Prospective Study of Color Duplex Ultrasonography Compared with Contrast Venography in Patients Suspected of Having Deep Venous Thrombosis of the Upper Extremities

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Background: **The optimal strategy for diagnosis of deep venous thrombosis (DVT) is less well established for the upper extremities than for the lower extremities. Duplex color ultrasonography can be difficult to perform in the upper extremities because of their anatomy, and contrast venography is often indicated. Moreover, limited data exist on the use of duplex color ultrasonography in this setting.**

Objective: **To determine the accuracy of duplex ultrasonography for diagnosis of DVT of the upper extremities.**

Design: **Prospective study of duplex ultrasonography compared with venography.**

Setting: **A teaching hospital in Amsterdam, the Netherlands.**

Patients: **126 consecutive inpatients and outpatients with suspected DVT of the upper extremities.**

Measurements: **Contrast venography was obtained after duplex ultrasonography and was judged independently. A three-step protocol, involving compression ultrasonography, color ultrasonography, and color Doppler ultrasonography, was used. Sensitivity, specificity, and likelihood ratios for ultrasonography as a whole were calculated. The independent value of each step was assessed.**

Results: **Venography and ultrasonography were not feasible in 23 of 126 patients (18%) and 1 of 126 patients (0.8%), respectively. Results of ultrasonography were inconclusive in 3 patients. Venography demonstrated thrombosis in 44 of 99 patients (44%); in 36 patients (36%), thrombosis was related to intravenous catheters or malignant disease. Sensitivity and specificity of duplex ultrasonography were 82% (95% CI, 70% to 93%) and 82% (CI, 72% to 92%), respectively. Venous incompressibility correlated well with thrombosis, whereas only 50% of isolated flow abnormalities proved to be thrombosis-related.**

Conclusions: **Duplex ultrasonography may be the method of choice for initial diagnosis of patients with suspected thrombosis of the upper extremities. However, in patients with isolated flow abnormalities, contrast venography should be performed.**

Ann Intern Med. 2002;136:865-872. www.annals.org
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The exact incidence of deep venous thrombosis (DVT) of the upper extremities is unknown. A prevalence of 2 cases per 1000 hospital admissions has been reported (1). Deep venous thrombosis of the upper extremities is increasingly recognized as causing high mortality and morbidity, similar to DVT of the leg (2, 3). Deep venous thrombosis of the upper extremities is closely associated with malignant disease and the use of central venous access lines (3–11). Nevertheless, few prospective studies on diagnosis and management of DVT of the upper extremities have been published. Contrast venography is generally considered the reference method for diagnosis of DVT of the upper extremities (2, 3). However, because of its inherent problems, such as availability, use of ionizing radiation, necessity of iodinated contrast media, and technical difficulties in obtaining intravenous access, researchers have searched for more appropriate, noninvasive methods.

Ultrasonography is widely available and has been used extensively for diagnosis of DVT of the lower extremities (12–18). However, only a few prospective studies have been done in limited numbers of patients to establish its role in the diagnosis of DVT of the upper extremities (3, 19–22). In addition, ultrasonography is problematic because of the anatomy of the upper extremities. The overlying bony structures and the inability to visualize the central intrathoracic venous system limit the value of compression ultrasonography. Therefore, duplex color ultrasonography has been proposed for diagnosis of DVT of the upper extremities (3, 19–24). We sought to assess the diagnostic accuracy of duplex color ultrasonography compared with contrast venography in patients suspected of having DVT of the upper extremities.

METHODS

Study Sample

From August 1996 to March 2001, 126 consecutive outpatients and inpatients with clinically suspected

Context

Venography is the standard test for diagnosing deep venous thrombosis of the upper extremities.

It is not an ideal test because it requires intravenous access and contrast media.

Ultrasonography is a widely available alternative test, but how feasible and accurate is it?

Contribution

In 126 consecutive patients with suspected upper-extremity thrombosis, venography and ultrasonography were not feasible in 18% and fewer than 1%, respectively.

When venography was used as the reference standard, the likelihood ratio for a positive result on ultrasonography was 4.5 (95% CI, 2.53 to 8.02). The likelihood ratio for a negative result was 0.2 (CI, 0.12 to 5.57).

Implications

Positive findings on ultrasonography are reasonably accurate for diagnosing deep venous thrombosis of the upper extremities.

–The Editors

DVT of the upper extremities were referred for diagnostic work-up. Three of these patients were referred twice, and 2 patients were referred three times. Patients were excluded if they were pregnant, were younger than 18 years of age, had renal failure prohibiting contrast venography, had a known allergy to iodinated contrast agents, or were unable to provide informed consent. Informed consent for duplex color ultrasonography and venography was obtained at referral from all but 2 patients, and the Institutional Review Board of the Academic Medical Center, Amsterdam, approved the study.

Contrast Venography

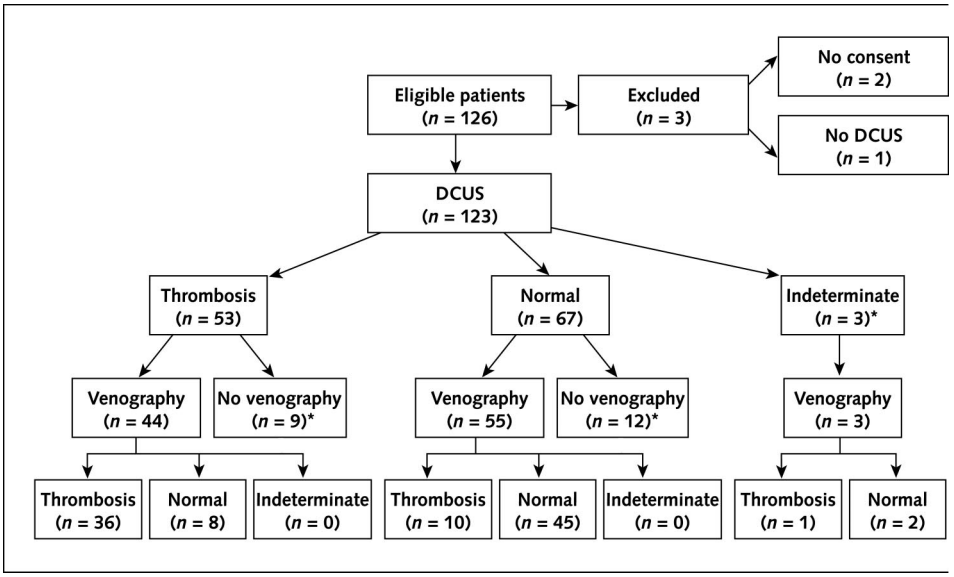
Contrast venography of the symptomatic extremity was performed by using digital subtraction angiography equipment (Polytron, Siemens, Erlangen, Germany). Standardized protocol consisted of a 30-mL contrast injection in the antecubital vein or, if this was not possible, in a more distal forearm vein in the affected arm. No tourniquet was applied. Patients were studied with the examined arm extended and with little abduction of the upper arm to prevent compression of the axillary vein by soft tissues. Low osmolar nonionic contrast was used at a concentration of 300 mg of iodine per liter (Omnipaque, Nycomed-Amersham, Oslo, Norway). All injections were performed by hand. Digital subtraction images of the brachial, axillary, subclavian, and superior caval veins were obtained at a rate of one frame per second. We defined DVT of the upper extremities as the presence of an intraluminal thrombus or persistent nonfilling of a venous segment in the presence of filling of collateral vessels, as demonstrated by contrast venography. All other findings were considered inadequate for interpretation.

Duplex Color Ultrasonography

Duplex color ultrasonography of the affected extremity was performed with assessment of the basilic, cephalic, axillary, and subclavian veins. The jugular and innominate veins were not included; because the first is visible only on ultrasonography and the second is visible only on venography, comparison is not possible. After identification of the relevant vessels, a three-step procedure was performed. This involved compression ultrasonography of the venous segments that could be reached, assessment of intravascular thrombus by using color ultrasonography, and flow measurements during respiration to determine the outflow of the venous system by using color Doppler ultrasonography. Patients were asked to perform the Valsalva maneuver to allow assessment of changes in flow pattern. Flow patterns of the unaffected veins in the upper extremities were used only in cases of doubt. All tests were performed by senior residents and staff radiologists who had adequate experience in duplex color ultrasonography, using normal departmental practice. We used three qualified ultrasonography machines that were updated but were not changed during the study (Sonos 2000, Hewlett Packard, Andover, Massachusetts; Aloka 1700 and 2000, Aloka, Tokyo, Japan); probes ranged from 4.5 to 7.5 MHz.

Duplex color ultrasonography was considered to demonstrate DVT if it showed noncompressibility of a venous segment, a visible intraluminal thrombus, or an abnormal flow pattern (absent flow or absence of phasic flow pattern indicating outflow obstruction) (3). If none of these findings were present, the results were considered normal. All other findings, lack of visualization,

Figure 1. **Flow of patients through the study.**



DCUS = duplex color ultrasonography. * Excluded from further analysis.

and performance of flow measurements were considered inadequate for interpretation.

Study Design

We performed a prospective comparative study in consecutive patients with clinically suspected DVT of the upper extremities. All patients underwent duplex color ultrasonography as the first test. Results were reported independently and within 4 hours before performance of the reference method, contrast digital venography. Because we followed departmental routine in our teaching hospital, a variety of qualified residents and staff personnel performed the ultrasonography and venography studies at any time during the day or evening. At all times, the radiologist who performed venography was blinded to the initial results on color duplex ultrasonography. Findings on duplex color ultrasonography were compared with those on contrast venography (the reference method). We also assessed potential factors associated with the cause of DVT of the upper extremities, such as the presence of malignant disease, indwelling catheters, or a hypercoagulable state.

Statistical Analysis

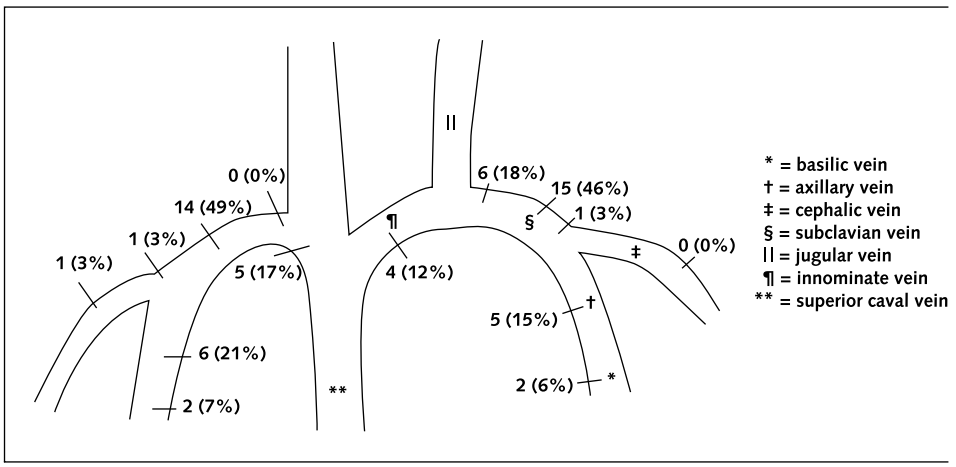
We calculated diagnostic accuracy (sensitivity and specificity), likelihood ratios (25), and 95% CIs for all findings except indeterminate findings on duplex color ultrasonography (because comparison with contrast venography was not possible). Patient groups in which DVT of the upper extremities was confirmed, excluded, or remained uncertain were compared by using the chi-square test. A P value less than 0.05 indicated statistical significance.

RESULTS

During the inclusion period, 126 patients were eligible for study enrollment. A total of 27 patients was excluded from the analysis. Contrast venography could not be performed in 16 patients because of medical or technical reasons (failure to obtain venous access, $n = 10$; renal failure, $n = 3$; pregnancy, $n = 2$; and iodinated contrast allergy, $n = 1$). Another 5 patients were excluded because of logistic reasons, and 2 patients declined to provide informed consent. Therefore, venography could not be performed in 23 of 126 patients (18%). In 1 patient, duplex color ultrasonography was not performed because of logistic reasons. Finally, results of duplex color ultrasonography were indeterminate in 3 patients, resulting in a conclusive rate of 98%. A flow diagram of patients is provided in **Figure 1**.

A total of 99 patients was available for evaluation after undergoing both duplex color ultrasonography and

Figure 2. **Distribution of 29 thrombi in the right upper-extremity veins and 33 thrombi in the left upper-extremity veins on digital subtraction venography.**



contrast venography. Forty-four patients were men, and 55 were women; the mean age of all patients was 54 years (range, 18 to 92 years). Deep venous thrombosis was demonstrated by contrast venography in 44 patients (44%). The distribution of thrombi in the veins of the right or left upper extremity on venography is shown in **Figure 2**. Eight patients had primary thrombosis of unknown cause, while an underlying cause could be shown in 36 patients (**Table 1**). Malignant disease was present in 63% of patients with proven DVT of the upper extremities and in 19 of 55 patients (35%) in whom DVT was excluded ($P < 0.01$).

Results on duplex color ultrasonography were compared with results on contrast venography (**Table 2**). Eight studies were false negative and 10 were false positive, resulting in a sensitivity and specificity of 82% (95% CI, 70% to 93%) and 82% (CI, 72% to 92%), respectively. The likelihood ratio was 4.5 (CI, 2.53 to 8.02) for a true-positive test result and 0.22 (CI, 0.12 to 0.42) for a true-negative test result.

Table 3 shows the correlation between criteria for absence or presence of DVT of the upper extremities on duplex color ultrasonography and findings on contrast venography. Isolated noncompressibility of a venous segment was relatively uncommon but correlated with DVT of the upper extremities in all cases. The identification of an intraluminal thrombus was highly correlated with DVT, while flow abnormalities were least correlated with DVT. Additional coincidental findings on duplex color ultrasonography were seen in 8 patients (solid mass, $n = 4$; cystic mass, $n = 2$; lymphadenopathy, $n = 1$; abscess, $n = 1$). Contrast venography revealed additional information in 5 patients (external compression of the vein, $n = 4$; pneumothorax, $n = 1$)

Table 1. **Identified Causes of Proven Deep Venous Thrombosis of the Upper Extremities in 44 Patients**

Identified Causes	Patients with Central Venous Catheters	Patients without Central Venous Catheters	All Patients
	n		*n (%)*
Malignant disease			
Lymphoma/leukemia	9	2	
Pancreas cancer	5	1	
Breast cancer	1	2	
Chest disorders (lung, pleura, esophagus)	0	3	
Other (gastrointestinal tract, ovary, urothelial, myeloma)	3	2	
Total	18	10	28 (63)
Central venous catheter without malignant disease			6 (14)
Hypercoagulable state			2 (5)
Protein C deficiency with central venous catheter			1
Factor II mutation			1
Primary thrombosis of unknown cause			8 (18)

DISCUSSION

Deep venous thrombosis of the upper extremities is increasingly encountered in clinical practice because of such factors as more frequent use of long-term indwelling venous catheters (2). To make the diagnosis, physicians must often rely on clinical suspicion and contrast venography. Venography is widely accepted as the reference method for establishing the presence or absence of DVT of the leg, although interpretation of venograms is subject to considerable observer variation (4% to 26%) (26, 27).

Only a few prospective studies have compared the sensitivity and specificity of duplex color ultrasonography with those of venography in DVT (**Table 4**). None of these studies disclosed much detail about observer variability of the reference tests. In our study, we performed a subanalysis of the first 62 consecutive venograms. The interobserver agreement was 94% (κ = 0.88 [CI, 0.77 to 0.99]) for a vascular radiologist and 76% (κ = 0.56 [CI, 0.33 to 0.79]) for an experienced general radiologist compared with consensus, showing that contrast venography, although imperfect, can be used as a reference test for assessment of DVT of the upper extremities.

We believe that errors in assessing thrombus on duplex ultrasonography and venography are probably independent. Although both procedures detect thrombus, they do so by using different techniques. Duplex color ultrasonography shows noncompressibility or flow abnormality of the vein, and venography shows a filling defect or absent vein. Because of overlying anatomic bony structures, such as the clavicle and sternum, venography can be expected to perform better in detecting more central thrombi. Jugular venous thrombosis, which is detectable by ultrasonography and not by venography, was excluded from our study.

If tests are considered independently, sensitivity and specificity are usually underestimated slightly (28). Regarding our study, we expect that the assessed sensitivity of 82% and specificity of 82% would be the lowest results in actual practice settings. Thirteen percent of our patients were unable to undergo contrast venography, largely because of medical conditions such as prohibited venous access due to extreme arm swelling or contraindications to iodinated contrast injection. In a study by Prandoni and colleagues (3), 4 of 62 patients (6.5%) were unable to undergo venography. This difference may be due to more severe illness in our study, which made intravenous access impossible. For example, 63% of our patients with proven DVT of the upper extremities had known malignant disease, compared with 30% in the group described by Prandoni and colleagues (3).

A possible methodologic failure of our study could be the lack of randomization of ultrasonography and venography. However, all patients referred for diagnostic work-up for suspected DVT of the upper extremities were asked to provide consent at referral, and contrast venography was performed regardless of the outcome of duplex ultrasonography. Furthermore, the diagnostic tests were performed independently by different radiologists who had no knowledge of the test results. We believe that this minimized the chance for bias. In three patients (2%), duplex color ultrasonography was considered indeterminate. One patient had positive results on venography, and two patients had negative results. Although these patients would not have influenced the

Table 2. **Duplex Color Ultrasonography Compared with Contrast Venography in 99 Patients with Suspected Deep Venous Thrombosis of the Upper Extremities***

Duplex Color Ultrasonography	Contrast Venography		
	Thrombus Present	Thrombus Absent	Total
	← *n* →		
Thrombus present	36	10	46
Thrombus absent	8	45	53
Total	44	55	99

* Three indeterminate results on duplex color ultrasonography were not accounted for.

Table 3. **Duplex Color Ultrasonography Criteria in Relation to Contrast Venography for the Presence or Absence of Deep Venous Thrombosis of the Upper Extremities**

Duplex Color Ultrasonography	Contrast Venography	
	Thrombus Present	Thrombus Absent
	n	
Noncompressibility	5	0
Intraluminal thrombus	24	3
Flow abnormality	7	7
Normal	8	45
Total	44	55

Table 4. **Performance Characteristics of Previous Studies of Consecutive Duplex Color Ultrasonography***

Study (Reference)	Year	Sensitivity	Specificity	Patients	Description
		%		*n*	
Prandoni et al. (3)	1997	100	93	58	Limited number of patients; relatively small number of patients with malignant disease
Falk and Smith (19)	1987	100	92	22	Small number of patients; normal volunteers included
Knudson et al. (20)	1990	78	92	91	Reference standard was venography, CT, and MRI
Baxter et al. (21)	1991	100	100	19	Small number of patients
Köksoy et al. (22)	1995	94	88	44	All patients had catheter-related thrombosis

* CT = computed tomography; MRI = magnetic resonance imaging.

performance characteristics of our study, they were excluded.

Ultrasonography is widely available and circumvents several of the disadvantages of contrast venography. In our study, duplex color ultrasonography could be performed in all but one patient. Compression ultrasonography and duplex color ultrasonography have been extensively validated for use in the diagnosis of lower-limb DVT (12–18). However, the upper extremities are anatomically much more complex than the lower extremities because of the shape of the axilla and the overlying bony structures. Therefore, it has been postulated that duplex color ultrasonography is more applicable to diagnosis of DVT of the upper extremities than of the lower extremities (29). In addition, it is more accurate than compression ultrasonography (3, 19–22).

In our study, the sensitivity and specificity of duplex color ultrasonography were 82% and 82%, respectively. These values compare slightly unfavorably with those found in Prandoni and colleagues' study of 58 patients (3), in which sensitivity was 100% (CI, 82% to 100%) and specificity was 93% (CI, 68% to 100%). Other small prospective studies have found ranges of 78% to 100% for sensitivity and 88% and 100% for specificity (19–22). The difference between these results and ours has several possible explanations. The prevalence of DVT of the upper extremities was 44% in our study, similar to that in previously reported studies (3, 19, 20). Our study describes one of the largest known cohorts with this disorder and examined a truly consecutive patient sample. Some of the other prospective studies published to date may have been affected by selection bias because only patients with more severe symptoms or catheter-related DVT of the upper extremities, and sometimes normal volunteers, were assessed (19–22).

Another possible explanation for the difference in diagnostic accuracy could be that our study followed standard clinical practice, which meant that a variety of trained personnel performed duplex color ultrasonography. It is well known that ultrasonography is operator dependent, and it is possible that some of the less experienced ultrasonographers influenced sensitivity and specificity. Other studies may have limited performance of ultrasonography to the best-qualified personnel, leading to relatively better results. Nevertheless, we opted to follow the usual routine at our institution to more closely reflect outcomes in clinical practice.

Each of the ultrasonographers did not separately assess the three criteria for the presence or absence of DVT, but noncompressibility of the veins accessible for ultrasonography was highly correlated with the presence of DVT. Findings are similar for use of compression ultrasonography in the lower-leg veins, which has been validated extensively (29). The visualization of thrombus in a venous segment was also highly correlated with DVT of the upper extremities, but changes in flow were not. The latter finding contradicts two previous publications, which showed very high correlation of flow abnormalities with DVT of the upper extremities (3, 22). In general, we believe that noncompressibility, presence of intraluminal thrombus on duplex color ultrasonography, or both would be sufficient for diagnosis of DVT of the upper extremities. Abnormal flow patterns, however, should be considered suggestive only, and patients with flow abnormalities in isolation should undergo subsequent contrast venography. In five of eight patients with false-negative results on duplex color ultrasonography, findings were correlated with the presence of thrombus in the proximal subclavian vein on the left side, just below the clavicle. One patient with false-negative results on duplex color ultrasonography had isolated innominate venous thrombosis. Therefore, al-

though normal results on duplex color ultrasonography are sufficient to exclude DVT of the upper extremities in most patients, contrast venography should still be considered if clinical suspicion for DVT is high. The likelihood ratio of a negative test result (0.22) also supports this conclusion; although relatively low, it does not indicate that negative results on ultrasonography render venography unnecessary.

The presence of malignant disease has been implicated as a risk factor for DVT. In several studies of thrombosis of the lower extremities, the risk increased from 1.5% for a first event to 7.5% for recurrent idiopathic DVT (30–32). In DVT of the upper extremities, a much higher proportion of patients have malignant disease (63% in our study and 24% to 62% in other studies [1, 3, 6–9]). In our study, the incidence of malignant diseases associated with DVT of the upper extremities was high because two thirds of affected patients also had a central intravenous access line in situ, which is an independent risk factor (7–11). Furthermore, in cases in which malignant disease was an isolated risk factor, the types of cancer seen involved lymph node metastases to the mediastinum or the axilla (breast, esophageal, and lung cancer).

Contrast venography could not be performed in a substantial portion of our sample. This is a potential problem in patients with inconclusive results on duplex color ultrasonography. Some early studies have shown that contrast-enhanced magnetic resonance venography could be used to diagnose DVT of the upper extremities (33, 34); however, this would not be ideal for patients in whom contrast venography is contraindicated because it would still require intravenous access. We anticipate that non–contrast-enhanced magnetic resonance venography sequences could be an alternative procedure in the future.

On the basis of our study and those in the literature, duplex color ultrasonography could be applied as the first-line diagnostic test in patients with suspected DVT of the upper extremities. However, in patients who have only flow abnormalities and in those with normal findings and a high clinical suspicion, additional contrast venography should be performed. In the future, patients who cannot have a contrast venous study but whose history strongly suggests DVT of the upper extremities will probably undergo magnetic resonance venography without the use of contrast. Further study of this issue is necessary.

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Acknowledgment: The authors thank B.A. Hutten of the Clinical Department of Epidemiology, Academic Medical Center, Amsterdam, for statistical support.

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COMMENTARY

This study's estimates of test performance are credible because of good study design. The authors obtained a representative study cohort by enrolling consecutive patients with suspected deep venous thrombosis (DVT) of the upper extremities. Consequently, their findings are likely to apply to patients in similar clinical settings. The authors made sure that each patient had the index test (duplex color ultrasonography) and the gold standard test (digital venography). This protocol helped them to avoid "partial verification bias," in which patients with negative results on the index test don't get the gold standard test. By failing to include patients with true-negative and false-negative results in the final tally of results, studies afflicted by work-up bias overestimate sensitivity and underestimate specificity.

The authors discuss the ability of negative results on color duplex ultrasonography to "exclude" DVT. They found that the likelihood ratio after such results is 0.22 (95% CI, 0.09 to 0.38). The likelihood ratio tells you how much the odds of disease change after a test result, according to the odds ratio form of Bayes' theorem (post-test odds = pretest odds × likelihood ratio). In this study, the prevalence of DVT was 44% among patients clinically suspected of DVT. If a patient's pretest odds were 1:1 (corresponding to a probability of 50%), the post-test odds of DVT after negative results on ultrasonography would be the pretest odds (1:1) times the likelihood ratio (0.22), which equals 0.22:1 (equivalent to a 18% probability). Does an 18% probability "exclude" DVT? The answer depends on the clinician's willingness to withhold anticoagulation when the probability of DVT is 18%.

—*The Editors*