Diagnostic and therapeutic management of venous and arterial disease
Bernardi, E.

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CHAPTER 2

SIMPLIFICATION OF THE DIAGNOSTIC MANAGEMENT OF PATIENTS WITH SUSPECTED DEEP VEIN THROMBOSIS


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* Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, The Netherlands; † Thromboembolism Unit, IRCCS Policlinico San Matteo, Pavia, Italy; ‡ Clinica Medica II, University Hospital of Padua, Italy; // Service of Angiology, University Hospital of Padua, Italy; § Department of Internal Medicine, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands; and ** Department of Clinical Epidemiology, Academic Medical Center, University of Amsterdam, The Netherlands

Abstract

Background - The standard diagnostic approach in patients with suspected deep vein thrombosis is to repeat the compression ultrasound examination after 1 week in all patients with an initial normal result. We hypothesized that a normal finding of a D-dimer assay safely obviates the need for repeat ultrasonography. In addition, we evaluated the potential value of a pre-test probability assessment for this purpose.

Methods - At presentation, consecutive outpatients with suspected thrombosis underwent independent assessment by means of ultrasonography of the proximal veins, a whole-blood D-dimer test and a pretest clinical model. Patients with normal ultrasonographic findings and an abnormal D-dimer assay result were scheduled for repeated ultrasonography. We evaluated the incidence of symptomatic venous thromboembolic complications during a 3-month follow-up, and the value of clinical pretest probability with ultrasonography or D-dimer in scenario analyses.
Results - We studied 1756 patients with prevalence of thrombosis of 22%. At entry, results of the D-dimer and ultrasonography were normal in 828 patients (47%). Of these, 6 returned with confirmed symptomatic venous thromboembolism (complication rate: 0.7%; 95% confidence interval [CI], 0.3% to 1.6%). Repeated ultrasonography was avoided in 61% of the patients with an initial normal test result. Scenario analyses disclosed that the complication rate was 1.6% (95% CI, 0.8% to 2.6%) in those with a low clinical pretest probability and a normal result of ultrasonography at referral, whereas this figure was 1.8% (95% CI, 0.9% to 3.3%) in patients with a low clinical probability result and a normal result of the D-dimer assay at referral.

Conclusions - It is safe to withhold repeated ultrasonography in patients with suspected deep vein thrombosis who have a normal results of ultrasonography and the SimpliRED D-dimer assay at presentation. The combination of a low clinical pretest probability with a normal result of compression ultrasonography or the D-dimer assay appears to be equally safe in refuting the diagnosis of deep vein thrombosis.

Introduction

During the past 2 decades, the diagnostic management of clinically suspected deep vein thrombosis of the lower extremity has considerably improved. Invasive diagnostic procedures such as contrast venography have gradually been replaced by non-invasive methods, most notably impedance plethysmography and compression ultrasonography. Results of both methods have shown a high accuracy for the diagnosis of symptomatic proximal vein thrombosis, but the sensitivity for non-occlusive or calf vein thrombi is much lower. Because these smaller thrombi may extend and give rise to pulmonary embolism, the concept of serial testing with repeated investigation during a 7- to 14-day period was introduced to rule out the disease. In 2 prospective studies, compression ultrasonography was shown to be superior to impedance plethysmography in detecting proximal venous thrombosis and in managing clinically suspected disease. Compression ultrasonography with an extended evaluation of the distal popliteal vein has recently been shown to safely reduce the number of investigations to 2 tests with an interval of one week. Although repeated testing remains mandatory to detect extending thrombi, the major disadvantage of this approach is that all patients with an initial normal ultrasonographic result need to undergo reinvestigation. Therefore, it has become desirable to develop new strategies that obviate the
need for repeated testing in those patients at very low risk for thrombosis. For this purpose, D-dimer assays and clinical pretest probability scores have been advocated. At present, only a limited number of prospective studies has evaluated the usefulness of these novel methods in the actual management of symptomatic patients, and it is unknown which approach is most useful and suitable for daily medical practice.

Therefore, we studied a large cohort of patients with clinically suspected deep vein thrombosis and tested the hypothesis that the combination of normal results of compression ultrasonography and a rapid whole-blood bedside D-dimer assay at referral can safely exclude the presence of thrombosis and obviate the need for serial testing. In addition, we assessed the potential value of a pretest clinical probability score in this setting.

**Methods**

**Patients**

From November 1, 1995, to January 31, 1999, consecutive outpatients with clinically suspected deep leg vein thrombosis, who were referred by their family physician to the thrombosis units of the participating centers, were eligible for the study. The referral pattern and the diagnostic process in these centers were comparable. The protocol was approved by the respective institutional review boards.

Patients were excluded if they were less than 18 years, had experienced a previous episode of deep vein thrombosis in the same leg without documented normalization of the ultrasonographic findings, had concurrent signs or symptoms suggestive of pulmonary embolism, had received anticoagulant treatment for more than 24 hours before referral, or were unable to return to the study center for follow-up because of geographical inaccessibility. Eligible patients had to give written informed consent.

**Diagnostic tests**

Compression ultrasonography was performed and the results were interpreted as described previously. The outcomes were categorized as normal or abnormal, ie, noncompressible.

For purposes of this study, we used the SimpliRED rapid whole-blood bedside D-dimer assay (AGEN Biomedical Ltd, Brisbane, Queensland). The test is performed on capillary blood samples drawn by means of a fingerstick method or on citrated venous blood samples. Agglutination occurs at D-dimer concentra-
tions of above 200 mg/L. The outcomes of the test were categorized as normal or abnormal.

The clinical pretest probability was assessed by means use of the clinical score model described by Wells et al.\textsuperscript{12} This quantitative clinical model stratifies patients with suspected deep vein thrombosis into high, moderate, or low probability for having deep vein thrombosis.

\textit{Study design}

At the day of referral, a compression ultrasonography of the proximal leg veins, the D-dimer assay, and the clinical pretest probability assessment were performed in all patients by 3 independent operators. Patients with an abnormal ultrasonographic result were considered to have deep vein thrombosis. Subsequent management decisions in patients with a normal ultrasonographic finding were based on the outcome of D-dimer assay, whereas information about the pretest clinical probability was used for a scenario analysis. In case of a normal D-dimer assay result, ultrasonography was not repeated, whereas patients with an abnormal D-dimer assay result were scheduled for repeated ultrasonography after 1 week. Patients with a normal D-dimer assay finding at presentation were considered not to have venous thrombosis, as were those with an abnormal D-dimer assay result and repeated normal results of ultrasonography. All patients were scheduled for a visit after 3 months and were instructed to contact the study center immediately if signs or symptoms of venous thromboembolism occurred before this visit. Objective testing was performed in these patients to confirm or refute the disease. Anticoagulant therapy was given only to patients with an abnormal ultrasound.

All deaths and suspected venous thromboembolic complications were reviewed by an independent blinded adjudication committee. Venous thromboembolism was considered present if: (1) symptomatic deep vein thrombosis was confirmed by new abnormal findings on compression ultrasonography or an intraluminal filling defect on results of ascending phlebography; (2) symptomatic pulmonary embolism was confirmed by a high-probability finding on a ventilation-perfusion lung scan or an abnormal angiographic finding; or (3) in case of death, pulmonary embolism was confirmed by autopsy findings or could not be ruled out confidently.

\textit{Statistical Analysis}

We hypothesised that a normal D-dimer assay result in combination with a normal initial ultrasound outcome would safely exclude the presence of deep vein
thrombosis in symptomatic outpatients at referral and obviates the need for repeated testing. Based on data from previous clinical studies that evaluated other noninvasive strategies, our new diagnostic strategy would be considered comparably safe if the upper limit of the 95% confidence interval (CI) of the total cumulative rate of symptomatic venous thromboembolic complications for 3 months was 2.0% or less. Assuming an expected prevalence of 30% for deep vein thrombosis, we calculated that a total of approximately 1500 consecutive symptomatic patients should be included to yield sufficiently narrow confidence intervals around the expected total venous thromboembolic complication rate of 1%. A venous thromboembolic complication was defined as either a pulmonary embolism between referral and repeated ultrasonography or as a pulmonary embolism or deep vein thrombosis during the 3-month follow-up that was confirmed by objective test results. We calculated the complication rate using the Kaplan-Meier survival analysis. The exact 95% CIs around the complication rates, were calculated using StatXact (Version 3.0; Cytel Software Corporation, Cambridge, Mass).

In addition, we performed a scenario analysis on the safety of other potential diagnostic strategies to exclude deep vein thrombosis at referral (ie, a low pretest clinical probability with a normal ultrasonographic finding; a low pretest clinical probability with a normal D-dimer assay finding, or each of these diagnostic methods alone) using the approach described in the previous paragraph. Finally, for all strategies, we determined the efficiency by calculating the proportion of patients from the initial cohort in whom initial and/or repeated ultrasonography could be avoided.

If the result or the D-dimer assay or the pretest probability were obtained with knowledge of the results of compression ultrasonography, the patient was excluded for the respective analyses.

Results

Patients

During the study period, 1899 consecutive outpatients with clinically suspected acute deep vein thrombosis of the lower extremity were referred. Of these, 143 (8%) were excluded for the following reasons: preexisting anticoagulant treatment for more than 24 hours (43%), a previous venous thrombosis in the same leg without normalisation of ultrasonographic findings (53%), geographic inaccessibility for follow-up (2%), and refusal of informed consent (2%). Therefore, 1756 patients entered the study. The mean age was 60 years (range,
18 to 96 years), and 1099 (63%) were female. Mean time since onset of symptoms was 7 days. The underlying disorders are shown in the following tabulation:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>13</td>
</tr>
<tr>
<td>Immobility or surgery in past 6 weeks</td>
<td>15</td>
</tr>
<tr>
<td>Recent trauma</td>
<td>15</td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>10</td>
</tr>
</tbody>
</table>

**Combined Compression Ultrasound and D-dimer Strategy**

Of the 1756 patients who entered the study, 17 were excluded from this analysis because the D-dimer assay was not performed or was performed with knowledge of the ultrasonographic results. Ultrasonographic findings were abnormal in 391 (22%) patients. Of the remaining 1348 patients with a normal compression ultrasonographic test result, the D-dimer assay finding was normal in 828 (61%). Of these patients, 19 returned during the 3-month follow-up with new or increased signs and symptoms of venous thromboembolism. In 6 of them, the venous thromboembolic event was confirmed by results of objective tests (2 had nonfatal pulmonary embolism and deep vein thrombosis developed in 4), whereas it was refuted in the other 13 patients, who did not receive anticoagulation therapy and had an uneventful follow-up. Therefore, the cumulative incidence of venous thromboembolic complications in this patient group was 0.7% (95% CI, 0.3% to 1.6%). Of the 520 patients with an abnormal D-dimer assay finding and a normal compression ultrasonographic finding at presentation, symptomatic pulmonary embolism developed in 2 (0.4%) (fatal in 1) before repeated testing. Of the remaining 518 patients, the results of repeated ultrasonography after 1 week were abnormal in 17 patients (3%). In the 501 patients with a normal result of serial ultrasonography, new or increased signs and symptoms of venous thromboembolism occurred in 21 patients during the 3-month follow-up. The disease was objectively confirmed in 9 of these patients (2 had pulmonary embolism [fatal in 1], and 7 had deep vein thrombosis), whereas it was refuted in the other 12, who did not receive anticoagulation therapy and had an uneventful follow-up. Hence, the incidence of symptomatic venous thromboembolic complications in patients with an abnormal D-dimer assay result at presentation and a normal result of repeated
ultrasonography was 2.1% (95% CI, 1.1% to 3.8%; Table 1). Overall, the strategy of combined ultrasonography and the D-dimer assay to limit repeated ultrasonography to patients with an abnormal D-dimer assay result was associated with an incidence of symptomatic venous thromboembolic complications of 1.3% (95% CI, 0.7% to 2.0%).

With this strategy, repeated ultrasonography could be avoided in 61% of the patients with an initial normal test result.

Scenario Analysis

Since the pretest probability score was also independently obtained in all patients at presentation, the potential value of various strategies combining clinical pretest probability with D-dimer and/or ultrasonographic testing results could be assessed.

Combined Compression Ultrasound and Clinical Pretest Probability Strategy

Of the 1756 patients who entered the study, 30 were excluded from this analysis because the pretest probability was not performed or was determined with knowledge of the ultrasonography result. The distribution of clinical pretest probability in the remaining 1726 patients is presented in Table 2, as well as the combined prevalence of venous thromboembolism at presentation or during follow-up. In 896 patients (51%), the pretest probability was scored as low. In 62 of these patients, the results of ultrasonography disclosed deep vein thrombosis at referral. During the 3-month follow-up of the remaining 834 patients, venous thromboembolism was diagnosed in 13 (3 pulmonary emboli [fatal in 1] and 10 deep vein thrombi; in 7 of the latter patients deep vein thrombosis was detected by routine ultrasonography after one week, which was scheduled because the D-dimer assay result was abnormal at presentation). Hence, the cumulative incidence of venous thromboembolism in patients with a low clinical pretest probability and a normal ultrasound result was 1.5% (95% CI, 0.8% to 2.6%).

This strategy would obviate the need for repeated ultrasonography in 62% of symptomatic patients with a normal ultrasonographic finding at presentation.

Combined D-dimer and Clinical Pre-test Probability Strategy

At presentation, 561 patients had a low pretest clinical probability and a normal D-dimer assay finding. Symptomatic venous thromboembolism was objec-
Table 1 - Clinical outcomes of the combined D-dimer and compression ultrasonography strategy in patients with sus-

<table>
<thead>
<tr>
<th>$ |$</th>
<th>11 (2.1%)</th>
<th>1.1% to 3.8%</th>
<th>[1.9% to 5.2%]</th>
<th>7 (3.3%)</th>
<th>250 (29.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (0.7%)</td>
<td>0.3% to 1.6%</td>
<td>...</td>
<td>...</td>
<td>828 (47.6)</td>
<td></td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>391 (22.5)</td>
<td></td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1739 (100.0)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>D-dimer assay findings at presentation</th>
<th>D-dimer assay findings at presentation</th>
<th>D-dimer assay findings at presentation</th>
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<tbody>
<tr>
<td>Normal ultrasonographic and abnormal</td>
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<td>Abnormal ultrasonographic and abnormal</td>
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<tr>
<td>All eligible patients</td>
<td>All eligible patients</td>
<td>All eligible patients</td>
</tr>
</tbody>
</table>

$\|$ Includes 2 patients with pulmonary embolism that occurred before repeated testing.

‡ These patients underwent repeat testing after 1 week and only received anticoagulant therapy when repeated results of ultrasonography became abnormal.

¶ These patients did not undergo repeat testing and did not receive anticoagulant therapy.

Data are given as (%) (95% CI).
Table 2 – Distribution of clinical pretest probability in 1726 patients with suspected venous thrombosis and the prevalence of venous thromboembolism *

<table>
<thead>
<tr>
<th>Pretest probability of deep vein thrombosis</th>
<th>Proportion of patients from initial cohort</th>
<th>Prevalence of venous thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>51% (49% to 53%)</td>
<td>8% (7% to 10%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>29% (27% to 31%)</td>
<td>27 (23% to 31%)</td>
</tr>
<tr>
<td>High</td>
<td>20% (18% to 22%)</td>
<td>66% (61% to 71%)</td>
</tr>
</tbody>
</table>

* Detected at presentation or during the 3-month follow-up. Data in parentheses are 95% CIs.

tively confirmed in 10 of these patients, by either abnormal ultrasonographic results at referral (7 patients) or recurrent signs and symptoms during the 3-month follow-up (3 patients: 1 with a nonfatal pulmonary embolism and 2 with deep vein thrombosis). The cumulative incidence of symptomatic venous thromboembolism in this subset of patients was 1.8% (95% CI, 0.9% to 3.3%). This strategy, in which deep vein thrombosis is excluded by the combination of a normal D-dimer and a low pretest probability, would obviate the need for initial ultrasonography in one-third of referred patients.

Other Strategies

A strategy in which deep vein thrombosis is excluded on the basis of a low pretest probability alone is associated with a cumulative incidence of symptomatic venous thromboembolism of 8.4% (95% CI, 6.6% to 10.4%), whereas if we used the D-dimer assay alone, this rate would be 2.8% (95% CI, 1.8% to 4.2%). Finally, a strategy in which none of the patients with a normal ultrasonographic finding at referral undergo repeated testing is associated with a cumulative incidence of venous thromboembolism of 2.5% (95% CI, 1.8% to 3.5%) during a 3-month follow-up.

Discussion

At present, the standard diagnostic approach for patients presenting with clinically suspected deep vein thrombosis of the lower limbs consists of a compression ultrasonography at referral and a repeated test after 1 week in those
patients with a normal initial ultrasonographic finding to detect extending thrombi initially limited to the calf veins. This strategy is safe, since it is associated with a low venous thromboembolic complication rate of approximately 1% during 3 months of follow-up. However, the need for repeated testing makes this approach highly inefficient, since the ultrasonographic finding will convert to abnormal in only a low percentage of patients.

The present study clearly shows that the need for repeat ultrasonography can be reduced by about 60% without a decrease in safety by using the SimpliRED D-dimer assay. The total venous thromboembolic complication rate for this novel strategy was 1.3% (95% CI, 0.7% to 2.0%), which is fully comparable to the present standard diagnostic approach.

To evaluate the potential safety and efficiency of other diagnostic strategies in their capacity to reduce the need for (repeated) ultrasonography, we independently and prospectively collected information about the clinical pretest probability at presentation, in addition to the ultrasound and D-dimer investigations. Scenario analysis shows that deep vein thrombosis cannot be safely refuted on the basis of a low clinical pretest probability or a normal SimpliRED D-dimer assay finding alone. The venous thromboembolic complication rate for a 3-month period in these patients was found to be as high as 8.4% (upper 95% confidence limit, 10.4%), and 2.8% (upper 95% confidence limit, 4.2%), respectively. Furthermore, diagnostic management based on either a SimpliRED D-dimer test only or a single ultrasound test is less safe than the combined ultrasound and D-dimer strategy. Despite the frequent assumption that the finding of a single compression ultrasonography is sufficient, our analysis shows clearly that a single ultrasound test of the upper leg to the to the proximal part of the deep calf veins is less safe than the strategy of combined ultrasonography and the D-dimer assay.

The total venous thromboembolic complication rate during a 3-month follow-up in patients with a normal ultrasonographic result and no further investigation was found to be 2.5% (upper 95% confidence limit, 3.5%), which is approximately twice the complication rate of the strategy of combined ultrasonography and the D-dimer assay (2.5% vs 1.3%; p = .048).

Diagnostic strategies in which the D-dimer assay is combined with the clinical pretest probability or the clinical pretest probability is combined with compression ultrasonography appear to be as safe and efficient as the combination the D-dimer assay and ultrasonography, particularly if one considers that approximately half of the venous thromboembolic complications in these strategies were diagnosed by routine initial or repeat ultrasonography as dic-
tated by the primary strategy evaluated in this study. Some of these thrombi might have regressed spontaneously. In our analysis, the venous thromboembolic complication rate in the subgroup of patients in which D-dimer was combined with the clinical pretest probability was 1.8% (95% CI, 0.9 to 3.3%). In these patients, ultrasonography can be completely avoided (approximately 30% of initial cohort). Therefore, in terms of reduction of ultrasonography, this strategy compares favourably with the strategy in which the D-dimer assay is combined with ultrasonography. Although this approach is very tempting, the safety and efficiency requires further clinical confirmation before daily use in clinical practice can be advocated. Recently, Wells and colleagues evaluated the safety of withholding treatment in patients with a normal ultrasonographic finding and a low pretest probability at presentation and observed a very low venous thromboembolic complication rate of 0.3% (95% CI, 0 to 1.7%) during the 3-month follow-up. In the present analysis, this figure was slightly higher, at 1.6% (95% CI, 0.8% to 2.6%). This strategy should be considered safe, although it has the potential disadvantage that the clinical pretest probability may become less accurate when used in routine clinical care. The high reproducibility of D-dimer assays may therefore have an advantage in this respect.

In our study, we made use of the SimpliRED D-dimer assay. Because this assay can be performed at bedside on whole-blood samples, it is very convenient for daily clinical care, in particular in the emergency department. The drawback of this assay, however, is that without proper experience, interpretation of the result may be difficult. Therefore, some institutions may be reluctant to use this specific D-dimer assay. In these institutions, implementation of this strategy with use of a quantitative D-dimer assay could be considered, since the various D-dimer assays have recently been shown to be interchangeable, due to the fact that the sensitivity-specificity ratio of each assay can be adapted to their intended role in clinical practice by varying their critical cut-off value.

Conclusions

The findings of this management study show that, for patients presenting with clinically suspected deep leg vein thrombosis, the diagnostic management strategy in which compression ultrasonography is combined with a D-dimer assay is a safe and more efficient alternative to the present standard approach of repeated ultrasonography. Two other diagnostic management strategies (the clinical model combined with compression ultrasonography and the D-dimer assay combined with the clinical model) appear to be equally safe and efficient.
in the exclusion of deep vein thrombosis at referral. However, further evaluation of these latter strategies is required before their use in daily clinical practice can be advocated.

Acknowledgement - We greatly appreciate the helpful suggestions of Dr. A.W.A. Lensing.

References