Diagnosing Pulmonary Embolism in Outpatients with Clinical Assessment, D-Dimer Measurement, Venous Ultrasound, and Helical Computed Tomography: A Multicenter Management Study

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PURPOSE: To evaluate a diagnostic strategy for pulmonary embolism that combined clinical assessment, plasma D-dimer measurement, lower limb venous ultrasonography, and helical computed tomography (CT).

METHODS: A cohort of 965 consecutive patients presenting to the emergency departments of three general and teaching hospitals with clinically suspected pulmonary embolism underwent sequential noninvasive testing. Clinical probability was assessed by a prediction rule combined with implicit judgment. All patients were followed for 3 months.

RESULTS: A normal D-dimer level (<500 μg/L by a rapid enzyme-linked immunosorbent assay) ruled out venous thromboembolism in 280 patients (29%), and finding a deep vein thrombosis by ultrasonography established the diagnosis in 92 patients (9.5%). Helical CT was required in only 593 patients (61%) and showed pulmonary embolism in 124 patients (12.8%). Pulmonary embolism was considered ruled out in the 450 patients (46.6%) with a negative ultrasound and CT scan and a low-to-intermediate clinical probability. The 8 patients with a negative ultrasound and CT scan despite a high clinical probability proceeded to pulmonary angiography (positive: 2; negative: 6). Helical CT was inconclusive in 11 patients (pulmonary embolism: 4; no pulmonary embolism: 7). The overall prevalence of pulmonary embolism was 23%. Patients classified as not having pulmonary embolism were not anticoagulated during follow-up and had a 3-month thromboembolic risk of 1.0% (95% confidence interval: 0.5% to 2.1%).

CONCLUSION: A noninvasive diagnostic strategy combining clinical assessment, D-dimer measurement, ultrasonography, and helical CT yielded a diagnosis in 99% of outpatients suspected of pulmonary embolism, and appeared to be safe, provided that CT was combined with ultrasonography to rule out the disease. **Am J Med. 2004;116:291–299.** ©2004 by Excerpta Medica Inc.

In recent years, extensive research has been devoted to developing noninvasive (1–4) and cost-effective (5,6) diagnostic strategies for pulmonary embolism, considering that angiography is costly and invasive. Moreover, even patients discharged without anticoagulant treatment based on a normal pulmonary angiogram have an approximately 1% 3-month risk of thromboembolic events (7,8).

Plasma D-dimer, a degradation product of cross-linked fibrin, has been studied extensively as a first-line test to rule out pulmonary embolism (1,9–11), but its use is not endorsed universally. Lower limb venous ultrasonography (12) has a low diagnostic yield when performed in patients with a nondiagnostic ventilation/perfusion (V/Q) lung scan or a negative helical computed tomography (CT) scan (13). Nevertheless, when used before other imaging modalities, it shows a proximal deep vein thrombosis in about 10% of patients suspected of pulmonary embolism (1,14). The sensitivity of single-detector helical CT may be as low as 70% (15,16). On the other hand, 15% of patients with clinical symptoms of pulmonary embolism and a negative helical CT scan have a deep vein thrombosis, and combining ultrasonography with CT may reduce the overall rate of false-negative results (16). Finally, the stratification of patients according

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This study was supported by a grant (32-61773.00) from the Swiss National Research Foundation; grants 97/4-T10 and 00/4-T9 from the Royal College of Physicians and Surgeons, Canada; a grant from La Fondation Québécoise pour le Progrès de la Médecine Interne and Les Internistes et Rhumatologues Associés de l'Hôpital du Sacré-Cœur, Montreal, Canada; and grant 2001/021 from the Direction of Clinical Research of the Angers University Hospital.

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Manuscript submitted June 2, 2003, and accepted in revised form September 11, 2003.

to the clinical probability of pulmonary embolism, whether assessed implicitly (1,17) or by a prediction rule (18,19), may reduce the requirement for invasive tests and resource use (1,2).

Therefore, we designed this prospective outcome study to evaluate the efficacy and safety of a diagnostic strategy combining clinical probability assessment, D-dimer measurement, lower limb ultrasonography, and helical CT in a multicenter cohort of unselected emergency department patients.

METHODS

Patients

Data were collected from October 1, 2000, to June 30, 2002, at three medical centers that serve as general or teaching hospitals (Geneva University Hospital, Geneva, Switzerland; University Hospital, Lausanne, Switzerland; and Angers University Hospital, Angers, France). The study was approved by the Ethics Committee of the Department of Medicine, Geneva University Hospital; the Ethics Committee of the Lausanne Medical School; and the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale des Pays de la Loire in Angers.

Consecutive patients presenting to the emergency department were eligible if there was suspicion of pulmonary embolism, defined as acute onset of new or worsening shortness of breath or chest pain without another obvious etiology. Among the 1290 screened patients, 258 patients (20.0%) were excluded according to the following predefined criteria: ongoing anticoagulant treatment for reasons other than venous thromboembolism (n = 43); contraindication to CT scan (known allergy to iodine contrast agents or at risk of allergic reaction) (n = 36); creatinine clearance below 30 mL/min as calculated by the Cockroft formula (n = 53) (20); informed consent impossible due to cognitive impairment (n = 24); patient refusal (n = 57); suspected massive pulmonary embolism with shock (n = 10); pregnancy (n = 9); estimated survival less than 3 months (n = 8); follow-up not possible (n = 11); and other reasons (n = 7). Another 67 patients (5.2%) were excluded because of protocol violations: diagnostic test not performed (D-dimer measurement: n = 1; ultrasonography: n = 21; helical CT: n = 17; pulmonary angiography: n = 17); and final diagnosis established by criteria different from those required by the study (n = 11). The final study sample consisted of 965 patients (75%).

An ancillary study comparing the Geneva prediction rule (19) and the Wells' rule (18) for assessing the clinical probability of pulmonary embolism in a subset of the study sample has been published (21).

Table 1. Prediction Rule for Evaluating the Clinical Probability of Pulmonary Embolism

Variable	Score*
Previous pulmonary embolism or deep vein thrombosis	+2
Heart rate >100 beats per minute	+1
Recent surgery	+3
Age (years)	
60–79	+1
≥80	+2
Pa_{CO_2}	
<4.8 kPa (36 mm Hg)	+2
4.8–5.19 kPa (36–38.9 mm Hg)	+1
Pa_{O_2}	
<6.5 kPa (48.7 mm Hg)	+4
6.5–7.99 kPa (48.7–59.9 mm Hg)	+3
8–9.49 kPa (60–71.2 mm Hg)	+2
9.5–10.99 kPa (71.3–82.4 mm Hg)	+1
Chest radiograph	
Platelike atelectasis	+1
Elevated hemidiaphragm	+1

* Clinical probability: low, 0 to 4 points; intermediate, 5 to 8 points; high, 9 or more points.
From Wicki et al (19).
Pa_{CO_2} = partial pressure of carbon dioxide, arterial; Pa_{O_2} = partial pressure of oxygen, arterial.

Study Design

The study was designed as a prospective management trial with a 3-month follow-up. Patients underwent clinical evaluation in the emergency department by the physicians in charge based on a previously published clinical prediction rule (19) prior to any other test (Table 1). Physicians filled out a standardized data collection form that also recorded risk factors for venous thromboembolism; symptoms and signs frequently encountered in pulmonary embolism, including symptoms or signs of deep vein thrombosis; a description of the electrocardiogram and chest radiograph; and the likelihood of an alternative diagnosis. As described previously (21), the physicians could override the prediction rule by implicit probability assessment in case of disagreement, in either direction. Hence, the final classification on which the diagnostic workup was based was an aggregate of the score and implicit clinical judgment.

Sequential noninvasive tests were then performed (Figure). The initial test was plasma D-dimer measurement by enzyme-linked immunosorbent assay (ELISA) ruling out pulmonary embolism when below the cutoff of 500 μg/L. Patients with D-dimer levels ≥500 μg/L proceeded to lower limb compression ultrasonography. An ultrasound showing a deep vein thrombosis warranted anticoagulant treatment without further testing. Patients with a normal ultrasound underwent helical CT, and patients in whom the scan showed pulmonary embolism

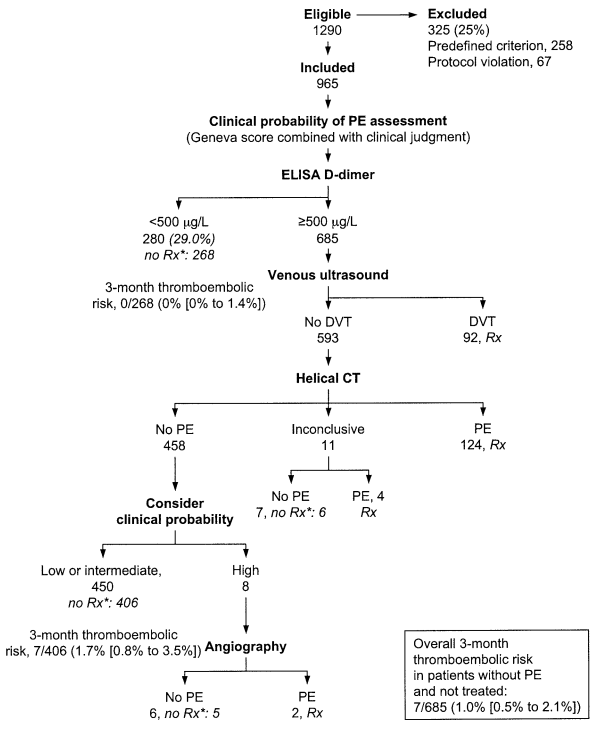

Figure. Flow chart summarizing the diagnostic process in the study. Several patients who were categorized as not having pulmonary embolism by the study criteria were anticoagulated during follow-up for reasons other than venous thromboembolism. The number of patients who were not anticoagulated at any time during follow-up is indicated in the Figure under the caption "no Rx." Those numbers were used to calculate the 3-month thromboembolic risk. Ranges in square brackets indicate 95% confidence intervals. CT = computed tomography; DVT = deep vein thrombosis; ELISA = enzyme-linked immunosorbent assay; PE = pulmonary embolism; Rx = treatment.

were treated accordingly. Patients were then stratified according to the clinical probability of pulmonary embolism as determined before D-dimer measurement and ultrasound were performed. Patients with a low or intermediate clinical probability and a negative CT scan and ultrasound were not treated with anticoagulants (unless another indication for anticoagulant treatment was present) and did not undergo further testing. Those with a high clinical probability of pulmonary embolism underwent pulmonary angiography. A small proportion of patients had an inconclusive CT scan due to technical reasons (e.g., insufficient contrast enhancement of the pulmonary arteries or motion artifacts). Ventilation/perfusion scintigraphy or pulmonary angiography was performed to reach a definite diagnosis in that subgroup.

Diagnostic Studies

Plasma D-dimer levels (rapid ELISA assay, Vidas DD; BioMérieux, Marcy l'Etoile, France) was assayed with an automated quantitative analyzer (22). Real-time, lower limb, B-mode venous compression ultrasonography of the common femoral and popliteal veins was performed within 24 hours in all patients. The criterion for diagnosing deep vein thrombosis was incomplete compressibility of the vein (23).

The protocols for performing helical CT varied among centers and over time. The following features were common to all centers and CT examinations throughout the study: pulmonary arteries were evaluated up to and including the segmental vessels from the level of the aortic arch to the lowest hemidiaphragm. Patients were examined during suspended inspiration or shallow breathing, depending on the degree of dyspnea. Each vessel was scored for the presence or absence of a clot, including subsegmental vessels, when visualized. A clot was considered to be present if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices. In Geneva and Angers, a single-detector CT was used for most of the study period (16) (Geneva: 81% of patients [348/430]; Angers: 80% of patients [227/251]). The acquisition parameters for single-detector CT were a total volume of 120 to 140 mL of nonionic contrast material injected with a power injector at 3 to 5 mL/s; imaging 12 to 15 seconds after initiation of the contrast material injection; scans performed at 3 mm per section with a pitch of 1.6 to 2.0, 120 kV, 200 mAs, requiring 1.0 second per rotation; and images reconstructed at 2- to 3-mm intervals. Multidetector CT (24) was used in all 251 patients from Lausanne and in the remaining patients from Geneva and Angers. The acquisition parameters for multidetector CT were a total volume of 100 to 120 mL of nonionic contrast material injected with a power injector at 3 to 5 mL/s; imaging 9 to 20 seconds after initiation of the contrast material injection; scans performed at 1 to 1.3 mm per section with a pitch of 1.25 to 1.75, 120 kV, 115 to 260 mAs; and images reconstructed at 0.6- to 0.8-mm intervals. For obese patients, slice thickness was sometimes increased to 2.5 mm. The technique for performing and interpreting lung scan and pulmonary angiography has been described elsewhere (14,25).

Outcomes

The outcome measurement for efficacy was the proportion of patients in whom a definite diagnosis could be made by the diagnostic strategy without an angiogram. Safety was assessed by the 3-month risk of thromboembolism in patients classified as not having pulmonary embolism and not anticoagulated at any time during follow-up except during the diagnostic workup. Diagnoses of venous thromboembolic events were established with usual criteria (deep venous thrombosis: abnormal ultrasonography; pulmonary embolism: high-probability V/Q scan, or helical CT or angiogram). Deaths were adjudicated as definitely caused by pulmonary embolism,

definitely unrelated to pulmonary embolism, or possibly due to pulmonary embolism. A 3-month thromboembolic risk of 4% (upper limit of the 95% confidence interval) was considered acceptable, as in similar outcome studies (1–3,26). Episodes of major bleeding (bleeding requiring transfusion, retroperitoneal, joint or cerebral hemorrhage) were also recorded. Three independent experts adjudicated outcome events.

3-Month Follow-up

Patients were followed by their family physicians and interviewed by telephone by one of the study coordinators at the end of the follow-up period. In 5% of patients, follow-up information was obtained by mail. The family physician was contacted whenever a possible event was disclosed by the interim history, and charts were reviewed if a patient was readmitted to a hospital for any cause.

Statistical Analysis

Characteristics of patients were compared by the chi-squared test with Fisher correction for small numbers for categorical variables and by the Mann-Whitney test for continuous variables (Statview 5.0 software for Windows; Abacus Concepts, Inc., Berkeley, California). The 95% confidence intervals for the incidence of thromboembolic and bleeding events during follow-up were calculated from the binomial distribution by means of Confidence Interval Analysis software (Trevor Bryant, University of Southampton, United Kingdom).

RESULTS

The 965 patients who met the inclusion criteria were younger (61 ± 19 years vs. 68 ± 20 years), had fewer comorbid conditions (1.2 ± 1.2 vs. 1.8 ± 1.4), and a lower prevalence of previously diagnosed heart failure (10% [95/965] vs. 18% [59/325]) as compared with patients who were excluded (Table 2). Nevertheless, the prevalence of pulmonary embolism was similar in both included and excluded patients (23% [n = 222] vs. 21% [n = 69]).

Diagnosis of Venous Thromboembolism

Only 5 (6.8%) of the 74 patients with a high clinical probability of pulmonary embolism had normal D-dimer levels (<500 μg/L), compared with 31% (275/891) of patients with a low or intermediate clinical probability ($P < 0.0001$) (Table 3). D-dimer and ultrasonography established a definite diagnosis in 38.5% of the entire cohort.

Helical CT scans were positive for pulmonary embolism in 124 patients (12.8%). The most proximal levels of the detected clots were the main pulmonary arteries in 37 patients (30%), the lobar arteries in 41 (33%), and the segmental vessels in 44 (35%). Only 2 patients had multiple subsegmental pulmonary emboli. No patient had an isolated subsegmental clot. Ultrasound and CT scans were negative in 458 patients, of whom clinical probability was low or intermediate in 450 who were considered as not having pulmonary embolism and not required to undergo further testing. Eight patients (0.8%) had a high clinical probability and underwent angiography, which showed pulmonary emboli in 2 patients (bilateral subsegmental embolus in 1 patient and bilateral lobar embolus in the other patient). CT scans could not be interpreted for technical reasons in 11 (1.9%) of the 593 patients who underwent helical CT. Pulmonary embolism was ruled out in 7 of these patients (normal pulmonary angiogram in 2 patients; normal V/Q lung scan in 4; combination of a low-probability V/Q scan, a low clinical probability, and a negative venous ultrasound in 1) and was established by a high-probability V/Q scan in the remaining 4 patients.

Assessment of Clinical Probability of Pulmonary Embolism

The prediction rule for pulmonary embolism could not be calculated in 194 patients (20%) because arterial blood gas analysis was either not performed (n = 137) or performed in patients receiving supplemental oxygen (n = 57). Clinical probability was assessed by implicit judgment in those patients. In the remaining 771 patients, physicians adopted the score assessment in 592 patients and there was disagreement in 179 patients (23%). The clinical probability as assessed by the score was increased in 126 patients (70% of disagreements) and decreased in 53 patients. Pulmonary embolism was diagnosed in 34 of the 522 patients in the low-probability group (7%; 95% confidence interval [CI]: 5% to 9%), 125 of the 369 patients in the intermediate-probability group (34%; 95% CI: 29% to 39%), and 63 of the 74 patients in the high-probability group (85%; 95% CI: 75% to 92%).

Follow-up

Three patients were lost to follow-up. The two patients who were classified as not having pulmonary embolism were aged 21 and 35 years, were in good health, and had a low clinical probability of pulmonary embolism. One had a D-dimer level of 123 μg/L and was discharged with a diagnosis of bronchitis. Pulmonary embolism was ruled out in the other patient by a negative ultrasound and CT scan; this patient was discharged with a diagnosis of bronchopneumonia and was alive at the end of the follow-up period.

Among the 743 patients in whom venous thromboembolism was considered to be absent according to the diagnostic strategy, 58 underwent anticoagulation during follow-up for reasons other than venous thromboembolism, mainly atrial fibrillation. In the 685 remaining patients, 7 had an acute venous thromboembolic event during the 3-month follow-up (1.0%; 95% CI: 0.5% to 2.1%). All thromboembolic events occurred in the 406 patients with a low-to-intermediate clinical probability of pulmonary embolism, a negative ultrasound, and a neg-

Table 2. Characteristics of the Study Sample (n = 965)

Characteristic	Number (%), Mean ± SD, or Median (Interquartile Range)
Pulmonary embolism	222 (23)
Age (years)	61 ± 19
Female sex	562 (58)
Risk factors	
Family history of deep vein thrombosis or pulmonary embolism	102 (11)
Previous deep vein thrombosis	129 (13)
Previous pulmonary embolism	89 (9)
Known heart failure	95 (10)
Paralysis	29 (3)
Chronic obstructive pulmonary disease	99 (10)
Cancer	89 (9)
Surgery within 1 month	57 (6)
Plaster cast within 12 weeks	13 (1)
Immobilization*	165 (17)
Oral contraceptives	69 (7)
Hormone replacement therapy	53 (6)
Clinical presentation	
Chest pain	678 (70)
Syncope	68 (7)
Dyspnea	634 (66)
Clinical presentation	
Symptoms of deep vein thrombosis	197 (20)
Hemoptysis	43 (5)
Elevated jugular venous pressure	108 (11)
Signs of deep vein thrombosis†	174 (18)
Signs of chronic venous insufficiency‡	199 (21)
Pleural effusion	137 (14)
Elevated hemidiaphragm	114 (12)
Band atelectasis	88 (9)
Heart rate (beats per minute)	86 ± 20
Systolic blood pressure (mm Hg)	140 ± 23
Temperature (°C)	36.9 ± 0.8
Respiratory rate (breaths per minute)	20 (8)
Pa_{O_2} (mm Hg)	75 ± 20
Pa_{CO_2} (mm Hg)	36 ± 6

* Bed rest >48 hours or travel >6 hours within 1 month.
† Unilateral lower limb edema and pain on palpation of the deep leg veins.
‡ Varicose veins, ochre dermatitis, or venous ulcers.
Pa_{CO_2} = partial pressure of carbon dioxide, arterial; Pa_{O_2} = partial pressure of oxygen, arterial.

ative helical CT scan, yielding a 3-month thromboembolic risk of 1.7% (95% CI: 0.8% to 3.5%), compared with 0% (95% CI: 0% to 1.4%) in the 268 patients with normal D-dimer levels. Two of these patients died of a possible pulmonary embolism (Table 4); the remaining 5 patients had nonfatal pulmonary embolism (n = 3) or distal deep vein thrombosis (n = 2). Nine (4.1%) of the patients with initial pulmonary embolism had a recurrent thromboembolic event (Table 4).

Major bleeding was observed in 7 of the 222 patients who underwent anticoagulation for pulmonary embolism (3.2%; 95% CI: 1.5% to 6.4%), of whom 2 died (risk of fatal hemorrhage: 0.9%; 95% CI: 0.2% to 3.2%) (Table 4). Overall 3-month mortality was 7.7% (95% CI: 4.8% to 11.9%) in patients with pulmonary embolism and 2.7% (95% CI: 1.7% to 4.1%) in those in whom the condition was ruled out.

DISCUSSION

We found our diagnostic algorithm to be safe and effective in outpatients. The overall 3-month risk of thromboembolism in patients classified as having no pulmonary embolism by the study algorithm was 1.0% (95% CI: 0.5% to 2.1%), which is in keeping with that found in

Table 3. Diagnostic Criteria According to the Clinical Probability of Pulmonary Embolism in the Study

	Clinical Probability of Pulmonary Embolism		
	Low (n = 522)	Intermediate (n = 369)	High (n = 74)
	Number (%)		
Pulmonary embolism*			
DVT shown by ultrasound	10 (1.9)	46 (12.5)	36 (48.6)
Positive CT scan	22 (4.2)	78 (21.1)	24 (32.4)
Positive angiogram	–	–	2 (2.7)
CT scan inconclusive†	2 (0.4)	1 (0.3)	1 (1.4)
No pulmonary embolism*			
D-dimer level <500 μg/L	238 (45.6)	37 (10.0)	5 (6.8)
Negative ultrasound and CT scan‡	245 (46.9)	205 (55.6)	–
Normal angiogram	–	–	6 (8.1)
CT scan inconclusive§	5 (1.0)	2 (0.5)	–

* As defined by the study criteria.
† Pulmonary embolism diagnosed by high-probability lung scan.
‡ Including low or intermediate clinical probability.
§ Pulmonary embolism ruled out by a normal pulmonary angiogram (n = 2); a normal V/Q lung scan (n = 1); or a combination of a low clinical probability, a low-probability V/Q scan, and a negative ultrasound (n = 1).
CT = computed tomography; DVT = deep vein thrombosis; V/Q = ventilation/perfusion.

other similar management studies (1,2,27–29) (Table 5) and with the risk in patients who were not anticoagulated based on a normal pulmonary angiogram (6). Admittedly, all thromboembolic events during follow-up occurred in low- or intermediate-probability patients who had a negative venous ultrasound and a negative CT scan, yielding a risk of 1.7% (95% CI: 0.8% to 3.5%) in that subgroup. However, that rate is still acceptable and similar to that found in a French management study (29) in which the same diagnostic criterion was applied (Table 5).

Pulmonary angiography was necessary in only 10 patients (1.0%). Adding the 17 patients who were excluded because the angiogram required by the study protocol was not performed, the frequency of angiography would still be only 2.7% in our cohort. Furthermore, performing D-dimer measurements as the first-line test followed by venous ultrasonography in patients with abnormal D-dimer levels reduced the number of CT scans required to reach a definite diagnosis (61.5% vs. 100% in other strategies based on CT [28,29]; Table 5), which may result in

Table 4. Venous Thromboembolic Events and Major Bleeding Events during the 3-Month Follow-up (Including Patients without Pulmonary Embolism Who Were Anticoagulated during Follow-up)

Events	Pulmonary Embolism (n = 222)	No Pulmonary Embolism (n = 743)
	Number (%)	
Thromboembolic events		
Fatal pulmonary embolism	4	0
Possible fatal pulmonary embolism	1	2
Nonfatal pulmonary embolism	0	3
Deep vein thrombosis (distal)	4	2
Total	9 (4.1)	7 (0.9)
Major bleeding events		
Fatal	2	2*
Nonfatal	5	5†
Total	7 (3.2)	7 (0.9)

* No anticoagulant treatment (cancer in 1 patient; multiple organ failure in 1 patient).
† Anticoagulant treatment for causes other than venous thromboembolism in 3 patients; spontaneous bleeding in 2 patients.

Table 5. Comparison of Various Diagnostic Strategies for Suspected Pulmonary Embolism Evaluated in Management Studies

		First Author (Reference)				
	Angiography Alone	Musset (29)	Van Strijen (28)	Wells (2)	Perrier (1)	Present Study
Number of tests performed per 1000 patients*						
D-dimer	–	–	–	1000	1000	1000
Venous ultrasound	–	1000	1453	317	642	710
Helical CT	–	1000	1000	2	–	615
V/Q lung scan	–	102†	–	530	534	9†
Angiography	1000	83†	16‡	3	113	10†
Costs of diagnostic tests ($)§	510,000	316,000	243,000	398,000	478,000	156,000
3-month nonfatal risk of thromboembolism‖ (95% confidence interval)	1.7% (1.0%–2.7%)	1.8% (0.8%–3.3%)	0.8% (0.3%–2.3%)	0.6% (0.2%–1.4%)	0.9 (0.2%–2.7%)	1.0% (0.5%–2.1%)
3-month risk of fatal thromboembolism‖ (95% confidence interval)	0.3% (0.02%–0.7%)	1.0% (0.4%–2.3%)	0.3% (0%–1.5%)	0% (0%–0.5%)	0% (0%–1.2%)	0.3% (0.1%–1.1%)

* The figures are extracted from the original studies and applied to a hypothetical cohort of 1000 patients.
† In patients with an inconclusive ultrasound or CT scan, or those with a high clinical probability of pulmonary embolism and a negative ultrasound and CT scan.
‡ In patients with an inconclusive CT scan.
§ Costs calculated for a hypothetical cohort of 1000 patients using U.S. costs extracted from reference 30: D-dimer: $12; ultrasound: $69; helical CT: $135; V/Q lung scan: $683; angiography: $510.
‖ In patients classified as without pulmonary embolism and not anticoagulated during the 3-month follow-up.
CT = computed tomography; V/Q = ventilation/perfusion.

substantial cost savings, as shown by a recent cost-effectiveness analysis (6).

Our study also confirms the accuracy of clinical probability assessment by the prediction rule with possible override by clinical judgment (21). The limitations of the prediction rule (19) have been described (21). Indeed, the score could be obtained for only 80% of patients, and clinicians overrode the score assessment using implicit clinical judgment in 23% of the patients in whom the score was available. We believe that combining implicit judgment with the score makes clinical sense, since prediction rules do not take into account rare but potentially important individual characteristics. Moreover, combining the two methods increased physician acceptance of the rule. The final classification of patients—an aggregate of score and implicit judgment—was not entirely standardized, but it had a fair accuracy and was probably more standardized than would have been using implicit assessment alone.

The study provides additional evidence on the safety and efficacy of a highly sensitive ELISA D-dimer assay as the first-line test for ruling out pulmonary embolism in outpatients. Indeed, none of the 268 patients with D-dimer levels <500 μg/L and who were not anticoagulated had a thromboembolic event during follow-up. Pooling these results with those from a previous study that used the same assay (1), the 3-month risk of thromboembolism in patients who were not anticoagulated based on the results of this particular ELISA test was 0% (95% CI: 0% to 0.9%; 0/423). However, those results cannot be extrapolated to other less sensitive assays or to the inpatient setting.

We chose to perform venous ultrasonography before thoracic imaging, which revealed unequivocal signs of proximal deep vein thrombosis in 9.5% of patients, whereas in a recent Dutch study in which ultrasonography was carried out after a normal helical CT scan, only two cases of thrombosis were found among the 248 patients (0.8%) (28). Venous ultrasonography also served to compensate for the limited sensitivity of single-slice helical CT. Indeed, previous studies (16,29) showed that 15% of patients with clinical symptoms of pulmonary embolism and a negative helical CT scan have a deep vein thrombosis. Hence, our results should not be interpreted as a validation of a negative CT scan to rule out pulmonary embolism. Furthermore, pending results of outcome studies using multidetector CT (24), CT should be combined with venous ultrasonography to exclude venous thromboembolism safely. Moreover, even if multidetector CT was proven to be safe as a single imaging modality for suspected pulmonary embolism, such a strategy would be considerably more resource intensive than a strategy that combined CT and other less expensive noninvasive tests (Table 5).

Generalization of our findings might be a concern since 25% of eligible patients were excluded. However, predefined exclusion criteria largely accounted for the differences between included and excluded patients. The mix of single- and multidetector CT scans is also a limitation, but was inevitable because of the continuous evolution of radiological technology. However, four of the five pulmonary emboli diagnosed during follow-up in patients without pulmonary embolism on initial workup occurred in the 183 patients evaluated by multidetector CT; this included the two deaths that were possibly attributable to pulmonary embolism. Hence, it is unlikely that the 3-month risk of thromboembolism would have been different had we used only multidetector machines.

In conclusion, our study shows that a diagnostic strategy combining clinical probability assessment, D-dimer measurement, venous ultrasonography, and helical CT is safe and effective in outpatients suspected of pulmonary embolism. However, this series was not designed to test the hypothesis that single-slice helical CT alone is safe for ruling out pulmonary embolism, and venous ultrasonography should imperatively be combined with CT to compensate for its limited sensitivity pending the results of ongoing studies of multidetector technology.

ACKNOWLEDGMENT

We gratefully acknowledge the skilled assistance of Catherine Ternisien, MD, Catherine Ridereau-Zins, MD, Alain Dauver, MD, Amel Benoit, MD, Alain Furber, MD, Philippe Geslin, MD, Gilles Berrut, MD, Thierry Urban, MD, and Alain Delhumeau, MD, in Angers; of Philippe de Moerloose, MD, Paul Cirafici, MD, Thierry Merminod, MD, Marc Righini, MD, Dominique Didier, MD, and Pascal Bachmann, in Geneva; and of all the physicians in the Departments of Emergency, Radiology, Angiology, and Nuclear Medicine in Angers, Lausanne, and Geneva. We would also like to thank Sylvain de Lucia, MD, in Geneva; Mathilde Marchand, MD, in Angers; and Dominique Gillis, MD, in Lausanne; for their help in data collection. Finally, we would like to thank all the residents who rotated in the emergency departments of the three centers for their invaluable collaboration throughout the study.

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