Management of venous thromboembolism. Etiology, diagnosis, prognosis and treatment

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Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study

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On behalf of the Antelope study group

Clinicians often deviate from the recommended algorithm for the diagnosis of pulmonary embolism (PE) consisting of ventilation-perfusion scintigraphy and pulmonary angiography. We assessed the safety of a new diagnostic algorithm which reduces the need for lung scintigraphy and avoids the use of angiography. Between May 1999 and April 2001, patients with a clinical suspicion of PE were prospectively investigated according to an algorithm in which the diagnosis of PE was excluded after a low clinical probability estimate and a normal D-dimer test result, a normal perfusion scintigraphy result, or a non-high probability scintigraphy result in combination with normal serial ultrasonography of the legs. In these patients anticoagulant treatment was withheld and they were followed-up for 3 months to record possible thromboembolic events. The primary outcome measure was the incidence of objectively confirmed thromboembolic events during follow-up in patients in whom the diagnosis of PE was considered to be excluded. A total of 631 patients were included. The diagnosis was refuted on the basis of a low clinical probability estimate and a normal D-dimer test result in 95 patients, normal perfusion scintigraphy in 161 and non-high probability lung scintigraphy followed by normal serial ultrasonography in 210 patients. Of these 466 patients, VTE complications during follow-up occurred in 6 (complication rate 1.3%, 95% CI: 0.5%-2.8%). In conclusion, the diagnosis of PE can be safely ruled out by a non-invasive algorithm consisting of D-dimer testing combined with a clinical probability estimate, lung scintigraphy, or serial ultrasonography of the legs (in case of non-diagnostic lung scintigraphy).
Although consensus statements have been formulated with regard to the optimal diagnostic approach in patients presenting with clinically suspected pulmonary embolism, surveys revealed that clinicians often deviate from the recommended algorithms. Most strategies encompass ventilation-perfusion scintigraphy followed by pulmonary angiography in case of a non-diagnostic result. The reasons for deviation include the often non-daily availability of ventilation scintigraphy (because of the short half-life and high costs of Krypton-81m) and the high proportion of non-diagnostic test results (40%-60% of all patients with suspected pulmonary embolism). Pulmonary angiography is also frequently omitted because of the invasive nature and perceived risks. As a consequence, physicians often fail to proceed with diagnostic testing but rather rely on their clinical judgment for treatment decisions, resulting in both over- and undertreatment. To improve this situation, more simple, easy to perform and reliable tests are needed.

Recently, apart from helical computed tomography, three non-invasive methods have emerged, i.e. D-dimer blood test, clinical probability estimates and serial ultrasonography of the legs. D-dimers are degradation products of cross-linked fibrin, which are elevated in the presence of thrombosis. The D-dimer test is best suitable as a method to rule out pulmonary embolism, when normal. The clinical probability estimate, based on information from the history and physical examination, can be assessed by either a formal numerical model or an informed intuitive estimate. This test in combination with other diagnostic modalities allows stratification for the likelihood of pulmonary embolism. Finally, serial leg testing performed over a period of 7-14 days in patients with a non-diagnostic ventilation-perfusion scintigram has been evaluated based on the concept that if (extending) deep vein thrombosis can be excluded, it is safe to withhold anticoagulants.

We designed an algorithm, which takes advantage of these three methods and obviates the need for angiography. Therefore, in consecutive patients with suspected pulmonary embolism, the combination of a normal D-dimer and a low clinical probability estimate was used as the first method to exclude pulmonary embolism. Subsequently, the remaining patients underwent lung scintigraphy and if non-diagnostic, serial ultrasonography of the legs was performed. We assessed the safety, feasibility and clinical acceptance of this approach.

Methods
Patients
This study was performed in three teaching hospitals in Amsterdam, The Netherlands, between May 1999 and April 2001 (Academic Medical Center, Vrije Universiteit Medical Center and Slotervaart Hospital). Consecutive in- and outpatients with a clinical suspicion of acute pulmonary
embolism were eligible. Patients were excluded if they had received vitamin K antagonists or heparin in a therapeutic dose for more than 24 hours, had already undergone objective testing for venous thromboembolism, were pregnant, were younger than 18 years of age, had an indication for thrombolysis, or if written informed consent could not be obtained. The study protocol was approved by the Institutional Review Boards.

Study design
Upon referral, the attending physician estimated the probability of pulmonary embolism bases on information from the medical history, physical examination and if available, chest X-ray, ECG and bloodgas analysis. He was asked to choose one of the following probability categories: <20%, 20-50%, 51-80 or >80%. The performance of this informed intuitive clinical probability estimate had been validated in the same study centres and yielded comparable predictive values as the clinical decision models 13. Subsequently, blood was drawn for D-dimer testing. If the probability of pulmonary embolism was less than 20% and the D-dimer normal, pulmonary embolism was excluded and anticoagulant therapy withheld. In all other cases, lung scintigraphy was performed. If normal, pulmonary embolism was ruled out and anticoagulant treatment was not instituted (or stopped).

After a high probability lung scan, anticoagulants were started or continued. If lung scintigraphy was non-diagnostic, serial leg ultrasonography was done on days 1, 3 or 4 and 7. Anticoagulant therapy was only instituted if ultrasonography was abnormal. All patients were followed for three months to record possible subsequent thromboembolic events. Each patient was contacted by telephone after 6 weeks and scheduled for a hospital visit after three months. Objective testing was performed in case of suspected thrombosis to confirm or refute the disease as described previously 14. An independent and blinded committee adjudicated all clinical events which occurred during follow-up (i.e. deaths and suspected episodes of venous thromboembolism).

Diagnostic Methods
A quantitative rapid immunoturbidimetric D-dimer assay was used (Tinaquant D-dimer, Roche Diagnostica, Mannheim, Germany) using a Hitachi system (Hitachi 912, Roche Diagnostica, Mannheim, Germany). The cut-off value was 0.5 microgram per millilitre.

Six-view perfusion lung scintigraphy was performed using 50-100MBq of 99mTc-Technetium-labeled macroaggregates of albumin, whereas 85Kr Krypton gas was employed for ventilation scintigraphy. Scans were interpreted using a lung segment reference chart 14 and reported as normal (no perfusion defects), high probability (at least one ventilation-perfusion mismatch of more than 75% of a segment), or non-diagnostic (defects not qualifying for high probability) 15.
Compression ultrasonography was performed and interpreted as described previously. The outcomes were categorised as normal or abnormal (i.e. non-compressible).

Outcomes

The primary (safety) outcome measurement was the incidence of clinically overt and objectively confirmed thromboembolic events during 3 months of follow-up in patients in whom the diagnosis of pulmonary embolism was considered to be excluded (i.e. patients with 1) a clinical probability estimate < 20% and a normal D-dimer; 2) normal perfusion scintigraphy and 3) non-high ventilation-perfusion scintigraphy and normal serial ultrasonography of the legs). Thromboembolic complication rates were also calculated separately for these three patient subgroups.

All deaths were classified by the adjudication committee using clinical reports of treating and/or family physicians and, if available, autopsy reports. Death was attributed to pulmonary embolism (i.e. confirmed by objective testing as well as cases in which embolism could not be ruled out as the possible contributing factor); other cardiovascular diseases; malignancy; or other causes.

The secondary outcomes were feasibility, clinical acceptance and duration of diagnostic process. Feasibility was defined as the proportion of patients who completed the diagnostic protocol without deviations. Protocol deviations occurred when the attending physicians overruled the protocol (e.g. performed angiography), when not all algorithm investigations were completed (e.g. not all repeat ultrasonograms) and when a clear alternative diagnosis emerged explaining the patients symptoms.

Clinical acceptance, although part of the feasibility outcome, was assessed separately as the proportion of patients in whom the protocol was violated because the attending physician felt uncomfortable with proceeding the investigations as planned. The duration of the diagnostic process was defined as the time interval between referral and the definitive diagnosis at presentation.

Statistical Analysis

Based on an expected incidence of complications of 1% and the need to exclude with 95% confidence (power 80%) that this incidence could be higher than 3%, 600 patients had to be recruited in the study (disease prevalence 25%). Exact 95% confidence intervals were calculated from the binomial distribution (SPSS Inc., Cary, NC, version 10.0 and CIA, version 1.0).

Results

During the study period, 923 consecutive patients with suspected pulmonary embolism were seen. Of these, 292 patients (32%) were excluded for the following reasons: anticoagulant treatment for more than 24 hours (82); prior objective diagnostic testing for pulmonary embolism (39); pregnancy
or age under 18 years (17); thrombolysis (3) and no informed consent (151). The latter group included patients who refused to participate, or who were unable to give consent because of a language barrier, mental disorders or being on a ventilator. Hence, the study population consisted of 631 patients, all of whom were followed-up for 3 months. The clinical and demographic characteristics of these patients are shown in Table 1. The clinical probability estimate was recorded in 627 patients (99%), and was less than 20% in 156 patients (25%), between 20% and 50% in 309 patients (49%), between 50% and 80% in 119 patients (19%) and more than 80% in the remaining 43 patients (7%). Of those patients for whom the chance of PE was estimated as <20%, 8% (95% CI: 5%-14%) eventually appeared to have pulmonary embolism. The prevalence of pulmonary embolism in the other probability categories was: 20%-50%: 15% (95% CI: 11%-19%); 50%-80%: 29% (95% CI: 21%-37%) and >80%: 67% (95% CI: 52%-81%). D-dimer results were available for 519 patients (82%); the test result was normal in 210 patients (40%).

Table 1. Baseline clinical and demographic characteristics of the 631 study patients with clinically suspected pulmonary embolism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>378 (60%)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>53 (18-94)</td>
</tr>
<tr>
<td>Outpatients, n (%)</td>
<td>413 (65%)</td>
</tr>
<tr>
<td>Median time since onset of symptoms, days (interquartile range)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td>Symptoms of DVT, n (%)</td>
<td>66 (10%)</td>
</tr>
<tr>
<td>Malignancy, n (%)</td>
<td>93 (15%)</td>
</tr>
<tr>
<td>Previous VTE, n (%)</td>
<td>74 (12%)</td>
</tr>
<tr>
<td>Immobilisation in past 4 weeks, n (%)</td>
<td>67 (11%)</td>
</tr>
<tr>
<td>Surgery in past 3 months, n (%)</td>
<td>108 (17%)</td>
</tr>
<tr>
<td>VTE in first degree relatives, n (%)</td>
<td>53 (8%)</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis, VTE = venous thromboembolism

Primary study outcome

Figure 1 details the outcomes of the diagnostic algorithm. In the 466 patients with clinically suspected venous thromboembolism in whom the diagnosis was excluded on the basis of a low clinical probability and normal D-dimer; a normal perfusion scan; or a non-diagnostic scintigram in combination with normal serial ultrasonography of the legs, venous thromboembolic complications occurred during 3-month follow-up in 1.3% (6 patients; 95% confidence interval [CI]: 0.5%-2.8%). Of all patients, 15% (95 patients) had the combination of a low clinical probability estimate and
non-invasive diagnostic work-up for suspected pulmonary embolism

**Figure 1.** VTE = venous thromboembolism, PE = pulmonary embolism, CUS = compression ultrasonography

normal D-dimer test result (84 were outpatients). During follow-up, 6 patients returned with symptoms suggestive of venous thromboembolism, but in all thrombosis was ruled out. The thromboembolic complication rate in this subgroup was therefore 0% (95% CI: 0%-3.8%). Of the remaining 536
patients, 161 had a normal perfusion scan. During follow-up there were 3 cases of suspected thrombosis which were all refuted by objective testing (venous thromboembolic complication rate 0%, 95% CI: 0%-2.3%). Of the 273 patients with a non-diagnostic lung scan, 224 underwent serial ultrasonography (in 49 patients the study protocol was violated, see for details later). Of the 210 patients with a non-diagnostic lung scan and normal serial ultrasonograms, 13 presented within the 3-month follow-up period with suspected thromboembolism, which was confirmed in 6 (complication rate 2.9%, 95% CI: 1.1%-6.1%). One of these patients died of end stage cancer with malignant pleural effusion in whom pulmonary embolism could not be ruled out, while 3 and 2 patients had an episode of symptomatic deep venous thrombosis and pulmonary embolism, respectively (Table 2).

Table 2. Details about the symptomatic venous thromboembolic complications during 3-months of follow-up in patients in whom the presence of pulmonary embolism was initially excluded

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Type of VTE complication</th>
<th>Time since initial investigation</th>
<th>Underlying disease</th>
<th>Findings at initial investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PI (fatal)</td>
<td>1 month</td>
<td>Oral cavity carcinoma with malignant pleural effusion and rib metastasis</td>
<td>CPI: 20-50% D-dimer: abnormal</td>
</tr>
<tr>
<td>2</td>
<td>DVT</td>
<td>2.5 month</td>
<td>Brain metastasis with unknown primary tumour</td>
<td>CPI: 20-50% D-dimer: abnormal</td>
</tr>
<tr>
<td>3</td>
<td>DVT</td>
<td>1.5 month</td>
<td>Renal insufficiency due to nephrosclerosis and amyloidosis</td>
<td>CPI: 50-80% D-dimer: abnormal</td>
</tr>
<tr>
<td>4</td>
<td>DVT</td>
<td>1.5 month</td>
<td>Sigmoid resection because of perforated diverticulitis</td>
<td>CPI: 50-80% D-dimer: abnormal</td>
</tr>
<tr>
<td>5</td>
<td>PI</td>
<td>3.5 weeks</td>
<td>Thrombophilia (factor V Leiden mutation)</td>
<td>CPI: 20-50% D-dimer: abnormal</td>
</tr>
<tr>
<td>6</td>
<td>PI</td>
<td>2 weeks</td>
<td>Non-small cell lung carcinoma</td>
<td>CPI: 20-50% D-dimer: abnormal</td>
</tr>
</tbody>
</table>

CPI: clinical probability estimate

Other diagnostic findings

A high probability ventilation-perfusion scan was obtained in 99 patients (Figure 1). Of the 224 patients with a non-diagnostic scintigraphy result, (serial) ultrasonography of the legs was abnormal in 14 patients (6%), with the great majority at referral (Figure 1). Thus, the prevalence of pulmonary embolism in those who completed the diagnostic algorithm was 20% (113 patients).

The diagnostic management was not completed according to protocol in 52 patients (8%). The main reason was incomplete serial ultrasonography in the patients with a non-diagnostic lung scan (36
patients). Thirteen did undergo ultrasonography on days 1 and 3 or 4, but not on day 7 (in all both tests were normal); in 14 patients it was performed only on day 1 (again all were normal), while in 9 patients serial ultrasonography was not done at all. None of these patients received anticoagulant treatment. During 3 months of clinical follow-up there was one unexplained sudden death (5 weeks after initial presentation) among these 36 patients. In this patient serial ultrasonography was performed on days 1 and 4 (which were normal), whereas a ventilation-perfusion scan performed shortly thereafter showed improvement. In 14 other cases the attending physician overruled the protocol. In 11 patients angiography was performed because of reluctance to proceed with ultrasonography (2 were abnormal), while in 3 patients an alternative diagnosis was obtained prior to lung scanning, which explained the chest symptoms (liver abscess, subcapsular liver bleed and abdominal aneurysm). One of the patients with a normal angiogram returned with suspected deep venous thrombosis after 10 days, which was confirmed by ultrasonography. Finally, the protocol was violated in the remaining 2 patients in whom anticoagulant therapy was instituted because of documented extensive superficial thrombophlebitis and arm vein thrombosis. Taken conservatively, the frequency of pulmonary embolism at presentation in this group in whom the protocol was not completed was 4 out of 52 patients (8%).

Secondary outcomes

Feasibility, clinical acceptance and time interval

In 92% of all 631 study patients with suspected pulmonary embolism the protocol could be entirely completed. For 5 of the 52 patients a good reason existed to deviate from the algorithm, i.e. an alternative diagnosis (3) and anticoagulant treatment was inevitable because of another manifestation of thrombosis (2). In 36 patients serial ultrasonography was not completed mainly because of non-compliance of the patients to return to the study center. Hence, in strict sense, the attending physician felt uncomfortable with proceeding the investigations as planned in 11 of the 631 study patients (1.7%, or clinical acceptance 98.3%). In the great majority of patients the investigations could be completed within 6 hours (Table 3). The clinical probability estimate, D-dimer test and scintigraphy were usually performed 1-2 hours after presentation.

Table 3. Time between referral and definite diagnosis

<table>
<thead>
<tr>
<th>Basis for diagnosis</th>
<th>Median time interval, hours (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low probability-normal D-dimer</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>Normal perfusion scintigraphy</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>High probability scintigraphy</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Non-high probability and first CUS</td>
<td>5 (2-24)</td>
</tr>
</tbody>
</table>

CUS=compression ultrasonography
Discussion

This study shows that a non-invasive diagnostic algorithm, which reduces the need for lung scintigraphy and completely avoids pulmonary angiography, is a safe, efficient and attractive diagnostic approach in the management of patients with suspected pulmonary embolism. The overall observed 3-month thromboembolic complication rate (1.3%, 95% CI: 0.5%-2.8%) in patients in whom the algorithm excluded pulmonary embolism (i.e., a normal D-dimer test result in combination with a low clinical probability; normal perfusion scintigraphy and non-high probability scintigraphy followed by normal serial ultrasonography of the legs) is similar to other generally accepted exclusion strategies. The use of D-dimer testing in combination with clinical probability obviates further diagnostic testing in approximately 15% of all referred patients. Finally, the studied algorithm is well accepted among clinicians with a low rate of protocol violations and could generally be performed within half a day.

Conventional methods to exclude pulmonary embolism which have been properly investigated, include pulmonary angiography and perfusion scintigraphy. The single prospective clinical outcome study in 480 consecutive patients with a normal angiogram in whom anticoagulant therapy was withheld showed a 3-month venous thromboembolic complication rate of 0.8% (95% CI: 0.2%-2.1%) 

Four studies evaluated the venous thromboembolic complication rate after normal perfusion scintigraphy. Of the 347 patients, 4 developed thromboembolic complications during at least 3 months of follow-up (1.2%, 95% CI: 0.3%-2.9%). Thus, the overall rate of 1.3% of subsequent symptomatic thromboembolic events in patients in whom our algorithm initially excluded pulmonary embolism, compares well with these traditional diagnostic modalities to rule out the disease.

Three aspects of our study findings require comment. The absence of venous thromboembolism during follow-up in patients with a normal D-dimer test result and low clinical probability adds to the growing evidence that this seems a simple, reliable and easy to perform diagnostic method to exclude venous thromboembolic disease. Thusfar, only one clinical outcome study has validated the safety of this strategy in patients presenting with suspected pulmonary embolism 

Wells and colleagues followed 437 outpatients with this combination and only one returned with a proven new episode of pulmonary embolism (3-month failure rate 0.2%, upper limit 95% CI: 1.3%). However, their study population is probably different from ours, as illustrated by the prevalence of pulmonary embolism at presentation (9% in the Canadian versus 20% in the present study) and the proportion of patients with a normal D-dimer and low clinical probability (46% versus 15%, respectively).

Secondly, the current recommendation is to perform pulmonary angiography after a non-high lung scan. Although this is a well validated approach, there exists great reluctance among clinicians to order angiography 

In the present study we used serial compression ultrasonography of the legs
performed at presentation and after 4 and 7 days to replace pulmonary angiography. The 3-month thromboembolic complication rate in patients with a non-diagnostic lung scan and normal serial ultrasonography was 2.9% (95% CI: 1.1%-6.1%). This failure rate appears higher as compared with the frequency of complications of leg testing reported by Hull et al. (1.9%, 95% CI: 0.8%-3.0%) and Wells and co-workers (0.5%, 95% CI: 0.1%-1.3%). It should be noticed however, that in these studies only patients with an adequate cardiorespiratory reserve or those with a low or moderate pretest probability were included, respectively. It is tempting to speculate that this might explain the difference in complication rates observed. However, there are two possible interpretations: our rate is indeed too high for all patients with a non-high ventilation-perfusion scan result and exclusion of certain patient categories is appropriate or this rate is acceptable and falls within the confidence intervals of the previous studies. We believe that the first interpretation is less likely, since the majority of our patients who returned with thromboembolic complications had a low to moderate clinical probability at presentation (Table 2).

Finally, a total of 52 patients (8% of the original cohort) did not complete the diagnostic algorithm. The main reasons were non-completion of ultrasonography (36 patients) and the performance of pulmonary angiography instead of serial ultrasonography, as requested by the attending physician (11 patients). The overall prevalence of venous thromboembolism in these 52 patients was 8%. Given this low figure, it is unlikely that these violations have biased our study findings. Therefore, we expect that our conclusions are valid for all patients presenting with clinically suspected pulmonary embolism and that the algorithm is generally well accepted by clinicians.

The present study did not evaluate newer imaging techniques such as helical computed tomography (CT), and magnetic resonance angiography (MRA). Although it is quite likely that in particular helical CT may become an important diagnostic tool in this setting, only limited data are at present available which suggest that this technique is safe in excluding pulmonary embolism when negative.

In conclusion, the non-invasive diagnostic algorithm evaluated appears a safe and attractive alternative to the current diagnostic strategy for pulmonary embolism.

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Appendix

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The Independent Blinded Adjudication Committee consisted of M. H. Prins (Chair), M. M. W. Koopman, S. Middeldorp and M. V. Huisman

Datamanagement was executed under the responsibility of the Department of Clinical Epidemiology and Biostatistics (A. Koolma, R. A. M. Breet)

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