

Papers

Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review

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Abstract

Objective To summarise the evidence supporting the use of rapid D-dimer testing combined with estimation of clinical probability to exclude the diagnosis of deep venous thrombosis among outpatients.

Data sources Medline (June 1993 to December 2003), the Database of Abstracts and Reviews (DARE), and reference lists of studies in English.

Selection of studies We selected 12 studies from among 84 reviewed. The selected studies included more than 5000 patients and used a rapid D-dimer assay and explicit criteria to classify cases as having low, intermediate, or high clinical probability of deep vein thrombosis of the lower extremity among consecutive outpatients.

Review methods Diagnosis required objective confirmation, and untreated patients had to have at least three months of follow up. The outcome was objectively documented venous thromboembolism. Two authors independently abstracted data by using a data collection form.

Results When the less sensitive SimpliRED D-dimer assay was used the three month incidence of venous thromboembolism was 0.5% (95% confidence interval 0.07% to 1.1%) among patients with a low clinical probability of deep vein thrombosis and normal D-dimer concentrations. When a highly sensitive D-dimer assay was used, the three month incidence of venous thromboembolism was 0.4% (0.04% to 1.1%) among outpatients with low or moderate clinical probability of deep vein thrombosis and a normal D-dimer concentration.

Conclusions The combination of low clinical probability for deep vein thrombosis and a normal result from the SimpliRED D-dimer test safely excludes a diagnosis of acute venous thrombosis. A normal result from a highly sensitive D-dimer test effectively rules out deep vein thrombosis among patients classified as having either low or moderate clinical probability of deep vein thrombosis.

Introduction

Deep vein thrombosis is a common condition that often presents a diagnostic challenge to clinicians. Seventy five per cent of outpatients who present with signs and symptoms suggestive of deep vein thrombosis do not have the disease.^{1 2} Most clinics and emergency facilities rely on venous ultrasound imaging as the initial diagnostic test of choice.³

One way to improve care and at the same time reduce the burden of ultrasound testing is to use a combination of two sim-

ple tests that, when combined, accurately exclude deep vein thrombosis. This use of two independent tests, each of which has high negative predictive value for a disease, is extremely useful in ruling out disease.⁴ Researchers into venous thrombosis now use this approach, combining D-dimer testing with estimation of the clinical probability of deep vein thrombosis.

D-dimer is one of the fibrin degradation products generated during fibrinolysis. D-dimer concentrations are raised in the setting of acute deep vein thrombosis,⁵ and normal concentrations are expected in the absence of acute venous thrombosis unless other, coexistent conditions that activate the coagulation system are present.⁶⁻⁹ Newer, less sensitive, whole blood, qualitative agglutination assays, particularly the SimpliRED D-dimer test (Agen Biomedical, Brisbane, Australia), and more highly sensitive, quantitative, enzyme linked immunosorbent assays (ELISAs) are sufficiently rapid for use in outpatients.^{10 11}

Two clinical probability tools to estimate the probability of venous thrombosis are widely used. The first, developed by Wells et al,^{2 12} uses a structured assessment of explicit historical and physical examination criteria (box) to stratify patients into low, moderate, and high risk of deep vein thrombosis.

A second clinical probability tool, developed by Perrier et al,^{13 14} also stratifies patients into the same three rating categories by using semistructured, implicit criteria. When each of these tools was used, fewer than 3% of patients with low probability

Wells clinical probability tool

Wells explicit assessment

- Active cancer
- Paralysis, paresis or recent plaster, or immobilisation of lower limb
- Recently bedridden for more than three days or major surgery in the past four weeks or more
- Localised tenderness
- Entire leg swollen
- Calf swelling >3 cm compared with asymptomatic leg
- Pitting oedema
- Collateral superficial veins
- Alternative diagnosis as likely or greater than deep vein thrombosis

Each positive response is 1 point, except if an alternative diagnosis is as likely as or greater than DVT, where 2 points are deducted. 0 or fewer points: low probability; 1-2 points: moderate probability; 3 or more points: high probability.

and fewer than 19% of patients with moderate probability had a deep vein thrombosis.^{12 13} A modified version of the Wells tool, which collapses the three risk categories into two—deep vein thrombosis likely and deep vein thrombosis unlikely—has been developed recently.¹⁵

Two general approaches have been used to evaluate the combined use of rapid D-dimer testing and clinical probability estimates.⁵ Firstly, accuracy studies have been conducted in which all patients underwent complete testing, and the results of each test were compared with the accepted criterion standard.¹⁶ Secondly, management studies have been reported in which patients were initially stratified into a low risk group and higher risk groups, on the basis of the result of either the D-dimer test or the clinical probability tool, and only the patients at higher risk were tested further by using the criterion standard. In these studies, patients classified as at low risk were simply followed over time to determine the incidence of thromboembolism.

This systematic review focuses on clinical studies that have evaluated the use of rapid D-dimer testing in conjunction with assessment of clinical probability.¹⁷ The primary outcome measure was the incidence of objectively confirmed symptomatic deep vein thrombosis and pulmonary embolism among patients with a normal D-dimer test result, stratified by the level of clinical probability.

Methods

Study identification

We searched Medline and the Database of Abstracts and Reviews (DARE) to identify identified clinical studies and systematic reviews. We searched Medline for English language publications from 1 June 1993 to 31 December 2003, using the following combination of medical subject headings, text words, and publication types: (“venous thrombosis” or “thrombophlebitis”) and (“D dimer” or “fibrin” or “fibrinogen degradation” or “FDP” or “fibrinogen degradation products” or “fibrin fibrinogen degradation products”) and (“comparative study” or “algorithms” or “predictive value of tests” or “prospective study” or “follow-up study”). We also reviewed the reference lists of the articles selected for inclusion.

Study selection

Two authors independently reviewed the titles and abstracts of the references identified to determine suitability for inclusion. If disagreement arose all three authors conferred to reach consensus.

Our 10 inclusion criteria were: clinical study; use of a rapid D-dimer assay on at least a subgroup of cases; estimation of the risk of deep vein thrombosis by using a validated clinical probability tool which categorised patients into those at low risk, at moderate or intermediate risk, and at high risk for deep vein thrombosis; prospective study of consecutive outpatients presenting with features of deep vein thrombosis; evaluation of outpatient data separately if inpatients were included; evaluation of deep vein thrombosis data separately if patients with pulmonary embolism were included; follow up of all patients by telephone or record review for at least three months; objective documentation of deep vein thrombosis by using venous compression ultrasound, venography, or impedance plethysmography; presentation of data that allowed us to calculate the sensitivity and specificity of the D-dimer assay, stratified by the clinical probability level; and presentation of data that allowed us to calculate the prevalence of thrombosis for each probability level. We excluded editorials, letters, and reviews.

We designed the selection criteria to limit the analysis to well defined populations of patients who had similar clinical presentations and adequate follow up. We adapted the assessment of the trials’ quality from the Cochrane methods group on systematic review of screening and diagnostic tests.¹⁸

We included only studies that used rapid D-dimer assays capable of providing results in less than one hour. Diagnosis of deep vein thrombosis required a persistent intraluminal filling defect in the deep venous system of the calf or leg when using venography, absence of compressibility of a deep vein of the leg in the transverse plane when using compression ultrasound, or abnormal venous outflow when using impedance plethysmography.¹⁹

We judged that venous thromboembolism, which includes both deep vein thrombosis and pulmonary embolism, was present if there was objective documentation at the time of the initial examination or during the three month follow up period.

Analysts were not blinded to authors, institutions, or journal.²⁰ In venous thromboembolic disease, a small number of collaborations are responsible for most of the publications. Blinding may have affected our ability to detect duplicate publication adversely.

Data extraction

Two authors independently extracted the data. If disagreement arose all three authors conferred to reach consensus. We did not quantify whether analysts agreed on the selection of trials and extraction of data. When relevant data from a study were missing or unclear we attempted to contact the primary author.

Statistical analysis

We first stratified results by the testing strategy and then analysed them. We included studies that did not perform D-dimer testing among patients with high clinical probability in the accuracy studies as long as patients classified as having low or moderate probability had the full testing.

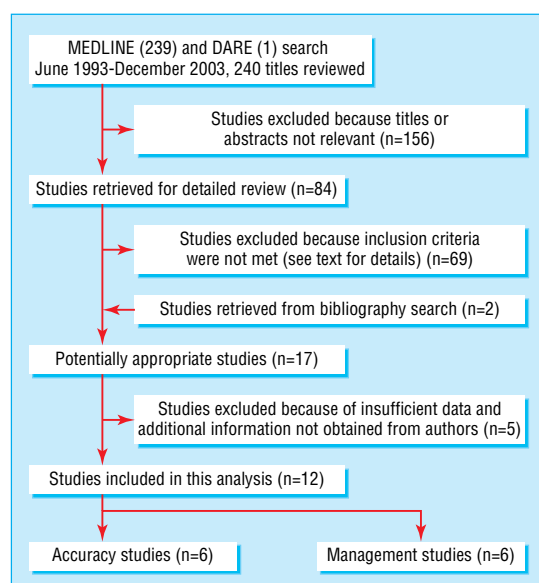
We calculated the three month cumulative incidence of deep vein thrombosis for all groups, along with the 95% confidence intervals.²¹ We then calculated the pooled incidence from a logistic meta-regression model, which included a random effect to allow for potential heterogeneity between studies.²² We calculated the pooled incidence for three groups: the accuracy studies, studies using the SimpliRED D-dimer assay, and studies using the highly sensitive D-dimer assay. We did not pool management studies because of the small number of studies contributing data in each clinical probability category. We used WinBUGS to estimate these models.²³

For pooling the accuracy studies, the model included indicator terms for clinical probability and the presence of prior deep vein thrombosis as variables at study level. The latter variable allowed us to calculate separate pooled estimates for studies including and excluding patients with prior deep vein thrombosis.

For pooling all studies using the SimpliRED D-dimer assay, the model included indicator terms for clinical probability and the presence of prior deep vein thrombosis as variables at study level. For pooling all studies using highly sensitive D-dimer assays, the model included an indicator term for high clinical probability as a variable at study level.

Characteristics of diagnostic test

We calculated pooled sensitivity, specificity, and negative likelihood ratios from a logistic meta-regression model that included an indicator term for use of the SimpliRED D-dimer



Selection process of studies for systematic review

assay and a random effect.²² We used WinBUGS to estimate the model.²³ The negative likelihood ratio was the probability that a patient will have a deep vein thrombosis and negative D-dimer test, divided by the probability that a patient without a deep vein thrombosis will have a negative D-dimer test. The lower the negative likelihood ratio, the better therefore the discriminative power of the D-dimer assay (a perfect test would have a negative likelihood ratio equal to negative infinity).²⁴

Results

Studies

We identified a total of 240 references. After review of titles and abstracts we retrieved 84 for detailed examination (figure). Sixty nine did not meet our inclusion criteria because they were letters, editorials, or reviews²⁵⁻³⁸; did not evaluate both a D-dimer assay and a clinical probability tool³⁹⁻⁷⁸; did not categorise patients into low risk, moderate or intermediate risk, and high risk for deep vein thrombosis¹⁵; were not prospective⁷⁹⁻⁸¹; included only inpatients or did not allow for separate analysis of outpatients⁸²⁻

83; included data that did not allow separate analysis of patients with a diagnosis of deep vein thrombosis and pulmonary embolism⁸⁹; or had follow up of less than three months' duration.⁹⁰⁻⁹²

We identified two additional studies from the reference list of the articles selected. Overall, 17 studies met our inclusion criteria; we subsequently excluded five because they contained insufficient data for analysis and attempts to contact the authors were unsuccessful.^{11 93-96} Ultimately we included 12 studies^{9 13 97-106} that had enrolled 5431 patients suspected of having deep vein thrombosis.

Accuracy studies

Six studies were accuracy studies (table 1).^{9 97-101} Two of these studies reported patients with low clinical probability only.^{97 98} Table 2 shows the results from the individual and pooled accuracy studies, stratified by clinical probability. Among the low clinical probability studies, those that included patients with prior history of deep vein thrombosis had higher rates of venous thromboembolism than those that excluded these patients (1.3% v 0.3%, $P=0.04$). We did not find this difference among the groups with moderate and high clinical probability ($P=0.5$ and $P=0.2$, respectively).

Management studies

Six studies were management studies (table 3).^{13 102-106} As table 4 shows, one management study used a highly sensitive D-dimer assay alone as the initial test,¹³ whereas the remaining studies combined clinical probability assessment with either a D-dimer assay or venous ultrasound. One study combined patients with low and moderate clinical probability into one group.¹⁰⁴ Results from the management studies were not pooled because the few available studies had small sample sizes, making synthesis unstable.

Tick et al first performed ultrasound testing on all patients, including those in the category of low clinical probability.¹⁰⁵ Patients with moderate or high clinical probability and a normal ultrasound result were then tested with the SimpliRED D-dimer assay. All 148 patients who had a normal D-dimer result remained disease free at three months (95% confidence interval 0.00% to 2.5%).

We analysed studies after pooling data based on the D-dimer assay used. As table 5 shows, among outpatients with a normal result from the SimpliRED D-dimer test and a low clinical prob-

Table 1 Cohort characteristics of accuracy studies

Study, year	Total No of cases	Total No of venous thromboembolism events (%)	Mean age (years)	Male sex (%)	D-dimer test*	Cut-off value	Reference standard	Laboratory technician blinded†	Radiologist blinded‡	Clinical probability tool§	Cases lost to follow up	Cases with prior deep vein thrombosis included
Bucek et al¶, 2002 ⁹⁷	93	2 (2.2*)	51	38	STA-LIA	0.5 µg/ml	Venous ultrasound	Unknown	Yes	Wells	10%	Yes (n=12)
Kraaijenhagen et al*, 2002 ⁹⁸	896	75 (0.8*)	60	37	SimpliRED	Any agglutination	Venous ultrasound	Unknown	Unknown	Wells	Unknown	Yes (10%)
Shields et al., 2002 ⁹⁹	102	17 (16.7)	50	52	SimpliRED	Any agglutination	Venous ultrasound	Unknown	Unknown	Wells	0	No
Anderson et al., 2000 ⁹	214	28 (13.1)	55	45	SimpliRED	Any agglutination	Venous ultrasound, venography	Yes	Unknown	Wells	3	No
Wells et al., 1998 ¹⁰⁰	496	83 (16.7)	56	Un-known	SimpliRED	Unknown	Venous ultrasound	Yes	Yes	Wells	Unknown	Unknown
Ginsberg et al., 1997 ¹⁰¹	398	68 (17.1)	61	35	SimpliRED	Any agglutination	Impedance plethysmography	Unknown	Yes	Wells	3	No

*STA-LIA (Diagnostica, Stago, France); SimpliRED (Agen Biomedical, Brisbane, Australia).

†Blinded to patient's clinical probability score and radiology result.

‡Blinded to patient's clinical probability score and D-dimer result.

§Wells et al., 1995². Wells et al., 1997¹².

¶Limited to low clinical probability only.

Table 2 Thromboembolic outcomes in accuracy studies

Potential testing schemes	Study, year	D-dimer test	No of patients (No of venous thromboembolism events)	Three month cumulative incidence of venous thromboembolism in% (95% CI)
Low clinical probability and a normal D-dimer result				
	Bucek et al., 2002 ⁹⁷	STA-LIA	48 (0)	0.0 (0 to 7.4)
	Kraaijenhagen et al., 2002 ⁹⁸	SimpliRED	561 (10)	1.8 (0.9 to 3.2)
	Shields et al., 2002 ⁹⁹	SimpliRED	32 (0)	0.0 (0.0 to 10.1)
	Wells et al., 1998 ¹⁰⁰	SimpliRED	206 (1)	0.5 (0.0 to 2.7)
	Ginsberg et al., 1997 ¹⁰¹	SimpliRED	178 (1)	0.6 (0.0 to 3.1)
	Anderson et al., 2000 ⁹	SimpliRED	97 (0)	0.0 (0.0 to 3.7)
Pooled*:				
	Included patients with history of deep vein thrombosis			1.3 (0.5 to 2.3)
	Excluded patients with history of deep vein thrombosis			0.3 (0.01 to 1.1)
Moderate clinical probability and a normal D-dimer result				
	Shields et al., 2002 ⁹⁹	SimpliRED	20 (0)	0.0 (0.0 to 16.8)
	Wells et al., 1998 ¹⁰⁰	SimpliRED	87 (3)	3.4 (0.7 to 9.8)
	Ginsberg et al., 1997 ¹⁰¹	SimpliRED	97 (3)	3.1 (0.6 to 8.8)
	Anderson et al., 2000 ⁹	SimpliRED	51 (3)	5.9 (1.2 to 16.2)
Pooled†				
				3.4 (1.3 to 6.9)
High probability and a normal D-dimer result				
	Shields et al., 2002 ⁹⁹	SimpliRED	7 (2)	29 (3.7 to 71.0)
	Wells et al., 1998 ¹⁰⁰	SimpliRED	7 (1)	14.3 (0.4 to 57.9)
	Ginsberg et al., 1997 ¹⁰¹	SimpliRED	5 (2)	40.0 (5.3 to 85.3)
	Anderson et al., 2000 ⁹	SimpliRED	15 (2)	13.3 (1.7 to 40.5)
Pooled†				
				21.0 (8.0 to 37.0)

*P value comparing studies that excluded and included patients with history of deep vein thrombosis was significant, P=0.04.
 †P value comparing studies that excluded and included patients with history of deep vein thrombosis were not significant (P=0.5 for moderate probability and P=0.3 for high probability).

ability of deep vein thrombosis, the three month incidence of venous thromboembolism was 0.5% (0.07% to 1.1%). Among outpatients with a normal result from a highly sensitive D-dimer test and low or moderate clinical probability of deep vein thrombosis, the three month incidence of venous thromboembolism was 0.4% (0.04% to 1.1%).

The estimated pooled sensitivity for the SimpliRED D-dimer assay was 87.5% (82.4% to 91.7%) and the specificity was 76.9% (65.4% to 86.2%), resulting in a negative likelihood ratio of 0.16. The estimated pooled sensitivity for the highly sensitive D-dimer assays was 97.7% (96.1% to 99.0%) and the specificity is 45.7% (28.0% to 66.6%), with a negative likelihood ratio of 0.05. The

differences in both the sensitivities and specificities were highly significant (P < 0.001 and P = 0.002, respectively).

Discussion

These findings provide strong evidence that the combination of low clinical probability for deep vein thrombosis, coupled with a normal SimpliRED D-dimer result, safely excludes a diagnosis of acute deep vein thrombosis, as the three month incidence was very low (0.5%). Because the SimpliRED D-dimer assay had a much lower sensitivity (about 88%) and thus lower negative predictive value than the highly sensitive ELISA and immunoturbidimetric assays,

Table 3 Cohort characteristics of management studies

Study, year	Total No of cases	Total venous thromboembolism events (%)	Mean age (years)	Male sex (%)	D-dimer test*	Cut-off value	Reference standard	Laboratory technician blinded†	Radiologist blinded‡	Clinical probability tool§	Total No of cases lost to follow up	Cases with prior deep vein thrombosis included
Bates et al., 2003 ¹⁰²	556	56 (10.1)	62	38	MDA	0.5 µg fibrin equivalent units/ml	Venous ultrasound	Yes	Unknown	Wells	0	No
Schutgens et al., 2003 ¹⁰⁴	812	317 (39.0)	Unknown	Unknown	Tinaquant	500 µg fibrin equivalent units/l	Venous ultrasound	Unknown	Unknown	Wells	15	No
Kearon et al., 2001 ¹⁰³	445	64 (14.4)	60	36	SimpliRED	Any agglutination	Venous ultrasound, impedance plethysmography, venography	Unknown	Unknown	Wells	Unknown	No
Perrier et al., 1999 ¹³	474	120 (25.3)	61	38	VIDAS	500 µg/l	Venous ultrasound, phlebography	Unknown	Yes	Implicit	4	Unknown
Tick et al., 2000 ¹⁰⁵	811	350 (43.2)	62	36	SimpliRED	Any agglutination	Venous ultrasound	Yes	Unknown	Wells	0	Unknown
Aguilar et al., 2002 ¹⁰⁶	134	26 (19.4)	71	48	STA-LIA	0.4 µg/ml	Venous ultrasound	Unknown	Yes	Wells	Unknown	Unknown

*MDA D-dimer assay (Organon Teknika, now bio-Mérieux, Durham, North Carolina); Tinaquant (Roche, Germany); SimpliRED (Agen Biomedical, Brisbane, Australia); VIDAS (bio-Mérieux, Durham, North Carolina); STA-LIA (Diagnostica Stago, Asnières sur Seine, France).

†Blinded to patient's clinical probability score and radiology result.

‡Blinded to patient's clinical probability score and D-dimer result.

§Wells et al. 1995²; Wells et al. 1997¹².

Table 4 Thromboembolic outcomes in management studies

Evaluation strategy	Study, year	D-dimer test	No of patients (No of venous thromboembolism events)	Three month cumulative incidence of venous thromboembolism in % (95%CI)
Normal D-dimer test alone				
No probability assessment, no further testing	Perrier et al, 1999 ¹³	VIDAS	127 (2)	1.6 (0.2 to 5.6)
Normal D-dimer test plus clinical probability				
Low clinical probability, no further testing	Kearon et al, 2001 ¹⁰³	SimpliRED	177 (1)	0.6 (0.0 to 3.1)
	Bates et al, 2003 ¹⁰²	MDA	193 (0)	0.0 (0.0 to 1.9)
Moderate clinical probability, no further testing	Aguilar et al, 2002 ¹⁰⁶	STA-LIA	35 (0)	0.0 (0.0 to 10.0)
	Bates et al, 2003 ¹⁰²	MDA	90 (1)	1.1 (0.0 to 6.0)
Low or moderate clinical probability, no further testing	Schutgens et al, 2003 ¹⁰⁴	Tinaquant	176 (1)	0.6 (0.0 to 2.0)
High clinical probability, ultrasound performed	Bates et al, 2003 ¹⁰³	MDA	20 (0)	0.0 (0.0 to 16.8)
	Schutgens et al, 2003 ¹⁰⁴	Tinaquant	39 (4)	10.3 (2.9 to 24.2)
Clinical probability plus venous ultrasound testing				
Low clinical probability	Tick et al, 2002 ¹⁰⁵	Not performed	280 (35)	12.5 (8.9 to 17.0)
Moderate or high clinical probability, normal ultrasound, normal D-dimer result	Tick et al, 2002 ¹⁰⁵	SimpliRED	148 (0)	0.0 (0.0 to 2.5)
Moderate or high clinical probability, normal ultrasound, abnormal D-dimer result	Tick et al, 2002 ¹⁰⁵	SimpliRED	83 (15)	18.1 (10.5 to 28.1)
Moderate clinical probability and normal D-dimer result	Kearon et al, 2001 ¹⁰³	SimpliRED	120 (7)	5.8 (2.4 to 11.7)
Moderate clinical probability and abnormal D-dimer result	Kearon et al, 2001 ¹⁰³	SimpliRED	68 (17)	25.0 (15.3 to 40.0)
High clinical probability and normal D-dimer result	Kearon et al, 2001 ¹⁰³	SimpliRED	8 (2)	25.0 (3.2 to 65.1)
High clinical probability and abnormal D-dimer result	Kearon et al, 2001 ¹⁰³	SimpliRED	41 (33)	80.5 (65.1 to 91.1)

nometric tests,¹⁰⁷ the use of this assay should be restricted to patients who have a low (less than or equal to 3%) probability of having deep vein thrombosis.^{12 13}

In comparison, the more sensitive D-dimer assays had a much higher sensitivity (about 98%) and negative predictive value, which other reviews have reported.¹⁰ A normal result from a highly sensitive D-dimer test effectively ruled out deep vein thrombosis among patients with either low or moderate clinical probability. Among patients with a moderate clinical probability (mean pre-test probability of disease of 19%^{12 13}) these assays had a negative likelihood ratio of 0.05 and a post-test probability of approximately 1%, which is sufficiently low to rule out deep vein thrombosis safely.

Trade off between sensitivity and specificity

It is possible that the number of cases with acute deep vein thrombosis that are missed as a consequence of using a lower sensitivity test such as SimpliRED negate the benefits associated with using this higher specificity test. However, because the highly sensitive D-dimer assays have lower specificity (detect more false positive cases), using one of these assays will result in fewer patients without deep vein thrombosis being excluded. This translates into more patients requiring venous ultrasound testing. Before any conclusions can be drawn regarding the D-dimer assay and testing strategy, a formal decision analysis is required that takes into consideration the test characteristics of ultrasound testing as well as the costs of misdiagnosis.

Table 5 Thromboembolic outcomes using SimpliRED or the highly sensitive D-dimer test

Potential testing scheme	Three month cumulative incidence of venous thromboembolism in % (95% CI)
Normal SimpliRED D-dimer result plus:	
Low clinical probability	0.5 (0.07 to 1.1)
Moderate clinical probability	3.5 (1.4 to 6.9)
High clinical probability	21.4 (8.5 to 37.9)
Normal highly sensitive D-dimer result plus:	
Low or moderate clinical probability	0.4 (0.04 to 1.1)
High clinical probability	6.4 (1.7 to 14.5)

Recent modification to Wells probability tool

Wells et al recently modified their clinical probability tool by consolidating the low, intermediate, and high probability groups into just two groups, deep vein thrombosis likely and deep vein thrombosis unlikely.¹⁵ They specifically divided the moderate probability group (1 or 2 points on the Wells score) into two groups and assigned those with the lower score of 1 to the lower probability group (deep vein thrombosis unlikely) and those with a score of 2 to a higher probability group (deep vein thrombosis likely). In addition, this new classification assigns 1 point for a prior history of deep vein thrombosis, whereas the original Wells model that was used in all previous studies did not explicitly account for a history of deep vein thrombosis. Thus, the results of our analysis cannot be applied to patients categorised by using this new probability classification scheme.

Other benefits of ultrasound testing

Although D-dimer testing combined with estimation of clinical probability can be used to rule out deep vein thrombosis, it is important to remember that venous ultrasound imaging may provide diagnostic information other than detection of the presence or absence of venous thrombosis. In the evaluation of the patient with leg swelling or pain, use of ultrasound may identify alternative causes of symptoms (such as Baker's cyst, calf haematoma, partial muscle rupture).¹⁰⁸⁻¹¹² Thus, ultrasound testing may still be useful among patients with calf swelling who have a normal D-dimer test and who do not have high clinical probability of having venous thrombosis.

Limitations of the study

Our study has some limitations. We were unable to include five studies that we originally identified as eligible but subsequently excluded because of limited detailed information about one or more subgroups. For three reasons, the exclusion of these studies is unlikely to have affected our results. Firstly, three of the studies compared the accuracy of different D-dimer assays on the same set of patients.¹¹⁻⁹⁶ Secondly, one study used a modified version of the Wells criteria to categorise risk groups, which prevented pooling and comparison of these findings with the other included studies.⁹⁵ Thirdly, one study included only 53

What is already known on this topic

Seventy five per cent of ambulatory patients who present with symptoms suspicious for deep vein thrombosis do not have the disease

Diagnosing deep vein thrombosis in an ambulatory setting may lead to excessive use of ultrasound testing

D-dimer testing and clinical probability assessment can safely reduce the need for ultrasound testing

What this study adds

A normal SimpliRED D-dimer test in patients at low risk can safely rule out deep vein thrombosis

A normal highly sensitive D-dimer test can safely rule out deep vein thrombosis in patients at low or moderate risk

Newer stratification models may reduce costly testing even further

patients who were tested by using an ELISA D-dimer assay, providing insufficient power to draw any conclusions.⁹³

Repeat ultrasound testing

Our analysis also does not deal with the question of when and how often ultrasound testing should be ordered among patients with a positive D-dimer test result and among patients who have a high clinical probability of deep vein thrombosis. More studies are needed to determine if repeat D-dimer or ultrasound testing is potentially useful in these subgroups of patients. Until these studies are completed, at least one repeat ultrasound test performed within one week is currently recommended.

Conclusion

Among outpatients with suspected deep vein thrombosis in whom the clinical probability of venous thrombosis is judged to be low or moderate, a normal, highly sensitive D-dimer result effectively excludes deep vein thrombosis, making ultrasound testing unnecessary. However, this conclusion includes the proviso that more prospective management studies using the different rapid D-dimer assays are needed in order to strengthen the level of this recommendation. Among outpatients classified as having low clinical probability of having deep vein thrombosis by using the original Wells criteria, strong evidence shows that a normal SimpliRED D-dimer assay safely excludes the presence of acute deep vein thrombosis.

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1 Heijboer H, Buller HR, Lensing AW, Turpie AG, Colly LP, ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med* 1993;329:1365-9.

- 2 Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet* 1995;345:1326-30.
- 3 Wells PS, Anderson DR. Diagnosis of deep-vein thrombosis in the year 2000. *Curr Opin Pulm Med* 2000;6:309-13.
- 4 Gordis L. *Epidemiology*. Philadelphia: W B Saunders, 1996.
- 5 Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. *Ann Intern Med* 1998;128:663-77.
- 6 Frost SD, Brotman DJ, Michota FA. Rational use of D-dimer measurement to exclude acute venous thromboembolic disease. *Mayo Clin Proc* 2003;78:1385-91.
- 7 Gouin-Thibault I, Samama MM. Laboratory diagnosis of the thrombophilic state in cancer patients. *Semin Thromb Hemost* 1999;25:167-72.
- 8 Hellgren M. Hemostasis during normal pregnancy and puerperium. *Semin Thromb Hemost* 2003;29:125-30.
- 9 Anderson DR, Wells PS, Stiell I, MacLeod B, Simms M, Gray L, et al. Management of patients with suspected deep vein thrombosis in the emergency department: combining use of a clinical diagnosis model with D-dimer testing. *J Emerg Med* 2000;19:225-30.
- 10 Keeling DM, Mackie IJ, Moody A, Watson HG. The diagnosis of deep vein thrombosis in symptomatic outpatients and the potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging. *Br J Haematol* 2004;124:15-25.
- 11 Schutgens RE, Haas FJ, Gerritsen WB, van der Horst F, Nieuwenhuis HK, Biesma DH. The usefulness of five D-dimer assays in the exclusion of deep venous thrombosis. *J Thromb Haemost* 2003;1:976-81.
- 12 Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350:1795-8.
- 13 Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999;353:190-5.
- 14 Miron MJ, Perrier A, Bounameaux H. Clinical assessment of suspected deep vein thrombosis: comparison between a score and empirical assessment. *J Intern Med* 2000;247:249-54.
- 15 Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003;349:1227-35.
- 16 Kruijff MJ, Leclercq MG, van der Heul C, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. *Ann Intern Med* 2003;138:941-51.
- 17 Irwig L, Tosteson AN, Gatsonis C, Lau J, Colditz G, Chalmers TC, et al. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med* 1994;120:667-76.
- 18 Cochrane Methods Group on Systematic Review of Screening and Diagnostic Tests. *Recommended methods*. Updated 6 June 1996. www.cochrane.org/contact/mwgfield.htm#40 (accessed 14 Sep 2004).
- 19 Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al. Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two centre paired-design prospective trial. *Thromb Haemost* 1995;74:1423-7.
- 20 Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001;135:149-64.
- 21 Fleiss JL. *Statistical methods for rates and proportions*. 2d ed. New York: Wiley, 1981.
- 22 Sutton A, Abrams K, Jones D, Sheldon T, Song F. *Methods for meta-analysis in medical research*. Chichester: John Wiley, 2000.
- 23 Spiegelhalter D, Thomas A, Best N. *WinBUGS Version 1.2 User manual*. Cambridge: MRC Biostatistics Unit, 1999.
- 24 Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. *Ann Intern Med* 2004;140:518-27.
- 25 Philbrick JT, Heim S. The D-dimer test for deep venous thrombosis: gold standards and bias in negative predictive value. *Clin Chem* 2003;49:570-4.
- 26 Hull RD, Stein PD, Ghali WA, Cornuz J. Diagnostic algorithms for deep vein thrombosis: work in progress. *Am J Med* 2002;113:687-8.
- 27 Jones S, Harrison M. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. SimpliRED and diagnosis of deep venous thrombosis. *Emerg Med J* 2001;18:120-2.
- 28 de Moerloose P, Bounameaux H, Perrier A, Reber G. Performances of the VIDAS D-dimer new assay for the exclusion of venous thromboembolism. *Thromb Haemost* 2001;85:185-6.
- 29 Sandrick K. Using new D-dimer tests to rule out venous thromboembolism. *CAP Today* 2000;14:40-2, 44, 46-7.
- 30 Heim SW. D-dimer testing in suspected DVT. *J Fam Pract* 1999;48:13.
- 31 Roy PM, Barbeau C, Ternisien C, Leftheriotis G. Diagnostic strategy in deep-vein thrombosis. *Lancet* 1998;351:1588.
- 32 Michiels JJ. Rational diagnosis of deep vein thrombosis (RADIA DVT) in symptomatic outpatients with suspected DVT: simplification and improvement of decision rule analysis for the exclusion and diagnosis of DVT by the combined use of a simple clinical model, a rapid sensitive D-dimer test and compression ultrasonography (CUS). *Semin Thromb Hemost* 1998;24:401-7.
- 33 Mauron T, Baumgartner I, ZBrun A, Demarmels Biasiutti F, Redondo M, Do DD, et al. SimpliRED D-dimer assay: comparability of capillary and citrated venous whole blood, between-assay variability, and performance of the test for exclusion of deep vein thrombosis in symptomatic outpatients. *Thromb Haemost* 1998;79:1217-9.
- 34 Bensoussan TA, Darnige L, Ducastel P. Rapid D-dimer testing to improve diagnosis of venous thromboembolism in emergency wards: fact or fiction? *Intensive Care Med* 1997;23:1287.
- 35 Michiels JJ, Freyburger G, van der Graaf F, Janssen M, Oortwijn W, van Beek EJ. Strategies for the safe and effective exclusion and diagnosis of deep vein thrombosis by the sequential use of clinical score, D-dimer testing, and compression ultrasonography. *Semin Thromb Hemost* 2000;26:657-67.
- 36 Michiels JJ, van der Meer J, Hamulyak K, Wollersheim H, Oortwijn WJ, Naaborg R. Diagnosis of deep vein thrombosis by the use of a rapid ELISA D-dimer test, CUS, and a clinical model: a cost-effectiveness analysis. *Clin Appl Thromb Hemost* 1999;5:219-21.

- 37 Aschwanden M, Labs K, Jeanneret C, Gehrig A, Jaeger K. Can a D-dimer assay, alone or combined with structured clinical risk assessment, rule out deep venous thrombosis in symptomatic patients? *West J Med* 2001;174:255-6.
- 38 Kelly J, Hunt BJ. A clinical probability assessment and D-dimer measurement should be the initial step in the investigation of suspected venous thromboembolism. *Chest* 2003;124:1116-9.
- 39 Johanning JM, Franklin DP, Thomas DD, Elmoro JR. D-dimer and calf circumference in the evaluation of outpatient deep venous thrombosis. *J Vasc Surg* 2002;36:877-80.
- 40 van der Graaf F, van den Borne H, van der Kolk M, de Wild PJ, Janssen GW, van Uum SH. Exclusion of deep venous thrombosis with D-dimer testing—comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as reference standard. *Thromb Haemost* 2000;83:191-8.
- 41 Larsen TB, Stoffersen E, Christensen CS, Laursen B. Validity of D-dimer tests in the diagnosis of deep vein thrombosis: a prospective comparative study of three quantitative assays. *J Intern Med* 2002;252:36-40.
- 42 Siragusa S, Terulla V, Pirrelli S, Porta C, Falaschi F, Anastasio R, et al. A rapid D-dimer assay in patients presenting at the emergency room with suspected acute venous thrombosis: accuracy and relation to clinical variables. *Haematologica* 2001;86:856-61.
- 43 Reber G, Bounameaux H, Perrier A, de Moerloose P. Performances of a new, automated latex assay for the exclusion of venous thromboembolism. *Blood Coagul Fibrinolysis* 2001;12:217-20.
- 44 Harper P, Marson C, Grimmer A, Monahan K, Humm G, Baker B. The rapid whole blood agglutination D-dimer assay has poor sensitivity for use as an exclusion test in suspected deep vein thrombosis. *N Z Med J* 2001;114:61-4.
- 45 Gosselin RC, Owings JT, Utter GH, Jacoby RC, Larkin EC. A new method for measuring D-dimer using immunoturbidometry: a study of 255 patients with suspected pulmonary embolism and deep vein thrombosis. *Blood Coagul Fibrinolysis* 2000;11:715-21.
- 46 Permpikul C, Chantavatharakorn K, Bouranasompop C, Chaiyasoot W. Whole blood agglutination D-dimer test for the diagnosis of deep vein thrombosis. *J Med Assoc Thai* 2000;83:732-6.
- 47 LaCapra S, Arkel YS, Ku DH, Gibson D, Lake C, Lam X. The use of thrombus precursor protein, D-dimer, prothrombin fragment 1.2, and thrombin antithrombin in the exclusion of proximal deep vein thrombosis and pulmonary embolism. *Blood Coagul Fibrinolysis* 2000;11:371-7.
- 48 Bradley M, Bladon J, Barker H. D-dimer assay for deep vein thrombosis: its role with colour Doppler sonography. *Clin Radiol* 2000;55:525-7.
- 49 Villa P, Ferrando F, Serra J, Faus H, Mira Y, Vaya A, et al. Quantification of D-dimer using a new fully automated assay: its application for the diagnosis of deep vein thrombosis. *Haematologica* 2000;85:520-4.
- 50 Sadouk M, Desmarais S, Patenaude JV, Lepage R. Comparison of diagnostic performance of three new fast D-dimer assays in the exclusion of deep vein thrombosis. *Clin Chem* 2000;46:286-7.
- 51 Farrell S, Hayes T, Shaw M. A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep vein thrombosis or pulmonary embolism in emergency department patients. *Ann Emerg Med* 2000;35:121-5.
- 52 Keeling DM, Wright M, Baker P, Sackett D. D-dimer for the exclusion of venous thromboembolism: comparison of a new automated latex particle immunoassay (MDA D-dimer) with an established enzyme-linked fluorescent assay (VIDAS D-dimer). *Clin Lab Haematol* 1999;21:359-62.
- 53 Lee AY, Julian JA, Levine MN, Weitz JL, Kearon C, Wells PS, et al. Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis. *Ann Intern Med* 1999;131:417-23.
- 54 Wahlander K, Tengborn L, Hellstrom M, Olmarker AH, Peterson LE, Stigendal L, et al. Comparison of various D-dimer tests for the diagnosis of deep venous thrombosis. *Blood Coagul Fibrinolysis* 1999;10:121-6.
- 55 Legnani C, Pancani C, Palareti G, Guazzaloca G, Coccheri S. Contribution of a new, rapid, quantitative and automated method for D-dimer measurement to exclude deep vein thrombosis in symptomatic outpatients. *Blood Coagul Fibrinolysis* 1999;10:69-74.
- 56 Wijns W, Daoud N, Droeshout I, Pradier O, Wautrecht JC, Golzarian J, et al. Evaluation of two D-dimer assays in the diagnosis of venous thromboembolism. *Acta Clin Belg* 1998;53:270-4.
- 57 Bernardi E, Prandoni P, Lensing AW, Agnelli G, Guazzaloca G, Scannapieco G, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. *BMJ* 1998;317:1037-40.
- 58 Escoffre-Barbe M, Oger E, Leroyer C, Grimaux M, Le Moigne E, Nonent M, et al. Evaluation of a new rapid D-dimer assay for clinically suspected deep venous thrombosis (Liatest D-dimer). *Am J Clin Pathol* 1998;109:748-53.
- 59 Wildberger JE, Vorwerk D, Kilbinger M, Piroth W, Hunter DW, Wienert V, et al. Bedside testing (SimpliRED) in the diagnosis of deep vein thrombosis. Evaluation of 250 patients. *Invest Radiol* 1998;33:232-5.
- 60 Freyburger G, Trillaud H, Labrousse S, Gauthier P, Javorschi S, Bernard P, et al. D-dimer strategy in thrombosis exclusion—a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. *Thromb Haemost* 1998;79:32-7.
- 61 Legnani C, Pancani C, Palareti G, Guazzaloca G, Fortunato G, Grauso F, et al. Comparison of new rapid methods for D-dimer measurement to exclude deep vein thrombosis in symptomatic outpatients. *Blood Coagul Fibrinolysis* 1997;8:296-302.
- 62 Mayer W, Hirschwehr R, Hippmann G, Otpadlik H, Bayer P, Partsch H. Whole-blood immunoassay (SimpliRED) versus plasma immunoassay (Nycocard) for the diagnosis of clinically suspected deep vein thrombosis. *Vasa* 1997;26:97-101.
- 63 Scarano L, Bernardi E, Prandoni P, Sardella C, Rossi L, Carraro P, et al. Accuracy of two newly described D-dimer tests in patients with suspected deep venous thrombosis. *Thromb Res* 1997;86:93-9.
- 64 Janssen MC, Heebels AE, de Metz M, Verbruggen H, Wollersheim H, Janssen S, et al. Reliability of five rapid D-dimer assays compared to ELISA in the exclusion of deep venous thrombosis. *Thromb Haemost* 1997;77:262-6.
- 65 Line BR, Peters TL, Keenan J. Diagnostic test comparisons in patients with deep venous thrombosis. *J Nucl Med* 1997;38:89-92.
- 66 Leroyer C, Escoffre M, Le Moigne E, Grimaux M, Cagnioncle O, Oger E, et al. Diagnostic value of a new sensitive membrane based technique for instantaneous D-dimer evaluation in patients with clinically suspected deep venous thrombosis. *Thromb Haemost* 1997;77:637-40.
- 67 Elias A, Aptel I, Huc B, Chale JJ, Nguyen F, Cambus JP, et al. D-dimer test and diagnosis of deep vein thrombosis: a comparative study of 7 assays. *Thromb Haemost* 1996;76:518-22.
- 68 Turckstra F, van Beek EJ, ten Cate JW, Buller HR. Reliable rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients. *Thromb Haemost* 1996;76:9-11.
- 69 D'Angelo A, D'Alessandro G, Tomassini L, Pittet JL, Dupuy G, Crippa L. Evaluation of a new rapid quantitative D-dimer assay in patients with clinically suspected deep vein thrombosis. *Thromb Haemost* 1996;75:412-6.
- 70 Brenner B, Pery M, Lanir N, Jabareen A, Markel A, Kaftori JK, et al. Application of a bedside whole blood D-dimer assay in the diagnosis of deep vein thrombosis. *Blood Coagul Fibrinolysis* 1995;6:219-22.
- 71 Wells PS, Brill-Edwards P, Stevens P, Panju A, Patel A, Douketis J, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation* 1995;91:2184-7.
- 72 Bouman CS, Ypma ST, Sybesma JP. Comparison of the efficacy of D-dimer, fibrin degradation products and prothrombin fragment 1+2 in clinically suspected deep venous thrombosis. *Thromb Res* 1995;77:225-34.
- 73 Tengborn L, Palmblad S, Wojciechowski J, Peterson LE, Stigendal L. D-dimer and thrombin/antithrombin III complex—diagnostic tools in deep venous thrombosis? *Haemostasis* 1994;24:344-50.
- 74 Hansson PO, Eriksson H, Eriksson E, Jagenburg R, Lukes P, Risberg B. Can laboratory testing improve screening strategies for deep vein thrombosis at an emergency unit? *J Intern Med* 1994;235:143-51.
- 75 Dale S, Gogstad GO, Brosstad F, Godal HC, Holtlund J, Mork E, et al. Comparison of three D-dimer assays for the diagnosis of DVT: ELISA, latex and an immunofiltration assay (Nycocard D-Dimer). *Thromb Haemost* 1994;71:270-4.
- 76 Arcelus JI, Caprini JA, Hoffman KN, Fink N, Size GP, Fareed J, et al. Laboratory assays and duplex scanning outcomes after symptomatic deep vein thrombosis: preliminary results. *J Vasc Surg* 1996;23:616-21.
- 77 Anderson DR, Wells PS, Stiell I, MacLeod B, Simms M, Gray L, et al. Thrombosis in the emergency department: use of a clinical diagnosis model to safely avoid the need for urgent radiological investigation. *Arch Intern Med* 1999;159:477-82.
- 78 Killick SB, Pentek PG, Mercieca JE, Clarke MF, Bevan DH. Comparison of immunofiltration assay of plasma D-dimer with diagnostic imaging in deep vein thrombosis. *Br J Haematol* 1997;96:846-9.
- 79 Walsh K, Kelaher N, Long K, Cervi P. An algorithm for the investigation and management of patients with suspected deep venous thrombosis at a district general hospital. *Postgrad Med J* 2002;78:742-5.
- 80 Schutgens RE, Esseboom EU, Haas FJ, Nieuwenhuis HK, Biesma DH. Usefulness of a semiquantitative D-dimer test for the exclusion of deep venous thrombosis in outpatients. *Am J Med* 2002;112:617-21.
- 81 Brimble KS, Ginsberg JS. Evaluation of the combination of a bedside D-dimer assay and enzyme-linked immunosorbent soluble fibrin assay in patients with suspected venous thromboembolism. *Thromb Res* 1997;88:291-7.
- 82 Houbouyan-Reveillard LL, Mihoubi A, Houdijk WF, Qanadli S, Joseph T, Courret JP, et al. Preliminary evaluation of two new rapid immunoturbidimetric D-dimer assays in patients with clinically suspected venous thromboembolism (VTE). *Thromb Haemost* 2000;84:770-4.
- 83 Hein-Rasmussen R, Tuxen CD, Winberg N. Diagnostic value of the Nycocard, Nycomed D-dimer assay for the diagnosis of deep venous thrombosis and pulmonary embolism: a retrospective study. *Thromb Res* 2000;100:287-92.
- 84 Le Blanche AF, Siguret V, Settegrana C, Bohus S, Le Masne de Chermont E, Andreux JP, et al. Ruling out acute deep vein thrombosis by ELISA plasma D-dimer assay versus ultrasound in inpatients more than 70 years old. *Angiology* 1999;50:873-82.
- 85 Aschwanden M, Labs KH, Jeanneret C, Gehrig A, Jaeger KA. The value of rapid D-dimer testing combined with structured clinical evaluation for the diagnosis of deep vein thrombosis. *J Vasc Surg* 1999;30:929-35.
- 86 Kozman H, Flemmer MC, Rahnema M. Deep venous thrombosis: prediction by D-dimer? *South Med J* 1997;90:907-10.
- 87 Shitri D, Heyd J, Raveh D, Rudensky B. Diagnostic value of the D-dimer test in deep vein thrombosis: improved results by a new assay method and by using discriminate levels. *Thromb Res* 2001;102:125-31.
- 88 Lennox AF, Delis KT, Serunkuma S, Zarka ZA, Daskalopoulou SE, Nicolaides AN. Combination of a clinical risk assessment score and rapid whole blood D-dimer testing in the diagnosis of deep vein thrombosis in symptomatic patients. *J Vasc Surg* 1999;30:794-803.
- 89 Bates SM, Grand'Maison A, Johnston M, Naguit I, Kovacs MJ, Ginsberg JS. A latex D-dimer reliably excludes venous thromboembolism. *Arch Intern Med* 2001;161:447-53.
- 90 Bucek RA, Quehenberger P, Feliks I, Handler S, Reiter M, Minar E. Results of a new rapid D-dimer assay (cardiac D-dimer) in the diagnosis of deep vein thrombosis. *Thromb Res* 2001;103:17-23.
- 91 Dryjski M, O'Brien-Irr MS, Harris LM, Hassett J, Janicic D. Evaluation of a screening protocol to exclude the diagnosis of deep venous thrombosis among emergency department patients. *J Vasc Surg* 2001;34:1010-5.
- 92 Blattler W, Kreis N, Blattler IK. Practicality and quality of outpatient management of acute deep venous thrombosis. *J Vasc Surg* 2000;32:855-60.
- 93 Cornuz J, Ghali WA, Hayoz D, Stoianov R, Depairon M, Yersin B. Clinical prediction of deep venous thrombosis using two risk assessment methods in combination with rapid quantitative D-dimer testing. *Am J Med* 2002;112:198-203.
- 94 Funsinn N, Calieze C, Biasiutti FD, Korte W, Z'Brun A, Baumgartner I, et al. Rapid D-dimer testing and pre-test clinical probability in the exclusion of deep venous thrombosis in symptomatic outpatients. *Blood Coagul Fibrinolysis* 2001;12:165-70.
- 95 Janes S, Ashford N. Use of a simplified clinical scoring system and D-dimer testing can reduce the requirement for radiology in the exclusion of deep vein thrombosis by over 20%. *Br J Haematol* 2001;112:1079-82.
- 96 Kovacs MJ, MacKinnon KM, Anderson D, O'Rourke K, Keeney M, Kearon C, et al. A comparison of three rapid D-dimer methods for the diagnosis of venous thromboembolism. *Br J Haematol* 2001;115:140-4.

- 97 Bucek RA, Koca N, Reiter M, Haumer M, Zontsich T, Minar E. Algorithms for the diagnosis of deep-vein thrombosis in patients with low clinical pretest probability. *Thromb Res* 2002;105:43-7.
- 98 Kraaijenhagen RA, Piovela F, Bernardi E, Verlato F, Beckers EA, Koopman MM, et al. Simplification of the diagnostic management of suspected deep vein thrombosis. *Arch Intern Med* 2002;162:907-11.
- 99 Shields GP, Turnipseed S, Panacek EA, Melnikoff N, Gosselin R, White RH. Validation of the Canadian clinical probability model for acute venous thrombosis. *Acad Emerg Med* 2002;9:561-6.
- 100 Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Lewandowski B. SimpliRED d-dimer can reduce the diagnostic tests in suspected deep vein thrombosis. *Lancet* 1998;351:1405-6.
- 101 Ginsberg JS, Kearon C, Douketis J, Turpie AG, Brill-Edwards P, Stevens P, et al. The use of d-dimer testing and impedance plethysmographic examination in patients with clinical indications of deep vein thrombosis. *Arch Intern Med* 1997;157:1077-81.
- 102 Bates SM, Kearon C, Crowther M, Linkins L, O'Donnell M, Douketis J, et al. A diagnostic strategy involving a quantitative latex d-dimer assay reliably excludes deep venous thrombosis. *Ann Intern Med* 2003;138:787-94.
- 103 Kearon C, Ginsberg JS, Douketis J, Crowther M, Brill-Edwards P, Weitz JI, et al. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and d-dimer testing. *Ann Intern Med* 2001;135:108-11.
- 104 Schutgens RE, Ackermans P, Haas FJ, Nieuwenhuis HK, Peltenburg HG, Pijlman AH, et al. Combination of a normal d-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation* 2003;107:593-7.
- 105 Tick LW, Ton E, van Voorthuizen T, Hovens MM, Leeuwenburgh I, Lobatto S, et al. Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography, and d-dimer test. *Am J Med* 2002;113:630-5.
- 106 Aguilar C, Martinez A, Del Rio C, Vazquez M, Rodriguez FJ. Diagnostic value of d-dimer in patients with a moderate pretest probability of deep venous thrombosis. *Br J Haematol* 2002;118:275-7.
- 107 Wilson DB, Gard KM. Evaluation of an automated, latex-enhanced turbidimetric d-dimer test (advanced d-dimer) and usefulness in the exclusion of acute thromboembolic disease. *Am J Clin Pathol* 2003;120:930-7.
- 108 White RH, McGahan JP, Daschbach MM, Hartling RP. Diagnosis of deep-vein thrombosis using duplex ultrasound. *Ann Intern Med* 1989;111:297-304.
- 109 Vayssairat M. D-dimer in venous thromboembolism. *N Engl J Med* 2004;350:192-4; author reply 192-4.
- 110 Elias A, Le Corff G, Bouvier JL, Benichou M, Serradimigni A. Value of real time B mode ultrasound imaging in the diagnosis of deep vein thrombosis of the lower limbs. *Int Angiol* 1987;6:175-82.
- 111 Mitchell DC, Grasty MS, Stebbings WS, Nockler IB, Lewars MD, Levison RA, et al. Comparison of duplex ultrasonography and venography in the diagnosis of deep venous thrombosis. *Br J Surg* 1991;78:611-3.
- 112 Bradley MJ, Spencer PA, Alexander L, Milner GR. Colour flow mapping in the diagnosis of the calf deep vein thrombosis. *Clin Radiol* 1993;47:399-402.

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