Management of Suspected Deep Venous Thrombosis in Outpatients by Using Clinical Assessment and D-Dimer Testing

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Background: **When deep venous thrombosis is suspected, objective testing is required to confirm or refute the diagnosis.**

Objective: **To determine whether the combination of a low clinical suspicion and a normal D-dimer result rules out deep venous thrombosis.**

Design: **Prospective cohort study.**

Setting: **Three tertiary care hospitals in Canada.**

Patients: **445 outpatients with a suspected first episode of deep venous thrombosis.**

Interventions: **Patients were categorized as having low, moderate, or high pretest probability of thrombosis and underwent whole-blood D-dimer testing. Patients with a low pretest probability and a negative result on the D-dimer test had no further diagnostic testing and received no anticoagulant therapy. Additional diagnostic testing was done in all other patients.**

Measurements: **Venous thromboembolic events during 3-month follow-up.**

Results: **177 (40%) patients had both a low pretest probability and a negative D-dimer result. One of these patients had deep venous thrombosis during follow-up (negative predictive value, 99.4% [95% CI, 96.9% to 100%]).**

Conclusion: **The combination of a low pretest probability of deep venous thrombosis and a negative result on a whole-blood D-dimer test rules out deep venous thrombosis in a large proportion of symptomatic outpatients.**

Ann Intern Med. 2001;135:108-111. www.annals.org

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Clinical assessment can stratify a patient's probability of having deep venous thrombosis but is insufficient on its own to establish or exclude the diagnosis (1–3). D-dimer is released into the circulation when cross-linked fibrin is degraded by plasmin; because patients with venous thromboembolism usually have elevated D-dimer levels, a normal D-dimer result can help to exclude this diagnosis (4–8).

After analyzing results of previous studies, we hypothesized that the combination of a low pretest probability of deep venous thrombosis and a negative D-dimer test result would exclude deep venous thrombosis (5, 7, 9). To test this hypothesis, we performed a prospective cohort study in which additional diagnostic testing and anticoagulant therapy were withheld in consecutive outpatients presenting with a suspected first episode of deep venous thrombosis who had a low pretest probability and a negative result on a whole-blood D-dimer test.

Methods

Patients

Consecutive outpatients with a first suspected episode of deep venous thrombosis who were referred to the thromboembolism service of any of three hospitals affiliated with McMaster University, Hamilton, Ontario, Canada, were potentially eligible for the study. Exclusion criteria have been described previously (5, 7). The institutional review boards of the participating hospitals approved the study.

Initial Assessment

After giving written informed consent, eligible patients underwent a standardized clinical assessment by a vascular technologist or a nurse who used a nine-item prediction rule to preliminarily categorize their pretest probability of deep venous thrombosis as low, moderate, or high (2). Patients were then seen by a physician who was aware of the prediction-rule results but could override the initial designation. Independent of the clinical assessment, all patients then underwent a whole-blood D-dimer test (SimpliRED, AGEN Biomedical, Ltd., Brisbane, Australia) that was performed at the bedside by a technologist, who interpreted the results as positive or negative (10). The physician's designation of pretest probability, along with the D-dimer test result, determined further management of the patient.

Deep venous thrombosis was ruled out in patients

Table. **Prevalence of Deep Venous Thrombosis according to Pretest Probability and D-Dimer Result***

D-Dimer Result	Pretest Probability of Deep Venous Thrombosis			Total
	Low	Moderate	High	
	← % (n/n) →			
Negative	0.6 (1/177)†	6 (7/120)‡	20 (2/8)	3 (10/307)
Positive	14 (4/29)	25 (17/68)‡	80 (33/41)‡	39 (54/138)
Total	2 (5/206)	13 (24/188)	69 (35/51)	14 (64/445)

* Because the intensity of the search for deep venous thrombosis was influenced by pretest probability and the results of D-dimer testing, the numbers in this table have the potential to yield a biased estimate of the accuracy of these assessments.
† No additional diagnostic testing was performed in patients with a low pretest probability and a negative D-dimer test result; isolated distal deep venous thrombosis was diagnosed during follow-up in one patient.
‡ Deep venous thrombosis was diagnosed by venography alone in 5 patients (1 patient with moderate pretest probability and negative D-dimer result, 1 patient with moderate pretest probability and positive D-dimer result, and 3 patients with high pretest probability and positive D-dimer result); clinical assessment or D-dimer results probably influenced the decision to perform venography in these patients.

with a low pretest probability and negative D-dimer results. Such patients had no further diagnostic testing, received no anticoagulants, and were followed for 3 months to monitor for development of deep venous thrombosis or pulmonary embolism. Suspected episodes of venous thromboembolism were confirmed or refuted according to a previously described evaluation standard (5, 11, 12).

On the day of presentation, all other patients (those with moderate or high pretest probability or a positive D-dimer result) underwent venous ultrasonography of the proximal veins (including the calf vein trifurcation) and impedance plethysmography. Venography was also done if the results of these two tests differed or if they were normal in a patient with a high pretest probability and a positive D-dimer result. Patients with normal findings on venous ultrasonography and impedance plethysmography who did not have venography received no anticoagulant therapy and underwent serial testing according to standard practice (12). At presentation and follow-up, diagnosis of deep venous thrombosis required noncompressibility of a proximal vein on venous ultrasonography or an intraluminal filling defect on venography (12).

Statistical Analysis

On the basis of a previous study (5), we expected that 45% of enrolled patients would have a low pretest probability and a normal D-dimer test result, and among these patients, 1% would have deep venous thrombosis. Thus, we calculated our sample size such that a 95% CI for a 1% prevalence of symptomatic events during follow-up among study patients with a low pretest probability and a negative D-dimer result would exclude a frequency of 5% (for a negative predictive value of at least 95%) (12). We estimated that enrollment of 400 patients would satisfy this requirement. The exact binomial distribution was used to calculate the 95% CIs.

Role of the Corporate Sponsor

D-dimer kits were donated by AGEN Biomedical, Ltd. The company had no role in designing or conducting the study, evaluating the data, or writing the manuscript.

RESULTS

Between November 1995 and June 1997, 445 patients were enrolled (mean age, 60 years; 239 [64%] women). According to the clinical assessments of the participating physicians, pretest probability of deep venous thrombosis was low in 206 patients (48%), moderate in 188 patients (42%), and high in 51 patients (11%) (**Table**). Results on D-dimer testing were negative in 307 patients (69%) and positive in 138 patients (31%) (**Table**).

Low Pretest Probability and a Negative D-Dimer Result

A total of 177 (40%) patients had a low pretest probability of deep venous thrombosis in combination with a negative D-dimer result. These 177 patients had no additional diagnostic testing or any anticoagulant treatment and were followed for 3 months. One patient, who was in this subgroup, had a confirmed episode of venous thromboembolism during follow-up. Three days after initial presentation, this patient returned to the clinic with persistent calf pain, and venography revealed isolated deep venous thrombosis of the calf. Therefore, the negative predictive value for subsequent symptomatic venous thromboembolism of low pretest probability of deep venous thrombosis combined with a negative D-dimer result was 99.4% (CI, 96.9% to 100%).

All Other Patients

Among the other 268 patients, who had moderate or high pretest probability or a positive D-dimer result, deep venous thrombosis was diagnosed in 63 on the day of presentation or during the subsequent week of serial testing (**Table**). No patient in this group experienced an episode of deep venous thrombosis or pulmonary embolism during the subsequent 3-month follow-up.

DISCUSSION

This study shows that it is safe to withhold further diagnostic testing and anticoagulant therapy in patients with a low pretest probability of deep venous thrombosis and a negative result on whole-blood D-dimer testing. The D-dimer test that we used provided a result within minutes (10), and 40% of patients had a low pretest probability and a negative result. Thus, this was a rapid and efficient method for excluding deep venous thrombosis.

In our study, clinical assessment of pretest probability had two components. First, a nine-item prediction rule (checklist) completed by a technologist or a nurse determined whether the patient had a low, moderate, or high pretest probability (2). Second, a physician could modify the preliminary designation of pretest probability. Physicians may have modified the patients' preliminary category because of disagreement on the completed items of the prediction rule or because they were influenced by factors that were not captured by the prediction rule; we did not evaluate this aspect. The method that physicians use to categorize pretest probability of deep venous thrombosis (for example, empirically or by prediction rule) does not appear to be critical to the validity of the assessment. In our study, physician-driven changes to the initial categorization of pretest probability did not alter the overall prevalence of deep venous thrombosis among patients assigned a low pretest probability (data not presented). Furthermore, others have shown a similar low prevalence of deep venous thrombosis in patients with a low pretest probability regardless of whether this assessment is performed empirically or by prediction rule (1, 13, 14).

The prevalence of thrombosis that has been reported in patients with suspected venous thromboembolism who have negative D-dimer results varies (4, 15, 16). The corresponding differences in negative predictive values among D-dimer tests has led to confusion. Three factors can largely account for these differences. First, some D-dimer assays are better (that is, they have a higher sensitivity and specificity) than others for differentiating patients who have venous thromboembolism from those who do not (17). Second, negative predictive value is generally higher with tests for deep venous thrombosis that are configured to have high sensitivity. However, because high sensitivity is achieved at the expense of specificity, this causes a high frequency of false-positive results, thereby reducing diagnostic utility. Third, the negative predictive value of a diagnostic test is inversely related to the prevalence of disease in the referral population; the lower the prevalence of disease, the higher the negative predictive value of a normal result. The whole-blood D-dimer assay used in this study has a sensitivity for venous thromboembolism of about 85% and a specificity of about 70% (4, 6). Therefore, although this D-dimer test has the advantage that it is negative in about two thirds of outpatients with suspected venous thromboembolism, the negative predictive value of this test, when used alone, is not high enough to exclude thrombosis. However, because the prevalence of venous thromboembolism is usually 10% or less in patients who have a low pretest probability of thrombosis (1, 5, 13, 14, 18), a negative result on a whole-blood D-dimer test reliably excludes thrombosis in this large subgroup.

Many noninvasive strategies can be used to diagnose deep venous thrombosis (12). This prospective management study establishes that the combination of a low pretest probability of thrombosis with a normal result on a whole-blood D-dimer test excludes a diagnosis of deep venous thrombosis in symptomatic outpatients.

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Acknowledgments: The authors thank J. Bennett, D. Ridgewell, and P. Stevens for providing technological and nursing assistance and collating the data. They also thank P. Massicotte, M. Andrew, P. Powers, M. Sternbach, and A. Patel for contributing patients.

Grant Support: Drs. Kearon and Douketis are Research Scholars of the Heart and Stroke Foundation of Canada, and Dr. Crowther is a Research Scholar of the Medical Research Council of Canada. Drs. Ginsberg and Weitz are Career Investigators of the Heart and Stroke Foundation of Ontario, and Dr. Weitz also holds the J. Fraser Mustard endowed chair in cardiovascular research at the Heart and Stroke Foun-

dation of Canada. The D-dimer kits were donated by AGEN Biomedical, Ltd. (Brisbane, Australia).

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