

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

Marieke J. H. A. Kruip, MD; Marjan J. Slob, MD; Joost H. E. M. Schijen, MD; Cees van der Heul, MD; Harry R. Büller, MD

Background: We designed a diagnostic strategy, based on clinical probability and D-dimer concentration, to select patients who were unlikely to have pulmonary embolism (PE), before further diagnostic workup was performed. The utility and safety of this strategy were evaluated in a prospective management study.

Methods: Consecutive patients with suspected PE had D-dimer testing and clinical probability assessment with a clinical decision rule. Patients with a low probability and a normal D-dimer concentration (<500 ng/mL) were considered not to have PE, and further diagnostic testing and anticoagulant therapy were withheld. In patients with a low probability and elevated D-dimer level or with a moderate or high probability, bilateral compression ultrasonography of the legs was performed. If deep venous thrombosis was detected, venous thromboembolism was diagnosed. If compression ultrasonogra-

phy was normal, pulmonary angiography was performed. All patients were followed up for 3 months.

Results: Of the 234 consecutive patients, 26% had the combination of a low probability and normal D-dimer level. During the follow-up period, none of these patients died and 3 patients had recurrent complaints of PE. In these 3 patients, PE was excluded by objective testing. The 3-month thromboembolic risk was therefore 0% (95% confidence interval, 0%-6%). The prevalence of PE in the entire population was 22%.

Conclusions: The combination of a low clinical probability and a normal D-dimer concentration appears to be a safe method to exclude PE, with a high clinical utility, and is readily accepted by clinicians.

Arch Intern Med. 2002;162:1631-1635

DIAGNOSING OR excluding pulmonary embolism (PE) is difficult because the clinical manifestations are nonspecific.¹

Less than 30% of patients presenting with signs and symptoms suggestive of PE actually have the disease confirmed by objective testing.²⁻⁴ As a result, the diagnostic approach has gradually changed from trying to confirm PE to also identifying the large proportion of patients who do not have the disease. Several methods have recently been advocated for excluding PE.

Clinical assessment has been used to stratify patients with suspected PE into low, moderate, and high clinical probability categories. Studies have been performed with the use of clinical judgment, as well as a structured algorithm, to achieve this stratification. However, in 3% to 28% of patients with a low clinical probability, PE was subsequently confirmed to be present.^{2,5-10} These figures are too high to safely exclude PE in symptomatic pa-

tients on the basis of the clinical probability assessment alone.

The finding of a normal plasma concentration of D dimer, the degradation product of cross-linked fibrin, was shown to be able to exclude PE accurately in most patients presenting with clinical suspicion. The sensitivity and negative predictive value vary depending on the type of D-dimer assay, but with the current rapid tests, both are usually high (90%-100% and 94%-100%, respectively).^{6,11-17} To safely exclude PE, the sensitivity should approach 100%. This is important because, for every 2% decrease in sensitivity, 1 per 1000 patients studied will die of recurrent PE as a result of inappropriately withholding anticoagulant therapy.¹⁸ Most D-dimer assays do not have a sufficiently high sensitivity to be safely used and accepted by clinicians as the only method to exclude PE.

Hence, the combination of clinical assessment and D-dimer concentration may be well suited to differentiate between patients who will probably have PE and those

From the Departments of Internal Medicine (Drs Kruip and van der Heul), Radiology (Dr Slob), and Pulmonology (Dr Schijen), St Elisabeth Hospital, Tilburg, and Department of Vascular Medicine, Academic Medical Centre, Amsterdam (Dr Büller), the Netherlands.

PATIENTS AND METHODS

PATIENTS

Consecutive inpatients and outpatients older than 16 years, with clinically suspected acute PE seen at St Elisabeth Hospital, Tilburg, the Netherlands, were prospectively included in the study between January 1, 1998, and May 31, 2000. The protocol was approved by the local ethics committees, and written informed consent was obtained from all patients.

STUDY DESIGN AND DIAGNOSTIC STUDIES

The clinical decision rule (CDR) was completed and the patients were stratified into low, moderate, and high clinical probability categories of PE. The CDR consists, as described elsewhere,⁷ of risk factors for PE, signs and symptoms from history and physical examination, chest radiography, oxygen saturation tests, and electrocardiography, as well as the likelihood of an alternative diagnosis for the patient's symptoms. The CDR was applied by a group of at least 10 attending physicians, who all received extensive instructions about how to use the rule before the start of the study. The plasma D-dimer concentration was then measured with a quantitative rapid enzyme-linked immunosorbent D-dimer assay (Vidas DD; bioMérieux, Inc, Paris, France). The concentration was expressed in nanograms per milliliter of fibrinogen equivalent units. The cutoff value, according to the manufacturer's instructions, was 500 ng/mL. All measurements were carried out in duplicate by a technician who was unaware of the outcome of the CDR and the patient's history.

Patients with a low probability of PE and a normal D-dimer test result (<500 ng/mL) did not undergo further diagnostic procedures and anticoagulant treatment was withheld. They were instructed to return to the thrombosis unit immediately when signs or symptoms of PE or deep venous thrombosis (DVT) recurred, and appropriate objective testing (CUS, lung scanning, or pulmonary angiography) was performed to confirm or refute the diagnosis.

In patients with a low probability of PE and elevated D-dimer concentration, or moderate or high clinical probability, first bilateral CUS of the legs was performed within 24 hours. The femoral vein was visualized in the supine position in its full length and the popliteal vein was investigated in the prone position to the trifurcation. Visualization of a clot, ie, not being able to compress the vein and lack of flow, was considered to be abnormal and to indicate the presence of DVT.

When a DVT was present, VTE was diagnosed and treatment with anticoagulants was initiated. If CUS was normal, selective pulmonary digital subtraction angiography was performed within 48 hours after initial presentation. A 7F Swan-Ganz flow-directed pulmonary angiography true-size catheter was positioned into a main pulmonary artery and selectively in the lobar arteries of both lungs. Subselective magnification series were obtained of lower, middle, and upper portions of both lungs with the catheter in lobar and segmental branches. Anteroposterior projections were obtained routinely; different projections and/or selective series were obtained if the initial images were not conclusive. Bilateral pulmonary angiography was performed in all patients. The following criteria were considered diagnostic of PE: a constant intraluminal filling defect or a persistent acute cutoff sign of an arterial pulmonary branch seen on more than 1 projection. In case of doubt, a second experienced radiologist was asked for his opinion and the diagnosis was made by means of consensus; if necessary, additional superselective series were performed.

THREE-MONTH FOLLOW-UP

All patients were reexamined by the study coordinator (M.J.H.A.K.) 1 week and 1 and 3 months after inclusion at the outpatient clinic or interviewed by telephone. Suspected venous thrombotic events (PE or DVT) were investigated by appropriate objective diagnostic methods within 48 hours of presentation. When a patient was readmitted to the hospital for any cause, the charts were reviewed. Venous thromboembolic events, as well as causes of death, were recorded and adjudicated independently.

who will not have this disease. Findings in recent studies in patients with suspected venous thromboembolism (VTE) support this assumption.^{6,7,19} The aim of the present study was to evaluate the utility and safety of a novel strategy in excluding PE in patients with a low clinical probability, according to a validated clinical decision rule,⁷ and a normal D-dimer concentration. In these patients, no further diagnostic investigations were performed and anticoagulant therapy was withheld. In the remaining patients we used compression ultrasonography (CUS), followed by pulmonary angiography if results were normal.

RESULTS

During the investigation period, 251 consecutive patients with clinically suspected PE were studied. Seventeen patients (7%) were excluded because of refusal or inability to give consent (5 patients), contraindications to pulmonary angiography (2 patients), and absence of

D-dimer measurement because of logistical problems (10 patients).

Thus, the study population available for analysis consisted of 234 patients. The mean age of this cohort was 51 years (SD, 17 years) and the prevalence of VTE was 22%. Of the total population, 83% presented as outpatients and 11% had a history of previous VTE (**Table**). The 3-month follow-up period was completed in all patients.

LOW CLINICAL PROBABILITY AND NORMAL D-DIMER CONCENTRATION

The **Figure** summarizes the results of the evaluated diagnostic strategy. The clinical probability of PE, according to the CDR, was low in 120 patients (51%), moderate in 74 patients (32%), and high in 40 patients (17%). Of the patients with a low clinical probability, 60 had a normal D-dimer concentration, so no further diagnostic procedures were performed and the patients did not re-

Clinical Characteristics of the 234 Study Patients With Clinically Suspected Pulmonary Embolism*

| Characteristic | Value |
|---|----------|
| Sex, No. (%) male | 84 (36) |
| Mean age, y (SD) | 51 (17) |
| Outpatient, No. (%) | 194 (83) |
| Previous VTE, No. (%) | 25 (11) |
| Duration of symptoms at presentation, No. (%) | |
| <1 d | 92 (39) |
| 1-3 d | 69 (29) |
| >3 d | 73 (31) |
| Risk period,† No. (%) | 50 (21) |
| Active malignancy,‡ No. (%) | 12 (5) |
| Symptoms of DVT, No. (%) | 23 (10) |

*VTE indicates venous thromboembolism; DVT, deep venous thrombosis.
 †Defined as period of immobilization, surgery, or trauma in the 3 months before presentation.
 ‡In the 6 months before presentation.

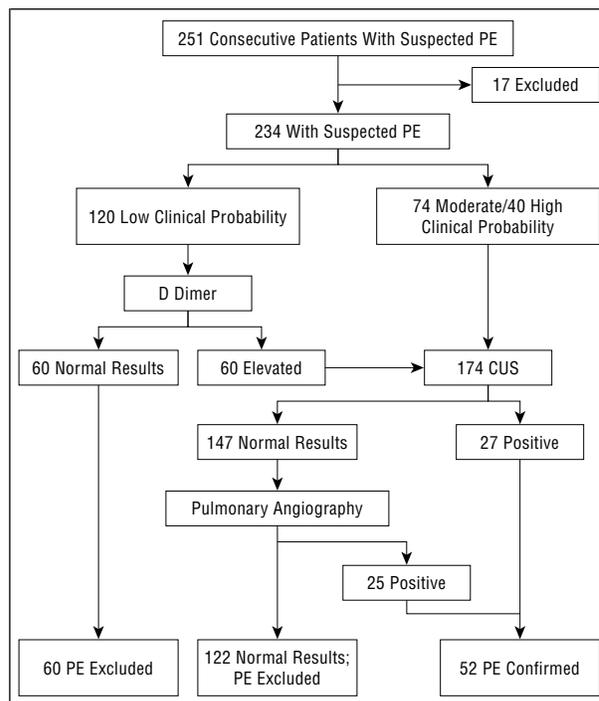
ceive anticoagulant therapy. This subgroup represents 26% of the original study cohort. Fifty-six of these presented as outpatients. Thus, in 4 (10%) of the 40 already hospitalized patients and in 56 (29%) of the 194 outpatients, PE was excluded by this diagnostic strategy. During the 3-month follow-up period, none of the patients with a low clinical probability and a normal D-dimer concentration died, and 3 returned with new complaints of PE (3, 14, and 16 days after initial presentation). In all 3 patients, PE was excluded (by normal pulmonary angiogram in 2 and normal perfusion scan result in 1). Hence, the subsequent rate of VTE in this patient group during follow-up was 0% (95% confidence interval [CI], 0%-6%).

PATIENTS WITH OTHER TEST OUTCOMES

Of the 174 patients with either a low clinical probability of PE but elevated D-dimer concentration or a moderate or high clinical probability, 27 had a DVT as detected by bilateral CUS. This subgroup with confirmed VTE by CUS represents 12% of the original study cohort. In the patients with a normal CUS (n=147), pulmonary angiography was performed. Pulmonary embolism was present in 25 patients. Thus, a total of 52 patients had documented VTE; hence, the overall prevalence was 22%. Of the 122 patients with normal pulmonary angiograms, 1 presented with suspected PE 10 days after the initial pulmonary angiogram. Pulmonary angiography was again performed and showed PE. Hence, the subsequent rate of VTE in patients with normal pulmonary angiograms was 0.8% (95% CI, 0.02%-4.50%). During the 3-month follow-up period of these 122 patients, a total of 4 patients died. The causes of death were cancer in 3 and progressive chronic obstructive pulmonary disease in 1.

ADDITIONAL OBSERVATIONS

In the present study, only patients with a low clinical probability of PE in combination with a normal D-dimer concentration were considered not to have PE. If we had added the patients with a moderate clinical probability and a normal D-dimer concentration to this group, a total of 85 (36%)



Results of the diagnostic strategy in 251 consecutive patients presenting with clinically suspected pulmonary embolism (PE). CUS indicates compression ultrasonography.

of the presenting cohort would have been spared further diagnostic procedures and anticoagulant therapy. One of these 85 patients had PE involving the segmental arteries, confirmed by pulmonary angiography (failure rate, 1.2%; 95% CI, 0.03%-6.40%). This patient was a 40-year-old woman who had recently had a neurosurgical operation (9 days before presentation) and who presented with a complaint of dyspnea of 3 days' duration. The remaining 149 patients, ie, those with a low or moderate clinical probability and an elevated D-dimer concentration or with a high clinical probability, would have undergone further diagnostic procedures, which would have revealed PE in approximately one third (51 patients).

The D-dimer concentration was measured in all patients. The result was normal in 100 patients (43%) of the study population. One of these 100 patients actually had PE in segmental arteries on pulmonary angiography (same patient as described above). The D-dimer concentration of this patient was 480 ng/mL. The sensitivity of the D-dimer assay was 98% (95% CI, 90%-100%) and the negative predictive value, 99% (95% CI, 95%-100%).

COMMENT

The primary finding of this study is that the combination of a low clinical probability of PE and a normal D-dimer concentration is able to exclude the disease safely in a substantial proportion (26%) of patients presenting with suspected PE. This new strategy was introduced in a large teaching hospital that previously used lung scanning and pulmonary angiography and was well accepted by the clinicians (physicians, internists, pulmonologists, and surgeons) involved in the diagnostic workup of such patients.

Furthermore, the present study confirms that the combination of CUS and pulmonary angiography is a feasible, effective, and safe subsequent diagnostic strategy. Performing CUS of the deep leg veins in patients with a moderate or high clinical probability or a low clinical probability and elevated D-dimers levels (n = 174) was worthwhile: 16% had DVT detected by ultrasonography, and anticoagulant treatment was initiated. Taken together, the use of the clinical probability assessment, D-dimer assay, and CUS, all noninvasive methods, was able to confirm or refute the diagnosis in 37% of the patients of the original study cohort. Pulmonary angiography was performed without any complication, confirming earlier observations,²⁰ although in 1 patient the initial PE was most likely missed. The outcome with respect to subsequent episodes of symptomatic VTE during the 3-month follow-up in patients with a low clinical probability and a normal D-dimer concentration (failure rate, 0%; 95% CI, 0%-6%) compared favorably with that of patients with normal pulmonary angiograms (failure rate, 0.8%; 95% CI, 0.02%-4.50%) and is in agreement with studies using normal perfusion scan results or serial ultrasound scan results to exclude VTE.^{4,6,7,19,21}

Only a limited number of prospective management studies with D-dimer, CDR, or a combination of both are available.^{6,7,19,21} Our observations of the combination of CDR and D-dimer are comparable with the findings of these studies. However, de Groot et al¹⁹ and Perrier et al⁶ used the combination only in patients with a nondiagnostic perfusion-ventilation lung scan result, whereas in the present study the combination was used as the first step in the diagnostic workup. Therefore, a larger proportion of our study cohort, approximately one quarter, was spared radiologic or nuclear investigations compared with these studies.

In a recent study by Perrier and colleagues,²¹ D-dimer measurements were used as the first test in the diagnostic workup of 444 outpatients with suspected PE. A total of 159 patients (36%) had normal D-dimer concentrations, and this method was used as the sole test to exclude VTE (subsequent failure rate was 0%; 95% CI, 0%-2.3%). If we had adopted a similar strategy, while we used exactly the same D-dimer assay, we would have missed 1 patient with significant PE, although our findings are still consistent with the CIs of that study. It should be noted that we studied both inpatients and outpatients and that combining clinical assessment and D-dimer testing was readily accepted by the specialists who see patients with suspected PE.

Several studies using CUS and pulmonary angiography in patients with suspected PE have been published. An abnormal venous ultrasonogram is found in 5% to 12% of patients with a nondiagnostic lung scan result.^{6,7,22-25} In a meta-analysis by van Rossum et al,²⁵ the prevalence of DVT in patients with clinically suspected PE was approximately 18%, and in patients with proven PE, 36% to 45% (range, 10%-93%). Our observations with respect to the proportion of patients with abnormal CUS are comparable with the findings in patients with a high-probability lung scan result but are higher than the proportion of patients with a nondiagnostic lung scan result.^{6,7,22-25} Investigations that assessed the validity and safety of pulmo-

nary angiography found that this method may be falsely negative in approximately 1% and that the morbidity and mortality rates associated with the test itself are very low (0.4% [95% CI, 0.09%-1.25%] and 0% [95% CI, 0%-0.53%], respectively), as was seen in the present study.^{2,20,26}

Some aspects of our study warrant comment. Although we studied a consecutive series of patients with suspected PE seen in a large teaching hospital, the total number of patients included is moderate. In particular, in the subgroup of patients with a low clinical probability of PE and a normal D-dimer concentration, there remains some uncertainty about the safety of withholding further diagnostic testing and anticoagulant treatment, since the upper limit of the 95% CI of the 3-month thromboembolic risk was 6%. Similar outcome studies using other strategies to exclude VTE usually had an upper limit of 4%.^{6,21,27-29} However, there is a wealth of evidence that D-dimer assays based on enzyme-linked immunosorbent assays are effective in excluding significant VTE. Therefore, it seems reasonable to conclude that a normal D-dimer concentration combined with a low clinical probability of PE is safe. Further studies are required to include patients with a moderate clinical probability.

We did not include perfusion-ventilation lung scanning in the present strategy. This is mainly because of the limited availability of, in particular, ventilation scanning and the often nondiagnostic test results. The strategy used in this study eliminates the need for nuclear medicine facilities, which may be relevant for those institutions without such services.

We conclude that the combination of a low clinical probability of PE, assessed by a CDR, and a normal D-dimer concentration contributes to the increasing body of evidence that this is a rapid and cost-effective method to exclude PE safely, and that this strategy is readily accepted. The combination of CUS and pulmonary angiography remains a valid and effective approach for patients with suspected PE.

Accepted for publication November 29, 2001.

We thank all physicians of the Internal Medicine, Pulmonology, and Radiology departments for participating in the study and treating the patients by the diagnostic strategy. We thank J. de Jongh-Leuvenink, PhD, and the technicians of the clinical chemical laboratory for performing the D-dimer assay.

Corresponding author and reprints: Marieke J. H. A. Kruij, MD, Department of Internal Medicine, St Elisabeth Hospital, Postbus 90151, 5000 LC, Tilburg, the Netherlands (e-mail: evert.janssen@zonnet.nl).

REFERENCES

1. Kearon C, Hirsh J. The diagnosis of pulmonary embolism. *Haemostasis*. 1995; 25:72-87.
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. Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. *Chest*. 1993;103:1553-1559.
4. Hull RD, Hirsh J, Carter CJ, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med*. 1983;98:891-899.

5. Ginsberg JS, Wells PS, Kearon C, et al. Sensitivity and specificity of a rapid whole-blood assay for D-dimer in the diagnosis of pulmonary embolism. *Ann Intern Med.* 1998;129:1006-1011.
6. 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;156:531-536.
7. 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.
8. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. *Chest.* 1985;88:819-828.
9. Huisman MV. Recurrent venous thromboembolism: diagnosis and management. *Curr Opin Pulm Med.* 2000;6:330-334.
10. Sanson BJ, Lijmer JG, MacGillivray MR, Turkstra F, Prins MH, Buller HR, for the ANTELOPE Study Group. Comparison of a clinical probability estimate and two clinical models in patients with suspected pulmonary embolism. *Thromb Haemost.* 2000;83:199-203.
11. van Beek EJ, van den Ende B, Berckmans RJ, et al. A comparative analysis of D-dimer assays in patients with clinically suspected pulmonary embolism. *Thromb Haemost.* 1993;70:408-413.
12. Ginsberg JS, Wells PS, Brill-Edwards P, et al. Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. *Thromb Haemost.* 1995;73:35-38.
13. Turkstra F, van Beek EJ, ten Cate JW, Buller HR. Reliable rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients. *Thromb Haemost.* 1996;76:9-11.
14. 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.
15. Demers C, Ginsberg JS, Johnston M, Brill-Edwards P, Panju A. D-dimer and thrombin-antithrombin III complexes in patients with clinically suspected pulmonary embolism. *Thromb Haemost.* 1992;67:408-412.
16. Sijens PE, van Ingen HE, van Beek EJ, Berghout A, Oudkerk M. Rapid ELISA assay for plasma D-dimer in the diagnosis of segmental and subsegmental pulmonary embolism: a comparison with pulmonary angiography. *Thromb Haemost.* 2000;84:156-159.
17. 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;75:11-13.
18. van Beek EJ, Schenk BE, Michel BC, et al. The role of plasma D-dimers concentration in the exclusion of pulmonary embolism [published correction appears in *Br J Haematol.* 1996;95:218]. *Br J Haematol.* 1996;92:725-732.
19. de Groot MR, van Marwijk Kooy M, Pouwels JG, Engelage AH, Kuipers BF, Buller HR. The use of a rapid D-dimer blood test in the diagnostic work-up for pulmonary embolism: a management study. *Thromb Haemost.* 1999;82:1588-1592.
20. Wallis JW, van Beek EJ, Reekers JA, van Rooij WJ, Oudkerk M. Reserve concerning pulmonary angiography in pulmonary embolism is not justified [in Dutch]. *Ned Tijdschr Geneesk.* 1997;141:578-581.
21. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet.* 1999;353:190-195.
22. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med.* 1998;129:1044-1049.
23. Hull RD, Raskob GE, Ginsberg JS, et al. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. *Arch Intern Med.* 1994;154:289-297.
24. Turkstra F, Kuijter 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;126:775-781.
25. van Rossum AB, van Houwelingen HC, Kieft GJ, Pattinama PM. Prevalence of deep vein thrombosis in suspected and proven pulmonary embolism: a meta-analysis. *Br J Radiol.* 1998;71:1260-1265.
26. Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation.* 1992;85:462-468.
27. Perrier A, Desmarais S, Goehring C, et al. D-dimer testing for suspected pulmonary embolism in outpatients. *Am J Respir Crit Care Med.* 1997;156:492-496.
28. Huisman MV, Buller HR, ten Cate JW, Heijermans HS, van der Laan J, van Maanen DJ. Management of clinically suspected acute venous thrombosis in outpatients with serial impedance plethysmography in a community hospital setting. *Arch Intern Med.* 1989;149:511-513.
29. Worsley DF, Palevsky HI, Alavi A. A detailed evaluation of patients with acute pulmonary embolism and low- or very-low-probability lung scan interpretations. *Arch Intern Med.* 1994;154:2737-2741.