Pulmonary embolism: advances in diagnosis and prognosis
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Citation for published version (APA):

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Chapter 5a

Application of a decision rule and a D-dimer assay in the diagnosis of pulmonary embolism

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Thrombosis and Haemostasis 2010;103:849-54
ABSTRACT

Background
Current strategies for diagnosing pulmonary embolism include a clinical decision rule (CDR), followed by a D-dimer assay in patients with an “unlikely” clinical probability. We assessed the implementation of the current guidelines for the diagnosis of pulmonary embolism.

Methods
A first questionnaire was sent to internists and pulmonologists to assess the proportion of physicians that adequately applied the guidelines. Two versions of a second questionnaire were sent presenting five hypothetical cases of which in two cases with an intermediate clinical probability an abnormal D-dimer test result was added to one version. We assessed the variation of the CDR and compared the proportions of a “likely” clinical probability between the two versions.

Results
A total of 65 physicians responded to the first questionnaire (response rate 75%). Half of the physicians (N=29; 46%) indicated that they use a CDR in all patients and 22 physicians (45%) indicated that they review the D-dimer result after they examined patients. Sixty-two physicians responded on the second questionnaire (response rate 36%). A shift was observed from an “unlikely” to a “likely” probability when an abnormal D-dimer test result was added to the clinical information (22% to 41%; p=0.22 and 26% to 50%; p<0.05).

Conclusion
Our findings indicate that physicians do not use the guidelines for diagnosis of pulmonary embolism consistently. Furthermore, the knowledge of an abnormal D-dimer test result before seeing the patient leads to a higher clinical decision rule score. Physicians should therefore first examine patients before taking note of the D-dimer test result.
INTRODUCTION

In the last decade much has changed in the diagnostic work-up of patients with clinically suspected pulmonary embolism. With the introduction of clinical probability assessment and D-dimer assays the proportion of patients in whom pulmonary embolism can be simply and safely excluded has improved significantly (1-4). Current guidelines for venous thromboembolism have been adjusted, based on performed studies, and this may have helped physicians in becoming more acquainted with these strategies (5,6). Although the strategies appear efficient, easy to apply and safe in clinical research settings, it is unknown whether this can be extrapolated to daily clinical practice. To what extent individual physicians are actually using these diagnostic strategies is even less clear.

With the popularity of the D-dimer assay, physicians have to be aware of pitfalls that come along with the use of this test. Since an abnormal D-dimer test result is non-specific, it is important that this assay is not used as a screening test (5,7). The test should also not be performed in patients with a “likely” clinical probability for pulmonary embolism, since they already need to undergo spiral CT testing. It has been established that false negative D-dimer test results appear in one per ten patients with a “likely” clinical probability (8).

In the emergency room setting, the D-dimer test is often ordered before the physician has examined the patient. It is conceivable that knowledge of the D-dimer assay outcome before examining the patient will influence the physician’s clinical probability estimation. In the ‘Wells rule’, a widely accepted clinical decision rule, the last item (alternative diagnosis less likely than pulmonary embolism) is a subjective element with an important contribution to the overall score, which may be interpreted differently if the physician is aware of a certain D-dimer test result (9).

Therefore, we performed a questionnaire based study to determine the use of clinical decision rules and D-dimer testing in patients with suspected pulmonary embolism. We analyzed whether physicians used these tests at all and if so, how consistently. In addition, we determined whether physicians were influenced by the knowledge of a D-dimer test result, when scoring the Wells clinical decision rule.

METHODS

First questionnaire

A first questionnaire was designed to determine which diagnostic strategies for pulmonary embolism were used in daily clinical practice. It specifically contained questions on the use of the clinical probability estimation and D-dimer testing. The responses were classified as using only a clinical decision rule, using it alternating with clinical judgment or using only clinical judgment. For the D-dimer assay, data were classified as using it never, sometimes, often or always; and for the interpretation of the test, whether this was done before examining the
Table 1. Wells score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent surgery or immobilization</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous PE or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Cut-off for PE “unlikely”</td>
<td>≤4</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; DVT, deep venous thrombosis. Adapted from: Wells et al. (9)

patient, after or both. A database was formed that contained all Dutch internists (n=1523) and pulmonologists (n=490) that are listed in the registries for Internal medicine and Pulmonology (Nederlandsche Internisten Vereeniging and Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose, respectively). The questionnaire was sent to a randomized sample of the physicians in the database and in case of no response, a reminder was sent.

Second questionnaire

In a separate second questionnaire, sent several months later, physicians were randomly assigned to two versions of this questionnaire in which five hypothetical patient cases with a clinical suspicion of pulmonary embolism were presented. The clinical probability of the cases varied from “unlikely” to “likely”. To assess the influence of the a-priori knowledge of the D-dimer test result, two versions were prepared for cases with an intermediate clinical probability of pulmonary embolism. In case 2, the D-dimer result was left out in version A and in version B, the clinical information included an abnormal D-dimer result of 1.8 mg/L. In the fourth case it was the other way around; version A was the version with an abnormal D-dimer result of 2.4 mg/L and it was left out in version B. Physicians received one of the two versions, and were not informed that there were two versions. They were told that the goal of this project was “to further evaluate the clinical decision rule”. The cut-off value for an abnormal D-dimer test result of > 0.5 mg/L was added to this questionnaire together with an example of a clinical decision rule, the ‘Wells rule’, illustrating the seven items of the rule and the cut-off value of 4 points (Table 1) (9).

Statistical analysis

In the first questionnaire, the proportions of physicians that applied evidence based diagnostic strategies were analyzed. We assessed the proportions of physicians that were aware of a clinical decision rule, that used it and that used it consistently. The same was done for the D-
dimer test. These data were also analyzed for several subgroups of physicians (field of specialization, working in a tertiary center, number of patients with pulmonary embolism seen per month).

For the second questionnaire, we analyzed the variation of the clinical decision rule score in the five cases, using descriptive statistics. An independent two sample T-test was used for the comparison between the two versions of cases 2 and 4. We compared the proportion of physicians that scored the cases as pulmonary embolism “likely” between the versions A and B (physicians that were informed about an abnormal D-dimer and those who were not). Since we wanted to observe a difference we sent the second questionnaire to more physicians compared to the first questionnaire. Statistical analyses were applied using SPSS version 14.0.2.

RESULTS

First questionnaire

Of the first questionnaire 87 copies were sent out to a randomized group which represented 4% of the 2013 physicians, of which 65 (75%) were completed and returned, including the reminder. The practice characteristics of the physicians are detailed in Table 2; 68% were internists, 32% were pulmonologists and the majority was male (86%). The practice characteristics of the 22 physicians that did not return the questionnaire did not differ from those included in this analysis (male gender n=19 (86%); academic center n=8 (36%); internists n=14 (64%); pulmonologists n=8 (36%)). All but two physicians indicated that they regularly examine patients with a clinical suspicion of pulmonary embolism, hence 63 questionnaires were analyzed.

Almost all physicians used a clinical probability test (N=60; 95%) to assess the clinical probability in patients with suspected pulmonary embolism, as is depicted in Figure 1. These physicians were divided equally in those using a clinical decision rule in all patients, or using it alternating with clinical judgment (N=29 and N=31, respectively). The remaining three physicians always used clinical judgment. Upon the question which clinical decision rule was used, the Wells rule was the only rule that was referred to by 46 physicians (71%), whereas the others could not report a specific decision rule.

All physicians indicated that they use a D-dimer test, of whom 53 (84%) indicated that they used this test always or very often. Four physicians (6%) reported to be always aware of the D-dimer result before they were seeing their patients. Half of the remaining physicians (N=22; 45%) reported to be aware of the result only after they examined the patients, whereas the others (N=27) reported that it varied between before and after.

When we compared the use of these tests among several subgroups (internists versus pulmonologists, academic versus non academic work settings and those physicians who see more than 5 patients with suspicion of VTE a month versus those who see less), only small differences were observed, which were not clinically relevant (data not shown).
Table 2. Practice characteristics of the 65 responding physicians.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>55 (86)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;35 years</td>
<td>4 (6)</td>
</tr>
<tr>
<td>36-45 years</td>
<td>31 (48)</td>
</tr>
<tr>
<td>46-55 years</td>
<td>21 (32)</td>
</tr>
<tr>
<td>&gt;55 years</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>44 (68)</td>
</tr>
<tr>
<td>Haematology</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Vascular Medicine</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Oncology</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Intensive Care</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Nephrology</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>21 (32)</td>
</tr>
<tr>
<td>Academic hospital</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Non-academic hospital</td>
<td>56 (86)</td>
</tr>
<tr>
<td>Patients PE/month, median (IQR)</td>
<td>3.0 (2-5)</td>
</tr>
</tbody>
</table>

IQR, inter quartile range.

Second questionnaire

The second questionnaire was sent to 172 physicians (representing 9% of the 2013 physicians) of whom 62 (36%) returned a completed questionnaire. The practice characteristics were as follows: 65% were internists, the remaining 35% were pulmonologists and 75% of the physicians were male. The practice characteristics of the non-responding physicians did not differ from those included in this analysis (data not shown). Case 1, 3 and 5 were similar for all physicians, whereas for the second and fourth case there were two different versions with respect to knowledge of D-dimer result. The clinical decision rule score per physician varied, although most physicians agreed on the scores of the first case (69% of the physicians scored 10 points) and the third case (89% scored 1 point), as is depicted in Figure 2. For cases 2, 4 and 5 with an intermediate clinical probability more variability in the clinical decision rule score was observed. Furthermore, a shift was observed between the two versions of cases 2 and 4 from an “unlikely” clinical probability to a “likely” clinical probability when an abnormal D-dimer test
result was added to the information. A total of 22% of physicians calculated a score >4 (PE “likely”) without the knowledge of an abnormal D-dimer versus 41% if the abnormal D-dimer was added to the information (p=0.22). For case 4, these percentages were 50% versus 26%, with or without information of an abnormal D-dimer test result, respectively (p<0.05; Figure 2).

DISCUSSION

This survey shows that the majority of responding internists and pulmonologists operate to a large extent according to the guidelines for diagnosing pulmonary embolism. However, the guidelines are not used consistently, since only half of the physicians indicate that they use a clinical decision rule in all patients. While clinical judgment is a respected method of clinical probability estimation, it is less efficient in withholding patients from additional imaging tests, and may be less safe in inexperienced physicians (10,11). In this study the scoring of the clinical decision rule was clear in those patients with a low or a high clinical probability, but variable and therefore arguably the same as one’s clinical judgment, in the cases in which diagnostic uncertainty for VTE was the greatest. While literature indicates that the interobserver variability of clinical judgment is inadequate if compared to explicit clinical decision rules, it is unclear whether this counts for all clinical probability groups (12). Although guidelines advise to assess the clinical probability before performing the D-dimer test, about one third of the responding physicians were already aware of the D-dimer result before
Figure 2. Distribution of the clinical decision rule score for the five hypothetical cases.
Case 1 was a patient with a high clinical probability for pulmonary embolism; 69% of the physicians scored 10 points with the decision rule. Case 3 was a patient with a low clinical probability; 89% scored 1 point. Case 5 was a patient with a moderate clinical probability; 26% scored 2.5 points and 55% scored 5.5 points. There were two versions of the cases 2 and 4: version A and B. The vertical dotted line stands for the cut-off value of the CDR for pulmonary embolism “unlikely” (≤4) or “likely” (>4). When an abnormal D-dimer test result was added to the patient information, it was clear that a higher proportion of the patients was scored as pulmonary embolism “likely” (2B and 4A).

they examined the patient. And even more important, physicians were influenced in scoring the clinical decision rule by the knowledge of an abnormal D-dimer test result. There is no information on which items contributed to the total score of the Wells rule, but the influence of the D-dimer test on the physician’s clinical probability estimation is probably caused by the
subjective element of the Wells rule ‘alternative diagnosis less “likely” than pulmonary embolism’. It appears that physicians may have more confidence in an objective blood test than in their own expertise. Due to its moderate specificity the D-dimer assay could also be abnormal in several other situations, and the influence on the clinical decision rule is therefore not justified. Furthermore, only a minority of the D-dimer tests have been evaluated in appropriate clinical trials concerning the exclusion of PE (13). Moreover, it has been shown that false negative D-dimers appear in almost 10% of the patients with a “likely” clinical probability, and physicians should therefore always first assess the clinical probability before taking notice of the D-dimer test result (8). Taken together, adherence to the guidelines was observed in less than a third of the physicians, which is in agreement with the literature, and this may result in unnecessary testing and a less safe strategy (14,15).

When we focus on the study restrictions, a questionnaire based survey will always have certain limitations, for example the retrospective character and that those that did not answer the questionnaire may have influenced the data. However, the characteristics of these physicians did not differ from those that participated. The response rate of 75% on our first questionnaire was higher than we had expected from response rates of other questionnaires sent to physicians (16,17). The lower response rate of 36% on the second questionnaire can be explained by the fact that no reminder was sent. It is plausible that those physicians that are familiar with diagnostic strategies would be more inclined to return the questionnaire. It can therefore be hypothesized that those who did not return the questionnaire are even less familiar with the diagnostic strategies for pulmonary embolism. Furthermore, the percentage of physicians represented in the first and second questionnaire of 4% and 9% respectively, is just a small proportion of the total database, which may affect the generalizability of our study. Finally, physicians may act differently in clinical practice from what they report in a questionnaire. Despite these limitations, we believe our results are a good reflection on how diagnostic strategies for pulmonary embolism in the Netherlands are applied.

In summary, although diagnostic strategies for pulmonary embolism have found wide implementation, there still are some pit-falls. Physicians assessing patients in emergency room settings should be cautious when requesting D-dimer assays and should always examine patients first before reviewing the D-dimer result. This will prevent physicians being influenced by a non-specifically elevated D-dimer result.

**REFERENCE LIST**

APPENDIX

Case 1
You are paged by an emergency room physician, who has just seen a 68-year old woman who had a curative hemicolecotomy four weeks earlier, because of a Dukes B colon carcinoma. She now complains of a swollen left leg and shortness of breath. Upon the physical exam, the respiratory rate is 24 per minute, the tension 110/75 mmHg, heart rate is 108 per minute and the left leg looks very suspect for deep vein thrombosis. The EKG shows a new right bundle branch block and on the chest X-ray some pleural effusion can be seen in the right pleural cavity.

CDR score: ............. points
A. You perform an ultrasound of the leg. If positive for thrombosis, you perform no further diagnostic tests.
B. You ask for a D-dimer test and let further diagnostic actions depend on the outcome of this test.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 2 – version 1
You see a 63-year old Indian man. His medical history contains a knee operation in 1980, complicated by deep vein thrombosis of that leg. He also has diabetes and mild hypertension. The patient explains he’s been having a severe flu for almost a week, but that he now also has shortness of breath and chest pain. Upon physical examination you find his body temperature is 37.7°C, the blood tension is 145/90 mmHg, he has an elevated heart rate (110/minute) and his respiratory rate is 20 per minute. The chest X-ray is normal. Besides tachycardia, the EKG shows no abnormalities.

CDR score: ............. points
A. You do not perform diagnostic testing for pulmonary embolism; you do not believe this disease as a possibility.
B. You ask for a D-dimer test and let further diagnostic actions depend on the outcome of this test.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 2 – version 2
Same case as version 1, only ‘D-dimer 1.8 mg/l’ was added to the information.

A. You request a troponin assay and ask the cardiologist to examine the patient.
B. You perform a CT scan to exclude or diagnose pulmonary embolism.
C. You perform a leg ultrasound. If this is negative for thrombosis, you perform a CT-scan.

Case 3
A man, 68 years old, who has an active carcinoma of the prostate, comes to see you in the outpatient clinic complaining of chest pain, cough, shortness of breath and a cold. The physical examination shows: body temperature T 37.5°C, tension 120/60 mmHg, heart rate 88/minuut. Auscultation of the lungs is normal and so are the chest X-ray and the EKG. Laboratory test: D-dimer 0.3 mg/l.
CDR score: .......... points
A. You do not perform diagnostic testing for pulmonary embolism; you do not believe this disease as a possibility.
B. You ask the patient to come back in two days, because you don’t fully trust the D-dimer and the clinical decision rule with his underlying malignancy.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 4 – version 1
You see a woman aged 61 years who stopped smoking 2 years ago. After her second pregnancy she had a DVT in the left leg. During the following 3 years she used oral contraceptives without any complications. The patient reports she has been coughing a lot more than usual during the past week. Five days ago, she had a fever when she measured her body temperature at home (38.4°C), but this was gone soon afterwards. Since one day, she has shortness of breath and a mild pain on the lateral side of the left thorax. With physical examination you find a body temperature of 37.2°C, her blood tension is 151/94 mmHg, the heart rate is 108 per minute, the respiratory rate is 22 per minute and no abnormalities are found by auscultations of the lungs. Both the chest X-ray and the EKG are normal. The D-dimer test is 2.4 mg/l.

CDR score: .......... points
A. You thoroughly re-examine the patient and the chest X-ray to exclude a rib fracture or pneumothorax.
B. You perform a CT scan to exclude or diagnose pulmonary embolism.
C. You refer the patient to a cardiologist.

Case 4 – version 2
Same case as version 1, except for leaving the D-dimer result is left out.

A. You do not perform diagnostic testing for pulmonary embolism; you do not believe this disease as a possibility.
B. You ask for a D-dimer test and let further diagnostic actions depend on the outcome of this test.
C. You perform a CT scan to exclude or diagnose pulmonary embolism.

Case 5
A 73-year old woman with no medical history reports to your outpatient clinic. After she fell with her rollator while doing groceries a week earlier, she had to rest several days because of a painful right knee. Since two days, she also developed some chest pain and also had some blood in her mouth with coughing. T 36.8°C, tension 115/68, heart rate 72/min. No abnormalities on auscultation. Lab: D-dimer 0.95 mg/l. There is some pleural effusion on the left side on the chest X-ray.

CDR score: .......... points
A. You perform an ultrasound of the right knee, and also check for DVT of the right leg.
B. You perform a CT scan to exclude or diagnose pulmonary embolism.
C. You refer the patient to a pulmonologist to perform a bronchoscopy.