Diagnosis of venous thrombosis and the post-thrombotic syndrome

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CHAPTER 2

Practical diagnostic management of patients with clinically suspected deep-vein thrombosis by clinical probability test, compression ultrasonography, and D-dimer test

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Purpose To evaluate a new non-invasive diagnostic strategy for ruling out deep vein thrombosis consisting of either a combination of low clinical probability and normal ultrasonography or a combination of moderate-to-high clinical probability, normal ultrasonography, and normal D-dimer test.

Subjects and Methods We studied 811 patients with clinically suspected deep vein thrombosis using a diagnostic management strategy that combined clinical probability, ultrasonography, and measurement of D-dimers. The primary endpoint was venous thromboembolism occurring during a 3-month follow-up.

Results Of the 280 patients (35%) with a low clinical probability, 30 (11%) had an abnormal initial ultrasonography and were treated. Of the other 250 untreated patients with low clinical probability and a normal ultrasonography, 5 (2%; 95% confidence interval [CI]: 1% to 5%) developed a nonfatal venous thromboembolism during follow-up. Of the 531 patients (65%) with a moderate-to-high clinical probability, 300 (56%) had an abnormal ultrasonography. Of the remaining 231 patients with a normal ultrasonography, 148 had a normal D-dimer test; none of these patients developed deep vein thrombosis during follow-up (0%; 95% CI: 0% to 3%). Of the 83 patients with an abnormal D-dimer test, 77 underwent repeat ultrasonography about 1 week later; none of the 64 patients with a second normal ultrasound developed symptomatic deep vein thrombosis during follow-up (0%; 95% CI: 0% to 6%).

Conclusion This management strategy, which combines clinical probability, ultrasonography, and D-dimer measurements, is practical and safe in ruling out deep vein thrombosis in patients with clinically suspected thrombosis and reduces the need for repeat ultrasonography.

Introduction

Because the clinical diagnosis of deep vein thrombosis is nonspecific, objective diagnostic tests are needed to confirm or refute the diagnosis. Noninvasive compression ultrasonography, which is widely used in the diagnostic work-up of these patients (1,2), has a high sensitivity and specificity for proximal vein thrombosis (3). However, owing to high intra- and interobserver variability, ultrasonography is less reliable for calf vein thrombosis, 20% to 30% of which progress to the proximal veins (3,4). It has therefore been considered necessary to follow patients who have the first normal ultrasonography to identify the relatively few patients in whom the test becomes abnormal (5,6). For example, in one study of 1702 patients with clinically suspected deep vein thrombosis, only 12 (0.9%) had an abnormal repeat ultrasonography 1 week after a normal test (6).

Two options have been proposed to avoid unnecessary repeat ultrasonography: the use of a D-dimer test and basing decisions on clinical probability. D-dimers are degradation products of cross-linked fibrin generated by plasmin, and their presence has a high sensitivity, moderate specificity, and high negative predictive value for deep vein thrombosis (7-14). Bernardi et al. (8) used the enzyme-linked immunosorbent assay (ELISA) D-dimer test in combination with ultrasonography. This combination resulted in an 87% reduction in repeat ultrasonography, with an incidence of venous thromboembolism during 3-month follow-up of only 0.4% in patients with normal ultrasonography and a normal ELISA D-dimer test. In another study, a normal ELISA D-dimer test had a negative predictive value of 99.3% at 3 months (9). The diagnostic algorithm for suspected deep vein thrombosis can also be simplified by use of a standardized clinical probability test. For example, Wells et al. developed a clinical model that enables physicians to stratify patients with clinically suspected deep vein thrombosis into categories with concomitant low (3%), intermediate (17%), and high (75%) risk of deep vein thrombosis (15,16).

We studied a combination of a clinical probability test, ultrasonography, and a D-dimer test in patients who were referred to nonacademic teaching hospitals with clinically suspected deep vein thrombosis. We evaluated the safety of withholding anticoagulant treatment in patients with a low clinical probability test and a normal ultrasonography, as well as in patients with a moderate-to-high clinical probability, a normal ultrasonography, and a normal D-dimer test. In patients with a moderate-to-high

clinical probability and an abnormal D-dimer test, ultrasonography was repeated 8 days later. Our primary endpoint was the incidence of venous thromboembolism during a 3-month follow-up.

Subjects and Methods

We performed a prospective cohort study in 921 consecutive outpatients with suspected deep vein thrombosis of the leg who were referred by their family physicians to one of the participating centers. Our study was carried out at four nonacademic teaching hospitals in The Netherlands: Eemland Ziekenhuis (presently known as Meander Medical Center) in Amersfoort, Ziekenhuis Hilversum, St. Elisabeth Ziekenhuis in Tilburg, and Amphia Ziekenhuis in Breda. After approval by the medical ethical committee, patients seen from November 1997 to August 2000 were included. All patients with suspected deep vein thrombosis were eligible for the study. Patients with any of the following criteria were excluded: treatment with anticoagulants for more than 48 hours before diagnosis, suspected pulmonary embolism, history of documented venous thromboembolism in the previous 6 months, age younger than 18 years, or allergy to contrast media. Eligible patients who gave informed consent were enrolled.

Clinical Probability Test

All patients were assessed clinically by the attending physician at the emergency department before undergoing ultrasonography and D-dimer testing. We used the Wells' criteria to estimate the pretest probability for deep vein thrombosis (Table 1) (15,16).

Table 1. The Wells' Clinical Probability Test

Clinical feature	Score*
Active cancer	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremity	1
Immobilisation for more than 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the venous system	1
Thigh and calf swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	-2

* A score of zero or less indicates a low clinical probability; a score of one point or more indicates a moderate-to-high clinical probability.

We combined the intermediate- and high-probability group into a “moderate-to-high” clinical probability category. The nine items included in the clinical model fell into three groups: signs of deep vein thrombosis, risk factors for deep vein thrombosis, and potential alternative diagnosis. Each item scored one point; when an alternative diagnosis was given, two points were subtracted. Patients were categorized as low clinical probability for deep vein thrombosis with a score of zero or less. Patients had a moderate-to-high probability when the score was one point or more.

Diagnostic Management Strategy

Patients with a low clinical probability underwent a single ultrasonography (see below). In our algorithm, a normal ultrasonography excluded the diagnosis of deep vein thrombosis, whereas an abnormal ultrasonography confirmed the diagnosis of deep vein thrombosis. These latter patients were treated with anticoagulants according to standard protocol, consisting of 5 to 10 days of therapeutic low-molecular-weight heparin followed by oral anticoagulants for 3 to 6 months.

Patients with a moderate-to-high clinical probability also underwent ultrasonography. A normal result was followed by D-dimer testing. According to our algorithm, a normal D-dimer test excluded the diagnosis of deep vein thrombosis. Those who had an abnormal D-dimer test underwent a repeat ultrasonography on day 8; a normal repeat study excluded the diagnosis of deep vein thrombosis. An abnormal initial or repeat ultrasonography confirmed the diagnosis, and patients were treated according to a standard protocol. Anticoagulants were withheld in all patients in whom the diagnosis of deep vein thrombosis was excluded; these patients were followed for 3 months to monitor the development of any symptomatic venous thromboembolic complications (Figure).

Ultrasonography

Ultrasonography, using real-time B mode with compression only, was performed using a standard 5- to 12-MHz linear array transducer. Veins were scanned in the transverse plane only. We examined the common femoral vein in the groin, and the popliteal vein at the knee joint extending down to the trifurcation of the calf veins (3). Results were judged as abnormal and called proximal vein thrombosis if a noncompressible segment was identified. The test was considered normal if all segments were fully compressible and no residual lumen was seen. No attempt to identify isolated calf vein thrombosis was made (3,6).

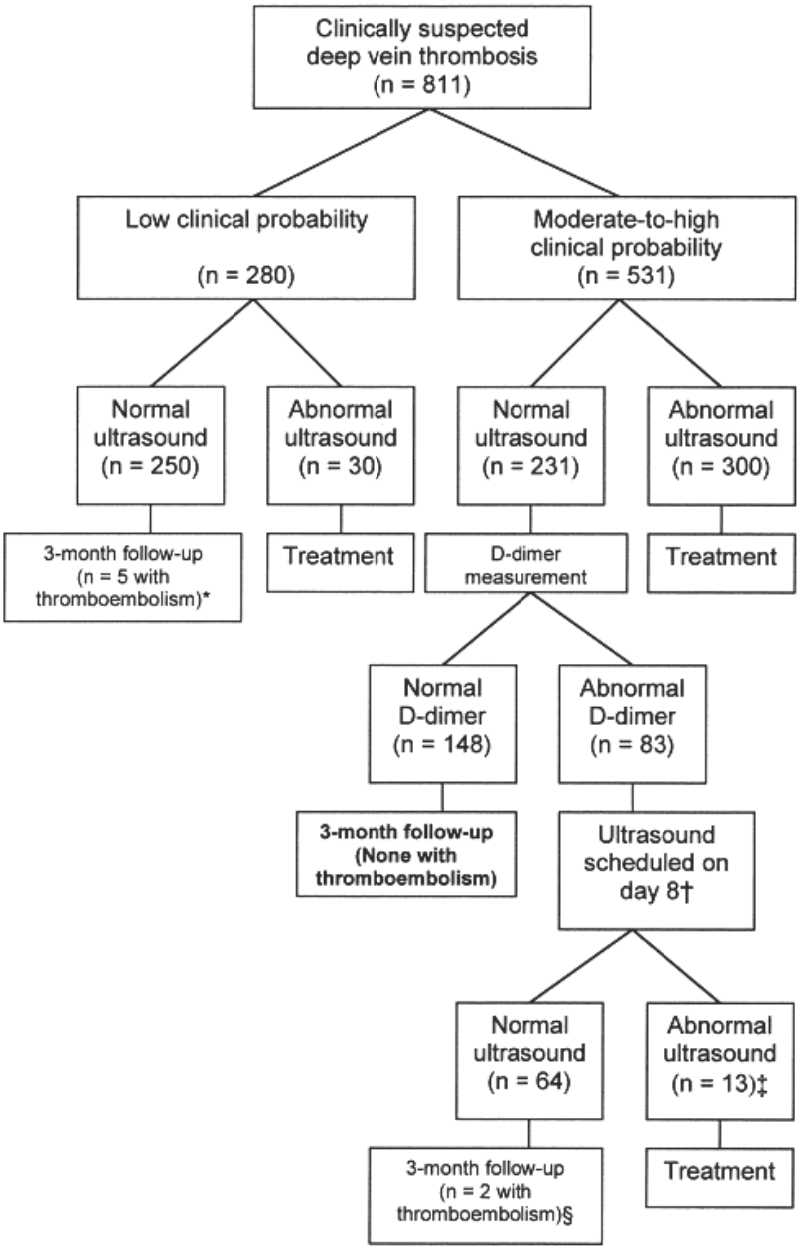

Figure. Study flow chart for patients with suspected deep-vein thrombosis. The 5 patients (*) with thromboembolism despite a normal ultrasound are described in Table 3. Repeat ultrasound was not performed in 6 patients (†). Two patients (‡) returned earlier with increased leg complaints, and 1 patient returned with pulmonary complaints. One patient who had refused the second ultrasonography on day 8 returned on day 14 with increased leg complaints. Two patients (§) had asymptomatic deep vein thrombosis diagnosed during follow-up.

D-dimer Test

We used the SimpliRED red cell agglutination assay (Agen Biomedical LTD, Brisbane, Australia) (10-14). All assays were performed using venous blood samples collected in laboratory citrate tubes according to the manufacturer's instructions by experienced laboratory technicians who were unaware of the results of the clinical probability test and ultrasonography. This assay is designed for use with freshly collected capillary or venous whole blood (10). The whole blood sample is mixed with a conjugate of a monoclonal antibody to D-dimer (3B6/22) linked to a monoclonal antibody to red blood cells (RAT-IC3/86). The detection limit is a whole blood D-dimer concentration of 0.2 mg/l corresponding to 0.4 mg/l Fibrinogen Equivalent Units (FEU). If any agglutination was present after 2 minutes, the test was considered to be positive.

Follow-up and Primary Endpoint

All patients had a 3-month follow-up and were asked to return to the study center at 3 months or immediately if they had signs or symptoms of venous thromboembolism or complications. Patients who did not return for follow-up assessment (n=24) were interviewed by telephone. Confirmatory testing with ultrasonography, phlebography, (spiral) computed tomographic scanning, ventilation perfusion (V-Q) lung scanning, or pulmonary angiography was performed in patients with suspected venous thromboembolic complications.

Statistical Analysis

We calculated the required sample size assuming an expected prevalence of 33% for deep vein thrombosis. We hypothesized that, among patients found by our management strategy not to have deep vein thrombosis, the rate of venous thromboembolism during a 3-month follow-up would be less than 2%. We calculated that 800 patients would be necessary to provide 95% confidence intervals (CI), which exclude a frequency of 5% of symptomatic thromboembolic events.

The outcome was the total rate of symptomatic venous thromboembolic complications during a follow-up of 3 months. We calculated the 95% confidence intervals with the binominal distribution.

Results

We evaluated 921 symptomatic outpatients for eligibility and excluded 75 patients for the following reasons: 19 had been treated with anticoagulants for more than 48 hours before diagnosis; 10 had

suspected pulmonary embolism; 1 had a history of documented venous thromboembolism in the previous 6 months; and 45 did not participate for other reasons, such as geographic inaccessibility, dementia, very old age, or mental incompetence. Of the remaining 846 eligible patients, 35 (4%) refused to participate. Thus, 811 patients were enrolled, of whom 522 (64%) were women. The mean (± SD) age was 62 ± 17 years (range, 18 to 99 years). The clinical probability test scored an alternative diagnosis as likely or greater than that of deep vein thrombosis in 361 patients (45%) (Table 2).

Table 2. Alternative Diagnoses among the 811 Patients

Alternative diagnosis	Number (%)
Erysipelas, cellulitis	89 (24)
Muscle tear, hematoma, trauma	65 (18)
Baker cyst	31 (9)
Superficial thrombophlebitis	30 (8)
Post-thrombotic syndrome	22 (6)
Lymphedema, lymphangitis	10 (3)
Edema due to heart failure	9 (2)
External compression due to malignancy	1 (1)
Other (gout, varices, arthritis, arterial thrombosis)	53 (15)
Not specified	51 (14)
Total*	361

* Some patients had more than one alternative diagnosis.

Patients with a Low Clinical Probability

Of the 811 enrolled patients, 280 (35%) had a low clinical probability of thromboembolism, of whom 30 (11%) had an abnormal ultrasonography (Figure).

During the 3-month follow-up of the remaining 250 untreated patients, 4 patients developed a deep vein thrombosis and 1 had a nonfatal pulmonary embolism, for a venous thromboembolic complication rate of 2% (95% CI: 1% to 5%). These 5 patients had increasing complaints within 2 weeks of the initial normal ultrasonography and returned to the hospital according to the physicians' instructions (Table 3).

Table 3. Patients with a Low Clinical Probability Test and an Initial Normal Ultrasonography in Whom Venous Thromboembolic Complications Were Diagnosed by Ultrasonography or V-Q Scanning during the 3-Month Follow-up

Patient	Diagnosis
31-year-old woman; third-term pregnancy, increased leg swelling on day 8	Ultrasonography shows femoral vein thrombosis
72-year-old man; treated for erysipelas,, increased leg swelling on day 15	Ultrasonography shows external iliac vein thrombosis
51-year-old woman; trauma, increased leg pain and swelling on day 5	Ultrasonography shows popliteal vein thrombosis
42-year-old woman; increased leg pain and pleuritic chest pain on day 10	Ultrasonography shows popliteal vein thrombosis; V-Q is not high probability for pulmonary embolism
44-year-old woman; increased leg pain and dyspnea on day 4	Ultrasonography is normal; V-Q is high probability for pulmonary embolism

Moderate-to-High Clinical Probability Test

Five hundred and thirty-one patients (65%) had a moderate-to-high clinical probability of thromboembolism, of whom 300 (56%) had ultrasonographic evidence of deep vein thrombosis (Figure). The remaining 231 patients had D-dimer measurements, of whom 148 (64%) had a normal D-dimer test. None of these 148 patients were treated, and none had a venous thromboembolism during the 3-month follow-up (0%; 95% CI: 0% to 3%).

In 83 (36%) of the 231 patients, the D-dimer test was abnormal. These patients were not treated with anticoagulants pending the results of a second ultrasonography that was scheduled on day 8. Nine of these patients had a deep vein thrombosis diagnosed with repeat ultrasonography. Three of these patients had returned to the hospital on days 2, 4, and 7 with increased complaints. Two complained of leg pain and swelling, which a second ultrasonography revealed to be a deep vein thrombosis. The third patient had symptoms of pulmonary embolism, and pulmonary angiography confirmed the diagnosis. In 7 patients, a repeat ultrasonography test was not performed because of patient refusal or logistic reasons. One patient, who had refused the second ultrasonography, returned to the hospital on day 14 with increased leg pain and swelling; an ultrasonography confirmed a deep vein thrombosis. The 6 remaining patients were followed for 3 months but did not develop venous thromboembolic complications.

None of the 64 patients with two normal serial ultrasonography results developed symptomatic deep vein thrombosis during follow-up (0%; 95% CI: 0% to 6%). However, 2 of these 64 patients developed asymptomatic deep vein thrombosis during follow-up. Both patients had cancer and had asymptomatic thrombosis diagnosed with routine computed tomographic scan during evaluation of their tumor.

Death during Follow-up

No deaths due to venous thromboembolic complications were reported during the 3-month follow-up. Of the 6 patients who died during that period, 4 had been diagnosed with, and treated for, deep vein thrombosis: 1 died of lung carcinoma, 1 of pancreas carcinoma, 1 of myocardial infarction, and 1 of unknown case. Of the 2 patients in whom deep vein thrombosis was not diagnosed, 1 died of lung carcinoma and the other patient died of unknown causes without suspected venous thromboembolism.

Discussion

This study shows that the combination of a low clinical probability test, as assessed by a standardized clinical score at the emergency department, combined with a normal ultrasonography can be used safely to exclude deep vein thrombosis in outpatients referred for evaluation of suspected deep vein thrombosis. Of 250 patients who met these criteria, only 5 had a thromboembolism during the 3-month follow-up. In patients with a moderate-to-high clinical probability for deep vein thrombosis, the combination of a normal ultrasonography and normal D-dimer test also excluded deep vein thrombosis, with no episodes of venous thromboembolic complications during follow-up, in 148 patients with these criteria. These rates of venous thromboembolic complication are consistent with those seen in other studies (6).

Ultrasonography fails to detect isolated calf vein thrombosis in some patients, and serial testing is considered necessary to detect clinically important venous thrombi that may extend proximally (4,17). In our study, combining clinical probability assessment, ultrasonography, and D-dimer measurements reduced the need for repeat ultrasonography by 83% (from 250 + 231 = 481 patients to 83 patients). Bernardi et al. (8) showed a similar 87% reduction in repeat ultrasonography using ELISA D-dimer as

an adjunct to ultrasonography. Fewer repeat ultrasonography examinations are convenient for patients and also cost-effective (18).

We used a qualitative assay for D-dimers. However, in a previous study, the combination of a low clinical probability test and a negative qualitative D-dimer test rules out deep vein thrombosis in symptomatic outpatients, with a venous thromboembolic complication rate of <1% (19). Although rapid ELISA D-dimer tests have greater sensitivity, we chose the qualitative assay because it was the most extensively studied test when our study was designed (11,12). This assay must be performed by experienced personnel, with whom it has a reported sensitivity of 97% (95% CI: 85% to 99%) (20). Alternatively, quantitative D-dimer tests, which have sensitivities ranging from 95% to 100%, can be used in our management strategy (13).

Patients with a positive D-dimer test but a normal repeat ultrasonography on day 8 were at low risk for venous thromboembolic complications during the 3-month follow-up, as was also seen in a previous study (8). We found a higher prevalence (41%) of deep vein thrombosis than did other studies (6,14-16), perhaps because all patients had been referred by a family physician. We believe that the safety of the algorithm that we used is strengthened by this higher prevalence of deep vein thrombosis. Our study was carried out in the emergency departments of nonacademic teaching hospitals and involved several physicians. This approach appears to be safe, provided a checklist is used for every patient to ensure that the management strategy is followed properly. Moreover, the attending physician should always instruct patients to return to the hospital if their symptoms worsen.

Many noninvasive combination strategies can be used to diagnose deep vein thrombosis. This management study shows that the combination of a low clinical probability test and a normal ultrasonography excludes the diagnosis of deep vein thrombosis in symptomatic outpatients. In patients with a moderate-to-high clinical probability who have normal ultrasonography and a normal D-dimer test, anticoagulant therapy can be withheld safely. This diagnostic strategy may simplify the management of the majority of patients with suspected deep vein thrombosis. It enables making treatment decisions on the day of referral without a substantial increase in the risk of venous thromboembolism-related morbidity and mortality, while saving health care costs.

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