Pulmonary embolism : diagnostic management and prognosis

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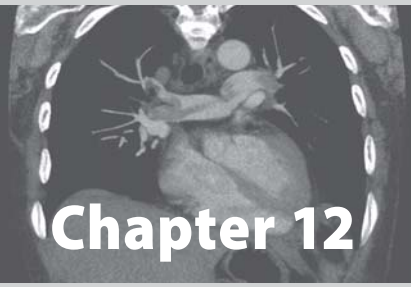

Chapter 12

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

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ABSTRACT

Aim

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).[4-8] This latter disease is further characterized by pulmonary arteriopathy and progressive right heart failure.[8] 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 favorable 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.[10-15]

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 (Leiden University Medical Center, 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 (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep vein thrombosis (DVT).[15,16] All patients fulfilling these criteria were included in this analysis. Patients were initially treated with at least 5 days of either unfractioned 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.[17] 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.[18]

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.[6,7] 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.[8] 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.[13,19] Apart from standard clinical work-up for expected acute PE, the included patients were not systematically screened for occult cancer in neither of the 2 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 3 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/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 analysis.

RESULTS

Patients

The diagnosis of acute PE had been established in 877 patients between January 1st 2001 and July 1st 2007 in the 2 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 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

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)

†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. PE=pulmonary embolism, SD=standard deviation, n=number, VCF=vena cava filter, COPD=chronic obstructive pulmonary disease, NA=not applicable.

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 4 patients after unprovoked acute PE (cumulative incidence 1.5%), and not in the patients with provoked PE or without PE (Table 2). The 4 patients diagnosed with CTEPH were all in stable clinical condition at the end of the follow-up period.

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. 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	0.75 ±0.029	54	0.84 ±0.024	8	0.96 ±0.015	2.1 (1.3-3.1)	10 (4.9-28)	6.0 (2.8-13)
CTEPH	4	0.99 ±0.007	0	*	0	*	*	*	*
Malignancy	23	0.91 ±0.017	8	0.98 ±0.007	8	0.97 ±0.010	4.4 (2.0-10)	2.5 (1.1-2.7)	0.78 (0.26-1.4)
Cardiovascular event	41	0.82 ±0.029	30	0.90 ±0.024	26	0.91 ±0.018	2.6 (1.5-3.8)	2.4 (1.2-3.7)	1.1 (0.72-1.5)
Mortality	67	0.72 ±0.038	193	0.60 ±0.026	29	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	0.42 ±0.038	252	0.47 ±0.028	58	0.76 ±0.041	0.98 (0.82-1.1)	2.6 (1.9-3.6)	2.9 (2.1-3.8)

§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; ‡combined endpoint; *could not be calculated due to 0-value. PE=pulmonary embolism, VTE=venous thromboembolism, CTEPH=chronic thromboembolic pulmonary hypertension, SE=standard error, n=number, CI=confidence interval.

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 2 to 3 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%), 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

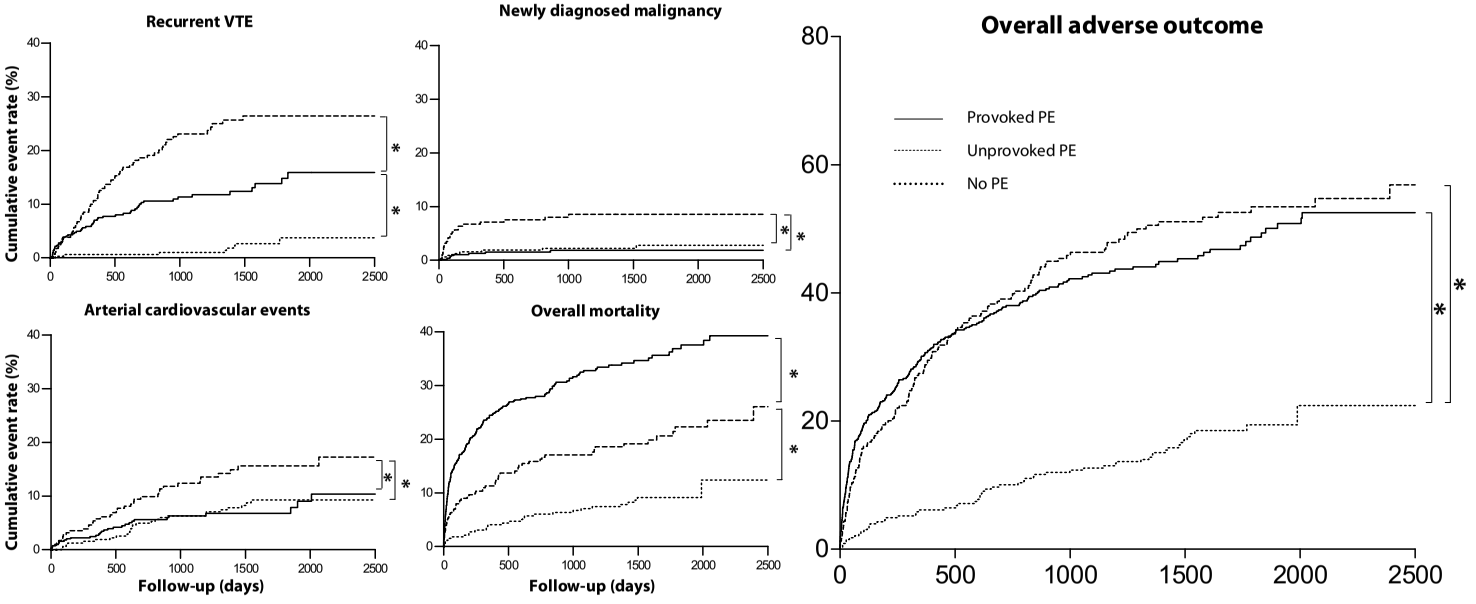

Figure 1. Cumulative adverse event rates by Kaplan-Meier life table method for recurrent venous thromboembolism (VTE), newly diagnosed malignancy, arterial cardiovascular events, mortality and the occurrence of the combined endpoint of adverse outcome in patients with provoked, unprovoked and no pulmonary embolism (PE); *p<0.05 by Log-Rank test.

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.

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

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

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.[6,7] 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 studies.[6,7,20] 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.[17] 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.[21] Sørensen et al have shown that patients in whom cancer was diagnosed within one 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.[21] 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.[11] Fourth, although the exact mechanism underlying the association between arterial cardiovascular events and VTE is unknown, evidence exists that both diseases are closely linked.[9,13] 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.[22] 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.[14,23] 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.[15] 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.[8]

Thus, we have combined 4 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 anti-thrombotic 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.[17,24-27] 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 three to six months.[17] 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 1 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 six 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 four 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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