Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism
van Es, Josien

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Combining Wells score including the D-dimer results in less need for CT-scanning in patients with suspected pulmonary embolism

J. van Es
L.F.M. Beenen
P.L. den Exter
R.A. Douma
I.C.M. Mos
K. Kaasjager
M.V. Huisman
P.W. Kamphuisen
S. Middeldorp
P.M.M. Bossuyt
**Abstract**

**Introduction:** The combination of an “unlikely” clinical decision rule and a negative D-dimer test result safely excludes pulmonary embolism (PE) in 30% of presenting patients. We aimed to simplify this diagnostic approach and to increase its efficiency.

**Methods:** We analysed data of a multicentre study of 723 consecutive patients with suspected PE. After constructing a logistic regression model including the D-dimer test result and Wells score items, we identified the most prevalent combinations of influential Wells items and subsequently developed a new clinical decision rule. The performance of this new clinical decision rule was externally validated in a separate dataset including 3306 patients with suspected PE.

**Results:** The prevalence of PE was 22%. Three Wells items were identified as significantly adding incremental value to the D-dimer test result: two clinical items (haemoptysis and clinical signs of deep vein thrombosis) and the subjective item (PE most likely). Based on the most frequent combinations of these three items we identified two groups: 1) none of these three items positive (41%), and 2) at least one of these items positive (59%). When applying a 1000 µg/L D-dimer threshold in group 1 and 500 µg/L in group 2, PE could be excluded without CT-scanning in 36%, whereas the false-negative rate was 1.2% (95% CI 0.04-3.3%). Alternatively, when a lower threshold of 900 µg/L and 400 µg/L was used, PE was excluded in 31%, and the false negative rate was 0.4% (95% CI 0.1-2.3%). In the validation cohort, the proportion of patients in whom PE could be excluded without CT-scanning, was 46% and 42% with false negative rates of 1.9% (95% CI 1.2-2.7%) and 1.4%, (95% CI 0.9-2.3%) for the two combinations of cut-off levels, respectively.

**Conclusion:** Combining items of the Wells rule with the D-dimer test result resulted in a simplified clinical decision rule, which additionally reduced the need for CT-scanning in patients with suspected PE. A prospective evaluation of this strategy would be required before implementation in clinical practice.
**INTRODUCTION**

The clinical presentation of patients with suspected acute pulmonary embolism (PE) is nonspecific and varies widely (1;2). The proportion of objectively proven PE by computerized tomography pulmonary angiography (CTPA-scan) in patients with suspected PE is relatively low: 20% to 30% of all patients undergoing CT-scanning for a clinical suspicion of PE (3;4). CT-scanning, being widely available among hospitals, has become the first-line imaging modality in patients with suspected PE (5), but is also associated with an increased lifetime risk of malignancy from radiation exposure and the risk of contrast nephropathy (6). These concerns encourage clinicians to seek a diagnostic strategy that safely reduces the number of CTPAs.

In the past decade, standardised clinical decision rules have been derived and implemented in clinical practice to determine the pre-test probability of PE. The most frequently validated and most commonly used clinical decision rule is the Wells rule (7). This score incorporates seven objective items from clinical history and physical examination and one subjective item, allowing the physician to indicate whether or not an alternative diagnosis is more likely than the presence of acute PE (Table 1) (7). The Wells rule was developed by selecting variables significantly associated with PE from an extended list of 40 items. These items were initially evaluated in univariate logistic regression analysis; significant variables that were retained after a step-wise backward elimination procedure in multivariable logistic regression were selected for the final clinical decision rule (7). Since unadjusted odds ratios calculated this way are known to have an upwards bias with lower values in replication studies, Gibson and colleagues derived and validated a simplified Wells score, assigning one point to all variables. The corresponding clinical decision rule uses a cut-off of one point; all patients with two points or more are referred for CT-scanning (Table 1) (8;9). This simplified Wells clinical decision rule showed to be as effective and safe as the original Wells rule (10). It probably is also easier to memorize, potentially leading to fewer mistakes in the acute care setting.

The Wells rule is used in combination with a high-sensitive D-dimer test (4;11). The sensitivity of the D-dimer, combined with a clinical decision rule, using a cut-off value of 500 µg/L was estimated at nearly 100%; its specificity, however, is only 30% to 40% (11;12). In patients with suspected PE, about 20% to 40% have an 'unlikely' result with the Wells score and a normal D-dimer test result (< 500µg/L). In these patients, PE can be safely excluded without CT-scanning (4;10).
The Wells clinical decision rule-D-dimer combination leads to CT-scanning in all patients with a slightly elevated D-dimer, even in patients with a Wells score of zero, although the accuracy of D-dimer testing has been demonstrated to be substantially different in this subgroup (13). In clinical practice, D-dimer-testing is often performed on a low threshold, regardless the Wells score (11). This results in more patients being referred for CTPA, which increases the number of CTPAs negative for the presence of PE, and decreases the proportion of patients in whom PE can safely be excluded without imaging. The aim of this study was therefore to derive a new clinical decision rule, combining the Wells items and D-dimer testing, with sensitivity similar to that of the original clinical decision rule but with an enhanced specificity, in order to safely reduce the number of (negative) CTPAs.

**METHODS**

**Development set**
To derive a new clinical decision rule, we analyzed data from 807 patients with clinically suspected PE included in a prospective multicentre cohort study, of which the design is reported in detail elsewhere (10). Briefly, the study population consisted of consecutive in- and outpatients in whom acute PE was clinically suspected. Clinically suspected acute PE was defined as sudden onset of dyspnea, deterioration of existing dyspnea, or sudden onset of pleuritic chest pain. Patients were identified in seven academic and non-academic hospitals in the Netherlands.

The attending physicians performed the clinical evaluation and collected demographic data and additional relevant information at baseline (10). For each included patient, the dichotomized Wells score (cut-off value 4) based on information obtained from history and physical examination. For study purposes, a high-sensitivity quantitative D-dimer test was performed in all patients (10). In case of an “unlikely” classification and a normal D-dimer result, PE was considered to be excluded (10). A CTPA-scan was performed in patients with a “likely” classification or in case the D-dimer test was abnormal (> 500 µg/L). The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree (10).

Patients were followed for three months and instructed to return to the hospital if symptoms of PE, DVT or bleeding events occurred and objective, imaging diagnostic tests were done if PE or DVT was suspected (10).
**Validation set**

For the validation set, data from a large prospective multicenter cohort study was used (4). This study evaluated the clinical effectiveness of an algorithm based on the dichotomized Wells score, D-dimer testing and CTPA-scanning in patients with suspected PE. The study design and results are reported elsewhere (4). In short, between November 2002 and August 2004, all consecutive in- and outpatients with clinically suspected acute PE in 12 hospitals in the Netherlands were eligible for this study. The institutional review boards of all participating hospitals had approved the study protocol.

The study group consisted of 3,306 patients. All underwent a sequential diagnostic work-up, consisting of clinical probability calculation, a D-dimer test, and CTPA-scanning. At admission, the clinical probability was calculated by the treating physician using the Wells score. According to the protocol, a D-dimer test was performed only in patients with a Wells score of 4 or less. PE was excluded by either an ‘unlikely’ Wells score (≤ 4) combined with a D-dimer test ≤ 500 μg/L or by a negative CTPA-scan in all other patients. PE was considered confirmed by a positive CTPA.

Patients were followed up by their family physicians and were interviewed by telephone by one of the study coordinators at the end of a three month follow-up period. The primary outcome measure was the estimated three-month thromboembolic risk in patients in whom PE was considered ruled out by the initial diagnostic work-up, and who had not received anticoagulants during follow-up (4).

**Statistical analysis**

We used multivariable logistic regression analyses, in which we added the original Wells items to the D-dimer test result, using PE as the dependent variable. The accuracy of the resulting model was evaluated by calculating the area under the Receiver Operating Characteristics curve (AUC).

We then calculated the frequency of the informative Wells variables. Based on the most frequent combinations and multivariable modelling, we aimed to develop a simple classification of the total group of patients based on the retained, most influencing Wells items. In each of the resulting subgroups we then identified a D-dimer threshold that would lead to a sensitivity rate comparable to that of the original Wells rule. Sensitivity of the new clinical decision rule was estimated using the proportion of patients with a positive clinical decision rule, relative to all patients with PE, as confirmed by CTPA. Specificity is estimated as the proportion of patients with a negative clinical decision rule.
result, relative to all patients without PE. The positive predictive value (PPV) was defined as the proportion of patients with a negative clinical decision rule with PE confirmed by CTPA relative to all positive clinical decision rules; the negative predictive value (NPV) was defined as the proportion of patients with a clinical decision rule unlikely with PE excluded by CTPA relative to all clinical decision rule classified as unlikely. Additionally, we calculated the false negative rates, defined as those patients who had PE in the diagnostic investigation or during follow-up. Besides, we assessed the number of patients who experienced DVT during follow-up. The clinical utility was assessed by calculating the proportion of patients in whom further diagnostic testing could be safely withheld. The safety as well as the clinical utility of the new clinical decision rule was compared to that of the original Wells rule at a cut-off ≤ 4 in combination with a normal D-dimer result (≤ 500 μg/L). The 95% confidence interval (CI) for the three months PE incidence rate in both the scores (for the Wells score in combination with a normal D-dimer test result) was calculated. A clinical decision rule was considered acceptable if the confidence interval around the observed diagnostic failure rate would not exceed 3% (14).

All p-values were two-tailed and statistical significance was defined as p < 0.05, except where indicated otherwise. All analyses were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill).

**RESULTS**

The development set consisted of 807 patients with clinically suspected PE. In 84 patients was no D-dimer test available, consequently these patients were excluded. Of the remaining 723 patients, 156 patients (22%) had PE. The mean age was 52 years (SD 17) and 441 patients (61%) were female, mean body mass index was 26 kg/m² (SD 5), and 92 female patients (13%) used estrogen containing drugs. With regard to the comorbidity, 67 patients (9%) had chronic obstructive pulmonary disease, 38 patients (5%) had heart failure and 90 patients (12%) had a malignancy. When using the regular Wells rule combined with the conventional D-dimer threshold, the number of patient in whom PE could be excluded was 160 (22%; 95% CI 19% to 25%). The PPV and NPV of this algorithm were 0.28 (95% CI 0.24-0.31) and 0.99 (95% CI 0.99-1.00), respectively.
Items of the new clinical decision rule

Table 1 shows the multivariable logistic regression model, fitted to the data in the development set, using the original Wells items. This table additionally depicts the coefficients for the same model, also including the D-dimer test result. When including the D-dimer test result in all items, only three of the seven Wells items were significantly associated with PE (at p < 0.2): two clinical items (haemoptysis, clinical signs of DVT) and the subjective item (PE most likely). All other items (history of DVT or PE, malignancy, immobilisation, and tachycardia) did not provide incremental value, conditional on the D-dimer test result.

Table 1. Multivariable logistic regression model, fitted to the data in the development set, using the original Wells items and the D-dimer result.

<table>
<thead>
<tr>
<th>Wells items and points</th>
<th>N (%)</th>
<th>Wells items</th>
<th>Wells items and D-dimer test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically suspected DVT</td>
<td>3 (5%)</td>
<td>3.94 (1.93-8.03)</td>
<td>2.99 (1.41-6.33)</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>1 (12%)</td>
<td>1.08 (0.91-1.90)</td>
<td>0.94 (0.51-1.74)</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5 (5%)</td>
<td>3.30 (1.56-6.99)</td>
<td>2.25 (0.96-5.28)</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3 (55%)</td>
<td>2.65 (1.76-3.98)</td>
<td>2.43 (1.56-3.77)</td>
</tr>
<tr>
<td>Heart rate ≥ 100 beats per minute</td>
<td>1.5 (21%)</td>
<td>1.59 (1.03-2.55)</td>
<td>1.29 (0.80-2.07)</td>
</tr>
<tr>
<td>Immobilization/surgery in past 4 weeks</td>
<td>1.5 (20%)</td>
<td>1.92 (1.23-3.00)</td>
<td>1.27 (0.77-2.09)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1 (12%)</td>
<td>2.86 (1.36-6.03)</td>
<td>2.84 (1.29-6.24)</td>
</tr>
<tr>
<td>D-dimer test result</td>
<td>-</td>
<td>1.58 (1.42-1.75)</td>
<td></td>
</tr>
</tbody>
</table>

CI confidence interval, DVT deep venous thrombosis, N number, PE pulmonary embolism

The corresponding model, including these three variables and the D-dimer test result had an AUC of 0.83 (95% CI 0.80-0.87) (Fig 1).
Figure 1. Receiver operating characteristic curves illustrating the diagnostic performance of the two clinical items (haemoptysis, clinical signs of deep venous thrombosis) and the subjective item (pulmonary embolism most likely), combined with the D-dimer test result in the derivation and validation cohort. The areas under the curve were 0.83 (95% confidence interval (CI) 0.80-0.87), 0.84 (95% CI: 0.83-0.86) and respectively.

Four combinations of the three remaining Wells items could be identified: (1) none of these items positive (n=298, 41%), (2) only the subjective item positive, none of the other two items positive (n=354, 49%) (3) one or two clinical items positive (n=26, 3.6%) (4) the subjective and one or more clinical items positive (n=45, 6.2%). Based on these frequencies, we then defined two groups (group 1) none of these items positive (41%), [group 2] the subjective item and/or one of the clinical items positive (59%) (Table 2).
New decision rule including Wells items and the D-dimer result

Table 2. The most prevalent (> 2%) combinations of the variables of the Wells rule in the derivation cohort and the validation cohort.

<table>
<thead>
<tr>
<th>Combination of variables</th>
<th>Derivation cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE is most likely diagnosis n (%)</td>
<td>345 (49)</td>
<td>1402 (50)</td>
</tr>
<tr>
<td>None of the items positive, n (%)</td>
<td>298 (41)</td>
<td>1135 (41)</td>
</tr>
<tr>
<td>PE is most likely diagnosis plus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoptysis, n (%)</td>
<td>18 (2.5)</td>
<td>78 (2.8)</td>
</tr>
<tr>
<td>clinical signs of DVT, n (%)</td>
<td>23 (3.2)</td>
<td>69 (2.5)</td>
</tr>
</tbody>
</table>

Based on this model, a novel clinical decision rule could be constructed that corresponds to the use of a variable D-dimer threshold, depending on the type and number of items positive. We calculated two different D-dimer cut-off levels: one for patients with none of these items positive (group 1), and one for the other subgroup (one or more of the three items positive) (group 2).

We assessed the cut-off levels of 1000 μg/L and 500 μg/L for the two groups, respectively: 1000 μg/L for group 1, and 500 μg/L for group 2. Using these cut-off levels we found the D-dimer to be negative in 83 patients in group 1 and 176 patients in group 2, respectively. This new rule had a positive predictive value of 22% at a negative predictive value of 99% for group 1 versus 37% and 99% for group 2. Overall, PE could be excluded in 259 patients (36%, 95% CI 32-39). Additionally, one patient with malignancy experienced DVT during follow-up, with none of the items positive and a D-dimer test result of 980 μg/L. Compared to the conventional method of the original Wells rule, combined with a normal D-dimer test result (cut-off value 500 μg/L), the number of patients in whom PE could be excluded increased from 160 to 259 (absolute increase 14%, relative increase of 62% (99/160)). The false negative rate increased from 0.6% (1/160, 95% CI 0.10-2.4%) to 1.2%, (3/259 95% CI 0.04-3.3).

We alternatively evaluated lower cut-off levels, leading to fewer negatives, but also a lower failure rate: 900 μg/L for group 1, and 400 μg/L for group 2. The PPV was 21% and 35%, at a NPV of 99% and 100%, for group 1 and 2, respectively. Using these cut-off levels we found the D-dimer test to be negative in 162 and 63 patients in the two groups respectively. PE could safely be excluded in 225 patients (31%, 95% CI 28 to 34%), with a false negative rate of 0.4% (1/225, 95% CI 0.1-2.3%). For this patient,
none of the three items was positive. None of the patients experienced DVT. Compared to the conventional algorithm, the number of patients in whom PE could be excluded increased from 160 to 225 patients (absolute increase 8.9%, relative increase 41% (65/160)). The false negative rate decreased from 0.6% (1/160, 95% CI 0.2-3.4) to 0.4% (1/225, 95% CI 0.10-2.4%).

Table 3 lists the test characteristics in terms of sensitivity, specificity, PPV and NPV of the new diagnostic strategy for the CDR combined with 1000/500 μg/L or 900/400 μg/L D-dimer cut-off levels. In Figure 2 the diagnostic steps of the new strategy are illustrated.

**Figure 2.** Diagnostic work up for suspected pulmonary embolism (PE), a combination three clinical items and two different cut-off points of the D-dimer.

CT computerized tomography, DVT deep venous thrombosis, PE pulmonary embolism

**Validation set**

The validation sample consisted of 3,306 patients with clinically suspected PE. In 515 patients with an unlikely clinical probability of PE, D-dimer test results were recorded only qualitatively and were therefore missing for this analysis. In another six patients, one of the Wells items was missing. Consequently these patients were excluded from
further analysis. Of the remaining 2785 patients, 491 patients were diagnosed with PE (17.6%). The clinical characteristics were similar to those of the patients in the derivation cohort. When using the original Wells rule combined with a conventional normal D-dimer test result, the number of patient in whom PE could be excluded was 989 (35%; 95% CI 34% to 37%). The PPV and NPV of this algorithm were 0.28 (95% CI 0.26-0.30) and 0.99 (95% CI 0.99-1.00), respectively (Table 3).

**Performance of the new clinical decision rule**

In 1135 (41%) patients of the validation set, none of the informative Wells items was positive; in the other 1649 patients (59%) one or more items were positive (Table 2). The corresponding model, including these three variables and the D-dimer test result had an AUC of 0.84 (95% CI 0.83-0.86) (Fig 1).

Applying the cut-off levels of 1000 μg/L for group 1, and 500 μg/L for group 2, the D-dimer test was negative in 782 and 500 patients, respectively. Using the cut off level of 1,000 μg/L for group 1, the PPV and NPV were 21% and 98%, respectively. For group 2, in which we used the lower, 500 μg/L cut-off, the PPV was 34% and the NPV 98%. Overall, PE could be excluded in 1295 patients (46%, 95% CI 45-48%) with a false negative rate of 1.9% (24/1295, 95% CI 1.2-2.7%). Compared to the conventional algorithm, the number of patients in whom PE could be excluded increased from 989 to 1295 (absolute increase 11%, relative increase of 31%). The false negative rate increased from 0.5% (5/989, 95% CI 0.2-1.2%) to 1.9% (24/1295, 95% CI 1.2-2.7%).

With the lower D-dimer positivity cut-offs (900 μg/L for group 1 and 400 μg/L for group 2), the PPV was 21% and 32%, the NPV 98% and 99%, Using these cut-off levels, the D-dimer test was negative in 762 and 403 patients, respectively. PE could safely be excluded in 1165 patients (41%, 95% CI 40-43%), with a false negative rate of 1.4% (17/1165, 95% CI 0.9-2.3%). Compared to the conventional algorithm, the number of patients in whom PE could be excluded increased from 989 to 1165 patients (absolute increase 7.0%, relative increase 18% (176/989). However, the false negative rate increased from 0.5% (5/989, 95% CI 0.2-1.2%) to 1.4% (17/1165, 95% CI 0.9-2.3%) (Table 3).
Table 3. Test characteristics of the new diagnostic strategy combined with D-dimer cut-off values 1000/500 μg/L * and 900/400 μg/L **, and the conventional Wells score with the the D-dimer test (cut-off 500 μg/L).

<table>
<thead>
<tr>
<th></th>
<th>New CDR including D-dimer cut-off levels 1000/500 μg/L *</th>
<th>New CDR including D-dimer cut-off levels 900/400 μg/L **</th>
<th>Wells score unlikely (&lt;4) and D-dimer cut-off 500 μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation cohort</strong>, n = 723</td>
<td>259 (36)</td>
<td>225 (31)</td>
<td>160 (22)</td>
</tr>
<tr>
<td>Number (%) of patients in whom PE can be excluded</td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
<td>PPV (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.98 (0.95-0.99)</td>
<td>0.45 (0.41-0.49)</td>
<td>0.33 (0.29-0.37)</td>
</tr>
<tr>
<td></td>
<td>0.99 (0.97-1.00)</td>
<td>0.40 (0.36-0.44)</td>
<td>0.31 (0.27-0.35)</td>
</tr>
<tr>
<td></td>
<td>0.99 (0.97-1.00)</td>
<td>1.00 (0.98-1.00)</td>
<td>0.99 (0.97-1.00)</td>
</tr>
<tr>
<td><strong>Validation cohort</strong>, n = 2785</td>
<td>1295 (64)</td>
<td>1165 (42)</td>
<td>989 (36)</td>
</tr>
<tr>
<td>Number (%) of patients in whom PE can be excluded</td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
<td>PPV (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.95 (0.93-0.97)</td>
<td>0.56 (0.53-0.57)</td>
<td>0.32 (0.29-0.34)</td>
</tr>
<tr>
<td></td>
<td>0.97 (0.95-0.98)</td>
<td>0.50 (0.48-0.52)</td>
<td>0.29 (0.27-0.31)</td>
</tr>
<tr>
<td></td>
<td>0.99 (0.97-0.99)</td>
<td>0.99 (0.98-0.99)</td>
<td>0.99 (0.99-1.00)</td>
</tr>
</tbody>
</table>

CDR clinical decision rule, NPV negative prospective value, PPV positive prospective value, PE pulmonary embolism.

Combining the results of the two cohorts

The number of patients in whom PE could be excluded in the 3508 patients in total of the two cohorts together, when assessing 1000 μg/L for group 1, and 500 μg/L for group 2, was 1554 patients (44%, 95% CI 43-46%), with a failure rate of 0.7% (27/3508, 95% CI 0.5-1.1%). Compared to the conventional algorithm the number of patients in whom PE could be excluded increased from 1149 (37%) to 1554 patients (absolute increase 7%, relative increase 35% (405/1149). The false negative rate increased from 0.5% (6/1149, 95% CI 0.2-1-1%) to 0.7% (27/3508, 95% CI 0.5-1.1%).

When using 900 μg/L and 400 μg/L for group 1 and 2 respectively, this number was 1390 patients (40% 95% CI 38.9-41.2%), with a false negative rate of 0.5% (18/3508, 95% CI 0.3-0.8%).
New decision rule including Wells items and the D-dimer result

Compared to the conventional method of the original Wells rule, combined with a normal D-dimer test result (cut-off value 500 μg/L), the number of patients in whom PE could be excluded increased from 1149 (37%) to 1390 patients (absolute increase 3%, relative increase 21% (241/1149). The false negative rate did not differ 0.5% (5/989, 95% CI 0.2-1.2%) versus 0.5% (18/3508, 95% CI 0.3-0.8%).

**DISCUSSION**

We derived a simple clinical decision rule in which Wells items and the D-dimer test are incorporated. Conditional on the D-dimer result, only a few of the Wells items proved to be of incremental value. The resulting rule therefore, was based on these three items and the D-dimer test result, with a different D-dimer threshold for those with no items positive versus those with one or more items positive. With this new clinical decision rule, approximately 36% (using the 1000/500 μg/L cut-off value) and 31% (using the 900/400 μg/L cut-off value) of patients with suspected PE can be withheld from further diagnostic imaging, a proportion substantially higher to that observed with the original Wells rule (22%).

In primary care, physicians already have access to a validated clinical decision rule for DVT, including 7 clinical items and the D-dimer, with a maximum of 13 points (16;17). A positive D-dimer result contributes for 6/13 points. Using this rule, the proportion suspected DVT referred for imaging tests could be reduced from 100% to 77%, at the expense of not referring 0.7% of all DVT cases. However, it is only recently demonstrated that for patients with suspected PE in primary care, the traditional Wells score followed by a D-dimer test safely excludes PE (18). Additionally, several studies addressed that using a higher cut-off level of the D-dimer, results in higher specificity without a relevant fall in sensitivity. Kline and colleagues recently doubled the threshold of the D-dimer, in a prospective study with 678 patients with suspected PE and an unlikely pretest probability (19). They found the threshold of 1000 μg/L to be safe to exclude PE in patients with a Wells score of ≤ 4 points. Similarly, in patients with suspected DVT, this study group has showed that in 860 patients with a first episode of suspected DVT, a D-dimer cut-off of 1000 μg/L is as safe as the conventional cut-off point of 500 μg/L in those with a low clinical probability (20). Other previous studies also demonstrated that a D-dimer cut-off value, adapted to the clinical probability category of the patient, has greater utility for exclusion of PE compared to the use of one D-dimer cut-off value regardless of the clinical probability (21;22). The proposed cut-off
value was kept at 500 µg/L for patients with an intermediate clinical suspicion of PE, but was doubled in patients with a low clinical suspicion, and halved in patients with a high clinical suspicion of PE. In a study by Kabrhel and colleagues, the conventional cut-off of 500 µg/L had an overall sensitivity of 94% (95% CI 91-97) and a specificity of 58% (95% CI 56-60). These rates were 88% (95% CI 83-92) and 75% (95% CI 74-76), respectively, when probability-dependent cut-offs were used (21).

Combining the items of the Wells rule with the D-dimer result resulted in a clinical decision rule with fewer items, one that has a sensitivity similar to that of the original Wells score / D-dimer combination, but substantially increased specificity. We showed the performance for two sets of cut-off points for the D-dimer test result: 1,000 plus 500 µg/L on the one hand, and 900 and 400 µg/L on the other. Obviously, the lower the cut-off level, the safer the strategy is. It is commonly accepted that the confidence intervals of the proportions of patients with PE at baseline or after three months with a diagnostic strategy for PE may not exceed 3% (13). The upper level of the confidence interval for the false negative rate of the novel decision rule, using 1000 µg/L and 500 µg/L, was 2.7%, and 3.3% in the validation set. Using the combination of cut-off levels of 900 and 400 µg/L, the upper levels of the 95% CI were 2.3% and 2.7% in the derivation set and validation set, respectively. Nevertheless, the false negative rates with this novel clinical decision rule are higher than applying the conventional Wells score with a D-dimer test result at a cut-off 500 µg/L. However, these false negative rates may not directly translate to failure rates if this strategy is applied in practice. There may be false positive CT-scans for PE, some of the PE cases during follow-up could be new thrombotic events and it has been suggested that not all PE cases confirmed by imaging are consequential (21;22). On the other hand, these false negative rates may be too high to allow this strategy to fully replace the current diagnostic strategy without further evaluation. Management studies could document the actual failure rate as well as any practical challenges when implementing this novel decision rule.

The conclusions of this study are strengthened by its large sample of patients, and its multicenter design, which enhance the extrapolation of our findings to other clinics. Limitations include that a D-dimer test was not performed in 84/807 patients of the derivation cohort, and that 515 patients of the validation set were excluded, because no qualitative D-dimer test was available. Furthermore, although our analysis was based on prospectively collected data and validated in an independent cohort, this analysis was done retrospectively. Therefore, our strategy would benefit from a prospective validation in a management study.
In summary, we have shown that combining the Wells items with the D-dimer test result in patients with suspected PE, using different thresholds for those with no Wells items positive than in the others, leads to a simple decision rule with comparable sensitivity, but substantially higher specificity, thereby increasing the number of patients in whom CT-scanning be withheld. This strategy needs further evaluation in management studies.

**Reference List**


