

## Deferral of assessment of pulmonary embolism

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### ABSTRACT

We evaluated a simplified algorithm for safely postponing diagnostic imaging for pulmonary embolism (PE). At the index visit, patients were identified as being at *high* or *low* risk of PE; the former received full dosage low molecular weight heparin while the latter were left untreated until performance of diagnostic imaging (max 72 hours). During this period, no thromboembolic events occurred in low-risk patients (0/211, 0.0% [upper 95% CI 0.9%]); only one event occurred in those at high-risk (1/125, 0.8% [upper 95% CI, 1.2]). Our study demonstrates that diagnostic imaging for PE can be safely deferred for up to 3 days.

Key words: pulmonary embolism, deferred tests, pretest clinical probability, D-dimer, low-molecular weight heparin

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Pulmonary embolism (PE) is a relatively common and potentially fatal condition that requires detection by appropriate and sensitive imaging.<sup>1-3</sup> When such imaging cannot be performed immediately (for example, in cases referred during the night or week-end or in poorly equipped institutions), physicians must decide whether to treat incompletely assessed patients or to hospitalize them until the imaging can be performed. Often, empirical protective anticoagulation with low molecular weight heparins (LMWH) is given to patients<sup>2,6</sup> but, critically, no clear-cut information is available about the need for such anticoagulation, its dosage and duration, or the time over which deferral of diagnostic procedures can be considered as safe. To provide information on these issues, we conducted a prospective clinical trial aimed at evaluating whether the use of a simplified algorithm can allow the diagnosis of PE to be safely delayed for up to 72 hours.

immediately performed were considered eligible for the study. Exclusion criteria were: (i) life-threatening conditions (i.e. hemodynamically unstable PE) or serious co-morbidities that required immediate hospitalization; (ii) relapse of a previously documented PE; (iii) current use of oral anti-coagulant therapy; (iv) history of bleeding or any other contraindication to heparin; (v) age younger than 18 years; (vi) life expectancy of less than 3 months; (vii) refusal to give informed consent.

### Intervention

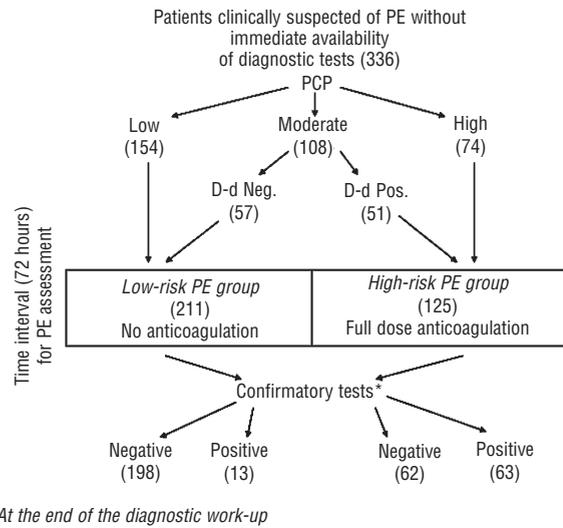
Patients were managed according to the protocol shown in Figure 1. At the index visit, the pretest clinical probability (PCP) of PE was assessed first, using Wells' score,<sup>4</sup> followed by a D-dimer assay.<sup>5,6</sup>

The risk of PE was then assessed: patients at *low-risk* (those with a low PCP or moderate PCP with a negative D-dimer test result) were discharged without anticoagulant therapy; patients at *high risk* (those with a moderate PCP and a positive D-dimer test or those with a high PCP) received therapeutic doses of LMWH; on-call emergency physicians had the option to hospitalize these patients. All patients underwent diagnostic imaging within 72 hours of the index visit.

### Design and Methods

#### Patients

Consecutive out-patients, presenting at the Emergency Department with suspected PE and in whom imaging could not be



**Figure 1.** PE: pulmonary embolism; PCP: pretest clinical probability; D-d neg: D-dimer negative result; D-d pos: D-dimer positive result.

### Diagnosis of pulmonary embolism

The presence or absence of PE was assessed as previously described;<sup>4-6</sup> briefly, all patients underwent ventilation-perfusion (V/Q) lung scanning or spiral computed tomography (CT) scanning (single- or multi-slice) within 72 hours of referral. Diagnostic tests were interpreted according to established criteria.<sup>3,7,8</sup> In cases of confirmed PE, patients received full-dose of anticoagulation. A semi-quantitative latex D-dimer assay (Dimertest®, Dade Behring, Deerfield, IL, USA) was used. The test was considered normal when values were < 200 ng/mL.<sup>9</sup> All diagnostic tests were performed by staff unaware of the results of the other investigations and interventions.

### Follow-up

Patients were monitored over the short-term and the long-term. Short-term follow-up was defined as the time between patient referral (index visit) and the completion of the diagnostic procedures (≤72 hours). During this period, patients were immediately re-evaluated in case of: (i) worsening respiratory symptoms; (ii) signs and symptoms suggestive of the development of venous thrombosis (DVT) of the legs; (iii) major and minor bleeding; and (iv) any other symptoms related to venous thromboembolism (VTE). The long-term follow-up (3 months) was used to record the incidence of PE in those patients in whom VTE had previously been ruled out. Patients were evaluated at the clinic or contacted by telephone. At any time during the follow-up, patients underwent objective testing in the case of signs or symptoms suggestive of recurrent VTE.

**Table 1.** Patients' characteristics.

Baseline features	Low-risk group (n=211)	High-risk group (n=125)	p value
Age in years (range)	59.3 (22-91)	60.3 (23-91)	n.s.
Sex (female/male)	98/113	59/66	n.s.
Time since onset of symptoms (days)	1.7	1.5	n.s.
Co-morbidity and cancer (%)	16 (7.5)	25 (19.2)	0.03
Median time of deferral of test (hours)	49.5	42.5	n.s.
Median time of protective anticoagulation (hours)	—	35.5	—

n.s.: not significant.

### Statistical analysis

Before initiating the study, we estimated that the primary event rate (PE and major bleeding) during the short-term follow-up would be less than 2%. We planned to include a sufficient number of patients to ensure that the upper limits of the 95% confidence intervals (CI) were less than 2.5%. This required a projected sample size of at least 300 patients.

The proportion of patients who developed VTE in each PCP group was determined as was the rate of occurrence of any thromboembolic event during the short- or long-term follow-up; related approximated 95% CI based on binomial distribution were calculated. Paired *t* tests and Pearson's  $\chi^2$  tests were used. A two-tailed *p* value <0.05 was considered statistically significant. All patients gave informed consent to their participation in the study, which was approved by the ethics review board of the University of Palermo.

## Results and Discussion

### Patients

Of 412 consecutive patients evaluated from January 1999 to December 2003, 76 were excluded from the study for the following reasons: life-threatening conditions or serious co-morbidities (n=28), concomitant use of oral anticoagulation (n=12), untested for D-dimer (n=11), no V/Q or CT lung scanning (n=14), history of objectively documented VTE (n=4) and refusal of informed consent (n=7). In total, 336 patients proved eligible for study entry. Table 1 shows the clinical characteristics of the 336 patients studied. Of these 211 (62.7%) were classified as being at low-risk and 125 (37.2%) as being at high-risk (Figure 1).

### Prevalence of pulmonary embolism

The prevalence of PE (determined at the time of imaging) was 6.1% ([13/211] 95% CI 2.7-9.3) in the low-risk group and 50.4% ([63/125] 95% CI 41.7-59.1) in the high-risk group. Overall, PE was confirmed in 76 (22.6%) of the 336 patients (95% CI 18.2-27) (Table 2).

### Short-term outcome

Tests were deferred for a median of 49 hours for patients considered as being at low-risk and for a median of 42.5 hours for those categorized as at high-risk. The median duration of LMWH treatment was 35.5 hours (Table 2). The patients' compliance was excellent; only four patients (1.2%) failed to conduct the course of LMWH. During the short-term follow-up, no thromboembolic events occurred in patients classified as being at low-risk of PE (0/211, 0.0% [upper 95% CI 0.9%]). In those considered at high-risk, one patient only had a worsening of symptoms; he underwent V/Q pulmonary scanning that showed a sub-segmental PE. None of the patients developed bleeding complications and none was lost to follow-up (Table 2).

### Long-term outcome and rate of hospitalization

Two hundred and sixty patients did not have PE at the time of imaging. No events occurred in patients at low-risk. Three patients at high-risk developed symptomatic VTE (Table 2). Two of them, with a previously negative V/Q scan, developed symptomatic DVT (on days 42 and 83). The other patient developed PE on day 53. Two patients with cancer died (10.5%) of complications. Neither of these patients showed symptoms of VTE or bleeding. None of the other patients died or developed bleeding complications; one patient was lost to follow-up (0.3%). The rate of hospitalization was low. During the entire follow-up, 86 (25.5%) patients were admitted to hospital; most of them belonged to the high-risk group (59/125, 47%).

The objective diagnostic assessment of PE requires appropriate imaging. When such resources are not available, the approach can prove highly unsatisfactory. Physicians commonly tend to hospitalize and/or treat patients with empirical anticoagulation irrespective of the actual risk of PE. Recently, it has been demonstrated that the combination of a low PCP and a negative D-dimer test safely rules out PE in symptomatic patients;<sup>10</sup> data from this and similar cohorts of patients were not available at the beginning of our study. However, emergency physicians are reluctant to forego diagnostic imaging (which can also furnish alternative diagnoses) even in patients at low risk of PE. Because of its 24-hour availability in most institutions, CT pulmonary scanning is often used alone as the main diagnostic test. However, its use as first-line imaging for diagnosing acute PE is still controversial, even when spiral detectors are used.<sup>11-14</sup> There is, therefore, the need to produce evi-

**Table 2. Short-term and long-term outcome.**

Categories of patients (n)	Prevalence of VTE at the time of diagnostic imaging n/N (%)	Events during the short-term follow-up n/N (%)	Events during the long-term follow-up n/N (%)
Low-risk group (211)	13/211 (6.1) [95% CI 2.7-9.3]	0/211 (0) [upper 95% CI, 0.9]	0/198 (0) [upper 95% CI, 1.0]
High-risk group (125)	63/125 (50.4) [95% CI 41.7-59.1]	1/125 (0.8) [upper 95% CI, 1.2]	3/62 (4.8) [upper 95% CI, 6.2]
All patients	76/336 (22.6) [95% CI 18.2-27]	1/336 (0.3) [upper 95% CI, 0.8]	3/260 (1.1) [upper 95% CI, 2.3]

CI: confidence intervals. \*This indicates patients in whom pulmonary embolism was excluded at the time of imaging.

dence-based data.

Recently, we have demonstrated that information on the PCP and D-dimer level, and the use of LMWH as a protective anticoagulant, may improve the management of patients clinically suspected of having VTE when objective tests are not available.<sup>15</sup> Our previous study was mainly focused on patients suspected of having DVT (about 80% of the cohort of patients) who are considered at lower risk of complications than are patients with PE.<sup>16</sup>

In the present investigation, we confirmed the safety of this approach in a population of patients suspected of having PE. Compared with the actual standard of giving protective anticoagulation to all patients with suspected PE, irrespective of thrombotic risk, our approach reduced the prescription of anticoagulant treatment to about one third (125/336 of patients), without increasing the patients' risk.

It could be argued that the prevalence of VTE we found in low-risk patients was high enough to warrant the administration of a course of protective anticoagulation, considering the low risk of bleeding connected with a short course of heparin; moreover, our strategy could discourage the decision to send these patients home. This argument is, in principle, a valid one; however, we found that no thrombotic events occurred during the short-term follow-up, which indicates that our approach was safe. This is particularly relevant if one bears in mind that heparin administration is associated with potentially dangerous side effects other than bleeding, such as heparin-induced thrombocytopenia.<sup>17</sup>

Our study also demonstrated that the rate of hospitalization could be consistently reduced; in our population only 25% of patients were admitted to hospital, and mainly because of concomitant other diseases.

In conclusion, this investigation demonstrated that a simple approach can allow safe deferral of imaging, thus permitting the planning of appropriate and sensitive diagnostic tests.

**Authors' Contributions**

SS was responsible for the conception and the design of the study, data handling and writing the manuscript. He also performed the statistical analysis. GM, AM, FF, AG, FP and RA contributed to the design of the study data handling and writing the manuscript. LLC was responsible for the laboratory analysis procedures. MCB, EM and MAB contributed to the collection of clinical data. GM also contributed to the revision of the paper. The order of the names of the authors reflects the time, work and scientific contribution of each of the authors.

**Conflict of Interest**

The authors reported no potential conflicts of interest.

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