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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 simple 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 inmmunosorbent 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.

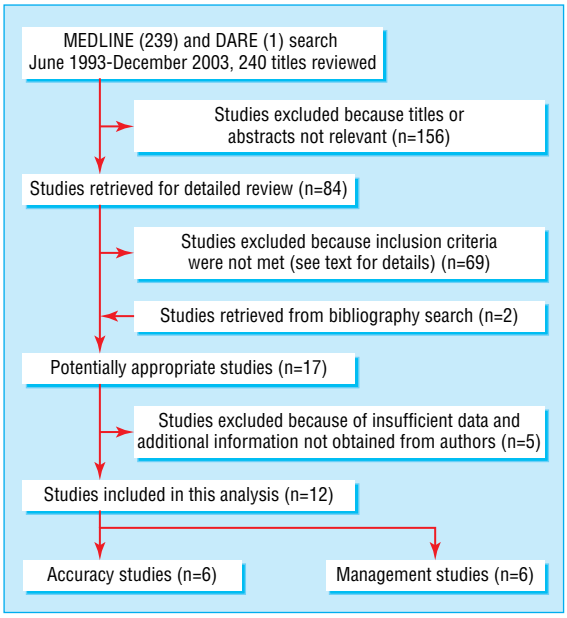
We calculated the three month cumulative incidence of deep vein thrombosis for all groups, along with the 95% confidence intervals.[21] We then calculated the pooled incidence from a logistic meta-regression model, which included a random effect to allow for potential heterogeneity between studies.[22] 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 reviews[25–38]; did not evaluate both a D-dimer assay and a clinical probability tool[39–78]; did not categorise patients into low risk, moderate or intermediate risk, and high risk for deep vein thrombosis[15]; were not prospective[79–81]; included only inpatients or did not allow for separate analysis of outpatients[82–88]; included data that did not allow separate analysis of patients with a diagnosis of deep vein thrombosis and pulmonary embolism[89]; 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, 1995[2]. Wells et al, 1997[12].
¶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 immunoturbi-

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, Asniéres 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.1995[2]; Wells et al 1997[12].

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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