in whom cancer was detected had developed symptomatic malignant disease or the cancer was an accidental finding during regular clinical care.

Statistical analysis

All patients were followed from the index event to the date of death or July 1st 2008, whichever came first. The Kaplan-Meier life table method was used to estimate the event free survival for all individual study endpoints and for the combined endpoint of adverse outcome in patients with unprovoked, provoked and without PE. For this latter analysis, the adverse event that occurred first was accounted for. The Log-Rank test was used for comparing the three study groups for statistical differences. A Cox proportional hazard model was used to calculate hazard ratios (HR) for adverse clinical events. HRs were adjusted for age, sex and in addition all further relevant patient demographics; recurrent VTE and CTEPH for initial treatment; malignancy for active smoking; cardiovascular events for active smoking, diabetes and use of anti-platelet, lipid-lowering or blood pressure-lowering medication; mortality for left sided heart failure, COPD and active malignancy; and overall adverse events for all above mentioned potential confounders. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analyses.

Results

Patients

The diagnosis of acute PE had been established in 877 patients between January 1st 2001 and July 1st 2007 in the two participating hospitals. Eleven patients were excluded because of geographical inaccessibility (1.3%), leaving 866 patients for analysis. In addition, 334 patients without PE were included. The final diagnosis in the 334 patients in whom acute PE was suspected but ruled out was infectious disease in 84 (25%), non infectious or malignancy associated pulmonary disease in 43 (13%), complications of an active malignancy in 47 (14%), musculoskeletal disease in 37 patients (11%), cardiovascular disease in 33 (9.9%), gastrointestinal disease in 17 (5.1%) and other/unknown in 73 patients (22%). General characteristics of the study patients are presented in Table 1: the patients without PE were

Table 1: Patient demographics.

	Unprovoked PE (n=308)	Provoked PE (n=558)	No PE (n=334)
Age at index event (years ±SD)	59±17*¶	55±18¶	48±17
Male sex (n, %)	149 (48)¶	261 (47)¶	123 (37)
Initial treatment†			
Low molecular/unfractioned heparin (n, %)	285 (93)	523 (94)	NA
Thrombolysis (n, %)	14 (4.5)	24 (4.3)	NA
Surgery, VCF or both (n, %)	9 (2.9)	11 (2.0)	NA
COPD† (n, %)	26 (8.4)	57 (10)	33 (9.9)
Left sided heart failure† (n, %)	16 (5.2)	26 (4.7)	11 (3.3)
Active malignancy† (n, %)	0 (0)*¶	201 (36)¶	46 (14)
Diabetes† (n, %)	18 (5.8)	27 (4.8)	17 (5.1)
Active smoking† (n, %)	102 (33)	172 (31)	110 (33)
Anti-platelet/lipid-lowering/blood pressure-lowering medication‡ (n, %)	151 (49)	240 (43)	147 (44)

PE=Pulmonary embolism, SD=standard deviation, n=number, VCF=vena cava filter; COPD=chronic obstructive pulmonary disease; NA=not applicable; †at index event; ‡at hospital discharge after index event; *p<0.05 vs. provoked PE; ¶p<0.05 vs. no PE. Continuous parameters were compared using ANOVA with Bonferroni post hoc testing; bivariate variables were compared by the Chi-Square test.

significantly younger than the patients with provoked and unprovoked PE (48 ±17 vs. 55 ±18 and 59 ±17 years respectively). In addition, the fraction of male patients was lowest in the patients without PE (37% vs. 47% and 48% respectively). Further, the presence of comorbidity and cardiovascular risk factors was similar between the three study groups, except for active malignancy, which was most frequently present in patients with provoked PE. Lastly, the patients with unprovoked and provoked PE received comparable anticoagulant treatment. The median follow-up period for the complete study population was 3.3 years.

Risk for recurrent VTE and CTEPH

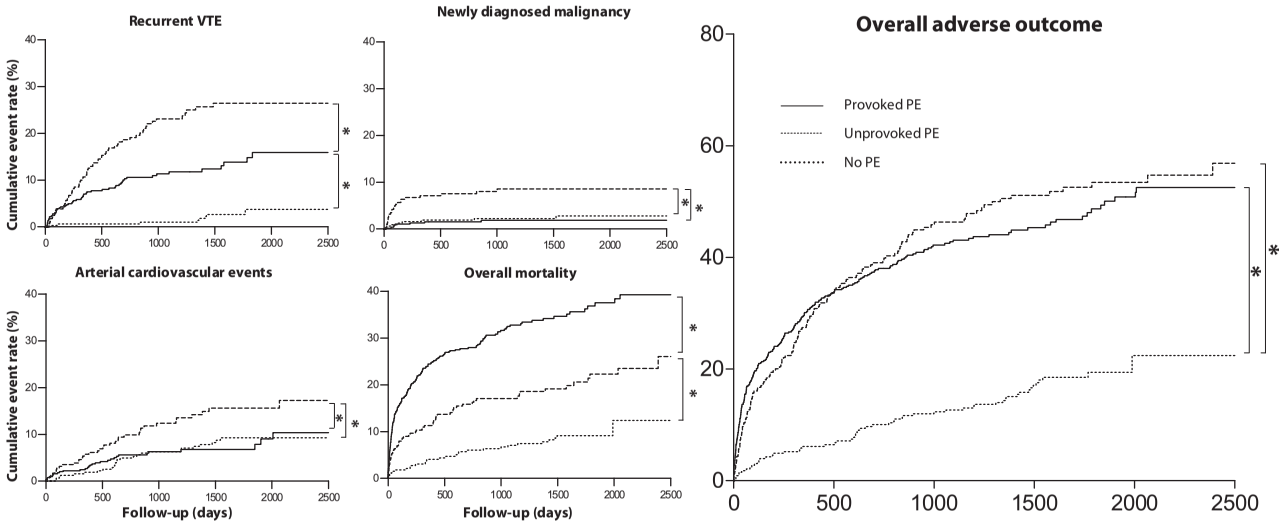
Symptomatic recurrent VTE was diagnosed in 64 (21%) patients with unprovoked PE and in 54 (9.7%) patients with provoked PE (Table 2, Figure 1) during follow-up. The adjusted HR for recurrent VTE was increased for patients with unprovoked versus provoked PE (2.1, 95% CI 1.3- 3.1) and versus patients without PE (10, 95% CI 4.9-28). Patients with provoked PE had higher risk on recurrences than the control patients as well (adjusted HR 6.0, 95% CI 2.8-13). Recurrent PE was fatal in 22 of the 118 patients initially diagnosed with PE (19%, 95% CI 12-27%), and in 1 of the 4 (25%, 95% CI 0.06-81%) VTE diagnoses in the control patients. Recurrences within the first 3 weeks after the index diagnosis were associated with significantly higher mortality (Odds Ratio 7.9, 95% CI 1.2-51). CTEPH was only diagnosed in four patients after unprovoked acute PE (cumulative incidence 1.5%), and not in the patients with provoked PE or without PE (Table 2). The four patients diagnosed with CTEPH were all in stable clinical condition at the end of the follow-up period.

Table 2: Event free survival and hazard ratios for patients with provoked and unprovoked acute PE.

Adverse event	Unprovoked PE		Provoked PE		No PE		HR† (95%CI) unprovoked vs provoked PE	HR† (95%CI) unprovoked vs no PE	HR† (95%CI) provoked vs no PE
	N (%)	Event free survival§ (±SE)	N (%)	Event free survival§ (±SE)	N (%)	Event free survival§ (±SE)			
Recurrent VTE	64 (21)	0.75±0.029	54 (9.7)	0.84±0.024	8 (2.4)	0.96±0.015	2.1 (1.3-3.1)	10 (4.9-28)	6.0 (2.8-13)
CTEPH	4 (1.3)	0.99±0.007	0 (0)	*	0 (0)	*	*	*	*
Malignancy	23 (7.5)	0.91±0.017	8 (1.4)	0.98±0.007	8 (2.4)	0.97±0.010	4.4 (2.0-10)	2.5 (1.1-2.7)	0.78 (0.26-1.4)
Cardiovascular event	41 (13)	0.82±0.029	30 (5.4)	0.90±0.024	26 (7.8)	0.91±0.018	2.6 (1.5-3.8)	2.4 (1.2-3.7)	1.1 (0.72-1.5)
Mortality	67 (22)	0.72±0.038	193 (35)	0.60±0.026	29 (8.7)	0.87±0.037	0.59 (0.43-0.82)	1.4 (1.1-1.8)	3.0 (2.0-4.5)
Adverse outcome‡	155 (50)	0.42±0.038	252 (45)	0.47±0.028	58 (17)	0.76±0.041	0.98 (0.82-1.1)	2.6 (1.9-3.6)	2.9 (2.1-3.8)

PE=pulmonary embolism, VTE=venous thromboembolism, CTEPH=chronic thromboembolic pulmonary hypertension, SE=standard error, n=number, CI=confidence interval. §Estimated by Kaplan-Meier life table method after 2500 days; †Hazard Ratio's were adjusted for age, sex and in addition all further relevant patient demographics; recurrent VTE and CTEPH for initial treatment, malignancy for active smoking, cardiovascular events for active smoking, diabetes and use of anti-platelet/lipid-lowering/blood pressure-lowering medication, mortality for left sided heart failure, COPD and active malignancy, and overall adverse events for all above mentioned; *could not be calculated due to 0-value, ‡ combined endpoint.

Figure 1: Cumulative adverse event rates by Kaplan-Meier life table method for recurrent VTE, diagnosis of malignancy, arterial cardiovascular events, mortality and the occurrence of any adverse event in patients with provoked, unprovoked or no PE.



VTE=venous thromboembolism, PE=pulmonary embolism, *=p<0.05.

Risk for malignancy and arterial cardiovascular events

The risk for cancer was higher for the patients after unprovoked PE than for the patients with provoked (adjusted HR 4.4, 95% CI 2.0-10) and without PE (adjusted HR 2.5, 95% CI 1.1-2.7; Table 2, Figure 1). There was no difference in the rate of newly diagnosed malignancies between patients with provoked and without PE (adjusted HR 0.78, 95% CI 0.26-1.4). In 27 of the 31 patients with PE (87%, 95% CI 70-96%) who were diagnosed with cancer, this malignancy was detected within the first year after the index PE. Patients with unprovoked PE suffered severe cardiovascular disease two to three times more often than the patients from the other two study cohorts (adjusted HR 2.6, 95% CI 1.5-3.8 and 2.4, 1.2-3.7 respectively; Table 2, Figure 1). Patients with PE, who suffered arterial cardiovascular events or were diagnosed with cancer had case fatality rates of 14% (95% CI 7.0-24) and 19% (95% CI 7.5-37) respectively.

Risk for mortality

In total, 259 (30%) patients with PE died, mainly as a result of a malignancy (110 patients, 13%). Furthermore, 67 (7.7%) patients died of (recurrent) PE, 6 (0.69%) because of severe bleeding from anticoagulant therapy, 30 (3.5%) of cardiovascular disease, 11 (1.3%) of non-malignant pulmonary disease and 35 (4.2%) of other causes. Twenty-nine patients without PE died during the study period (8.7%): 1 of acute PE (0.30%), 1 of myocardial infarction (0.30%),

Table 3: Yearly overall event free survival for patients with unprovoked, provoked and without acute PE.

Follow-up period	Unprovoked PE (n=308)		Provoked PE (n=558)		Overall PE (n=866)	No PE (n=334)	
	NLFA	Event free survival§ (±SE)	NLFA	Event free survival§ (±SE)	Event free survival§ (±SE)	NLFA	Event free survival§ (±SE)
1 year	212	0.70±0.026	379	0.68±0.020	0.69±0.016	298	0.94±0.014
2 years	151	0.59±0.028	280	0.61±0.021	0.60±0.017	275	0.90±0.017
3 years	108	0.52±0.030	195	0.56±0.022	0.54±0.018	265	0.87±0.019
4 years	78	0.48±0.031	122	0.54±0.023	0.51±0.018	203	0.84±0.021
5 years	52	0.45±0.032	76	0.50±0.025	0.48±0.019	78	0.80±0.024
6 years	31	0.44±0.034	37	0.48±0.027	0.46±0.021	26	0.77±0.038
7 years	14	0.42±0.038	16	0.47±0.028	0.45±0.024	9	0.76±0.041

PE=pulmonary embolism, SE=standard error, n=number, NLFA=number left for analysis. §Estimated by Kaplan-Meier life table method.

4 of non-ischemic heart diseases (1.2%), 3 of non-malignant pulmonary disease (1.2%), 12 of malignancies (3.6%) and 8 by other causes (2.4%). Risk for overall mortality in patients after unprovoked PE was lower than in patients after provoked PE (adjusted HR 0.59, 95% CI 0.43-0.82; Table 2, Figure 1). Intriguingly, the patients with unprovoked PE who by definition did not suffer from active malignancies at time of the index event, were at higher risk for dying than the non-cancer patients with provoked PE (adjusted HR 1.8, 95% CI 1.3-2.5). Patients with unprovoked as well as with provoked PE had higher risks for death than the control patients (adjusted HR 1.4, 95% CI 1.1-1.8 and 2.9, 95% CI 2.1-3.8 respectively).

Risk for overall adverse outcome

The prognostic differences between patients with unprovoked and provoked PE disappeared after combining all adverse events to one pooled endpoint of adverse outcome (adjusted HR 0.98, 95% CI 0.82-1.1; Table 2, Figure 1). Nonetheless, both groups had significantly worse prognosis than the control patients without PE (adjusted HR 2.6, 95% CI 1.9-3.6 and 2.9, 2.1-3.8 respectively). Importantly, the fraction of PE patients without any event after 1 year was only 69% and decreased to 60% after 2 years and 50% after 4 years (Table 3, Figure 1). These numbers were applicable to both patients with unprovoked as well as with provoked PE. The patients without PE had significant higher event free survival with 84% of the patients surviving without any of the adverse events after a follow-up period of 4 years.

Discussion

We aimed to evaluate the long term overall prognosis of patients after acute PE. Two important conclusions can be drawn from this analysis. First, we have demonstrated that after 1 year of follow-up, only 70% of the patients are free of adverse outcome and notably, after a period of 4 years, half of the patients developed one or more serious clinical complications. A control cohort consisting of patients in whom PE was suspected but ruled out had significantly higher event free survival. Second, although risks for the occurrence of specific adverse events differed significantly between patients with unprovoked and provoked PE, the risk of the combined endpoint of adverse outcome was similar between the two patient groups, both higher than for the control patients without PE.

The importance of our findings is underlined by the complication specific prognosis, which is poor for all adverse events studied in this analysis. First, the index PE itself had a mortality rate of 5.2%, which compares well to the existing literature.[1-4] Second, recurrent VTE was diagnosed in 118 patients. Previous studies have shown that thrombotic recurrences are associated with increased mortality.[5,7] The case fatality rate in our study was 19% in the complete study period and even 60% within the first 3 weeks after the index diagnosis. This 3 weeks mortality rate is comparable to the range of 51-79% that was reported in earlier stud-

ies.[5,7,23] In addition, according to the latest ACCP guidelines, recurrent VTE should be treated with long term anticoagulant therapy (Grade 1A), which is associated with an increased risk of often severe bleeding complications.[20] Third, cancer diagnosed at the same time as or shortly after the diagnosis of VTE is a bad prognostic sign, as this is associated with more advanced stages of cancer and a poor prognosis.[18] Sørensen *et al* have shown that patients in whom cancer was diagnosed within 1 year after the diagnosis of VTE had an increased risk of distant metastasis at the time of diagnosis and a relatively low rate of survival compared to patients with cancer without a history of VTE.[18] In our population, cancer diagnosed after the index PE proved to be fatal in 19% of the cases within the follow-up period. The association between unprovoked PE and the subsequent development of clinically overt cancer is most likely explained by the fact that these cancers are already present at the time of, and may even be causally related to the PE, although not yet detected.[17] Fourth, although the exact mechanism underlying the association between arterial cardiovascular events and VTE is unknown, evidence exists that both diseases are closely linked.[10,13] The observation that control patients without PE and patients with provoked PE have the same risk for arterial cardiovascular events, which is significantly lower than for patients after unprovoked PE, supports the hypothesis that a shared but yet unidentified mechanism causes events in both the venous and the arterial system.[13]

Arterial events such as myocardial infarction or stroke have great implications for the patients' health and lead to high morbidity and mortality rates and decreased quality of life.[15] Lastly, four patients were diagnosed with CTEPH (cumulative incidence in patients with unprovoked PE 1.5%). This percentage is relatively low compared to some recent studies reporting incidences of 3.8% and even 8.8% in patients after PE.[12,16] This discrepancy might very well be explained by different selection criteria than in previous studies, or by underdiagnosis of CTEPH in our cohort, although the included patients with PE were systematically screened for the presence of pulmonary hypertension.[14] Even though none of our four patients with CTEPH died during the study period, it has previously been shown in larger cohorts that the prognosis of patients with CTEPH is rather poor, unless a successful pulmonary endarterectomy is achievable.[6]

Thus, we have combined four very serious complications of PE as well as all-cause mortality in this analysis. The pooled endpoint of adverse outcome was reached by 50% or more of the patients with PE after 4 years of follow-up, which is significantly more than for the control patients. Remarkably, this overall prognosis is comparable for patients with unprovoked and patients with provoked PE. This latter observation was mainly driven by the malignancy related high mortality rates in the patients with provoked PE. Further analysis showed that patients with unprovoked PE have in fact the highest risk on non-malignancy related mortality and all the other included endpoints. These findings emphasize that acute PE is an important clinical problem with poor prognosis for short and long term survival and the occurrence of serious thrombotic or non-thrombotic adverse events.

Many risk stratification and screening strategies including intensified or prolonged antithrombotic therapy regimes to identify and treat patients with high risk for PE-related mortality, recurrent VTE or detection of cancer have been proposed, but all remain insufficient or controversial.[20,24-27] An earlier study concluded that treatment of heparin and anticoagulants is not enough for all PE patients.[28] Our results, although almost 30 years later, confirm this conclusion and once more emphasize the poor overall prognosis of patients with acute PE. In current clinical practice and despite the increased risk for serious clinical complications, patients with a first episode of acute PE stop their anticoagulant therapy usually after 3-6 months.[20] From then on, they are usually no longer subject to clinical supervision by a medical specialist. Importantly, by lack of scientific based evidence and proven cost-efficacy, standard screening for classic cardiovascular risk factors, hidden cancer or CTEPH is at this moment not part of routine clinical work-up of patients with PE. Our results underline the importance of close clinical surveillance in the first months after PE, especially in those patients with unprovoked PE, to evaluate the basic risks for future adverse events and in addition, treat patients accordingly. Therefore, future outcome studies should focus on 1) better individual assessment of the risk for recurrent venous thromboembolism and CTEPH to enable the physician to identify those patients who could benefit from prolonged anticoagulant therapy or specific screening for pulmonary hypertension; 2) effectiveness of cardiovascular risk factor evaluation and proper treatment measures to prevent arterial cardiovascular events; and 3) effect of specific screening programs for underlying malignancies, to achieve very early identification of hidden malignancies thereby potentially improving the patients' prognosis.

Our study has strengths and limitations. Our findings are likely to be generalizable to most patients with PE since we have included all consecutive patients diagnosed with this disease in an academic and non-academic teaching hospital independently of their clinical condition or comorbidity. Even though our study endpoints are severe clinical events that are likely to be recorded in detail, we have additionally verified the accuracy and completeness of the data from the medical charts with the surviving patients. Only 11 patients with PE (1.3%) who could not be reached due to geographical inaccessibility, were excluded. Furthermore, our findings are in accordance with the extensive literature on this subject, although we are the first to combine all adverse events into one pooled endpoint. We acknowledge that we were not able to report on all bleeding events, which are important complications in the clinical course of acute PE. Nonetheless, the adverse effect of bleeding is often transient and the period at risk is limited to the first 6 months after diagnosis in the majority of patients. Moreover, the most severe bleedings that resulted in mortality could in fact be accounted for.

We conclude that acute PE remains a very serious clinical condition with high mortality and high risk on PE associated severe complications. Remarkably, there was no difference in the pooled risk for adverse outcome of patients with unprovoked and provoked PE, although the risk on all separate endpoints except for overall mortality was markedly higher for the patients with unprovoked PE. Physicians should be well aware of the fact that in 4 years time,

half of the patients diagnosed with acute PE has died or is diagnosed with cancer, recurrent VTE, CTEPH or arterial cardiovascular disease. The challenge of future trials remains to enable the treating physician to use accurate prediction tools for adjusting treatment regimes and clinical surveillance to the personalized prognosis of the individual patient.

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Chapter 9

Comparison of risk profile and clinical outcome of patients after acute pulmonary embolism in university and non-university hospitals

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J Thromb Haemost. 2010 Feb; 8(2): 407-9

Abstract

Background

Current knowledge on diagnostic management and treatment of patients with acute pulmonary embolism (PE) is partly derived from outcome studies including patients from university hospitals alone. It is debatable whether these data are applicable to patients in non-university hospitals. The aim of this study was to compare baseline characteristics and clinical outcome of patients with PE treated in university hospitals versus patients treated in non-university hospitals.

Methods

Post-hoc analysis on data derived from Christopher study, a prospective multicenter management study.

Results

A total of 399 (59%) patients with PE presented to a university hospital and 275 (41%) to a non-university teaching hospital. The characteristics of patients from the university and non-university hospitals were different with respect to female ratio (46% vs. 56%, Odds Ratio [OR] 0.65, 95% confidence interval [CI] 0.47-0.88), outpatient ratio (73% vs. 84%, OR 0.53, 95%CI 0.36-0.79), presence of immobilization (37% vs. 23%, OR 2.0, 95%CI 1.4-2.8) and the presence of active malignancy (19% vs. 12%, OR 1.6, 95%CI 1.1-2.5). Risk on venous thromboembolic recurrence (3.3% vs. 2.6% OR 1.3, 95%CI 0.50-3.3) and mortality (9.0% vs 6.9% OR 1.3, 95%CI 0.75-2.4) were higher for patients in university than in non-university hospitals. Bleedings occurred twice more often in patients from university hospitals (4.3% vs 2.2% OR 2.0, 95%CI 0.77-5.1).

Conclusion

Physicians should be aware of differences in patient characteristics and outcome between university and non-university hospitals when interpreting results from large clinical trials and applying these to their everyday medical practice.

Introduction

Current knowledge regarding diagnostic management and treatment of patients with acute pulmonary embolism (PE) is mainly derived from large outcome studies including patients from university and non-university hospitals or university hospitals alone.[1-4] A common perception of university hospitals is that they treat more severely ill patients than non-university hospitals.[5] Therefore, it must be debated whether data on the diagnostic management and treatment of patients with acute PE derived from university hospitals are relevant and applicable to everyday patient care in non-university hospitals, and vice-versa. We hypothesized that patients from university hospitals would be a population with more comorbidity than in non-university hospitals. Accordingly, we investigated differences between baseline risk factors predicting adverse clinical outcome (e.g. higher age, immobilization, cancer and cardiopulmonary comorbidity) in patients with established acute PE in university and non-university hospitals. In addition, the clinical outcome of these patient groups was compared.

Methods

We performed a post-hoc analysis on data obtained from a large multicenter prospective cohort follow-up study.[2] In this study, executed from November 2002 until September 2004, consecutive hemodynamic stable patients with computed tomography proven acute PE were followed for a period of 3 months to document the occurrence of recurrent symptomatic venous thromboembolic events. All patients were treated according to the previously followed guidelines.[6] Furthermore, all patients were treated as inpatients and hemodynamically instable patients were excluded from the study. Therefore, no patient was treated with fibrinolytic drugs or vena cava filter. Secondary endpoints were all-cause mortality and bleeding complications. Follow-up consisted of a hospital visit or telephone interview with the patient after 3 months. Patients were instructed to contact the study center immediately in case of complaints suggestive of PE, deep vein thrombosis (DVT) or bleeding. In case of clinically suspected DVT, PE or bleeding objective tests were performed to confirm the diagnosis. 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 (*i.e.* a high probability lung scan), a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography, or confirmation of a new PE at autopsy. The objective criterion of a new DVT was a new, non-compressible 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. 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. Bleeding was considered clinically relevant when the episode did not qualify as a major bleeding but included one of the following: epistaxis requiring intervention, formation of a large hematoma visible on the skin or spontaneous macroscopic hematuria.[7] All patients were treated with therapeutic doses of unfractionated or low molecular weight heparin followed by vitamin K antagonist for a period of at least 6 months. Patients diagnosed as outpatients as well as inpatients were eligible. The study was executed in 12 hospitals in the Netherlands, of which five were university hospitals. Non-university hospitals differed in size from 330 to 1386 patient beds and university hospitals from 715 to 1100 patient beds. All participating centers had comparable services including emergency units, intensive care units and 24-hour access to a CT scan. A total of 673 patients with acute PE completed 3 months follow-up with one patient lost to follow-up (0.15%).

Results

The baseline characteristics of the included patients are shown in Table 1. A total of 399 (59%) patients attended a university hospital and 275 (41%) a non-university teaching hospital. The characteristics of patients from the university and non-university hospitals were different with respect to female ratio (46% vs. 56%, Odds Ratio [OR] 0.65, 95% confidence interval [CI] 0.47-0.88), outpatient ratio (73% vs. 84%, OR 0.53, 95% CI 0.36-0.79), presence of immobilization (37% vs. 23%, OR 2.0, 95% CI 1.4-2.8) and the presence of active malignancy (19% vs. 12%, OR 1.6, 95% CI 1.1-2.5). The rates of adverse clinical events are presented in Table 2. Overall 55 patients died; of these, 11 patients died because of fatal recurrent PE and two died because of fatal hemorrhage. The cause of death in the remaining patients was mainly malignancy or cardiovascular disease. The time of death ranged from 1 to 90 days, with a median of 22 days. Risk of venous thromboembolic recurrence (3.3% vs. 2.6% OR 1.3, 95% CI 0.50-3.3) and mortality (9.0% vs. 6.9% OR 1.3, 95% CI 0.75-2.4) was higher for patients in university than in non-university hospitals. Furthermore, bleeding occurred in 23 patients, and was fatal in two of these. Both fatal bleeding events occurred out of hospital, while seven of the eight non-fatal major bleedings occurred in the hospital and 7 of 13 clinically relevant

Table 1. Baseline characteristics

Characteristics	University hospital (n=399)	Non-university teaching hospital (n=275)	OR
Age (years)	56± 18	59±18	NS
Female gender	183 (46)	156 (56)	0.65 (0.47-0.88)
Duration of complaints (days)	5.9±11	6.4±10	NS
Outpatients	294 (73)	231 (84)	0.53 (0.36-0.79)
Risk factors for VTE			
Paralysis	23 (5.8)	15 (5.5)	NS
Immobilization	151 (37)	65 (23)	2.0 (1.4-2.8)
Recent surgery	33 (8.3)	34 (12)	NS
History of VTE	69 (17)	48 (17)	NS
Heart failure	26 (6.5)	14 (5.1)	NS
COPD	34 (8.5)	28 (10)	NS
Active malignancy	89 (19)	41 (12)	1.6 (1.1-2.5)
Clinical findings			
Hemoptysis	37 (9.3)	19 (6.9)	NS
Tachycardia	143 (35)	104 (37)	NS

Categorical data are displayed as No (%). Numerical data are displayed as means ± standard deviation. VTE= venous thromboembolism, COPD = chronic obstructive pulmonary disease, OR = Odds Ratio

Table 2. Adverse clinical outcome in a three months follow-up period

	University hospital (n=399)	Non-university teaching hospital (n=274)
Total recurrences	13 (3.3)	7 (2.6)
Fatal recurrent PE	6 (1.5)	5 (1.8)
Non-fatal recurrent PE	2 (0.5)	1 (0.4)
Non-fatal recurrent DVT	5 (1.3)	1 (0.4)
All bleeding complications	17 (4.3)	6 (2.2)
Fatal bleeding	1 (0.3)	1 (0.4)
Major bleeding	7 (1.8)	1 (0.4)
Clinically relevant bleeding	9 (2.3)	4 (1.5)
All cause mortality	36 (9.0)	19 (6.9)

Data are displayed as No (%).
PE = pulmonary embolism, DVT = deep vein thrombosis

bleedings occurred in the hospital. Hemorrhagic complications occurred twice more often in patients from university hospitals (4.3% vs. 2.2% OR 2.0, 95% CI 0.77-5.1). These bleeding complications were strongly associated with the baseline presence of active malignancy (OR 3.4, 95% CI 1.5-7.9).

Discussion

Our data demonstrate that patients with acute PE presenting to university hospitals are different from patients presenting to non-university hospitals regarding gender, proportion of outpatients and malignancy. Especially the latter two are established risk factors for adverse events and mortality in the first 3 months following acute PE.[8] To our best knowledge, there were no different characteristics between the hospitals other than being a university hospital, which could have biased these study observations. According to our hypothesis we identified differences in baseline characteristics and observed a higher rate of adverse clinical events in patients from university hospitals than in patients from non-university hospitals. Of note, we found a significant association between bleeding and malignant comorbidity. This association has been described previously and thus underlines the validity of our study results.[9] Of note, correlations between additional patient demographics were not studied. A limitation of our study is that although we have performed a post hoc analysis of a reasonable large patient cohort, the study might have included too few patients to detect a significant difference between the patient cohorts.

In summary, we have identified important differences in demographics, comorbidity and clinical outcome between patients diagnosed with PE in university and in non-university hospitals. Physicians should be aware of these differences when interpreting results from large clinical trials and applying these to their everyday medical practice.

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