

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

Tonya L Fancher, Richard H White, Richard L Kravitz

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 simple tests that, when combined, accurately exclude deep vein thrombosis.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 a fibrin degradation product generated during fibrinolysis. D-dimer concentrations are raised in the setting of acute deep vein thrombosis, and normal concentrations are expected in the absence of acute venous thrombosis unless other, coexistent conditions that activate the coagulation system are present. 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.^{5,6}

Two clinical probability tools to estimate the probability of venous thrombosis are widely used. The first, developed by Wells et al,^{2,7} 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,^{8,9} 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 and fewer than 19% of patients with moderate probability had a deep vein thrombosis.^{7,8} 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.¹⁰

This systematic review focuses on clinical studies that have evaluated the use of rapid D-dimer testing in conjunction with assessment of clinical probability.

Division of General Medicine,
University of California at Davis,
Patient Support Services Building,
Suite 2400,
Sacramento, California 95817,
USA

Tonya L Fancher
assistant professor
Richard H White
professor of medicine

Center for Health Services Research
in Primary Care,
2103 Stockton Blvd,
Sacramento, CA 95817, USA

Richard L Kravitz
*professor of medicine
and director*

Correspondence to:
T L Fancher
Tonya.Fancher@ucdmc.
ucdavis.edu

BMJ 2004;329:821-4



This is the abridged version of an article that was posted on bmj.com on 21 September 2004: <http://bmj.com/cgi/doi/10.1136/bmj.38226.719803.EB>

Table 1 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 ¹²	STA-LIA	48 (0)	0.0 (0 to 7.4)
	Kraaijenhagen et al., 2002 ¹³	SimpliRED	561 (10)	1.8 (0.9 to 3.2)
	Shields et al., 2002 ¹⁴	SimpliRED	32 (0)	0.0 (0.0 to 10.1)
	Wells et al., 1998 ¹⁵	SimpliRED	206 (1)	0.5 (0.0 to 2.7)
	Ginsberg et al., 1997 ¹¹	SimpliRED	178 (1)	0.6 (0.0 to 3.1)
	Anderson et al., 2000 ⁸	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 ¹⁴	SimpliRED	20 (0)	0.0 (0.0 to 16.8)
	Wells et al., 1998 ¹⁵	SimpliRED	87 (3)	3.4 (0.7 to 9.8)
	Ginsberg et al., 1997 ¹⁶	SimpliRED	97 (3)	3.1 (0.6 to 8.8)
	Anderson et al., 2000 ¹¹	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 ¹⁴	SimpliRED	7 (2)	29 (3.7 to 71.0)
	Wells et al., 1998 ¹⁵	SimpliRED	7 (1)	14.3 (0.4 to 57.9)
	Ginsberg et al., 1997 ¹⁶	SimpliRED	5 (2)	40.0 (5.3 to 85.3)
	Anderson et al., 2000 ¹¹	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).

Methods

Study identification

We searched Medline and the Database of Abstracts and Reviews (DARE) to identify clinical studies and systematic reviews (see bmj.com). We also reviewed the reference lists of the articles selected for inclusion.

Our 10 inclusion criteria are detailed on bmj.com. In brief we included studies using a rapid D-dimer assay, a validated clinical probability tool to estimate the risk of deep vein thrombosis, and an objective documentation of deep vein thrombosis; follow up of all patients had to be for at least three months.

Statistical analysis

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 assay and a random effect. We used WinBUGS to estimate the model (see bmj.com for more details).

Results

Studies

We identified a total of 240 references and, 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. Ultimately we included 12 studies^{8-11,21} that had enrolled 5431 patients suspected of having deep vein thrombosis.

Accuracy studies

Six studies were accuracy studies (table 1 and bmj.com).¹¹⁻¹⁶ Two of these studies reported patients with low clinical probability only.^{12,13} 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 (see bmj.com).^{8,17-21} One management study used a highly sensitive D-dimer assay alone as the initial test,⁸ whereas the remaining studies combined clinical probability assessment with either a D-dimer assay or venous ultrasound (table 2). One study combined patients with low and moderate clinical probability into one group.¹⁹ Results from the management studies were not pooled because the few available studies had small sample sizes, making synthesis unstable.

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 deep vein thrombosis, where 2 points are deducted. 0 or fewer points: low probability; 1-2 points: moderate probability; 3 or more points: high probability.

Table 2 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 ¹⁸	SimpliRED	177 (1)	0.6 (0.0 to 3.1)
	Bates et al, 2003 ¹⁷	MDA	193 (0)	0.0 (0.0 to 1.9)
Moderate clinical probability, no further testing	Aguilar et al, 2002 ²¹	STA-LIA	35 (0)	0.0 (0.0 to 10.0)
	Bates et al, 2003 ¹⁷	MDA	90 (1)	1.1 (0.0 to 6.0)
Low or moderate clinical probability, no further testing	Schutgens et al, 2003 ¹⁹	Tinaquant	176 (1)	0.6 (0.0 to 2.0)
High clinical probability, ultrasound performed	Bates et al, 2003 ¹⁷	MDA	20 (0)	0.0 (0.0 to 16.8)
	Schutgens et al, 2003 ¹⁹	Tinaquant	39 (4)	10.3 (2.9 to 24.2)
Clinical probability plus venous ultrasound testing				
Low clinical probability	Tick et al, 2002 ²⁰	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 ²⁰	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 ²⁰	SimpliRED	83 (15)	18.1 (10.5 to 28.1)
Moderate clinical probability and normal D-dimer result	Kearon et al, 2001 ¹⁸	SimpliRED	120 (7)	5.8 (2.4 to 11.7)
Moderate clinical probability and abnormal D-dimer result	Kearon et al, 2001 ¹⁸	SimpliRED	68 (17)	25.0 (15.3 to 40.0)
High clinical probability and normal D-dimer result	Kearon et al, 2001 ¹⁸	SimpliRED	8 (2)	25.0 (3.2 to 65.1)
High clinical probability and abnormal D-dimer result	Kearon et al, 2001 ¹⁸	SimpliRED	41 (33)	80.5 (65.1 to 91.1)

Tick et al first performed ultrasound testing on all patients, including those in the category of low clinical probability.²⁰ 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. Among outpatients with a normal result from the SimpliRED D-dimer test and a low clinical probability of deep vein thrombosis, the three month incidence of venous thromboembolism was 0.5% (0.07% to 1.1%) (table 3). 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 tests,²² 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.^{7, 8}

In comparison, the more sensitive D-dimer assays had a much higher sensitivity (about 98%) and negative predictive value, which other reviews have reported.⁵ 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%^{7, 8}) 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.

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.¹⁰ 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,

Table 3 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)

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

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.

Limitations of the study

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.^{6 23 24} 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.²⁵ Thirdly, one study included only 53 patients who were tested by using an ELISA D-dimer assay, providing insufficient power to draw any conclusions.²⁶

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.

We thank Samantha Vincent and the staff at BMJ Knowledge for help with the early phases of the literature review and Benjamin Chan and Jessica Utts for their statistical expertise.

Contributors: See bmj.com.

Funding: We acknowledge the US Health Resources and Services Administration's Faculty Development in Primary Care Grant 1 D55 HP 00232 in supporting TLF's Primary Care Outcomes Research Fellowship.

Competing interests: RHW has been reimbursed by bio-Mérieux, Inc, Durham, North Carolina, the manufacturer of the VIDAS and MDA D-dimer assays, for participation as a consultant in a one day meeting.

- 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.
- 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.
- Wells PS, Anderson DR. Diagnosis of deep-vein thrombosis in the year 2000. *Curr Opin Pulm Med* 2000;6:309-13.
- Gordis L. *Epidemiology*. Philadelphia: W B Saunders, 1996.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Kraaijenhagen RA, Piovello 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.
- Shields GP, Turnipseed S, Panacek EA, Melnikoff N, Gosseiln R, White RH. Validation of the Canadian clinical probability model for acute venous thrombosis. *Acad Emerg Med* 2002;9:561-6.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Funfsinn N, Caliezi 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.
- 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.
- 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.

(Accepted 13 August 2004)

doi 10.1136/bmj.38226.719803.EB