

# An Evaluation of D-Dimer in the Diagnosis of Pulmonary Embolism

## A Randomized Trial

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**Background:** It may be safe to omit additional diagnostic testing in selected patients with suspected pulmonary embolism (PE) who have a negative D-dimer test, but this approach has never been evaluated in a randomized, controlled trial.

**Objective:** To determine if additional diagnostic testing can be safely withheld in patients with suspected PE who have negative erythrocyte agglutination D-dimer test results.

**Design:** Randomized comparisons in 2 subgroups of a prospective multicenter study.

**Setting:** 7 university hospitals.

**Patients:** 1126 outpatients or inpatients with suspected PE; of these, 456 patients with negative erythrocyte agglutination D-dimer test results were randomly assigned to the intervention groups. Patients were classified into 2 clinical probability groups: those with a low clinical probability of PE (low-probability group) and those with a moderate or high clinical probability of PE, a nondiagnostic ventilation-perfusion lung scan, and no evidence of proximal deep venous thrombosis on bilateral ultrasonography (moderate- or high-probability group).

**Interventions:** The experimental intervention for both probability groups was no further diagnostic testing for PE. The control intervention for the low-probability group was a ventilation-perfusion lung scan followed by ultrasonography of the proximal deep veins of the legs on the same day. If the lung scan was nondiagnostic, ultrasonography of the legs was repeated 7 and 14 days later. The control intervention for the moderate- or high-probability group was ultrasonography of the proximal deep veins of the legs after 7 and 14 days. In the control and experimental groups, anticoagulation was withheld or withdrawn if PE was not diagnosed.

**Measurements:** Symptomatic venous thromboembolism (VTE) during 6 months of follow-up.

**Results:** Prevalence of VTE was 15.2% in the 1126 enrolled patients. In the low-probability group, VTE occurred during follow-up in 0 of 182 patients who had no additional diagnostic testing and in 1 of 185 patients who had additional testing (difference, -0.5 percentage point [95% CI, -3.0 to 1.6 percentage points]). In the moderate- or high-probability group, VTE occurred during follow-up in 1 of 41 patients who had no additional diagnostic testing and in 0 of 41 patients who had additional testing (difference, 2.4 percentage points [CI, -6.4 to 12.6 percentage points]).

**Limitations:** The authors could not enroll 2000 patients as originally planned; 3 randomly assigned patients did not receive the allocated intervention, and 7 received inadequate follow-up. Personnel who performed follow-up evaluations were not blinded to the results of diagnostic testing at enrollment or to allocation group assignments.

**Conclusion:** In patients with a low probability of PE who have negative D-dimer results, additional diagnostic testing can be withheld without increasing the frequency of VTE during follow-up. Low clinical probability and negative D-dimer results occur in 50% of outpatients and in 20% of inpatients with suspected PE.

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\*For other persons and institutions who participated in this study, see the Appendix, available at [www.annals.org](http://www.annals.org).

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**D**-Dimer is a fibrin-derived fragment that is released into the circulation when cross-linked fibrin is broken down by the fibrinolytic system (1, 2). Because elevated levels of D-dimer are common in patients with venous thromboembolism, negative D-dimer test results can help to exclude pulmonary embolism (2-9). In a previous cohort study (6), we showed that negative erythrocyte agglutination D-dimer test results had the potential to exclude pulmonary embolism in 2 subgroups of patients: those with a low clinical probability of embolism and those with a moderate or high clinical probability of embolism who had nondiagnostic ventilation-perfusion lung scan and no proximal deep venous thrombosis on venous ultrasonography. However, management decisions were not made on the basis of D-dimer test results in the earlier study.

Several subsequent management studies also supported the safety of withholding anticoagulant therapy and addi-

tional diagnostic testing in patients with a low clinical suspicion of pulmonary embolism who have negative erythrocyte agglutination D-dimer test results (2, 4, 7, 10). However, to our knowledge, the safety of using negative D-dimer test results to exclude pulmonary embolism has never been compared with additional diagnostic testing in

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Appendix

Appendix Table

Conversion of figures and tables into slides

a randomized, controlled trial (11). Consequently, we studied 2 subgroups of patients with suspected pulmonary embolism and negative erythrocyte agglutination test results: patients with a low clinical probability of pulmonary embolism and those with a moderate or high clinical probability of pulmonary embolism who had a nondiagnostic ventilation–perfusion lung scan and no proximal deep venous thrombosis on venous ultrasonography. Our goal was to test the hypothesis that patients with negative D-dimer test results who do not undergo further testing for pulmonary embolism will not have a higher frequency of venous thromboembolism during follow-up than patients who receive usual diagnostic testing and management.

## METHODS

### Patients

Inpatients and outpatients with suspected pulmonary embolism who were referred to the thrombosis service of 7 university-affiliated hospitals were prospectively assessed for enrollment (Figure 1). The referring physicians included primary care physicians, general internists, surgeons, and emergency department physicians. Patients were excluded if they had undergone ventilation–perfusion lung scan or venous ultrasonography, had received full-dose heparin therapy for more than 24 hours or long-term warfarin therapy, had a comorbid condition that limited their expected survival to less than 3 months, had a contraindication to radiographic contrast, or were asymptomatic within 7 days of presentation. Pregnant women were excluded, as were individuals who resided in a location where they could not access follow-up. Some patients were also excluded because their physicians considered them to be inappropriate candidates for the study (for example, they were scheduled to have surgery). The institutional review boards of all participating centers approved the study, and patients provided written informed consent.

### Clinical Assessment

Before any diagnostic testing was performed, a physician or nurse from the thrombosis service used the Wells 7-item prediction rule (12) to categorize the patient's clinical probability of pulmonary embolism as either low or moderate to high (Table 1). The clinician was not allowed to assign a clinical probability that differed from the prediction rule.

#### Patients with Low Clinical Probability of Pulmonary Embolism

D-Dimer testing with the SimpliRED assay (Agen Biomedical Ltd., Brisbane, Australia) was performed on all patients with a low clinical probability of pulmonary embolism (Figure 2). With this qualitative red cell agglutination assay, a drop of whole blood obtained from a venipuncture or finger stick is mixed for 2 minutes with a test reagent that contains a bivalent antibody that binds to both D-dimer and erythrocyte membranes. In the presence of elevated D-dimer levels, the test reagent induces aggluti-

### Context

Is it safe to withhold additional testing in patients with suspected pulmonary embolism (PE) and negative D-dimer test results?

### Contribution

This randomized trial evaluated the effect of further testing after negative D-dimer test results in patients with low pretest probability (group A) or moderate or high pretest probability (group B) of PE. At 6 months, 0 of 182 (group A) and 1 of 41 (group B) patients with no further testing had had symptomatic venous thromboembolism, compared with 1 of 185 (group A) and 0 of 41 (group B) patients with further testing.

### Cautions

Few moderate- or high-probability patients were studied.

### Implications

Additional diagnostic testing seems unnecessary in patients with low pretest probability of PE and negative D-dimer test results.

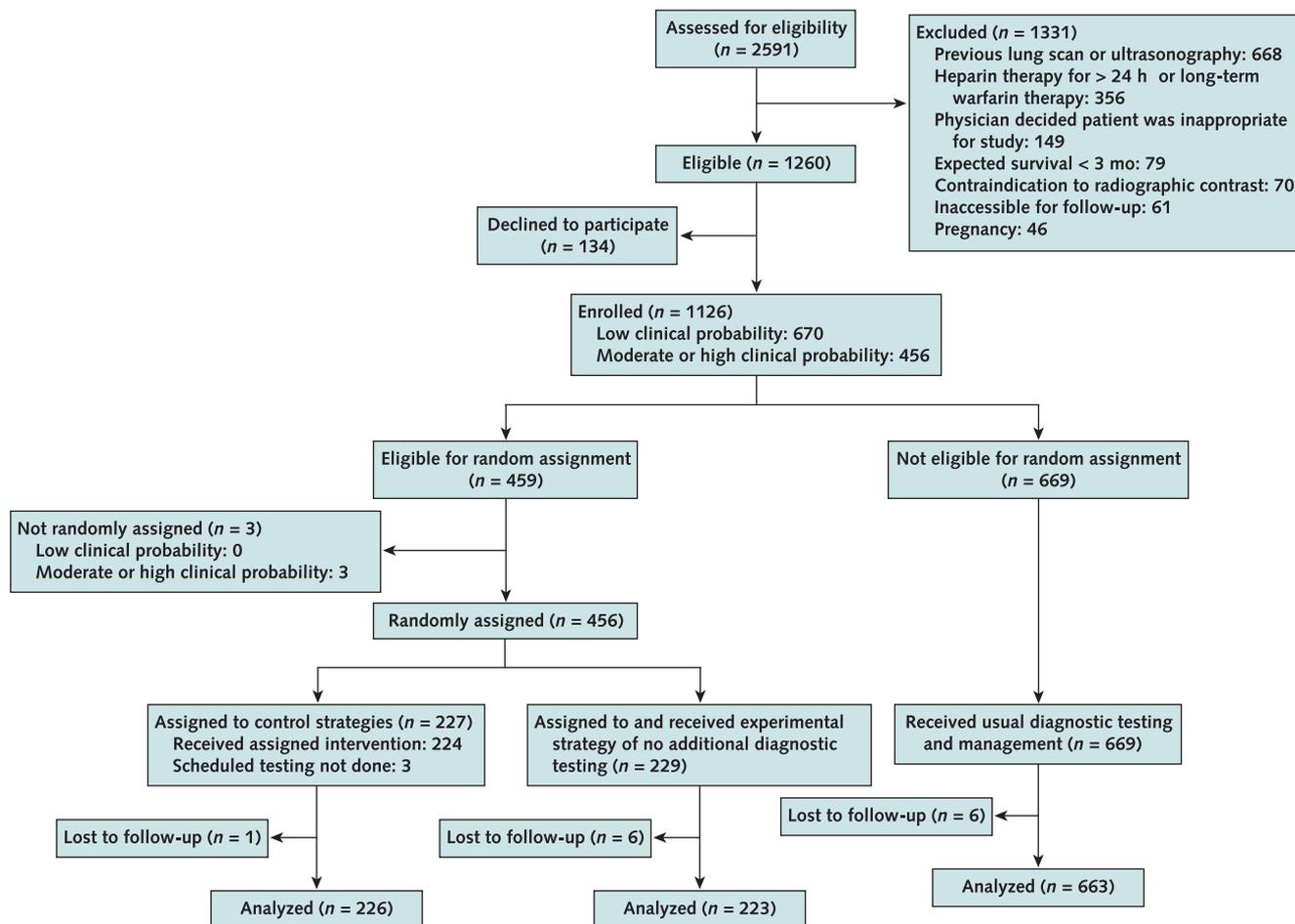
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nation of erythrocytes. Any agglutination is considered a positive result and no agglutination is considered a negative result.

Patients with negative D-dimer test results were randomly assigned to 1) receive no additional diagnostic testing and no treatment with anticoagulant therapy or 2) undergo additional diagnostic testing, starting with a ventilation–perfusion lung scan (Figure 2). If the lung scan showed no abnormalities, pulmonary embolism was excluded; if there were 1 or more segmental perfusion defects that were normally ventilated, the scan was considered diagnostic for pulmonary embolism (“high-probability scan”); and if there were perfusion defects that did not meet criteria for a “high-probability scan,” the scan was considered nondiagnostic. Patients with nondiagnostic lung scans underwent bilateral ultrasonography of the proximal veins of the legs. The sole criterion for diagnosis of deep venous thrombosis was inability to fully compress the lumen of the deep veins with application of ultrasonography probe pressure anywhere from the common femoral vein to the calf vein trifurcation (13); if deep venous thrombosis was present, pulmonary embolism was diagnosed. If ultrasonography results were normal, the test was repeated after 7 and 14 days (serial ultrasonography); anticoagulant therapy was only given if deep venous thrombosis developed.

A ventilation–perfusion lung scan was performed on all patients with positive D-dimer test results. Results of the lung scan dictated subsequent management, as previously described (Figure 2).

Figure 1. Study flow diagram.



**Patients with Moderate or High Clinical Probability of Pulmonary Embolism**

A ventilation–perfusion lung scan was performed on all patients with a moderate or high clinical probability of pulmonary embolism; the lung scan findings determined

subsequent management, as previously described (Figure 3). Patients with a nondiagnostic lung scan, normal bilateral venous ultrasonography results, and negative D-dimer test results were randomly assigned to receive either no additional diagnostic testing or serial ultrasonography (Figure 3).

Table 1. Clinical Model for Predicting the Pretest Probability of Pulmonary Embolism\*

| Clinical Characteristics                                           | Score |
|--------------------------------------------------------------------|-------|
| Active cancer (treatment within 6 mo or palliative)                | 1     |
| Surgery or bedridden for ≥3 d during past 4 wk                     | 1.5   |
| History of deep venous thrombosis or pulmonary embolism            | 1.5   |
| Hemoptysis                                                         | 1     |
| Heart rate of >100 beats/min                                       | 1.5   |
| Pulmonary embolism judged to be the most likely diagnosis          | 3     |
| Clinical signs and symptoms compatible with deep venous thrombosis | 3     |

\* A total score of ≤4 indicates a low probability of pulmonary embolism (also termed “pulmonary embolism unlikely” in other reports [9, 12]). A score of 4.5 to 6 indicates a moderate probability of pulmonary embolism; a score of >6 indicates a high probability of pulmonary embolism [12].

**Randomization Protocol**

A biostatistician used a computer program to generate separate randomization sequences, equal in proportion and stratified by clinical center, for each of the 2 eligible groups of patients. Allocations were concealed in consecutively numbered, sealed, opaque envelopes that were distributed to each of the clinical centers. Patients opened the next consecutively numbered envelope at that clinical center to determine their group allocation; this allocation group could not be changed by opening another envelope.

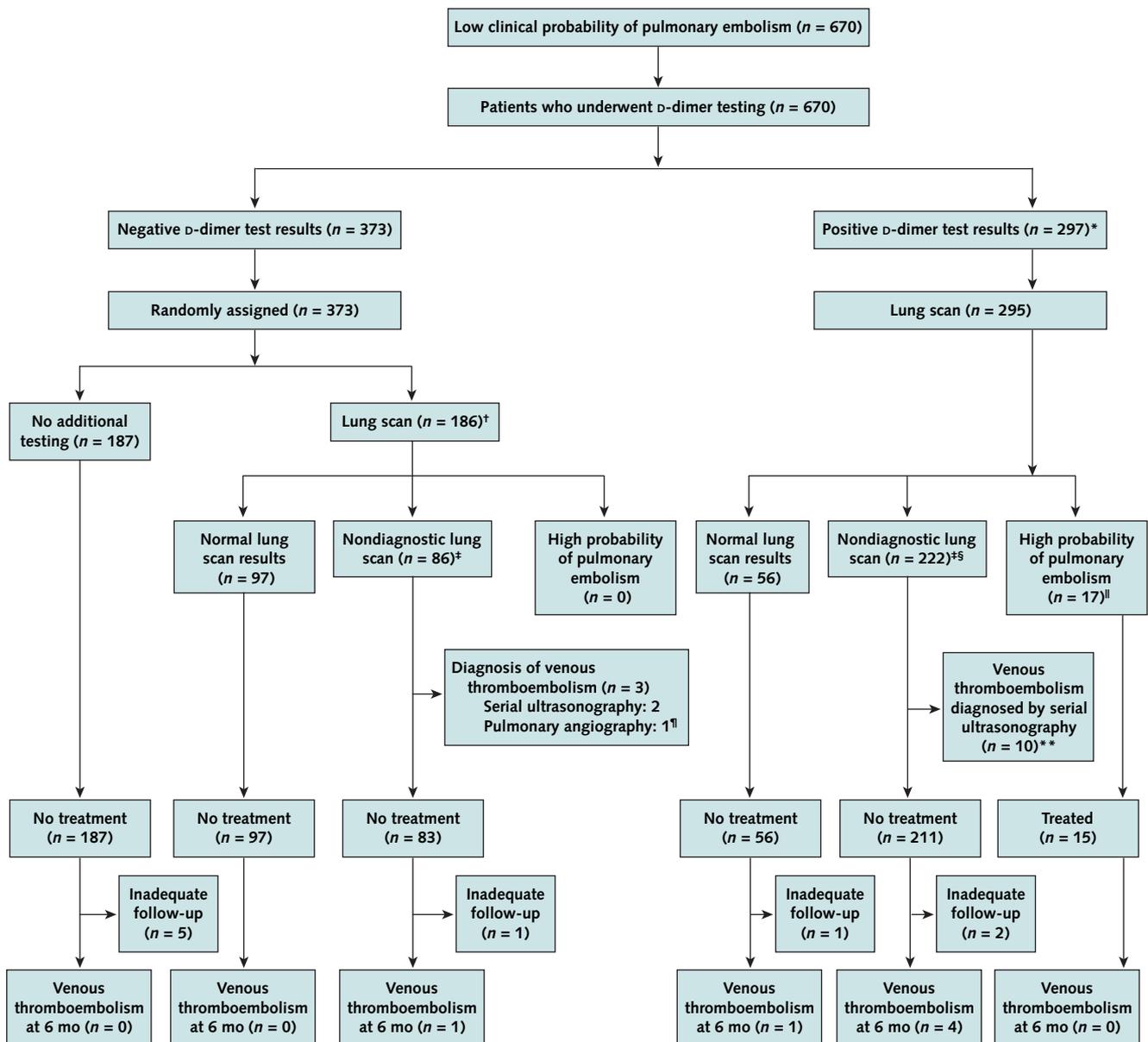
**Follow-up and Outcome Measures**

All enrolled patients, including those who did not undergo randomization, were followed for 6 months to determine if venous thromboembolism developed after initial

diagnostic testing. In addition, patients were alerted to the symptoms of deep venous thrombosis and pulmonary embolism and were advised to return to the hospital immediately if any of these symptoms developed. In patients with suspected deep venous thrombosis, venography or com-

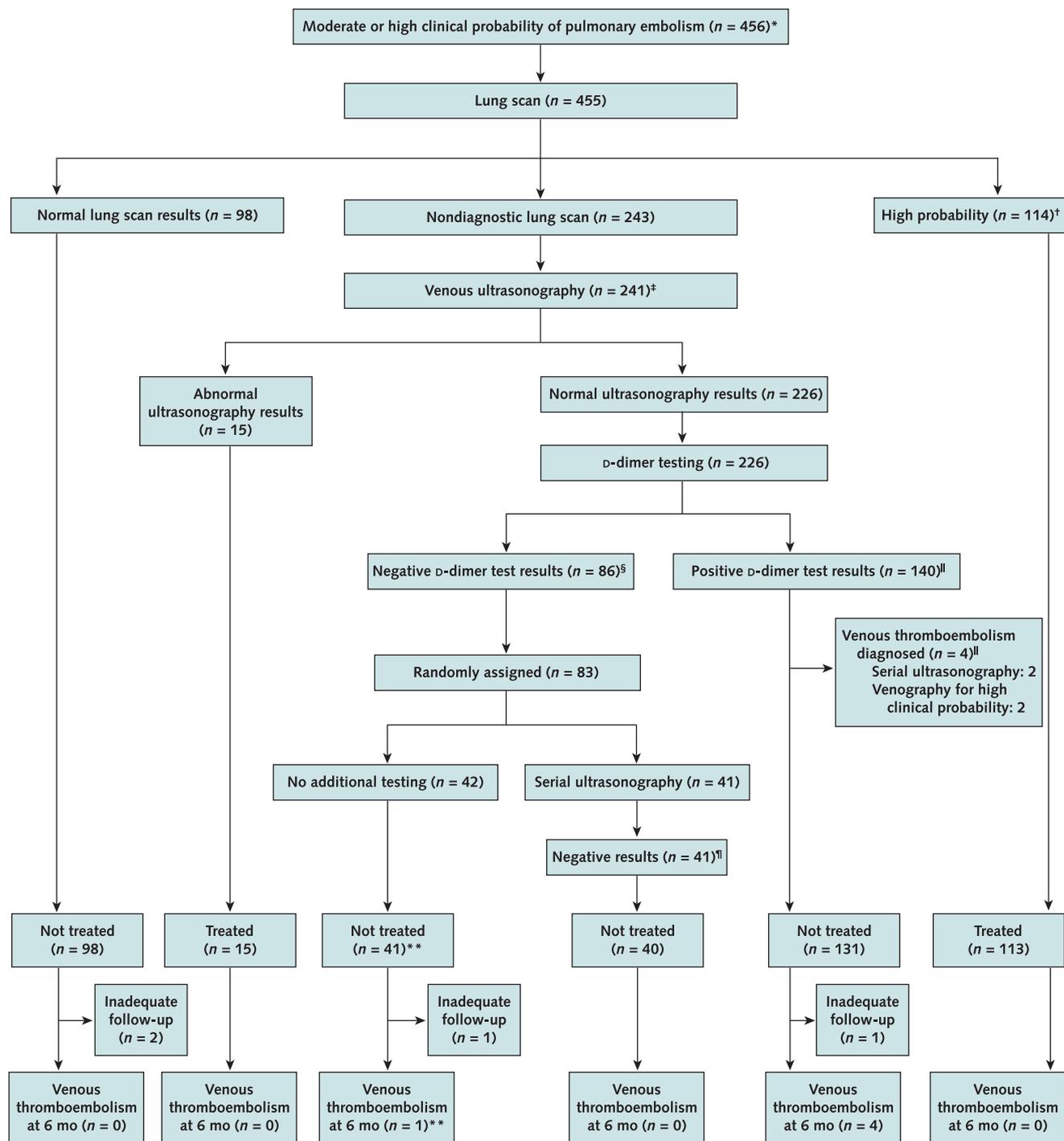
pression ultrasonography of the proximal deep veins was performed. Ultrasonography was repeated if the initial results were normal (13). In patients with suspected pulmonary embolism, a ventilation–perfusion lung scan was performed. If the lung scan was nondiagnostic, the patient

Figure 2. Diagnostic algorithm and patient outcomes for patients with a low clinical probability of pulmonary embolism.



High probability = ventilation–perfusion lung scan showed a high probability for pulmonary embolism; nondiagnostic = nondiagnostic ventilation–perfusion lung scan; normal = normal ventilation–perfusion lung scan; serial ultrasonography = serial bilateral ultrasonography of the proximal deep veins. \*Ventilation–perfusion lung scan was not performed in 2 patients: 1 patient had a myocardial infarction, and radioisotope was not available for 1 patient. Neither patient was treated with anticoagulant therapy or had venous thromboembolism during follow-up. †Three patients did not have ventilation–perfusion lung scan, were not treated with anticoagulant therapy, and did not have venous thromboembolism at follow-up. ‡Patients with a nondiagnostic lung scan had bilateral venous ultrasonography of the proximal veins on the day of presentation and after 7 and 14 days (serial ultrasonography). §One patient started anticoagulant therapy for atrial fibrillation. ¶Two patients were judged to not have pulmonary embolism and were not treated: One had normal pulmonary angiography results, and 1 had normal serial venous ultrasonography results. Neither patient had venous thromboembolism during follow-up. ¶One patient had subsegmental pulmonary embolism on pulmonary angiography that was performed contrary to the protocol. \*\*One patient who was treated for pulmonary embolism died suddenly on day 50, possibly from recurrent pulmonary embolism.

Figure 3. Diagnostic algorithm and outcomes for patients with a moderate or high probability of pulmonary embolism.



High probability = ventilation–perfusion lung scan showed a high probability for pulmonary embolism; nondiagnostic = nondiagnostic ventilation–perfusion lung scan; normal = normal ventilation–perfusion lung scan; serial ultrasonography = serial bilateral ultrasonography of the proximal deep veins. \*Pulmonary embolism was diagnosed in 1 critically ill patient on the basis of presence of proximal deep venous thrombosis on ultrasonography; the patient did not have a ventilation–perfusion lung scan. †One patient was judged to not have pulmonary embolism on the basis of normal spiral computed tomography and venous ultrasonography results and was not treated. ‡Two patients did not have venous ultrasonography performed. Neither patient was treated with anticoagulant therapy or had venous thromboembolism during follow-up. §Three eligible patients were not randomly assigned: The physician chose to perform bilateral venography in 1 patient, and 2 patients were mistakenly sent for additional testing. None of these 3 patients was treated with anticoagulant therapy or had venous thromboembolism during follow-up. ¶Patients with high clinical probability were considered for pulmonary angiography or for venography followed by serial ultrasonography if the venography results were normal. Of 19 such patients, 2 had deep venous thrombosis on venography and were treated for pulmonary embolism. Moderate-probability patients were to have serial ultrasonography; of 121

underwent compression ultrasonography of the proximal deep veins or pulmonary angiography (5). D-Dimer testing was not used to evaluate suspected venous thromboembolism during follow-up. In patients who died, pulmonary embolism was reported as the cause of death if there was substantive evidence or if the death was sudden and of uncertain cause. Among patients who were randomly assigned, episodes of bleeding and deaths were evaluated as secondary outcomes. Study personnel who performed routine and unscheduled follow-up assessments were not precluded from knowing initial test results or randomization group assignments. A central adjudication committee reviewed information regarding all suspected outcome events; members of this committee were unaware of test results at enrollment or patients' group assignments. Subject to availability, data provided to this committee included case report forms, clinic notes, original investigations (for example, lung scans and venography), interpreted reports of original investigations, and autopsy reports.

### Statistical Analysis

Among each randomized group of patients with a low clinical probability for pulmonary embolism and a negative D-dimer result, the 95% CIs around the observed proportion of patients who had symptomatic venous thromboembolism during follow-up should be narrow (that is,  $\pm 2\%$ ). We used this requirement as the basis for sample size. On the basis of findings from our previous study, we expected 44% of enrolled patients to have a low clinical probability of pulmonary embolism and negative D-dimer results, 1% of whom would have symptomatic venous thromboembolism during 6 months of follow-up (7). We originally planned to enroll 2000 patients to satisfy these requirements; however, a slower-than-expected enrollment rate prompted a blinded interim analysis that showed a very low prevalence of symptomatic venous thromboembolism during follow-up among all randomly assigned patients, and the study was therefore stopped early. Patients who did not complete follow-up are noted and are not included in outcome calculations. We calculated 95% CIs for proportions; to calculate CIs for differences between proportions, we applied the modified Wilson score method by using Confidence Interval Analysis software, version 2.1 (University of Southampton, Southampton, United Kingdom) (14, 15).

### Role of the Funding Sources

The Canadian Institutes of Health Research (formerly known as the Medical Research Council of Canada; grant MT-14092) funded the study, and Agen Biomedical Ltd. (Brisbane, Australia) donated the D-dimer kits. The fund-

ing sources had no role in study design or execution, collection of data, writing the manuscript, or the decision to submit the manuscript for publication.

## RESULTS

Patients were enrolled from July 1998 through October 2002. A total of 2591 patients met the inclusion criteria; 1126 of these were eligible, provided informed consent, were enrolled in the study, and had a standardized assessment of clinical probability of pulmonary embolism (Tables 1 and 2; Figure 1).

### Low Clinical Probability of Pulmonary Embolism

Clinical probability of pulmonary embolism was low in 670 (60%) patients (Figure 2). Of these patients, 373 (56%) had negative D-dimer test results and 297 (44%) had positive D-dimer test results.

### Low Clinical Probability and Negative D-Dimer Results

As shown in Figure 2 and Table 2, 373 patients with a low clinical probability of pulmonary embolism and negative D-dimer results were randomly assigned to receive no additional diagnostic testing ( $n = 187$ ) or a ventilation-perfusion lung scan, the results of which would determine the need for additional diagnostic testing ( $n = 186$ ).

Of 187 patients who had no additional testing, none was diagnosed with pulmonary embolism at presentation and none received anticoagulant therapy. Five patients did not complete 6 months of follow-up; of the 182 with adequate follow-up, none (CI, 0.0% to 2.1%) had venous thromboembolism, none had bleeding, and 3 died of causes unrelated to thromboembolism (1 each of cancer, chronic obstructive pulmonary disease, and cardiac failure).

In the group that underwent additional testing, 3 of 186 patients had pulmonary embolism at enrollment and received anticoagulant therapy (Figure 2). One patient did not complete 6 months of follow-up; of those who completed follow-up (including the 3 patients who were treated for pulmonary embolism), 1 (0.5% [CI, 0.1% to 3.0%]) had venous thromboembolism, none had bleeding, and 7 died (1 each of possible pulmonary embolism, sepsis, cancer, motor vehicle accident, cardiac failure, pericardial disease, and leukemia).

During 6 months of follow-up, the frequency of venous thromboembolism was similar in the 2 groups (difference,  $-0.5$  percentage point [CI,  $-3.0$  to  $1.6$  percentage points]).

such patients, 2 had ultrasonography results showing deep venous thrombosis that was subsequently treated. Five other patients were treated with anticoagulant therapy: 2 for initial pulmonary embolism despite nondiagnostic testing (not counted as pulmonary embolism in the analysis), 1 for atrial fibrillation, and 2 for temporary venous thromboembolism prophylaxis after major orthopedic surgery. None of these 9 treated patients had venous thromboembolism during follow-up. ¶One patient was treated with anticoagulant therapy for atrial fibrillation and did not have venous thromboembolism during follow-up. \*\*One patient was treated with anticoagulant therapy because of a history of recurrent venous thromboembolism and congenital heart disease. This patient was diagnosed with pulmonary embolism during follow-up after stopping anticoagulant therapy.

Table 2. Patient Characteristics

| Characteristic                            | All Patients<br>(n = 1126)* | Randomly Assigned Patients                               |                                 |                                                                                                                                       |                                 |
|-------------------------------------------|-----------------------------|----------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
|                                           |                             | Low Clinical Probability and Negative<br>D-Dimer Results |                                 | Moderate or High Clinical Probability,<br>Nondiagnostic Lung Scan, Normal<br>Ultrasonography Results, and<br>Negative D-Dimer Results |                                 |
|                                           |                             | No Additional Testing<br>(n = 187)                       | Additional Testing<br>(n = 186) | No Additional Testing<br>(n = 42)†                                                                                                    | Additional Testing<br>(n = 41)‡ |
| Mean age (SD), y                          | 57 (17)                     | 47 (18)                                                  | 46 (17)                         | 54 (19)                                                                                                                               | 56 (17)                         |
| Men, n (%)                                | 391 (35)                    | 51 (27)                                                  | 61 (33)                         | 19 (45)                                                                                                                               | 14 (34)                         |
| Outpatients, n (%)                        | 564 (50)                    | 131 (70)                                                 | 137 (74)                        | 24 (57)                                                                                                                               | 20 (49)                         |
| Active cancer, n (%)                      | 153 (14)                    | 9 (5)                                                    | 11 (6)                          | 3 (7)                                                                                                                                 | 5 (12)                          |
| Previous venous thromboembolism,<br>n (%) | 130 (12)                    | 5 (3)                                                    | 12 (6)                          | 10 (24)                                                                                                                               | 8 (20)                          |

\* Includes 670 (60%) patients with low clinical probability, 385 (34%) with moderate clinical probability, and 71 (6%) with high clinical probability.

† Of 42 patients who received no additional testing, 37 (88%) had a moderate clinical probability and 5 (12%) had a high clinical probability.

‡ Of 41 patients who underwent additional testing, 38 (93%) had a moderate clinical probability and 3 (7%) had a high clinical probability.

### Low Clinical Probability and Positive D-Dimer Results

Of 297 patients with a low clinical probability of pulmonary embolism and positive D-dimer test results, pulmonary embolism was diagnosed by scheduled testing in 24 patients (Figure 2). Three patients did not complete 6 months of follow-up. Of 294 patients who did have adequate follow-up, 5 (2.0% [CI, 0.7% to 3.9%]) had venous thromboembolism (Figure 2; Appendix Table, available at [www.annals.org](http://www.annals.org)).

### Moderate or High Clinical Probability of Pulmonary Embolism

Clinical probability of pulmonary embolism was moderate or high in 456 patients (40%), 243 of whom had a nondiagnostic lung scan (Figures 1 and 3). Of these, 241 had venous ultrasonography at presentation; the diagnostic study showed deep venous thrombosis in 15 patients whereas 226 had normal results. Of those with normal ultrasonography results, D-dimer test results were negative in 86 patients and positive in 140 patients. Of the 86 patients with negative D-dimer test results, 83 were randomly assigned to receive either additional testing or no additional testing. Of the 140 patients with positive D-dimer test results, additional scheduled testing was diagnostic for pulmonary embolism in 4 patients.

Of the 375 patients who had a moderate or high clinical probability for pulmonary embolism but were not randomly assigned, 3 had inadequate follow-up and 4 had venous thromboembolism during follow-up (Figure 3; Appendix Table, available at [www.annals.org](http://www.annals.org)). Of 83 patients with a nondiagnostic lung scan, normal venous ultrasonography results, and negative D-dimer results, 42 were randomly assigned to receive no additional diagnostic testing and 41 were randomly assigned to receive serial venous ultrasonography (Figure 3; Table 2).

Of the 42 patients who received no further testing, 1 was treated with anticoagulant therapy contrary to the protocol (history of recurrent venous thromboembolism and

congenital heart disease), 1 did not complete follow-up, and 1 (2.4% [CI, 0.1% to 12.6%]) had venous thromboembolism during follow-up (Appendix Table, available at [www.annals.org](http://www.annals.org); Figure 3). The episode of venous thromboembolism occurred in the patient who was treated with full-dose anticoagulation at presentation (Appendix Table, available at [www.annals.org](http://www.annals.org)). There were no deaths or episodes of bleeding in this group.

Of the 41 patients who underwent additional testing, 1 was treated with anticoagulant therapy (for atrial fibrillation). All completed follow-up, and none (CI, 0.0% to 8.6%) was found to have venous thromboembolism or bleeding (Appendix Table, available at [www.annals.org](http://www.annals.org)). One person in this group died of complications related to dementia.

Therefore, during 6 months of follow-up, the frequency of venous thromboembolism was similar in the 2 groups (difference, 2.4 percentage points [CI, -6.4 to 12.6 percentage points]).

### Overall Prevalence of Pulmonary Embolism at Initial Presentation and during Follow-up

Of 1126 enrolled patients, 160 (14.2%) had pulmonary embolism diagnosed at initial presentation or by serial venous ultrasonography. Of 952 patients who did not have pulmonary embolism diagnosed initially, 11 (1.2% [CI, 0.6% to 2.1%]) had venous thromboembolism during follow-up (not including 14 patients whose study follow-up was incomplete). Overall prevalence of venous thromboembolism was 15.2%.

### Comparison of Inpatients and Outpatients

Inpatients were older and had a higher prevalence of cancer, a lower prevalence of low clinical probability of pulmonary embolism, a lower prevalence of negative D-dimer test results among patients with low clinical probability, and a higher overall prevalence of pulmonary embolism (Table 3). In each category of clinical probability for

pulmonary embolism, the prevalence of pulmonary embolism was similar in inpatients and outpatients.

## DISCUSSION

Our study shows that it is safe to withhold additional diagnostic testing in outpatients and inpatients with suspected pulmonary embolism if they have a low pretest clinical probability and negative erythrocyte agglutination D-dimer test results. Although similarly safe in the 2 groups, the clinical utility of D-dimer testing was greater in outpatients because this combination of findings was more than twice as common in outpatients as in inpatients. There were too few patients in the second randomized subgroup (patients with moderate or high clinical probability of pulmonary embolism, a nondiagnostic ventilation–perfusion lung scan, no proximal deep venous thrombosis on ultrasonography, and negative D-dimer test results) to be able to conclude that additional diagnostic testing can be safely withheld in such patients.

Several D-dimer tests of varying accuracy and technical complexity have been used as exclusionary tests for pulmonary embolism (1, 2). We used the SimpliRED assay because it is a point-of-care test, has a higher specificity (approximately 75%) for venous thromboembolism than most other D-dimer tests, and retains moderately high sensitivity (approximately 90%) (6). Consistent with our findings, previous cohort studies and related meta-analyses suggest that it is safe to withhold additional diagnostic testing in patients who have a low clinical suspicion of pulmonary

embolism and negative erythrocyte agglutination D-dimer test results (2, 4, 7). However, the findings of cohort studies have greater potential for bias than randomized trials. Furthermore, such studies cannot directly compare the outcomes achieved with different approaches to diagnosis of pulmonary embolism (11).

At the beginning of our trial, we used a prediction rule score of 1.5 or less to categorize patients as having a low clinical probability of pulmonary embolism. However, of the first 231 patients enrolled, only 13% (rather than the expected 44%) were categorized as having both a low clinical probability of pulmonary embolism and negative D-dimer results. This prompted the steering committee to question if a higher prediction rule score could be used to identify patients who had a low clinical probability because use of a higher score would increase the proportion of patients in the study who had both a low clinical probability and negative D-dimer test results. Further analysis of the first 231 patients found that use of a score of 4 or less (instead of 1.5 or less) increased the number who had a low clinical probability and negative D-dimer results from 30 (13%) to 71 (31%); none of these 71 patients had pulmonary embolism at presentation or during follow-up. Reanalysis of data from the original study that was used to derive the prediction rule (6) also demonstrated that there was a very low prevalence of pulmonary embolism (2.1%) among patients with a prediction rule score of 4 or less who had negative D-dimer results. These characteristics were categorized as “pulmonary embolism unlikely” in the

**Table 3. Comparison of Enrolled Inpatients and Outpatients\***

| Characteristic                                                                                                                                                                             | Inpatients<br>(n = 562) | Outpatients<br>(n = 564) | P Value† |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------------|----------|
| Mean age (SD), y                                                                                                                                                                           | 60 (18)                 | 49 (18)                  | <0.001   |
| Men, n (%)                                                                                                                                                                                 | 214 (38)                | 177 (31)                 | 0.018    |
| Active cancer, n (%)                                                                                                                                                                       | 101 (18)                | 52 (9)                   | <0.001   |
| Previous venous thromboembolism, n (%)                                                                                                                                                     | 65 (12)                 | 65 (12)                  | 1        |
| Clinical probability                                                                                                                                                                       |                         |                          | <0.001   |
| Low, n (%)                                                                                                                                                                                 | 283 (50)                | 387 (69)                 |          |
| Moderate, n (%)                                                                                                                                                                            | 234 (42)                | 151 (27)                 |          |
| High, n (%)                                                                                                                                                                                | 45 (8)                  | 26 (5)                   |          |
| Prevalence of venous thromboembolism according to clinical probability‡                                                                                                                    |                         |                          |          |
| All patients, n/n (%)                                                                                                                                                                      | 108/556 (20)            | 63/557 (11)              | 0.002    |
| Low, n/n (%)                                                                                                                                                                               | 17/278 (6)              | 16/383 (4)               | 0.25     |
| Moderate, n/n (%)                                                                                                                                                                          | 69/233 (30)             | 30/148 (20)              | 0.043    |
| High, n/n (%)                                                                                                                                                                              | 22/45 (49)              | 17/26 (65)               | 0.178    |
| Low clinical probability and negative D-dimer results, n (%)                                                                                                                               | 105 (19)                | 268 (48)                 | <0.001   |
| Prevalence of venous thromboembolism with low clinical probability and negative D-dimer results, n/n (%)§                                                                                  | 1/103 (1)               | 2/264 (1)                | 1        |
| Moderate or high clinical probability, nondiagnostic lung scan, normal ultrasound of proximal veins, and negative D-dimer results, n (%)                                                   | 42 (7)                  | 44 (8)                   | 0.9      |
| Prevalence of venous thromboembolism with moderate or high clinical probability, nondiagnostic lung scan, normal ultrasonography of proximal veins, and negative D-dimer results, n/n (%)§ | 0/41 (0)                | 1/44 (2)                 | 1        |

\* For calculation of prevalence of pulmonary embolism, denominators do not include the 13 enrolled patients who did not complete follow-up.

† Student *t*-test for means; Fisher exact test for proportions; 2-tailed *P* value.

‡ Includes pulmonary embolism diagnosed at initial presentation and venous thromboembolism diagnosed during 6 months of follow-up in patients with no initial diagnosis of pulmonary embolism.

§ Includes pulmonary embolism diagnosed at initial presentation (patients randomly assigned to receive additional testing) and venous thromboembolism diagnosed during 6 months of follow-up of patients with no initial diagnosis of pulmonary embolism (both groups).

subsequent report, which contains the details of these analyses (12). On the basis of this evidence, the original trial was stopped and the current trial was restarted using a prediction rule score of 4 or less to identify patients with a low clinical probability of pulmonary embolism. Only data that were collected after restarting this study are included in this report. The findings of the current study confirm the validity of using a prediction rule score of 4 or less to identify patients with a low probability of pulmonary embolism (5% prevalence of pulmonary embolism). The prevalence of pulmonary embolism was similar in outpatients and inpatients who had the same clinical suspicion of embolism; therefore, our study demonstrates that the clinical model works similarly in the 2 groups of patients. Consistent with our findings, a recent large cohort study (9) also used the combination of a score of 4 or less with this clinical prediction rule (termed “pulmonary embolism unlikely” in that study) and negative D-dimer results to successfully exclude pulmonary embolism.

Our study’s strengths included its randomized design, independent adjudication of outcomes, complete follow-up in nearly all enrolled patients, inclusion of inpatients and outpatients, participation of multiple clinical centers, and independent interpretation of test results at initial presentation. Furthermore, most eligible patients consented to the study. These features reduce potential for bias and support the generalizability of our findings.

The study had 4 main limitations. First, approximately one half of the patients who satisfied the inclusion criteria were excluded from participating. The most common reasons for exclusion were previous initiation of diagnostic testing or administration of anticoagulant therapy for more than 24 hours; therefore, the high proportion of exclusions is not expected to have undermined the study’s validity. Second, study personnel were not blinded to the results of diagnostic testing or to group assignment, which could have biased assessment of outcomes. Third, the study enrolled fewer patients than planned, which reduced the precision of the study’s findings. Fourth, of the 6 patients with a low clinical probability of pulmonary embolism and negative D-dimer test results who had inadequate follow-up, 5 were randomly assigned to receive no additional testing. However, even if all of these patients were assumed to have had venous thromboembolism during follow-up, the rate of thrombosis would only be 2.7% in this group.

Since this study was performed, computed tomography pulmonary angiography has become an established diagnostic test for pulmonary embolism (8, 9, 16, 17). Compared with ventilation–perfusion lung scan, computed tomography angiography is more widely available, is rarely nondiagnostic (10% vs. 50%) (5, 8, 9, 16, 17), and often yields clinically important information about alternative diagnoses in patients who have not had a pulmonary embolism (9, 18). However, computed tomography pulmonary angiography is associated with substantial exposure to

radiation, high costs, and complications from radiographic contrast. Consequently, our main finding remains highly relevant. Future studies are required to refine the combined use of currently available tests for pulmonary embolism, to identify which tests are optimal for predefined populations of patients (for example, inpatients or those with cancer), and to identify new tests that further improve on current diagnostic modalities.

We conclude that pulmonary embolism can be excluded in patients who have a low clinical probability of pulmonary embolism and negative erythrocyte agglutination D-dimer test results and that further diagnostic testing is not beneficial to this population. These findings are present in approximately 50% of outpatients and 20% of inpatients with suspected pulmonary embolism.

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**Appendix Table. Characteristics of Patients with Venous Thromboembolism during 6 Months of Follow-up and without Pulmonary Embolism Diagnosis at Initial Presentation\***

| Clinical Probability | Initial Assessment and Diagnostic Testing |                 |                                                                                                        | Days after Enrollment | Venous Thromboembolism Outcome Event |                                                                                                                                                                                                                                                                                   |
|----------------------|-------------------------------------------|-----------------|--------------------------------------------------------------------------------------------------------|-----------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | Original Presentation                     | D-Dimer Results | Other Testing                                                                                          |                       | Event                                | Circumstances                                                                                                                                                                                                                                                                     |
| Low                  | Outpatient                                | Positive        | Nondiagnostic lung scan; normal initial US results and no serial US                                    | 13                    | Probable PE                          | Breathless, acute deterioration, normal electrocardiography results; metastatic cancer                                                                                                                                                                                            |
| Low                  | Inpatient                                 | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 69                    | Possible fatal PE                    | Cardiac arrest with ventricular fibrillation; metastatic cancer                                                                                                                                                                                                                   |
| Low                  | Inpatient                                 | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 84                    | Possible fatal PE                    | Cardiac arrest with ventricular tachycardia; coronary artery disease                                                                                                                                                                                                              |
| Low                  | Outpatient                                | Positive        | Normal lung scan                                                                                       | 105                   | Proximal DVT                         | Admitted to hospital with sepsis and liver failure, diagnosed 8 days later                                                                                                                                                                                                        |
| Low                  | Inpatient                                 | Negative        | Randomly assigned to additional testing; nondiagnostic lung scan; normal serial US results             | 109                   | Possible fatal PE                    | Chest pain, witnessed arrest, no diagnostic testing                                                                                                                                                                                                                               |
| Low                  | Outpatient                                | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 162                   | Arm DVT                              | Cancer and indwelling central line                                                                                                                                                                                                                                                |
| Moderate             | Inpatient                                 | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 22                    | PE                                   | No unusual circumstances                                                                                                                                                                                                                                                          |
| Moderate             | Inpatient                                 | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 30                    | Proximal DVT and PE                  | No unusual circumstances                                                                                                                                                                                                                                                          |
| Moderate             | Inpatient                                 | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 42                    | Proximal DVT                         | No unusual circumstances                                                                                                                                                                                                                                                          |
| Moderate             | Outpatient                                | Negative        | Nondiagnostic lung scan; normal initial US results; randomly assigned to receive no additional testing | 103                   | PE                                   | Contrary to the protocol, received anticoagulant therapy for history of recurrent venous thromboembolism and congenital heart disease; subsequently stopped warfarin therapy and pulmonary embolism was diagnosed 10 d later despite uncertainty that lung scan findings were new |
| Moderate             | Inpatient                                 | Positive        | Nondiagnostic lung scan; normal serial US results                                                      | 153                   | Proximal DVT                         | No unusual circumstances                                                                                                                                                                                                                                                          |

\* DVT = deep venous thrombosis; PE = pulmonary embolism; US = ultrasonography of the proximal veins.

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**APPENDIX**

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