

REGULAR ARTICLE

# Clinical probability assessment and D-dimer determination in patients with suspected deep vein thrombosis, a prospective multicenter management study

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## KEYWORDS

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## Abstract

**Objectives:** To investigate the reliability of a combined strategy of clinical assessment score followed by a local D-dimer test to exclude deep vein thrombosis. For comparison D-dimer was analysed post hoc and batchwise at a coagulation laboratory. **Design:** Prospective multicenter management study. **Setting:** Seven hospitals in southern Sweden. **Subjects:** 357 patients with a suspected first episode of deep vein thrombosis (DVT) were prospectively recruited and pre-test probability score (Wells score) was estimated by the emergency physician. If categorized as low pre-test probability, D-dimer was analysed and if negative, DVT was considered to be ruled out. The primary outcome was recurrent venous thromboembolism (VTE) during 3 months of follow up. **Results:** Prevalence of DVT was 23.5% (84/357). A low pre-test probability and a negative D-dimer result at inclusion was found in 31% (110/357) of the patients of whom one (0.9%, [95% CI 0.02—4.96]) had a VTE at follow up. Sensitivity, specificity, negative predictive value and negative likelihood ratio for our local D-dimer test in the low probability group were 85.7%, 74.5%, 98.2%, and 0.19 respectively compared to 85.6%, 67.6%, 97.9% and 0.23 using batchwise analysis at a coagulation laboratory. **Conclusion:** Pre-test probability score and D-dimer safely rule out DVT in about 30% of

outpatients with a suspected first episode of DVT. One out of 110 patients was

## Introduction

Although patients with suspected deep vein thrombosis are common in hospital emergency departments, relatively few actually have deep vein thrombosis (DVT) [1,2]. In recent years, new diagnostic methods involving assessment of clinical probability and the use of D-dimer analysis have proven safe and have simplified the diagnostic strategy of these patients [3,4]. Recent studies have shown that low clinical probability and a negative D-dimer result exclude DVT in 30–50% of outpatients with suspected deep vein thrombosis and safely obviate the need for further diagnostic testing [5,6].

According to Bayes' theorem the probability that a patient has the disease following diagnostic testing is determined by the estimated probability prior to the test (pretest probability) and the accuracy of the test [7]. In Scandinavia several studies indicate a higher prevalence (30–50%) of confirmed DVT in outpatients than observed in many other countries [8–10]. This would of course affect the PTP and increase the risk for false negative results and decrease the diagnostic exclusion rate. Furthermore, since D-dimer assays are not standardized and actually measure different products of the fibrin degradation the performance varies substantially between assays and populations [11,12]. Because of these limitations many clinicians hesitate to implement this diagnostic strategy.

The purpose of this study was to examine whether a combined strategy of a clinical assessment score done in the emergency ward followed by a local D-dimer test was safe for the patients in a clinical setting where the prevalence of DVT in outpatients was high. We also wanted to address the question of whether D-dimer methods used locally were as reliable as the same method used in batch analysis under optimal circumstances with reduced variability from inter-assay differences.

## Methods

### Study design and patients

This study was performed between December 2003 and December 2005. Adult patients with a suspected first episode of DVT were potentially eligible for inclusion. Seven centres in southern Sweden, serving approximately 1 million residents, participated in the study. A total of 491 outpatients were consecutively evaluated for the study over the 2-year recruitment period. Patients were either self-referred, referred from primary care physicians or to a lesser extent sent in from other clinics. The patients were enrolled immediately on their arrival to the emergency dept. Enrollment was possible 24 h/day, 7 d/week. One hundred and seven patients were excluded due to one of the following exclusion criteria: previous VTE (n = 54), duration of symptoms > 10 days (n = 37), inability or unwillingness to provide informed consent (n = 9), symptoms suspicious for pulmonary embolism (n = 3), pregnancy (n = 1), ongoing anticoagulation (n = 1), contraindication to contrast media (n = 1) and co morbid condition likely to shorten survival to less than 3 months (n = 1). Another 27 patients were excluded due to inadequate or missing case report forms, written informed consent or lost blood samples. Site-specific investigators (see acknowledgement) were responsible for collecting data on each site and the central database was compiled by the authors of this paper.

The regional center research ethics board in Lund approved the study, and all patients provided written informed consent before enrollment.

All patients were evaluated by the emergency physician on duty, who was briefly introduced to the Wells score. Pre-test probability for DVT according to Wells' nine item score [3] was determined (Table 1). Patients were categorized as having low, intermediate or high pre-test probability. Patients with a low pretest probability underwent immediate, local, D-dimer testing. Patients with low clinical probability and negative result on the D-dimer test had no further diagnostic testing for DVT and received no anticoagulant therapy. These patients were followed for VTE events and were either contacted by telephone or seen at an outpatient clinic after 3 months. Patients who couldn't be reached by telephone or didn't return to the outpatient clinic, were checked for VTE events in the medical charts and diagnostic imaging databases at each local hospital. Patients who presented again with symptoms consistent with DVT or pulmonary embolism underwent objective testing with contrast venography and / or compression ultrasonography (CUS) of the leg and ventilation/perfusion scintigraphy and / or computed tomography of the lungs respectively.

**Table 1** Pretest clinical probability (Wells' score)

Pretest clinical probability, (Wells' score) (1)	
-Active cancer	1
-Paresis, paralysis or recent plaster or immobilization of lower limb	1
-Bedridden > 3 days or major surgery < 4 weeks	1
-Localized tenderness	1
-Entire leg swollen	1
-Calf swelling > 3 cm compared with asymptomatic leg	1
-Pitting oedema	1
-Collateral superficial veins	1
-Alternative diagnosis as likely or greater than DVT	-2

Simplified clinical model for assessment of DVT.

*High probability:* 3 or more points.

*Intermediate probability:* 1–2 points.

*Low probability:* 0 or less points.

Patients with intermediate / high clinical probability or positive D-dimer test were further investigated with contrast venography and / or CUS. DVT was diagnosed if an intraluminal filling defect was present in two views or if noncompressibility was present in the common femoral, superficial femoral or popliteal vein respectively. If the CUS was negative, further evaluation with comprehensive ultrasound (including calf veins) or contrast venography was performed.

For D-dimer analysis, venous blood was collected in 5 ml vacuum tubes (Becton-Dickinson, Franklin Lakes, USA) containing sodium-citrate (3.8%), and centrifuged at 3600 ×g for 10 minutes at 4 °C within 30 minutes of collection. The plasma was aliquoted and one aliquot was used for the local D-dimer analysis. The others were frozen at -70 °C for later analysis in batch with Auto Dimer® (Biopool® International Umeå, Sweden) on the BCS™ Coagulation Analyser (Dade-Behring, Marburg, Germany). The cut off value used for the post-hoc batch analyses, was set to

0.25 mg L<sup>-1</sup>, according to manufacturers' recommendation.

The local D-dimer tests used were Auto Dimer® in 92% of the patients, measured on Thrombolyser™ Compact XR (Behnk Electronic, Norderstedt, Germany) or Sysmex CA 1500 and 7000 coagulation analysers (Dade-Behring, Marburg, Germany), Nycocard® D-Dimer assay (Axis-Shield PoC AS, Oslo, Norway) with the Nycocard® READER was used in 6% and, STA-LIA® D-dimer in 2%, measured on STA-R®, Diagnostica Stago, Asnieres, France). All tests were performed according to manufacturers' instructions. Lab personnel performing the D-dimer assay were not aware of the patients pre-test probability assessment.

## Statistical methods

Our primary outcome was the proportion of patients who had a venous thromboembolic event during 3-month follow-up among those for whom the diagnosis of DVT had been excluded by a low clinical probability and a negative D-dimer test. On the basis of previous studies in Scandinavia showing prevalence rates of DVT ranging from about 30–50% in outpatients with suspected DVT [8– 10] , we estimated that approximately 40% of the patients would be categorized as having low pre-test probability and that the prevalence of DVT in this group would be about 10%. The generally accepted requirement for safely ruling out DVT and withholding anticoagulant therapy is a false negative rate of less than 2% during follow up which is achieved by a negative contrast venography or a comprehensive compression ultrasonography [13,14] . Based on the sensitivity and specificity of the Autodimer, 85% and 46% respectively [15,16] , we estimated that the Auto Dimer® assay would have a negative predictive value of at least 98% in the low probability group. We calculated that the sample size needed to reach a power of 80% (2.5% risk level, one-sided test for the lower boundary of a CI of 95%, reaching a NPV of 95%) was 140 patients in the low probability, negative D-dimer cohort. The 2-sided 95% CI was calculated by using the exact method for obtaining the confidence interval for a binominal proportion except for likelihood ratios (LR) where calculations were based on a method described by Bolboaca et al. [17] .

## Results

Three hundred and fifty-seven patients were considered eligible and entered the study. The prevalence of DVT (final diagnosis) was 23.5% (84/357) of which 52 (63%) were considered proximal DVTs (proximal thrombosis if the thrombus was located in the popliteal or more proximal veins). The median age was 62 years and 138 (39%) were men. Other patient characteristics are shown in Table 2 . Of the 357 patients entering the study, 159 (45%) were categorized as having a low, 141 (39%) intermediate, and 57 (16%) as having a high pre-test probability for DVT.

### Low probability cohort

Of the 159 patients with low probability, 110 (69%) had a negative D-dimer and were not targeted to go through further diagnostic testing for DVT. In this category however, 11 patients underwent diagnostic imaging (venography (n =4), CUS (n =6) or both (n =1)) based on the physicians clinical judgement, overriding the low probability of the Wells' score or, when ultrasonography was used, because suspicion of differential diagnoses to DVT, and where the ultrasound examiner investigated the veins as well. One of these patients was diagnosed with a distal DVT (CUS). This patient was considered as “missed” DVT in the outcome analysis. In one patient with positive D-dimer, DVT was ruled out by clinical judgement. Over the 3 month follow up period, 1 patient (0.9%, [95% CI, 0.02— 4.96%]) subsequently developed distal DVT confirmed by venography on day 9 after initial presentation. This patient was at inclusion diagnosed for superficial thrombophlebitis and had a recent history of a long distance flight, she was initially sent home with elastic stockings and Hirudoid® ointment. Five patients returned and underwent diagnostic testing for VTE during follow up, (CUS (n =1), venography (n =3), V/P-scintigraphy (n =1)). In all these patients VTE was ruled out and anticoagulant treatment was withheld. Two patients were admitted to the hospital due to acute coronary syndrome and received low molecular heparin (enoxaparin 1 mg/kg b.i.d) for 1 and 3 days respectively and one patient received warfarin treatment from day 53. These patients were not excluded. No patient was lost to follow up. Fig. 1 , flowchart.

**Table 2** Demographic data, results of categorization of patients according to the pretest clinical probability score and of D-dimer testing

	All patients (n=357)	Patients with DVT (n=84)	Patients without DVT (n=273)	p-values *
Low probability	159 (45%)	14 (17%)	145 (53%)	<0.001
Intermediate	141 (39%)	37 (44%)	104 (38%)	0.28
High probability	57 (16%)	33 (39%)	24 (9%)	<0.001
Age (median)	62 (33, 82) **	67 (32, 83)	60 (33, 81)	0.62
Men	138 (39%)	34 (40%)	104 (38%)	0.72
Heredity	62 (17%)	16 (19%)	46 (17%)	0.48
Smoking	66 (18%)	12 (14%)	54 (20%)	0.46
BMI	26 (21,33) ** (n=188)	26 (20, 33) (n=62)	26 (22, 33) (n=126)	0.52
D-dimer local (neg)	110 (31%)	2 (2%)	125 (46%)	<0.001
D-dimer batch (mg/L)	0.26 (0.06, 1.88) ** (n=350)	1.40 (0.31, 6.92) (n=80)	0.18 (0.05, 0.64) (n=270)	<0.001

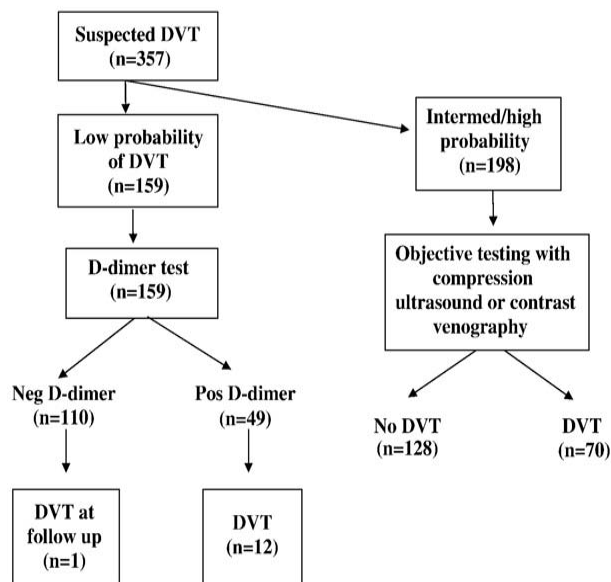
\* Mann-Whitney U test was used for comparison between patients with and without DVT. Chi-squared test was used for nominal variables.

\*\* Median (10th, 90th percentiles).

In patients categorized as having low clinical probability our local D-dimer methods had a sensitivity and specificity of 85.7% (95% CI, 57 to 98%) and 74.4% (95% CI, 67 to 81%) respectively with a negative predictive value of 98.2% (95% CI, 94 to 100%) and a negative likelihood ratio (LR-) of 0.19 (95% CI, 0.06 to 0.67). This gives an exclusion rate of about 30%. Post-hoc batch analysis with the Auto Dimer® gives a sensitivity, specificity, negative predictive value and LR-of 84.6% (95% CI, 55 to 98%), 67.6% (95% CI, 59 to 75%), 97.9% (95% CI, 93 to 100%) and 0.23 (95% CI, 0.07 to 0.79) respectively. The concordance between the local D-dimer assay and the batch was 89% with a kappa value (κ) of κ =0.76.

### Intermediate/high probability cohort

The prevalence of DVT was 26% in the intermediate and 58% in the high probability group. The frequency of negative D-dimer (post-hoc batch analysis) was 44% and 14% respectively giving a sensitivity, specificity, NPV and PPV of 94.1% (95% CI, 86 to 98%), 51.9% (95% CI, 43 to 61%), 94.3% (95% CI, 86 to 98%) and 51.2% (95% CI, 42 to 60%). Contrast venography was the main diagnostic method used in this cohort (78% of the patients) and in 10% of the patients both CUS and venography was performed. Two patients in the intermediate group were not examined with CUS / venography, DVT was ruled out by clinical judgement of the responsible physician. One patient in the intermediate group was diagnosed as having DVT although venography was considered normal.



## Discussion

Assessment of clinical pre-probability scores and the use of D-dimer testing has simplified the diagnostic strategies for DVT and reduced the need for diagnostic imaging. Implementing these strategies into the diagnostic workup lowers costs [18], reduces inconvenience for the patients and is timesaving for both staff and patients at the emergency departments.

In this study we demonstrate that anticoagulation therapy can be safely withheld in almost 1/3 of outpatients with suspected DVT by using a non-invasive diagnostic strategy including clinical assessment and D-dimer. The safety of this approach was demonstrated, since only one of 110 patients who had DVT ruled out at inclusion was diagnosed with a DVT (distal). However, due to the limited sample size, the upper limit of the 95% CI reached 4.96%.

To our knowledge no other published prospective management study has used a combination of a moderate sensitive D-dimer [11] and clinical probability assessment to rule out DVT without objective imaging testing, in a clinical setting with a high prevalence of DVT and where the assessment was made by physicians with relatively low clinical experience, including many junior residents.

In the low probability cohort, comparison between locally used D-dimer assays (mainly Auto Dimer®, 92%) and post-hoc batch analysis with the Auto Dimer® method demonstrates an acceptable 89% concordance. The observed difference can probably be explained by the fact that in 8% of the patients a different D-dimer assay was used, analyses were made on different coagulation instruments and reagent batches.

The present study has strengths and limitations. Identification and inclusion of patients was done entirely by the physician at the emergency unit. This could have affected the inclusion rate of patients with intermediate/high clinical probability, since including these patients into the study would slow down the diagnostic workup. This would explain why the prevalence of DVT in the study population was lower than expected. The fact that the physicians chose to refer eleven of the patients in the low probability-negative D-dimer group to diagnostic imaging and in one of these patients a distal DVT was revealed, is worth considering, but consistent with other studies which indicate that the sensitivity of the D-dimer test is lower for distal thrombosis [10]. Indeed the good outcome in the present and other recent management studies probably indicate that a negative D-dimer test does not exclude all distal DVTs, but excludes DVT that require treatment. We also believe that this is a strength of this study, showing that the strategy was used in the daily clinical practice, leaving open the possibility to override the clinical prediction score and use empirical clinical judgment, a better approach than strict adherence to the diagnostic algorithm [19].

The decision to stop inclusion before we reached the calculated 140 patients (low probability, negative D-dimer) needed to reach a power of 80% was mainly based on the fact that the inclusion rate successively decreased during the study as the diagnostic algorithm studied became implemented as clinical routine, probably a result of the guidelines from the Swedish National Board of Health and Welfare on diagnosis of VTE established in 2004. Continued inclusion of patients at this low rate would have increased the risk for inclusion bias.

The effect of clinical experience on the predictive power of the Wells' score in the diagnosis of DVT is a matter of debate [19,20]. In our study, the diagnostic strategy was handled by physicians only briefly introduced to the Wells clinical assessment score. No specialized research staff or vascular experts were involved in the diagnostic workup of these patients. In spite of this only one out of 110 patients was diagnosed with a DVT during follow-up. These results are comparable with the results from other clinical management trials [5,21] here in a routine emergency setting.

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