Clinically Suspected Acute Recurrent Pulmonary Embolism: A Diagnostic Challenge

M. Nijkeuter, H. Kwakkel- van Erp, M. Sohne, L.W. Tick, M.J.H.A. Kruip, E.F. Ullmann,
M.H.H Kramer, H.R. Büller, M.H. Prins, F.W.G. Leebeek, M.V.Huisman

On behalf of the Christopher Study Investigators

Accepted for publication in Thrombosis and Haemostasis

Basilica Sanctuario di S. Domenico,
Bologna, Italia
Chapter 7

Abstract

Background
It is unknown whether strategies validated for diagnosing pulmonary embolism (PE) are valid in patients with a history of PE.

Objective
To investigate whether a diagnostic algorithm consisting of sequential application of a clinical decision rule (CDR), a quantitative D-dimer test and computed tomography (CT) safely ruled out a clinical suspicion of acute recurrent PE.

Methods
Data were obtained from a diagnostic outcome study of patients suspected of PE. Acute recurrent PE was ruled out by an unlikely probability of PE (CDR score ≤ 4 points) combined with a normal D-dimer test (≤500 ng/ml) or by a normal CT in all other patients. The primary outcome was the incidence of acute recurrent venous thromboembolism during three months of follow-up in patients with normal tests and not treated with anticoagulants.

Results
Of 3306 patients suspected of acute PE, 259 patients (7.8%) had a history of PE of whom 234 were not treated with anticoagulants. The probability of PE was unlikely in 82 of 234 patients (35%) and 42 had a normal D-dimer test (18%), excluding recurrent PE. None of these patients had a thrombotic event during follow-up (0%, 95%CI: 0-6.9). A CT was indicated in all other patients (192) and ruled out recurrent PE in 127 patients (54%). Only one patient with a negative CT had a fatal recurrent PE during follow-up (0.8%; 95%CI: 0.02-4.3).

Conclusions
This prospective study demonstrates the safety of ruling out a clinical suspicion of acute recurrent PE by a simple diagnostic algorithm in patients with a history of PE.
Clinical Suspected Acute Recurrent Pulmonary Embolism: A Diagnostic Challenge

Introduction

In recent years many studies have focused on improving the diagnostic management of patients with suspected acute pulmonary embolism (PE) by developing clinical decision rules and implementing computed tomography (CT)\(^1\)-\(^3\). However, the management of patients with suspected recurrence is problematic, since it is unclear whether currently used strategies are valid in patients with a prior history of proven PE. In the literature there are no studies that investigated the diagnostic accuracy of objective tests in patients with a history of PE, despite the fact that it is well established that 10-20% of patients with PE will have a recurrence during the first two years after stopping anticoagulant treatment\(^4\)-\(^5\). In particular, no study has reported on the safety of withholding anticoagulant therapy on the basis of normal diagnostic tests in patients with a clinical suspicion of recurrent PE. The consequences of misdiagnosis of acute recurrent PE are major. Incorrectly concluding that acute recurrent PE is present exposes the patient to prolonged - and often life-long - anticoagulation\(^6\) with its attendant costs, inconvenience, and bleeding risks. Incorrectly concluding that acute recurrent PE is absent puts the patient at high risk of ongoing PE, which may be fatal. Objective diagnosis of acute recurrent PE in clinically suspected patients is relevant because in parallel it has been shown that patients clinically suspected of recurrent Deep Vein Thrombosis (DVT), only 20-30% have objective recurrent DVT demonstrated by diagnostic methods. Moreover, the accurate diagnosis of acute recurrent PE is important because it is generally accepted to treat patients with two or more episodes of objectively diagnosed PE indefinitely with anticoagulants\(^6\). An objective diagnosis is problematic since it may be difficult to distinguish new from old thrombo-emboli. It has been estimated that the percentage of patients with residual pulmonary thrombi is 50% six months after an initial diagnosis of PE\(^7\).

Recently, in a large, prospective cohort study we investigated the safety of a diagnostic algorithm consisting of a clinical decision rule (CDR), quantitative D-dimer test and CT in excluding clinically suspected PE\(^8\). The aim of the present study is to investigate whether this diagnostic algorithm can also be safely used to exclude the diagnosis of recurrent PE in patients presenting with a clinical suspicion of acute recurrent PE.

Methods

Study design

This study was part of a large, prospective management study in 5 academic and 7 general hospitals in the Netherlands performed between November 2002 and December 2004\(^8\). This study evaluated the safety of excluding PE by a diagnostic algorithm consisting of a CDR, a quantitative D-dimer test and CT. All patients were followed for a period of three months to document the occurrence of symptomatic venous thrombo-embolic events (VTE).
Study patients
All consecutive in- and outpatients with a clinical suspicion of recurrent PE, defined as a sudden onset of dyspnea, a deterioration of existing dyspnea or sudden onset of pleuritic chest pain without another apparent cause, were eligible for the study. All patients had a history of confirmed PE, with or without DVT. Previous pulmonary embolism was diagnosed by one of the following; a CT-scan demonstrating PE, a high-probability VQ-scan, an intermediate VQ-scan with CUS demonstrating DVT or pulmonary angiography showing PE. Patients were not systematically screened for the existence of chronic thrombo-embolic pulmonary arterial hypertension.
Exclusion criteria were: age under 18 years, treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 hours prior to inclusion, a life expectancy of less than three months, pregnancy, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance less than 30 ml/min), logistic reasons, geographic inaccessibility precluding follow up or hemodynamic instability. Patients who were treated with anticoagulants at admission and/or during follow-up were excluded from the present analysis because the safety of withholding anticoagulants could not be established in these patients. The Institutional Review Boards (IRB’s) of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants, depending on the requirements of the local IRB’s.

Diagnostic work-up
The dichotomized clinical decision rule according to Wells was used to determine pre-test probability for PE (Table 1). Patients were designated as PE unlikely if the CDR was ≤ 4 points, and PE likely in case of a CDR > 4 points. In patients with a CDR indicating PE unlikely, a D-dimer test was performed. In patients with a normal D-dimer concentration, the diagnosis of recurrent PE was considered excluded. Patients with a CDR indicating PE likely and patients with an abnormal D-dimer test underwent CT. Single-row detector as well as multi-row detector systems were used. In case of a normal CT, recurrent PE was considered excluded. The criterion for the diagnosis of a recurrent PE was the presence of signs of acute PE, i.e. a central filling defect or complete occlusion of a vessel on CT. All patients in whom the diagnosis of recurrent PE was excluded were withheld from anticoagulant treatment and were followed for three months to document the occurrence of symptomatic venous thrombo-embolic events, diagnosed by objective imaging tests.
### Clinical decision rule according to Wells et al.

| Clinical signs and symptoms of deep vein thrombosis (DVT) (minimum of leg swelling and pain with palpation of the deep veins) | 3.0 |
| Alternative diagnosis less likely than PE | 3.0 |
| Heart rate > 100/minute | 1.5 |
| Immobilization (> 3 days) or surgery in the previous 4 weeks | 1.5 |
| Previous PE or DVT | 1.5 |
| Hemoptysis | 1.0 |
| Malignancy (on treatment, treated in the last 6 months or palliative) | 1.0 |

Clinical probability of PE unlikely ≤ 4 points, clinical probability of PE likely > 4 points.

### Outcome

The primary outcome of the study was the incidence of symptomatic, recurrent venous thrombo-embolic events during three months follow-up in patients in whom recurrent PE was excluded and who were not treated with anticoagulants. Symptomatic recurrent VTE was considered to have occurred if recurrent PE or DVT was documented objectively or if there was a death in which PE was a contributing cause or could not be ruled out. A diagnosis of PE or DVT was made, based on a priori defined and generally accepted criteria. The criteria for the objective diagnosis of DVT were a non-compressible venous segment during compression ultrasonography or an intraluminal filling defect on venography. The criteria for the objective diagnosis of recurrent PE were signs of acute PE, i.e. a central filling defect or complete occlusion on CT a filling defect or a cut-off of a vessel of more than 2.5 mm on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan) or PE confirmed by autopsy. An independent adjudication committee, whose members were unaware of the results of the diagnostic algorithm, evaluated all suspected venous thrombo-embolic events and deaths.

### Statistical analysis

The incidences of symptomatic recurrent VTE confirmed by objective testing were calculated for a) the group in which recurrent PE was excluded based on a CDR indicating PE unlikely combined with a normal D-dimer test and b) the group of patients in which recurrent PE was excluded based on a normal CT. Exact 95% confidence intervals (CI) were calculated around the observed incidences using JavaStat software (http://statpages.org/confint.html). Descriptive parameters were calculated using the SPSS software, version 11 (SPSS, Inc., Chicago, Illinois). The univariate relation between baseline characteristics and outcome was examined by chi-square statistics for categorical variables and t-tests for continuous variables. Fisher’s Exact test was used when the expected values were less than five. A level of significance of 0.05 (two-tailed) was used in all tests. Excluding recurrent PE was considered safe in case of a three-month thrombo-embolic failure rate not exceeding that of the upper confidence level of normal pulmonary angiography (upper 95%CI: 2.7) in patients in whom the diagnosis was excluded and who were not treated with anticoagulants.
Chapter 7

Results

Patients
A total of 3503 patients were eligible of which 197 were excluded because of predefined exclusion criteria or no informed consent (Figure 1). Of 3306 patients with a clinical suspicion of PE who were included in the diagnostic management study, 259 patients (7.8%, 95%CI: 6.9-8.8) had a history of PE. Of these, 25 patients were treated with anticoagulants (9.7%) and they were excluded from the present analysis. The baseline characteristics of the 234 remaining patients with previous PE are demonstrated in Table 2. Mean age was 55 years, 61% was female and the median time since the prior PE was 4 years. The 25th percentile of time since previous PE was 1.7 years, the 75th percentile was 7.2 years and the 90th percentile 15.1 years.

Table 2
Baseline demographic and clinical characteristics of 234 patients with a history of PE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>55 (18)</td>
</tr>
<tr>
<td>Female sex</td>
<td>142 (61)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>214 (91)</td>
</tr>
<tr>
<td>Duration of complaints in days, median (IQR)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>Time since previous PE in years, median (IQR)*</td>
<td>4 (2-7)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Immobilization or recent surgery</td>
<td>20 (9)</td>
</tr>
<tr>
<td>COPD with treatment</td>
<td>39 (17)</td>
</tr>
<tr>
<td>Heart failure with treatment</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Oestrogen useª</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Clinical symptoms of DVT</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Heart rate (beats per minute &gt;100)</td>
<td>40 (17)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>12 (5)</td>
</tr>
<tr>
<td>PE at baseline</td>
<td>63 (27)</td>
</tr>
</tbody>
</table>

*SD= standard deviation, ^IQR= interquartile range, ^missing data in 31 patients, * of females only

Results of the diagnostic algorithm
In 63 of 234 patients, recurrent PE was diagnosed (prevalence 26.9%, 95%CI: 21.4-33.1). Compared to patients in whom recurrent PE was excluded, patients with recurrent PE were older (62 versus 52 years, p<0.001), were more often male (56% versus 33%, p=0.002) and had more risk factors for PE, i.e. paralysis (11% versus 1%, p=0.002), immobilization or surgery in last four preceding weeks (17% versus 5%, p=0.003) and malignancy (14% versus 7%, p=0.08).
Clinically Suspected Acute Recurrent Pulmonary Embolism: A Diagnostic Challenge

Chapter 7

Clinically suspected pulmonary embolism (n=3503)

Study patients (n=3306)

Excluded (n=184)
- No consent (n=13)

No previous PE (n=3050)

Previous PE (n=259 (7.8%))

Anticoagulant treatment (n=25)

No anticoagulant treatment, n=234

PE unlikely (n=82)
- D-dimer normal (n=42)
  - Recurrent PE excluded (n=42)
    - 3-month F.U.: 0 VTE
    - Failure rate: 0%
    - 95%CI: 0-6.9%

PE likely (n=152)
- D-dimer abnormal (n=40)
- CT indicated (n=192)
  - CT: no recurrent PE (n=127)
    - 3-month F.U.: 1 fatal PE
    - Failure rate: 0.8%
    - 95%CI: 0.02-4.3
  - CT: recurrent PE (n=63)
    - Anticoagulant treatment
    - 3-month F.U.: 1 DVT
  - CT not performed (n=2)

Failure rate 0%
95%CI: 0-6.9%
Failure rate 0.8%
95%CI: 0.02-4.3

3-month F.U.: 0 VTE
Failure rate 0%
95%CI: 0-6.9%
3-month F.U.: 1 fatal PE
Failure rate 0.8%
95%CI: 0.02-4.3
Anticoagulant treatment
3-month F.U.: 1 DVT
Chapter 7

Excluding recurrent PE by a CDR indicating “recurrent PE unlikely” and a normal D-dimer test
Of 234 patients with clinically suspected recurrent PE, 82 patients (35%) had a CDR indicating PE unlikely and were subsequently tested for D-dimer concentration. D-dimer tests were normal in 42 of 82 patients (51%) with unlikely PE, representing 18% of the total study population. Recurrent PE was excluded in these patients and during the three-months follow-up, completed in all patients, none of the 42 patients returned with a symptomatic recurrent venous thrombo-embolic event (0%, 95%CI: 0-6.9) (Table 3).

Excluding recurrent PE by helical CT
Of the 234 patients with a clinical suspicion of recurrent PE, 152 patients (65%) had a CDR indicating PE likely and 40 patients had a CDR indicating PE unlikely but had an abnormal D-dimer test. Of these 192 patients, 190 underwent CT. In 63 of 190 patients, recurrent PE was diagnosed (prevalence 26.9%, 95%CI: 21.4-33.1). CT was normal in 89 patients and suggested an alternative diagnosis (pneumonia, pleural effusion, malignancy etc.) in 38 patients (127 of 234 patients; 54% overall). During the three-month follow-up period, one of the patients in whom PE was excluded by CT died suddenly and was adjudicated as a possible fatal recurrent pulmonary embolism. Therefore, the 3-month thrombo-embolic failure rate in patients in whom CT had excluded PE was 0.8% (1/127; 95%CI: 0.02-4.3) (Table 3).
In two patients the protocol was violated and a CT was not performed. During follow-up, an arm vein thrombosis was diagnosed in one patient and this patient was treated with anticoagulants. The other patient was not treated with anticoagulants and follow-up was uneventful. If these two patients had been included, the failure rate in patients who were assigned to undergo a CT would have been 1.6% (2/129; 95%CI: 0.2-5.5).
The 3-month thrombo-embolic failure rate of the whole strategy of sequential application of CDR, D-dimer test and CT was 1.2% (2/171; 95%CI: 0.1-4.2)(Table 3).

Table 3
Safety of the diagnostic algorithm in patients with previous PE

<table>
<thead>
<tr>
<th>n (%)</th>
<th>3-m VTE failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>CDR unlikely and normal D-dimer</td>
<td>42</td>
</tr>
<tr>
<td>PE excluded by CT</td>
<td>127</td>
</tr>
<tr>
<td>PE excluded by CT + protocol violations</td>
<td>129</td>
</tr>
<tr>
<td>Whole strategy</td>
<td>171</td>
</tr>
</tbody>
</table>

Additional observations
The prevalence of PE in patients with a CDR indicating unlikely PE was 14.6% (12/82; 95%CI: 7.8-24.2) versus 33.6% (51/152; 95%CI: 26.1-41.7) in patients with a CDR
indicating likely PE. Of 168 multi-row detector CT scans, 54 patients were diagnosed with PE (32%; 95%CI: 25–40%). Of 21 patients with single-row detector systems, 9 patients were diagnosed with PE (43%; 95%CI: 22–66). The diagnostic algorithm could be followed according to the protocol in 232 of 234 patients (99.1%).

Discussion

A simple diagnostic algorithm consisting of sequential application of a CDR, a quantitative D-dimer test and a CT appears to be safe in excluding PE in patients with clinically suspected recurrent PE. A clinical decision rule indicating PE unlikely combined with a normal D-dimer test excluded recurrent PE without the need for additional CT in approximately one-fifth of our total study population suspected of recurrent PE. CT ruled out recurrent PE in all other patients. However, the relatively wide confidence intervals of the 3-month thrombo-embolic risk of the whole strategy (95%CI: 1.2 (0.1–4.2) do not permit to conclude that our approach is as safe as pulmonary angiography.

To our knowledge, this is the first prospective study assessing the value of a standardized diagnostic strategy in patients with clinically suspected acute recurrent pulmonary embolism. In two recent studies evaluating CT in patients with clinically suspected PE a history of venous thrombo-embolism was present in 14% and 19% of the study population respectively, but a separate analysis was not given either with respect to the clinical outcome after a normal CT or accuracy of CT in patients with a prior PE.

We chose to limit the study to patients with a history of PE and did not allow patients with DVT. Patients presenting with DVT have reported scintigraphic evidence of silent PE in 40–50% of cases. Including patients with prior DVT in our analysis would have led to a falsely increased feasibility of our algorithm since approximately half of those patients would have been patients with a first suspicion of PE.

Our study warrants additional comment on possible limitations. First, the absence or presence of PE was not verified by pulmonary angiography, the gold standard. However, the clinical outcome after a 3-month follow-up period is widely accepted as an appropriate alternative to establish the safety of excluding PE by a diagnostic strategy, given a near complete follow-up. Although by design, it was not the objective of our study, we cannot exclude the possibility of false-positive CT-scans and overdiagnosis of PE, especially because old thrombi may have mistakenly been judged to be new thrombi and consequently treated as a recurrent PE. Although we used criteria of acute PE to diagnose recurrent PE, the natural evolution of pulmonary clots is currently unknown and it cannot be excluded that signs of acute PE persist longer than is generally presumed. However, the observed 27% prevalence of recurrent PE is fully in line with similar observations in patients with clinically suspected recurrent DVT and does not suggest overdiagnosis in our patients.

Second, although in our study only patients presenting with an acute sudden onset of dyspnea, a deterioration of existing dyspnea or sudden acute onset of pleuritic chest pain
without another apparent cause were included, we could not fully exclude the existence of chronic thrombo-embolic pulmonary hypertension as an explanation for the patient’s symptoms because we did not systematically screen all patients on CTEPH.

Third, the clinical decision rule consisted of the item “history of VTE” and as a consequence, all patients scored 1.5 points with this item. The discriminative power of the clinical decision rule was expected to be different in patients with prior VTE, and indeed, 35% of our population had a CDR indicating PE unlikely while in our overall cohort in the original study population 67% had a CDR indicating “PE unlikely”. In addition, the combination of a CDR indicating PE unlikely and a normal D-dimer test was present in nearly one-fifth of patients compared to one-third in the original study population. Nevertheless, the prevalence of PE in patients with PE unlikely versus PE likely remained different, i.e. 14.6% versus 33.6%, indicating that the CDR we used is still clinically useful in distinguishing patients with a low and high risk for recurrent PE. Fourth, although our study contains the largest sample of patients with a clinical suspicion of recurrent PE reported, the 95% confidence limits of the three-month thrombo-embolic failure rate were rather wide and, exceeded that of the upper confidence limit of normal pulmonary angiography (2.7%)\(^1\). Finally it may be criticized that an observation period of three months may be too short to conclude that recurrent PE can be safely excluded. However, three months is a widely used period in diagnostic studies on the safety of excluding PE and any thrombo-embolic event occurring more than three months after a clinical suspicion is raised, is unlikely to be related to the first symptoms.

In conclusion, in patients with a prior history of PE who present with a clinical suspicion of a recurrent PE, either a CDR indicating recurrent PE unlikely combined with a normal quantitative D-dimer test or either a CT in all other patients appears safe in excluding recurrent PE. Larger studies are needed to confirm the safety of excluding recurrent PE by this simple algorithm.
Reference List

Chapter 7


