Effectiveness of Managing Suspected Pulmonary Embolism Using an Algorithm Combining Clinical Probability, D-Dimer Testing, and Computed Tomography

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THE MAIN CHALLENGE IN THE DI-agnostic workup of patients with clinically suspected pulmonary embolism is to accurately and rapidly distinguish the approximately 25% of patients who have the disease and require anticoagulant treatment from the 75% who do not.[1,2] A number of new approaches have improved the diagnostic process for pulmonary embolism. The first is the combination of a clinical decision rule such as the Wells score,[3] which categorizes patients as low, intermediate, or high clinical probability of pulmonary embolism, with a D-dimer test. Several management studies have shown that pulmonary embolism can be safely ruled out without the need for additional imaging in patients with low clinical probability and a normal D-dimer test result, occurring in 20% to 40% of patients.[3-5] In these studies, 3 categories of likelihood were used. However, a retrospective analysis suggested that the clinical utility of the Wells score could be further increased by using 2 instead of 3 categories of clinical probability, dichotomizing patients as either likely or unlikely to have had a pulmonary embolism,[3] but no large prospective studies evaluating this dichotomization have been carried out.

Context Previous studies have evaluated the safety of relatively complex combinations of clinical decision rules and diagnostic tests in patients with suspected pulmonary embolism.

Objective To assess the clinical effectiveness of a simplified algorithm using a dichotomized clinical decision rule, D-dimer testing, and computed tomography (CT) in patients with suspected pulmonary embolism.

Design, Setting, and Patients Prospective cohort study of consecutive patients with clinically suspected acute pulmonary embolism, conducted in 12 centers in the Netherlands from November 2002 through December 2004. The study population of 3306 patients included 82% outpatients and 57% women.

Interventions Patients were categorized as "pulmonary embolism unlikely" or "pulmonary embolism likely" using a dichotomized version of the Wells clinical decision rule. Patients classified as unlikely had D-dimer testing, and pulmonary embolism was considered excluded if the D-dimer test result was normal. All other patients underwent CT, and pulmonary embolism was considered present or excluded based on the results. Anticoagulants were withheld from patients classified as excluded, and all patients were followed up for 3 months.

Main Outcome Measure Symptomatic or fatal venous thromboembolism (VTE) during 3-month follow-up.

Results Pulmonary embolism was classified as unlikely in 2206 patients (66.7%). The combination of pulmonary embolism unlikely and a normal D-dimer test result occurred in 1057 patients (32.0%), of whom 1028 were not treated with anticoagulants; subsequent nonfatal VTE occurred in 5 patients (0.5% [95% confidence interval {CI}, 0.2%-1.1%]). Computed tomography showed pulmonary embolism in 674 patients (20.4%). Computed tomography excluded pulmonary embolism in 1505 patients, of whom 1436 patients were not treated with anticoagulants; in these patients the 3-month incidence of VTE was 1.3% (95% CI, 0.7%-2.0%). Pulmonary embolism was considered a possible cause of death in 7 patients after a negative CT scan (0.5% [95% CI, 0.2%-1.0%]). The algorithm was completed and allowed a management decision in 97.9% of patients.

Conclusions A diagnostic management strategy using a simple clinical decision rule, D-dimer testing, and CT is effective in the evaluation and management of patients with clinically suspected pulmonary embolism. Its use is associated with low risk for subsequent fatal and nonfatal VTE.

JAMA. 2006;295:172-179   www.jama.com

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Another advancement is computed tomography (CT), which has emerged as a prominent imaging technique for the exclusion or confirmation of pulmonary embolism, as well as the detection of alternative diagnoses.[6-10] However, a critical missing piece of information has been whether it is safe to withhold anticoagulation treatment after a CT that is negative for pulmonary embolism.[11,12] In a recent study,[13] recurrent venous thromboembolism (VTE) occurred in 1.7% of patients who initially had a low or intermediate probability for pulmonary embolism using the Geneva score,[14] an abnormal D-dimer test result, normal bilateral compression ul-

trasound (CUS) of the leg veins, and a normal multidetector-row CT scan. In that study, all patients with high probability for pulmonary embolism had to undergo pulmonary angiography after normal CT and normal CUS. A more efficient strategy would consist of an algorithm with a dichotomized decision rule, D-dimer testing, and CT, in which pulmonary embolism is considered excluded in patients with an unlikely clinical probability score and a normal D-dimer test result, while CT is used in all other patients as the sole imaging method to make management decisions. Therefore, we performed a prospective study in a large cohort of

consecutive patients with clinically suspected pulmonary embolism to evaluate the effectiveness of this novel management strategy.

METHODS
Study Design
The Christopher Study was a prospective cohort study evaluating a diagnostic algorithm consisting of sequential application of a clinical decision rule, D-dimer testing, and CT within 24 hours of presentation (**FIGURE**). All patients were followed up for a period of 3 months after presentation to document the occurrence of subsequent symptomatic VTE.

Figure. Diagnostic Flowchart
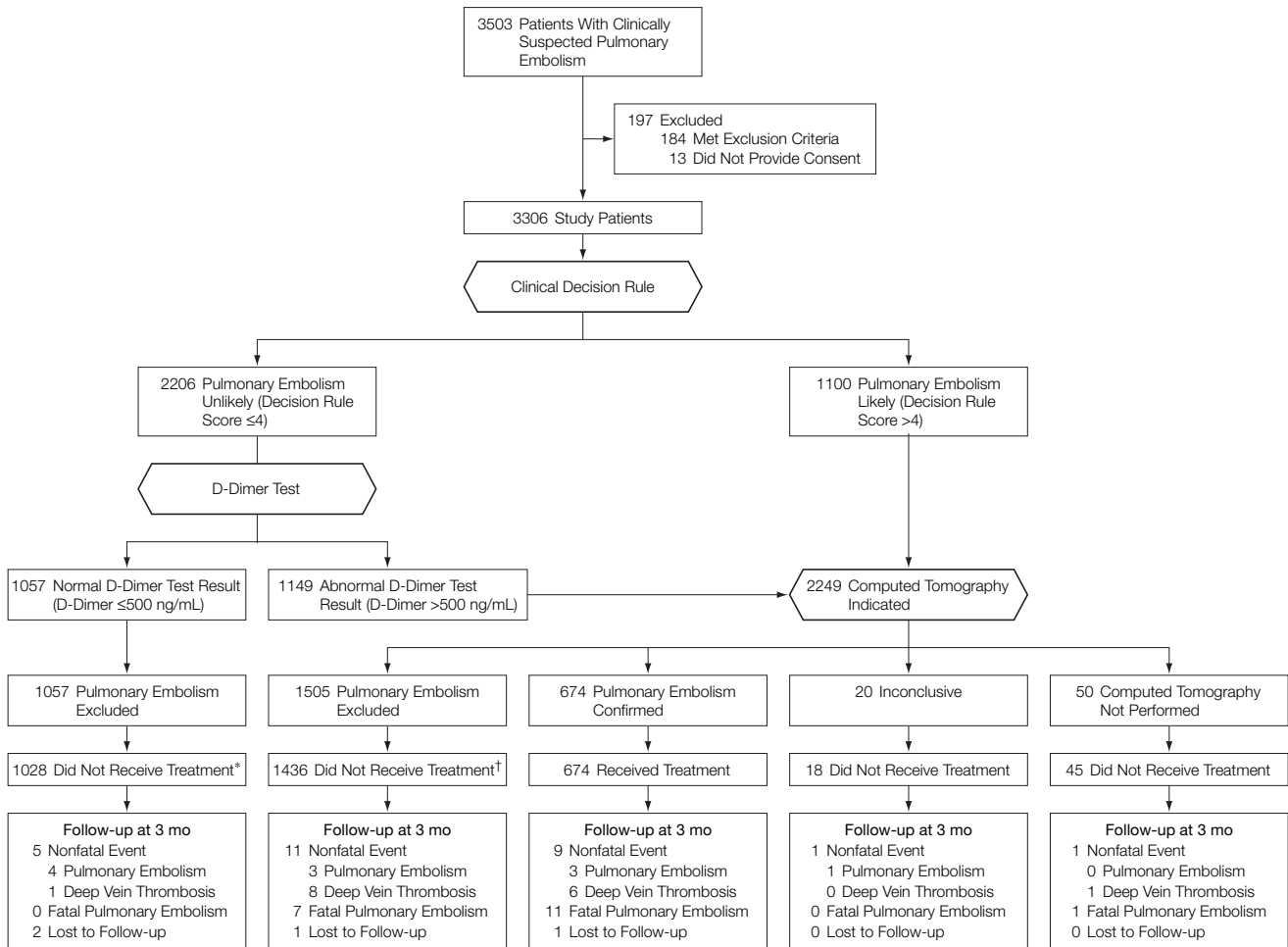
*Excludes 29 patients treated with anticoagulant therapy for reasons other than venous thromboembolism.
†Excludes 69 patients treated with anticoagulant therapy for reasons other than venous thromboembolism.

Table 1. Clinical Decision Rule*

Variable	Points
Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins)	3.0
Alternative diagnosis less likely than pulmonary embolism	3.0
Heart rate >100/min	1.5
Immobilization (>3 d) or surgery in the previous 4 wk	1.5
Previous pulmonary embolism or deep vein thrombosis	1.5
Hemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 mo or palliative)	1.0

*Clinical probability of pulmonary embolism unlikely: 4 or less points; clinical probability of pulmonary embolism likely: more than 4 points. Source: Wells et al.[3]

Patients

Consecutive patients with clinically suspected pulmonary embolism, defined as a sudden onset of dyspnea, sudden deterioration of existing dyspnea, or sudden onset of pleuritic chest pain without another apparent cause, were potentially eligible for the study. Patients presenting to the emergency ward (outpatients) and inpatients were eligible. Patients presenting to an outpatient office were sent directly to the emergency department for evaluation. Patients were recruited between November 2002 and September 2004.

Exclusion criteria were treatment with therapeutic doses of unfractionated or low-molecular-weight heparin for more than 24 hours, life expectancy less than 3 months, pregnancy, geographic inaccessibility precluding follow-up, age younger than 18 years, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance <30 mL/min [<0.5 mL/s]), logistic reasons (eg, unavailability of CT, patient too ill to undergo CT scanning), or hemodynamic instability. Five academic and 7 general urban hospitals in the Netherlands participated. The institutional review boards of all participating hospitals approved the study protocol, and written or oral informed consent was obtained from all participants.

Clinical Decision Rule and D-Dimer Assay

Patients with clinically suspected pulmonary embolism were evaluated by an attending physician using a validated clinical decision rule (**TABLE 1**).[3] Pulmonary embolism was classified as "unlikely" with a clinical decision rule score of 4 or less points, and "likely" with a score of more than 4 points. This cutoff was chosen because it has been shown to give an acceptable VTE diagnostic failure rate of 1.7% to 2.2% in combination with a normal D-dimer test result.[3] An estimated 300 attending physicians in the participating hospitals used the clinical decision rule with the study participants.

In patients with a clinical decision rule indicating pulmonary embolism unlikely, a D-dimer concentration was measured, using either the VIDAS D-dimer assay (Biomerieux, Marcy L'Etoile, France) or the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of 500 ng/mL or less was defined as normal. In patients with pulmonary embolism unlikely and a normal D-dimer test result, the diagnosis of pulmonary embolism was considered excluded and anticoagulant treatment was withheld. Those patients who had a combination of clinical decision rule indicating pulmonary embolism unlikely with an abnormal D-dimer test result, or who had a clinical decision rule indicating pulmonary embolism likely, underwent CT.

Radiological Evaluation

Computed tomography was performed using either single-detector row or multidetector-row systems. Patients were examined during suspended inspiration. The single-detector row CT parameters were 3-mm slice thickness with a 2-mm reconstruction interval at 120 kV/140 mAs, 120 to 140 mL of nonionic contrast material containing 350 mg of iodine per mL with an injection speed of 3.0 mL/s and an injection delay of 16 seconds. Multidetector-row CT parameters were 1.25-mm slice thickness with a 1.2-mm reconstruction interval at 120 kV/120 mAs, 80 to 100 mL of nonionic contrast material containing 350 mg of iodine per mL with an injection speed of 4.0 mL/s and bolus tracking in the common pulmonary artery to get optimal contrast opacification of the pulmonary arteries.

The pulmonary arteries were evaluated up to and including the subsegmental vessels from the level of the aortic arch to the lowest hemidiaphragm. Pulmonary embolism was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least 2 adjacent slices. These patients received low-molecular-weight heparin or unfractionated heparin, followed by vitamin K antagonists, according to local practice. In patients without pulmonary embolism, the presence or absence of an alternative diagnosis was recorded and anticoagulant treatment was withheld. The CT was considered inconclusive if the images could not be interpreted because of motion artifacts due to movements of the patient or the heart or if there was insufficient contrast enhancement of the pulmonary arteries. The management of patients in whom the CT could not be performed or who had an inconclusive CT scan was left to the discretion of the attending physician.

The decision of the presence or absence of pulmonary embolism was made by trained attending radiologists who were blinded to any specific patient clinical information. By protocol design they knew that a patient referred for CT either had a D-dimer level that was above 500 ng/mL or a clinical decision rule score that was higher than 4 points, but did not know which of these items was the reason for performing a CT scan.

Outcome Measures

The primary outcome of the study was the incidence of symptomatic VTE events during 3 months of follow-up, defined as fatal pulmonary embolism, nonfatal pulmonary embolism, or deep vein thrombosis (DVT). An independent adjudication committee, whose members were unaware of the patient's allocation within the diagnos-

tic algorithm, evaluated all suspected VTE and deaths. A diagnosis of pulmonary embolism or DVT was based on a priori defined and generally accepted criteria.[15] Deaths were classified as caused by pulmonary embolism in case of confirmation by autopsy, in case of an objective test positive for pulmonary embolism prior to death, or if pulmonary embolism could not be confidently excluded as the cause of death.

Follow-up consisted of a scheduled outpatient visit or telephone interview at 3 months. Patients were additionally instructed to contact the study center or their general practitioner immediately in the event of symptoms suggestive of DVT or pulmonary embolism. At each visit, information was obtained on complaints suggestive of VTE, including acute onset of dyspnea, acute worsening of existing dyspnea, acute onset of chest pain, unilateral leg swelling and leg pain, as well as interval initiation of anticoagulants. In case of clinically suspected DVT or pulmonary embolism, objective diagnostic tests were required, including CUS for suspected DVT, and ventilation-perfusion scintigraphy or CT for suspected pulmonary embolism. In case of death, information was obtained from the general practitioner, from the hospital records, or from autopsy.

Statistical Analysis

The 2 primary analyses were incidence of symptomatic VTE during follow-up, confirmed by objective testing, in (1) the group of patients in whom anticoagulant treatment was withheld based on a classification of pulmonary embolism unlikely by clinical decision rule and a normal D-dimer test result, and (2) the group of patients in whom anticoagulant treatment was withheld based on a CT scan that excluded pulmonary embolism. Additional analyses were performed for fatal pulmonary embolism in these groups, as well as among the patients with a normal CT scan and an alternative diagnosis on CT separately.

Sample size was based on an assumption of a 1% incidence of VTE in both patient groups[5,9] and a goal to keep the upper limit of the 95% confidence interval (CI) below 2.7%, which has been reported as the upper limit of the range of recurrent VTE after a normal angiogram.[16] We calculated that approximately 1000 patients would have to be included in each group, using a 2-sided type I error of .05 and a type II error of .20. Since we expected that approximately 30% of patients would have a classification of pulmonary embolism unlikely by clinical decision rule and a normal D-dimer test result,[5] a total study population of 3300 patients was needed.

Exact 95% CIs were calculated around the observed incidences using StatXact software, version 5 (Cytel Software Corp, Cambridge, Mass). Descriptive parameters were calculated using SPSS software, version 11.5 (SPSS Inc, Chicago, Ill). For statistical differences, the Fisher exact test was used; statistical significance was set at $P<.05$.

RESULTS

Study Patients

A total of 3503 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 184 (5.3%) were excluded because of predefined exclusion criteria: more than 24 hours of low-molecular-weight heparin (n=50), life expectancy less than 3 months (n=47), pregnancy (n=26), geographic inaccessibility precluding follow-up (n=20), renal insufficiency (n=26), logistic reasons (n=10), age younger than 18 years (n=4), and allergy to intravenous contrast agent (n=1). In addition, 13 patients refused consent (Figure). The final study population of 3306 participants included 2701 (81.7%) outpatients and 605 (18.3%) inpatients; the baseline demographic and clinical characteristics of the 3306 study patients are shown in TABLE 2.

Results of Diagnostic Algorithm

Of the 3306 included patients, 2206 (66.7%) had a clinical decision rule in-

Table 2. Baseline Demographic and Clinical Characteristics of Study Population (N = 3306)*

Characteristic	Value
Age, mean (SD), y	53.0 (18.4)
Female	1897 (57.4)
Outpatients	2701 (81.7)
Duration of complaints, median (IQR), d	2 (1-5)
Paralysis	91 (2.8)
Immobilization or recent surgery	610 (18.5)
Previous venous thromboembolism	480 (14.5)
COPD with treatment	341 (10.3)
Heart failure with treatment	243 (7.4)
Malignancy	476 (14.4)
Estrogen use, women	438 (23.1)
Clinical symptoms of deep vein thrombosis	190 (5.7)
Heart rate >100/min	867 (26.2)
Hemoptysis	176 (5.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
*Data are presented as number and percentage unless otherwise indicated.

dicating pulmonary embolism unlikely and were tested for D-dimer concentrations (Figure). The prevalence of pulmonary embolism in these patients was 12.1% (266/2206; 95% CI, 10.7%-13.5%) vs 37.1% (408/1100; 95% CI, 34.2%-40.0%) in those with a clinical decision rule indicating pulmonary embolism likely ($P<.001$). Among the 1149 patients classified as unlikely but with an abnormal D-dimer test result, the prevalence of pulmonary embolism was 23.2% (266/1149). D-dimer test results were normal in 1057 (32.0%) patients, and in these patients, pulmonary embolism was considered excluded. Of the 2206 patients undergoing D-dimer testing, 968 (44%) had a VIDAS D-dimer test performed; 1238 patients (56%) had a Tinaquant D-dimer test.

Of the 2249 patients with either abnormal D-dimer concentrations (n=1149) or a clinical decision rule indicating pulmonary embolism likely (n=1100), 2199 underwent CT. In the other 50 patients a CT was indicated but not performed because of lack of venous access, extreme obesity, DVT confirmed by CUS prior to CT, or a deteriorating clinical condition prior to CT. Multidetector-row CT was performed in 1939 patients and single-detector row CT in 260 patients. Computed tomography excluded pulmonary embolism

Table 3. Venous Thromboembolic Events (VTEs) During 3-Month Follow-up (n = 3138)*

Variable	No.	Total VTEs, No. (%) [95% CI]	Fatal Pulmonary Embolism, No. (%) [95% CI]
Pulmonary embolism unlikely and normal D-dimer test result	1028	5 (0.5) [0.2-1.1]	0 (0) [0.0-0.3]
Pulmonary embolism excluded by CT	1436	18 (1.3) [0.7-2.0]	7 (0.5) [0.2-1.0]
CT normal	764	9 (1.2) [0.5-2.2]	3 (0.4) [0.1-1.1]
CT alternative diagnosis	672	9 (1.3) [0.6-2.5]	4 (0.6) [0.1-1.5]
Pulmonary embolism diagnosed by CT	674	20 (3) [1.8-4.6]	11 (1.6) [0.8-2.9]

Abbreviations: CI, confidence interval; CT, computed tomography.
*A total of 168 patients were excluded due to treatment with anticoagulation outside of protocol, inconclusive CT, or CT not performed.

in 1505 patients (45.5% of the study population). In these patients, 702 (21.2% of the study population) had additional diagnostic information visualized on CT: pneumonia (n=212), pleural effusion (n=163), malignancy (n=50), and other diagnoses (n=277). Pulmonary embolism was confirmed in 674 patients (20.4% of the study population). Computed tomography was inconclusive in 20 patients (0.9%). Hence, the diagnostic algorithm could be completed according to the protocol in 3256 patients (98.5%) and allowed a management decision in 3236 patients (97.9%).

Patients With Pulmonary Embolism Unlikely and Normal D-Dimer Test Result

Of the 1057 patients with the combination of a clinical decision rule indicating pulmonary embolism unlikely and a normal D-dimer test result, 29 patients (2.7%) were treated with oral anticoagulants during follow-up for various reasons other than VTE. Three of the 1028 remaining patients returned with symptomatic VTE events (2 nonfatal pulmonary embolism, 1 DVT) during the 3-month follow-up. In 25 patients, the protocol was violated and a CT or a ventilation-perfusion scan was performed while not indicated. Pulmonary embolism was diagnosed in 2 of these 25 patients. Therefore, the incidence of VTE was 5 of 1028 (0.5% [95% CI, 0.2%-1.1%]) (TABLE 3). Two patients were lost to follow-up (0.2%). In a "worst case" scenario, in which these 2 patients would have developed VTE, the incidence of VTE would have been 7 of 1028 (0.7%

[95% CI, 0.3%-1.4%]). There were no fatal pulmonary embolisms. Eight (0.8%) of the 1057 patients died of other causes.

Of the study population, 605 were inpatients, and 56 of these had a decision rule indicating pulmonary embolism unlikely and a normal D-dimer test result (9.3%). No VTE was observed at follow-up in these patients (VTE rate, 0% [95% CI, 0%-6.4%]). The results for inpatients and outpatients were comparable (VTE rate, 0% [95% CI, 0%-6.4%] vs 0.5% [95% CI, 0.2%-1.2%]). There were no significant differences between patients at academic and general hospitals.

The VIDAS D-dimer assay had a true-negative rate of 44.2% (428/968 patients) and the Tinaquant D-dimer assay had a true-negative rate of 50.8% (629/1238 patients) (P<.002). The negative predictive values for the VIDAS and Tinaquant assays were 100% (95% CI, 99.1%-100%) and 99.2% (95% CI, 98.1%-99.7%), respectively.

Patients With CT Excluding Pulmonary Embolism

Of the 1505 patients in whom CT excluded pulmonary embolism, 69 (4.6%) received anticoagulants during follow-up for various reasons other than VTE. Of the 1436 patients who did not receive anticoagulant treatment, 18 experienced VTE events during the 3-month follow-up (1.3% [95% CI, 0.7%-2.0%]). Eleven of these patients had nonfatal symptomatic thromboembolic events (3 pulmonary embolism and 8 DVT). Fatal pulmonary embolism was presumed to have occurred in the other 7 patients (0.5% [95% CI,

0.2%-1.0%]); it was proven by autopsy in 2 and attributed as the cause of death in 5 (TABLE 4). Follow-up was incomplete in one of the 1436 patients (0.1%). In a "worst case" scenario in which this patient would have developed VTE, the incidence of VTE would have been 19 of 1436 (1.3% [95% CI, 0.8%-2.1%]).

Rates of VTE during follow-up were comparable for inpatients and outpatients (1.4% ([95% CI, 0.4%-3.1%]) vs 1.2% [95% CI, 0.7%-2.1%], respectively). Among the patients who did not receive anticoagulants, similar incidences of VTE were observed in those with a normal CT scan (9/764 [1.2%] {95% CI, 0.5%-2.2%}) and those with additional diagnostic information on CT (9/672 [1.3%] {95% CI, 0.6%-2.5%}) (Table 3). Similar incidences of VTE were observed in untreated patients who underwent multidetector-row CT (14/1266 [1.1%] {95% CI, 0.6%-1.9%}) vs single-detector row CT (4/170 [2.4%] {95% CI, 0.6%-5.9%}).

Twenty patients returned with symptoms of pulmonary embolism during follow-up. Computed tomography was again used as the diagnostic method in 13 of these 20 patients and was normal in all. No VTE was demonstrated at later follow-up.

The overall mortality rate in patients in whom CT excluded pulmonary embolism was 8.6% (129 patients).

Patients With CT That Was Inconclusive or Not Performed

Of the 20 patients with an inconclusive CT scan, pulmonary embolism was demonstrated by ventilation-perfusion lung scan in 2 patients, and they received anticoagulant treatment. During follow-up, 1 of the 18 remaining patients had a nonfatal VTE event. Of the 50 patients in whom CT was indicated but not performed, 3 had pulmonary embolism demonstrated by ventilation-perfusion lung scan, and 2 patients had DVT demonstrated by CUS; during follow-up, 1 of the remaining 45 patients had a fatal pulmonary embolism, while DVT occurred in

1 patient. The mortality rate for inconclusive CT was 5% (1/20) and for CT not performed, 14% (7/50).

Patients With Pulmonary Embolism Confirmed by CT

Of the 674 patients in whom CT demonstrated pulmonary embolism, 20 patients (3.0%) had a recurrent VTE despite anticoagulant treatment. This included 11 fatal pulmonary embolism, 3 nonfatal pulmonary embolism, and 6 DVT. One patient was lost to follow-up. The overall mortality in this group was 7.2% (55 patients).

COMMENT

This large cohort study of 3306 consecutive patients with clinically suspected pulmonary embolism demonstrates that the use of a diagnostic algorithm consisting of a dichotomous decision rule, D-dimer testing, and CT scan can guide treatment decisions with a low risk for subsequent pulmonary embolism. No further diagnostic testing was necessary in the third of our patients who had an unlikely clinical probability score in combination with a normal D-dimer test result, with a 3-month incidence of VTE of 0.5%. Computed tomography effectively ruled out pulmonary embolism in all other patients without using other imaging tests (3-month incidence of VTE in those with a negative CT of 1.3%). The algorithm was pragmatic in that it could be completed in 98.5% of the eligible patients and allowed a management decision in 97.9%.

Other management studies have documented the safety of a low clinical probability in combination with a normal D-dimer concentration for the exclusion of pulmonary embolism.[3-5,17] In these studies, the rate of VTE during follow-up ranged from 0% to 1.5%. However, because the sample size was limited, upper confidence limits were as high as 6.0%.[3-5,15]

In contrast to our simple algorithm, a recent study[13] used a more complex flowchart with sequential testing that included clinical probability assessment, D-dimer assay, CUS, CT, as well as pulmonary angiography to exclude pulmonary embolism in patients with high likelihood and negative workup. As the authors pointed out, their study was not a true outcome study, since CUS was performed in all patients with abnormal D-dimer levels, and patients with abnormal CUS and a normal CT scan were treated with anticoagulation. That study had a smaller sample size (674 patients) and a higher rate of exclusion (25% vs 5.6% in our study).

To improve the simplicity and utility of their decision rule, Wells et al proposed changing their model from the original 3 categories (low, moderate, high) to 2 categories (pulmonary embolism unlikely and pulmonary embolism likely).[3] Our study is the

Table 4. Deaths Attributed to Pulmonary Embolism

Patient Sex	Age, y	Results of Computed Tomography	Anticoagulant Therapy	Past Medical History	Time of Death After Enrollment, d	Circumstances of Death
Male	60	Normal	No	COPD, alcohol abuse	3	Sudden death at home
Female	65	Alternative diagnosis: pulmonary metastases	No	Colon cancer; multiple metastases in liver, spleen, adrenal glands	18	Dehydration due to chemotherapy-induced diarrhea; morphine for pain complaints; sudden death
Male	46	Normal	No	Multiple myeloma	40	Bedridden due to complaints of pain associated with myeloma; sudden death at home; autopsy result: pulmonary embolism
Female	69	Alternative diagnosis: interstitial pneumonia	No	Progressive dyspnea in past half year due to interstitial pneumonia	41	Computed tomography at day 34 showed pulmonary embolism; progressive respiratory insufficiency; ventilator dependency; palliative care; autopsy result: pulmonary embolism and bilateral pneumonia
Female	60	Alternative diagnosis: pericarditis carcinomatosa	No	COPD, breast cancer	75	Immobilization in electric wheelchair in nursing home; gradual worsening, cardiac failure due to pericarditis
Female	77	Alternative diagnosis: pneumonia; at review, a subsegmental pulmonary embolism had been missed at inclusion	No	Hypertension	86	Collapse on street with swollen face
Female	31	Normal	No	Pulmonary embolism in 2002, diabetes, renal insufficiency, estrogen use	94	Antibiotics for CAPD peritonitis; sudden death

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; COPD, chronic obstructive pulmonary disease.

first to prospectively validate the safety of the dichotomized score in combination with the D-dimer assay. Compared with a combination using the 3-category classification, this approach has the potential to increase the number of patients in whom pulmonary embolism can be excluded by approximately 50%.[3,17]

Despite concerns that the sensitivity of CT for pulmonary embolism is lower than that of pulmonary angiography,[18,19] the observed risk of subsequent symptomatic VTE in those patients in whom pulmonary embolism was excluded by CT was comparable to the risk reported after a normal pulmonary angiogram (3-month incidence, 1.3% [95% CI, 0.7%-2.0%] vs 1.7% [95% CI, 1.0%-2.7%],[16] respectively). In addition, in our study fatal pulmonary embolism occurred in 0.5% (95% CI, 0.2%-1.0%) of patients in whom CT had excluded pulmonary embolism, compared with 0.3% (95% CI, 0.02%-0.7%) after normal pulmonary angiography.[16] Computed tomography has the potential advantage of providing additional diagnostic information for the presenting symptoms in patients without pulmonary embolism.

Several potential limitations in our study require comment. First, the absence of pulmonary embolism was not verified by pulmonary angiography. However, the clinical outcome after a 3-month follow-up is widely accepted as an appropriate alternative to establish the safety of a diagnostic strategy, given a near-complete follow-up.[20]

Second, while our cohort study has the strength of minimal loss to follow-up (3 patients, 0.1%) and independent blinded adjudication of all outcomes, a randomized controlled study design would have allowed a direct comparison to other validated strategies.

Third, CT was again used to exclude pulmonary embolism in 13 of 20 patients who returned during follow-up with symptoms after CT had excluded pulmonary embolism at baseline. Although these could represent false-negative results, these patients were not treated and further follow-up was uneventful, making this unlikely.

Fourth, the use of multidetector-row CT has the potential for overdiagnosis by imaging very small peripheral subsegmental emboli. Because patients did not undergo confirmatory pulmonary angiography, our study design did not permit assessing the false-positive rate of CT scans. Only 10% of our patients underwent single-detector row CT, so we could not make a meaningful comparison of the impact of each test. However, the overall prevalence of pulmonary embolism in our study (20%) is comparable to the prevalence in a previous multicenter study performed with single-detector row CT (24%).[9] This does not support a concern that multidetector-row CT technology will lead to a high number of false-positive results.

Finally, a definitive cause of death could not be established for all patients with normal test results who died during follow-up. However, pulmonary embolism was assigned as the cause of death if it could not be confidently excluded, a conservative assumption that strengthens our conclusions about low risk for this strategy.

The generalizability of our findings should be considered. The baseline clinical characteristics and the incidence of pulmonary embolism for our study population are comparable with those observed in other population-based studies, except for a somewhat younger mean age.[5,10,12] The low proportion of patients excluded and the enrollment of consecutive patients who were referred to both academic and nonacademic hospitals further supports broad applicability of these results, as does the similar rates of VTE during follow-up between inpatients and outpatients.

In conclusion, a diagnostic management strategy using a simple clinical decision rule, D-dimer testing, and CT is as effective as other more complex diagnostic strategies in the evaluation and management of patients with clinically suspected pulmonary embolism. Its use is associated with low risk for subsequent fatal and nonfatal VTE.

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REFERENCES

1. Lee AY, Hirsh J. Diagnosis and treatment of venous thromboembolism. *Annu Rev Med*. 2002;53: 15-33.

2. 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;263:2753-2759.

3. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83:416-420.

4. Kruip MJ, Slob MJ, Schijen JH, et al. 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;162:1631-1635.

5. Ten Wolde M, Hagen PJ, MacGillavry MR, et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism: results of a management study. *J Thromb Haemost*. 2004;2:1110-1117.

6. Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. *Circulation*. 2004;109:2160-2167.

7. 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;132:227-232.

8. Mullins MD, Becker DM, Hagspiel KD, et al. The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. *Arch Intern Med*. 2000;160:293-298.

9. van Strijen MJ, de Monye W, Schiereck J, et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. *Ann Intern Med*. 2003;138: 307-314.

10. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multi-center outcome study. *Lancet*. 2002;360:1914-1920.

11. Moores LK, Jackson WL Jr, Shorr AF, et al. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. *Ann Intern Med*. 2004;141:866-874.

12. 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;116:291-299.

13. Perrier A, Roy P-M, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med*. 2005;352:1760-1768.

14. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med*. 2001;161:92-97.

15. Büller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695-1702.

16. van Beek EJ, Brouwerst EM, Song B, et al. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism—a critical review. *Clin Radiol*. 2001;56:838-842.

17. Wolf SJ, McCubbin TR, Feldhaus KM, et al. Prospective validation of Wells criteria in the evaluation of patients with suspected pulmonary embolism. *Ann Emerg Med*. 2004;44:503-510.

18. Van Strijen MJ, De Monye W, Kieft GJ, Pattynama PM, 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.

19. Perrier A, Bounameaux H. Validation of helical computed tomography for suspected pulmonary embolism: a near miss? *J Thromb Haemost*. 2005;3: 14-16.

20. Kruip MJ, Leclercq MG, van der Heul C, et al. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies: a systematic review. *Ann Intern Med*. 2003;138:941-951.