

Withholding Anticoagulation after a Negative Result on Duplex Ultrasonography for Suspected Symptomatic Deep Venous Thrombosis

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Background: Negative results on simplified compression ultrasonography cannot rule out symptomatic deep venous thrombosis (DVT) without further testing, such as repeated ultrasonography several days later. Repeated testing is costly and inconvenient, and patients are sometimes less likely to return for follow-up tests.

Objective: To determine the rate of venous thromboembolism when anticoagulation is withheld in patients with symptoms of DVT of the leg after negative results on a single examination with comprehensive duplex ultrasonography.

Design: Prospective clinical cohort study.

Setting: Peripheral vascular laboratory of a tertiary care academic hospital.

Patients: 445 consecutive patients in whom a first episode of symptomatic DVT was suspected.

Intervention: The researchers examined the entire leg with comprehensive duplex ultrasonography, using compression and Doppler techniques. Anticoagulation was withheld from the group with negative results. Patients were observed for thromboembolic events for 3 months.

Measurements: All patients who had new or progressive symptoms or signs of venous thromboembolism during follow-up underwent objective testing.

Results: Comprehensive duplex ultrasonography yielded normal results in 384 patients (86.3%) and showed DVT in 61 patients (13.7%). Nineteen cases of DVT (31.1%) were isolated to the deep veins of the calf. Nine patients in the negative cohort (2.3%) were excluded from analysis because they received anticoagulation for reasons unrelated to venous thromboembolism. Three of 375 patients (0.80% [95% CI, 0.16% to 2.33%]) in the normal cohort had symptomatic venous thrombosis during the 3-month follow-up. All 384 patients in the negative cohort completed follow-up.

Limitations: The study was conducted at a single tertiary care center by a peripheral vascular staff with substantial experience in duplex ultrasonography, which may limit the applicability of the results to other institutions. Pregnant patients were excluded.

Conclusions: It is safe to withhold anticoagulation after negative results on comprehensive duplex ultrasonography in nonpregnant patients with a suspected first episode of symptomatic DVT of the leg. New or progressive symptoms should prompt further testing.

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Ultrasonography is the most commonly used test in the United States for diagnosis of deep venous thrombosis (DVT) of the leg (1–4). The term *ultrasonography* has been applied to a variety of diagnostic techniques. The most researched technique, simplified compression ultrasonography, is highly sensitive and specific for symptomatic proximal venous thrombosis but does not detect thrombosis in the distal veins of the calf (1–8). Distal DVT may propagate proximally and lead to venous thromboembolism. Therefore, a second examination with simplified compression ultrasonography performed 5 to 7 days later is necessary to detect unvisualized calf vein thrombi that have propagated proximally (9–12).

Repeated testing is inconvenient, and not all patients are able to return for serial tests (9, 10, 12). Many follow-up tests that yield normal results must be performed to detect relatively few patients with disease (9–13). In the United States, approximately 500 000 patients are evaluated annually for DVT (14). Given that results are normal on approximately 80% of initial ultrasonography examinations (15), and only 2% of patients have abnormal results on serial testing 5 to 7 days later (9, 10), as many as 390 000 repeated tests may be performed annually without detecting disease.

A single noninvasive study that safely rules out DVT would be useful. Comprehensive duplex ultrasonography, which examines the deep veins from the inguinal ligament to the level of the malleolus, has not been tested prospectively to determine whether it is adequate to detect clinically important calf DVT and make routine repeated scanning unnecessary. To determine whether negative results on a single examination with comprehensive duplex ultrasonography are adequately sensitive to justify withholding anticoagulation in patients with symptoms of DVT of the leg, we performed a prospective cohort study of consecutive patients in whom a first episode of this disorder was suspected. The primary end point was the rate of venous thromboembolism (including death attributed to venous thromboembolism) when anticoagulant therapy was withheld from patients on the basis of negative results on a single examination with comprehensive duplex ultrasonography. We used 3 months of clinical follow-up to test the validity of this approach (16–18).

METHODS

Patients

From April 2000 through July 2001, we enrolled consecutive adult patients who were referred to a tertiary care

Context

Simplified compression ultrasonography is useful in detecting deep venous thrombosis (DVT), but repeated testing is required 5 to 7 days later to detect proximal propagation from an unvisualized calf vein. Comprehensive duplex ultrasonography examines deep veins from the inguinal ligament to the malleolus.

Contribution

Consecutive patients with suspected symptomatic first episodes of DVT underwent comprehensive duplex ultrasonography. Anticoagulation was withheld if results were negative, regardless of symptoms or clinical signs. On 3-month follow-up, the overall rate of symptomatic venous thrombosis was 0.8%.

Implications

An acceptably low risk for false-negative results on comprehensive duplex ultrasonography may obviate the need for repeated testing in the vast majority of patients with suspected first episodes of DVT.

—The Editors

hospital's peripheral vascular laboratory for a suspected first episode of symptomatic DVT of the leg. Vascular technologists determined the absence of a history of DVT and referred patients to a study clinician, who then performed a history and physical examination and determined eligibility. Criteria for exclusion were previous DVT, pregnancy, technical inability to perform comprehensive duplex ultrasonography, anticipated inability to obtain long-term follow-up (for example, because of homelessness), more than 24 hours of therapeutic anticoagulation before ultrasonography, no informed consent, or long-term anticoagulation planned for another diagnosis (for example, atrial fibrillation). A priori, we determined that patients treated with therapeutic anticoagulation during the 3-month follow-up period for diagnoses unrelated to venous thromboembolism (for example, joint replacement surgery) would be excluded from analysis to avoid confounding results.

Descriptive data, including a score of pretest probability of DVT calculated by using a validated scoring system (19), were collected for each patient. Patients then underwent objective testing for DVT by comprehensive duplex ultrasonography. The LDS Hospital Institutional Review Board approved the study, and all enrolled patients provided written informed consent.

Objective Testing for DVT

Comprehensive, real-time B-mode ultrasonography with color Doppler analysis was performed immediately after enrollment by using the technique described by Talbot (20). Registered vascular technologists performed all ultrasonography, and 1 of 2 certified vascular surgeons on

the hospital staff interpreted the results. Vascular technologists and interpreting physicians were blinded to the enrollment clinicians' assessment and the pretest probability score. A high-resolution, electronically focused linear array transducer with a 3.5- to 10-MHz variable frequency probe (model 5000 scanner, ATL Corp., Bothell, Washington) was used for all studies.

Comprehensive duplex ultrasonography was used to examine the deep veins of the symptomatic leg in all patients. Proximally, patients were examined from the level of the inguinal ligament to the adductor canal in the supine position. The popliteal vein was examined to its trifurcation in the upper calf, and the remainder of the calf veins were examined to the level of the malleolus. Compressibility was assessed at 2-cm intervals in the transverse plane. Interpreting physicians were required by protocol to characterize the study results as negative (DVT absent) if all imaged venous segments were fully compressible or as abnormal (DVT present) if a noncompressible segment was identified. Thus, the sole criterion for the diagnosis of DVT was noncompressibility of the vein. Doppler interrogation of each of these segments was performed, as was imaging distally to the level of the medial malleolus for supplemental information. Anticoagulation was withheld if the initial results of comprehensive duplex ultrasonography were negative (the negative cohort), regardless of symptoms or clinical signs.

Long-Term Follow-up

All patients were instructed to return to the hospital immediately if they experienced symptoms or signs of venous thromboembolism. All patients in the negative cohort were interviewed at least 3 months after study enrollment and queried for specific symptoms of venous thromboembolism, institution of new medications, hospitalization, surgery, diagnostic testing, and general health. We also comprehensively reviewed each patient's electronic medical record, which included all inpatient, outpatient, diagnostic, and pharmacy services.

The primary outcome measure was venous thromboembolism (DVT, pulmonary embolism, or paradoxical embolism) verified by objective testing or by death from venous thromboembolism. The minimum follow-up period of 3 months was chosen on the basis of previous studies (9, 16–18). Patients in whom DVT was suspected because of progressive symptoms were evaluated with repeated ultrasonography and continued long-term follow-up. Those in whom pulmonary embolism was suspected were evaluated with lung scanning, pulmonary angiography, or computed tomography angiography in conjunction with ultrasonography of the legs (21–24).

Methodologic Issues and Avoidance of Bias

We minimized selection bias by sequentially enrolling consecutive patients. Verification bias (25) was avoided because all negative results were verified by 3 months of clinical follow-up for venous thromboembolism. Previous studies

have verified that repeated ultrasonography is a highly sensitive technique for detecting DVT missed on initial ultrasonography (9–11, 15). This makes the potential incorporation bias (26) introduced by repetition of the diagnostic method less relevant.

Experienced vascular surgery staff interpreted comprehensive duplex ultrasonography studies according to predefined criteria for negative and positive results. We limited interobserver variability by using a priori criteria for positive and negative results (20) and by using only 2 interpreters. A previous study found that interobserver agreement is high for this technique (27).

An independent adjudication committee blinded to the study hypothesis reviewed all deaths, characterizing them as insidious or abrupt and indicating whether they were caused by venous thromboembolism. Adjudicators with substantial experience in clinical trials of venous thromboembolism reviewed all records and diagnostic tests of patients in whom venous thromboembolism was suspected during the follow-up period, categorizing venous thromboembolism as present, absent, or indeterminate. A simple majority resolved disputes. Adjudicators were not involved in the care of any patients in the study and were provided with hospital and physician records, death certificates, and imaging studies.

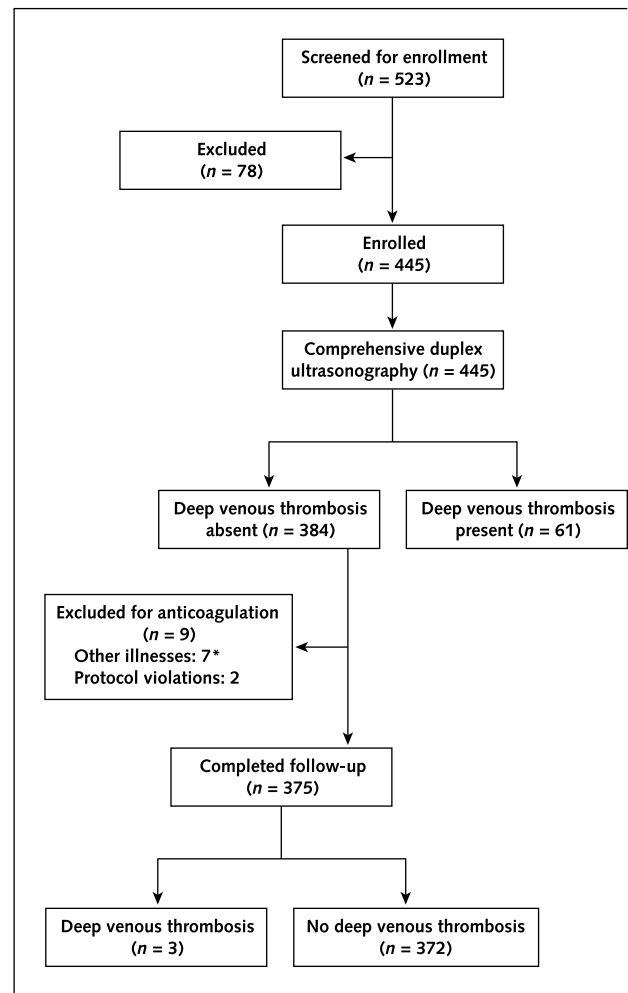
Statistical Analysis

A priori, we hypothesized that the upper boundary of the exact 2-sided 95% CI for the rate of venous thromboembolism would be less than 2.6% when anticoagulant therapy was withheld after negative results on a single examination with comprehensive duplex ultrasonography. We chose 2.6% because this was the event rate observed after a single simplified compression test in a previous study (9). The sample size required to perform equivalence testing was prohibitive, so we enrolled sufficient participants to produce a negative cohort large enough to allow calculation of an exact 2-sided 95% CI of approximately $\pm 1.5\%$. We estimated that 30% of the original sample would have positive results on ultrasonography and that the event rate would be 0.9% in the negative cohort. Therefore, an initial sample size of 500 patients would be needed to yield a negative cohort of 350 patients. With the hypothesized event rate, the upper limit of an exact 2-sided 95% CI (0% to 2.29%) would exclude the published event rate of 2.6% (9). The exact 2-sided 95% CI was calculated with Microsoft Excel 9.0 (Microsoft Corp., Redmond, Washington), using the exact method for obtaining a confidence interval for a binomial proportion (28).

Role of the Funding Source

Funding for the study was provided through a grant from the Deseret Foundation, a private philanthropic organization. The Deseret Foundation had no role in the collection, analysis, or interpretation of the data or in the submission of the study for publication and has no finan-

Figure. Enrollment and analysis of patients.



*Of the 384 patients enrolled who showed no signs of deep venous thrombosis on comprehensive duplex ultrasonography the negative cohort, 9 were excluded from the analysis because of use of therapeutic anticoagulants (7 for diagnoses not related to venous thromboembolism and 2 in violation of protocol).

cial interest in diagnostic equipment or therapeutic agents used for venous thromboembolism.

RESULTS

Patients

Of the 523 consecutive patients evaluated, 445 (85.1%) were eligible and 78 (14.9%) were excluded. Reasons for exclusion were unwillingness or inability to provide informed consent ($n = 34$), anticipated inability to obtain follow-up (no telephone, traveling from outside the country, homeless, or indigent) ($n = 13$), therapeutic anticoagulation for more than 24 hours ($n = 13$), pregnancy ($n = 3$), ultrasonography not technically possible (morbid obesity [$n = 1$] and massive interstitial edema [$n = 1$]), and not referred for first-episode DVT ($n = 1$). In addition, 12 patients initially indicated no history of DVT but were excluded because further interview by the study clinician revealed previous DVT (Figure).

Table 1. Therapeutic Anticoagulation Used in the Negative Cohort*

Patients, n	Time after Enrollment†	Duration of Anticoagulation	Comments
3	15–88 d	6–12 wk	Joint replacement surgery
1	88 d	Permanent	Recurrent atrial fibrillation in patient with pre-existing paroxysmal atrial fibrillation and history of valve replacement surgery
1	77 d	Permanent	Recurrent atrial fibrillation in patient with history of paroxysmal atrial arrhythmias
1	26 d	12 wk	Thrombosis of upper-extremity hemodialysis graft
1	52 d	12 wk	Upper-extremity thrombosis in subclavian vein complicating central venous catheter
1	Immediate	6 mo	Protocol violation; initial comprehensive duplex ultrasonography showed thrombus in superficial veins near anastomosis at saphenofemoral junction
1	Immediate	6 mo	Protocol violation; therapeutic anticoagulation given when comprehensive duplex ultrasonography showed superficial thrombophlebitis

* Patients described in this table were excluded from analysis because they used therapeutic anticoagulants during the follow-up period.

† Enrollment and initial ultrasonography took place on day 0.

Objective Testing for DVT

Comprehensive duplex ultrasonography did not show acute DVT in 384 patients (86.3%) (the negative cohort) and showed acute DVT in 61 patients (13.7%) (the abnormal cohort). Nineteen cases of DVT (31.1%) were isolated to the peroneal or posterior tibial veins of the calf, and 31 (50.8%) were detected in both the calf and proximal deep veins. The remaining 11 cases (18.0%) were in the proximal veins with no evidence of calf DVT. All patients with DVT were treated with therapeutic anticoagulation.

Long-Term Follow-up

All 384 patients in the negative cohort completed the minimum follow-up period of 3 months (range, 3 to 23.9 months; median, 5.1 months). Nine patients in the negative cohort (2.3%) received therapeutic anticoagulants during 3-month follow-up (Table 1) and were excluded from analysis to avoid confounding results. Seven (1.8%) received anticoagulants for diagnoses unrelated to venous thromboembolism, and 2 (0.5%) received anticoagulants in violation of protocol: one for a superficial venous thrombus that was within 1 cm of the saphenofemoral junction, and the other from the treating physician for superficial thrombophlebitis. None had venous thromboembolism

during 3-month follow-up. Anticoagulation was withheld in the remaining 375 patients (97.7%) in the negative cohort. All 61 patients in the abnormal cohort were treated with anticoagulation according to standard clinical practice. The clinical characteristics of the analyzed patients are shown in Table 2.

Twenty-two of the 375 patients who remained in the negative cohort for analysis during the 3-month period (5.9% [CI, 3.71% to 8.75%]) had symptoms of recurrent venous thromboembolism (Table 3). Repeated comprehensive duplex ultrasonography revealed 3 cases of DVT: 1 proximal and 2 isolated to the calf. Therefore, the overall rate of symptomatic venous thrombosis was 0.80% (CI, 0.16% to 2.33%) in the negative cohort within 3 months of initial comprehensive duplex ultrasonography. All 3 patients presented with increased leg swelling.

Of the remaining patients in the negative cohort in whom venous thromboembolism was suspected during follow-up, 15 (4.0% [CI, 2.25% to 6.52%]) had progressive leg symptoms that prompted repeated comprehensive duplex ultrasonography. Of these, 13 (3.5% [CI, 1.85% to 5.86%]) had no evidence of DVT. One patient noted shortness of breath among numerous symptoms at the time of evaluation, but the treating physician did not pursue further diagnostic evaluation for pulmonary embolism. Anticoagulants were withheld, and long-term follow-up of this patient was extended for 3 months from the event without further clinical evidence of venous thromboembolism. Two patients (0.5% [CI, 0.06% to 1.92%]) had inconclusive results on repeated comprehensive duplex ultrasonography. Anticoagulants were withheld, and these 2 patients were followed for 3 months from the second ultrasonography scan without evidence of venous thromboembolism.

Pulmonary embolism was suspected in the remaining 4 patients (1.1% [CI, 0.29% to 2.71%]). In 3 patients, diagnostic testing excluded the disorder, as detailed in Table 3. In the fourth patient, a spiral computed tomography pulmonary angiogram showed no pulmonary embolism, but DVT was ruled out only by unilateral comprehensive duplex ultrasonography. Therefore, follow-up of this patient was extended for 3 additional months without further clinical evidence of venous thromboembolism. This patient received no anticoagulants.

Six patients in the negative cohort (1.6% [CI, 0.58% to 3.45%]) died during the 3-month follow-up period. None of the deaths were due to venous thromboembolism (Table 4).

DISCUSSION

Previous studies have shown that it is safe to withhold anticoagulants once 2 compression ultrasonography examinations limited to the common femoral vein in the groin and the popliteal vein are performed 5 to 7 days apart and yield negative results (9, 10). One such examination is not sufficient because undetected calf vein thrombi can propa-

Table 2. Characteristics of Analyzed Patients*

Characteristic	All Analyzed Patients (n = 436)†	Negative Cohort (n = 375)†	Abnormal Cohort (n = 61)
Pretest probability score for DVT, n (%)‡			
Low	165 (37.8)	157 (42.0)	8 (13.1)
Moderate	208 (47.7)	180 (48.0)	28 (45.9)
High	63 (14.5)	38 (10.1)	25 (41.0)
Mean age ± SD (range), y	56.3 ± 17.3 (19–95)	56.1 ± 17.3 (19–93)	58.3 ± 17.4 (24–95)
Men, n (%)	145 (33.3)	117 (31.2)	28 (45.9)
Symptoms at presentation, n (%)			
Pain	356 (81.7)	307 (81.9)	49 (80.3)
Swelling	168 (38.5)	133 (35.5)	35 (57.4)
Median duration of symptoms (range), d	7 (0 to >90)	7 (0 to >90)	5 (0 to 90)
Clinical conditions, n (%)			
Active cancer	26 (6.0)	18 (4.8)	8 (13.1)
History of cancer	33 (7.6)	29 (7.7)	4 (6.6)
Congestive heart failure	24 (5.5)	22 (5.9)	2 (3.3)
Hospitalized in the past 6 mo	116 (26.6)	98 (26.1)	18 (29.5)
Surgery in the past 6 mo	93 (21.3)	77 (20.5)	16 (26.2)
Immobilization	13 (3.0)	7 (1.9)	6 (9.8)
Bedridden	58 (13.3)	44 (11.7)	14 (23.0)
Postpartum	7 (1.6)	7 (1.9)	0 (0)
Family history of DVT	82 (18.8)	70 (18.7)	12 (19.7)
Clinical signs at presentation, n (%)			
Asymmetric edema	91 (20.9)	70 (18.7)	21 (34.4)
Size difference > 3 cm	66 (15.1)	51 (13.6)	15 (24.6)
Localized tenderness	222 (51.0)	181 (48.3)	41 (67.2)
Collateral veins	1 (0.2)	1 (0.3)	0 (0)
Location of DVT on initial ultrasonography, n (%)			
Isolated proximal			11 (18)
Isolated distal			19 (31)
Both			31 (51)

* DVT = deep venous thrombosis.

† These groups exclude the 9 patients in Table 1 who had normal results on initial duplex ultrasonography but received anticoagulant therapy during follow-up for reasons unrelated to venous thromboembolism or because of protocol violation.

‡ Based on Wells et al. (19).

gate proximally, with potentially serious complications (9, 10, 15). Fatal pulmonary embolism has occurred before the common femoral vein and the popliteal vein could be examined again (9, 13). Although the technique of com-

prehensive duplex ultrasonography used in our study takes 15 to 30 minutes longer than simplified compression ultrasonography, the second study required for follow-up of the latter method consumes substantial resources and is not

Table 3. Characteristics of Suspected Recurrent Venous Thromboembolism

Patients, n	Time to Presentation of Symptoms after Enrollment, d*	Diagnostic Testing/Results	Comments
Suspected DVT			
3	1, 10, 64	Comprehensive duplex ultrasonography/positive	
13	3–61	Comprehensive duplex ultrasonography/negative	
2	7, 66	Comprehensive duplex ultrasonography/inconclusive	Anticoagulants withheld and no signs or symptoms of venous thromboembolism during >3 additional mo of follow-up (143 d, 131 d, respectively) after diagnostic testing
Suspected pulmonary embolism			
1	1	Ventilation–perfusion lung scan/normal	
1	27	Pulmonary angiography/negative	
1	1	CT angiography/negative	
1	19	Bilateral comprehensive duplex ultrasonography/negative	
1	19	CT angiography/negative	
1	19	Unilateral comprehensive duplex ultrasonography/negative	No signs or symptoms of venous thromboembolism during >3 additional mo (92 d) of follow-up after diagnostic testing

* Enrollment and initial ultrasonography took place on day 0.

Table 4. Description of the 6 Deaths in the Negative Cohort

Acuity of Death	Time to Death after Enrollment, d*	Comments
Insidious	11	Death due to disseminated intravascular coagulation following Denver shunt placement to relieve obstructing pancreatic carcinoma
Abrupt	69	Death due to myocardial infarction. Previously documented coronary artery disease and myocardial infarction
Abrupt	46	Death due to thalamic stroke. Previous placement of porcine mitral valve and maze procedure for permanent atrial fibrillation
Insidious	66	Death due to metastatic rectal carcinoma while receiving hospice care
Insidious	59	Death due to traumatic head injury sustained in a fall
Abrupt	3	Death due to brain herniation following subarachnoid hemorrhage

* Enrollment and initial ultrasonography took place on day 0.

always practical (29). Previous investigators have considered the role of a single examination of the entire deep venous system with duplex ultrasonography (15, 30–32), but this approach has been the subject of only limited study. Our trial was designed to address this issue directly, adding data that evaluate the safety of withholding anticoagulant therapy after only 1 examination of the symptomatic leg with comprehensive duplex ultrasonography.

We found that it is safe to withhold anticoagulants after negative results on 1 examination of the affected leg with comprehensive duplex ultrasonography. Venous thrombosis occurred in 3 of 375 patients (0.8%) when anticoagulants were withheld after negative results on examination of the proximal and distal deep veins of the affected leg. Only 1 of these 3 patients developed proximal DVT, and no patient developed symptomatic pulmonary embolism or paradoxical embolism attributable to venous thromboembolism or died of this disorder. Furthermore, because our patient sample was sufficiently large, the upper limit of the 95% CI for recurrent thromboembolic disease was 2.33%. These results compare favorably with results from similar studies of repeatedly normal simplified compression ultrasonograms (9, 10, 15) or 1 negative simplified duplex ultrasonogram combined with normal results on a whole-blood D-dimer test (12, 13). In these studies, patients who were not treated after negative test results had a risk of less than 3.3% for subsequent venous thromboembolic disease (9, 10, 12, 13, 15).

Most investigators have chosen to evaluate serial simplified duplex ultrasonography because duplex ultrasonography has low sensitivity for isolated calf vein thrombi (9, 10, 15). Reduced sensitivity is thought to reflect failure to

detect small calf thrombi that are unlikely to propagate proximally and embolize (8, 33). It has further been suggested that patient habitus, especially obesity, results in frequent inability to image calf veins (5, 9). However, recent studies have suggested that such imaging of the calf is sensitive enough to exclude clinically significant thrombosis and have excluded very few patients because of inability to obtain images (31, 32). The exclusion of only 2 patients in our study for this reason is consistent with these results. Our study provides the most formal results to date suggesting that comprehensive duplex ultrasonography detects clinically important venous thrombosis in the calf and can replace routine repeated testing.

When the ultrasonography examination is extended to include the calf veins, additional patients will receive a diagnosis of isolated calf vein thrombosis. Nineteen of the 445 patients in our study (4.3%) had DVT isolated to the calf. The specificity of technically adequate duplex examinations of calf veins is high (8, 30), making it unlikely that additional patients were unnecessarily exposed to the risks associated with anticoagulants. However, clinicians may choose to withhold anticoagulation from patients with DVT isolated to the calf, provided that they repeat the duplex examination to investigate extension of these thrombi into proximal deep veins (9, 10, 15).

Although we enrolled many consecutive patients and the demographic characteristics of our cohort appear similar to those of patients evaluated in previous studies (9, 10, 15), our results may not apply to all patients with suspected DVT. We excluded pregnant patients, and isolated iliac venous thrombosis is known to complicate pregnancy (34). Comprehensive duplex ultrasonography does not detect isolated iliac venous thrombosis. Similarly, our results may not apply to patients for whom technical factors, such as prominent swelling or overlying wounds, limit the ability to visualize the deep venous system of the calf. In this situation, repeated simplified duplex examinations or venography is preferable. Also, our study was performed at a single institution with an experienced staff of technologists and interpreters.

In summary, withholding anticoagulant treatment in patients with suspected acute DVT after 1 examination with comprehensive duplex ultrasonography is associated with a low rate of venous thromboembolism during 3-month follow-up. Our observations suggest that 1 comprehensive duplex examination is a reasonable alternative to 2 simplified compression duplex examinations performed 5 to 7 days apart. Basing treatment on the results of a single examination with comprehensive duplex ultrasonography would substantially reduce the inconvenience associated with evaluation of suspected DVT and would reduce the risk to patients who do not return for serial testing.

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