ORIGINAL ARTICLE

Multidetector-Row Computed Tomography in Suspected Pulmonary Embolism

Arnaud Perrier, M.D., Pierre-Marie Roy, M.D., Olivier Sanchez, M.D., Grégoire Le Gal, M.D., Guy Meyer, M.D., Anne-Laurence Gourdier, M.D., Alain Furber, M.D., Marie-Pierre Revel, M.D., Nigel Howarth, M.D., Alain Davido, M.D., and Henri Bounameaux, M.D.

ABSTRACT

BACKGROUND

Single-detector–row computed tomography (CT) has a low sensitivity for pulmonary embolism and must be combined with venous-compression ultrasonography of the lower limbs. We evaluated whether the use of D-dimer measurement and multidetector-row CT, without lower-limb ultrasonography, might safely rule out pulmonary embolism.

METHODS

We included 756 consecutive patients with clinically suspected pulmonary embolism from the emergency departments of three teaching hospitals and managed their cases according to a standardized sequential diagnostic strategy. All patients were followed for three months.

RESULTS

Pulmonary embolism was detected in 194 of the 756 patients (26 percent). Among the 82 patients with a high clinical probability of pulmonary embolism, multidetector-row CT showed pulmonary embolism in 78, and 1 patient had proximal deep venous thrombosis and a CT scan that was negative for pulmonary embolism. Of the 674 patients without a high probability of pulmonary embolism, 232 (34 percent) had a negative D-dimer assay and an uneventful follow-up; CT showed pulmonary embolism in 109 patients. CT and ultrasonography were negative in 318 patients, of whom 3 had a definite thromboembolic event and 2 died of possible pulmonary embolism during follow-up (three-month risk of thromboembolism, 1.7 percent; 95 percent confidence interval, 0.7 to 3.9). Two patients had proximal deep venous thrombosis and a negative CT scan (risk, 0.6 percent; 95 percent confidence interval, 0.2 to 2.2). The overall three-month risk of thromboembolism in patients without pulmonary embolism would have been 1.5 percent (95 percent confidence interval, 0.8 to 3.0) if the D-dimer assay and multidetector-row CT had been the only tests used to rule out pulmonary embolism and ultrasonography had not been performed.

CONCLUSIONS

Our data indicate the potential clinical use of a diagnostic strategy for ruling out pulmonary embolism on the basis of D-dimer testing and multidetector-row CT without lower-limb ultrasonography. A larger outcome study is needed before this approach can be adopted.

From the Service of General Internal Medicine (A.P.) and the Division of Angiology and Hemostasis (G.L.G., H.B.), Department of Internal Medicine, and the Service of Radiodiagnosis and Interventional Radiology, Department of Medical Radiology and Informatics (N.H.), Geneva Faculty of Medicine and Geneva University Hospital, Geneva; the Emergency Department (P.-M.R.), the Service of Radiology (A.-L.G.), and the Service of Cardiology (A.F.), Angers University Hospital, Angers, France; and the Service of Pneumology (O.S., G.M.), the Service of Radiology (M.-P.R.), and the Emergency Department (A.D.), Hôpital Européen Georges-Pompidou, Paris. Address reprint requests to Dr. Perrier at the Service of General Internal Medicine, Geneva University Hospital, Rue Micheli-du-Crest 24, CH-1211 Geneva 14, Switzerland, or at arnaud.perrier@medecine.unige.ch.

N Engl J Med 2005;352:1760-8.

Computed tomography (CT) is increasingly being used as the main thoracic imaging technique in suspected pulmonary embolism.[1-4] First-generation single-detector–row helical CT scanners have a 90 percent specificity but only a 70 percent sensitivity for pulmonary embolism.[5-8] In series in which venous-compression ultrasonography of the lower limbs and single-detector–row helical CT were performed in all patients with clinically suspected pulmonary embolism,[7,9] the proportion of patients with deep venous thrombosis despite findings on CT that were negative for pulmonary embolism was 6 to 9 percent. The implication of this finding is that lower-limb ultrasonography must be combined with CT to improve the overall diagnostic yield. In two recent outcome studies,[9,10] patients without a high clinical probability of pulmonary embolism who were left untreated on the basis of negative findings on single-detector CT and lower-limb compression ultrasonography had a 1 to 2 percent risk of a thromboembolic event within three months, a finding that is similar to that for patients who were left untreated after pulmonary angiography showed no abnormalities.[11]

The advent of multidetector-row CT scanners has improved the visualization of the segmental and subsegmental pulmonary arteries.[12,13] This development has raised the possibility that pulmonary embolism might be safely ruled out without the use of lower-limb venous ultrasonography, at least in patients without a high probability of pulmonary embolism — a change in strategy that could save both money and other resources. If that hypothesis were true, the diagnosis of deep venous thrombosis in a patient with clinically suspected pulmonary embolism and negative findings on multidetector-row CT should be uncommon, and the three-month risk of thromboembolism in patients with a negative multidetector-row CT scan should be low.

Therefore, we conducted a prospective study to assess whether a strategy of D-dimer measurement and multidetector-row CT, without the use of lower-limb ultrasonography, might safely rule out pulmonary embolism in patients admitted to the emergency department for clinically suspected pulmonary embolism.

METHODS

PATIENTS

Consecutive patients who presented to the emergency department were eligible if there was a suspicion of pulmonary embolism, which was defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause. Among the 1014 screened patients, 185 (18 percent) were excluded from the study for the following reasons: a contraindication to CT (i.e., a known allergy to iodine contrast agents or a risk of allergic reaction) (7 patients); impaired renal function, defined as a creatinine clearance below 30 ml per minute, as calculated by the Cockcroft–Gault formula[14] (38); pregnancy (7); ongoing anticoagulant therapy for a reason other than venous thromboembolism (38); a decision not to participate in the study (41); inability to give informed consent (15); a life expectancy of less than three months (9); a diagnosis that had been made before admission (3); unavailability for follow-up (10); hospitalization in another institution for more than 24 hours before admission (3); inability to undergo CT because of hemodynamic instability (3); transfer to another facility (1); absence of peripheral venous access (1); and other reasons (9).

Another 73 patients (7.2 percent) were excluded because of the following violations in study protocol: clinical probability was not assessed (14 patients); diagnostic tests were not performed, including D-dimer measurement (4), ultrasonography (15), CT (8), and angiography (7); tests were inadequately performed despite a negative D-dimer test (2); a decision was made by the physicians in charge to prescribe anticoagulants, despite the absence of pulmonary embolism according to the study criteria (5); or the diagnosis was not confirmed according to study criteria in patients whose CT scan was inconclusive for technical reasons (17) or because of the presence of isolated subsegmental pulmonary embolism (1). Hence, the final study cohort consisted of 756 patients (75 percent of the screened population).

STUDY DESIGN

The study was designed as a prospective management trial with a three-month follow-up. Data were collected from August 1, 2002, to November 30, 2003, at three participating medical centers that serve as general and teaching hospitals (Geneva University Hospital, Geneva; Angers University Hospital, Angers, France; and Hôpital Européen Georges-Pompidou, Paris). The study was approved by the ethics committees of Geneva University Hospital and Angers University Hospital, and all patients provided written informed consent before they were enrolled.

Drs. Perrier, Bounameaux, Roy, and Meyer designed the study. A research assistant gathered the data in each center, and the local study coordinator checked the data. Drs. Perrier and Le Gal performed the analysis and vouch for the data and the analysis. All the authors participated in the interpretation of the data and approved the final version of the article. Dr. Perrier drafted the manuscript.

Before any other test was administered, patients underwent clinical evaluation in the emergency department by the physicians in charge with the use of the Geneva score.[10,15,16] The Geneva score is based on seven variables: age, previous deep venous thrombosis or pulmonary embolism, recent surgery, heart rate, the partial pressure of arterial oxygen, the partial pressure of arterial carbon dioxide, and the findings on chest radiography (e.g., band atelectasis or hemidiaphragm elevation). It allows the classification of patients into three categories of clinical probability of pulmonary embolism (low, intermediate, or high), corresponding to an increasing prevalence of pulmonary embolism. As previously described,[10,16] the physicians in the emergency department could override the score by clinical judgment in case of disagreement. Clinical judgment was also used when the Geneva score could not be computed because of the unavailability of arterial-blood gas measurements while the patient was breathing ambient air.

Sequential noninvasive tests were then performed and stratified according to the clinical probability of pulmonary embolism (Fig. 1). In patients without a high clinical probability (i.e., either a low or intermediate probability), we measured plasma D-dimer levels by enzyme-linked immunosorbent assay (ELISA) and ruled out pulmonary embolism in patients with a level below the cutoff value of 500 μg per liter. Patients with a D-dimer level of 500 μg per liter or above underwent proximal venous-compression ultrasonography of the lower limbs and multidetector-row CT. CT that was positive for pulmonary embolism or ultrasonography that showed a deep venous thrombosis warranted anticoagulant treatment, whereas such therapy was withheld in patients in whom both tests were negative. In patients with a high clinical probability of pulmonary embolism, we did not obtain a D-dimer measurement, since the D-dimer test is negative in less than 10 percent of such patients and the probability of pulmonary embolism is still 12 to 23 percent when the test is negative in the subgroup that has a 65 to 80 percent prevalence of pulmonary embolism.[17] These patients thus proceeded directly to CT and lower-limb ultrasonography. Patients in whom either test was positive were treated, but those with a high clinical probability and negative findings on both CT and ultrasonography proceeded to pulmonary angiography, and their cases were managed accordingly. The results of CT scanning were deemed inconclusive if technical problems (i.e., insufficient contrast enhancement of the pulmonary arteries or motion artifacts) precluded a definitive interpretation. Patients with isolated subsegmental pulmonary embolism (defined as CT evidence of embolism in a single subsegmental vessel) were also considered to have had an inconclusive CT, since the positive predictive value of that finding is low (25 percent in the Evaluation du Scanner Spiralé dans l'Embolie Pulmonaire [ESSEP] study[9]). Patients with an inconclusive CT result proceeded to ventilation–perfusion lung scanning or pulmonary angiography. Ventilation–perfusion scanning confirmed pulmonary embolism in the case of a high-probability pattern[18] and ruled it out when the result was normal[19] or of low probability in a patient with a low clinical probability of pulmonary embolism and an absence of proximal deep venous thrombosis.[20] In all other instances, ventilation–perfusion scanning was followed by pulmonary angiography for final adjudication.

DIAGNOSTIC STUDIES

Plasma D-dimer was assayed by an automated quantitative analyzer (rapid ELISA assay, Vidas DD Exclusion, BioMérieux).[21] Lower-limb B-mode venous-compression ultrasonography was performed within 24 hours after admission by trained staff blinded to the results of CT. The examination consisted of a real-time B-mode examination of the common femoral and popliteal veins. The criterion for diagnosing deep-vein thrombosis was incomplete compressibility of the vein.[22]

The protocol for multidetector-row CT consisted of an evaluation of the pulmonary arteries up to and including the subsegmental vessels. The patients were examined during a breath hold or shallow breathing, depending on the degree of dyspnea. A clot was considered present if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material. Four-slice multidetector-row CT was used in 89 percent of the patients, including all the patients in Angers and Paris and 81 of 137 patients (59 percent) in Geneva; the remaining 56 patients in Geneva were

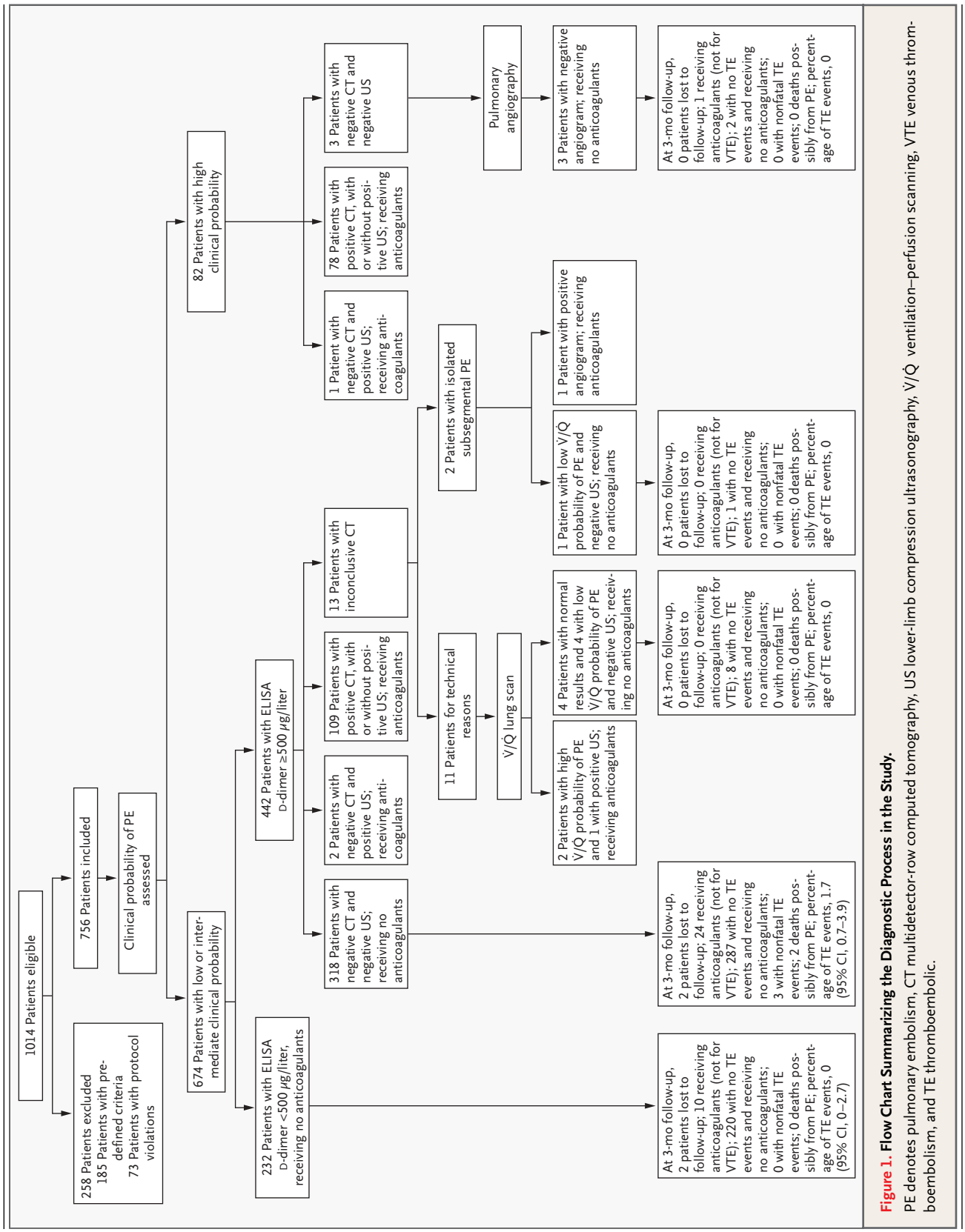

Figure 1. Flow Chart Summarizing the Diagnostic Process in the Study.

PE denotes pulmonary embolism, CT multidetector-row computed tomography, US lower-limb compression ultrasonography, V̇/Q̇ ventilation–perfusion scanning, VTE venous thromboembolism, and TE thromboembolic.

Table 1. Characteristics of the 756 Patients in the Study.

Characteristic	Value*
Age — yr	60±19
Male sex — no. (%)	302 (40)
Risk factors for venous thromboembolism — no. (%)	
Family history of venous thromboembolism†	103 (14)
Previous venous thromboembolism	142 (19)
Known heart failure	60 (8)
Stroke	7 (1)
Chronic obstructive lung disease	74 (10)
Surgery within past 1 mo	37 (5)
Bed rest (>48 hr) within past 1 mo	109 (14)
Lower-limb plaster cast within past 1 mo	18 (2)
Cancer	75 (10)
Current hormone-replacement therapy	51 (7)
Current oral-contraceptive use	48 (6)
Current pregnancy or post partum	13 (2)
Symptoms of pulmonary embolism — no. (%)	
Dyspnea	538 (71)
Chest pain	480 (63)
Syncope or malaise	188 (25)
Recent cough	173 (23)
Unilateral lower-limb pain	137 (18)
Hemoptysis	35 (5)
Clinical findings	
Central temperature — °C	37.3±0.8
Respiratory frequency — breaths per min	21±6
Heart rate — beats per min	88±20
Systolic blood pressure — mm Hg	138±24
Chronic venous insufficiency — no. (%)	97 (13)
Varicose veins — no. (%)	122 (16)
Signs of deep venous thrombosis — no. (%)‡	72 (10)
Distention of neck veins — no. (%)	42 (6)

* Plus–minus values are means ±SD.
† A family history of venous thromboembolism was defined as the presence of the disorder in at least one first-degree relative.
‡ Signs of deep venous thrombosis were unilateral calf edema and pain on palpation of the deep veins.

examined by 16-slice multidetector-row CT. The acquisition parameters for multidetector-row CT were injection of a total volume of 100 to 120 ml of nonionic contrast material (iodine concentration, 300 to 350 mg per milliliter) with a power injector at 3 to 5 ml per second; imaging 9 to 20 seconds after initiation of the contrast-material injection; scanning performed at 1.0 to 1.3 mm per section with a pitch of 1.25 to 1.75, 120 kV, and 115 to 260 mA; and reconstruction of images 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 scanning and pulmonary angiography has been described elsewhere.[23,24]

OUTCOMES

The main outcome was the proportion of patients with proximal deep venous thrombosis and negative findings on CT. The secondary outcome was an estimate of the three-month risk of thromboembolism if lower-limb ultrasonography had not been performed — in other words, the sum of the proportion of patients with deep venous thrombosis and negative CT results and of the three-month risk of thromboembolism among patients in whom pulmonary embolism was considered to have been ruled out by the initial diagnostic workup and anticoagulant therapy was not administered during follow-up.

Diagnoses of venous thromboembolic events during follow-up were established with the usual criteria — for deep venous thrombosis, on the basis of abnormal results on ultrasonography; and for pulmonary embolism, ventilation–perfusion scanning showing a high-probability pattern or CT or angiography showing pulmonary embolism. Deaths were adjudicated as definitely caused by pulmonary embolism, definitely unrelated to pulmonary embolism, or possibly due to pulmonary embolism. A three-month risk of thromboembolism of 4 percent (upper limit of the 95 percent confidence interval) was considered acceptable, as in previous outcome studies.[10,25,26] Three independent experts adjudicated the outcome events.

THREE-MONTH FOLLOW-UP

Patients were followed up by their family physicians and were interviewed by telephone by one of the study coordinators at the end of the follow-up period. 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 the hospital for any cause.

STATISTICAL ANALYSIS

The exact 95 percent confidence intervals for proportions were calculated from the binomial distribution with use of the Confidence Interval Analysis software program.

RESULTS

STUDY POPULATION

The 756 patients had a mean (±SD) age of 60±19 years, and 60 percent were female. The characteristics of the patients are shown in Table 1. The overall prevalence of pulmonary embolism in this cohort was 26 percent (194 of 756 patients).

DIAGNOSTIC WORKUP

The diagnostic workup is detailed in Figure 1, and the respective diagnostic yield of the criteria used in this series is summarized in Table 2.

Patients with a High Clinical Probability of Pulmonary Embolism

CT scanning showed a pulmonary embolism in 78 of the 82 patients (95 percent) who had a high clinical probability of pulmonary embolism; 37 of these 78 patients had proximal deep venous thrombosis (47 percent; 95 percent confidence interval, 37 to 58). Only one patient had proximal deep venous thrombosis and negative findings on CT, and that patient was treated. The other three patients had negative findings on both ultrasonography and CT, and subsequent angiography was negative in all three.

Patients without a High Clinical Probability of Pulmonary Embolism

Among the 674 patients without a high clinical probability of pulmonary embolism, the D-dimer level was below 500 μg per liter in 232 patients (34 percent; 95 percent confidence interval, 31 to 38). The remaining patients proceeded to CT and venous ultrasonography. CT showed pulmonary embolism in 109 patients, of whom 36 also had a deep venous thrombosis (33 percent; 95 percent confidence interval, 25 to 42), and they all were treated. CT scanning and ultrasonography were negative in 318 patients. Two patients with negative CT scans had a proximal deep venous thrombosis (0.6 percent; 95 percent confidence interval, 0.2 to 2.2) and were treated.

Among 13 patients, the CT scan was considered inconclusive, according to the study criteria. In 11 patients, the scan was technically inadequate for interpretation. Further testing established pulmonary embolism in three patients and ruled it out in eight patients, who were not treated (Fig. 1 and Table 2). In the other two patients, CT revealed an isolated subsegmental embolus. One of these patients — who had a low clinical probability of pulmonary embolism, a low-probability ventilation–perfusion lung scan, and no proximal deep venous thrombosis — was not treated, whereas the other was treated with anticoagulants on the basis of a positive angiogram. The overall proportion of patients (both those without a high probability of pulmonary embolism and those with a high probability) who had deep venous thrombosis and negative findings on

Table 2. Yield of the Diagnostic Criteria Used in the Series.*

Diagnostic Criterion	Clinical Probability of Pulmonary Embolism	
	Not High	High
	no. of patients (%)	
Presence of pulmonary embolism		
CT positive	109 (95)	78 (99)
CT negative, DVT on ultrasonography	2 (2)	1 (1)
CT inconclusive		
Technical reasons†	3 (3)	—
Isolated subsegmental pulmonary embolism‡	1 (1)	—
All patients	115	79
Absence of pulmonary embolism		
D-Dimer level <500 μg/liter	232 (42)	—
CT negative, no DVT on ultrasonography	318 (57)	—
Angiogram negative	—	3 (100)
CT inconclusive		
Technical reasons¶	8 (1)	—
Isolated subsegmental pulmonary embolism§	1 (<1)	—
All patients	559	3

* CT denotes multidetector-row computed tomography, and DVT deep venous thrombosis. Percentages may not sum to 100 because of rounding.
† Two patients had ventilation–perfusion scans showing a high probability of pulmonary embolism, and one patient had deep venous thrombosis on ultrasonography.
‡ Angiography in this patient showed an isolated subsegmental pulmonary embolism.
¶ Four patients had normal ventilation–perfusion scans, and four patients had a low clinical probability of pulmonary embolism, low-probability ventilation–perfusion scans, and negative findings on ultrasonography.
§ This patient had a low clinical probability of pulmonary embolism, a low-probability ventilation–perfusion scan, and negative findings on ultrasonography.

Table 3. Anatomical Distribution of Pulmonary Emboli Visualized by CT, According to the Most Proximal Level of the Pulmonary Arterial Tree.*

Most Proximal Level	Clinical Probability of Pulmonary Embolism		
	Not High	High	Total
	no. of patients (%)		
Main pulmonary artery	30 (28)	30 (38)	60 (32)
Lobar level	31 (28)	34 (44)	65 (35)
Segmental level	37 (34)	11 (14)	48 (26)
Multiple subsegmental levels	11 (10)	3 (4)	14 (7)
Any level	109	78	187

* CT denotes multidetector-row computed tomography.

CT was 3 of 324 (0.9 percent; 95 percent confidence interval, 0.3 to 2.7).

Anatomical Distribution of Emboli

The anatomical distribution of the pulmonary emboli, according to the most proximal vessel that was affected and to the clinical probability category, is detailed in Table 3.

FOLLOW-UP AND OUTCOMES

Pulmonary Embolism Ruled Out by Initial Diagnostic Workup

In all 4 patients lost to follow-up (0.5 percent of the entire cohort of 756), pulmonary embolism had been ruled out by the initial diagnostic workup; 2 patients without a high clinical probability of pulmonary embolism had a negative D-dimer assay, and 2 patients had negative findings on CT and lower-limb ultrasonography. During follow-up, 35 of the 562 patients in whom pulmonary embolism had been ruled out received anticoagulation therapy for reasons other than venous thromboembolism (atrial fibrillation or flutter, 26 patients; cardiomyopathy, 2; and other indications, 7), leaving 523 patients for the assessment of the three-month thromboembolic risk. There were no thromboembolic events among the 220 patients with a normal D-dimer level who did not receive anticoagulation therapy (0 percent; 95 percent confidence interval, 0 to 2.7). Of the patients without a high probability of pulmonary embolism who had negative findings on CT scanning and ultrasonography, three patients had a thromboembolic event, and 2 of the 26 deaths in this group were adjudicated as possibly due to pulmonary embolism (Table 4). Therefore, the three-month risk of thromboembolism among the 292 patients who did not receive anticoagulation therapy during follow-up was 1.7 percent (95 percent confidence interval, 0.7 to 3.9). The overall three-month risk of thromboembolism among the 523 patients who did not have pulmonary embolism and were not receiving treatment was 1.0 percent (95 percent confidence interval, 0.4 to 2.2). With the addition of the three patients with proximal deep venous thrombosis and negative findings on CT scanning, the maximum three-month risk of thromboembolism would have been 1.5 percent (95 percent confidence interval, 0.8 to 3.0) if ultrasonography had not been included in the diagnostic workup. There were 24 deaths that were not related to venous thromboembolism in this group, which were caused by cancer (18 patients), respiratory failure (3), septic shock (2), and cardiac disease (1).

Pulmonary Embolism Indicated by Initial Diagnostic Workup

Four of the 194 patients with pulmonary embolism (2.1 percent; 95 percent confidence interval, 0.9 to 4.5) had recurrent venous thromboembolism. There were 11 deaths (5.7 percent; 95 percent confidence interval, 3.2 to 9.9) from cancer (5), septic shock (2), recurrent pulmonary embolism (2), initial pulmonary embolism (1), and an indeterminate cause (1).

DISCUSSION

This study shows that the proportion of patients with proximal deep venous thrombosis despite negative findings on multidetector CT is very low (0.9 percent; 95 percent confidence interval, 0.3 to 2.7). Therefore, the improvement of the overall detection rate of pulmonary embolism by venous ultrasonography was marginal in this series, and the three-month thromboembolic risk in patients left untreated if pulmonary embolism had been ruled out on the sole basis of a negative multidetector CT scan would have been 1.5 percent (95 percent confidence interval, 0.9 to 2.7), similar to that of pulmonary angiography[11] and other recent outcome studies.[9,10,25,26] This raises the possibility that the use of ELISA measurement of plasma D-dimer levels and multidetector CT scanning might safely rule out pulmonary embolism in patients without a high probability of pulmonary embolism without performing lower-limb ultrasonography. Since ultrasonography is costly and labor-intensive and not all centers have access to the technique, forfeiting ultrasonography would possibly reduce costs. It would also mean that small centers with equipment

Table 4. Thromboembolic Events during the Three-Month Follow-up among Five Patients in Whom Pulmonary Embolism Was Initially Ruled Out.*

Patient	Risk Factors for VTE	Initial Diagnostic Workup	Initial Diagnosis	Follow-up
89-Yr-old woman	None	Intermediate clinical probability, positive D-dimer test, negative US and CT	Left ventricular failure	Day 24: pulmonary embolism
74-Yr-old woman	Bed rest	Intermediate clinical probability, positive D-dimer test, negative US and CT	Anxiety and hyperventilation	Day 13: proximal DVT
57-Yr-old woman	Cancer	Intermediate clinical probability, positive D-dimer test, negative US and CT	Pain and hyperventilation	Day 11: upper extremity DVT
45-Yr-old woman	Cancer, bed rest	Intermediate clinical probability, positive D-dimer test, negative US and CT	Bronchopneumonia	Day 89: sudden death
79-Yr-old man	History of VTE, COPD	Intermediate clinical probability, positive D-dimer test, negative US and CT	Left ventricular failure	Day 2: sudden death

* VTE denotes venous thromboembolism, US lower-limb venous-compression ultrasonography, CT multidetector-row computed tomography, DVT deep venous thrombosis, and COPD chronic obstructive pulmonary disease.

to perform multidetector CT but not venous ultrasonography could safely work up patients with suspected pulmonary embolism without a referral.

The advent of an imaging technique allowing the visualization of very small peripheral emboli[12,13] raises the concern of overdiagnosis. In this study, we could not calculate the false positive rate of multidetector-row CT since scans showing pulmonary embolism were not verified by other tests. Nevertheless, the anatomical distribution of emboli in the pulmonary arterial tree (Table 3) was similar to that in our previous series conducted with the use of single-detector CT,[7] except for the presence of multiple subsegmental clots in 7 percent of patients. That proportion is similar to that of the landmark Prospective Investigation of Pulmonary Embolism Diagnosis study, which showed subsegmental emboli in 6 percent of patients with the use of pulmonary angiography.[18] Isolated subsegmental emboli were identified in only 2 of the 191 patients with CT evidence of venous thromboembolism (1.0 percent), as compared with 12 of 290 patients in the ESSEP study.[9] The overall prevalence of pulmonary embolism in this cohort (26 percent) has only slightly risen as compared with a previous multicenter study from our group (23 percent).[10] Therefore, our findings do not support the fear that multidetector CT technology entails a substantial risk of overdiagnosis.

This series adds to the body of data on the performance of an already well-validated ELISA D-dimer assay in suspected pulmonary embolism.[10,25,27] No thromboembolic event occurred during the follow-up period in the 220 patients with a normal D-dimer test who were left untreated throughout. Hence, pooled data from our two previous studies[10,25] and this series provide a precise estimate of the three-month thromboembolic risk in patients in whom pulmonary embolism is ruled out on the basis of a normal D-dimer test: 0 of 643 patients (0 percent; 95 percent confidence interval, 0 to 0.4).

Our study has some limitations. First, generalization of our findings might be a concern, since 25 percent of screened patients were excluded. However, the characteristics of the patients who were included in this cohort are representative of those among patients admitted to emergency departments for suspected pulmonary embolism in all recent series.[10,25,26,28] Moreover, none of the 73 patients who were excluded because of protocol violations (7 percent) who had negative findings on CT scanning had a thromboembolic event during follow-up. Second, this series is not a true outcome study, since venous ultrasonography was performed in all patients with an abnormal D-dimer level, and those with deep venous thrombosis and negative findings on CT were treated with anticoagulant therapy. Our results should be confirmed in a proper outcome study in which the decision to withhold anticoagulation would be made on the basis of negative find-

ings on multidetector-row CT alone in patients with an abnormal D-dimer level.

In summary, our study shows that the proportion of patients with deep venous thrombosis despite negative findings on multidetector-row CT scanning is below 1 percent and that ruling out pulmonary embolism with the use of D-dimer measurement and multidetector CT would entail a three-month thromboembolic risk of around 1.5 percent. This raises the possibility that such a strategy might be safe in patients who are admitted to emergency centers for suspected pulmonary embolism, a hypothesis that should now be evaluated in a proper outcome study.

Supported by a grant from the Hirsch Fund of the University of Geneva.

Dr. Perrier, Dr. Le Gal, and Dr. Roy report having served as consultants for BioMérieux. Dr. Bounameaux, Dr. Sanchez, Dr. Meyer, Dr. Davido, Dr. Gourdier, Dr. Furber, Dr. Revel, and Dr. Howarth have no relationships with companies that make products relevant to this study.

We are indebted to Catherine Ridereau, Georges Leftheriotis, Catherine Ternisien, Alain Dauver, and Alain Delhumeau in Angers; to Philippe de Moerloose, Thierry Merminod, Marc Righini, Dominique Didier, and Pascal Bachmann in Geneva; and to all physicians in the departments of emergency, radiology, angiology and hemostasis, and nuclear medicine in Paris, Angers, and Geneva; to Patrick Bandelier and Ariane Testuz in Geneva, Nicole Sorin and Céline Priou in Angers, and Delphine Wermert in Paris for their help in data collection; and to all the residents of the emergency departments of the three centers for their invaluable collaboration throughout the study.

REFERENCES

1. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 2003;58:470-83.
2. Fedullo PF, Tapson VF. The evaluation of suspected pulmonary embolism. N Engl J Med 2003;349:1247-56.
3. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies: a systematic review. Ann Intern Med 2003;138:941-51.
4. Goldhaber SZ. Pulmonary embolism. Lancet 2004;363:1295-305.
5. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. Ann Intern Med 2000;132:227-32.
6. Mullins MD, Becker DM, Hagspiel KD, Philbrick JT. The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. Arch Intern Med 2000;160:293-8.
7. Perrier A, Howarth N, Didier D, et al. Performances of helical computed tomography in unselected outpatients with suspected pulmonary embolism. Ann Intern Med 2001;135:88-97.
8. van Strijen MJL, de Monye W, Kieft GJ, Pattynama PMT, Prins MH, Huisman MV. Accuracy of single-detector spiral CT in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients with abnormal perfusion scintigraphy. J Thromb Haemost 2005;3:17-25.
9. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002;360:1914-20.
10. Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004;116:291-9.
11. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism — a critical review. Clin Radiol 2001;56:838-42.
12. Ghaye B, Szapiro D, Mastora I, et al. Peripheral pulmonary arteries: how far in the lung does multi-detector row spiral CT allow analysis? Radiology 2001;219:629-36.
13. Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. Circulation 2004;109:2160-7.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
15. Wicki J, Perneger TV, Junod A, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med 2001;161:92-7.
16. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment for suspected pulmonary embolism. Am J Med 2002;113:269-75.
17. Righini M, Aujesky D, Roy PM, et al. Clinical usefulness of D-dimer depending on clinical probability and cutoff value in outpatients with suspected pulmonary embolism. Arch Intern Med 2004;164:2483-7.
18. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990;263:2753-9.
19. Hull RD, Raskob GE, Coates G, Panju AA. Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. Chest 1990;97:23-6.
20. Perrier A, Miron MJ, Desmarais S, et al. Using clinical evaluation and lung scan to rule out suspected pulmonary embolism: is it a valid option in patients with normal results of lower-limb venous compression ultrasonography? Arch Intern Med 2000;160:512-6.
21. de Moerloose P, Desmarais S, Bounameaux H, et al. Contribution of a new, rapid, individual and quantitative automated D-dimer ELISA to exclude pulmonary embolism. Thromb Haemost 1996;75:11-3.
22. Lensing AWA, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N Engl J Med 1989;320:342-5.
23. Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. Lancet 1991;337:196-200.
24. Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med 1996;156:531-6.
25. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999;353:190-5.
26. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 2001;135:98-107.
27. Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Buller HR. Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: a prospective management study. Arch Intern Med 2002;162:1631-5.
28. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998;129:997-1005.