The role of plasma D-dimer concentration in the exclusion of pulmonary embolism

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Summary. Objective. To determine the role of four ELISA D-dimer assays in the exclusion of pulmonary embolism.

Design. Blinded comparison using pulmonary angiography and/or lung scintigraphy as a reference method.

Setting. A secondary and tertiary referral centre.

Patients and methods. Consecutive patients with suspected pulmonary embolism underwent lung scintigraphy, followed by angiography if a non-diagnostic result was obtained. Comorbid conditions resulting in elevated plasma D-dimer levels were defined a priori. Cut-off levels for 100% sensitivity were determined. A decision-analytic model was used to determine effectiveness and costs in the management pulmonary embolism.

Main outcome measures. The exclusion efficacy of the various assays at a sensitivity of 100%, and cost-effectiveness.

Results. A total of 179 patients were included (78 inpatients and 101 outpatients; 74 patients had comorbid conditions). Pulmonary embolism could be adequately excluded in between 8% and 18% of all patients, and in between 3% and 7% and 11% and 27% of inpatients and outpatients, respectively, depending on the assay used. D-dimer assays could exclude pulmonary embolism in <5% of patients with comorbid conditions, whereas this increased to 14–32% in outpatients without comorbid conditions. A cost-effectiveness analysis showed a cost reduction of 10% at a specificity of 30%, largely due to a 28% decrease in angiography requirements. Furthermore, for every 2% decrease in sensitivity, one per 1000 evaluated patients would die as a result of inadequately treated pulmonary embolism.

Conclusion. D-dimer ELISA assays may have a role in the exclusion of pulmonary embolism in symptomatic outpatients, where the application may reduce angiography by 30% and costs by 10%.

Keywords: pulmonary embolism, diagnosis, D-dimer, ELISA, cost-effectiveness.

Clinically suspected pulmonary embolism is a frequent and difficult diagnostic challenge. Several studies have shown that annually about three per 1000 people are suspected of this disorder (Anderson et al., 1991; van Beek et al., 1991), whereas only 30% will have the diagnosis confirmed (Hull et al., 1983; PIOPED, 1990; McBride et al., 1986). To establish or exclude pulmonary embolism often requires multiple, sometimes invasive, and costly diagnostic procedures. Although in recent years several major advances have been made, such as the clinical validity of a normal perfusion lung scan to refute pulmonary embolism or a high probability scan result as sufficient proof for the diagnosis to warrant long-term anticoagulant therapy, there remains controversy over the best strategy for the 50–60% of symptomatic patients who have neither of the above lung scan results. In these patients with lung scan results that are designated as non-diagnostic (Hull & Raskob, 1991; Moser, 1990), several management strategies are currently proposed. They vary from pulmonary arteriography in all patients to the use of (in various combinations) clinical decision rules (Patil et al., 1993; Stein et al., 1993a), tests for the detection of deep venous thrombosis (Kruit et al., 1991; Stein et al., 1999b; Hull et al., 1994) or computed tomography (Remy-Jardin et al., 1992; Teigen et al., 1993).

Recently, several investigators have assessed the potential value of detecting certain markers of coagulation or fibrinolysis activation, based on the concept that increased levels in peripheral blood reflect the presence of thrombosis in the circulation. In particular, the utility of measuring the degradation product of cross-linked fibrin (D-dimer) in plasma
has been evaluated in patients with clinically suspected pulmonary embolism (Bounameaux et al, 1991; Leitha et al, 1991; Demers et al, 1992; Harrison et al, 1993; Goldhaber et al, 1993). From these studies it has become apparent that the majority of patients with pulmonary embolism have an elevated plasma D-dimer concentration. However, patients with clinical conditions mimicking pulmonary embolism often have similar concentrations. Therefore the most promising application of this test lies in the exclusion of pulmonary emboli in symptomatic patients, i.e. in those patients with normal plasma D-dimer concentrations (Harrison et al, 1993; Goldhaber et al, 1993; Ginsberg et al, 1993; van Beek et al, 1993; Bounameaux et al, 1994). Such an approach is only acceptable if virtually none of the patients with pulmonary embolism is missed, so that, in the future, anticoagulant treatment can be safely withheld in patients with symptoms suggesting pulmonary embolism and normal D-dimer test results.

With this high requirement of a sensitivity approaching 100% with a consequent negative predictive value of 100%, it becomes important to assess how many patients of the initial cohort with clinically suspected pulmonary embolism can be safely identified and spared further investigation and treatment. Furthermore, it is unknown whether there is an advantage to using this test in all symptomatic patients or to limit the determination to certain subgroups, such as outpatients or those without diseases known to be associated with intravascular fibrin deposition. Finally, there is controversy whether the D-dimer test should be used early or later in the diagnostic work-up of patients suspected of having pulmonary emboli (Bounameaux et al, 1991; Harrison et al, 1993; Perrier et al, 1994; Quinn et al, 1994).

We therefore undertook a cross-sectional study in a consecutive series of patients with clinically suspected pulmonary embolism. First we estimated, for four different assays, the plasma D-dimer concentration which yielded a sensitivity of 100%. Subsequently, we calculated the percentage of patients from the entire cohort in whom D-dimer was able to exclude pulmonary emboli in all patients and in certain subgroups: newly seen or admitted patients (outpatients), previously admitted patients (inpatients) and patients with or without comorbid conditions. Finally, using a decision-analytic model, the best time to perform D-dimer tests in order to obtain the highest diagnostic utility was determined.

MATERIALS AND METHODS

Patients. Consecutive patients (both in- and outpatients), who underwent diagnostic work-up for clinically suspected pulmonary embolism in two large teaching hospitals in Amsterdam, The Netherlands, were eligible for inclusion into the study. Clinical and demographic characteristics were prospectively collected. All patients underwent lung scintigraphy. Perfusion lung scintigraphy was performed using 99mTc-Technetium-labelled macro-aggregates of albumin (Sorin Biomedica, Vercelli, Italy), while ventilation images were obtained using 81mKrypton gas (Cygne by, Eindhoven, The Netherlands). Lung scans were classified as normal, high probability for pulmonary embolism (defined as one or more segmental perfusion defects with normal ventilation), or non-high probability (non-diagnostic) (PIOPED, 1990; Hull et al, 1985; Lensing et al, 1992).

All patients with non-diagnostic lung scan results underwent pulmonary angiography. Selective intra-arterial pulmonary angiography was performed using low-osmolar contrast media. Angiography was considered to demonstrate pulmonary emboli if a filling defect or an acute cut-off of an arterial branch with a diameter of 2-5 mm or more was seen in two projections (PIOPED, 1990; Dalen et al, 1971).

Patients were classified as having pulmonary embolism if a high probability lung scan result was obtained or if pulmonary emboli were shown on pulmonary angiography. Pulmonary embolism was excluded if a normal lung scan or angiogram was obtained and 6 months follow-up was uneventful with respect to symptomatic venous thromboembolism.

The study was approved by the respective Institutional Review Boards and written informed consent was obtained from all patients.

Plasma samples. Prior to heparinization, blood was collected from each patient. Platelet-poor plasma was obtained by centrifuging 9 ml of venous blood collected into 1 ml of 0-105M sodium citrate solution (Becton Dickinson, New Jersey, U.S.A.) for 20 min at 3000rpm (1200g) at 15°C. All samples were stored at −70°C. Assays were performed within 6 months of blood collection. All samples were analysed in duplicate, without knowledge of the results of the other diagnostic tests that were performed.

Four ELA plasma D-dimer assays were evaluated: Dimertest I (Agen Test Technologies, Acacia Ridge, Qld, Australia), Enzygnost D-dimer (Behringwerke, Marburg, Germany), Fibrinostika FbDP (Organon Teknika, Boxtel, The Netherlands) and Asserachrom D-dil (Diagnostica Stago, Asnières, France). The discriminant values used for raised plasma D-dimer levels were 50 µg/l, 40 µg/l, 550 µg/l and 400 µg/l, respectively.

Study design. Since the basis of the clinical utility of D-dimer tests rests with the safe exclusion of pulmonary embolism, we first determined, in all patients, the cut-off value for each assay. In order to have optimal confidence that a normal D-dimer would exclude pulmonary embolism, the D-dimer plasma concentration corresponding to the lowest value observed in patients with proven pulmonary embolism was determined. By definition, this leads to a sensitivity of 100%. Subsequently, we calculated the exclusion efficacy as the percentage of patients of the entire group in whom the diagnosis would have been adequately excluded by the finding of normal plasma D-dimer concentration.

Since the presence of other disorders may increase plasma D-dimer levels, subgroup analyses were performed to evaluate the influence of comorbid conditions and of prior admission (i.e. the development of symptoms in outpatients or in patients already admitted for other reasons). The comorbid conditions were identified a priori according to previously published definitions (Demers et al, 1992). Briefly, patients were classified as having comorbid conditions if the following circumstances or disorders were present: <10d following either surgery, trauma, myocardial infarction or cerebrovas-
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Malaria accident; sepsicaemia, diffuse intravascular coagulation or acute infection; pregnancy or <30 d post partum; active collagen vascular disease; or metastatic cancer.

Finally, with the use of a decision-analytic model, we attempted to define the optimal place of the plasma D-dimer assay in the diagnostic management of patients with clinically suspected pulmonary embolism. Based on previously reported analyses, we selected two strategies which are widely used and were previously shown to be cost-effective (PIOPED, 1990; Oudkerk et al, 1993; Hull et al, 1994). The analysis for each of these two strategies was expanded with the inclusion of D-dimer as a first test or as an additional test only in patients with non-diagnostic lung scan results, resulting in two groups of strategies.

The main assumptions in this model are related to complications of invasive diagnostic methods, complications of anticoagulant therapy and the natural history of pulmonary embolism (Oudkerk et al, 1993). From several reports in the literature, the morbidity and mortality related to pulmonary angiography was estimated to be 1-9% and 0-2%, respectively (Dalen et al, 1971; Mills et al, 1980; Stein et al, 1992). The risk of major bleeding due to anticoagulant therapy was estimated at 1%, whereas fatal haemorrhage was thought to occur in 0-25% of patients, for a 3-month course of anticoagulants (Hull et al, 1982; Levine et al, 1992; van der Meer et al, 1993). The natural history of untreated pulmonary embolism can only be properly derived from one study, in which non-fatal recurrence was observed in 26% and fatal recurrence in 26% of untreated patients (Barritt & Jordan, 1960). For further details of these and other assumptions the reader is referred to the full paper (Oudkerk et al, 1993).

Group I comprised [1] perfusion-ventilation lung scintigraphy with ultrasonography of the deep leg veins if the lung scan result was non-diagnostic and pulmonary angiography if ultrasonography was normal; patients were treated if the lung scan was high probability, if ultrasonography was abnormal or if angiography showed pulmonary emboli; [2] D-dimer as a first test, followed by strategy [1] if the D-dimer level was above the cut-off level; [3] perfusion-ventilation lung scintigraphy with D-dimer if the lung scan result was non-diagnostic, ultrasonography of the leg if the D-dimer was above the cut-off level, and pulmonary angiography if ultrasonography was normal; treatment as in the first strategy.

Group II contained the following strategies: [4] perfusion-ventilation lung scintigraphy with pulmonary angiography if the lung scan result was non-diagnostic; patients were treated if the lung scan was high probability or if angiography shows pulmonary emboli; [5] D-dimer as a first test, followed by strategy [4] if the D-dimer level was above the cut-off level. Finally, the sixth strategy includes perfusion-ventilation lung scintigraphy with D-dimer if the lung scan result was non-diagnostic and angiography if the plasma D-dimer

Table I. Clinical and demographic characteristics of 179 patients with clinically suspected pulmonary embolism.

<table>
<thead>
<tr>
<th></th>
<th>Inpatients (n = 78)</th>
<th>Outpatients (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>40/38</td>
<td>36/65</td>
</tr>
<tr>
<td>Mean age (range) (years)</td>
<td>58.5 (22–92)</td>
<td>56.5 (18–82)</td>
</tr>
<tr>
<td>Scintigraphic and angiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal perfusion lung scan</td>
<td>21 (27%)</td>
<td>40 (40%)</td>
</tr>
<tr>
<td>Normal angiogram</td>
<td>19 (24%)</td>
<td>26 (26%)</td>
</tr>
<tr>
<td>High-probability lung scan</td>
<td>33 (43%)</td>
<td>25 (24%)</td>
</tr>
<tr>
<td>Abnormal angiogram</td>
<td>5 (6%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Referring specialty/service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine (including pulmonology)</td>
<td>48 (61%)</td>
<td>47 (47%)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>0 (0%)</td>
<td>41 (41%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>16 (21%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (18%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Risk factors for venous thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent surgery and/or trauma*</td>
<td>13 (17%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>7 (9%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Paralysis or paresis of lower limb(s)</td>
<td>10 (13%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Recent cerebral or myocardial infarction*</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Coexisting diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18 (23%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>18 (23%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Acute infection</td>
<td>13 (17%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Active collagen vascular disease</td>
<td>4 (5%)</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

*Recent is defined as within 10 d for inclusion into the study.

concentration was above the cut-off level: therapy as in strategy [4].

For comparison, we included an imaginary strategy which assumes correct diagnosis and therapy in all patients without diagnostic tests, the so-called clairvoyant strategy.

Data analysis. The McNemar $\chi^2$-test was used to compare differences between the defined subgroups. A $P$ value of $<0.05$ was regarded as statistically significant.

The cost-effectiveness analysis was performed using previously presented assumptions (Oudkerk et al. 1993). These assumptions consisted of prevalence of pulmonary embolism and deep venous thrombosis, sensitivity and specificity of diagnostic tests (angiography, lung scintigraphy and ultrasonography of the leg veins), morbidity and mortality of angiography and anticoagulant therapy, morbidity and mortality in the natural history of pulmonary embolism, and costs of procedures and therapy. Additionally, we assumed that the D-dimer assay was available 24 h per day and costs 40 ECU (or 35 UK £) per patient. The sensitivity of the D-dimer assay was set at 98%, and a specificity of 30% was used for base-line analysis. The efficacy of the various strategies was assessed in terms of mortality, morbidity, costs, and percentage of patients requiring pulmonary angiography.

A sensitivity analysis was performed, which varied one parameter each time. The tested parameters (and the range evaluated) were: specificity of D-dimer assay (10–50%), sensitivity of D-dimer assay (90–100%), prevalence of pulmonary embolism (20–50%), risk of major haemorrhage (0.5–5%), sensitivity (96–100%) and specificity (92–100%) of pulmonary angiography.

RESULTS

Study subjects
A total of 203 consecutive patients with clinically suspected pulmonary embolism were entered into the study. In 24 (12%) patients with a non-diagnostic lung scan result, angiography could not be performed due to existing contraindications (12 manifest heart failure, two myocarditis, three severe pulmonary hypertension, three severe dyspnoea with inability to lie flat, two thrombocytopenia $<20 \times 10^9$/l, and two renal failure). Since no definite diagnosis could be obtained in these patients, they were excluded from the analysis. Hence, 179 patients, of whom 78 were inpatients and 101 were outpatients, were evaluated.

The clinical, demographic characteristics and scintigraphic and angiographic findings of the studied patients are listed in Table I. The mean age of the study population was 56.5 years; almost three-quarters of the patients had no known risk factors for thromboembolism, whereas malignant disease was present in 16%. The mean delay between onset of symptoms and presentation was 2 d (range 0–60 d). Pulmonary embolism was excluded in 106 patients (61 normal perfusion lung scan and 45 normal pulmonary angiogram), whereas emboli were demonstrable in the remaining 73 patients (58 high probability lung scan and 15 positive angiogram), for a prevalence of pulmonary embolism of 41%.

| Percentage of patients adequately excluded by D-dimer |
|---------|--------|
| n       | Range  |
| All patients | 179   | 8–18%   |
| Inpatients   | 78    | 3–6%    |
| Outpatients  | 101   | 11–27%  |
| Presence of comorbidity | 74    | 0–5%    |
| Absence of comorbidity | 105   | 13–27%  |
| Outpatients without comorbidity | 76    | 14–32%  |

*For definition of comorbid conditions see Materials and Methods section.

Exclusion of pulmonary embolism
The discriminant plasma concentrations of the four D-dimer assays were applied, and their value for the adequate exclusion of pulmonary embolism in all patients, and separately for in- and outpatients, presenting with clinical suspicion of this disorder, was determined. These results are described in Table II. The percentage of patients which could be excluded varied from 8% to 18% in all patients. This increased to up to 27% if only outpatients were assessed. All methods performed equally badly in inpatients.

When patients were grouped according to the presence or absence of comorbid conditions which may independently raise plasma D-dimer levels, the exclusion rate of all assays in patients with comorbidity was insufficient to be clinically useful (Table II). For all assays the exclusion rate was significantly better (varying from 13% to 27%) in patients without comorbidity conditions, and this improved only marginally if solely outpatients without comorbidity conditions were analysed.

Cost-effectiveness analysis
The efficacy (in terms of mortality and morbidity rates), the estimated average cost per patient for diagnosis and treatment and the angiography rate required in the various management strategies for the entire study population of patients with clinically suspected pulmonary embolism, are shown in Table III. For reference, a theoretical (clairvoyant) strategy is given. The first three strategies all contain ultrasonography, but this test is omitted in the last three strategies. Addition of the D-dimer assay to the diagnostic strategies does not result in any significant change in the mortality rates, whereas morbidity decreases to a slightly lower level. Furthermore, regardless of the strategy employed, there is an approximate 10% cost-reduction in addition to a 25–28% reduction in the number of patients requiring pulmonary angiography. The timing for performing the D-dimer assay, either as an initial screening test or later in the diagnostic process, does not have major effects on the parameters of the cost-effectiveness analysis.
Table III. Efficacy in terms of mortality and morbidity, costs and percentage of patients requiring pulmonary angiography in various diagnostic-therapeutic strategies.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mortality rate (%)</th>
<th>Morbidity rate (%)</th>
<th>Costs/patient (ECU*)</th>
<th>Angiography required (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct in all (clairvoyant)</td>
<td>0.69</td>
<td>0.92</td>
<td>652</td>
<td>0</td>
</tr>
<tr>
<td>1. Perfusion-ventilation scan with ultrasonography if scan shows non-high probability and angiography if ultrasound is normal; treatment if scan shows high probability, if ultrasound is abnormal, or if angiography shows pulmonary embolism</td>
<td>0.87</td>
<td>2.17</td>
<td>1265</td>
<td>61.8</td>
</tr>
<tr>
<td>2. D-dimer followed by strategy 1 if D-dimer elevated</td>
<td>0.97</td>
<td>1.97</td>
<td>1131</td>
<td>44.4</td>
</tr>
<tr>
<td>3. Perfusion-ventilation scan with D-dimer if scan shows non-high probability; ultrasonography if D-dimer elevated and angiography if ultrasound is normal; treatment as strategy 1</td>
<td>0.97</td>
<td>1.97</td>
<td>1131</td>
<td>44.4</td>
</tr>
<tr>
<td>4. Perfusion-ventilation scan with angiography if scan shows non-high probability; treatment if scan shows high probability or if angiogram shows pulmonary embolism</td>
<td>0.94</td>
<td>2.41</td>
<td>1254</td>
<td>72.2</td>
</tr>
<tr>
<td>5. D-dimer followed by strategy 4 if D-dimer elevated</td>
<td>1.04</td>
<td>2.19</td>
<td>1133</td>
<td>54.4</td>
</tr>
<tr>
<td>6. Perfusion-ventilation scan with D-dimer if scan shows non-high probability and angiography if D-dimer elevated; treatment as strategy 4</td>
<td>0.98</td>
<td>2.14</td>
<td>1171</td>
<td>54.4</td>
</tr>
</tbody>
</table>

ECU = European Currency Unit.

Table IV. Sensitivity analysis and effects on mortality and costs of strategy using perfusion-ventilation lung scintigraphy, plasma D-dimer test, ultrasonography and angiography.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line</th>
<th>Range</th>
<th>Effects on mortality</th>
<th>Effects on costs</th>
<th>Effects on angiography rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity dimer</td>
<td>30%</td>
<td>50–10%</td>
<td>Increase with decreasing specificity (0.90–0.94%)</td>
<td>Less costs-savings with decreasing specificity (13–1% costs-savings)</td>
<td>Less reduction with decreasing specificity (43–9% reduction)</td>
</tr>
<tr>
<td>Sensitivity D-dimer</td>
<td>98%</td>
<td>100–90%</td>
<td>Increase 0.085% with every 2% decrease in sensitivity (0.83–1.25%)</td>
<td>Increasing costs-savings with decreasing sensitivity (7–10% costs-savings)</td>
<td>Virtually unchanged (29% reduction)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>30%</td>
<td>20–50%</td>
<td>Increase (0.66–1.44%) with increasing prevalence</td>
<td>Less costs-savings with increasing prevalence (10–3% costs-savings)</td>
<td>Decreasing reduction with increasing prevalence (37–24% reduction)</td>
</tr>
<tr>
<td>Sensitivity angiography</td>
<td>98%</td>
<td>90–100%</td>
<td>Decrease (1.06–0.88%) with increasing sensitivity</td>
<td>Unchanged (8% costs-savings)</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Specificity angiography</td>
<td>96%</td>
<td>90–100%</td>
<td>Unchanged (0.92%)</td>
<td>Less costs-savings (9–7%) with increasing specificity</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Haemorrhagic complications</td>
<td>1.25%</td>
<td>0.5–5%</td>
<td>Increase (0.84–1.16%) with increasing incidence</td>
<td>Not calculated</td>
<td>Not calculated</td>
</tr>
</tbody>
</table>

* Base-line values for strategy without D-dimer test: mortality 0.87%, costs 1265 ECU, angiography rate 61.8%.
† Morbidity always less in strategy employing D-dimer than in strategy without D-dimer.

The results of the sensitivity analysis, which varied each of our assumptions, are described in Table IV. With decreasing specificity for the D-dimer test, mortality is virtually unaffected, whereas costs-savings are rapidly decreasing and the angiography rate returns to the 60–70% required in strategies which do not apply D-dimer (Table III). The influence of the sensitivity of the D-dimer assay on mortality is high: for every 2% reduction in sensitivity, mortality increases by approximately one per 1000 investigated patients, but extra costs-savings are marginal and the angiography rate is not further reduced as compared to the angiography rate with a D-dimer sensitivity of 100%. Finally, changes in the prevalence of pulmonary embolism do not substantially affect the outcomes of the present analysis.

The sensitivity and specificity of pulmonary angiography have little influence on the outcome of the analysis. However, increasing haemorrhagic complications result in an increasing mortality of 0.7% for every 1% increase in bleeding complications.

DISCUSSION

The use of blood tests, such as plasma D-dimer methods, in the diagnosis of pulmonary embolism may have several advantages, such as its non-invasive nature, relatively low cost, and ease of use. Ideally, the proper evaluation of any diagnostic test, including the D-dimer assay, should involve three consecutive steps (Sackett et al, 1985; Böllner et al, 1991). First, the technical aspects of the various D-dimer assays, such as intra- and inter-assay variability and the definition of normal and abnormal values, should be determined. The second step involves testing the accuracy of the D-dimer assay in a blind fashion in consecutive patients with or without a specific disease. Finally, clinical utility and validity should be ascertained.

We previously addressed the first step, and showed that the more accurate but laborious ELISA plasma D-dimer methods are preferred (van Beek et al, 1993). The results of the present investigation clearly demonstrate that D-dimer assays should only be used in excluding pulmonary embolism. Furthermore, it is shown that the highest clinical utility of this assay lies in excluding outpatients, where it may be used either as a screening test or following perfusion-ventilation lung scintigraphy.

It should be noted that, in order to make the D-dimer assay a reliable tool in the diagnostic work-up of patients with clinically suspected pulmonary embolism, one must use a cut-off value which results in virtually no patients with pulmonary embolism going unnoticed; hence, a sensitivity and negative predictive value approaching 100%. Acceptance of sensitivity < 100% (Harrison et al, 1993; Goldhaber et al, 1993) may have serious adverse effects, as shown in our sensitivity analysis. It was calculated that one per 1000 evaluated patients with clinically suspected pulmonary embolism would die for every 2% decrease in sensitivity. Hence, in the present phase of evaluation of D-dimer assays standards need to be set high, because in subsequent application in clinical practice accuracy indices tend to be slightly lower.

Our analysis indicates that the D-dimer method was virtually unable to exclude pulmonary embolism in inpatients. This could in part be explained by the fact that pulmonary embolism was diagnosed in 35% of outpatients and in 49% of inpatients, resulting in relatively fewer patients with possible normal D-dimer values in inpatients. Furthermore, comorbid conditions were present in 87% of inpatients and only 25% of outpatients (P < 0.001), which further reduced the possibility of obtaining a normal D-dimer value in inpatients. These findings of the effects of comorbid conditions and prior admission are in agreement with recent Canadian and Swiss studies (Demers et al, 1992; Raimondi et al, 1993).

The study population consisted of consecutive in- and outpatients with symptoms suggestive for pulmonary embolism and prevalence of proven pulmonary emboli of approximately 40%. When taking into account that lung scan criteria may vary, the distribution of the lung scan findings in normal, high probability and non-high probability categories is in accordance with earlier studies (Hull et al, 1983; PIOPED, 1990; Goldhaber et al, 1993). Therefore we believe that our findings are relevant for all patients with symptomatic pulmonary embolism seen in a teaching hospital.

The place of D-dimer assays in a diagnostic strategy is currently debated (Bounameaux et al, 1991; Harrison et al, 1993; Perrier et al, 1994; Quinn et al, 1994). In our decision-analytic model there did not appear to be a substantial difference between using D-dimer assays as an initial screening test or after an abnormal lung scan result has been obtained. In both applications of the D-dimer test a moderate cost-reduction of 10% was observed. This is largely the result of a reduced requirement to perform angiography and depends significantly on the specificity of the ELISA method used. If the specificity of the assay decreases below 20–25% this beneficial effect on the angiography rate and costs disappears. The observed difference between the various ELISA methods illustrates the risk of extrapolating the findings with one method to other assays.

Although not analysed in this study, the time required to perform the D-dimer assay may be another factor in deciding the optimal place. When performed as a first test, a time delay for further testing of several hours may be incurred. On the other hand, when the test is performed later, this delay is less likely to be important. In clinical practice virtually all symptomatic patients will be treated with anticoagulants pending a definitive diagnosis. Since the outcome of using D-dimer as an initial test is similar to its use following lung scintigraphy, it is probably best to use the test in patients with abnormal lung scan findings.

The institution of heparin therapy could influence plasma D-dimer levels. A previous study showed that minimal changes will not have a significant effect within the first 24 h. However, since more definitive data on this important issue are lacking, the plasma samples should preferably be obtained before heparinization takes place.

The cut-off values for a sensitivity of 100% clearly determine the specificity and consequently the number of patients in whom pulmonary embolism could be adequately
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cluded. One could argue that one patient could thus negatively influence the results in our series. However, the cut-off values never relied on a single low value. In patients with proven pulmonary embolism, several patients had lower D-dimer plasma concentrations which led to the determination of the appropriate cut-off values.

Finally, the present decision-analytic model does not take the prior probability of disease into account. Several reports have suggested that the use of this information (in combination with the D-dimer test result) may further improve clinical management (Stein et al., 1993a; Patil et al., 1993; Perrier et al., 1994).

In conclusion, the observations in this study suggest that the use of studied D-dimer assays in patients with clinically suspected pulmonary embolism should be limited to outpatients, where the application appears cost-effective. Moreover, it appears that the tests should be used following lung scintigraphy. We believe that a sensitivity approaching 100% must be maintained in order to guarantee safe practice in the adequate exclusion of pulmonary embolism. This practice, however, needs to be confirmed in carefully designed management studies.

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