Diagnostic strategy for excluding pulmonary embolism in primary care
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Citation for published version (APA):
Lucassen, W. A. M. (2013). Diagnostic strategy for excluding pulmonary embolism in primary care

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CHAPTER 5

ALTERNATIVE DIAGNOSES OF PULMONARY EMBOLISM IN PRIMARY CARE

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M van Heugten, L Rietjens, H ten Cate, MH Prins, HR Büller, AW Hoes
KGM Moons, R Oudega, HEJH Stoffers

Submitted
ABSTRACT

Introduction
Pulmonary Embolism (PE) often presents with non-specific symptoms and is a frequently missed diagnosis. A list of alternative diagnoses of PE might help the primary care physician when his differential diagnosis includes PE. This study aims to report the most common alternative diagnoses in patients in whom the primary care physician suspected PE. Additionally, we investigate whether the Wells rule combined with a point of care D-dimer test not only may exclude PE but also other serious diagnoses.

Methods
This study is a secondary analysis of the Amsterdam Maastricht Utrecht study on thromboembolism that validated the use of the Wells clinical decision rule for PE combined with point of care D-Dimer testing in patients suspected of PE in primary care. After medical history and physical examination, all patients were referred to secondary care and diagnosed according to local hospital protocols. Patients were followed-up for 3 months.

Results
The most frequent alternative diagnoses after excluding PE (n=516) were: non-specific thoracic pain/dyspnoea (42.6%), pneumonia (13.0%), myalgia (11.8%), asthma/COPD (4.8%), panic disorder/hyperventilation (4.1%) and respiratory tract infection (2.3%). Patients with a Wells score of >4 or a positive D-Dimer test were significantly more often diagnosed with a clinically serious disease that needs immediate medical treatment.

Conclusion
In primary care patients suspected of PE, the most common alternative diagnoses besides PE were thoracic pain/dyspnoea e.c.i., pneumonia and myalgia. A low probability of PE according the Wells rule and point of care D-dimer testing may also help to exclude other serious diseases than PE.
Introduction

Pulmonary embolism (PE) often presents with non-specific mild symptoms and is a frequently missed but potentially life-threatening diagnosis. In patients presenting with sudden unexplained (or deterioration of existing) dyspnoea, pain on inspiration and/or unexplained cough symptoms primary care physicians have to differentiate between frequently occurring clinically less serious diseases such as myalgia and more rare serious diseases such as PE and pneumonia. Several clinical decision rules to exclude PE have been proposed and validated. One of the most validated and used clinical decision rule is the Wells rule. The Amsterdam Maastricht Utrecht Study on thromboembolism (AMUSE-2) recently showed the safety of the use of the Wells clinical decision rule for PE combined with D-dimer testing in primary care.

The Wells rule combines 7 items into a score to calculate the pretest probability of PE (Table 5.1). The rule includes the attending physician’s judgment of whether an alternative diagnosis is less or more likely than PE. The subjective character of this specific criterion and its moderate reproducibility is the main point of criticism to the Wells rule. However, clinical judgment has been shown to improve the accuracy of clinical decision rules for PE. Furthermore, Klok et al. showed that the subjective criterion has a high predictive value in comparison to the other variables of the Wells rule. A list of alternative diagnoses of PE might thus help physicians in judging this subjective criterion and in judging the probability of PE in suspected patients.

Bagattini et al. investigated common alternative diagnoses of PE in secondary care. They found that the most frequent discharge diagnoses in emergency ward patients in whom PE was ruled out were nonspecific chest pain, bronchopneumonia, and heart failure. Alternative diagnoses of PE as seen in primary care, however, have not been investigated yet. In this secondary analysis of the AMUSE-2 study we aim to report the most common alternative diagnoses in patients in whom the primary care physician suspected PE. Additionally, we investigated whether the Wells rule combined with a point of care D-dimer test may not only exclude PE but also other serious diagnoses.
Table 5.1. Wells Clinical Decision Rule for Pulmonary Embolism

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

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism

Methods

**Study design and population**

This study is a preplanned sub-analysis of the AMUSE-2 data: a prospective cohort-study evaluating the safety of the diagnostic strategy of the Wells PE rule and a point of care D-dimer test in ruling out PE in primary care patients in the Netherlands between July 2007 and December 2010. We enrolled patients suspected of PE. Suspicion of PE was based on the presence of at least one of the following symptoms: unexplained (sudden) dyspnoea, deterioration of existing dyspnoea, pain on inspiration, or unexplained cough.

**Data collection**

After written informed consent, the primary care physician documented information on the patient’s history and physical examination and applied the Wells PE rule using a standard form. Subsequently the point of care Simplify D-dimer test (Clearview, Inverness Medical, Bedford, UK) was performed. Primary care physicians were asked to refer all patients to secondary care for further diagnostic work-up regardless of the outcome of the Wells rule and the point of care D-dimer test. In secondary care, the diagnostic strategy was based on current guidelines and routine care protocols. We retrieved medical information, including hospital discharge letters, about the investigations done to establish the diagnosis. In addition, all patients were followed up for 3 months. After these 3 months,
primary care physicians were asked to document the final diagnosis of each patient by completing a case record form. The primary care physician could choose one or more of the following predefined diagnoses: PE, deep vein thrombosis (DVT), pneumonia, (exacerbation of) chronic obstructive pulmonary disease (COPD), coronary insufficiency, aneurysm aortae, trauma thorax, malignancy, pneumothorax, myalgia, panic disorder, nonspecific thoracic pain/dyspnoea or other. When ‘other’ was chosen, the primary care physician was asked to write down the patient’s final diagnosis. No criteria for the clinical diagnoses were provided. If more than one final diagnosis was reported, the main diagnosis explaining the signs and symptoms which originally resulted in PE suspicion was included in the current analyses.

**Outcomes**
The primary outcome of this sub-study is the prevalence of each alternative diagnosis after excluding PE in primary care patients suspected of PE. In order to analyze the association between the clinical probability for PE (as assessed by Wells score and result of D-dimer test) and the type or severity of the final diagnosis, we divided the alternative diagnoses in two categories: Clinical serious diseases, leading to immediate medical treatment including pneumonia, pneumothorax, pleuritis, pericarditis, atelectasis, aneurysm aortae thoracalis, heart failure, asthma/COPD, respiratory tract infection, endocarditis, atrial fibrillation and lung cancer. Clinical less serious diseases, not leading to any treatment other than supportive care (e.g. pain-killing in case of musculo-skeletal pain) including nonspecific thoracic pain/dyspnoea, myalgia and panic disorder/hyperventilation. At least two investigators assessed the 3-months follow-up forms completed by the primary care physician and hospital discharge letters before assigning patients to one of the two above described categories. In case of disagreement a third investigator was involved and disagreements were resolved by discussion.

**Statistical Analysis**
Statistical analyses were performed by using IBM Statistical Package for the Social Sciences software (version 19; SPSS; Chicago, IL, USA).
Descriptive statistics were used to describe the baseline characteristics and to report the prevalence of the alternative diagnoses. Corresponding ninety-five percent confidence intervals (95% CI) were calculated for each alternative diagnosis by using Fisher’s exact test. In order to investigate the association between the probability of PE and type or severity of the alternative diagnosis, we performed subgroup analyses for patients with a Wells score >4 or a positive point of care D-Dimer test and patients with a Wells score of ≤4 and a negative point of care D-Dimer test. A threshold of 4 was introduced based on previous studies showing a high efficiency and safety at this cutoff point.²,³ Odds ratios (OR) and corresponding 95% CI for the alternative diagnoses by probability of PE were calculated by Mantel-Haenszel common odds ratio.

Missing values on items of the Wells PE rule or point of care Simplify D-dimer test results were observed in 24 patients. Missing data was not completely at random and therefore deletion of the subjects with missing values would not only lead to a loss of statistical power but also to biased results.⁹ To minimize the effect of selective missing, we imputed missing values using multiple imputation techniques. Imputation techniques are based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects.¹⁰;¹¹

**Results**

Over a three-year period, primary care physicians collected data of 662 patients suspected of PE. One or more of the predefined exclusion criteria were met in 64 patients, leaving 598 patients. VTE was present in 73 patients (prevalence 12.2%). Since a clear final diagnosis was missing in 9 (1.5%) patients, a total of 516 patients in whom PE was excluded were included in the analyses of the current study. One hundred and forty-nine patients (29%) were classified as having a clinically serious disease and 367 patients (71%) as having a clinically less serious disease (Figure 5.1).

Baseline characteristics of both groups are shown in Table 5.2. The mean age was 47 years and 72% was female. Patients with a clinically less serious disease were younger than patients with a clinically serious disease. Patients diagnosed with a serious disease were
Alternative diagnoses of PE

Excluded patients N=64
- VKA or LMWH use N=28
- Pregnant N=15
- Age ≤ 18 years N=3
- Unable to follow-up N=18

Study patients (Amuse2) N=598

Diagnosis missing N=9 (15%)

Patients suspected of PE N=662

Pulmonary Embolism N=73

Patients with alternative diagnosis N=516

Clinically less severe diseases N=367 (71.1%)
- Thoracic pain/dyspnoea eci 220 (42.6%)
- Myalgia 61 (11.8%)
- Panic disorder/hyperventilation 21 (4.1%)
- Other clinically less severe diseases† 65 (12.6%)

Clinically severe diseases N=149 (28.9%)
- Pneumonia 67 (13.0%)
- Asthma/COPD 25 (4.8%)
- Respiratory tract infection 12 (2.3%)
- Heart failure 7 (1.4%)
- Pericarditis 6 (1.2%)
- Lung cancer 5 (1.0%)
- Other clinically severe diseases* 27 (5.2%)

Abbreviations: PE, Pulmonary Embolism; VKA, Vitamin K Antagonist; LMWH, Low Molecular Weight Heparin; COPD, Chronic Obstructive Pulmonary Disease.

†Other clinically less serious diseases: other diagnoses (e.g. bronchial hyperactivity, collaps eci, trauma thorax, influenza, sinusitis) made by a PCP or hospital physician not leading to any treatment other than supportive care (e.g. painkilling).

*Other clinically serious diseases: coronary insufficiency (n=3), atrial fibrillation (n=3), pleuritis (n=3), pneumothorax

Figure 5.1. Flow chart study population
Table 5.2. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Baseline characteristics:</th>
<th>Clinically serious disease N=149</th>
<th>Clinically less serious disease N=367</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age - years</td>
<td>52±16</td>
<td>45±16</td>
<td>-</td>
</tr>
<tr>
<td>range</td>
<td>18-88</td>
<td>17-91</td>
<td>-</td>
</tr>
<tr>
<td>Females - no. (%)</td>
<td>99 (66.4%)</td>
<td>270 (73.6%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained sudden onset dyspnoea - no. (%)</td>
<td>94 (63.1%)</td>
<td>189 (51.5%)</td>
<td>1.6 (1.1 - 2.4)</td>
</tr>
<tr>
<td>Pain on inspiration - no. (%)</td>
<td>116 (77.9%)</td>
<td>294 (80.1%)</td>
<td>0.9 (0.5 - 1.4)</td>
</tr>
<tr>
<td>Unexplained cough - no. (%)</td>
<td>63 (42.3%)</td>
<td>98 (26.7%)</td>
<td>2.0 (1.3 - 3.0)</td>
</tr>
<tr>
<td><strong>Wells CDR for PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs and symptoms suggestive for DVT - no. (%)</td>
<td>11 (7.4%)</td>
<td>18 (4.9%)</td>
<td>1.5 (0.7 - 3.4)</td>
</tr>
<tr>
<td>PE most likely diagnosis - no. (%)</td>
<td>88 (59.1%)</td>
<td>179 (48.8%)</td>
<td>1.5 (1.0 - 2.2)</td>
</tr>
<tr>
<td>Heart rate &gt;100 bpm - no. (%)</td>
<td>51 (34.2%)</td>
<td>34 (9.3%)</td>
<td>5.1 (3.1 - 8.3)</td>
</tr>
<tr>
<td>Immobilisation or surgery - no. (%)</td>
<td>20 (13.4%)</td>
<td>50 (13.6%)</td>
<td>1.0 (0.6 - 1.7)</td>
</tr>
<tr>
<td>Previous DVT or PE - no. (%)</td>
<td>9 (6.0%)</td>
<td>56 (15.3%)</td>
<td>0.4 (0.2 - 0.7)</td>
</tr>
<tr>
<td>Haemoptysis - no. (%)</td>
<td>9 (6.0%)</td>
<td>7 (1.9%)</td>
<td>3.3 (1.2 - 9.0)</td>
</tr>
<tr>
<td>Active malignancy - no. (%)</td>
<td>7 (4.7%)</td>
<td>13 (3.5%)</td>
<td>1.3 (0.5 - 3.4)</td>
</tr>
<tr>
<td>Wells PE rule score &gt;4 - no. (%)</td>
<td>44 (29.5%)</td>
<td>78 (21.3%)</td>
<td>1.6 (1.0 - 2.4)</td>
</tr>
<tr>
<td>Simplify point-of-care D-Dimer positive - no. (%)</td>
<td>64 (43.0%)</td>
<td>100 (27.2%)</td>
<td>2.0 (1.4 - 3.0)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation; CDR, clinical decision rule; PE, pulmonary embolism; DVT, deep vein thrombosis; bpm, beats per minute
more likely to have presented with an unexplained sudden onset of dyspnoea, unexplained cough, a heart rate of more than 100 beats per minute and haemoptysis. Furthermore, patients with a clinically serious disease were more likely to have a Wells risk score of more than 4 points or a positive point of care D-Dimer test than patients with a less serious disease (Table 5.2).

Common alternative diagnoses
The most common alternative diagnoses after excluding PE were non-specific thoracic pain/dyspnoea (42.6%; 95%CI 38.3%-47.0%), pneumonia (13.0%; 95%CI 10.2%-16.2%), myalgia (11.8%; 95%CI 9.2%-15.0%), (exacerbation of) asthma/COPD (4.8%; 95%CI 3.2%-7.1%), panic disorder/hyperventilation (4.1%; 95%CI 2.5%-6.2%), respiratory tract infection (2.3%; 95%CI 1.2%-4.0%), heart failure (1.4%; 95%CI 0.5%-2.8%), pericarditis (1.2%; 95%CI 0.4%-2.5%) and lung cancer (1.0%; 95%CI 0.3%-2.2%). Other less frequent alternative diagnoses are presented in Figure 5.1.

Alternative diagnoses by probability for PE
There was a significant association between probability for PE and severity of the alternative diagnoses, p=0.001. Patients with a Wells score of >4 or a positive point of care D-Dimer test were less often diagnosed with a clinically less serious disease than patients with a low probability (OR 0.5; 95% CI 0.3-0.7). Consequently, patients with a high probability of PE were more likely to have a clinical serious disease (OR 2.1; 95%CI 1.4-3.1) leading to immediate medical treatment than patients with a Wells score of ≤4 and a negative point of care D-Dimer test. Especially pneumonia was strongly associated with a high probability of PE (OR 2.7; 95% CI 1.6-4.8, p=0.001). No difference was seen in the prevalence of respiratory tract infection between high risk and low risk patients (Table 5.3).
### Table 5.3. Odds Ratios for alternative diagnoses by probability for pulmonary embolism

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>High Probability Wells &gt; 4 or positive D-dimer N=254</th>
<th>Low Probability Wells ≤ 4 and negative D-dimer N=262</th>
<th>Total N=516 OR (95% CI; p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically less serious diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>161 (63.4%; 57.1 - 69.3)</td>
<td>206 (78.6%; 73.2 - 83.4)</td>
<td>0.5 (0.3 - 0.7)</td>
</tr>
<tr>
<td>Nonspecific thoracic pain/dyspnoea</td>
<td>97 (38.2%; 32.2 - 44.5)</td>
<td>123 (46.9%; 40.8 - 53.2)</td>
<td>0.7 (0.5 - 1.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23 (9.1%; 5.8 - 13.3)</td>
<td>38 (14.5%; 10.5 - 19.4)</td>
<td>0.6 (0.3 - 1.0)</td>
</tr>
<tr>
<td>Panic disorder/hyperventilation</td>
<td>8 (3.1%; 1.4 - 6.1)</td>
<td>13 (5.0%; 2.7 - 8.3)</td>
<td>0.6 (0.3 - 1.5)</td>
</tr>
<tr>
<td>Other clinical less serious diagnosis*</td>
<td>33 (13.0%; 9.1 - 17.8)</td>
<td>32 (12.2%; 8.5 - 16.8)</td>
<td>1.1 (0.6 - 1.8)</td>
</tr>
<tr>
<td>Clinically serious diagnoses</td>
<td>93 (36.6%; 30.7 - 42.9)</td>
<td>56 (21.4%; 16.6 - 26.8)</td>
<td>2.1 (1.4 - 3.1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>47 (18.5%; 13.9 - 23.8)</td>
<td>20 (7.6%; 4.7 - 11.5)</td>
<td>2.7 (1.6 - 4.8)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>10 (3.9%; 1.9 - 7.1)</td>
<td>15 (5.7%; 3.2 - 9.3)</td>
<td>0.7 (0.3 - 1.5)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>6 (2.4%; 0.9 - 5.1)</td>
<td>6 (2.3%; 0.8 - 4.9)</td>
<td>1.0 (0.3 - 3.2)</td>
</tr>
<tr>
<td>Other clinical serious diagnosis†</td>
<td>30 (12.3%; 22.9 - 42.8)</td>
<td>15 (6.1%; 9.3 - 25.2)</td>
<td>2.2 (1.2 - 4.2)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CI, Confidence Interval.

* other clinical less serious diagnoses: other diagnoses (e.g. bronchial hyperactivity, collapse, trauma thorax, influenza, sinusitis) made by a PCP or hospital physician not leading to any treatment other than supportive care (e.g. painkilling).

† other clinical serious diagnoses: coronary insufficiency (n=3), atrial fibrillation (n=3), pleuritis (n=3), pneumothorax (n=2), atelectasis (n=2), rib fracture (n=2), obstructive sleep apnoea syndrome (n=2), multiple myeloma (n=1), metastatic colon carcinoma (n=1), endocarditis (n=1), lymphadenopathy eci (n=1), urosepsis diabetes (n=1), diabetes mellitus de novo (n=1), sarcoidosis (n=1), acute aortic dissection (n=1), systemic lupus erythematosus (n=1), Langerhans cell histiocytosis (n=1).
Discussion

Main findings

In this analysis of a large prospective study performed in primary care including patients suspected of PE, we found that the most common alternative diagnoses of PE were thoracic pain/dyspnoe e. ci., myalgia and pneumonia. To our knowledge, this is one of the first studies presenting alternative diagnoses of PE in suspected primary care patients and our results correspond to reported alternative diagnoses in secondary care in the literature.\textsuperscript{7} Furthermore, we showed that high risk patients, with either a positive Wells rule or positive D-dimer test, in whom the diagnosis of PE was excluded, were more often diagnosed with clinically serious diseases than low risk patients. More than 60\% of the patients with a clinically serious disease had a Wells score of >4 or a positive D-Dimer test.

Interpretation

Our results are consistent with previously published studies showing a high proportion of patients with clinically serious diseases in patients with a high clinical probability of PE.\textsuperscript{12;13} The association in our study between risk class and severity of the final diagnosis may be partly explained by high D-dimer levels. It is known from literature that pneumonia, malignancy, coronary syndromes and heart failure are associated with high D-dimer levels.\textsuperscript{12;14-18} This corresponds with our finding of an increased proportion of having pneumonia in patients with a positive D-Dimer test result. Unfortunately, a significant association between D-dimer and malignancy, heart failure or coronary syndrome could not be noted due to the small number of patients in the subgroups resulting in large 95\% CI. Additional to D-Dimer, also the items ‘heart rate >100 beats per minute’ and ‘haemoptysis’ of the Wells clinical decision rule have contributed to the association between the probability for PE and severity of the alternative diagnosis. From these results we may conclude that a low Wells score and negative D-dimer test not only exclude PE, but also reduces the probability of other clinically serious diseases for which patients need to be referred to the hospital. This emphasizes the usefulness of the diagnostic strategy of the Wells rule combined with point of care D-dimer testing in primary care.
Limitations

Some limitations of this study have to be mentioned. First, although we asked primary care physicians to refer all patients to secondary care, 17% of the patients were not sent to the hospital for further diagnostic work-up. No referral to secondary care usually means less systematic diagnostic work-up. This may have resulted in an underreporting of less clinically serious diagnoses in those patients without referral and thus selection bias can not be excluded. Nevertheless, all patients were followed-up in primary care for three months and the reported final diagnosis according to the primary care physician for these patients was included in the present analysis. For 1.5% of the patients no alternative diagnosis was reported. All these patients had a follow-up without VTE.

Second, in 30% of the patients without a confirmed PE but with a clinically serious alternative diagnosis, it was not clear if objective testing was performed to confirm these diagnoses. In these patients the presence of the alternative diagnoses may thus be mainly based on clinical features. Since this also occurs in daily clinical primary care, we think that our study is still a good representation of daily practice.

Third, the original study was designed to validate the diagnostic strategy of excluding PE in primary care by using the Wells clinical decision rule for PE and point of care D-dimer testing. Therefore, potentially important characteristics of the alternative diagnoses may not have been recorded. Hence, we were not able to identify risk factors and predictors for the alternative diagnoses. This deserves more attention in future studies.

Conclusion

In conclusion, we found that the most common alternative diagnoses, besides PE, in primary care patients suspected of PE were nonspecific thoracic pain/dyspnoea, pneumonia and myalgia. Furthermore, we found that a low probability of PE may not only exclude PE but also other serious diseases. Otherwise, patients with a high probability of PE but without PE, often have a clinically serious diagnosis that needs medical treatment. This emphasizes the usefulness of the Wells rule and D-dimer point of care testing in the differentiation between high and low risk patients for clinically serious diseases in primary care patients suspected of PE. Although approximately
80% of the primary care patients with a high probability of PE will not be diagnosed with PE, referral to secondary care seems still warranted to diagnose and treat potential other clinical serious diseases.

Reference List


