

Does This Patient Have Deep Vein Thrombosis?

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CLINICAL SCENARIO

A 60-year-old man referred with suspected deep vein thrombosis (DVT) cut the plantar surface of his left foot on glass 10 days ago and has been resting in bed. He presents with left leg pain, mild calf swelling, redness, and heat. There is no history of a previous DVT or known family history of venous thromboembolism. Physical examination shows the patient is febrile and has pitting edema of the left calf. The calf erythema is hot, tender, and well demarcated. Enlarged left inguinal lymph nodes are present. He has long-standing diabetes mellitus and the diagnoses that seem most likely are cellulitis or deep venous thrombosis. Can a clinical probability estimate of DVT reliably determine a pretest probability that can be used in decision making?

CLINICAL EVALUATION AND CLINICAL PREDICTION RULES

Deep vein thrombosis occurs frequently with an estimated annual incidence of 0.1% in white populations,^{1,2} creating considerable morbidity. Complications include postphlebotic syndrome and chronic thromboembolic

Context Outpatients with suspected deep vein thrombosis (DVT) have nonspecific signs and symptoms. Missed DVT diagnosis may result in fatal pulmonary embolism. Since many patients may have DVT, a selective and efficient diagnostic process is needed.

Objective To systematically review trials that determined the prevalence of DVT using clinical prediction rules either with or without D-dimer, for the diagnosis of DVT.

Data Sources English- and French-language studies were identified from MEDLINE from 1990 to July 2004 and supplemented by a review of all relevant bibliographies.

Study Selection We included studies that prospectively enrolled consecutive, unselected outpatients with suspected DVT and applied clinical prediction rules before D-dimer testing or diagnostic imaging. All studies included sufficient information to allow the calculation of the prevalence of DVT for at least 1 of the 3 clinical probability estimates (low, moderate, or high). We required that patients be followed up for a minimum 3-month period. Unless the clinical model incorporated prior DVT, studies were excluded if patients with a history of prior DVT were enrolled.

Data Extraction Two reviewers independently reviewed and abstracted data for estimating the prevalence of DVT, sensitivity, specificity, and likelihood ratios (LRs) of D-dimer in each of the 3 clinical probability estimates. Data for the D-dimer in all studies were pooled and analyzed as high-sensitivity/low-specificity test or a moderate-sensitivity/moderate-specificity test.

Data Synthesis Fourteen studies involving more than 8000 patients used 1 clinical prediction rule for diagnosing DVT, of which 11 incorporated D-dimer testing in the diagnostic algorithm. The prevalence of DVT in the low, moderate, and high clinical probability groups was 5.0% (95% CI, 4.0%-8.0%), 17% (95% CI, 13%-23%), and 53% (95% CI, 44%-61%), respectively. The overall prevalence of DVT was 19% (95% CI, 16%-23%). Pooling all studies, the sensitivity, specificity, and negative LRs of D-dimer testing in the low probability group were 88% (95% CI, 81%-92%), 72% (95% CI, 65%-78%), and 0.18% (95% CI, 0.12-0.18); in the moderate probability group: 90% (95% CI, 80%-95%), 58% (95% CI, 49%-67%), and 0.19% (95% CI, 0.11-0.32); and in the high probability group: 92% (95% CI, 85%-96%), 45% (95% CI, 37%-52%), and 0.16% (95% CI, 0.09-0.30). The LRs for a normal result on a high or moderately sensitive D-dimer assay among patients with: (1) low clinical suspicion were 0.10 (95% CI, 0.03-0.37) and 0.20 (95% CI, 0.12-0.31); (2) moderate clinical suspicion were 0.05 (95% CI, 0.01-0.21) and 0.23 (95% CI, 0.13-0.39); and (3) high clinical suspicion were 0.07 (95% CI, 0.03-0.18) and 0.15 (95% CI, 0.10-0.38).

Conclusions Diagnostic accuracy for DVT improves when clinical probability is estimated before diagnostic tests. Patients with low clinical probability on the predictive rule have prevalence of DVT of less than 5%. In low-probability patients with negative D-dimer results, diagnosis of DVT can be excluded without ultrasound; in patients with high clinical suspicion for DVT, results should not affect clinical decisions.

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pulmonary hypertension, while pulmonary embolism causes death in 1% to 8% of affected patients despite treatment.³⁻⁵ Although anticoagulant therapy decreases the risk of recurrent thrombosis, the treatment also increases the risk of major hemorrhage and other potentially serious consequences, such as heparin-induced thrombocytopenia. Therefore, diagnostic strategies must correctly diagnose DVT when present and safely rule out DVT when absent. The desire to not miss a patient with DVT combined with the large number of nonspecific signs and symptoms makes DVT part of the differential diagnosis in most patients presenting with leg pain or swelling. Unfortunately, the nonspecific signs and symptoms force clinicians to investigate many patients who do not have DVT. In the past, clinical assessment was not quantified in the diagnostic assessment in patients with suspected DVT and prior to 1995, the approach was to image all patients with suspected DVT.^{6,7} This approach was inefficient because most patients with suspected DVT did not have the disorder (DVT rates ranging from 10%-25%).⁷⁻⁹ Because imaging for calf DVT is relatively inaccurate and often inadequate,^{10,11} serial testing in which only the proximal veins were evaluated and negative testing repeated 1 week later was the standard. Several studies performed in the last decade successfully incorporated clinical assessment into the diagnostic approach.

In a previous Rational Clinical Examination, we outlined how categorizing patients as having a low clinical probability for DVT eliminates the need for serial testing and categorizing patients as high clinical probability selects those in whom a negative ultrasound result may be a false-negative.¹² We also emphasized that false-positive ultrasound results were most likely when patients had a low clinical probability for DVT. The clinical prediction rule⁸ described in that article had not been widely evaluated. We conducted a new systematic

review to determine the accuracy of the same clinical prediction rule for DVT.

The incorporation of D-dimer testing into diagnostic algorithms has simplified the treatment of a patient presenting with suspected DVT.¹³⁻¹⁶ Clinical trials demonstrate safe, feasible, and validated approaches for the treatment of patients with suspected DVT. However, it is also clear that D-dimer assays differ with respect to sensitivity and specificity. Recent meta-analyses summarize the accuracy of various D-dimer assays compared with gold standard imaging tests for DVT.^{17,18}

Diagnostic algorithms work by combining the pretest probability estimate (or clinical suspicion) with the likelihood ratio (LR) of a diagnostic test result, providing an accurate probability of disease after testing.¹⁹ Given the consequences of failing to detect DVT, a strategy that produces probability of 1% or less after testing should provide reassurance that additional tests are unnecessary. The combination of a low or unlikely clinical probability estimate with a negative D-dimer safely rules out DVT.¹³ What is not clear are the following questions: (1) whether the clinical prediction rule (eg, Wells et al¹³) can be used reliably across a broad range of at-risk population; (2) what is an estimated pooled risk of DVT in each pretest category and; (3) how should pretest clinical probability estimates be used with different D-dimer assays. To date, 3 studies have evaluated the literature on clinical prediction rules for the diagnosis of DVT but all have limitations.²⁰⁻²² Specifically, they included studies and data that either did not use the model or used the model incorrectly by including patients with prior DVT (the most recent changes to the model include a point for patients with prior DVT). Indeed, Goodacre et al²² report that exclusion of persons with a history of thromboembolism is associated with improved diagnostic performance of the model by Wells et al¹³; however,

they did not report summary prevalence data, one article only reported events rates in follow-up, and none reported LR data in combination with D-dimer testing. We conducted a systematic review to determine the accuracy of clinical prediction rules for DVT and D-dimer assays in conjunction with the clinical probability estimate.

METHODS

Study Identification

We searched for English- and French-language clinical studies that used a clinical prediction model or clinical assessment in the DVT diagnostic process. To evaluate the role of D-dimer, we also sought studies that used D-dimer in combination with clinical assessment. Published studies were identified by searching MEDLINE from January 1, 1990, to July 1, 2004, using the medical subject headings: *venous thrombosis* or *thrombophlebitis*, *fibrin* or *fibrinogen degradation products* and *predictive value of tests* and the key words: *DVT*, *D-dimer*, *diagnosis*, *sensitivity*, *specificity*, *clinical probability*, *clinical model*, or *decision rule*. We supplemented the MEDLINE search by scrutinizing the reference lists of all articles selected for inclusion, review articles retrieved, and review of our own reference library of over 4200 articles.

Study Selection

To be included in the review, all of the following criteria were required: (1) enrollment of consecutive outpatients with symptoms and signs of suspected DVT; (2) prospective trial design involving a minimum 3-month follow-up; (3) objective documentation of all venous thromboembolic events (DVT and pulmonary embolism); (4) exclusion of patients with prior DVT unless the clinical model adjusted for the history of prior DVT or the reviewers could make that adjustment; (5) assessment of patients using a validated clinical rule to estimate the clinical probability of DVT prior to D-dimer testing or diagnostic imaging; (6) if D-dimer testing

was performed, it must have been drawn prior to other diagnostic tests (although D-dimer testing was not a requirement for study inclusion); (7) available data on the prevalence of DVT in at least 1 of the 3 risk estimate categories (low, moderate, or high); (8) evaluation of proximal DVT and; (9) study quality graded A or B using the scheme previously appearing in the Rational Clinical Examination series, adapted from Holleman and Simel²³ as shown:

Level 1: Independent, blinded comparison of symptom or sign results with a criterion standard of diagnosis among a large number of consecutive patients (≥ 300) with suspected DVT;

Level 2: Independent, blinded comparison of symptom or sign results with a criterion standard of diagnosis among consecutive patients (< 300) with suspected DVT.

Data Extraction

Two authors independently reviewed and abstracted data for determining: (1) prevalence of DVT in low, moderate, and high clinical probability groups; (2) sensitivity and specificity; and (3) LRs of D-dimer testing in each of the 3 clinical probability groups.

Statistical Analysis

Data were imported into the Comprehensive Meta-Analysis software program version 2.1.97 (Biostat Inc, Englewood, NJ) and analyzed using a random-effects model.

For each study, the overall prevalence of DVT and the prevalence among patients with low, moderate, or high clinical probability estimate were calculated. We confirmed the sensitivity and specificity and 95% confidence intervals (CIs) for each study that included D-dimer testing. The positive and negative LRs for each clinical probability estimate according to the D-dimer subset were calculated. A positive LR is a measure of how strongly a positive result increases the odds of disease and a negative LR is measure of how well a negative result decreases the odds of disease. The

easiest way to interpret LRs is to keep in mind that the likelihood of a disease outcome increases when the LR is greater than 1, the likelihood of disease decreases if the LR is less than 1, and an LR close to 1 does not change the likelihood. We also calculated the pooled LR because, unlike diagnostic odds ratios (ORs), the LRs can be used for clinical decisions.

Studies were grouped into 2 subsets depending on the accuracy of the D-dimer that was used: (1) high sensitivity; (2) moderate sensitivity, according to Stein et al,¹⁸ and the same calculations were performed. Diagnostic ORs were calculated with correction for 100% sensitivities by adding 0.5 to each cell of the 2×2 table.^{24,25} The diagnostic OR is a single indicator of diagnostic test performance reflecting its overall accuracy. Using the random-effects model of DerSimonian and Laird, the pooled estimates for the diagnostic OR overall as well as for the 2 subsets of D-Dimer assays were calculated. For the 2 subsets of D-dimer assays, we evaluated differences between the sensitivity and specificity of the assays, between the low and moderate clinical probability groups, and moderate and high pretest probability groups using a χ^2 test.

RESULTS

After reviewing all titles and abstracts, we identified 67 of 274 articles for further review. Of the 67 articles, 14 met the inclusion criteria involving 8239 patients (TABLE 1).^{9,13-15,26-35} The only studies eligible used the Wells clinical prediction rule (TABLE 2). One study reported D-dimer data on an earlier study so it was not included in the calculation of prevalence.²⁷ Eleven of the 14 studies evaluating 5690 patients incorporated D-dimer testing into the diagnostic algorithm.^{9,13-15,27-34}

Does the Clinical Prediction Rule Accurately Categorize the Pretest Probability Estimate?

To be useful, the clinical probability estimate for DVT must be reproduc-

ible. Put another way, when assessing the same patient or different patient populations presenting with suspected DVT, the clinical prediction rule should yield similar estimates for the risk of DVT. All studies included in this systematic review used the same clinical prediction rule. The pooled prevalence of DVT in the studies included in this meta-analysis was 19% (95% CI, 16%-23%). The pooled prevalence of DVT in the low, moderate, and high clinical probability groups was 5.0% (95% CI, 4.0%-8.0%), 17% (95% CI, 13%-23%), and 53% (95% CI, 44%-61%), respectively (FIGURE). Interobserver reliability has not been widely evaluated, but the reported studies included many different physicians with a wide range of clinical experience, including junior residents.

Applying the Wells¹³ criteria, the patient would have a score of zero summed by pitting edema (1 point), bed rest (1 point), and an alternative diagnosis (cellulitis) at least as likely as DVT (-2 points). Using the clinical prediction rule, the clinician concludes that the patient has a low clinical probability of having an acute DVT. The data suggest that the clinician should be confident that the prevalence of DVT is around 5%. Would additional tests lower the likelihood of DVT below 5%?

D-Dimer Testing

D-Dimer is a degradation product of a cross-linked fibrin blood clot. Levels of D-dimer are typically elevated in patients with acute venous thromboembolism. D-Dimer levels may also be increased by a variety of nonthrombotic disorders including recent major surgery, hemorrhage, trauma, pregnancy, cancer, or acute arterial thrombosis.³⁶ D-Dimer assays are, in general, sensitive but nonspecific markers so that a positive D-dimer result is not useful to "rule in" the diagnosis of DVT. Instead, the value of the D-dimer is with a negative test result that works to lower the likelihood of the diagnosis.

Table 1. Summary of Studies of Deep Vein Thrombosis Diagnosis Involving Clinical Prediction Rule ± D-Dimer Testing in Outpatients

Source	Evidence Quality Level	Outpatient Population	Had Ultrasound, %	Requiring Serial Ultrasound, %	D-Dimer Assay	Score	Prior DVT Excluded	Prevalence of DVT, %
Anderson et al, ²⁶ 1999	1	447	100	27	N/A	Wells	Yes	13.1
Anderson et al, ²⁷ 2000	2	214	100	N/A	Moderate sensitivity	Wells	Yes	13.1
Miron et al, ²⁸ 2000	2	270	N/A	N/A	High sensitivity	Wells empirical estimate*	Yes	21.1
Kearon et al, ²⁹ 2001	1	445	60	N/A	Moderate sensitivity	Wells	Yes	14.4
Aguilar et al, ³⁰ 2002	2	134	100	0	High sensitivity	Wells	Not stated	NA
Bucek et al, ³¹ 2002	2	99 Patients with low clinical probability	74	0	High sensitivity	Wells	No†	NA
Kraaijenhagen et al, ¹⁵ 2002	1	1756	100	47	Moderate sensitivity	Wells	Yes	24.2
Shields et al, ³² 2002	2	102	100	0	Moderate sensitivity	Wells	Yes	16.7
Tick et al, ³³ 2002	1	811	100	10	Moderate sensitivity	Wells	Yes	42.5
Anderson et al, ³⁴ 2003	1	1075	71	19	Moderate sensitivity	Modified Wells‡	No	17.9
Bates et al, ⁹ 2003	1	556	49	7	High sensitivity	Wells	Yes	10.1
Schutgens et al, ¹⁴ 2003	1	812	78	38	High sensitivity	Wells	Yes	39.0
Wells et al, ¹³ 2003	1	1082	62	18	Moderate sensitivity	Modified Wells‡	No	15.7
Stevens et al, ³⁵ 2004	1	436	100	0	Not done	Wells	Yes	13.9

Abbreviations: DVT, deep vein thrombosis; IPG, impedance plethysmography; overall prevalence not available.

*Did not report D-dimer data; clinical prediction tool data from this prospective study was analyzed retrospectively.

†Only results for patients without prior DVT used in analysis (n = 87).

‡Modified Wells Score including 1 point for a history of prior DVT.

Table 2. Simplified Clinical Model for Assessment of Deep Vein Thrombosis*

Clinical Variable	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)†	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

Abbreviation: DVT, deep vein thrombosis.

*Scoring method indicates high probability if score is 3 or more; moderate if score is 1 or 2; and low if score is 0 or less.

†In patients with symptoms in both legs, the more symptomatic leg was used.

The ability of a negative D-dimer result to “rule out” DVT depends on the type of assay. D-Dimer assays are categorized as high sensitivity vs moderate sensitivity. The efficiency of a negative result to rule out DVT increases proportionately with the sensitivity of the assay, but it is inversely related to the prevalence of venous thromboem-

bolism. On the other hand, the specificity of the particular D-dimer assay and the population under study affect its ability to exclude the diagnosis of DVT. For instance, use of a less specific assay or the testing of hospitalized patients who are currently ill limits its value due to the expected number of false-positive results.

The incorporation of D-dimer testing into diagnostic algorithms simplifies the management of a patient's case presenting with suspected DVT. Since the last review, numerous trials evaluated the accuracy of D-dimer and its incorporation into the diagnostic approach in patients with suspected DVT. Recent meta-analyses summarize the accuracy of various D-dimer assays compared with gold standard imaging tests for DVT.

Returning to the clinical scenario outlined earlier, a D-dimer test is performed. The hospital uses a moderately sensitive D-dimer assay. Does the type of D-dimer assay matter? Does the D-dimer result affect the already low probability of DVT?

How Will D-Dimer Testing Simplify DVT Diagnosis?

Although a variety of quantitative and qualitative D-dimer assays are available and with all involving specific

monoclonal antibodies, 2 methods have been extensively investigated: enzyme-linked immunosorbent assays and whole-blood assays. There is wide variation in the sensitivity, normal reference ranges, and cut-off points among different assays. Current available assays can be divided into highly sensitive or moderately sensitive tests.¹⁸ A recent meta-analysis of different D-dimer assays shows that the enzyme-linked immunosorbent assays and certain immunoturbidimetric tests are highly sensitive ($\geq 95\%$) but less specific (approximately 40% at a cut-off value of 500 ng/mL) for excluding DVT.¹⁸ In general, other D-dimer methods such as whole-blood and quantitative latex agglutination assays are moderately sensitive ($\approx 85\%$) but more specific ($> 65\%$). Therefore, the probability after testing varies according to the D-dimer assay used. Before clinicians use a particular D-dimer assay to revise their clinical probability estimate, they should be aware of the differences and interpret the results accordingly. The use of D-dimer testing has improved the diagnostic process in suspected DVT, but the D-dimer result itself does not serve as the reference standard for the presence or absence of DVT.

The pooled sensitivity, specificity, and negative LR of the D-dimer test in the low clinical probability group were 88% (95% CI, 81%-92%), 72% (95% CI, 65%-78%), and 0.18% (95% CI, 0.12%-0.28%), respectively. Among patients with moderate clinical probability estimate, the pooled values were 90% (95% CI, 80%-95%), 58% (95% CI, 49%-67%), and 0.19% (95% CI, 0.11%-0.32%), respectively; among patients with high clinical probability estimate the results were 92% (95% CI, 85%-96%), 45% (95% CI, 37%-52%), and 0.16% (95% CI, 0.09%-0.30%), respectively. The specificity of D-dimer testing decreased as the clinical suspicion for DVT increased from low to moderate, and from moderate to high ($P < .001$) with no change in the sensitivity ($P = .51, .28$, respectively). The lower

specificity of D-dimer testing among patients with a high clinical suspicion for DVT might be due to more comorbid conditions (eg, surgery or cancer) that can cause high D-dimer levels.³⁷

Among patients in this group, the number of false-positive D-dimer results can exceed the number of negative results, thereby limiting its use. The pooled estimates for diagnos-

Figure. Prevalence of Deep Vein Thrombosis

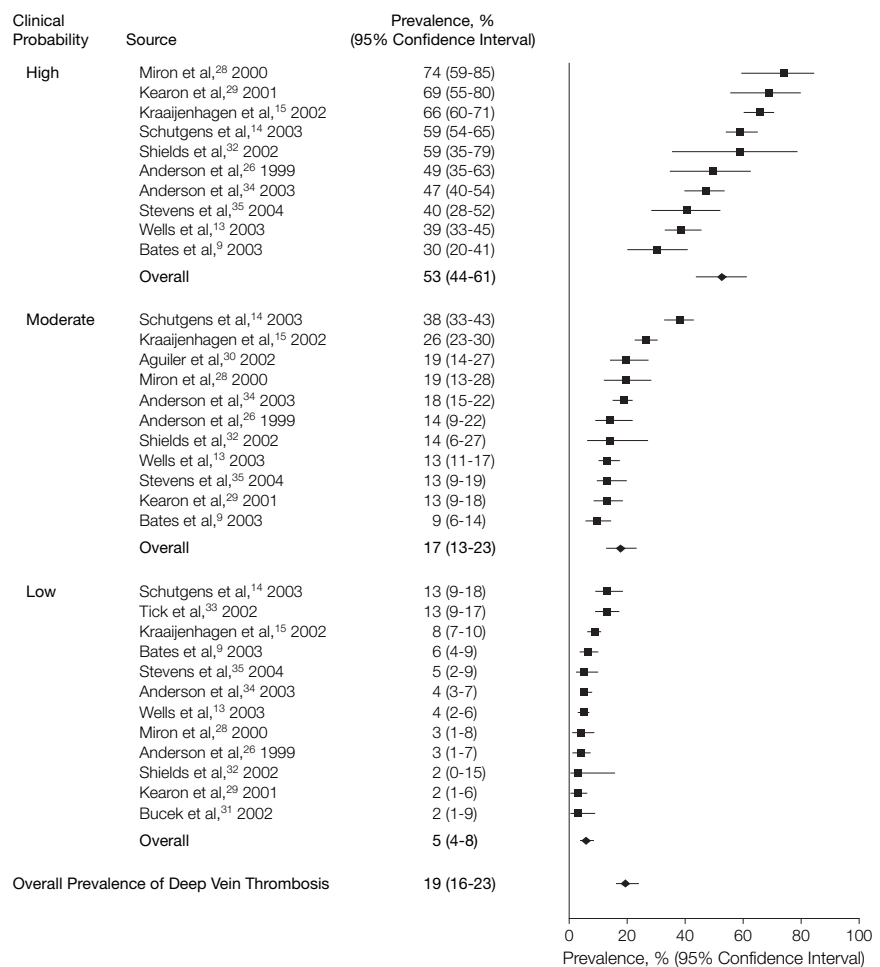


Table 3. Accuracy Measures for D-Dimer Pooling of All Studies

Measures	Clinical Pretest Probability (95% Confidence Interval)		
	Low	Moderate	High
Sensitivity, %	88 (81-92)	90 (80-95)	92 (85-96)
Specificity, %	72 (65-78)	58 (49-67)	45 (37-52)
Negative predictive value	99 (98-99)	96 (94-97)	84 (77-89)
Positive predictive value	17 (13-20)	32 (25-41)	66 (56-75)
Positive likelihood ratio	3.3 (2.6-4.1)	2.1 (1.8-2.5)	1.6 (1.5-1.8)
Negative likelihood ratio	0.18 (0.12-0.28)	0.19 (0.11-0.32)	0.16 (0.09-0.30)
Diagnostic OR	17 (9.9-28)	14 (8.6-21)	12 (5.7-25)

Abbreviation: OR, odds ratio.

tic OR for D-dimer tests in the low, moderate, and high clinical probability groups were 17 (95% CI, 9.9-28), 14 (95% CI, 8.6-21), and 12 (95% CI, 5.7-25), respectively; that is the diagnostic OR did not differ between clinical probability estimates despite a variation in sensitivity and specificity. These data are summarized in TABLE 3. Since the literature suggests

that D-dimer assays can be broadly considered as high-sensitivity or moderate-sensitivity assays, we analyzed the eligible D-dimer studies in these categories.

Moderate-Sensitivity D-Dimer Assays

The sensitivity, specificity, negative predictive values, positive and negative LRs,

and their respective 95% CIs for the studies that used moderate-sensitivity D-dimer assays are demonstrated in TABLE 4. Data are presented for each clinical probability estimate category. The negative LRs are not sufficiently low to exclude DVT without ultrasound among patients with moderate and high pretest probability estimates. Among these patients, the probability after testing for

Table 4. Accuracy Measures in the Moderate-Sensitivity D-Dimer Studies

Clinical Probability Before Testing	Study	Sensitivity, %	Specificity, %	NPV, %	LR+ (95% CI)	LR- (95% CI)
Low	Wells et al, ¹³ 2003	93	73	100	3.7 (2.9-4.6)	0.10 (0.01-1.41)
	Kraaijenhagen et al, ¹⁵ 2002	87	67	98	2.6 (2.3-3.1)	0.20 (0.11-0.36)
	Kearon et al, ²⁸ 2001	80	88	99	6.4 (3.6-11.4)	0.23 (0.04-1.31)
	Anderson et al, ²⁷ 2000	90	85	99	6.7 (4.3-10.4)	0.12 (0.01-1.68)
	Anderson et al, ³⁴ 2003	85	73	99	3.2 (2.5-4.1)	0.20 (0.07-0.58)
	Shields et al, ³² 2002	NE	80	98	5.0 (2.7-9.3)	0.32 (0.03-3.50)
	Weighted average (95% CI)	86 (79-92)	78 (71-83)	99 (98-99)	4.0 (3.0-5.4)	0.20 (0.12-0.31)
Moderate	Wells et al, ¹³ 2003	94	60	98	2.4 (2.0-2.8)	0.10 (0.03-0.38)
	Anderson et al, ³⁴ 2003	80	72	94	2.9 (2.4-3.6)	0.27 (0.17-0.43)
	Kraaijenhagen et al, ¹⁵ 2002	94	57	96	2.2 (2.0-2.5)	0.11 (0.05-0.21)
	Shields et al, ³² 2002	93	53	98	2.1 (1.5-3.0)	0.14 (0.01-1.97)
	Kearon et al, ²⁸ 2001	71	69	94	2.3 (1.6-3.2)	0.42 (0.23-0.80)
	Anderson et al, ²⁷ 2000	67	84	94	4.2 (2.0-9.0)	0.40 (0.16-1.00)
	Weighted average (95% CI)	85 (73-93)	66 (58-73)	95 (93-97)	2.4 (2.1-2.7)	0.23 (0.13-0.39)
High	Wells et al, ¹³ 2003	83	44	79	1.5 (1.2-1.9)	0.39 (0.20-0.77)
	Anderson et al, ³⁴ 2003	84	48	77	1.6 (1.3-2.0)	0.34 (0.20-0.56)
	Shields et al, ³² 2002	80	71	71	2.8 (0.8-9.4)	0.28 (0.07-1.06)
	Kraaijenhagen et al, ¹⁵ 2002	98	44	91	1.7 (1.5-2.1)	0.05 (0.02-0.14)
	Kearon et al, ²⁸ 2001	94	43	75	1.7 (1.0-2.6)	0.13 (0.03-0.59)
	Anderson et al, ²⁷ 2000	87	87	87	6.5 (1.8-24.0)	0.15 (0.04-0.57)
	Weighted average (95% CI)	90 (80-95)	49 (40-58)	81 (74-86)	1.7 (1.5-1.9)	0.20 (0.10-0.38)

Abbreviations: CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NE, not estimable; NPV, negative predictive value.

Table 5. Accuracy Measures in the High-Sensitivity D-Dimer Studies

Clinical Probability Before Testing	Study	Sensitivity, %	Specificity, %	NPV, %	LR+ (95% CI)	LR- (95% CI)
Low	Bates et al, ⁹ 2003	97	69	100	3.3 (2.7-3.9)	0.04 (0-0.65)
	Schutgens et al, ¹⁴ 2003	96	51	99	2.0 (1.7-2.4)	0.07 (0.01-0.51)
	Bucek et al, ³¹ 2002	83	53	99	2.1 (1.7-2.6)	0.32 (0.03-3.99)
	Weighted average (95% CI)	95 (82-99)	58 (45-71)	99 (97-100)	2.4 (1.7-3.3)	0.10 (0.03-0.37)
Moderate	Bates et al, ⁹ 2003	94	52	99	2.0 (1.6-2.4)	0.11 (0.02-0.76)
	Schutgens et al, ¹⁴ 2003	100	40	99	1.7 (1.5-1.9)	0.01 (0-0.16)
	Aguilar et al, ³⁰ 2002	98	32	99	1.5 (1.3-1.7)	0.06 (0-0.85)
	Weighted average (95% CI)	98 (91-100)	41 (31-52)	99 (96-100)	1.7 (1.5-1.9)	0.05 (0.01-0.21)
High	Bates et al, ⁹ 2003	98	40	98	1.7 (1.3-2.1)	0.06 (0-0.85)
	Schutgens et al, ¹⁴ 2003	98	34	90	1.5 (1.3-1.7)	0.07 (0.03-0.20)
	Weighted average (95% CI)	97 (94-99)	36 (29-43)	92 (81-97)	1.5 (1.4-1.7)	0.07 (0.03-0.18)

Abbreviations: LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value.

DVT is greater than 1% (see negative predictive values in TABLE 5). When combined with a negative D-dimer result, diagnostic imaging and anticoagulant therapy can be safely withheld for patients with a low clinical probability estimate since the negative LR (0.20; 95% CI, 0.12-0.31) is such that the probability after testing for DVT is less than 1%.

High-Sensitivity D-Dimer Assays

The sensitivity, specificity, negative predictive values, positive and negative LRs, and their respective 95% CIs for the studies that used high-sensitivity D-dimer assays are demonstrated in Table 5. When combined with a negative D-dimer result, diagnostic imaging and anticoagulant therapy can be safely withheld in patients with a low (LR, 0.10; 95% CI, 0.03-0.37) or moderate clinical probability estimate (LR, 0.05; 95% CI, 0.01-0.21) because they create a probability estimate after testing for DVT of less than 1%. With a high clinical probability estimate, a normal D-dimer result does not have an LR low enough so that the probability of DVT becomes less than 1%. These results suggest pooling D-dimer data may not be appropriate. TABLE 6 demonstrates the probabilities after testing for the different clinical probability estimates according to the D-dimer results and the table notes provide an explanation of the application of Bayes theorem. Assessing the clinical impact of different sensitivity D-dimer assays on venous thromboembolic outcomes requires assumptions about the proportions of patients in each clinical probability category, since they have not been compared in head-to-head comparisons. This type of assessment is best performed by a formal decision analysis in which D-dimer assay accuracies and DVT prevalence are varied and this is beyond the scope of this article. We would suggest that comparative studies are required to provide more definitive conclusions.

Are Serial Ultrasounds Needed?

Should a negative D-dimer result after a normal ultrasound suggest a need for serial ultrasonography?

Table 6. Probabilities by Clinical Probability Estimate Combined with D-Dimer Assays After Testing*

	Clinical Probability Estimate†		
	Low	Moderate	High
Point estimate for deep vein thrombosis likelihood	5	17	53
Probability for positive D-dimer after testing (high sensitivity)	11	25	63
Probability for negative D-Dimer after testing (high sensitivity)	0.5	1	8.6
Probability for positive D-dimer after testing (moderate sensitivity)	17	34	67
Probability for negative D-dimer after testing (moderate sensitivity)	0.9	4.4	19

*Probability after testing from application of Bayes Theorem.

†Posttest odds = pretest odds × likelihood ratio; pretest odds derived from pretest probability as follows: pretest odds = pretest probability/(1 - pretest probability). Similarly posttest probability derived from posttest odds by posttest odds/(1 + posttest odds). For example using a negative result with a high-sensitivity D-dimer if patient is low pretest probability then pretest odds = 0.05/.95 = 0.052. Next posttest odds = 0.052 X 0.10 (from Table 5) = 0.0052. Convert to posttest probability by 0.052/1.0052 = 0.052 or 0.5%.

Five studies reported sufficient data to enable the determination of the LR for a negative D-dimer result when the clinical probability estimate was moderate or high and the initial ultrasound was normal (data not shown).^{9,13-15,34} Two studies used a high-sensitivity D-dimer.^{9,14} Since the probability of DVT after an initially negative ultrasound is low, the LR for a negative D-dimer result ranges from 0.22 to 0.45 and results in a probability of DVT of less than 1% after testing. Thus, regardless of the clinical probability estimate, a negative D-dimer result using a moderately sensitive D-dimer assay combined with a negative initial ultrasound safely obviates the need for serial ultrasonography. However, caution must be used when performing D-dimer testing in patients with prolonged symptoms of suspected DVT or after a prolonged period of heparin therapy (>24 hours).³⁸

SCENARIO RESOLUTION

The clinician has already determined that the patient has a low pretest probability for DVT. The D-dimer result is now determined to be negative and therefore the probability of DVT after testing is sufficiently low (<1%) that the diagnosis can be safely ruled out. If the D-dimer result had been positive, the patient would

require ultrasound imaging. In patients with low pretest probability, the combination of a normal ultrasound and positive D-dimer result also reliably excludes clinically important DVT without the need for follow-up ultrasound (probability after testing <1%). If the ultrasound result is abnormal, it is usually considered predictive of DVT, although the probability after testing may be as low as 90%. Therefore, consideration should be given that it may be a false-positive result. Small, isolated, single-vein, nonocclusive ultrasound results have been reported to be falsely positive, mostly since they represent chronic DVT.³⁹

BOTTOM LINE

Outpatients presenting with suspected DVT should be initially assessed using a validated clinical prediction rule. The clinical prediction published by Wells et al¹³ has been assessed and validated in multiple clinical studies and can accurately categorize outpatients as low, moderate, or high clinical probability. Using this model, less than 5% of outpatients classified as low clinical probability have DVT. No other prediction tools met our eligibility criteria. A recent study suggests the prediction rule may not work in the primary care setting but limitations in the design of that study (in par-

ticular, failure to prospectively apply the rule as the diagnostic strategy) necessitate further research in primary care.⁴⁰ Validation studies of the model are required for hospitalized patients.

Incorporating D-dimer testing into a diagnostic algorithm further simplifies the management of a patient's case when he or she presents with suspected DVT. Once the clinical probability has been estimated, the D-dimer result can be combined to determine if DVT can be safely ruled out without use of diagnostic imaging. Currently, the diagnosis of DVT can be excluded without the need for ultrasound by using a combination of low clinical probability estimate and a negative D-dimer result, and this strategy should apply to as much as 40% of patients referred with suspected DVT. It should be kept in mind that ultrasound may provide information helpful to establish an alternative diagnosis but ultrasound imaging for DVT is not required for every patient. Although the data are more limited, it seems likely that serial testing after an initially normal ultrasound result can

be confined to high-probability patients with positive D-dimer results. Patients with moderate probability and a negative high-sensitivity D-dimer can have DVT ruled out.

Among patients with high clinical probability estimates, a normal D-dimer result does not have a sufficiently low LR. Therefore, all high-probability patients require diagnostic imaging to safely rule out DVT. Thus, D-dimer assays should not affect initial management for patients with a high probability of a DVT, because all of them require diagnostic imaging.

The specificity of D-dimer assays decreases as the clinical probability estimate increases; this leads to more false-positive test results, thereby limiting its utility. This emphasizes that D-dimer should not be used as a screening test and indeed some advocate that D-dimer assays should not be used for patients at high risk for a false-positive result, ie, elderly patients, patients with cancer, and hospitalized patients.

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Society in its full sense . . . is never an entity separable from the individuals who compose it. No individual can arrive even at the threshold of his potentialities without a culture in which he participates. Conversely, no civilization has in it any element which in the last analysis is not the contribution of an individual.

—Ruth Benedict (1887-1948)