A Randomized Trial of Diagnostic Strategies after Normal Proximal Vein Ultrasonography for Suspected Deep Venous Thrombosis: D-Dimer Testing Compared with Repeated Ultrasonography

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Background: **With suspected deep venous thrombosis and normal results on proximal vein ultrasonography, a negative D-dimer result may exclude thrombosis and a positive D-dimer result may be an indication for venography.**

Objective: **To evaluate and compare the safety of 2 diagnostic strategies for deep venous thrombosis.**

Design: **Randomized, multicenter trial.**

Setting: **Four university hospitals.**

Patients: **810 outpatients with suspected deep venous thrombosis and negative results on proximal vein ultrasonography.**

Interventions: **Erythrocyte agglutination D-dimer testing followed by no further testing if the result was negative and venography if the result was positive (experimental) or ultrasonography repeated after 1 week in all patients (control).**

Measurements: **Symptomatic deep venous thrombosis diagnosed initially and symptomatic venous thromboembolism during 6 months of follow-up.**

Results: **Nineteen of 408 patients (4.7%) in the D-dimer group and 3 of 402 patients (0.7%) in the repeated ultrasonography group initially received a diagnosis of deep venous thrombosis ($P < 0.001$). During follow-up of patients without a diagnosis of deep venous thrombosis on initial testing, 8 patients (2.1% [95% CI, 0.9% to 4.0%]) in the D-dimer group and 5 patients (1.3% [CI, 0.4% to 2.9%]) in the repeated ultrasonography group developed symptomatic venous thromboembolism (difference, 0.8 percentage point [CI, −1.1 to 2.9 percentage points]; $P > 0.2$). Venous thromboembolism occurred in 1.0% (CI, 0.2% to 2.8%) of those with a negative D-dimer result.**

Limitations: **Seventy patients (8.6%) deviated from the diagnostic protocols, and 9 patients (1.1%) had inadequate follow-up.**

Conclusion: **In outpatients with suspected deep venous thrombosis who initially had normal results on ultrasonography of the proximal veins, a strategy based on D-dimer testing followed by no further testing if the result was negative and venography if the result was positive had acceptable safety and did not differ from the safety of a strategy based on withholding anticoagulant therapy and routinely repeating ultrasonography after 1 week.**

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Venous compression ultrasonography is currently the diagnostic test of choice for suspected deep venous thrombosis (1, 2). Noncompressibility of the proximal veins is usually diagnostic for deep venous thrombosis, whereas normal compressibility reliably excludes proximal deep venous thrombosis (1). Ultrasonography of the distal (calf) deep veins is less accurate and is more difficult to perform than evaluation of the proximal veins (1). However, fewer than one fifth of symptomatic deep venous thromboses are confined to the distal veins, and these thrombi are associated with a very low risk for symptomatic pulmonary embolism unless they extend into the proximal veins (1). If distal deep venous thrombosis is going to extend into the proximal veins, this usually occurs within a week of presentation (1). Consequently, in patients with suspected deep venous thrombosis, it is safe to withhold anticoagulant therapy if results on ultrasonography of the proximal veins are normal (1). However, because 1% to 2% of patients with normal results on initial ultrasonography have thrombi that subsequently extend into the proximal veins, ultrasonography must be repeated after 1 week to detect these cases (1, 2). This management approach is costly and inconvenient and causes anxiety because of diagnostic uncertainty before repeated testing. Therefore, a test that reduces the need for repeated ultrasonography in patients who have normal results on initial ultrasonography would be valuable.

D-Dimers are molecules that circulate when thrombi are broken down by the fibrinolytic system (3). Elevated levels of D-dimer usually occur in patients with deep venous thrombosis, and a normal D-dimer level can be used to exclude this diagnosis (3–8). We and other investigators have shown that a negative result on erythrocyte agglutination D-dimer test (SimpliRED, AGEN Biomedical Ltd., Brisbane, Australia) is valuable for excluding deep venous thrombosis and pulmonary embolism (3, 4, 6–11). This assay has advantages over other D-dimer tests because it can be performed at the bedside and yields a result within minutes.

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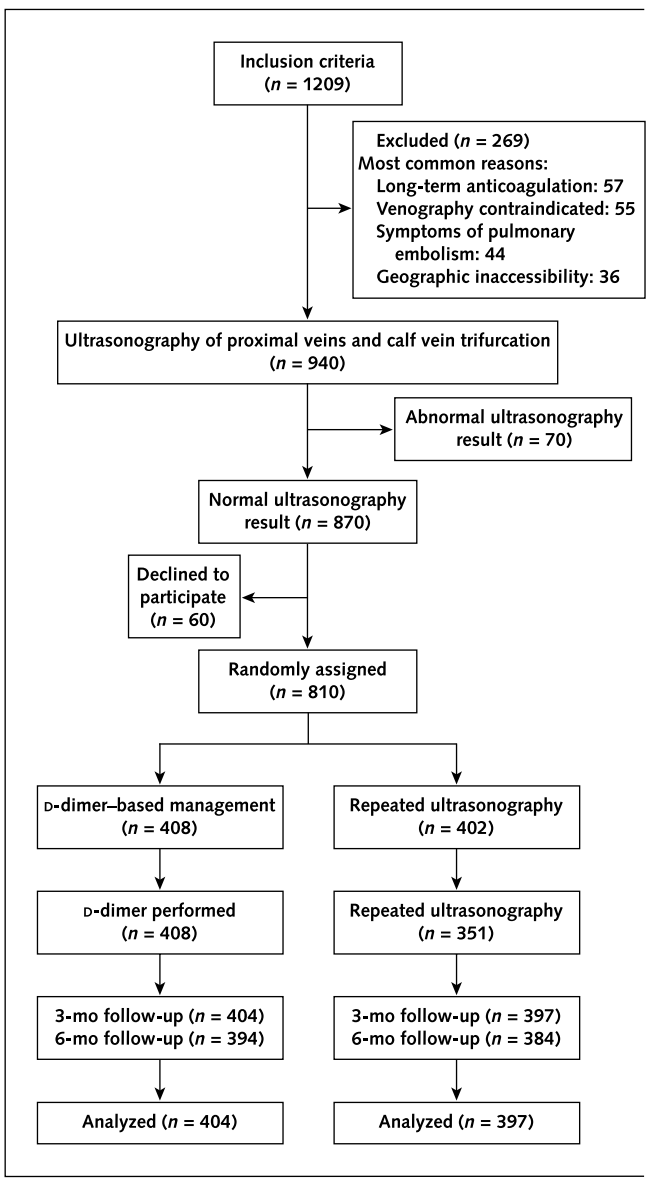
We hypothesized that the combination of a negative D-dimer result and a normal result on ultrasonography of the proximal veins would exclude thrombosis and obviate the need for follow-up ultrasonography after 1 week in outpatients with suspected deep venous thrombosis. We also hypothesized that, compared with routinely repeating ultrasonography after 1 week, performance of venography in those with a positive D-dimer result would reliably indicate or exclude deep venous thrombosis and result in fewer cases of symptomatic venous thromboembolism during follow-up. To test these hypotheses, we performed a randomized trial in which outpatients with suspected deep venous thrombosis who had normal results on ultrasonography of the proximal veins were managed according to the results of D-dimer testing or by routinely repeating ultrasonography after 1 week.

Figure 1. **Trial profile.**



Context

Physicians use several strategies to diagnose deep venous thrombosis (DVT).

Contribution

This trial randomly assigned 810 outpatients with suspected DVT and negative results on proximal vein ultrasonography to repeated ultrasonography at 1 week or D-dimer testing followed by no further tests if results were negative and venography if results were positive. Repeated ultrasonography diagnosed fewer DVTs than the D-dimer strategy (0.7% vs. 4.7%). In both groups followed for 6 months, only 1% to 2% of patients without DVT on initial testing developed symptomatic thromboembolism.

Implications

In patients with suspected DVT and negative results on proximal vein ultrasonography, a D-dimer–based strategy that minimizes additional assessments had similar safety to repeated ultrasonography.

–The Editors

METHODS

Patients

Consecutive outpatients with suspected first episodes of deep venous thrombosis who were referred by primary care and hospital-based physicians to the thrombosis services of 4 university-affiliated hospitals were potentially eligible. We excluded patients if they had a life expectancy of less than 6 months, had a contraindication to venography, were receiving full-dose heparin therapy for more than 48 hours, were receiving long-term warfarin therapy, had no symptoms within 5 days of presentation, had symptoms of pulmonary embolism, or were pregnant or if geographic inaccessibility precluded follow-up visits. The institutional review boards of the participating centers approved the study, and all patients provided written informed consent.

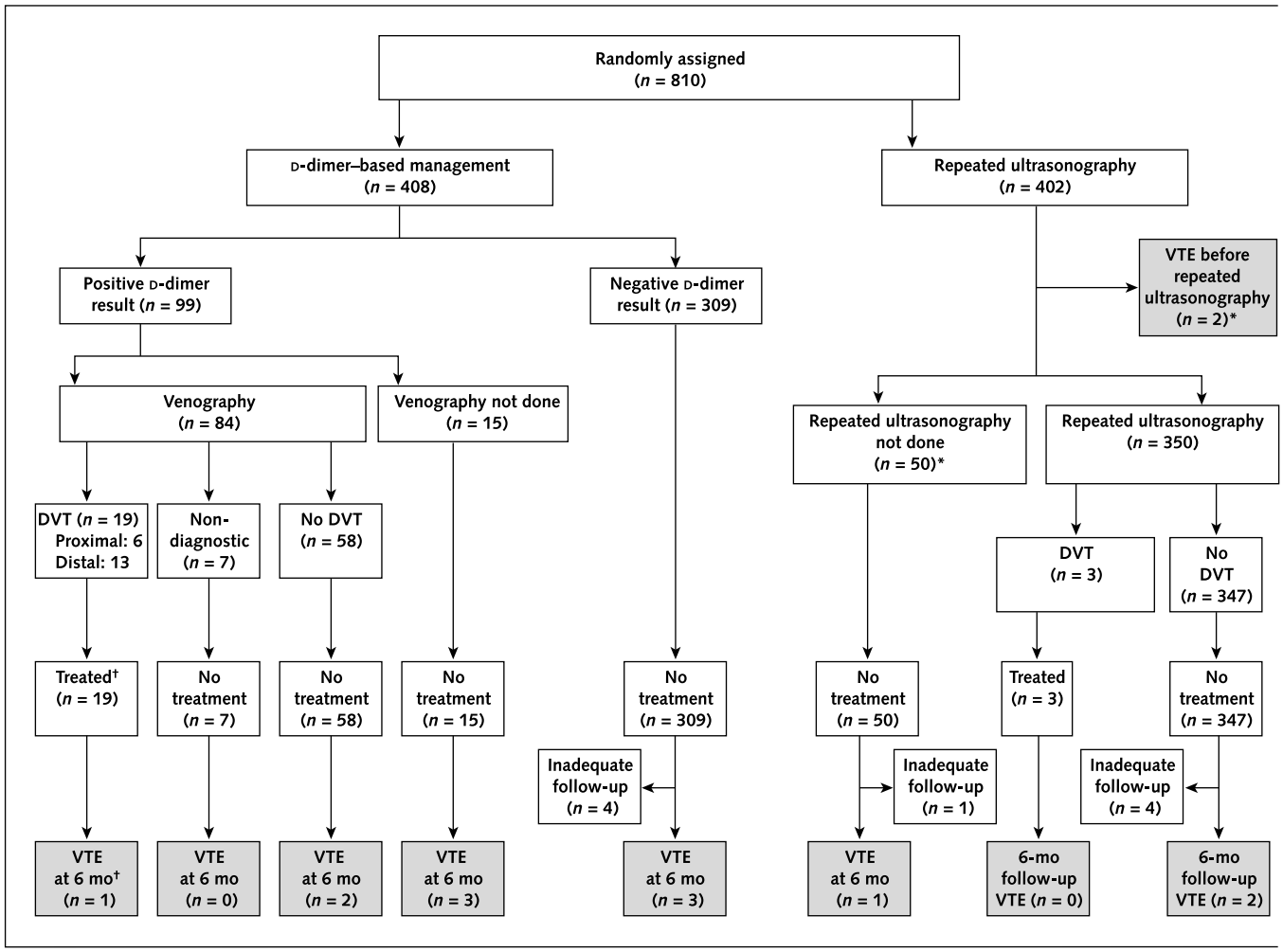
Management before Randomization

All patients had compression ultrasonography of the deep veins of the symptomatic leg or legs, with examination of the common femoral, femoral, and popliteal veins (including the trifurcation of the calf veins) (1). Patients with abnormal results on ultrasonography received a diagnosis of deep venous thrombosis and were not eligible for randomization. Consenting patients with normal ultrasonography were eligible for randomization (**Figures 1** and **2**).

Randomization and Diagnostic Strategies

A research statistician performed computer-generated randomization, stratified by clinical center, with random block sizes of 2 to 8 participants, and this allocation sequence was transferred to consecutively numbered, sealed, opaque envelopes that were distributed to the clinical cen-

Figure 2. **Diagnostic algorithm and patient outcomes for all randomly assigned patients.**



Shaded boxes indicate outcome assessments. *Includes 1 patient with deep venous thrombosis (*DVT*) that was diagnosed by unscheduled venography on the day of presentation. †One patient was treated with an inferior venacaval filter, without anticoagulant therapy, and had a subsequent fatal pulmonary embolism. VTE = venous thromboembolism.

ters. According to the directions contained in these envelopes, enrolled patients were allocated to a D-dimer–based diagnostic strategy or a repeated ultrasonography diagnostic strategy (**Figures 1** and **2**).

D-Dimer–Based Strategy

D-dimer testing was performed by 1 or 2 thrombosis service technologists or nurses at each site who had extensive previous experience with this test (4, 6, 7, 10, 12). With this D-dimer test (SimpliRED), a drop of whole blood obtained from a venipuncture or fingerstick is mixed with a test reagent for 2 minutes (13). The test reagent contains a bispecific antibody, 1 part of which binds to site 3B6/22 on the γ chain of the D-dimer, while the other part binds to erythrocyte membranes. In the presence of elevated D-dimer levels, the bispecific antibody induces agglutination of the patient's erythrocytes. Any agglutination is considered a positive result, whereas no agglutination is considered a negative result.

Patients with a negative D-dimer test result had no further diagnostic testing and were not treated with anticoagulation. Those with a positive D-dimer test result had venography performed the same day. If venography showed deep venous thrombosis, patients were treated with anticoagulants for at least 3 months. If deep venous thrombosis was not diagnosed (normal or nondiagnostic venogram), no further testing was performed and patients did not receive anticoagulant therapy.

Repeated Ultrasonography Strategy

All patients were scheduled to have ultrasonography of the proximal veins repeated after 1 week and did not receive anticoagulant therapy unless the second ultrasound was abnormal.

Follow-up and Outcome Measures

All randomly assigned patients, including those who received a diagnosis of deep venous thrombosis by venog-

raphy or repeated ultrasonography, were contacted by telephone or attended the clinic after 3 and 6 months to determine whether venous thromboembolism or bleeding had developed. In addition, we alerted patients about the symptoms of deep venous thrombosis, pulmonary embolism and bleeding, and advised them to return to the hospital immediately if such symptoms occurred. We evaluated suspected deep venous thrombosis with ultrasonography of the proximal veins, followed by venography if the ultrasound was not diagnostic for thrombosis (1, 2). We initially evaluated suspected pulmonary embolism with ventilation–perfusion lung scanning. If the lung scan was not diagnostic, patients underwent additional testing with bilateral ultrasonography of the proximal veins, bilateral venography, or pulmonary angiography (14). We did not use D-dimer testing to evaluate suspected deep venous thrombosis or pulmonary embolism during follow-up. Other than abnormal bleeding, we did not monitor adverse outcomes related to diagnostic testing and resultant treatment. We classifed deaths as due to pulmonary embolism (when there was substantive evidence) or another cause. A central adjudication committee, whose members were unaware of patient allocation groups, reviewed and classified information on all suspected outcome events and deaths. Subject to availability, data provided to this committee included study case report forms, clinic notes, original investigations (for example, lung scans and venograms), interpretation reports for original investigations, and autopsy reports.

Statistical Analysis

We based sample size on the requirement of narrow (that is, ±2%) 95% CIs around the observed proportion of patients who would have symptomatic venous thromboembolism during 6 months of follow-up (the primary outcome measure) in each randomized group. On the basis of previous reports, we expected this proportion to be about 1.5% for both groups (1, 4). Originally, we planned to randomly assign 640 patients to satisfy these requirements. However, we found the prevalence of deep venous thrombosis diagnosed by initial ultrasonography to be lower than expected. Suspecting that the frequency of venous thromboembolism during follow-up might also be lower than expected, we decided to extend enrollment to 800 patients to accrue additional data that would narrow the 95% CIs associated with rates of outcome events. Our decision to increase sample size to 800 patients, which was based on feasibility considerations rather than formal statistical arguments, was made without knowledge of interim results. We considered the small group of patients who completed 3 months but not 6 months of follow-up to have adequate follow-up for inclusion in calculations of outcomes. We noted those who did not complete 3 months of follow-up and excluded them from these calculations. We calculated 95% CIs for binomial proportions, and for differences between proportions, by using the modified Wilson score method (Confidence Interval Analysis [CIA], version 2.1, University of Southampton, Southampton, United Kingdom) (15). We used the Fisher exact test to compare proportions.

Table 1. **Baseline Characteristics of Randomly Assigned Patients**

Characteristic	D-Dimer Group (n = 408)	Repeated Ultrasonography Group (n = 402)
Age, *y*	59	60
Men, *n (%)*	154 (38)	153 (38)
Median duration of symptoms, *d*	8	8
Pretest probability, *n (%)**		
Low	259 (63)	261 (65)
Moderate	123 (30)	107 (27)
High	22 (5)	31 (8)
Not available	4 (1)	3 (1)
Active cancer, *n (%)*	33 (8)	24 (6)

* Clinical probability for deep venous thrombosis was assessed by using a structured clinical model as described by Wells et al. (16).

Role of the Funding Sources

The National Health Research Development Program of Health Canada funded the study (grant 6606-5620-400), and AGEN Biomedical Ltd. donated the D-dimer kits. The funding sources had no role in study design or execution, collection of data, or writing of the manuscript. Authors had full access to data files.

RESULTS

Over a 3-year period, 1209 patients met inclusion criteria. Of these, 269 patients were early exclusions (**Figure 1**). Of the remaining 940 patients, 70 had deep venous thrombosis on initial ultrasonography. Of 870 eligible patients, 810 gave informed consent and were randomly assigned to the D-dimer group (408 patients) or the repeated ultrasonography group (402 patients) (**Table 1** and **Figures 1** and **2**).

D-Dimer–Based Strategy

D-Dimer test results were negative in 309 patients, and no patient was treated with anticoagulants (contrary to the protocol, 2 patients underwent venography, which yielded normal results).

D-Dimer test results were positive in 99 of 408 patients (24%) (**Figure 2**). Venography was performed in 84 of these patients and showed deep venous thrombosis in 19 (isolated calf vein thrombosis in 13 patients and proximal thrombosis in 6 patients), normal results in 58, and nondiagnostic results in 7. Venography was not completed in 15 patients with a positive D-dimer test result because of withdrawn consent (5 patients), failed attempt (3 patients), or unspecified reasons (7 patients). None of the 80 patients who had a positive D-dimer test result but did not receive a diagnosis of deep venous thrombosis by venography was treated with anticoagulants. Of the 19 patients who received a diagnosis of deep venous thrombosis, 1 had a

venacaval filter inserted without anticoagulation because of a previous intracerebral bleeding episode and the others received heparin or low-molecular-weight heparin (16 patients) and at least 3 months of warfarin therapy (18 patients).

Four patients did not complete 3 months of follow-up (10 others had follow-up at 3 months but not at 6 months). These 4 patients had a negative D-dimer result at presentation (**Figure 2**). Of the 404 patients with adequate follow-up, 9 (2.2% [95% CI, 1.0% to 4.2%]) had symptomatic venous thromboembolism within 6 months, of which 2 cases were classified as fatal pulmonary embolism (**Table 2**). Six episodes of venous thromboembolism (6.1% [CI, 2.3% to 12.7%]) occurred among the 99 patients who had a positive D-dimer test result (at initial presentation, venography yielded normal results in 2 patients, was declined by 2 patients, was unsuccessful in 1 patient, and showed proximal deep venous thrombosis in 1 patient) (**Figure 2**, **Table 2**). Three episodes of venous thromboembolism (1.0% [CI, 0.2% to 2.8%]) occurred among the 305 patients who had a negative D-dimer test result (**Figure 2**, **Table 2**). An additional 26 patients had suspected episodes of venous thromboembolism excluded. No episodes of bleeding occurred. Eleven patients assigned to the D-dimer strategy died: 7 of cancer, 2 of pulmonary embolism, 1 of liver failure, and 1 of unknown causes (family physician excluded pulmonary embolism but would not provide cause of death).

Repeated Ultrasonography Strategy

Contrary to the protocol, 3 patients assigned to repeated ultrasonography underwent venography on the day of presentation (proximal deep venous thrombosis was diagnosed in 1 patient [**Figure 2**, **Table 2**] and results on venography were normal in 2 patients). One patient returned with persistent leg symptoms, and proximal deep venous thrombosis was diagnosed by venography before the second ultrasonography was scheduled to occur. Ultrasonography was repeated 1 week after the initial normal test results in 350 patients (88% of scheduled patients), and deep venous thrombosis was diagnosed in 3 of these patients (0.9% [CI, 0.2% to 2.5%]). Scheduled ultrasonography after 1 week was not performed in 50 patients because of patient nonadherence (31 patients), misunderstanding (4 patients), or other reasons (15 patients). No patient who had normal results on repeated ultrasonography or who did not have repeated ultrasonography performed was treated with anticoagulants. Of the 3 patients in whom deep venous thrombosis was diagnosed by repeated ultrasonography, 2 patients were treated with initial heparin or low-molecular-weight heparin and all 3 patients received warfarin for at least 3 months.

Five patients did not complete 3 months of follow-up (13 others had follow-up at 3 months but not at 6 months). Four of these patients had normal results on ultrasonography at 1 week, and 1 patient did not have repeated ultrasonography after 1 week (**Figure 2**). Of the 397 patients with adequate follow-up, in addition to the 2 episodes that were diagnosed during the first week (noted earlier), 3 patients (0.8% [CI, 0.2% to 2.2%]) had symptomatic venous thromboembolism during follow-up (**Table 2**). At initial presentation, 2 of these 3 patients had normal results on repeated ultrasonography at 1 week, and 1 patient had a normal result on venography (done contrary to protocol) and did not have repeated ultrasonography. An additional 23 patients had suspected episodes of venous thromboembolism excluded. One bleeding episode, fatal intracranial bleeding without anticoagulant therapy,

Table 2. **Venous Thromboembolism Diagnosed by Unscheduled Testing during 6 Months of Follow-up***

Randomization Group	Event	Time after Randomization, *d*	D-Dimer Result at Presentation	Clinical Probability	Comments
D-dimer	Proximal DVT	1	Negative	High	
D-dimer	Proximal DVT	4	Positive	Moderate	Failed scheduled venography
D-dimer	Proximal DVT	4	Negative	Moderate	
D-dimer	Fatal PE	11	Positive	Moderate	Proximal DVT at presentation and subsequent suspected fatal PE despite inferior vena caval filter (contraindication to anticoagulation).
D-dimer	Proximal DVT	14	Positive	Low	Declined scheduled venography
D-dimer	Proximal DVT	25	Negative	Low	
D-dimer	Proximal DVT and nonfatal PE	27	Positive	Moderate	Declined scheduled venography
D-dimer	Fatal PE	94	Positive	Low	Normal scheduled venography; lung cancer; no diagnostic testing before death but PE suspected
D-dimer	Nonfatal PE	152	Positive	Low	Normal scheduled venography
Repeated ultrasonography	Proximal DVT	0		Low	Venography performed contrary to protocol
Repeated ultrasonography	Proximal DVT	2		Low	Unscheduled venography for persistent symptoms
Repeated ultrasonography	Proximal DVT	23		Moderate	Normal venography at presentation and repeated ultrasonography not done
Repeated ultrasonography	Proximal DVT	26		High	Normal repeated ultrasonography
Repeated ultrasonography	Proximal DVT	44		Low	Normal repeated ultrasonography

* Note: 19 episodes of deep venous thrombosis diagnosed by scheduled venography in patients who were randomly assigned to D-dimer testing and had a positive result and 3 episodes of deep venous thrombosis diagnosed by scheduled repeated ultrasonography after 1 week in patients randomly assigned to have repeated ultrasonography are not included in this table. DVT = deep venous thrombosis; PE = pulmonary embolism.

occurred. Eleven patients randomly assigned to this group died: 5 because of cancer, 4 because of cardiac disease, 1 because of intracranial bleeding, and 1 because of trauma.

Comparison of the 2 Diagnostic Strategies

Scheduled diagnostic testing resulted in diagnosis and treatment of 19 patients (4.7%) who were assigned to the D-dimer strategy compared with 3 patients (0.7%) who were assigned to the repeated ultrasonography strategy ($P < 0.001$).

During 6 months of follow-up of patients who were not found to have deep venous thrombosis by scheduled diagnostic testing, venous thromboembolism occurred in 8 of 385 patients (2.1% [CI, 0.9% to 4.0%]) in the D-dimer group and 5 of 394 patients (1.3% [CI, 0.4% to 2.9%]) in the repeated ultrasonography group (includes 1 case of deep venous thrombosis that was diagnosed by unscheduled venography at initial presentation) (difference, 0.8 percentage point [CI, −1.1 to 2.9 percentage points]; $P > 0.2$).

During 6 months of follow-up of all randomly assigned patients, including those who were treated for deep venous thrombosis that was diagnosed by scheduled testing, venous thromboembolism occurred in 9 of 404 patients (2.2% [CI, 1.0% to 4.2%]) in the D-dimer group and 5 of 397 patients (1.3% [CI, 0.5% to 2.9%]) in the repeated ultrasonography group (difference, 1.0 percentage point [CI, −1.0 to 3.0 percentage points]; $P > 0.2$).

Discussion

Our study shows that the 2 diagnostic strategies used to manage outpatients with suspected deep venous thrombosis and normal results on initial ultrasonography of the proximal veins had similar safety. Only about 2% of patients from each group returned with symptomatic venous thromboembolism during 6 months of follow-up. Also, a negative result on an erythrocyte agglutination D-dimer test reliably excluded subsequent venous thromboembolism in patients without proximal deep venous thrombosis on ultrasonography (negative predictive value, 99.0%). Routine venography in patients with a positive D-dimer test result led to the diagnosis and treatment of more episodes of deep venous thrombosis ($n = 19$) than did repeating ultrasonography after 1 week and treating only those who had abnormal results on repeated ultrasonography ($n = 3$). The overall finding that the repeated ultrasonography strategy had safety similar to that of a strategy that resulted in more frequent diagnosis and treatment suggests that many calf thrombi do not progress to more severe deep venous thrombosis or pulmonary embolism. Moreover, an aggressive invasive approach to diagnosing and treating deep venous thrombosis that is confined to the calf veins may not be warranted.

Other than those we evaluated, 3 diagnostic strategies seem to safely manage patients with suspected deep venous thrombosis who have normal results on ultrasonography of the proximal veins at presentation. First, D-dimer testing is performed, and only patients with positive results have ultrasonography repeated after 1 week (7, 8, 17). The low frequency of venous thromboembolism that we observed after negative results on repeated ultrasonography indirectly supports this management strategy. Second, clinical probability of deep venous thrombosis is assessed, and the combination of a low clinical probability of thrombosis and normal ultrasonography results is used to exclude the diagnosis. Ultrasonography is repeated only in those with a moderate or high clinical suspicion of thrombosis (7, 16, 18). We suggest that this is also a reasonable diagnostic approach. Of 261 patients with a low clinical probability of thrombosis who were randomly assigned to the repeated ultrasonography group, 1.9% received a diagnosis of venous thromboembolism (1 by venography at presentation, 1 before repeated ultrasonography, 2 by repeated ultrasonography, and 1 during follow-up after negative ultrasonography results). Third, having found the proximal veins to be normal, we could base the decision to treat or not to treat patients on the results of ultrasonography of the calf veins (19, 20). Disadvantages of this approach are that calf vein ultrasonography is time-consuming, is less accurate than ultrasonography of the proximal veins (1), and is likely to result in unnecessary treatment of many patients who either do not have thrombosis (that is, those with false-positive ultrasound findings) or have small thrombi that will resolve spontaneously. A safe alternative to performing ultrasonography as the initial diagnostic test is to exclude deep venous thrombosis on the basis of a negative result on a D-dimer test that is highly sensitive for thrombosis (5, 8) or the combination of a negative result on a D-dimer test that is less sensitive for thrombosis (such as that used in our study) and a low clinical probability for thrombosis (6–8).

Strengths of our study include the use of a randomized design, independent adjudication of study outcomes, and a minimum of 3 months of follow-up in almost all patients. Only 1.1% of patients were lost to follow-up. Even if thrombosis had occurred in the 4 patients from the D-dimer group and none of the 5 patients from the repeated ultrasonography group who were lost to follow-up, the absolute frequency of thrombosis during follow-up among those who were found to not have deep venous thrombosis by scheduled diagnostic testing would only be 1.8 percentage points higher (CI, −0.3 to 4.2 percentage points) in the D-dimer group. Limitations of our study include the fact that clinical assessment of the probability of deep venous thrombosis was not incorporated into either management strategy and that the study protocol was not followed in 8.6% of patients. Most of the protocol deviations resulted from failure to complete repeated ultrasonography.

Many D-dimer tests, with varying accuracy and technical complexity, have been used to exclude deep venous thrombosis (3, 8). We used the SimpliRED test because it has a higher specificity for venous thromboembolism than most other D-dimer tests (about 75%) while retaining

moderately high sensitivity (about 85%) (9, 10). These characteristics yield a comparatively low frequency of false-positive results and a high negative predictive value when used in combination with other noninvasive tests for venous thromboembolism (4, 6, 8–11). In addition, this D-dimer assay is convenient to perform and can provide a result within minutes.

In conclusion, a negative D-dimer test result obviates the need to repeat ultrasonography after 1 week in most outpatients with suspected deep venous thrombosis who have a normal initial examination of the proximal veins. A strategy that included routine venography in patients with positive D-dimer test results did not reduce the frequency of venous thromboembolism during follow-up compared with a less invasive strategy of repeating ultrasonography and treating only those patients with positive repeated test results.

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