15 December 1998 Volume 129 Number 12

Annals of Internal Medicine

Use of a Clinical Model for Safe Management of Patients with Suspected Pulmonary Embolism

Philip S. Wells, MD, MSc; Jeffrey S. Ginsberg, MD; David R. Anderson, MD; Clive Kearon, MD, PhD; Michael Gent, MSc; Alexander G. Turpie, MD; Janis Bormanis, MD; Jeffrey Weitz, MD; Michael Chamberlain, MD; Dennis Bowie, MD; David Barnes, MD; and Jack Hirsh, MD

Background: The low specificity of ventilation–perfusion lung scanning complicates the management of patients with suspected pulmonary embolism.

Objective: To determine the safety of a clinical model for patients with suspected pulmonary embolism.

Design: Prospective cohort study.

Setting: Five tertiary care hospitals.

Patients: 1239 inpatients and outpatients with suspected pulmonary embolism.

Interventions: A clinical model categorized pretest probability of pulmonary embolism as low, moderate, or high, and ventilation–perfusion scanning and bilateral deep venous ultrasonography were done. Testing by serial ultrasonography, venography, or angiography depended on pretest probability and lung scans.

Measurements: Patients were considered positive for pulmonary embolism if they had an abnormal pulmonary angiogram, abnormal ultrasonogram or venogram, high-probability ventilation–perfusion scan plus moderate or high pretest probability, or venous thromboembolic event during the 3-month follow-up. All other patients were considered negative for pulmonary embolism. Rates of pulmonary embolism during follow-up in patients who had a normal lung scan and those with a non–high-probability scan and normal serial ultrasonogram were compared.

Results: Pretest probability was low in 734 patients (3.4% with pulmonary embolism), moderate in 403 (27.8% with pulmonary embolism), and high in 102 (78.4% with pulmonary embolism). Three of the 665 patients (0.5% [95% CI, 0.1% to 1.3%]) with low or moderate pretest probability and a non–high-probability scan who were considered negative for pulmonary embolism had pulmonary embolism or deep venous thrombosis during 90-day follow-up; this rate did not differ from that in patients with a normal scan (0.6% [CI, 0.1% to 1.8%]; $P > 0.2$).

Conclusion: Management of patients with suspected pulmonary embolism on the basis of pretest probability and results of ventilation–perfusion scanning is safe.

This paper is also available at http://www.acponline.org.

Ann Intern Med. 1998;129:997-1005.

Because the signs and symptoms of pulmonary embolism are nonspecific, objective diagnostic tests are warranted when this event is suspected (1, 2). Many algorithms have been suggested for the diagnosis of pulmonary embolism, but there is no standardized approach. Pulmonary angiography is the gold standard diagnostic test, but this technique is invasive, expensive, not readily available, and labor intensive. Moreover, its results can be difficult to interpret. In addition, 1.6% of patients with a normal pulmonary angiogram develop pulmonary embolism during 1-year follow-up, usually in the first month (3, 4). Consequently, noninvasive ventilation–perfusion lung scanning is usually performed first in patients with suspected pulmonary embolism. A normal scan essentially rules out the diagnosis of pulmonary embolism (5), and a high-probability scan has a high positive predictive value (except in patients with a low pretest probability) (6, 7). However, more than 50% of patients with suspected pulmonary embolism have so-called non–high-probability ventilation–perfusion scans; angiography would demonstrate pulmonary embolism in less than 25% of these patients. Given the limitations of angiography and the fact that most pulmonary emboli originate from thrombi in the deep veins of the leg (7), investigation for deep venous thrombosis by using ultrasonography is an alternative. It is relatively safe to withhold anticoagulation in patients with suspected pulmonary embolism who have no evidence of deep venous thrombosis on serial impedance plethysmography (8); however, impedance plethysmography is not widely used, and we recently demonstrated that it is significantly less sensitive

See related articles on pp 1006-1011 and pp 1044-1049.

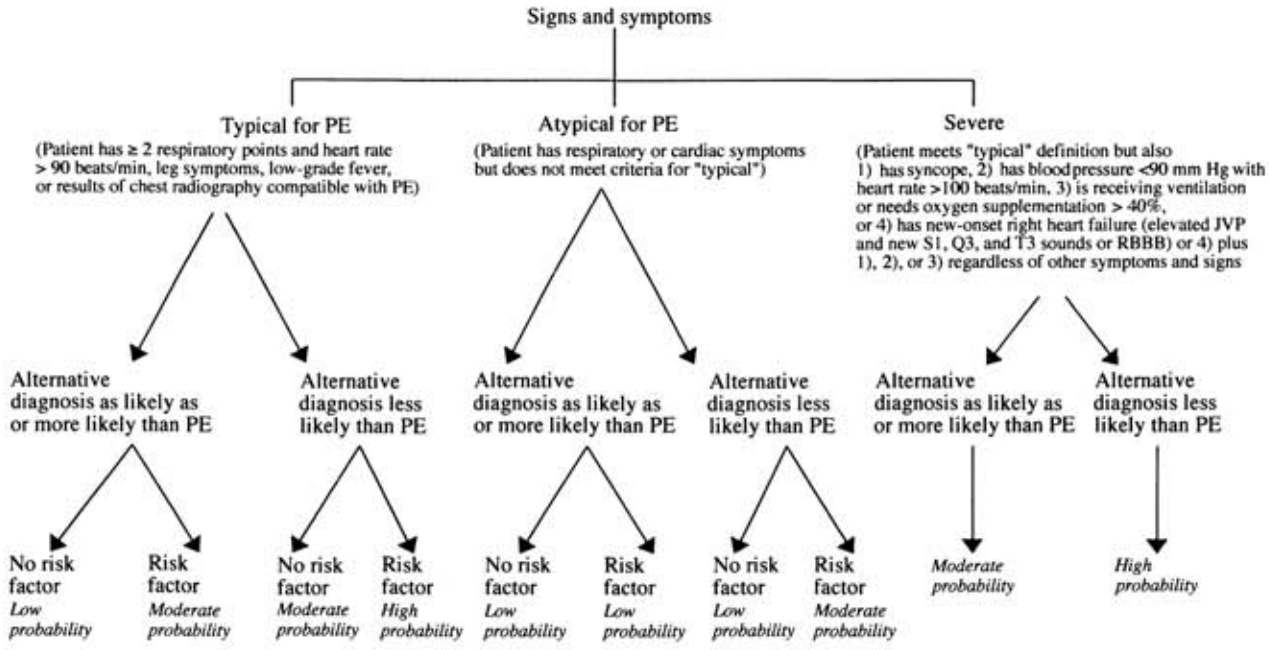

Figure 1. Algorithm for the clinical model to determine the pretest probability of pulmonary embolism (*PE*). Respiratory points consist of dyspnea or worsening of chronic dyspnea, pleuritic chest pain, chest pain that is nonretrosternal and nonpleuritic, an arterial oxygen saturation less than 92% while breathing room air that corrects with oxygen supplementation less than 40%, hemoptysis, and pleural rub. Risk factors are surgery within 12 weeks, immobilization (complete bedrest) for 3 or more days in the 4 weeks before presentation, previous deep venous thrombosis or objectively diagnosed pulmonary embolism, fracture of a lower extremity and immobilization of the fracture within 12 weeks, strong family history of deep venous thrombosis or pulmonary embolism (two or more family members with objectively proven events or a first-degree relative with hereditary thrombophilia), cancer (treatment ongoing, within the past 6 months, or in the palliative stages), the postpartum period, and lower-extremity paralysis. JVP = jugular venous pressure; RBBB = right bundle-branch block.

than ultrasonography (9, 10). Two studies (6, 11) have demonstrated that clinical assessment of the pretest probability of pulmonary embolism may be a useful adjunct to lung scanning, but neither study used explicit criteria.

The optimal strategy for investigating patients with suspected pulmonary embolism should combine clinical assessment, ventilation–perfusion scanning, and venous ultrasonography of the lower extremities. We reasoned that patients with non–high-probability ventilation–perfusion scans and a low or moderate pretest clinical probability of pulmonary embolism (as determined by a clinical prediction rule) could be safely managed with serial ultrasonography. Further testing would be required in patients with a high clinical probability and a non–high-probability scan and in patients with a low clinical probability and a high-probability scan.

Methods

Development of the Clinical Model

Our group (consisting of physicians trained in respiratory medicine, hematology, thrombotic diseases, epidemiology, and radiology) previously developed a useful clinical model for patients with suspected deep venous thrombosis by reviewing the literature and coming to a consensus on a scoring system. The system combined well-established risk factors for venous thrombosis, clinical signs and symptoms, and determination of whether an alternative diagnosis was likely (12). We applied the same strategy in patients with suspected pulmonary embolism. We used criteria from the published literature (13, 14) to establish a pilot model by consensus. This preliminary model was tested in a pilot study of 91 patients with suspected pulmonary embolism and was subsequently refined. The final clinical model is shown in **Figure 1**.

First, a history was taken and a physical examination was performed; the latter included chest radiography, oxygen saturation tests, and electrocardiography (if indicated). A checklist of signs and symptoms was completed to determine whether the patient met our definition of a severe, typical, or atypical clinical presentation. The presence of an alternative diagnosis that was as likely as or more likely than pulmonary embolism to account for the patient's signs and symptoms was determined. This determination was based on signs and symptoms and results of routine tests (blood gas, chest X radiography, or electrocardiography). We defined an alternative diagnosis as any other illness that could fit the patient's symptom complex if it was supported by the history or by physical, laboratory, and radiologic findings. The alternative diagnosis did not have to be related to previous disorders: For exam-

ple, it was possible to enroll a patient with an alternative diagnosis of pneumonia if the physician still thought that pulmonary embolism could not be ruled out. Finally, established risk factors for venous thromboembolism were totalled. Patients could then be classified as having a low, moderate, or high probability of pulmonary embolism.

Management Study

Patient Sample

Five Canadian centers (McMaster University Medical Centre and the Hamilton Civics Hospitals, Hamilton; Ottawa Civic Hospital, Ottawa; and Queen Elizabeth II Health Sciences Centre, Halifax) participated in the study from September 1993 to May 1996. Consecutive inpatients and outpatients with suspected pulmonary embolism whose symptoms had lasted less than 30 days were potentially eligible. Exclusion criteria were 1) suspected upper-extremity deep venous thrombosis as the source of the pulmonary embolism, 2) no symptoms of pulmonary embolism for more than 3 days before presentation, 3) use of anticoagulation for more than 72 hours, 4) expected survival of less than 3 months (a criterion introduced halfway through the study because the death rate, albeit not due to pulmonary embolism, was higher than expected), 5) contraindication to contrast media, 6) pregnancy, 7) geographic inaccessibility precluding follow-up, 8) age younger than 18 years, and 9) inability to obtain permission from the patient or the patient's attending physician.

Investigations on the Day of Presentation

After informed consent was obtained, all patients were evaluated by a physician to determine the pretest clinical probability of pulmonary embolism by using the clinical model. Ventilation–perfusion scanning was performed, and the results were interpreted by the hospitals' nuclear medicine physicians. These physicians had no knowledge of other results or the patients' signs, symptoms, or risk factors. Their scan interpretations were used to manage patients. Ventilation–perfusion scans were interpreted as 1) normal (no perfusion defects), 2) high probability (≥1 segmental or greater perfusion defects with normal ventilation or ≥2 large subsegmental perfusion defects [>75% of a segment]) with normal ventilation, or 3) non–high probability (ventilation–perfusion defects that did not qualify as high probability or normal) (7). A lung segment reference chart was used to interpret the scans (15). In a random sample of 570 patients, the scans were interpreted by using the revised Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria (16) and were compared with the

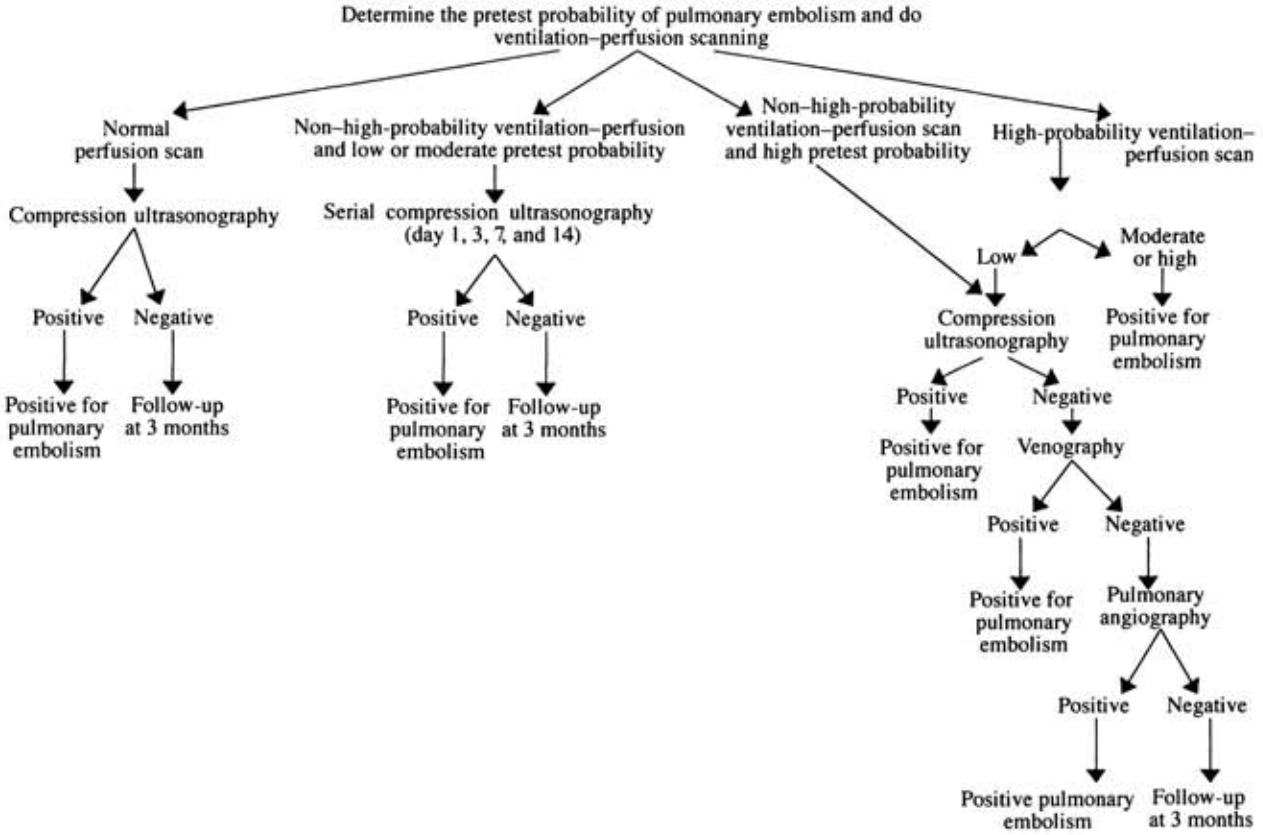

Figure 2. Diagnostic strategy used in patients with suspected pulmonary embolism.

results derived by using the criteria described above. After ventilation–perfusion scanning was completed, bilateral compression ultrasonography from the common femoral vein to the trifurcation of the calf veins (but not below) was performed. Lack of vein compressibility was considered diagnostic of deep venous thrombosis.

Subsequent Management Strategy

Patient management was based on the results of clinical pretest probability, ventilation–perfusion scanning, and ultrasonography (**Figure 2**). In our management strategy, patients underwent contrast venography and pulmonary angiography if the clinical pretest probability and ventilation–perfusion scan were discordant (high clinical probability with a non–high-probability ventilation–perfusion scan or low clinical probability with a high-probability ventilation–perfusion scan). Contrast venography was performed as described elsewhere (17). If the venogram was normal, patients received intravenous heparin and pulmonary angiography was performed within 24 hours. Pulmonary angiography was performed by using standard techniques (11). Pulmonary embolism was diagnosed if there was a constant intraluminal filling defect or an abrupt cut-off in vessels larger than 2.5 mm in diameter. Low- and moderate-probability patients with non–high-probability ventilation–perfusion scans are statistically the most likely group to have false-positive results on ultrasonography. Therefore, we attempted to perform confirmatory venography in these patients. If the venogram was inadequate or could not be obtained, the final diagnosis was made on the basis of the result of ultrasonography or angiography was performed.

Patients were classified as positive for pulmonary embolism if one or more of the following occurred: an abnormal result on pulmonary angiography, ultrasonography, or venography; a high-probability ventilation–perfusion scan plus moderate or high pretest probability; or a venous thromboembolic event within the 3-month follow-up period. All other patients were classified as negative for pulmonary embolism.

Treatment and Follow-up

Anticoagulant therapy was withheld in patients who were negative for pulmonary embolism. Patients were followed for 3 months and were instructed to return at once if they developed symptoms or signs suggestive of pulmonary embolism or deep venous thrombosis. If at any time venous thromboembolism was suspected, patients were investigated by using a standardized approach (**Figure 3**). After 3 months, all patients returned for a follow-up appointment or were contacted by telephone.

Statistical Analysis

The primary analysis was a comparison of the rate of venous thromboembolism during the 3-month follow-up in patients who had a low or moderate pretest probability, non–high-probability ventilation–perfusion scans, and normal serial compression ultrasonograms with the rate in patients who had normal perfusion scans and normal initial ultrasonograms. This comparison was performed because a normal ventilation–perfusion scan is usually considered to exclude pulmonary embolism and we hypothesized a priori that the rates of venous thromboembolism in these two groups would be the same. Sample size was determined by adapting the equivalence test procedure described by Dunnett and Gent (18). We believed that an acceptable rate of deep venous thrombosis or pulmonary embolism in the follow-up period after normal serial testing in patients with non–high-probability ventilation–perfusion scans and low or moderate pretest clinical

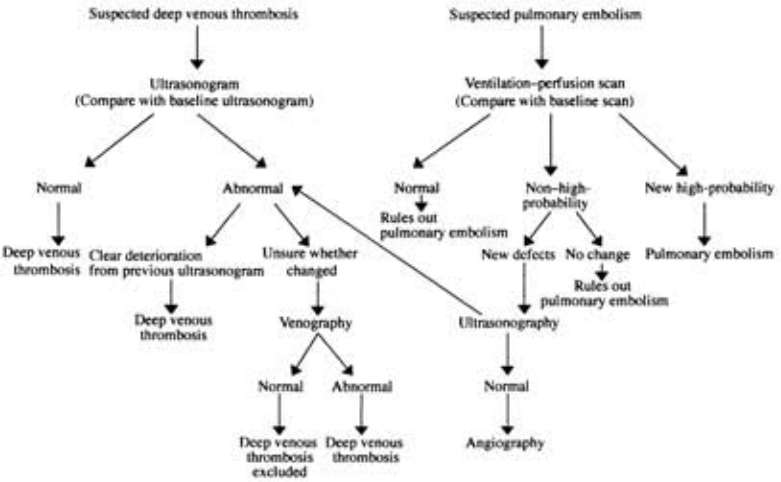

Figure 3. Algorithm for investigation of patients with suspected deep venous thrombosis or pulmonary embolism during 3-month follow-up.

Table 1. Rates of Pulmonary Embolism According to Pretest Probability of Pulmonary Embolism and Results of Ventilation–Perfusion Lung Scanning

Pretest Probability of Pulmonary Embolism	Normal Perfusion (95% CI)	Lung Scanning Result (95% CI)		Total (95% CI)
		Non–High Probability	High Probability	
	← % →			
Low	1.2 (0.2–3.4)	2.9 (1.5–4.9)	33 (17–54)	3.4 (2.2–5.0)
Moderate	0 (0–4.9)	12.1 (8.0–16.2)	100*	27.8 (23.4–32.2)
High	13 (3.2–52.7)	47 (37.9–72)	100*	78.4 (69.2–86.0)
Total	1.2 (0.3–3.0)	8.4 (6.5–10.7)	89.3 (83.7–93.6)	17.5 (15.4–19.6)

* By definition, the probability of pulmonary embolism was 100% in these groups.

probability would be 4%; this was the rate of pulmonary embolism in the normal/near-normal category used in PIOPED. Most physicians seem to consider such scan results acceptable to exclude pulmonary embolism. We accepted that the rate of events on follow-up in the patients with normal perfusion scans would be 1%. In this case, with the null hypothesis (probability of pulmonary embolism during follow-up in patients with non–high-probability lung scans minus the probability of pulmonary embolism during follow-up in patients with a normal lung scan = 3%) and the alternative hypothesis (probability = 1%), 550 patients with non–high-probability lung scans would provide a power of 84% to demonstrate that the difference between the two groups is unlikely to be more than 3%. We judged that a 3% difference would be clinically acceptable.

Results were assessed by using a chi-square test. Confidence intervals were calculated from the binomial distribution. To determine the interobserver reliability of the clinical model, two independent observers obtained same-day assessments in 58 patients. Agreement was determined by using a weighted κ test. The rates of abnormal ultrasonography results in the three pretest probability categories were compared by using a 3×2 chi-square test. This analysis was performed for all patients regardless of lung scanning results and in patients with high-probability lung scans.

Results

Patients

A total of 1885 consecutive, symptomatic patients were evaluated, of whom 484 were ineligible because of prolonged anticoagulant therapy ($n = 158$), expected survival less than 3 months ($n = 89$), geographic inaccessibility ($n = 68$), contraindication to contrast media ($n = 60$), inability to contact the attending physician ($n = 57$), pregnancy ($n = 23$), suspected upper-extremity deep venous thrombosis ($n = 17$), symptoms resolved for more than 72 hours ($n = 7$), and age younger than 18 years ($n = 5$). Of the 1401 eligible patients, 147 declined to participate, 2 had inadequate ventilation–perfusion scans, and 13 moved from the study region and were lost to follow-up. Thus, 1239 patients were evaluated.

Pretest Probability and Rates of Pulmonary Embolism

Of the 1239 evaluable patients, 734 were determined to have a low pretest probability (of whom 25 [3.4%] had pulmonary embolism), 403 had a moderate pretest probability (of whom 112 [27.8%] had pulmonary embolism), and 102 had a high pretest probability (of whom 80 [78.4%] had pulmonary embolism). **Table 1** shows the breakdown of patients with pulmonary embolism according to pretest probability and result of ventilation–perfusion scanning. The difference in the prevalence of pulmonary embolism in the three categories was statistically significant ($P < 0.001$).

The proportion of patients with pulmonary embolism in the three pretest probability categories was compared among centers. The clinical model performed similarly in all five centers ($P > 0.2$). Sixteen physicians were involved in the study. The weighted κ value for interobserver reliability for the clinical model was determined in a subset of 58 patients to be 0.86; this value represents an excellent level of agreement.

Ventilation–Perfusion Lung Scanning

Of the 1239 patients analyzed, 334 (27%) had normal ventilation–perfusion scans, 736 (59%) had non–high-probability scans, and 169 (14%) had high-probability scans. When events in the 3-month follow-up period were included, 4 patients (1.2%) in the normal ventilation–perfusion scan group, 62 patients in the non–high-probability scan group (8.4%), and 151 patients (89%) in the high-probability scan group were positive for pulmonary embolism. Results obtained by using the PIOPED criteria are shown in **Table 2.**

Table 2. Rates of Pulmonary Embolism According to Pretest Probability of Pulmonary Embolism and Results of Ventilation–Perfusion Lung Scanning (by PIOPED Criteria)*

Pretest Probability of Pulmonary Embolism	Normal Perfusion	Lung Scan Result			Total†
		Low Probability	Intermediate Probability	High Probability	
	←		*n/n*	→	*n/n (%)*
Low	2/162	0/113	1/69	4/13	7/357 (2 [0.8–4.0])
Moderate	0/40	5/54	8/41	32/33	45/168 (27 [20.3–34.2])
High	0/3	2/8	5/8	21/24	28/43 (65 [49.1–79.0])
Total‡	2/205 (1 [0.1–3.5])	7/175 (4 [1.6–8.1])	14/118 (12 [6.6–19.1])	57/70 (81.4 [70.3–89.7])	

* PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.
† Values in square brackets are 95% CIs.
‡ Values in parentheses and square brackets are (percentage of patients [95% CI]).

Management Strategy

Primary Analysis

Rates of venous thromboembolic events during the 3-month follow-up did not differ between patients with normal perfusion scans and normal initial ultrasonograms (2 of 332 [0.6%; 95% CI, 0.3% to 3.0%]) and those with non–high-probability ventilation–perfusion scans, low or moderate pretest probability, and normal serial ultrasonograms (3 of 665 [0.5%; CI, 0.1% to 1.3%]; $P > 0.2$). Normal serial ultrasonography had a negative predictive value of 99.5%. The results of ultrasonography are shown in **Figure 4**. Serial conversion occurred in 14 of 679 patients (2.0%): 7 on day 3, 4 on day 7, and 3 on day 14. Thus, if the day 7 and 14 ultrasonograms had not been obtained, the follow-up event rate could have been as high as 1.3%. Three-month follow-up information was obtained by telephone for 58% of patients. All other patients were interviewed for their follow-up visit and underwent ultrasonography at 3 months. Asymptomatic deep venous thrombosis was not detected in any of these patients.

Secondary Analyses

Twenty-seven of the 169 patients (16%) with high-probability ventilation–perfusion scans had a low pretest probability. Eight patients were initially confirmed to have pulmonary embolism (by ultrasonography in 5 patients, venography in 1, and angiography in 2). One patient had pulmonary embolism during follow-up, but this patient did not comply with the protocol by declining to undergo venography and angiography. A comparison of ultrasonographic results in patients with high-probability ventilation–perfusion scans showed that the ultrasonogram was abnormal in 5 of 27 patients (19%) with low pretest clinical probability, 31 of 75 patients (40%) with moderate pretest probability, and 35 of 60 patients (58%) with high pretest probability. These differences are statistically significant ($P < 0.001$). When all ventilation–perfusion scan groups are combined, ultrasonograms were abnormal in 17 of 734 patients (2.3%) with low pretest probability, 56 of 396 patients (14.1%) with moderate pretest probability, and 46 of 102 patients (45%) with high pretest probability ($P < 0.001$) (**Table 3**).

Seventy-two patients died during the study. Sixteen of these patients had an initial diagnosis of pulmonary embolism, and 56 were considered negative for pulmonary embolism. All deaths were adjudicated by an independent panel, and none was judged to have been caused by pulmonary embolism (**Table 4**).

Discussion

We developed a clinical model for use in patients with suspected pulmonary embolism. The model accurately classified patients as having low, moderate, or high probability of pulmonary embolism. Reproducibility of the model is suggested by the similar accuracy in the five centers, and the interobserver reliability of the model was validated. The validity of the clinical model is further suggested by the significantly different rates of deep venous thrombosis detected by ultrasonography in patients with low, moderate, and high pretest probability of pulmonary embolism. We recognize that our model may overestimate the overall rate of pulmonary embolism in patients whom we considered to have a moderate pretest probability, because these patients were considered positive for pulmonary embolism if the ventilation–perfusion scan indicated high probability. However, almost 90% of these patients have angiographic evidence of pulmonary embolism (6), and treatment is generally recommended in these patients. By incorporating the pretest probability into the diagnostic approach for patients with suspected pulmonary embolism, we tested a management strategy that reliably diagnosed pulmonary embolism in more than 96% of patients by using only ventilation–perfusion scanning and bilateral leg vein ultrasonography. The strategy outlined in **Figure 2** resulted in only 46 of 1239 patients (3.7%) requiring

venography or angiography, and only 6 of 1022 (0.6%) patients considered negative for pulmonary embolism had events on follow-up. None of these events was massive pulmonary emboli or iliofemoral deep venous thrombosis.

It is difficult to estimate the number of tests that our strategy avoids. In the PIOPED study, 54% of patients with suspected pulmonary embolism had moderate or high pretest probabilities and nondiagnostic scans. It would not be unreasonable to perform angiography in all of these patients. Another study demonstrated that only 15% of patients with non–high-probability scans go on to angiography, but a remarkable proportion (28%) were treated with anticoagulants without receiving a final diagnosis (19). In our study, only 3.7% of patients required angiography or venography; thus, our strategy provides a marked reduction in the need for invasive tests. It is evident that our approach is a safe, noninvasive strategy for the management of patients with non–high-probability ventilation–perfusion scans. We validated the use of serial ultrasonography in patients with non–high-probability ventilation–perfusion scans and a low or moderate pretest probability, a group that represented more than 95% of our patients with non–high-probability ventilation–perfusion scans. Because pulmonary embolism and deep venous thrombosis are manifestations of the same disease and because this approach is safe in patients with suspected deep venous thrombosis, it seemed reasonable to hypothesize that serial ultrasonography would be safe (20–22). In addition, we identified two small but clinically important subgroups in which further invasive diagnostic tests are justified: 1) patients with a low pretest clinical probability of pulmonary embolism, a high-probability ventilation–perfusion scan, and a normal ultrasonogram and 2) patients with high pretest clinical probability of pulmonary embolism, a non–high-probability scan, and a normal ultrasonogram.

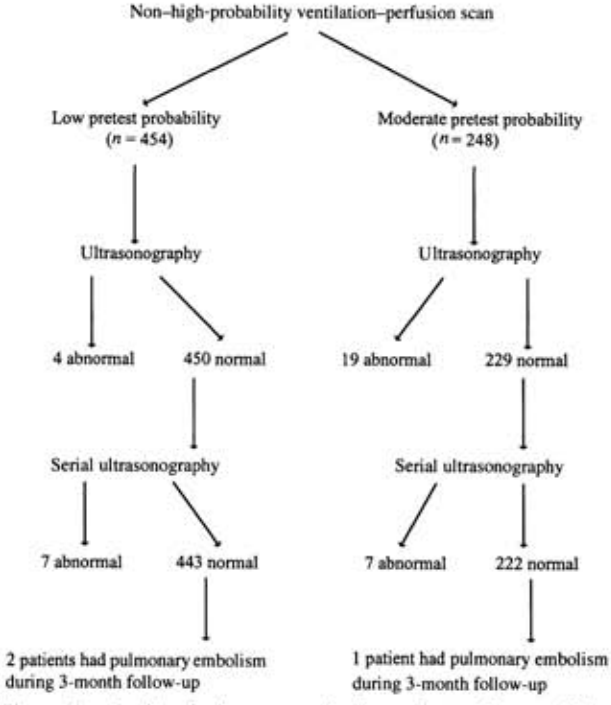

Figure 4. Results of ultrasonography in patients with non–high-probability ventilation–perfusion scans and low or moderate pretest probability of pulmonary embolism.

Table 3. Rates of Abnormal Results on Initial Ultrasonography According to Ventilation–Perfusion Scanning Results and Pretest Probability

Pretest Probability of Pulmonary Embolism	Normal Perfusion	Lung Scan Result		Total
		Non–High Probability	High Probability	
	n/n (%)			
Low	1/253 (1.2)	11/454 (2.4)*	5/27 (19)	17/734 (2.3)
Moderate	0/73 (0)	26/248 (10.5)†	30/75 (40)‡	56/396 (14.1)‡
High	1/8 (13)	10/34 (29)	35/60 (58)	46/102 (45)
Total	2/334 (0.6)	47/736 (6.3)	70/162 (43)	119/1232 (9.7)

* Seven of 11 patients had an abnormal result on serial testing.
† Seven of 26 patients had an abnormal result on serial testing.
‡ Three patients had inadequate ultrasonography results and four did not undergo ultrasonography.

Because physicians are willing to rule out pulmonary embolism in patients with normal ventilation–perfusion scans (5), we believed that the rate of venous thromboembolism during 3-month follow-up in patients with normal perfusion scans should be equivalent to that found with any strategy in which angiography is limited. We chose to use Hull diagnostic criteria for scan interpretation instead of the PIOPED criteria because a previous noninvasive management strategy had used these criteria; a high degree of observer agreement has been demonstrated with these criteria; and Hull criteria, which make no distinction between low- and intermediate-probability scans, are easier to remember. Nonetheless, because we expected that some physicians would be more familiar with the PIOPED criteria, we also scored the ventilation–perfusion scans of 570 randomly selected patients according to the PIOPED system. We found no advantage to using the PIOPED criteria. None of the 113 patients (CI, 0% to 3.2%) with a low pretest probability and a low probability scan according to the PIOPED criteria had pulmonary embolism; this does not statistically significantly differ from the 3.4% rate of pulmonary embolism (CI, 2.2% to 5.0%) in patients with low pretest probability and non–high-probability scans according to Hull criteria. Thus, either the PIOPED or Hull criteria can be used in our strategy, with the same results.

The role of ultrasonography in patients with suspected pulmonary embolism is somewhat controversial. Although Bradley and Alexander (23) reported

Table 4. Cause of Death According to Whether Pulmonary Embolism Was Initially Diagnosed

Cause of Death	Deaths		
	Patients with Pulmonary Embolism Initially	Patients with No Pulmonary Embolism Initially	Total
	← n →		
Metastatic cancer	8	34	42
Congestive heart failure	0	11	11
Renal failure	2	2	4
Pneumonia	0	5	5
Liver failure	1	1	2
Sepsis	1	0	1
Myocardial infarction	3	3	6
Stroke	0	1	1

high rates of deep venous thrombosis detected by ultrasonography in patients with non–high-probability scans, their study was limited by small numbers (20 patients) and selected enrollment. In another study, Turkstra and colleagues (24) indicated that ultrasonography may be of low usefulness in patients apparently similar to those in our study. However, we believe that Turkstra and colleagues' study was limited because ultrasonography was done only on the day of presentation and only in the common femoral vein and popliteal vein regions. We performed serial testing and more extensive imaging of leg veins in our study. This may account for the fact that 43% of our patients with high-probability ventilation–perfusion scans had an abnormal ultrasonogram compared with only 30% in the study by Turkstra and colleagues. In addition, the latter study may have overestimated the rate of pulmonary embolism by considering all high-probability scans positive. The PIOPED study showed that the rate of pulmonary embolism with high-probability scans was 96% if clinical probability was high, 88% if clinical probability was moderate, and 50% if clinical probability was low. It is unlikely that all patients in Turkstra and colleagues' study had high clinical probability. In addition, false-positive ultrasonographic results are more likely with the two-region compression used by Turkstra and colleagues, but no attempt was made to adjust for this in the study design or interpretation (10). These limitations all bias toward a lower usefulness for ultrasonography. We used venography to confirm cases in which the ultrasonographic result was statistically most likely to be false-positive (low or moderate pretest probability with non–high-probability ventilation–perfusion scans). Thus, false-positive results are not likely to be common with our approach. However, in our study, only 10% of all patients with suspected pulmonary embolism had an abnormal ultrasonogram, and serial conversions occurred in only 2% of patients in whom ultrasonography was performed.

Our study has some limitations. Because the clinical model was used predominantly by physicians who have expertise in thromboembolic diseases, it may not be suited for use by all physicians. Patients were entered consecutively, and we included both hospitalized and ambulatory patients; nonetheless, the demographic characteristics of our patients may differ from those of patients presenting in other centers. Although the eligibility criterion was simply "suspected pulmonary embolism," it was informally agreed that patients should have dyspnea or chest pain not clearly due to another condition. This lack of a definable symptom complex as an eligibility criterion may limit the generalizability of our findings. Another potential limitation is the critical role of determining whether an alternative diagnosis that was as likely as or more likely than pulmonary embolism accounted for the patient's signs and symptoms. This depends on the physician judgment, which will vary according to physician experience. Overall, 60% of patients had an alternative diagnosis (such as pneumonia, musculoskeletal pain, viral pleuritis, postoperative atelectasis, pulmonary neoplasm, or anxiety). An alternative diagnosis was made in 65% of the patients without pulmonary embolism and 29% of those with pulmonary embolism. Our strategy is designed to reduce invasive tests and, as such, it may be best to assume that an alternative diagnosis does not exist in cases of doubt.

Despite these potential limitations, the model seems to be reproducible and most of the necessary information easily elicited. The high frequency of telephone follow-up did not allow us to determine the frequency of asymptomatic events during follow-up, but no events were detected in patients who reported for ultrasonography at 3 months. Therefore, we cannot accurately comment on asymptomatic events during the 3-month follow-up, but it is unlikely that a significant number of events occurred. Moreover, we were more concerned with symptomatic events during follow-up, and it is unlikely that telephone follow-up would miss symptomatic events.

Depending on local costs of ultrasonography and angiography, the serial ultrasonography approach, although very safe, may not save money. On the other hand, it is important to note that only 3.4% of all patients with a low clinical probability had pulmonary embolism. Because this rate is not dissimilar to the rate of pulmonary embolism in patients with normal and near-normal ventilation–perfusion scans, it may not be worthwhile to perform lung scans or ultrasonography in such patients. However, we believe that the optimal strategy may include the high negative predictive value of certain D-dimer tests (25), much as we have proposed in patients

with suspected deep venous thrombosis (26). Decreasing the number of serial tests performed (that is, eliminating the test on day 7 or 14) would also increase efficiency and decrease the cost of our approach with almost no loss in safety.

We have shown that our clinical model can be used to select patients with non–high-probability ventilation–perfusion scans in whom serial ultrasonography is appropriate. When the pretest probability is discordant with the result of ventilation–perfusion scanning (high pretest probability but non–high-probability ventilation–perfusion scan or low pretest probability but high-probability ventilation–perfusion scan) and the ultrasonogram is normal, pulmonary angiography is indicated. In our study, venography was performed in the hope that it would eliminate the need for angiography, but this was not the case. Therefore, patients in whom more invasive testing is indicated can proceed directly to angiography. Application of the model and its use in the strategy that we described represent a safe, effective, and largely noninvasive means of managing patients with suspected pulmonary embolism.

From University of Ottawa, Ottawa, Ontario, Canada; McMaster University, Hamilton, Ontario, Canada; and Dalhousie University, Halifax, Nova Scotia, Canada.

Grant Support: By the National Health Research and Development Program of Canada (#6606-5283-403). Drs. Wells, Kearon, and Anderson are recipients of Research Scholarships from the Heart and Stroke Foundation of Canada. Drs. Ginsberg and Weitz are recipients of Career Investigator Awards from the Heart and Stroke Foundation of Ontario. Dr. Hirsh is a Distinguished Professor of the Heart and Stroke Foundation of Canada.

Requests for Reprints: Philip S. Wells, MD, MSc, Suite 467, 737 Parkdale Avenue, Ottawa, Ontario K1Y 1J8, Canada.

Current Author Addresses: Dr. Wells: Suite 467, 737 Parkdale Avenue, Ottawa, Ontario K1Y 1J8, Canada.
Dr. Ginsberg: McMaster University Medical Centre, Room 3w15, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada.
Drs. Anderson, Bowie, and Barnes: QEII Health Sciences Centre, 1278 Tower Road, Halifax, Nova Scotia B3H 1V8, Canada.
Dr. Kearon, Mr. Gent, and Drs. Weitz and Hirsh: HCH Research Centre, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.
Dr. Turpie: Hamilton General Hospital, Hamilton, Ontario L8L 2X2, Canada.
Dr. Bormanis: Suite 465, 737 Parkdale Avenue, Ottawa, Ontario K1Y 1J8, Canada.
Dr. Chamberlain: 1053 Carling Avenue, Ottawa, Ontario K1Y 4B3, Canada.

References

1. **Hildner FJ, Ormond RS.** Accuracy of the clinical diagnosis of pulmonary embolism. JAMA. 1967;202:567-70.
2. **Sasahara AA, Sharma GV, Barsamian EM, Schoolman M, Cella G.** Pulmonary thromboembolism. Diagnosis and treatment. JAMA. 1983;249: 2945-50.
3. **Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, et al.** Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation. 1992;85:462-8.
4. **Henry JW, Relyea B, Stein PD.** Continuing risk of thromboemboli among patients with normal pulmonary angiograms. Chest. 1995;107:1375-8.
5. **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.
6. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA. 1990;263:2753-9.
7. **Hull RD, Carter CJ, Jay RM, Ockleford PA, Hirsh J, et al.** Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion scan. Ann Intern Med. 1983;98:891-9.
8. **Hull RD, Raskob GE, Coates G, Panju AA, Gill GJ.** A new noninvasive management strategy for patients with suspected pulmonary embolism. Arch Intern Med. 1989;149:2549-55.
9. **Anderson DR, Lensing AW, Wells PS, Levine MN, Weitz JI, Hirsh J.** Limitations of impedance plethysmography in the diagnosis of clinically suspected deep-vein thrombosis. Ann Intern Med. 1993;118:25-30.
10. **Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al.** Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two centre paired-design prospective trial. Thromb Haemost. 1995; 74:1423-7.
11. **Perrier A, Bounameaux H, Morabia A, de Moerloose P, Slosman D, Didier D, 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.
12. **Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al.** Accuracy of clinical assessment of deep-vein thrombosis. Lancet. 1995; 345:1326-30.
13. **Celi A, Palla A, Petruzzelli S, Carrozzi L, Jacobson A, Cella G, et al.** Prospective study of a standardized questionnaire to improve clinical estimate of pulmonary embolism. Chest. 1989;95:332-7.
14. **Hoellerich VL, Wigton RS.** Diagnosing pulmonary embolism using clinical findings. Arch Intern Med. 1986;146:1699-704.
15. **Lensing AW, van Beek EJ, Demers C, Tiel-van Buul MM, Yakemchuk V, van Dongen A, et al.** Ventilation-perfusion lung scanning and the diagnosis of pulmonary embolism: improvement of observer agreement by the use of a lung segment reference chart. Thromb Haemost. 1992;68:245-9.
16. **Gottschalk A, Sostman HD, Coleman RE, Juni JE, Thrall J, McKusick KA, et al.** Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. J Nucl Med. 1993; 34:1119-26.
17. **Rabinov K, Paulin S.** Roentgen diagnosis of venous thrombosis in the leg. Arch Surg. 1972;104:134-44.
18. **Dunnett CW, Gent M.** Significance testing to establish equivalence between treatments, with special reference to data in the form of 2 × 2 tables. Biometrics. 1977;33:593-602.
19. **Schluger N, Henschke C, King T, Russo R, Binkert B, Rackson M, et al.** Diagnosis of pulmonary embolism at a large teaching hospital. J Thorac Imaging. 1994;9:180-4.
20. **Huisman MV, Büller HR, ten Cate JW, van Royen EA, Vreeken J, Kersten MJ, et al.** Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest. 1989;95:498-502.
21. **Kruit WH, de Boer AC, Sing AK, van Roon F.** The significance of venography in the management of patients with clinically suspected pulmonary embolism. J Intern Med. 1991;230:333-9.
22. **Sluzewski M, Koopman MM, Schuur KH, van Vroonhoven TJ, Ruijs JH.** Influence of negative ultrasound findings on the management of in- and outpatients with suspected deep-vein thrombosis. Eur J Radiol. 1991;13: 174-7.
23. **Bradley MJ, Alexander L.** The role of venous colour flow Doppler to aid the non-diagnostic lung scintigram for pulmonary embolism. Clin Radiol. 1994; 50:232-4.
24. **Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR.** Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med. 1997;126:775-81.
25. **Ginsberg JS, Wells PS, Brill-Edwards P, Donovan D, Panju A, van Beek EJ, et al.** Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. Thromb Haemost. 1995;73:35-8.
26. **Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Lewandowski B.** SimpliRED D-dimer can reduce the diagnostic tests in patients with suspected deep vein thrombosis [Letter]. Lancet. 1998;351:1405-6.