High D-dimer concentrations can predict malignancy in patients presenting with deep venous thrombosis

R.E.G. Schutgens\textsuperscript{1}, F.J.L.M. Haas\textsuperscript{2}, M.M.J. Beckers\textsuperscript{3} and D.H. Biesma\textsuperscript{3}

Departments of \textsuperscript{1}Haematology, University Hospital Utrecht, and Departments of \textsuperscript{2}Clinical chemistry and \textsuperscript{3}Internal Medicine, St. Antonius Hospital Nieuwegein, The Netherlands
SUMMARY

BACKGROUND Venous thromboembolism can be related to malignancy, but routine screening for cancer in patients with deep venous thrombosis (DVT) is a matter of debate.

METHODS In consecutive outpatients with proven DVT, D-dimer measurement was done at presentation. Patients were followed for a median of 31 months and the occurrence of malignancy was documented. In a proportion of the patients, daily measurements of D-dimers were performed for 4 consecutive days.

RESULTS Forty-nine (22%) of 218 patients with DVT had or developed cancer: 28 patients were known with cancer, in 8 patients cancer was discovered at time of presentation with DVT and during follow-up 13 patients developed cancer. The prevalence of cancer in patients with initial D-dimer levels < 4000 µg/l was 16% as compared to 35% in patients with D-dimer levels > 4000 µg/l (p=0.005). After 4 days of treatment, the prevalence of cancer was 14% when D-dimer levels were < 4000 µg/l, compared to 46% when they were still > 4000 µg/l (p=0.02). Of the patients with thrombosis and cancer, 78% (38/49) was older than 60 years. D-dimer levels at age > 60 did not discriminate in the presence or absence of cancer. In younger patients, initial D-dimer levels of < 4000 µg/l were associated with a cancer prevalence of 3% compared to 23% at levels > 4000 µg/l (p=0.001). After 4 days of treatment, cancer prevalences were 0% and 100% in younger patients with D-dimer levels < and > 4000 µg/l respectively (p=0.003).

CONCLUSIONS High D-dimer concentrations at presentation and persistently high D-dimer levels during the first days of treatment are indicators of an increased change for overt or occult forms of cancer, especially in patients younger than 60 years.
INTRODUCTION

The development of venous thromboembolism is associated with transient risk factors for thrombosis like surgery or trauma, and permanent risk factors (such as factor V Leiden, the prothrombin mutation, protein C and S deficiency, antithrombin deficiency, lupus anticoagulant and hyperhomocysteinemia). Venous thromboembolism can also be related to malignancy (1-5). The incidence of malignancy in patients with thrombosis is 7-26% (6-10). Patients with cancer are at higher risk of developing venous thromboembolism, which has been observed especially in postoperative patients with cancer and in patients receiving chemotherapy (11).

Although several studies have tried to define clinical conditions in which cancer is more frequent in venous thromboembolism (3,6,10,12,13), there is still debate about routine screening for occult malignancy. It would be of interest if certain patients with thrombosis could be identified as having an increased risk of having malignancy. The mechanism of the hypercoagulable state in cancer is complex and many markers of blood clotting activation are disturbed (2,14,15). Increased concentrations of D-dimers, specific markers of fibrinolysis, can be found in patients with cancer (18-19). As in many patients suspected for venous thromboembolism a D-dimer measurement is now being performed according to more recently developed diagnostic strategies (20-24), it is of interest to know whether the D-dimer concentration can be used as a predictor for cancer as cause for venous thromboembolism in these patients.

The aim of this study is to investigate whether the initial height of the D-dimer level in patients with deep venous thrombosis or early changes in D-dimer levels during treatment for deep venous thrombosis can differentiate between patients with and without cancer.
PATIENTS AND METHODS

Consecutive outpatients with proven deep venous thrombosis of the leg were included in this study from July 1998 to October 2001. Ineligibility criteria were the use of anticoagulants, pregnancy and not documented recanalisation after a previous history of deep venous thrombosis in the ipsilateral leg. Thrombosis was diagnosed using real-time B-mode compression ultrasonography, where lack of compressibility was the criterion for an abnormal result; a vein was considered fully compressible if no residual lumen was seen. In all patients, a D-dimer measurement was done using the Tina-quant® quantitative latex assay (Roche, Mannheim, Germany) at presentation. D-dimer values above 8000 µg/l FEU (Fibrinogen Equivalent Units) were not diluted further and were reported as > 8000 µg/l FEU. Treatment for thrombosis was started immediately and was given as a once daily subcutaneous injection with a low molecular weight heparin (dalteparin; dose adjusted to weight). Oral acenocoumarol was started simultaneously. Patients were treated with dalteparin for at least 5 subsequent days until the INR was > 2.0. We documented the presence of previously known malignancy and the type of malignancy that was detected at the moment of thrombosis or developed during follow-up. Data on the follow-up period were obtained by checking the medical records in the participating hospital from July 1998 to February 2002, by sending a questioner to the patient's general practitioner and by checking the national database network and registry of histo- and cytopathology.

We had the intention to measure D-dimer levels daily for a period of at least four days after the start of anticoagulation. The day of presentation was considered to be day 0. This study was, however, restricted to the first 57 patients, because in 1999, we lost the opportunity for this clinical follow-up and daily D-dimer measurements due to the decision to treat patients with deep venous thrombosis at home.

Statistics

As D-dimer values > 8000 µg/l FEU were not diluted, no linear comparison between the groups could be made. We have made clusters for the D-dimer levels, with ranges 0-2000, 2001-4000, 4001-6000 and > 6000 µg/l FEU. We used the Fisher's exact method with two-tailed p-values for comparison between the clusters.
RESULTS

In total, 218 (102 men and 116 women) consecutive outpatients with proven deep venous thrombosis of the leg were included. Of the total of 218 patients, 49 (22%) patients had or developed cancer; 28 were already known with cancer at the moment of thrombosis, 8 had cancer discovered at presentation with thrombosis and 13 developed malignancy during follow up (Table 1). The median follow up was 31 months (range 4-54 months). In the 8 patients who had cancer discovered at presentation, all but one had metastatic disease. In the 13 patients who developed cancer during follow-up, 3 had metastatic disease. The median time to the development of cancer in the latter 13 patients was 15 months (range 3-36 months). The total prevalence of cancer in patients with deep venous thrombosis that were not previously known with cancer was 11% (21/190). The prevalence of cancer during follow-up was 7% (13/182). Of the 218 patients, 102 (47%) was older than 60 years. In these 102 patients, the prevalence of cancer was 37% (38/102). This was significantly higher than the prevalence of cancer in patients younger than 60 years (10% (12/116); p=0.0003). The median age in patients with cancer was higher than in patients without cancer: 67.9 years (range 30-88) versus 55.0 years (range 18-90) (p<0.001). Of the patients with thrombosis and cancer, 78% (38/49) was older than 60 years. Of the 13 patients that developed cancer in the follow up, 85% (11/13) was older than 60 years. At initial D-dimer levels of 0-2000 µg/l FEU, the prevalence of cancer in the total group was 12% (7/59), at levels 2001-4000 µg/l FEU 19% (13/69), at levels 4001-6000 µg/l FEU 33% (9/27) and at levels > 6000 µg/l FEU 32% (20/63). Comparing the lowest with the highest cluster, this difference was statistical significant (p=0.009). The prevalence of cancer in patients with a D-dimer < 4000 µg/l FEU was 16% (20/128) as compared to 32% (29/90) (p=0.005) in patients with D-dimer levels > 4000 µg/l FEU (Table 2). In patients older than 60 years, there was no difference in cancer prevalence between patients with D-dimer levels above or under 4000 µg/l FEU (p=0.7). In patients younger than 60 years, the prevalence of cancer was 3% when D-dimer levels were < 4000 µg/l FEU, and 23% when D-dimer levels were > 4000 µg/l FEU (p=0.001).

D-dimer levels were measured at 4 consecutive days after the start of anticoagulation in 57 patients with proven deep venous thrombosis. All
patients had D-dimer levels > 500 µg/l FEU at presentation. There was a significant decrease in D-dimer levels over time. At presentation (day 0), 25 (44%) of the 57 patients had a D-dimer concentration in the highest cluster (> 6000 µg/l FEU); at day 4 only 8 (14%) patients had a D-dimer concentration > 6000 µg/l FEU (p<0.001). Similarly, at presentation 10 (18%) of the 57 patients had D-dimer levels in the lowest cluster (0-2000 µg/l FEU), where at day 4 these values were 23/57 (40%) (p=0.01). However, at day 4 only 2 (4%) of the 57 patients returned to normal D-dimer levels (< 500 µg/l FEU).

Of these 57 patients, there were 12 (21%) patients with cancer; 6 were already known with cancer, 2 had cancer discovered at presentation and in 4 patients cancer developed during follow up. In 4 of the 6 patients who were not previously known with cancer, the D-dimer levels remained > 4000 µg/l FEU at day 4. Comparing the D-dimer levels in patients with and without cancer, there was a significant difference at day 4. At day 4, 6 (50%) of the 12 patients with cancer had D-dimer levels > 4000 µg/l FEU, whereas in the 45 patients without cancer only 7 (16%) had D-dimer levels > 4000 µg/l FEU (p=0.02). The prevalence of cancer in patients with D-dimer levels < 4000 µg/l FEU at day 4 was 14% (6/44), as compared to 46% (6/13) in patients with D-dimer levels > 4000 µg/l FEU (p=0.02) (Table 2).

Of these 57 patients, 29 (51%) were over 60 years old. In these patients, 10 (34%) had cancer. A D-dimer concentration > 4000 µg/l FEU at day 4 in these patients was associated with a cancer prevalence of 36% compared to 33% at lower D-dimer concentrations (p=1.0). In patients younger than 60 years (n=28), 2 had cancer. These two patients both had D-dimer concentrations > 4000 µg/l FEU at day 4. The remaining 26 patients had no cancer and they all had a D-dimer concentration < 4000 µg/l FEU at day 4. These differences were statistical significant (p=0.003) (Table 2).
### Table 1. Types of malignancy in outpatients with deep venous thrombosis.

Of the 49 patients with cancer, 28 were previously known with cancer, 8 had cancer discovered at presentation with deep venous thrombosis and 13 developed cancer during follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Previously known (n)</th>
<th>At presentation (n)</th>
<th>During follow-up (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8</td>
<td>-</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Other hematologic</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
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<tr>
<td>Breast</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Ovarium</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>8</td>
<td>13</td>
<td>49</td>
</tr>
</tbody>
</table>

### Table 2. Prevalence of cancer in patients with deep venous thrombosis according to D-dimer concentrations at presentation and after 4 days of treatment and according to age. Values are reported as percentage (n).

<table>
<thead>
<tr>
<th>D-dimer concentration (µg/l FEU)</th>
<th>At presentation</th>
<th>At day 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 4000 &lt; 4000</td>
<td>&lt; 4000 &lt; 4000</td>
<td></td>
</tr>
<tr>
<td>Total group</td>
<td>16 32</td>
<td>14 46</td>
<td>0.005 0.02</td>
</tr>
<tr>
<td>(20/128) (29/90)</td>
<td>(6/44) (6/13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>35 40</td>
<td>33 36</td>
<td>0.7 1.0</td>
</tr>
<tr>
<td>(18/52) (20/50)</td>
<td>(6/18) (4/11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>3 23</td>
<td>0 100</td>
<td>0.005 0.003</td>
</tr>
<tr>
<td>(2/76) (9/40)</td>
<td>(0/26) (2/2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

This study shows that in patients with deep venous thrombosis, high D-dimer concentrations at presentation and during the first days of treatment are indicators of an increased change for overt or occult forms of cancer. The prevalence of cancer in patients with thrombosis reported in literature varies from 7 to 26% (6-10) and corresponds well with the cancer prevalence of 22% in our study. Reports on the incidence of occult cancer in idiopathic deep venous thrombosis vary from 8% to 26% (9,25,26). So far, routine screening for cancer in every patient with deep venous thrombosis has not been recommended (12). There are some reports that identify patients with thrombosis with an increased risk of having cancer. A recent report identified the presence of bilateral deep venous thrombosis as an independent predictive factor of cancer discovery with a hazard ratio of 6.28 compared with unilateral one (27). The risk of developing cancer in the first year after diagnosis of thrombosis is 4 to 7 times higher in patients with idiopathic thrombosis compared to patients with secondary thrombosis (25,28).

We found that if the initial D-dimer concentration was > 4000 µg/l FEU, the prevalence of cancer was significantly higher than at D-dimer levels < 4000 µg/l FEU (32% versus 16%). Also, if the D-dimer levels after 4 days of treatment were still > 4000 µg/l FEU, the prevalence of cancer was significantly higher than if D-dimer levels were < 4000 µg/l FEU: 46% versus 14%. This implicates that the D-dimer concentration at presentation and after 4 days of treatment with oral anticoagulants can select patients that are at a higher risk of having cancer. Cushman et al found no association of baseline D-dimer with the occurrence of cancer-associated venous thrombosis (29). However, that study was conducted in unsymptomatic patients with a high prevalence of a normal D-dimer concentration. They used quintiles where the lowest quintile (D-dimer 2-69 µg/l) was compared with the highest quintile (278-7429 µg/l). In our study, performed in symptomatic patients with proven deep venous thrombosis, the D-dimer levels were all > 500 µg/l. Another difference is that the comparison of D-dimers in our study was performed at the time of the thrombosis, and not in the periods before.

We confirm the findings of Ranft et al, who found that 71% of patients with deep venous thrombosis and occult cancer were over 60 years old (8). In our study, 78% of the patients with thrombosis and cancer were older
than 60 years and of the patients that developed cancer in the follow up, 85% was older than 60 years. Similarly, in a recent study in patients with thrombosis, 21% of the patients over 60 years old developed cancer, compared to 5% in patients younger than 60 years old (10). This shows that the chance of having cancer in patients with deep venous thrombosis increases with aging and this might be a stimulus to screen for occult malignancy in patients older than 60 years. In our study, determination of a D-dimer has no value in defining a subgroup of elderly with an increased prevalence of cancer. However, in younger patients, we found a significant difference in the prevalence of cancer when comparing D-dimer levels above and under 4000 µg/l: 23% versus 3% for D-dimers at presentation and 100% versus 0% for D-dimers at day 4 of treatment. Therefore, especially in younger patients with deep venous thrombosis, D-dimers might be useful as indicators for underlying malignancy. A possible explanation for this age-dependency may be the fact that D-dimer concentrations will be frequently elevated in the elderly due to co-morbidity and general vessel damage (16;30-34).

In conclusion, we found that patients with deep venous thrombosis and a D-dimer concentration > 4000 µg/l at presentation and after 4 days of treatment are at higher risk for developing cancer, especially when they are younger than 60 years. Cancer-related deep venous thrombosis most frequently occurs in patients older than 60 years. Our results argue for a larger study towards cost-effectiveness of screening for a malignancy in patients older than 60 years and in patients younger than 60 years with initially high and persistently elevated D-dimer levels.
REFERENCE LIST

D-dimers can predict cancer in DVT


