Diagnostic strategy for excluding pulmonary embolism in primary care
Lucassen, W.A.M.

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CHAPTER 1

GENERAL INTRODUCTION
AND OUTLINE OF THE THESIS
'Pulmonary embolism (PE) is more common than is usually supposed and is often overlooked because not considered in differential diagnosis’ was written in The Lancet in 1910.1 Nowadays, more than 100 years after the publication in this journal, the statement is still true and PE remains a frequently missed or delayed diagnosis in particular because the diagnosis is not even considered.2 In 2009 the omission of the diagnosis resulted in a warning at the Dutch medical disciplinary council. An obese woman was progressively short of breath and complained of chest pain two weeks after a varicose vein operation. The general practitioner considered ‘cardial’, ‘pleural effusion’ or ‘panic’ as possible explanations, as he wrote down in his report. His most probable diagnosis ‘hyperventilation’ appeared wrong. The woman died of pulmonary embolism 5 days after the first consultation.3 In 2010 a missed diagnosis resulted again in a warning at the tribunal. A 43 year old, healthy prisoner complained of chest pain, decreased exercise tolerance and tachycardia. He had never experienced those complaints before. Repeatedly and with different physicians he was diagnosed with hyperventilation. Three weeks after his first complaint he died of massive pulmonary embolism. His persistent symptoms were based on (small) multiple pulmonary emboli.4 In an analysis of disciplinary law verdicts concerning family physicians, Gaal and colleagues concluded that most incidents with serious health consequences were related to missing potentially severe diagnoses and they stressed the importance of an increase in quality of diagnosing potentially serious diseases in primary care.5

**Pulmonary embolism in primary care**

In patients consulting their primary care physician (PCP) with symptoms suggestive of pulmonary embolism, such as sudden unexplained (or deterioration of existing) dyspnoea, pain on inspiration or unexplained cough symptoms, the PCP can not do anything but refer to secondary care for further evaluation. In secondary care only 10-20% of these referred patients are diagnosed with pulmonary embolism. A large proportion of the remaining patients have alternative diagnoses that the PCP herself/himself could have treated. Referral of all patients with suspected PE to secondary care is not only a burden for patients and unsatisfactory for PCPs but is also
not a very cost-effective strategy. To increase the effectiveness and management of patients suspected of PE PCPs require accurate diagnostic tools that enables them to discriminate between patients who need a referral for further diagnostic work-up and patients in whom PE can be safely excluded and do not need to be referred.

**Incidence of pulmonary embolism in primary care**

The incidence of pulmonary embolism correlates strongly with age. It is extremely uncommon in childhood (0.0 per 1000 inhabitants yearly) but increases to 1.0 per 1000 in elderly people (above 75 years) with hardly any difference between women and men. In an average Dutch general practice (2350 patients) about 0.5 patients will be diagnosed with PE yearly. Because the suspicion of PE will arise about 8 times more often a Dutch general practitioner will see approximately 4 patients with suspected PE annually.

PE is a potentially lethal disease if left untreated. Mortality rates up to 30% of untreated PE are based on historical studies, which were small and methodologically flawed. Analysis of untreated or missed PE in ambulatory patients reveals a more realistic mortality rate of approximately 5%.

**Pulmonary embolism in secondary care**

**Clinical presentation**

The clinical presentation of pulmonary embolism can vary greatly depending on the extent of obstruction of the vascular bed. In case of massive PE, patients might present with a circulatory collapse (hypotensive shock) but to the other extreme, a person with small peripheral emboli may have few or even not any symptoms at all. The classical presentation of PE is of one with acute shortness of breath, pleuritic chestpain and haemoptysis, but this patient is hardly ever seen. Knowledge of the clinical characteristics of patients with acute PE derives from secondary care studies.

**History**

Dyspnoea is the most common symptom; it occurs in 3 out of four patients with PE. Dyspnoea is usually present at rest but one in six patients complains of dyspnoea with exertion only. Orthopnoea, often associated with heart failure, exists in one third of PE-
patients. Pleuritic pain is present in less than half of all patients. Two-fifths of patients complain of lower limb pain. Haemoptysis occurs in only a minority of patients (<10%).

**Physical examination**

Tachypnoea (>20/min.) exists in more than half of the patients and tachycardia (>100/min) in more than a quarter of patients. Fever above 38.5 is rarely seen. Examination of the lungs identifies abnormalities in about one third of both suspected patients finally diagno-sed with PE and in suspected patients finally not diagnosed with PE.\(^\text{9;10}\)

Chest pain that is reproduced by palpation is thought to be caused by pathology of the musculoskeletal chest wall and may prompt physicians to discard PE as the cause. However Le Gal and colleagues showed that in suspected PE-patients chest pain with palpation is not associated with a lower prevalence of PE.\(^\text{11}\)

One third of all PE-patients show calf swelling plus pain with palpation of the deep veins. Oxygen saturation measurement is not of great value. A normal oxygen saturation does not exclude pulmonary embolism but a low saturation puts the physician on the track of lung pathology.

**In conclusion**

The broad range (of severity) of clinical findings in patients with pulmonary embolism makes it a difficult and an easy to miss diagnosis.\(^\text{9}\)

Both history and physical examination are neither specific nor sensitive for PE. There is no individual clinical sign or even a combination of these that can be used to confirm or safely exclude the diagnosis.

**Diagnosing pulmonary embolism**

In the second half of the last century ventilation-perfusion lung scanning was usually performed as a first step in patients suspected of having pulmonary embolism. A normal scan was considered to rule out the diagnosis of PE and a high-probability scan confirmed the diagnosis. However more than 50% of the patients had a so called non-high probability scan. In these patients a pulmonary angiography, at that time being the gold standard diagnostic test, was required but this technique is invasive, expensive and labor intensive.\(^\text{12}\)

Moreover, as PE was only present in 20% of suspected
patients, unnecessary imaging occurred in a large number of patients without PE.\textsuperscript{13} Therefore, Wells and colleagues incorporated the clinical probability of PE into the diagnostic work up. They showed that only 0.5\% of patients with a low or moderate clinical probability and a non-high-probability scan, who received no anticoagulant treatment, had PE in a three month follow-up period. Incorporating the clinical probability increased significantly the specificity of ventilation-perfusion lung scanning.\textsuperscript{14}

As the diagnostic strategy using clinical assessment of PE-probability and ventilation-perfusion scanning was rather complicated Wells and colleagues simplified the strategy and showed that combining probability assessment using their clinical decision rule and D-dimer testing could safely exclude PE in secondary care patients without the need for additional ventilation-perfusion scanning or other imaging tests. In 46\% of patients with a negative strategy PE occurred in only 1.7\% of patients during a three month follow-up period.\textsuperscript{15} A large Dutch secondary care management study showed that in 32\% of suspected patients with a negative strategy, not treated with anticoagulants, PE occurred in only 0.5\% of patients during a three month follow-up period.\textsuperscript{16} Several prospective studies confirmed the safety of withholding additional diagnostic testing and treatment in patients (either inpatients or outpatients) with suspected PE if they had the combination of a low clinical probability (as assessed with different clinical decision rules or with the unstructured clinical estimate) and a negative D-dimer test. All these studies were performed in secondary care.\textsuperscript{17-19} Hence, the first step in the diagnostic work-up of patients with suspected PE is assessment of the clinical probability. If the probability is high (or likely) additional investigation is required. If the probability is low/intermediate (or unlikely), D-dimer testing is the next step. If the D-dimer test is positive additional investigation is required. If the D-dimer test is negative PE is considered safely excluded (Figure 1.1). In the last decade of the previous century computed tomography pulmonary angiography (CTPA) was introduced and is currently the first line imaging test in patients with a high (or likely) clinical probability or a positive D-dimer test.
Assessment of PE-probability using clinical gestalt or using a clinical decision rule

Physicians are able to stratify patients in different groups of clinical probability using empirical clinical assessment (‘clinical gestalt’).\textsuperscript{20} However such empirical assessment depends on the physician’s subjective judgement and experience, thereby showing considerable interobserver variability. To objectify and standardize this clinical probability assessment various decision rules have been developed. Wells and colleagues developed a decision rule using logistic regression (Table 1.1a).\textsuperscript{15} The rule only contains clinical variables which makes the rule also suitable for primary care. One of 7 items is the physician’s judgment of whether PE is more likely than an alternative diagnosis. This criterion however is subjective and therefore submitted to inter-doctor variation. Therefore other rules contain-
ing only objective items were developed. Both the Geneva-rule and (revised) Pisa-rules require the result of either a chest X-ray, blood gas analysis or ECG-interpretation and are therefore less feasible for use in primary care. The revised Geneva-rule, containing only clinical variables was constructed and can also be used in primary care (Table 1.1b). The clinical decision rules all assign different weights to the variables. To facilitate computation of the scores the Wells rule and the revised Geneva-rule have recently been simplified, assigning one point to all items (except for heart-rate in the simplified revised Geneva). Both the Wells rule and the revised Geneva might stratify patients into two levels (low and high) or three levels of probability (low, intermediate and high). No clinical decision rule is considered sensitive enough to exclude pulmonary embolism safely without additional D-dimer testing and none of these clinical decision rules was validated in primary care. Before implementing a clinical decision rule in primary care it needs to be validated in the proper setting of primary care. Owing to differences in spectrum of disease, symptoms and doctors’ experience encouraging results from secondary care may not be applicable in primary care.

### D-dimer tests

The process of thrombosis is physiologically accompanied by fibrinolysis with the aim to degrade the clot. D-dimers are degradation products of cross-linked fibrin and are generated during fibrinolysis. D-dimer is not a single entity in plasma but a mixture of heterogeneous fibrin degradation products. The D-dimer test is based on the complex formation of an antibody against the D-dimer molecule. Different assays use different types of monoclonal anti-D-dimer-antibodies. The D-dimer test is used to exclude venous thromboembolism. A negative D-dimer test has a high sensitivity (low false negative rate) and a high negative predictive value for the presence of venous thromboembolism. The specificity however is rather low due to the fact that increased levels of D-dimers are not only found in venous thromboembolism but also in many other conditions such as pregnancy, cancer and infections. D-dimer levels are also age-dependent (higher in the elderly).
Table 1.1.a/b Clinical decision rules suitable for use in primary care

### a. Wells rule

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical signs and symptoms of DVT (minimum of leg swelling</td>
<td>3.0</td>
</tr>
<tr>
<td>and pain with palpation of the deep veins)</td>
<td></td>
</tr>
<tr>
<td>2. Alternative diagnosis less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>3. Heart rate $&gt;100$/min</td>
<td>1.5</td>
</tr>
<tr>
<td>4. Immobilization ($&gt;3$days) or surgery in the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>5. Previous PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>6. Haemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>7. Malignancy (receiving treatment, treated in the last 6 months or</td>
<td>1.0</td>
</tr>
<tr>
<td>palliative)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical probability of PE:
- Unlikely: $\leq 4$ points
- Likely: $>4$ points

<table>
<thead>
<tr>
<th>Clinical probability for PE:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>$&lt;2$ points</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2-6 points</td>
</tr>
<tr>
<td>High</td>
<td>$&gt;6$ points</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism.

### b. revised Geneva-rule

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age $&gt;65$ y</td>
<td>1</td>
</tr>
<tr>
<td>2. Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>3. Surgery (under general anaesthesia) or fracture (of the lower limbs)</td>
<td>2</td>
</tr>
<tr>
<td>within 1 month</td>
<td></td>
</tr>
<tr>
<td>4. Active malignant condition (solid or hematologic malignant condition</td>
<td>2</td>
</tr>
<tr>
<td>currently active or considered cured $&lt;1$y)</td>
<td></td>
</tr>
<tr>
<td>5. Unilateral lower-limb pain</td>
<td>3</td>
</tr>
<tr>
<td>6. Haemoptysis</td>
<td>2</td>
</tr>
<tr>
<td>7. Heart rate</td>
<td></td>
</tr>
<tr>
<td>75-94 beats/min</td>
<td>3</td>
</tr>
<tr>
<td>$\geq 95$ beats/min</td>
<td>5</td>
</tr>
<tr>
<td>8. Pain on lower-limb deep venous palpation and unilateral oedema</td>
<td>4</td>
</tr>
</tbody>
</table>

Clinical probability for PE:
- Unlikely: $\leq 5$ points
- Likely: $>5$ points

<table>
<thead>
<tr>
<th>Clinical probability for PE:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>$&lt;4$ points</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-10 points</td>
</tr>
<tr>
<td>High</td>
<td>$&gt;10$ points</td>
</tr>
</tbody>
</table>
D-dimer tests are available as laboratory based and as point of care tests. These point of care or near patient-tests can be performed during the consultation and results are ready available within 10-15 minutes. For some point of care tests no additional equipment is necessary, which makes these tests easily accessible for use in the primary care setting.

Two major groups of D-dimer tests are available: quantitative tests in which the result is expressed in a number and qualitative tests in which the result is expressed in a positive or negative score.

**Computed tomography for PE**

In computed tomography a motorized table moves the patient through the CT imaging system. At the same time a source of x-rays rotates within the circular opening and a set of x-ray detectors rotates in synchrony on the far side of the patient. After intravenous administration of 80-100ml of iodinated contrast medium an image is produced by irradiating the patient from several directions with a narrow beam of X-rays. The intensity of transmitted X-rays will be measured with detectors. With a spiral CT-scan the X-ray tube continuously makes circular movements while the patient is moved slowly through the centre of the CT scanner (Figure 1.2). The X-ray tube describes a spiral movement around the patient hence the name spiral CT or helical CT. All the data are processed by a computer to produce a series of image slices representing a three-dimensional view of the chest.\(^\text{34}\) To reduce scanning time and improve resolution current CT-machines typically have multiple rows of detectors operating side by side, so that many slices (currently up to 64) can be imaged simultaneously.

The negative predictive value of a normal multi-slice CT-scan is regarded high enough to exclude PE without the need for additional imaging.\(^\text{35}\) In the Christopher-study the three months incidence of venous thromboembolism in patient with a normal CT-scan not treated with anticoagulants was 1.3%\(^\text{16}\), Perrier et al found an incidence of 1.7%.\(^\text{19}\)

With the increase in the number of detectors one is increasingly able to detect even small pulmonary emboli. Since the introduction of multi-detector CTPA the incidence of pulmonary embolism increased significantly. The suggestion is that these additional cases are often
Figure 1.2. Spiral CT-scan
(Reproduced with permission 34 Copyright Massachusetts Medical Society)

small, subsegmental emboli.36 The clinical significance of these small emboli is not entirely clear. They can be a precursor to larger emboli and might have more impact in patients with a poor cardiopulmonary status.37 Alternatively the trapping of smaller emboli could be an important physiological function of the lung.38 In the past these emboli would have remained untreated and probably would not have led to complications. Further research is needed to determine the need for treatment of these small emboli.

An important disadvantage of CT-scanning is the contrast-induced nephropathy in 2-5% of patients.39 Another major disadvantage of CT-scanning is the relatively high radiation exposure and the increased (though small) risk for radiation induced carcinogenesis,
which emphasizes the importance of excluding PE with the combination of an unlikely Wells decision rule and a negative D-dimer test in particular in younger women thereby reducing the number of patients undergoing unnecessary imaging.\textsuperscript{34}

**Compression ultrasonography of the legs in patients with suspected PE**

Pulmonary embolism usually arises from deep venous thrombosis (DVT) of the lower extremities.\textsuperscript{40,41} Compression ultrasonography of the leg veins could provide indirect evidence for the presence of PE in patients with clinically suspected PE.\textsuperscript{42} The detection of DVT would anyhow provide a rationale for anticoagulant treatment without the requirements of further diagnostic investigation. However bilateral compression ultrasound has been demonstrated to have a relatively low sensitivity (many false-negatives) for the diagnosis of asymptomatic DVT in patients presenting with symptoms of pulmonary embolism. Given that the prevalence of PE may be only 10\% to 30\% in the evaluation of suspected patients, this further reduces the utility of screening all patients initially with bilateral ultrasonography. The exception may be the patient with suspected PE with clinical signs of DVT in which case the likelihood of detection of DVT with ultrasonography is increased about 4-fold.\textsuperscript{43,44}

**Outline of this thesis**

The previous AMUSE-1 (Amsterdam, Maastricht, Utrecht, Study on thrombo-Embolism) showed that primary care physicians can safely exclude deep vein thrombosis with a clinical decision rule and D-dimer testing, thereby reducing the need for referral to secondary care of patients with clinically suspected DVT by almost 50\%.\textsuperscript{45} Many participating physicians asked whether a similar approach could also be possible for their patients with suspected PE. This thesis aims to evaluate the safety of a strategy to exclude pulmonary embolism in primary care patients with clinically suspected pulmonary embolism using the Wells PE-decision rule and a qualitative point of care D-dimer test. If the safety of this strategy is confirmed the primary care physician can distinguish between suspected PE-patients she/he can safely manage in primary care
and patients who need referral to secondary care for further testing. Chapter 2 describes a scenario-analysis that calculates the expected results of such a management strategy. The Wells rule at different cutoff values in combination with a qualitative point of care D-dimer test is applied in secondary care outpatients suspected of PE. Chapter 3 presents the results of a meta-analysis that compares the test-characteristics of gestalt (physicians’ unstructured estimate) and different clinical decision rules for suspected PE-patients and assesses failure-rates (missed cases) when used in combination with D-dimer testing. Chapter 4 shows the results of AMUSE-2 (Amsterdam, Maastricht, Utrecht, Study on thrombo-Embolism), a prospective validation study performed in primary care evaluating a diagnostic strategy using the Wells clinical decision rule and a point of care qualitative D-dimer test. Chapter 5 describes the alternative diagnoses in patients in whom pulmonary embolism was rejected. In patients in whom the PCP excluded PE using a negative Wells rule and a negative D-dimer test the PCP still faces a diagnostic dilemma. Are these patients suffering from any other clinically relevant disease? Chapter 6 answers this question and assesses the additional value of the CRP-test in these patients. In patients referred to secondary care CTPA is the preferred imaging test. Chapter 7 looks at the accuracy of the CTPA with the assessment of three expert radiologists as the reference standard. The general discussion (Chapter 8) follows a 35 year old female patient suspected of having pulmonary embolism in the process of applying the diagnostic strategy using clinical probability assessment and the D-dimer test.

Reference List

1 Anonymous. The diagnosis of pulmonary embolism. Lancet 175, 1633-1634. 11-6-1910.

CHAPTER I


4 Rijksen WP, Crul BVM. Hyperventilatie blijkt longembolie. Medisch Contact 50. 16-12-2010.


