Combination of a Normal D-Dimer Concentration and a Non-High Pretest Clinical Probability Score Is a Safe Strategy to Exclude Deep Venous Thrombosis

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Background—Serial ultrasonography is reliable for the diagnosis of deep venous thrombosis in symptomatic patients, but the low prevalence of thrombosis in this group renders the approach costly and inconvenient to patients. We studied the clinical validity of the combination of a pretest clinical probability score and a D-dimer test in the initial evaluation of patients suspected of deep venous thrombosis.

Methods and Results—Patients with a normal D-dimer concentration (<500 fibrin equivalent units [FEU] g/L) and a non-high probability score (<3) had no further testing. Patients with a normal D-dimer concentration and a high probability score (≥3) underwent one ultrasonogram. Serial ultrasonography was performed in patients with an abnormal D-dimer concentration. Patients were followed for 3 months. A total of 812 patients were evaluable for efficacy. Only 1 of 176 patients (0.6%; 95% CI, 0.02% to 3.1%) with a normal D-dimer concentration and a non-high probability score developed thrombosis during follow-up. A normal D-dimer concentration and a high probability score were found in 39 patients; 3 of them (7.7%; 95% CI, 1.6% to 20.9%) had thrombosis at presentation, and one (2.8%; 95% CI, 0.07% to 14.5%) developed pulmonary embolism during follow-up. In 306 of 597 patients (51.3%) with an abnormal D-dimer concentration, thrombosis was detected by serial ultrasonography. Six patients (2.1%; 95% CI, 0.8% to 4.4%) developed thrombosis during follow-up. No deaths due to thromboembolism occurred during follow-up. The total need for ultrasonography was reduced by 29%.

Conclusion—The combination of a non-high pretest clinical probability score and a normal D-dimer concentration is a safe strategy to rule out deep venous thrombosis and to withhold anticoagulation. (Circulation. 2003;107:593-597.)

Key Words: thrombosis ■ D-dimer tests ■ fibrin fragment D ■ fibrin fibrinogen degradation products ■ ultrasonics

Deep venous thrombosis can be diagnosed or rejected accurately by serial compression ultrasonography. In 2 studies with a follow-up period of, respectively, 3 and 6 months, venous thromboembolic complications were found in only 0.6% and 0.7% of patients with suspected deep venous thrombosis after normal serial ultrasonography.1,2 Serial ultrasonography, however, is inefficient because only 17% to 24% of patients suspected of deep venous thrombosis actually has it,1-6 and only 0.9% develop it after the initial normal ultrasonogram.2 Other noninvasive diagnostic tests, such as the pretest clinical probability score5-7 and the D-dimer measurement,4,7-14 are the subject of studies to reduce the need for ultrasonography. It has been proven safe to withhold anticoagulant treatment in patients with a low pretest clinical probability score and normal initial ultrasonogram7 and in patients with a normal D-dimer and normal ultrasonogram at first presentation.3,11,14 The next step, which is the subject of the present study, is to investigate the safety of the combination of a non-high pretest clinical probability score and a normal D-dimer level to replace ultrasonography as the initial test in the diagnostic management of patients suspected of having deep venous thrombosis.

Methods

Patients
This investigation was a prospective cohort study in 4 large, nonacademic, teaching hospitals in the Netherlands. All outpatients with clinical symptoms of deep venous thrombosis of the leg, who were referred by their general practitioners, were potentially eligible for the study. Exclusion criteria were pregnancy; previous deep venous thrombosis in the ipsilateral leg without documentation of recanalization; a concomitant clinical suspicion of pulmonary em-
bolism; the use of unfractionated heparin, low-molecular-weight heparin, or any form of oral anticoagulant in the past month; geographic impossibility for follow-up; and life expectancy <3 months. Patients entering the study were asked for informed consent. The medical ethics committees of the participating centers approved the study.

Procedures

Eligible patients who gave informed consent were assessed by one of the study physicians or local residents, and a single pretest clinical probability score according to Wells et al. was performed. Patients were considered to have a low or moderate (“non-high”) suspicion for having deep venous thrombosis when the score was <3 and a high suspicion when the score was ≥3. We performed the Tinaquant quantitative latex D-dimer assay (Roche, Germany) in all patients. Previous reports have validated this test using venography. An abnormal test was defined as a D-dimer value >499 fibrin equivalent units (FEU)/L. The pretest clinical probability score was performed by physicians who were not previously aware of the D-dimer concentration.

Ultrasonography, using real-time B-mode with compression, was done with a 7.5 MHz and/or a 5.0 MHz transducer. Two areas of the leg were examined: the common femoral vein at the inguinal ligament and the popliteal vein at the knee-joint line traced down to the point of the trifurcation of the calf veins. Veins were scanned in the transverse plane only. Lack of compressibility was the sole criterion for an abnormal result; a vein was considered fully compressible if no residual lumen was seen.

Patients with a non-high pretest clinical probability score and a normal D-dimer concentration had no further investigations (Figure). The patients with a high pretest clinical probability score and a normal D-dimer concentration underwent a single ultrasonogram at presentation. Patients with an abnormal D-dimer (irrespective their pretest clinical probability score) had repeated ultrasonography (with a second ultrasonogram after 1 week). Patients who had no further investigations and patients with normal ultrasonography results did not receive anticoagulation. These patients were followed for 3 months, and data from this 3-month follow-up were obtained by visit or telephone contact with the patient or the general practitioner. Patients were instructed to contact their physician when symptoms of their leg worsened or when symptoms of pulmonary embolism occurred. Worsening of complaints of the leg, new complaints of the leg or respiratory tract, or an objective clinical change in the patient were followed by objective testing using ultrasonography, ventilation-perfusion scintigraphy, or pulmonary angiography. The primary outcome of this study was the development of thromboembolic processes (deep venous thrombosis or pulmonary embolism) during the 3-month follow-up period.

Statistics

For calculation of 95% confidence intervals (CI), the exact binomial method was used.

Results

During the study period, 902 consecutive outpatients with suspected deep venous thrombosis were referred. Of these patients, 827 (92%) were eligible and gave informed consent. There were 75 ineligible patients (Table 1). Of the 827 patients included in the study, 812 patients were fully evaluable (mean age, 59±17 years; 518 women [64%]). None of the patients used tranexamic acid. The 15 patients who were not fully evaluable were excluded from the final analysis of the study (ie, the 3-month thromboembolic risk): one patient (with normal serial ultrasonography) was lost to follow-up, 6 patients received oral anticoagulation for reasons other than thromboembolism during follow-up, 4 patients had a protocol violation, and 4 patients died during follow-up. The 4 patients who died all had a positive D-dimer and normal serial ultrasonography, and the cause of death was not

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>No.</th>
</tr>
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<tbody>
<tr>
<td>Pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Previous deep venous thrombosis in the ipsilateral leg without documentation of recanalization</td>
<td>6</td>
</tr>
<tr>
<td>Concomitant clinical suspicion of pulmonary embolism</td>
<td>3</td>
</tr>
<tr>
<td>The use of unfractionated heparin, low-molecular-weight heparin, or any form of oral anticoagulant in the past month</td>
<td>50</td>
</tr>
<tr>
<td>Geographic impossibility for follow-up</td>
<td>3</td>
</tr>
<tr>
<td>Life expectancy &lt;3 months</td>
<td>1</td>
</tr>
<tr>
<td>No informed consent obtained (8 refused and 3 were mentally incapable of signing)</td>
<td>11</td>
</tr>
</tbody>
</table>
related to thrombosis. None of these 15 patients had venous thromboembolism at the time of exclusion from the study.

The main results of this study are given in Table 2. Deep venous thrombosis or pulmonary embolism was diagnosed in 317 patients (39%) during the entire study period. Deep venous thrombosis was diagnosed at initial screening in 309 patients by single or serial ultrasonography; 8 of the remaining 503 patients (1.6%; 95% CI, 0.7% to 3.1%) developed deep venous thrombosis or pulmonary embolism during the 3-month follow-up period. No deaths due to venous thromboembolism were observed during the follow-up period.

In the group of patients with a non-high pretest clinical probability score and normal D-dimer concentration, deep venous thrombosis was found during follow-up in one patient (0.6%; 95% CI, 0.02% to 3.1%). This patient returned to the hospital because of worsening of complaints 2 days after first presentation; at that time, the D-dimer was abnormal and a deep calf vein thrombosis was detected by a single ultrasonogram. This patient seemed to be heterogeneous for the factor V Leiden mutation. The diagnostic strategy performed in this group had a negative predictive value of 99.4% (95% CI, 96.9% to 100%). There were no deaths in this group. The prevalence of deep venous thrombosis in these three clinical probability groups was 22%, 51%, and 68%, respectively.

Three of the 39 patients (7.7%; 95% CI, 1.6% to 20.9%) with a normal D-dimer concentration and a high pretest clinical probability score had deep venous thrombosis on ultrasonography at presentation; one of the remaining 36 patients (2.8%; 95% CI, 0.07% to 14.5%) developed pulmonary embolism at 71 days after initial screening. At that time, the D-dimer concentration was abnormal and repeated ultrasonograms remained normal. This patient seemed to have an abdominal localized non-Hodgkin lymphoma that impaired lymph drainage from the legs. The negative predictive value of this regimen was 97.2% (95% CI, 85.8% to 99.9%). No deaths were reported in this group.

In patients with an abnormal D-dimer concentration (n=597), 291 had deep venous thrombosis detected by the first ultrasonogram, and 15 patients had it detected by the second ultrasonogram. Six of the 291 patients (2.1%; 95% CI, 0.8% to 4.4%) with normal serial ultrasonography developed venous thromboembolism during the 3-month follow-up period (3 deep venous thromboses and 3 pulmonary embolisms). Of these 6 patients, one was heterogeneous for the factor V Leiden mutation, one had a non-Hodgkin lymphoma, and one had a previous history of venous thromboembolism and was using oral contraceptives. The diagnostic strategy in the group with abnormal D-dimer concentrations was 19% (114 of 597 patients), 41% (243 of 597 patients), and 40% (240 of 597 patients), respectively. The prevalence of deep venous thrombosis in these three clinical probability groups was 22%, 51%, and 68%, respectively.

If exclusion of deep venous thrombosis was based on a normal D-dimer concentration alone (ie, not using the pretest clinical probability score), we would have missed deep venous thrombosis in 5 of 215 patients (2.3%; 95% CI, 0.8% to 5.3%) with a normal D-dimer concentration; this strategy would have a negative predictive value of 97.7% (95% CI, 94.7% to 99.2%). The sensitivity of the D-dimer was 98.4% (95% CI, 96.4% to 99.5%; 312 of 317 patients), and its specificity was 42.4% (95% CI, 38.1% to 46.8%; 210 of 495 patients).

Analysis of the clinical probability score in the 812 patients showed that 24.8% (201 of 812 patients) had a low probability score, 40.9% (332 of 812 patients) a moderate score, and 34.3% (279 of 812 patients) a high probability score. The prevalence of deep venous thrombosis in these 3 probability categories was 12.9%, 37.7%, and 59.5%, respectively. The sensitivity of the D-dimer in patients with a low probability score was 96.2%, the negative predictive value was 98.9%, and specificity was 51.4%. In patients with a moderate score, the values were 100%, 100%, and 39.6%, respectively. In patients with a high probability score, the D-dimer had values of 97.6%, 90.5%, and 33.6%, respectively.

The total number of ultrasonograms performed in this study was 949; if a strategy of serial ultrasonography was performed in all patients in this study, we would have performed 1335 ultrasonograms. Our diagnostic strategy led to a reduction of 29% in the need for ultrasonograms.

### Table 2. Prevalence of Venous Thromboembolism According to D-Dimer Result and Pretest Clinical Probability Score

<table>
<thead>
<tr>
<th>Group</th>
<th>n (%)</th>
<th>VTE During Follow-Up, n (%; 95% CI)</th>
<th>Overall VTE, n (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal D-dimer and non-high score</td>
<td>176 (22)</td>
<td>1 (0.6; 0.02–3.1)</td>
<td>1 (0.6; 0.02–3.1)</td>
</tr>
<tr>
<td>Normal D-dimer and high score</td>
<td>39 (5)</td>
<td>1 (2.8; 0.07–14.5)</td>
<td>4 (10.3; 2.9–24.2)</td>
</tr>
<tr>
<td>Normal D-dimer</td>
<td>215 (26)</td>
<td>2 (0.9; 0.1–3.4)</td>
<td>5 (2.3; 0.8–5.3)</td>
</tr>
<tr>
<td>Abnormal D-dimer</td>
<td>597 (74)</td>
<td>6 (2.1; 0.8–4.4)</td>
<td>312 (52.3; 48.3–56.3)</td>
</tr>
<tr>
<td>Total</td>
<td>812 (100)</td>
<td>8 (1.6; 0.7–3.1)</td>
<td>317 (39.0; 35.7–42.4)</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism and includes deep venous thrombosis and pulmonary embolism.

### Discussion

This study indicates that it is relatively safe to withhold anticoagulation in outpatients suspected of having deep venous throm-
bosis who have a normal D-dimer test and a non-high pretest clinical probability score. This approach will reduce the need for compression ultrasonography. The role of the pretest clinical probability score and/or the D-dimer concentration in the diagnostic management of deep venous thrombosis has been the objective of many different studies.\textsuperscript{4,14,16,17} All suggested diagnostic regimens may not exceed the failure rates (percentage of missed deep venous thrombosis) of 0.6% and 0.7% that have been reported in 2 landmark studies on the safety of serial ultrasonography.\textsuperscript{1,2} The failure rate of 0.6% (95% CI, 0.02% to 3.1%) in our study for patients with a non-high pretest clinical probability score and a normal D-dimer concentration is comparable with the studies in which serial ultrasonography has been used. Therefore, we conclude that this regimen can replace serial ultrasonography in this subgroup of patients with suspected deep venous thrombosis.

A part of the follow-up in our patients was provided by their general practitioner. In the Netherlands, patients see their general practitioner on a regular basis, and the general practitioner provides follow-up of their patients for many diseases. In case of hospitalization, the general practitioner will always be notified. At 3 months, patients were seen by a physician in one of the participating institutes or by their general practitioner or they were contacted by telephone by a physician in one of the participating institutes. If a telephone contact revealed continuos complaints of the leg, patients were seen by their general practitioner or a physician. A similar method of follow-up has also been used in other management studies on the diagnosis of venous thromboembolism.\textsuperscript{5,18}

The prevalence of deep venous thrombosis in our study population was relatively high (39%), especially compared with other recent studies.\textsuperscript{1,2,5–7,14,16,17} In our institutes, this prevalence has been that high for several years. Because the participating centers in this study are the only institutes for diagnosing thrombosis in the region and because we used consecutive patients, we do not think that this high prevalence is due to some kind of bias. A possible explanation for the prevalence might be the referral pattern of the general practitioners. Despite this high prevalence, exclusion of deep venous thrombosis without performing an ultrasonogram was possible in 22% of the patients. The need for ultrasonography in the entire study population was reduced by \(\approx 30\%\), which creates an economical advantage and less inconvenience for patients and radiology staffs. Our results also open the possibility for general practitioners to rule out deep venous thrombosis in a substantial number of patients without presenting those patients to the emergence wards.

Where previous reports excluded deep venous thrombosis using the combination of a normal D-dimer concentration and only a low pretest clinical probability score,\textsuperscript{16,17} we show that deep venous thrombosis can also be excluded in patients with a normal D-dimer concentration and a low and moderate pretest clinical probability score. However, a D-dimer assay with high sensitivity is an important prerequisite in our strategy. Because the sensitivity of the D-dimer assay in previous reports (using the SimpliRed D-dimer assay) was only 85%,\textsuperscript{16,17} one needs to rely more extensively on the pretest clinical probability score for a safe exclusion of deep venous thrombosis. However, because of the probability of an alternative diagnosis, this score is highly subjective and shows large interobserver variability.\textsuperscript{19} The D-dimer assay used in our study had a sensitivity of 98.4% and a negative predictive value of 97.7%. For exclusion of deep venous thrombosis in patients with a non-high pretest clinical probability score and a normal D-dimer concentration, we recommend the use of a D-dimer assay with at least a sensitivity and negative predictive value as high as the one used in the present study.

Leaving out the pretest clinical probability score from our strategy would have led to an increase in the percentage of missed venous thromboembolism from 0.6% (95% CI, 0.02% to 3.1%) to 2.3% (95% CI, 0.8% to 5.3%) in patients with a normal D-dimer concentration. Because of the small number of missed thromboembolic processes, however, the confidence intervals overlap. However, this possible additional value of a simple pretest clinical probability score was achieved despite the fact that it was performed by more than 20 junior residents in 4 different hospitals. Therefore, we recommend using the combination of the pretest clinical probability score and a D-dimer test instead of using the D-dimer test alone to exclude deep venous thrombosis, as suggested by some authors.\textsuperscript{11} The use of the pretest clinical probability score had only a limited effect on the total number of patients in whom serial ultrasonography can be avoided: 39 of the 215 patients (18.1%) with a normal D-dimer concentration underwent a single ultrasonogram because of high pretest clinical probability.

The overall failure rate of the diagnostic strategy in our study was 1.6% (95% CI, 0.7% to 3.1%). In the patients in our study in whom serial ultrasonography was performed, the failure rate was 2.1% (95% CI, 0.8% to 4.4%). This higher percentage can be explained by the fact that only patients with a positive D-dimer assay and, therefore, a higher a priori chance of having deep venous thrombosis underwent serial ultrasonography.

In conclusion, the combination of a non-high pretest clinical probability score and a normal D-dimer concentration is a safe strategy to rule out deep venous thrombosis without performing ultrasonography in symptomatic outpatients. The need for ultrasonography can be reduced by \(\approx 30\%\) using this strategy.

References
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Circulation. 2003;107:593-597; originally published online January 6, 2003;
doi: 10.1161/01.CIR.0000045670.12988.1E
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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