Value of D-Dimer Testing for the Exclusion of Pulmonary Embolism in Patients With Previous Venous Thromboembolism

Grégoire Le Gal, MD; Marc Righini, MD; Pierre-Marie Roy, MD; Oliver Sanchez, MD; Drahomir Aujesky, MD, MSc; Arnaud Perrier, MD; Henri Bounnameaux, MD

Background: D-dimer levels remain elevated in many patients after completion of a 6-month anticoagulant drug course for a first episode of venous thromboembolism (VTE), which may limit the clinical usefulness of D-dimer testing for ruling out a possible recurrence.

Methods: We assessed the safety and usefulness of D-dimer testing in patients with suspected pulmonary embolism (PE) who had experienced a previous VTE. We analyzed data from 2 outcome studies that enrolled 1721 consecutive emergency department patients with clinically suspected PE. Information on the existence of a previous VTE was abstracted from the database. All the patients underwent a sequential diagnostic work-up, including an enzyme-linked immunosorbent assay D-dimer test and a 3-month follow-up.

Results: The proportion of confirmed PE was 24.1% (415/1719); PE was ruled out by a negative D-dimer test result in 32.7% (462/1411) of the patients without previous VTE but in only 15.9% (49/308) of the patients with previous VTE (P<.001). The 3-month thromboembolic risk was 0% (95% confidence interval, 0.0%-7.9%) in patients with previous VTE and a negative D-dimer test result. The 2-fold lower chance of a negative D-dimer test result in patients with previous VTE was independent of older age, active malignancy, fever, and recent surgery.

Conclusions: In patients with suspected PE and previous VTE, a negative D-dimer test result seems to allow safely ruling out a recurrent event. However, the proportion of negative results is lower in such patients, definitely reducing the clinical usefulness of the D-dimer test in that subgroup.

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Diagnosis of recurrent venous thromboembolism (VTE) is a difficult challenge.1-2 Plasma D-dimer measurement is widely used as a first-line test in patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE).3-4 Although available D-dimer assays are heterogeneous, most allow ruling out VTE in combination with clinical assessment when the results are negative: in patients with a low clinical probability for whole-blood agglutination assays5 and in patients without a high clinical probability for the most sensitive tests (enzyme-linked immunosorbent assay [ELISA] and some immunoturbidimetric assays).6-7

See also pages 147, 169, and 181

In inpatients,8 during pregnancy9 or post partum,10 in elderly patients,11 and in cancer patients,12 the clinical usefulness of the D-dimer value, defined as the proportion of patients in whom the suspicion of VTE may be ruled out based on a negative D-dimer test result, is lower, although the sensitivity and negative predictive value of the test remain high enough to safely rule out VTE. For example, this proportion is only 5% in patients older than 80 years compared with 60% in patients 40 years or younger.11 Recently, Palareti et al13 reported on the value of D-dimer testing to predict the recurrence of VTE. Among patients who were given a 6-month anticoagulant drug course for a first episode of VTE, 40% still had an elevated D-dimer level 1 month after withdrawal of oral anticoagulant drug treatment, probably reflecting the persistence of a hypercoagulable state. This finding is compounded by a higher recurrence rate in such patients.13 However, a high proportion of patients with persistent D-dimer elevation may limit the clinical usefulness of D-dimer testing in cases of suspected recurrent events in patients with previous VTE. Therefore, we assessed the safety and usefulness of D-dimer testing in patients with suspected PE and a previous episode of VTE and whether a history of VTE is independently associated with positive D-dimer test results.

Original Investigation: Value of D-Dimer Testing for the Exclusion of Pulmonary Embolism in Patients With Previous Venous Thromboembolism

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METHODS

PATIENTS

We analyzed the combined data from 2 prospective multicenter cohort studies3,4 that included 1721 consecutive patients admitted to the emergency department with suspected PE. These outcome studies were designed to evaluate diagnostic strategies for PE, combining clinical probability assessment, plasma D-dimer measurement, lower limb venous compression ultrasonography, and helical computed tomography (CT).

Briefly, all the consecutive patients admitted to the emergency department of 3 general and teaching hospitals were included if they had clinical suspicion of PE, defined as the acute onset of new or worsening shortness of breath or chest pain without any other obvious etiology. The exclusion criteria consisted of (1) ongoing anticoagulant drug treatment, (2) contraindication to CT (known allergy to contrast iodine agents or at risk for allergic reaction, creatinine clearance level <30 mL/min [<0.50 mL/s] calculated using the Cockcroft formula, or current pregnancy), (3) suspected massive PE with shock, and (4) an estimated life expectancy of less than 3 months. The first study3 was conducted at Geneva University Hospital, Centre Hospitalier Universitaire Vaudois (Lausanne), and Angers University Hospital between October 1, 2000, and June 30, 2002. Of 1290 eligible patients, 258 were excluded because of contraindications to CT and 67 because of protocol violations. Thus, the final study population comprised 965 patients. The second study4 was conducted at Geneva University Hospital, Angers University Hospital, and the Hôpital Européen Georges Pompidou between August 1, 2002, and November 30, 2003. Of 1014 eligible patients, 185 were excluded because of contraindications to CT and 73 because of protocol violations. Thus, the final study population comprised 756 patients. Both studies were approved by the ethics committee of each participating institution, and written informed consent was obtained from all the patients. All the participating hospitals serve as general public hospitals for the surrounding population and as referral institutions for a larger population. Most patients included in these studies were first seen in the emergency department primarily or by their general practitioner.

DIAGNOSTIC WORKUP

All the patients underwent a sequential diagnostic workup. At admission to the emergency department, the physicians in charge completed a clinical evaluation of the patient before any specific tests for suspected PE were performed. They completed a standardized data form for each patient, recording demographic characteristics, risk factors (including the presence of previous DVT or PE), clinical signs and symptoms of VTE, results of electrocardiography and chest radiography, and the presence of an alternative diagnosis to PE and its likelihood compared with that of PE. Based on that information, they assigned each patient to a clinical probability category using the Geneva prediction rule,14 with possible override by implicit assessment in case of disagreement with their clinical judgment.15 Sequential tests were then performed, including plasma D-dimer measurement using a rapid ELISA (VIDAS D-Dimer Exclusion; bioMérieux, Marcy-l’Etoile, France). Pulmonary embolism was ruled out by (1) a D-dimer level below the cutoff value of 500 µg/L, except in patients with a high clinical probability of PE in the second study; (2) negative lower limb venous compression ultrasonographic findings and negative helical CT findings in patients with a low or intermediate clinical probability of PE; or (3) normal ventilation-perfusion lung scan findings or normal pulmonary angiographic findings in patients with a high clinical probability of PE or with inconclusive helical CT findings. Pulmonary embolism was established by (1) finding a proximal DVT on lower limb ultrasonography, (2) positive helical CT findings, or (3) high-probability ventilation-perfusion lung scan findings or positive findings on pulmonary angiograms in patients with a high clinical probability of PE and negative compression ultrasonography and helical CT findings and in patients with inconclusive helical CT findings.

3-MONTH FOLLOW-UP

Patients were followed up by their family physicians and were interviewed by telephone by a study coordinator at the end of follow-up. The family physician was contacted when a possible event was disclosed by the interim history, and medical records were reviewed if a patient was readmitted to the hospital for any cause. The outcome was an estimate of the 3-month thromboembolic risk in patients in whom PE was considered ruled out by the initial diagnostic workup and who were not anticoagulated during follow-up. Diagnoses of VTE events during follow-up were established using the usual criteria (DVT: abnormal ultrasonographic findings; and PE: high-probability ventilation-perfusion lung scan findings or a CT scan or angiogram showing PE). Deaths were adjudicated as definitely caused by PE, definitely unrelated to PE, or possibly due to PE by 3 independent experts.

DATA ANALYSIS

Characteristics of patients with and without a personal history of VTE were compared using t tests for the continuous variable (age) and χ2 tests for the nominal categorical variables (sex, familial history of VTE, recent surgery, active malignancy, current pregnancy or post partum, body temperature ≥38.5°C, alternative diagnosis more likely than that of PE, and pretest clinical probability of PE). The proportion of patients with confirmed PE and the proportion with negative D-dimer test results were also compared using a χ2 test. The 3-month thromboembolic rate in untreated patients on the basis of a negative D-dimer test result and the sensitivity and specificity of the D-dimer test were computed along with 95% confidence intervals (CIs) in each group. The number of patients needed to test by D-dimer measurement to rule out 1 PE was computed as 1 divided by the proportion of patients with negative D-dimer test results in each group.16 χ2 Tests were used to compare the proportion of patients with negative D-dimer test results in those with and without factors known to be associated with higher D-dimer values: age, active malignancy, infection, current pregnancy or post partum, and recent surgery. Age was dichotomized using the median value (<63 vs ≥63 years). We used the presence of a body temperature of 38.5°C or greater as a surrogate for infection because that item was not recorded as such in the database. We then performed a multivariate logistic regression analysis to test for an independent association between previous VTE and the chance of a negative D-dimer test result, adjusting for potential confounders significantly associated with a negative result in univariate analyses. Inpatients3 and patients undergoing long-term oral anticoagulant therapy were not included in the original studies from which the present data are abstracted.

RESULTS

Previous VTE was recorded in 308 (17.9%) of the 1721 included patients with clinically suspected PE. Two patients were excluded from further analysis because in-
formulation on history of VTE was not available. The proportion of confirmed PE in the study population was 24.1% (415/1719). Patients had a median age of 63 years (range, 18-98 years), and 59% were women. Characteristics of patients with and without previous VTE are given in Table 1. Patients with previous VTE were 8 years older (67 vs 59 years) and more likely to have a family history of VTE (17.2% vs 10.8%) than those without previous VTE. Only 26.3% of the patients with previous VTE had a low clinical probability of PE compared with 58.2% of those without previous VTE. Finally, PE was confirmed in 40.3% of patients with previous VTE compared with only 20.6% of those without previous VTE.

**VALUE OF THE D-DIMER TEST**

Performances on the D-dimer test in patients with and without a history of VTE are given in Table 2. The D-dimer level was less than 500 µg/L in 462 (32.7%) of the 1411 patients with suspected PE and without history of VTE compared with 49 (15.9%) of the 308 who had experienced an event in the past (P<.001). The number of patients needed to test to rule out 1 PE was 3.1 in patients without previous VTE and 6.3 in those with a previous episode. In the second study, although D-dimer testing was not necessary in patients with a high clinical probability of PE, it was performed in 73 of the 82 high-probability patients, and the results were positive in all cases. The 9 remaining patients had PE during initial workup and were arbitrarily considered to have a positive D-dimer test result for the estimation of specificity and positive predictive value. During 3-month follow-up, 22 patients with a negative D-dimer test result received oral anticoagulant drug therapy for indications other than VTE (mainly cardiac arrhythmias), 18 without and 4 with previous VTE. Three patients were lost to follow-up.

In patients in whom PE was considered ruled out by a negative D-dimer test result and who did not receive anticoagulant agents, there were no thromboembolic events during 3-month follow-up in patients with previous VTE (0/45; 0%; 95% CI, 0%-7.9%) or in patients without previous VTE (0/441; 0%, 95% CI, 0%-0.9%). The specificity of the D-dimer test was lower in patients with previous VTE (27% vs 41% [95% CI, 21%-33% vs 38%-44%]).

**PREDICTORS OF AN ELEVATED D-DIMER LEVEL**

The proportion of patients with a negative test result according to the presence or absence of previous VTE and of factors known to be associated with higher D-dimer concentrations (age, active malignancy, fever, recent surgery, and current pregnancy or post partum) and the crude odds ratios (ORs) for the association between these factors and a negative D-dimer test result are given in Table 3. Age, active malignancy, fever, and recent surgery demonstrated statistically significant associations, whereas current pregnancy or post partum was not significantly associated with D-dimer test negativity. For example, only 9.6% of patients with recent surgery had a negative D-dimer test result compared with 30.9% of those who had not undergone an operation (OR, 0.2; 95% CI, 0.1-0.5; P<.001).

Previous VTE was also associated with a significant reduction in the probability of a negative D-dimer test result (15.9% vs 32.7% in patients without history of VTE; OR, 0.4; 95% CI, 0.3-0.5; P<.001). After adjustment for other factors associated with a positive D-dimer test result in univariate analysis (age, active malignancy, fever, and recent surgery), a history of VTE remained strongly associated with an approximately 2-fold decreased chance of a negative D-dimer test result (OR, 0.5; 95% CI, 0.3-0.7; P<.001).

**COMMENT**

The present study shows that in patients with a history of VTE and suspected PE, a negative D-dimer test result safely rules out a recurrent event. However, the propor-
tion of patients with negative D-dimer test results is lower in such patients, and the clinical usefulness of the test is reduced in this setting. The approximately 2-fold reduced chance of a negative result in patients with previous VTE is independent of factors known to be associated with higher D-dimer values, such as advancing age, active malignancy, fever, and recent surgery.

This study has several limitations. First, although 308 patients had a history of VTE, only 43 had a negative test result and were not given anticoagulant agents because of the higher proportion of confirmed cases of PE and the lower proportion of patients with negative D-dimer test results in this group. Consequently, the 95% CI for the 0%–3-month thromboembolic rate (0%-7.9%) remains too wide to allow a definite conclusion. The accepted upper margin of the 95% CI for the 3-month thromboembolic risk to consider a test as safely ruling out PE is 3%. On the other hand, all published management studies in which PE was ruled out on the basis of a negative highly sensitive D-dimer test result demonstrated the safety of this strategy, regardless of whether included patients had a history of VTE. Moreover, to date, except in patients with a high clinical probability of PE—in which the proportion of PE might be too high to ensure sufficient negative predictive value despite high ELISA D-dimer test sensitivity—no clinical setting has been formally identified as being associated with a lower negative predictive value of a negative D-dimer test result. Thus, we believe that the available data are convincing enough to allow ruling out PE on the basis of a negative D-dimer test result in patients with previous VTE. Although the usefulness of this test is limited in these patients, D-dimer testing might still avoid many more invasive and time-consuming diagnostic tests and hence may be cost-effective despite the relatively low proportion of negative test results (16%). Its usefulness will be further limited if a less sensitive D-dimer test is used because these tests allow ruling out the diagnosis of PE only in low-probability patients; in the present analysis, 26.3% of patients with a history of VTE were classified as having a low clinical probability of PE vs 58.2% of patients without such a history.

In the somewhat different setting of DVT, Rathbun et al recently published the results of a management study in which a highly sensitive D-dimer test was used to exclude DVT in 300 patients with a previous episode of DVT and a suspected recurrent event. The final prevalence of DVT was 18.0% (54/300), and 134 patients (44.7%) had a negative D-dimer test result. During 3-month follow-up, only 1 patient experienced proven recurrent VTE (0.8%; 95% CI, 0%-4.1%). The usefulness of D-dimer testing was higher in this trial: 1 of 2.2 patients had negative D-dimer test results compared with 1 of 6.3 in the present analysis. This difference might be explained by the difference in the D-dimer test that was used or by the fact that D-dimer testing was performed regardless of the clinical probability. The location of VTE might also play a role if the proportion of patients with persistently elevated D-dimer levels is higher after an episode of PE than after an episode of DVT.

Another limitation of this study is that we do not have detailed information on the previous episode of VTE, for example, on neither the location of VTE (DVT or PE) nor the delay between the previous episode and the suspicion of PE leading to patient inclusion. We only know, because it was an exclusion criterion, that patients were not receiving oral anticoagulant drug therapy when included in the study. However, subgroup analysis according to the delay since the previous episode would have been of interest. Indeed, approximately 40% of patients still had elevated D-dimer levels 3 months after oral anticoagulant drug therapy withdrawal, but little is known about the long-term evolution of D-dimer levels. Moreover, the reasons for these persistently elevated D-dimer levels after a first episode of VTE remain unknown. Hypotheses include persisting thrombotic/thrombolytic activity (hypercoagulable state) and a constitutional high basal level in some individuals. In fact, elevated D-dimer levels in the absence of acute VTE have been shown to be associated with the occurrence of a first episode of VTE in a report from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study.

Our data also confirm that some clinical factors are associated with higher D-dimer levels. Patients with a history of recent surgery or with an age greater than the median age of the cohort had a 5-fold reduced chance of a negative D-dimer test result. Similarly, active malignancy and a body temperature of 38.5°C or greater as a surrogate for infectious/inflammatory diseases were associated with a 3- and 2-fold reduced chance of a negative D-dimer test result, respectively.

Table 3. Factors Associated With the Chance of a Negative D-Dimer Test Result in Patients With Suspected PE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previous VTE</th>
<th>No Previous VTE</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;63 y</td>
<td>107 (12.5)</td>
<td>404 (46.8)</td>
<td>0.2 (0.1-0.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>17 (10.4)</td>
<td>494 (31.8)</td>
<td>0.3 (0.1-0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surgery &lt;1 mo</td>
<td>9 (9.6)</td>
<td>502 (30.9)</td>
<td>0.2 (0.1-0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Central temperature ≥38.5°C</td>
<td>15 (19.2)</td>
<td>481 (30.1)</td>
<td>0.6 (0.3-1.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Current pregnancy or post partum</td>
<td>10 (43.5)</td>
<td>501 (29.6)</td>
<td>1.8 (0.8-4.2)</td>
<td>.16</td>
</tr>
<tr>
<td>Personal history of VTE</td>
<td>49 (15.9)</td>
<td>462 (32.7)</td>
<td>0.4 (0.3-0.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

*Adjusted for age, active malignancy, recent surgery, and fever.
In conclusion, in patients with suspected PE and a history of previous VTE, a negative ELISA D-dimer test result allows safely ruling out this diagnosis. However, the usefulness of the test is reduced because the proportion of patients with a history of VTE and a negative D-dimer test result is lower than that in patients without previous VTE. The association between a history of VTE and a negative D-dimer test result is independent of other factors known to be associated with high D-dimer values.

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Correspondence: Grégoire Le Gal, MD, EA 3878 (GETBO), Department of Internal Medicine and Chest Diseases, Centre Hospitalier Universitaire de la Cavale Blanche, Boulevard Tanguy Prigent, 29609 Brest CEDEX, France (gregoire.legal@chu-brest.fr).

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