Patient Outcomes after Acute Pulmonary Embolism
A Pooled Survival Analysis of Different Adverse Events

Frederikus A. Klok, Wendy Zondag, Klaas W. van Kralingen, Arie P. J. van Dijk, Jouke T. Tamsma, Fenna H. Heyning, Hubert W. Vliegen, and Menno V. Huisman

1Section of Vascular Medicine, Department of General Internal Medicine-Endocrinology, 2Department of Pulmonary Medicine, and 3Department of Cardiology, LUMC, Leiden; 4Department of Cardiology, Radboud University Nijmegen Medical Centre, Nijmegen; 5Department of Hematology, Medical Center Haaglanden, The Hague, The Netherlands

Rationale: There is a lack of information on the long-term prognosis of patients with acute pulmonary embolism (PE).

Objectives: To assess the long-term risk for adverse events after 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, cancer, arterial cardiovascular events and chronic thromboembolic pulmonary hypertension. Hazard ratios (HR) for all endpoints and a combined endpoint were calculated and adjusted for potential confounders.

Measurements and Main Results: Three hundred eighty 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 a lower overall risk for mortality than patients with provoked PE (HR, 0.59; 95% confidence interval [CI], 0.43–0.82), but a higher risk for nonmalignancy-related mortality (HR, 1.8; 95% CI, 1.3–2.5). Recurrent venous thromboembolism (HR, 2.1; 95% CI, 1.3–3.1), cancer (HR, 4.4; 95% CI, 2.0–10), cardiovascular events (HR, 2.6; 95% CI, 1.5–3.8) and chronic thromboembolic pulmonary hypertension (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.

Conclusions: 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.

Keywords: pulmonary embolism; cohort study, arterial cardiovascular events; mortality; malignancy

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 to mortality occurs in approximately 2 to 6% of patients with hemodynamically stable PE and in 30% or more of patients with PE presenting with hemodynamic instability or 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 nonthrombotic 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 than population controls of being subsequently diagnosed with cancer as well as with arterial cardiovascular events (9, 10). The prognosis of patients diagnosed with unprovoked PE, that is, 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 yet been reported. Knowledge of this short- and long-term prognosis after acute PE is of great importance insofar as this should guide clinical decision making regarding treatment regimes, specific preventive screening programs, and follow-up

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients who survive the acute thromboembolic episodes face increased risk of several serious clinical complications as recurrent venous thrombosis, pulmonary hypertension, cancer, arterial cardiovascular events and death by comorbid conditions. The combined risk for these adverse events and the difference in prognosis between patients with provoked and unprovoked disease, is not known yet.

What This Study Adds to the Field

Our analysis indicates that the fraction of patients without events after 1 year was only 70%, and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years for the overall population. Control patients without PE had significantly better prognosis. Furthermore, although the risks for the different complications varied between patients with provoked and unprovoked disease, the risk for the combined endpoint did not differ between both groups. This unexpectedly high risk of adverse events underlines the need for individualized, better risk stratification and screening programs for patients after acute pulmonary embolism to improve their prognosis.
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 those with provoked PE and to a control group of patients for whom PE was suspected but was ruled out.

METHODS

Patients

The original admission charts of all consecutive inpatients 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, high probability ventilation perfusion scintigraphy [VQ-scans], or intermediate probability VQ-scan in combination with objectively diagnosed deep vein thrombosis (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 of 2.0 to 3.0 (17).

In patients with severe acute PE presenting with hemodynamic instability, anticoagulant treatment was preceded by the administration of thrombolytic drugs, thrombectomy, or surgical embolectomy, according to the judgment of the attending clinician. The control cohort consisted of patients for whom PE was clinically suspected but was ruled out by either an unlikely probability (Wells rule ≤4 points) combined 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 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 peripartum period and use of oral contraception, or hormone replacement therapy (1). All-cause mortality and 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 computed-tomography pulmonary angiography or (2) a new high probability perfusion defect revealed by VQ-scan or (3) any new defects after earlier normalization of the scan (6, 7). Criteria for the diagnosis of CTEPH were mean pulmonary artery pressures assessed by right heart catheterization exceeding 25 mm Hg, 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 either 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 1, 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 for 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 antiplatelet/lipid-lowering/blood pressure–lowering medication; mortality for left-sided heart failure, chronic obstructive pulmonary disease, and active malignancy; and overall adverse events for all the 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 1, 2001 and July 1, 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 for whom acute PE was suspected but ruled out was infectious disease in 84 (25%), noninfectious 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

<table>
<thead>
<tr>
<th>TABLE 1. PATIENT DEMOGRAPHICS</th>
</tr>
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<tbody>
<tr>
<td>Unprovoked PE</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age at index event, years ± SD</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Initial treatment</td>
</tr>
<tr>
<td>Low molecular/unfractioned heparin</td>
</tr>
<tr>
<td>Thrombolysis</td>
</tr>
<tr>
<td>Surgery, VCF, or both</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Left sided heart failure</td>
</tr>
<tr>
<td>Active malignancy</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Active smoking</td>
</tr>
<tr>
<td>Antiplaque/lipid-lowering/blood pressure-lowering medication</td>
</tr>
</tbody>
</table>

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; NA = not applicable; PE = pulmonary embolism; VCF = vena cava filter.

Values are n (%) unless otherwise noted.

† At index event.

‡ At hospital discharge after index event.

* P < 0.05 vs. provoked PE.

< 0.05 vs. no PE. Continuous parameters were compared using analysis of variance with Bonferroni post hoc testing; bivariate variables were compared using the Chi-Square test.
without PE were significantly younger than the patients with provoked and unprovoked PE (48 ± 17 vs. 55 ± 18 and 59 ± 17 yr of age, 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 (HR, 2.1; 95% CI, 1.3–3.1) and unprovoked versus patients without PE (HR, 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, Figure 1). There was no difference in the rate of newly diagnosed malignancies between patients with provoked PE and those 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 HR, 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 nonmalignant 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 nonischemic heart diseases (1.2%), 3 of nonmalignant pulmonary disease, 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 noncancer 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 HR, 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 HR, 2.9; 95% CI, 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 significantly higher event-free survival with 84% of 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 demonstrated that after

### TABLE 2. EVENT-FREE SURVIVAL AND HAZARD RATIOS FOR PATIENTS WITH PROVOKED AND UNPROVOKED ACUTE PE

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Unprovoked PE</th>
<th>Provoked PE</th>
<th>No PE</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Event-free Survival‡ (± SE)</td>
<td>Event-free Survival‡ (± SE)</td>
<td>Event-free Survival‡ (± SE)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>64 (0.75 ± 0.029)</td>
<td>54 (0.84 ± 0.024)</td>
<td>8 (0.96 ± 0.015)</td>
</tr>
<tr>
<td>CTEPH</td>
<td>4 (0.99 ± 0.007)</td>
<td>0 (0.98 ± 0.007)</td>
<td>0 (0.97 ± 0.010)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>23 (0.91 ± 0.017)</td>
<td>8 (0.90 ± 0.024)</td>
<td>26 (0.91 ± 0.018)</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>41 (0.82 ± 0.029)</td>
<td>30 (0.60 ± 0.026)</td>
<td>29 (0.87 ± 0.037)</td>
</tr>
<tr>
<td>Mortality</td>
<td>67 (0.72 ± 0.038)</td>
<td>193 (0.70 ± 0.026)</td>
<td>58 (0.76 ± 0.041)</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>155 (0.42 ± 0.038)</td>
<td>252 (0.47 ± 0.028)</td>
<td>58 (0.76 ± 0.041)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; HR = hazards ratio; PE = pulmonary embolism, VTE = venous thromboembolism.

* Hazard ratios were adjusted for age, sex, and 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 antiplatelet/lipid-lowering/blood pressure-lowering medication, mortality for left sided heart failure, COPD and active malignancy, and overall adverse events for all above mentioned.

† Estimated by Kaplan-Meier life table method after 2,500 days.

‡ Could not be calculated due to 0-value.

§ Combined endpoint.
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 for 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-week 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 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 and colleagues 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 with 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

<table>
<thead>
<tr>
<th>Follow-up period, years</th>
<th>Unprovoked PE (n = 308)</th>
<th>Provoked PE (n = 558)</th>
<th>Overall PE (n = 866)</th>
<th>No PE (n = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>212</td>
<td>0.70 ± 0.026</td>
<td>379</td>
<td>0.68 ± 0.020</td>
</tr>
<tr>
<td>2</td>
<td>151</td>
<td>0.59 ± 0.028</td>
<td>280</td>
<td>0.61 ± 0.021</td>
</tr>
<tr>
<td>3</td>
<td>108</td>
<td>0.52 ± 0.030</td>
<td>195</td>
<td>0.56 ± 0.022</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>0.48 ± 0.031</td>
<td>122</td>
<td>0.54 ± 0.023</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>0.45 ± 0.032</td>
<td>76</td>
<td>0.50 ± 0.025</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>0.44 ± 0.034</td>
<td>37</td>
<td>0.48 ± 0.027</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>0.42 ± 0.038</td>
<td>16</td>
<td>0.47 ± 0.028</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: PE = pulmonary embolism; NLFA = number left for analysis.
* Estimated by Kaplan-Meier life table method.

Figure 1. Cumulative adverse event rates by Kaplan-Meier life table method for recurrent VTE, newly diagnosed malignancy, arterial cardiovascular events, mortality, and the occurrence of the combined endpoint of adverse outcome in patients with provoked, unprovoked, or no PE. VTE = venous thromboembolism, PE = pulmonary embolism. *P < 0.05 by log-rank test.
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 with some recent studies reporting incidences of 3.8 and even 8.8% in patients after PE (14, 23). This discrepancy might 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 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 of nonmalignancy-related mortality and all the other included endpoints. These findings emphasize that acute PE is an important clinical problem with a poor prognosis for short-term and long-term survival and the occurrence of serious thrombotic or nonthrombotic adverse events. Many risk stratification and screening strategies, including intensified or prolonged antithrombotic therapy regimes, to identify and treat patients with a 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 3 to 6 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 not part of the routine clinical work-up of patients with PE. Our results underscore 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 to 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 preventive treatment measures to inhibit arterial cardiovascular events; and (3) effect of specific screening programs for underlying malignancies to achieve 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 insofar as we have included all consecutive patients diagnosed with this disease in an academic and nonacademic 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 malignancy-related 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 died or were 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.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References


