Venous thrombosis in cancer patients: Prediction, diagnosis and management
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Safety and feasibility of a diagnostic algorithm combining clinical probability, D-dimer and ultrasonography in suspected upper extremity deep vein thrombosis: a prospective management study

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Submitted

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| ABSTRACT |

**Background**
Although well-established for suspected lower limb deep vein thrombosis (DVT), the use of an algorithm combining a clinical decision score, D-dimer and ultrasonography has not been evaluated in suspected upper extremity DVT (UEDVT).

**Objective**
To assess the feasibility and safety of a new diagnostic algorithm in patients with clinically suspected UEDVT.

**Design**
Diagnostic management study.

**Setting**
16 different hospitals in Europe and the United States.

**Patients**
406 in- and -outpatients with suspected UEDVT

**Measurements**
The algorithm consisted of the sequential application of the Constans’ clinical decision score, D-dimer testing and ultrasonography. Patients were first categorized as UEDVT likely or unlikely and in those with an unlikely score and a normal D-dimer, UEDVT was excluded. All other patients underwent (repeated) compression ultrasonography. The primary outcome was the three-month incidence of symptomatic UEDVT and pulmonary embolism in patients with a normal diagnostic work-up.

**Results**
The algorithm was feasible and completed in 390 of the 406 patients, i.e. 96%. In 87 (21%) patients an unlikely score combined with a normal D-dimer excluded UEDVT. In 103 (25%) and 54 (13%) patients a diagnosis of UEDVT or superficial vein thrombosis was made, respectively. Of the 249 patients with a normal diagnostic work-up, one developed UEDVT during follow-up for an overall failure rate of 0.40% (95%CI: 0.0-2.2%).

**Limitations**
This study was not powered to show the safety of the various sub-strategies. Furthermore, D-dimer measurement was performed locally.

**Conclusions**
The combination of a clinical decision score, D-dimer and ultrasonography can safely and effectively exclude venous thrombosis of the upper extremity. If confirmed by other studies, this algorithm has potential as standard approach to suspected UEDVT.
INTRODUCTION

Venous thromboembolism affects approximately two to three per 1000 persons each year (1,2). Traditionally, most attention has been drawn to the correct diagnosis of deep vein thrombosis (DVT) of the leg and pulmonary embolism (3-6). Because of the more widespread use of central venous catheters, the incidence of clinically suspected upper extremity deep vein thrombosis (UEDVT) is increasing (7). In addition, the complication rate of UEDVT is higher than previously appreciated; in particular pulmonary embolism may be present in 10-25% of these patients (8-10).

The reference standard for the diagnosis of UEDVT is contrast venography which is an invasive test, requiring the use of ionizing radiation. Ultrasonography has several potential advantages such as being non-invasive, it can be repeated easily, and allows the evaluation of the deep as well as the superficial venous system. While in many hospitals ultrasonography has in fact replaced venography for clinically suspected UEDVT, the diagnostic accuracy of ultrasonography is still unclear, as confirmed in a recent systematic review in a total of 346 patients (11).

Correctly confirming the presence of UEDVT is important in view of the risk of pulmonary embolism, prevention of the post-thrombotic syndrome, as well as avoiding unnecessary exposure to anticoagulants. At present, a diagnostic algorithm combining clinical probability assessment, D-dimer testing and ultrasonography is widely used and well validated in suspected DVT of the leg (4,12). Of all patients presenting with suspected UEDVT, the diagnosis can be confirmed in approx. 30% (13). Therefore, effective and simple tools for confirming or refuting the diagnosis are needed.

Recently, Constans and colleagues developed and validated a clinical decision score based on four items (Table 1). When dividing the patients into low, medium and high clinical probability, they reported an incidence of UEDVT of 12%, 20% and 70%, respectively (13). In patients with suspected UEDVT, D-dimer measurement has only been tested in a series of 52 consecutive patients (14).

A combined diagnostic algorithm would be clinically attractive. In the present study we therefore prospectively evaluated the safety and feasibility of an algorithm using the Constans’ clinical decision score, followed by D-dimer and if indicated compression ultrasonography. Furthermore, we assessed the prevalence of deep and superficial vein thrombosis in these patients presenting with suspected UEDVT.

METHODS

Patients

In- and -outpatients with suspected UEDVT were potentially eligible for this study. Patients were recruited between January 2010 and June 2012 in 16 different hospitals in six European countries and the United States. Pre-defined exclusion criteria were: use of anticoagulants in therapeutic dosages longer than 24 hours before inclusion, prior UEDVT in the same arm, a life
expectancy of less than three months, hemodynamic instability, age younger than 18 years and previous participation in the study. The institutional review boards of all hospitals approved the study protocol and written informed consent was obtained from all participants.

**Study design and outcome measures**

This was a prospective management study evaluating a new diagnostic algorithm for clinically suspected UEDVT. The algorithm consisted of the sequential application of the Constans’ clinical decision score (Table 1), D-dimer testing, ultrasonography, and if indicated repeated ultrasonography (Figure 1). All patients were followed up for three months to document the occurrence of symptomatic UEDVT or pulmonary embolism. In addition, patients were instructed to contact the general practitioner or the emergency department in case of worsening complaints. In case of death during follow-up the cause of death was ascertained if available by autopsy, otherwise by interviewing the treating physician. All suspected events were adjudicated by an independent committee whose members were unaware of the patient’s allocation within the diagnostic algorithm.

<table>
<thead>
<tr>
<th>Item</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous material present (central venous catheter or pacemaker thread)</td>
<td>1</td>
</tr>
<tr>
<td>Localized pain</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral edema</td>
<td>1</td>
</tr>
<tr>
<td>Other diagnosis at least as plausible</td>
<td>-1</td>
</tr>
<tr>
<td>Probability for UEDVT</td>
<td></td>
</tr>
<tr>
<td>If ≤ 1 : unlikely</td>
<td></td>
</tr>
<tr>
<td>If ≥ 2: likely</td>
<td></td>
</tr>
</tbody>
</table>

The primary outcome was the cumulative three-month incidence of objectively confirmed symptomatic UEDVT and pulmonary embolism in patients with an initial work-up excluding deep and superficial vein thrombosis of the upper extremity. Pulmonary embolism was defined as a (new) intraluminal filling defect in subsegmental or more proximal branches on spiral CT scan, or as a new intraluminal filling defect or an extension of an existing defect more than 2.5 mm in diameter on the pulmonary angiogram, or a new perfusion defect of at least 75% in a segment with normal ventilation on ventilation perfusion lung scintigraphy.

The main study question was to establish the safety of withholding anticoagulants in patients with a negative work-up based on the overall diagnostic strategy. Additionally, the safety of withholding anticoagulants was evaluated in the following subgroups of patients with suspected UEDVT:

1. patients with an unlikely score and normal D-dimer
2. patients with an unlikely score and a normal ultrasonography
3. patients with a likely score and a normal ultrasonography, or a likely score plus abnormal D-dimer and a normal repeated ultrasonography
Figure 1. Diagnostic flow-chart. DVT: deep vein thrombosis. SVT: superficial vein thrombosis.
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Clinical decision rule and D-dimer
First, physicians evaluated all patients by the clinical decision score of Constans and colleagues (13). We chose to dichotomize the score in a category ‘UEDVT unlikely’ with a score of one or less, and ‘UEDVT likely’ with a score of two or three, thereby taking the low and intermediate probability groups together. This dichotomization simplified the diagnostic algorithm, whereas it allows the classification of about 50% of the patients in the unlikely category, similar to the proportion of suspected leg DVT patients with an unlikely Wells’ score (15).

In patients with an unlikely score, D-dimer was measured using the locally available D-dimer method, which could be either a quantitative latex assay or an ELISA method. In patients with an unlikely score and a normal D-dimer, ultrasonography was not performed and anticoagulant treatment was withheld (Figure 1). Patients with a likely score or an unlikely score in combination with an abnormal D-dimer underwent ultrasonography.

Ultrasoundography
All examinations were performed by skilled ultrasonographers. UEDVT was confirmed in case of non-compressibility or evidence of thrombus material within the brachial, axillary, subclavian, brachiocephalic or internal jugular vein. In the absence of thrombus in the deep veins, the examination was extended to the superficial vein system. Superficial venous thrombosis (SVT) was confirmed in presence of non-compressibility of the cephalic, basilic, median antebrachial, median antecubital or accessory cephalic veins.

In case of technical problems or anatomical barriers that hampered appropriate visualization of (part of) the deep veins, the ultrasound result was considered indeterminate and repeated after three to five days. If again indeterminate, venography or CT-venography was mandatory. In case of a good interpretable ultrasound result without evidence of UEDVT or SVT in a patient with an abnormal D-dimer and likely score, the ultrasonography was repeated after three to five days.

Statistical analysis
A failure was defined as symptomatic and objectively confirmed UEDVT or pulmonary embolism within three months, after the initial work-up had excluded the presence of deep and superficial vein thrombosis. The failure rate of the diagnostic algorithm with its two-sided 95% confidence intervals (CI) was calculated (16). The upper limit of the 95% CI was set at a maximum of 3%, which is a commonly accepted margin to conclude about the safety of a diagnostic strategy (17). With an anticipated failure rate of 1%, it was calculated that a sample size of 400 patients would have allowed to detect a difference between the null hypothesis of 3% failures and the alternative proportion of 1% failures with a power of 90% and a significance level of 5%. We calculated failure rates and 95% CI’s also for parts of the strategy. Descriptive parameters were calculated using SPSS software, version 16 (SPSS Inc., Chicago, Ill). The T-test was used for comparisons if appropriate and the border for
statistical significance was set at $P < 0.05$. This study was registered in the international trial register of clinical trials.gov (NCT01324037).

**Funding**
No external funding sources were involved in this study.

## RESULTS

### Study patients
A total of 460 patients with suspected UEDVT were eligible, of whom 22 patients refused informed consent and 32 patients were excluded because of pre-defined exclusion criteria, including anticoagulant treatment for more than 24 hours (16 patients), previous UEDVT (6 patients) and a life-expectancy of less than 3 months (6 patients). Therefore, the study population consisted of 406 patients (Table 2).

**Excluding UEDVT based on an unlikely score, combined with a normal D-dimer or a normal ultrasound**
Of the 406 patients included 203 (50%) had a clinical decision score indicating UEDVT unlikely and therefore D-dimer was measured (Figure 2). This was omitted in three patients who underwent compression ultrasonography right away, constituting a protocol violation. One of these patients had UEDVT and the other two had no thrombosis.

A normal D-dimer test was found in 87 of the remaining 200 patients, and in these patients anticoagulants were withheld without further testing, except for five patients in whom ultrasonography was performed and showed no thrombosis. Hence, in 21% (95% CI 17–25%) of all patients the diagnosis UEDVT could be excluded without ultrasonography.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>56</td>
<td>(17)</td>
</tr>
<tr>
<td>Male sex</td>
<td>182</td>
<td>(45)</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>384</td>
<td>(95)</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>141</td>
<td>(35)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>24</td>
<td>(5.9)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>137</td>
<td>(34)</td>
</tr>
<tr>
<td>Confirmed pulmonary embolism*</td>
<td>2</td>
<td>(0.5)</td>
</tr>
<tr>
<td><strong>Referral by:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient ward</td>
<td>83</td>
<td>(20%)</td>
</tr>
<tr>
<td>Emergency room</td>
<td>130</td>
<td>(32%)</td>
</tr>
<tr>
<td>General physician</td>
<td>95</td>
<td>(23%)</td>
</tr>
<tr>
<td>Outpatient ward</td>
<td>77</td>
<td>(19%)</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>(4.8%)</td>
</tr>
</tbody>
</table>

* Simultaneous with UEDVT
Figure 2. Results of the diagnostic work-up. DVT: deep vein thrombosis. SVT: superficial vein thrombosis. ND: not done (outcomes are given in the results section). * One patient had two indeterminate ultrasounds and needed venography, which was negative.
None of these patients developed symptomatic venous thromboembolism (failure rate 0.0%; 95% CI 0.0–4.2%).

Of the 203 patients with an unlikely score, 113 had an abnormal D-dimer test result (56%) and underwent ultrasonography, except one patient who died of a rapidly progressive malignant disease. UEDVT was diagnosed in 12 patients, SVT in 25 patients, while thrombosis (deep and superficial) was excluded in the remaining 73 patients. The ultrasound was inconclusive in two other patients, and a repeated test after three to five days showed no thrombosis. Therefore, UEDVT and SVT were excluded by ultrasonography in 75 patients with an unlikely score of whom none received anticoagulant treatment. In the three months of follow-up, one patient returned after two months with persisting complaints of the arm, and compression ultrasonography revealed UEDVT. Therefore, the failure rate of this part of the algorithm was 1.3% (one out of 75; 95% CI 0.0–7.2%).

Two of the 203 patients died during follow-up, one patient had a documented myocardial infarction and the other patient died of progressive cancer without a suspicion of pulmonary embolism.

Excluding UEDVT based on a likely score with a normal (repeated) ultrasound
All 203 patients with a likely score underwent compression ultrasonography, which showed UEDVT in 86 patients (42%), SVT in 29 patients (14%), no thrombosis in 83 patients (41%) and was indeterminate in five patients (2.5%). In 77 of the 83 patients without thrombosis, D-dimer was measured to assess the need for repeated ultrasonography. In six patients, D-dimer testing was not performed, whereas in two of them the ultrasonography was repeated, as if the D-dimer would have been high, and showed no thrombosis. All six patients were followed up. Of the 77 patients with a normal ultrasound and an available D-dimer test result, the D-dimer was normal in 26 patients, after which UEDVT and SVT were considered excluded. The 51 patients with an abnormal D-dimer had an indication for repeated ultrasonography, which was done in 45 patients and revealed UEDVT in three of them, whereas in the other 42 patients UEDVT/SVT was excluded. In six patients, the ultrasound was not repeated while indicated, because of a clear improvement in clinical symptoms (five patients) and a rapid deterioration in the clinical situation due to advanced cancer (one patient).

Finally, in five patients the first ultrasonography was inconclusive. Upon repeated ultrasonography, one patient had UEDVT, three patients had no UEDVT, while in the remaining patient ultrasonography remained inconclusive. Subsequent venography excluded thrombosis in this case.

To summarize, in a total of 84 patients with a likely score, UEDVT and SVT were excluded by either (repeated) ultrasonography or in combination with a normal D-dimer, including the 12 patients with protocol violations. None of these patients received anticoagulants and none returned with recurrent symptoms. Hence, the failure rate was 0% (95% CI 0.0–4.3%). In this group of patients with a likely score, five patients died during follow-up, all had known cancer and died of disease progression, without evidence for pulmonary embolism.
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Feasibility and overall safety of excluding UEDVT and SVT

The diagnostic algorithm was feasible and completed in 390 of the 406 patients (96%). Taken together, the diagnostic algorithm ruled out UEDVT and SVT in 249 of the 406 patients (61%; 95% CI 57-66%). One patient returned to the hospital with documented recurrent VTE, hence, the overall safety of this approach revealed a failure rate of 0.40% (95% CI 0.0-2.2%). In all patients in whom the diagnostic procedures were not completed according to protocol, the follow-up was uneventful.

Confirmed deep or superficial vein thrombosis of the arm

In a total of 103 patients the diagnosis UEDVT was established (prevalence 25%; 95% CI 21-30%) with thrombosis involving the following veins: subclavian (n=76), axillary (n=59), brachial (n=36), internal jugular (n=23) and the brachiocephalic vein (n=10). In the patients with an unlikely probability, the prevalence of UEDVT was 6.4% (13/203), compared to 44% (90/203) in the patients with a likely probability.

In another 54 patients isolated SVT was diagnosed (prevalence 13%, 95% CI 10-17) in the following veins: cephalic (n=38), basilic (n=12), median antebrachial (n=11), median antecubital (four patients) and the accessory cephalic veins (three patients). The majority of these patients were treated with anticoagulants (41/54; 76%) for a planned median duration of one month (range: one week-12 months). None of these patients with SVT developed UEDVT during follow-up (0%; 0.0-6.6%).

| DISCUSSION |

This study demonstrates that a non-invasive diagnostic algorithm combining the Constans’ clinical score, D-dimer and ultrasonography is safe in excluding UEDVT and SVT, and feasible in 96% of patients. In this population of patients presenting with clinically suspected UEDVT the prevalence of UEDVT (25%) and SVT (13%) was appreciable, making a comprehensive diagnostic work-up desirable. The failure rate of 0.40% with an upper confidence interval of 2.2% compares favorably with similar strategies used for excluding DVT of the leg. When confirmed by other studies, this algorithm could become the standard diagnostic approach for patients with suspected UEDVT.

Several aspects of the design and findings of the present study require comment. First, we assessed the clinical probability of UEDVT using the score developed by Constans and colleagues (13) and dichotomized this score to improve its applicability. Although the incidence of UEDVT in the likely group was somewhat lower than the initially reported incidence of 70% in the high probability group, the discriminative ability of the score remained good, with an incidence of UEDVT of 6.4% in the unlikely versus 44% in the likely probability group.

Second, D-dimer levels were measured locally, and both ELISA and quantitative latex assays, which have shown similar accuracy for clinically suspected DVT, were allowed (18).
The local cut-off values of the D-dimer tests were used as already validated in patients with suspected DVT of the leg and pulmonary embolism. A normal D-dimer together with an unlikely score was able to exclude UEDVT and SVT in 21% of all patients, which saves time and imaging costs.

Third, we anticipated a relatively high frequency of indeterminate ultrasonography study results, as the position of the clavicle might hamper proper imaging. However, the ultrasonography was indeterminate in only seven of 406 patients (1.7%). In six of them a repeated ultrasonography three to five days later completed the diagnostic evaluation, while a single patient required contrast venography. The ultrasonography needed to be repeated in 51 patients with a likely score, an abnormal D-dimer and a normal first ultrasonography, i.e. 13% of all patients, which clearly adds to the complexity of the diagnostic work-up. However, this turned out to be an essential part of the algorithm, since if abolished, three UEDVTs would have been missed. Of note, our imaging protocol dictated first the assessment of the deep veins and then the superficial veins. The evaluation of the upper extremity superficial vein system is simple, requires little extra time and it proved to be clinically relevant since SVT was found in 13% of all patients.

Fourth, the diagnostic algorithm was not followed in 4% of the cases, a rate that is comparable to similar management studies (5). The three month follow-up was uneventful in all these patients except one who died a few days later as a result of rapid cancer progression. Strengths of this study are the completeness of the follow-up and the central adjudication of the suspected outcomes.

Although this study was not powered to show the safety of the various sub-strategies to exclude UEDVT and SVT (Constans’ score and D-dimer alone or Constans’ score, D-dimer plus (repeated) ultrasonography), the safety findings in these sub-strategies seemed consistent with the overall safety outcome.

Finally, the incidence of UEDVT in this cohort is comparable to other published series. We included both inpatients and outpatients of whom 34% had cancer and venous catheters were present in 35%. As there was no signal that the strategy performed better or worse in one of these subgroups, we believe that the algorithm is applicable to a wide spectrum of patients presenting with suspected UEDVT.

In conclusion, a diagnostic management strategy using the Constans’ clinical score, D-dimer testing and (repeated) ultrasonography, can safely and effectively exclude deep and superficial vein thrombosis in patients presenting with suspected UEDVT. This approach is attractive as it is simple, quick, non-invasive and very similar to the well established algorithm for suspected DVT of the leg which could facilitate its implementation in clinical practice.


