ORIGINAL ARTICLE

Evaluation of D-Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis

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ABSTRACT

BACKGROUND

Several diagnostic strategies using ultrasound imaging, measurement of D-dimer, and assessment of clinical probability of disease have proved safe in patients with suspected deep-vein thrombosis, but they have not been compared in randomized trials.

METHODS

Outpatients presenting with suspected lower-extremity deep-vein thrombosis were potentially eligible. Using a clinical model, physicians evaluated the patients and categorized them as likely or unlikely to have deep-vein thrombosis. The patients were then randomly assigned to undergo ultrasound imaging alone (control group) or to undergo D-dimer testing (D-dimer group) followed by ultrasound imaging unless the D-dimer test was negative and the patient was considered clinically unlikely to have deep-vein thrombosis, in which case ultrasound imaging was not performed.

RESULTS

Five hundred thirty patients were randomly assigned to the control group, and 566 to the D-dimer group. The overall prevalence of deep-vein thrombosis or pulmonary embolism was 15.7 percent. Among patients for whom deep-vein thrombosis had been ruled out by the initial diagnostic strategy, there were two confirmed venous thromboembolic events in the D-dimer group (0.4 percent; 95 percent confidence interval, 0.05 to 1.5 percent) and six events in the control group (1.4 percent; 95 percent confidence interval, 0.5 to 2.9 percent; P=0.16) during three months of follow-up. The use of D-dimer testing resulted in a significant reduction in the use of ultrasonography, from a mean of 1.34 tests per patient in the control group to 0.78 in the D-dimer group (P=0.008). Two hundred eighteen patients (39 percent) in the D-dimer group did not require ultrasound imaging.

CONCLUSIONS

Deep-vein thrombosis can be ruled out in a patient who is judged clinically unlikely to have deep-vein thrombosis and who has a negative D-dimer test. Ultrasound testing can be safely omitted in such patients.

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Suspected deep-vein thrombosis is a common condition, with a lifetime cumulative incidence of 2 to 5 percent. Untreated deep-vein thrombosis can result in pulmonary embolism, a potentially fatal outcome. Anticoagulant therapy reduces both morbidity and mortality from venous thromboembolism, and early diagnosis is therefore important. Accurate diagnosis of deep-vein thrombosis minimizes the risk of thromboembolic complications and averts the exposure of patients without thrombosis to the risks of anticoagulant therapy.

We previously determined that the use of a clinical model allows physicians to categorize accurately the probability that a patient has deep-vein thrombosis before tests are performed.[1] Subsequently, analysis of our data suggested that this model could be used to categorize patients into two groups without sacrificing patient safety, as long as clinical probability was used in combination with D-dimer testing.

D-Dimer is a marker of endogenous fibrinolysis and should therefore be detectable in patients with deep-vein thrombosis. Several studies have shown the D-dimer assay to have a high negative predictive value and D-dimer to be a sensitive but nonspecific marker of deep-vein thrombosis.[2-4] However, the safety and added value of relying on a negative D-dimer test to exclude a diagnosis of deep-vein thrombosis remain controversial, and D-dimer testing has not previously been evaluated in a randomized trial.

We hypothesized that the use of D-dimer testing in patients with suspected deep-vein thrombosis would reduce the need for ultrasound imaging and rule out deep-vein thrombosis in a higher proportion of patients on the day of presentation, while not compromising safety, as reflected by a small number of thromboembolic events during three months of follow-up.

Table 1. Clinical Model for Predicting the Pretest Probability of Deep-Vein Thrombosis.*

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as deep-vein thrombosis	−2

* A score of two or higher indicates that the probability of deep-vein thrombosis is likely; a score of less than two indicates that the probability of deep-vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

METHODS

STUDY PARTICIPANTS

Consecutive outpatients with suspected deep-vein thrombosis were potentially eligible for the study. Patients were excluded if they were suspected to have pulmonary embolism, if they had a life expectancy of less than three months, if they had used therapeutic doses of anticoagulant agents (defined by an international normalized ratio >2.0 for oral anticoagulants or treatment doses of low-molecular-weight heparin) for more than 48 hours, if they were pregnant, if they were under 18 years of age, if they resided where they were inaccessible to follow-up, if their symptoms had resolved for more than 72 hours before presentation, if they were allergic to the contrast agent, or if they refused or were unable to give consent.

SETTING AND LOCATIONS

The patients were recruited from the thrombosis units of five academic health centers. Patients were also recruited from our emergency departments in the last quarter (six months) of the study. The research ethics committee of each institution approved the study, and all participants gave written informed consent.

INTERVENTIONS

All patients were first evaluated by physicians using a clinical model (Table 1). Patients with a score of less than two were considered unlikely, and those with a score of two or more were considered likely, to have deep-vein thrombosis. Consecutive patients were randomly assigned either to undergo ultrasound imaging alone (control group) or to undergo D-dimer testing; those in the latter group then underwent ultrasound imaging if they had been judged clinically likely to have deep-vein thrombosis or if

they were judged clinically unlikely but the D-dimer test was positive (Fig. 1 and 2).

Control Group

All patients in the control group underwent ultrasound imaging of the proximal veins. For patients who had been judged clinically unlikely to have deep-vein thrombosis, the diagnosis of deep-vein thrombosis was excluded if the ultrasound test was negative. For those who had been judged likely to have deep-vein thrombosis, a second ultrasound examination was performed one week later if the first test was negative.

D-Dimer Group

D-Dimer testing was performed with either the SimpliRED assay (Agen Biomedical) or the IL-Test (Instrumentation Laboratory). For the SimpliRED test, the result was considered negative if no agglutination was seen. For the IL-Test, the result was considered negative if the value was less than 200 μg per liter.[5] We previously demonstrated that these D-dimer

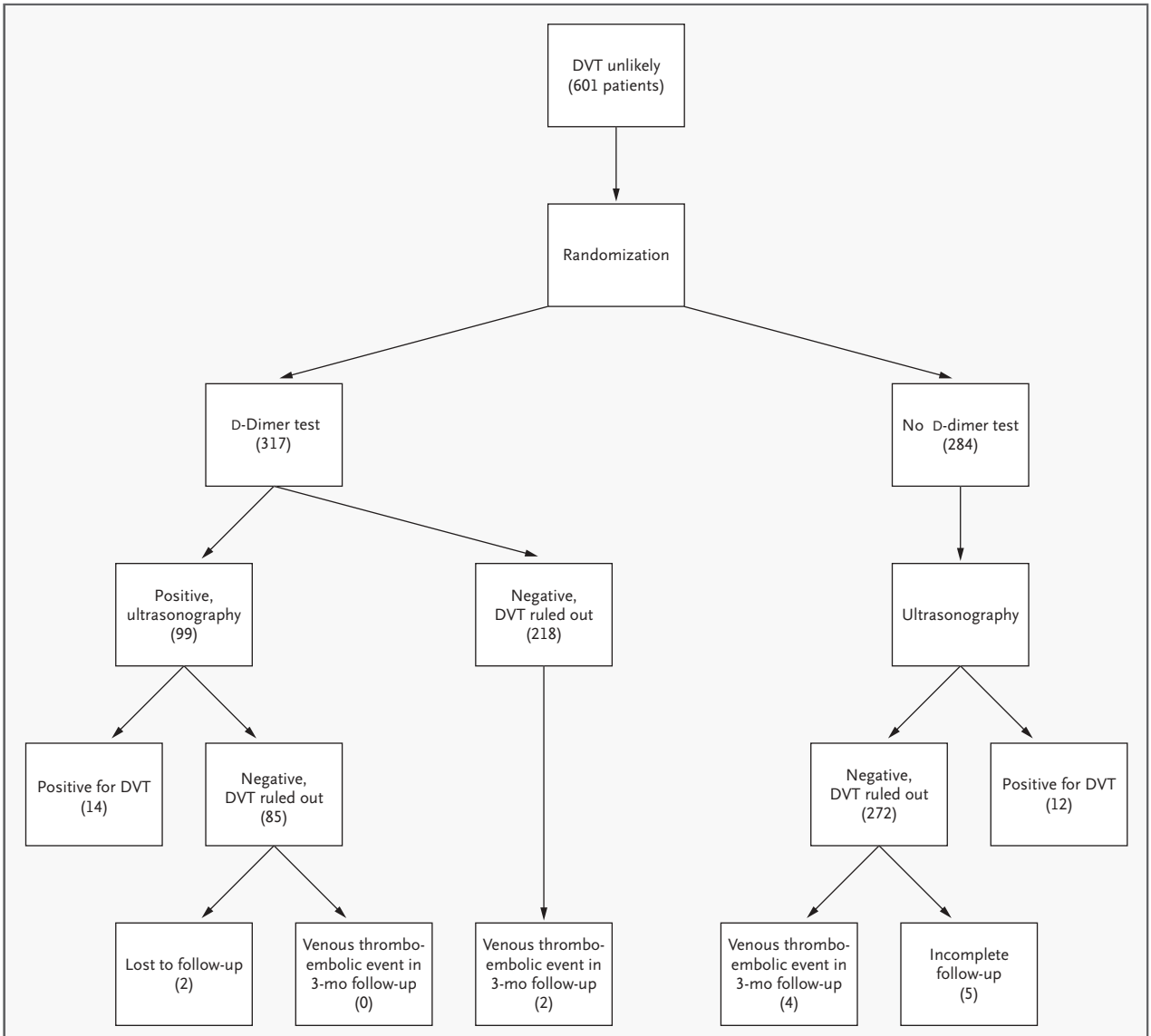

Figure 1. Diagnostic Algorithm and Patient Outcomes in the Group Judged Clinically Unlikely to Have Deep-Vein Thrombosis (DVT).
Two patients refused follow-up, and three were lost to follow-up.

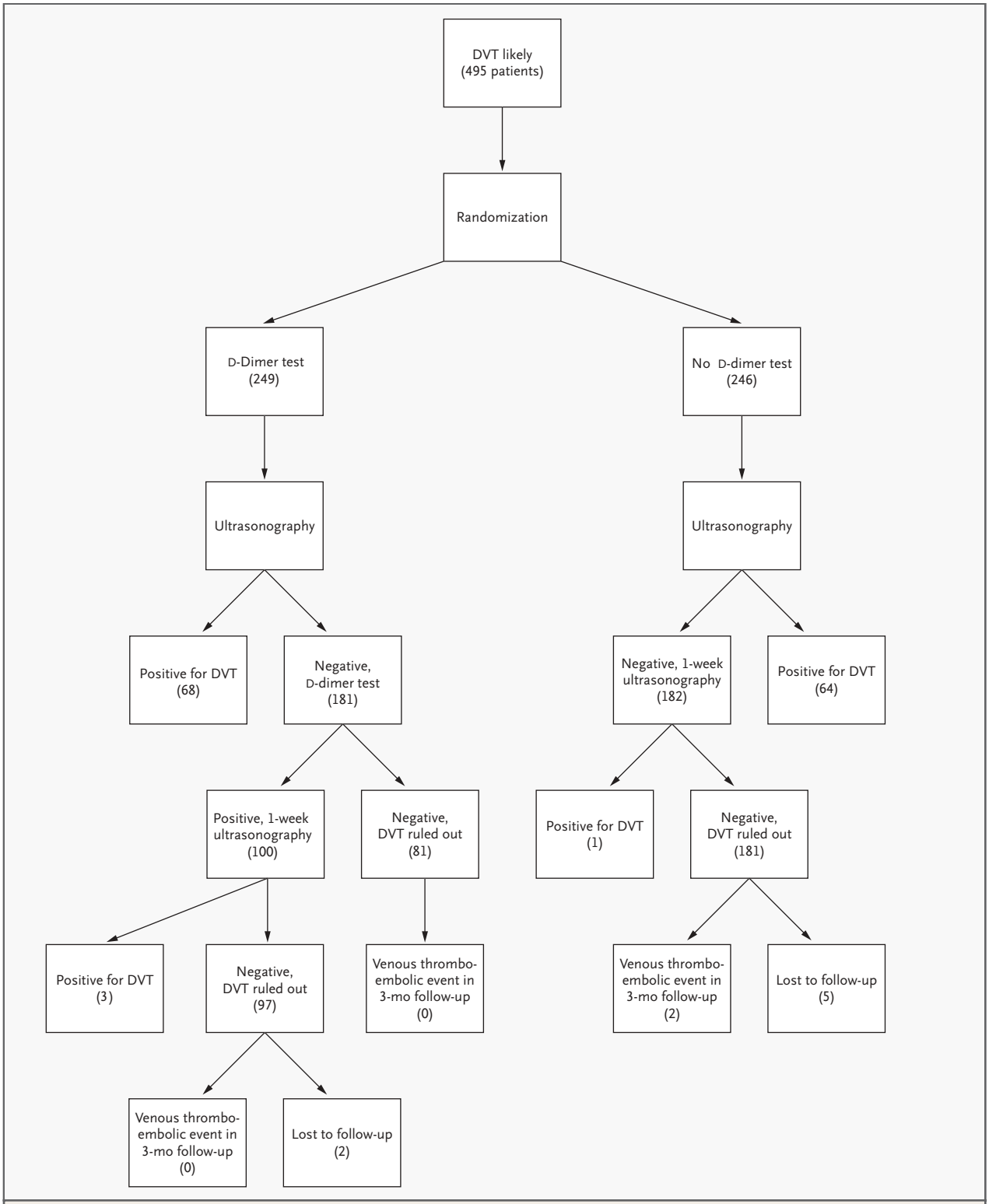

Figure 2. Diagnostic Algorithm and Patient Outcomes in the Group Judged Clinically Likely to Have Deep-Vein Thrombosis (DVT).

assays have similar negative predictive values in our patient population.[5] Patients who had been judged clinically unlikely to have deep-vein thrombosis and whose D-dimer test was negative underwent no ultrasound imaging. All other patients underwent an ultrasound test. A second test was performed only in the patients judged clinically likely to have deep-vein thrombosis who had an initial negative ultrasound test and a positive D-dimer test.

Venous Ultrasound Imaging

Ultrasonography was performed with a high-resolution 5- or 7.5-MHz linear-array transducer. The deep veins were evaluated for compressibility at 1-cm intervals from the common femoral vein to the point where the popliteal vein joins the calf veins. In patients with no history of deep-vein thrombosis, deep-vein thrombosis was diagnosed if the vein was noncompressible. In patients with a history of deep-vein thrombosis, deep-vein thrombosis was diagnosed if there was a new noncompressible site or if the diameter of a clot had increased by at least 4 mm from a previous measurement.[6,7] If the change in clot diameter was 1 mm or less, recurrence was ruled out. If the clot diameter had increased by 1.1 to 3.9 mm, the ultrasound examination was repeated one week later or venography was performed.

RANDOMIZATION

Randomization was performed in computer-generated blocks, with block sizes ranging from 4 to 12 and with stratification according to the history of previous deep-vein thrombosis and according to center. The randomization assignments were concealed in opaque envelopes. The study nurse opened the envelopes sequentially after the patient consent form had been signed and the clinical probability of deep-vein thrombosis had been determined. The ultrasonographers and the laboratory technicians performing the D-dimer tests were unaware of the patients' assignments.

SURVEILLANCE AND FOLLOW-UP

Patients receiving a diagnosis of deep-vein thrombosis were treated with conventional anticoagulant therapy. Other patients were asked to report to or call the study center if they had symptoms compatible with venous thromboembolism, and their condition was reviewed one week and three months after presentation.

OUTCOMES

All suspected outcome events were evaluated in a standardized way by an adjudication panel that was unaware of the patients' assignments, as previously described.[8-10] The primary outcome was the development of proximal deep-vein thrombosis or pulmonary embolism within three months in patients in whom deep-vein thrombosis had initially been ruled out.

CALCULATION OF SAMPLE SIZE

On the basis of our previous studies, we expected a rate of thromboembolic complications of 0.8 percent during the three-month follow-up period among patients in the control group in whom deep-vein thrombosis had been ruled out.[1,11] The study had sufficient power to detect an increase of 0.8 percent in the rate of thromboembolic complications in the D-dimer group as compared with the control group. An increase of 0.8 percent was chosen to correspond to an absolute rate of 1.6 percent, since this was the rate of follow-up events in two studies employing serial ultrasound imaging alone.[12,13] A sample of 500 patients per group would have 80 percent power with a two-tailed alpha error of less than 0.05 to ensure that the two diagnostic strategies were equivalent in effectiveness within 0.8 percent and that the 95 percent confidence interval for this difference in proportions would be 0.5 percent in favor of the D-dimer strategy or 2 percent in favor of the control strategy.[14]

STATISTICAL ANALYSIS

The primary analysis compared the rates of proximal deep-vein thrombosis and pulmonary embolism during the three-month follow-up among patients in the control and D-dimer groups in whom deep-vein thrombosis had initially been ruled out. Fisher's exact test was used to compare proportions. The mean number of ultrasound tests per patient in each group was compared by Student's t-test. Statistical significance was considered to have been achieved if the two-tailed P value was less than 0.05. The binomial distribution was used to determine 95 percent confidence intervals for proportions (SPSS, version 10.0, and SAS, version 8.1, Unix platform).

RESULTS

STUDY PATIENTS

A total of 1285 outpatients were screened, of whom 1096 were eligible, provided informed consent, and

were randomized (Fig. 3). Of these, 530 were assigned to the control group and 566 to the D-dimer group. The base-line characteristics of the two groups were similar (Table 2). The difference in the numbers of patients in the two groups was due to stratification and to the loss of randomization envelopes in the emergency departments of our institutions.

PATIENT OUTCOMES

Of the 1082 patients who completed follow-up, 83 (16.0 percent) in the control group and 87 (15.5 percent) in the D-dimer group had proximal deep-vein thrombosis or pulmonary embolism, for an overall prevalence of 15.7 percent. Four hundred ninety-five (45.7 percent) were categorized as likely to have deep-vein thrombosis; 138 of these patients (27.9 percent; 95 percent confidence interval, 23.9 to 31.8 percent) had proximal deep-vein thrombosis or pulmonary embolism. Five hundred eighty-seven (54.3 percent) were categorized as unlikely to have deep-vein thrombosis; 32 of these patients (5.5 percent; 95 percent confidence interval, 3.8 to 7.6 percent) had proximal deep-vein thrombosis or pulmonary embolism. These rates include events that occurred during the three-month follow-up.

Of the 520 control patients who completed follow-up, 279 were categorized as unlikely and 241 as likely to have deep-vein thrombosis. Sixteen patients in the former group had venous thromboembolic events (5.7 percent; 95 percent confidence interval, 3.3 to 9.2 percent), of which four occurred during follow-up (1.4 percent; 95 percent confidence interval, 0.4 to 3.8 percent). Sixteen patients

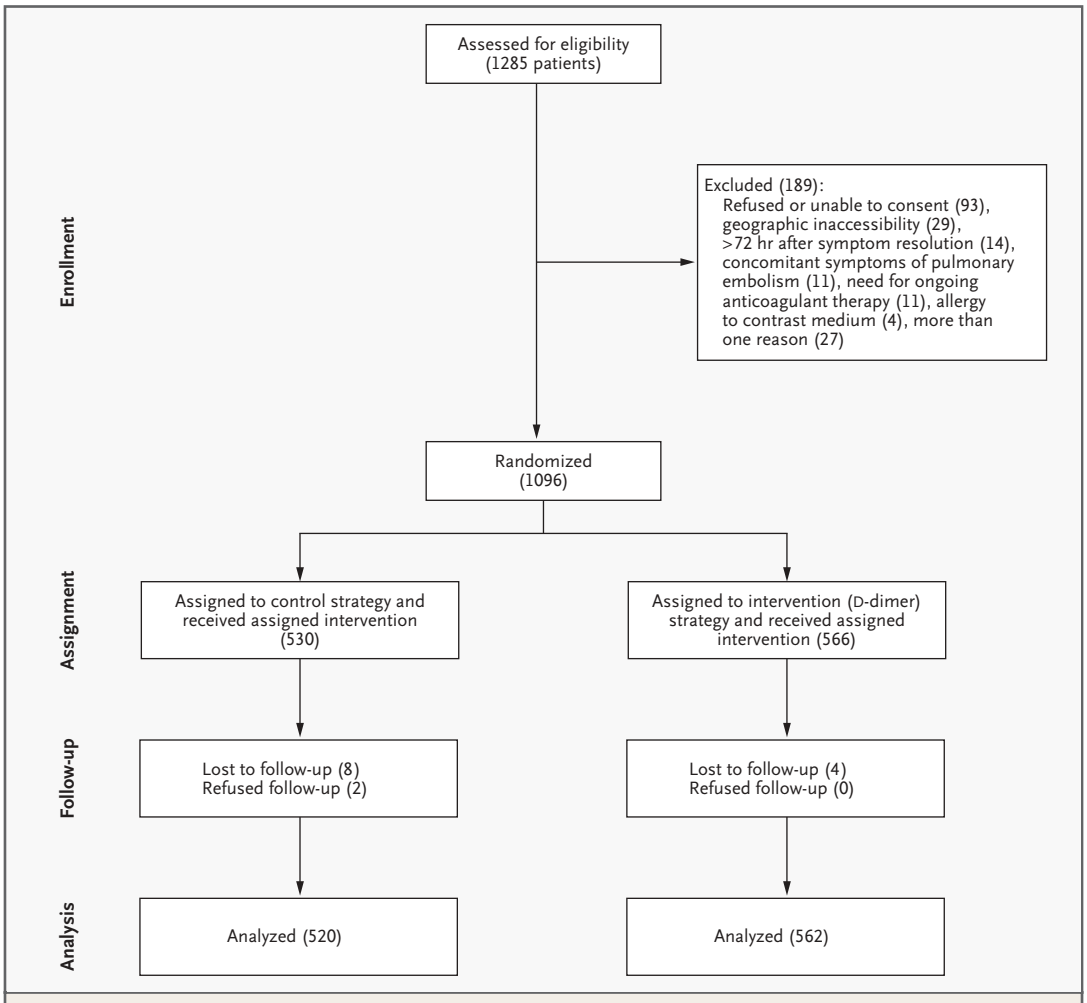

Figure 3. Profile of the Trial.

returned during follow-up: seven with suspected pulmonary embolism and nine with suspected deep-vein thrombosis. The four events seen on follow-up were all pulmonary emboli that were confirmed by high-probability ventilation perfusion scanning on days 10, 59, 65, and 70 after initial presentation. In two patients, the pulmonary embolism developed during a subsequent hospitalization.

Of the 241 control patients categorized as likely to have deep-vein thrombosis, 67 (27.8 percent; 95 percent confidence interval, 22.1 to 33.5 percent) had venous thromboembolic events: 64 had deep-vein thrombosis at presentation, 1 had deep-vein thrombosis at the one-week repeated ultrasound examination (0.5 percent of patients in whom this examination was performed), and 2 had pulmonary embolism during follow-up. Twelve patients returned during follow-up: three with suspected pulmonary embolism and nine with suspected deep-vein thrombosis. In two patients, pulmonary embolism was confirmed (on days 14 and 21 of follow-up). In one of these cases, the diagnosis was equivocal, even after spiral computed tomography and pulmonary angiography, but the patient was treated with anticoagulant therapy.

Overall, in the control group 6 of the 443 patients (1.4 percent; 95 percent confidence interval, 0.5 to 2.9 percent) in whom deep-vein thrombosis was initially considered to have been ruled out had confirmed thromboembolism during the three-month follow-up.

Of the 562 patients randomly assigned to the D-dimer group who completed follow-up, 315 were categorized as unlikely and 247 as likely to have deep-vein thrombosis. Sixteen patients in the former group had venous thromboembolic events (5.1 percent; 95 percent confidence interval, 2.9 to 8.1 percent), two of which occurred during follow-up (0.6 percent; 95 percent confidence interval, 0.1 to 2.4 percent). Two hundred eighteen patients (38.8 percent of the entire D-dimer group who completed follow-up) had a negative D-dimer test and therefore did not undergo ultrasound testing. Seventeen of these patients returned during follow-up: 4 with suspected pulmonary embolism and 13 with suspected deep-vein thrombosis. Two of these patients (0.9 percent; 95 percent confidence interval, 0.1 to 3.3 percent) had proximal deep-vein thrombosis on days 4 and 14 of follow-up. Ninety-seven had a positive D-dimer test and underwent ultrasound imaging, which confirmed proximal deep-vein thrombosis in 14 patients and was negative in 83, none of whom subsequently had deep-vein thrombosis. The negative predictive value of the D-dimer test was 99.1 percent (95 percent confidence interval, 96.7 to 99.9 percent), and the positive predictive value was 14.1 percent (95 percent confidence interval, 7.95 to 22.6 percent).

Table 2. Demographic and Clinical Characteristics of the Patients.

Characteristic	D-Dimer Group (N=566)	Control Group (N=530)
Mean age — yr	58.6	58.3
Mean duration of symptoms — days	7.8	7.9
Sex — M/F	248/318	212/318
No. clinically unlikely/no. clinically likely to have deep-vein thrombosis	317/249	284/246
Prior venous thromboembolic event — no. of patients (%)	102 (18.0)	100 (18.9)
Cancer — no. of patients (%)	51 (9.0)	46 (8.7)
Surgery or immobilization — no. of patients (%)	82 (14.5)	75 (14.2)

Of the 247 patients in the D-dimer group who were categorized as likely to have deep-vein thrombosis, 71 (28.7 percent; 95 percent confidence interval, 23.1 to 34.4 percent) had deep-vein thrombosis: 68 at presentation and 3 at the one-week repeated ultrasound examination (3 percent of the 100 patients who had this examination). None had deep-vein thrombosis or pulmonary embolism during follow-up (95 percent confidence interval, 0 to 2.0 percent). Nine patients returned during follow-up: two with suspected pulmonary embolism and seven with suspected deep-vein thrombosis. The negative predictive value of the D-dimer test was 89.0 percent (95 percent confidence interval, 80.7 to 94.6 percent), and the positive predictive value was 38.6 percent (95 percent confidence interval, 31.0 to 46.7 percent).

Among all patients who underwent D-dimer testing, two (0.4 percent; 95 percent confidence interval, 0.05 to 1.5 percent) in whom deep-vein thrombosis was initially ruled out had thromboembolic events during follow-up. In the entire D-dimer group, the negative predictive value was 96.1 percent (95 percent confidence interval, 93.3 to 98.0 percent).

There was no significant difference between the rates of various thromboembolic events on follow-up in the D-dimer and control groups (0.4 percent [2 of 477] vs. 1.4 percent [6 of 443], respectively; P=0.16). The 95 percent confidence interval for the

observed difference of 0.93 percent between the two groups was –0.2 to +2.2 percent. The mean number of ultrasound tests per patient was 1.34 in the control group and 0.78 in the D-dimer group (P=0.008).

Venography was performed in 11 patients, 5 of whom had prior deep-vein thrombosis and an abnormal ultrasound test at presentation but no baseline ultrasound test for comparison; venography showed evidence of previous deep-vein thrombosis and ruled out acute thrombosis in all 5. Among patients categorized as likely to have deep-vein thrombosis, 74 percent of control patients and only 40 percent of patients in the D-dimer group had a repeated ultrasound examination. In the entire study population, a definitive diagnosis was made on the day of presentation in 82 percent of the D-dimer group and 65 percent of the control group (P< 0.001). Twenty patients died during the study, 10 of whom initially received a diagnosis of deep-vein thrombosis. Sixteen deaths were due to metastatic cancer, two to renal failure, one to sepsis, and one to ischemic cardiac disease. None of the deaths were due to pulmonary embolism.

DISCUSSION

We have demonstrated that in patients presenting with suspected deep-vein thrombosis, a diagnostic strategy using D-dimer testing and clinical judgment to select patients for ultrasound imaging is as safe and feasible as a strategy combining clinical judgment with ultrasound imaging for all patients. The addition of D-dimer testing to the diagnostic algorithm has the potential to make the diagnosis of deep-vein thrombosis in outpatients more convenient and economical. In patients who are considered clinically unlikely to have deep-vein thrombosis and who have a negative D-dimer test, the diagnosis of deep-vein thrombosis can safely be excluded without the need for further diagnostic testing. Use of the D-dimer test also reduces the need for repeated ultrasound testing in patients who are likely to have deep-vein thrombosis and establishes a definitive diagnosis on the day of presentation in a larger proportion of patients.

Diagnostic strategies that have proved safe in patients with suspected deep-vein thrombosis have used repeated ultrasound testing, ultrasonography combined with D-dimer testing, and clinical probability estimation combined with ultrasonography. Several previous studies have suggested that the high negative predictive value of D-dimer testing in outpatients with suspected deep-vein thrombosis may be used as part of a diagnostic algorithm.[11,15-17] The value of combining clinical estimation of probability with imaging tests has been confirmed in other studies.[18-21] We and others have demonstrated the potential for the use of D-dimer testing to simplify diagnosis further.[11,22] However, none of these strategies have previously been compared in a randomized trial. Our study demonstrates that the use of D-dimer testing to rule out deep-vein thrombosis benefits from consideration of clinical probability. First, the negative D-dimer result in patients who were unlikely to have deep-vein thrombosis eliminated the need for ultrasound testing in over 38 percent of the patients in the D-dimer group. In the group judged likely to have deep-vein thrombosis, we were able to limit the need for a repeated test to the patients with positive D-dimer results. This strategy has the additional advantage of increasing the proportion of patients who will have a positive result on the repeated test. Venous thromboembolism developed on follow-up in only 0.4 percent of patients in whom deep-vein thrombosis was ruled out. Finally, the overall number of ultrasound examinations was reduced to 0.78 test per patient. Our results are likely to be valid, because study assignment was randomized and the outcomes were determined by persons blinded to the patients' assignments. Referral bias was unlikely to be the explanation for the equivalence of the two strategies, since there was no difference between the groups in the number of patients referred during follow-up for suspected recurrence.

This study confirms the validity of modifying our previous clinical model for the diagnosis of deep-vein thrombosis, which categorized patients into high-, moderate-, and low-probability groups, to one that categorizes patients as likely or unlikely to have deep-vein thrombosis.[1,11,21] The addition to the scoring system of one point for a previous diagnosis of deep-vein thrombosis allows the model to be used in patients with previous thrombosis, a group we had excluded from earlier studies.

Our study has two potential limitations. First, we evaluated only outpatients. Given the results of our previous study, our approach is likely to be safe in hospitalized patients, but validation studies are required.[23] Second, the use of only two different D-dimer assays may be considered a limitation. However, the two assays have similar accuracies. We therefore believe our diagnostic strategy should work, regardless of which D-dimer assay is used,

provided that the assay chosen has a sensitivity and specificity similar to those obtained with the SimpliRED or IL-Test D-dimer assays.[5] We used D-dimer assays with lower sensitivities than those reported for rapid enzyme-linked immunosorbent assays of D-dimers. Because the tests we used have the advantage of greater specificity, they have the potential to rule out deep-vein thrombosis in a much larger proportion of patients; hence they seemed more suitable for use in outpatients. If more sensitive rapid enzyme-linked immunosorbent assays of D-dimers are used, the outcomes should be as safe, but it is possible that the reduction in the use of ultrasound imaging will be less.

In conclusion, incorporating D-dimer testing into a diagnostic strategy with clinical estimation of pretest probability and ultrasound imaging simplifies the diagnosis of deep-vein thrombosis in outpatients without compromising safety.

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REFERENCES

1. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997;350:1795-8.
2. Wells PS, Brill-Edwards P, Stevens P, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. Circulation 1995; 91:2184-7.
3. Freyburger G, Trillaud H, Labrouche S, et al. D-dimer strategy in thrombosis exclusion — a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. Thromb Haemost 1998;79:32-7.
4. Brill-Edwards P, Lee A. D-dimer testing in the diagnosis of acute venous thromboembolism. Thromb Haemost 1999;82:688-94.
5. Kovacs MJ, MacKinnon KM, Anderson D, et al. A comparison of three rapid D-dimer methods for the diagnosis of venous thromboembolism. Br J Haematol 2001;115: 140-4.
6. Koopman MMW, Büller HR, ten Cate JW. Diagnosis of recurrent deep vein thrombosis. Haemostasis 1995;25:49-57.
7. Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. Ann Intern Med 1998; 128:663-77. [Erratum, Ann Intern Med 1998; 129:425.]
8. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990; 263:2753-9.
9. Gottschalk A, Juni JE, Sostman HD, et al. Ventilation-perfusion scintigraphy in the PIOPED study. I. Data collection and tabulation. J Nucl Med 1993;34:1109-18.
10. Wells PS, Anderson DR, Rodger MA, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 2001;135:98-107.
11. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Lewandowski B. SimpliRED D-dimer can reduce the diagnostic tests in suspected deep vein thrombosis. Lancet 1998;351:1405-6.
12. Heijboer H, Büller HR, Lensing AWA, Turpie AGG, Colly LP, ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. N Engl J Med 1993; 329:1365-9.
13. Sluzewski M, Koopman MMW, Schuur KH, van Vroonhoven TJMV, Ruijs JHJ. Influence of negative ultrasound findings on the management of in- and outpatients with suspected deep-vein thrombosis. Eur J Radiol 1991;13:174-7.
14. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials 1982;3:345-53.
15. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999;353: 190-5.
16. Bates SM, Grand'Maison A, Johnston M, Naguit I, Kovacs MJ, Ginsberg JS. A latex D-dimer reliably excludes venous thromboembolism. Arch Intern Med 2001;161: 447-53.
17. Kraaijenhagen RA, Piovella F, Bernardi E, et al. Simplification of the diagnostic management of suspected deep vein thrombosis. Arch Intern Med 2002;162:907-11.
18. Lennox AF, Delis KT, Serunkuma S, Zarka ZA, Daskalopoulou SE, Nicolaides AN. Combination of a clinical risk assessment score and rapid whole blood D-dimer testing in the diagnosis of deep vein thrombosis in symptomatic patients. J Vasc Surg 1999; 30:794-803.
19. Janes S, Ashford N. Use of a simplified clinical scoring system and D-dimer testing can reduce the requirement for radiology in the exclusion of deep vein thrombosis by over 20%. Br J Haematol 2001;112:1079-82. [Erratum, Br J Haematol 2001;114:738.]
20. Aguilar C, Martinez A, Martinez A, Del Rio C, Vazquez M, Rodriguez FJ. Diagnostic value of d-dimer in patients with a moderate pretest probability of deep venous thrombosis. Br J Haematol 2002;118:275-7.
21. Anderson DR, Wells PS, Stiell I, et al. Management of patients with suspected deep vein thrombosis in the emergency department: combining use of a clinical diagnosis model with D-dimer testing. J Emerg Med 2000;19:225-30.
22. Kearon C, Ginsberg JS, Douketis J, et al. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. Ann Intern Med 2001;135:108-11.
23. Wells PS, Anderson DR, Bormanis J, et al. Application of a diagnostic clinical model for the management of hospitalized patients with suspected deep-vein thrombosis. Thromb Haemost 1999;81:493-7.