

Articles

Value of assessment of pretest probability of deep-vein thrombosis in clinical management

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Summary

Background When ultrasonography is used to investigate deep-vein thrombosis, serial testing is recommended for those who test negative initially. Serial testing is inconvenient for patients and costly. We aimed to assess whether the calculation of pretest probability of deep-vein thrombosis, with a simple clinical model, could be used to improve the management of patients who present with suspected deep-vein thrombosis.

Methods Consecutive outpatients with suspected deep-vein thrombosis had their pretest probability calculated with a clinical model. They then underwent compression ultrasound imaging of proximal veins of the legs. Patients at low pretest probability underwent a single ultrasound test. A negative ultrasound excluded the diagnosis of deep-vein thrombosis whereas a positive ultrasound was confirmed by venography. Patients at moderate pretest probability with a positive ultrasound were treated for deep-vein thrombosis whereas patients with an initial negative ultrasound underwent a single follow-up ultrasound 1 week later. Patients at high pretest probability with a positive ultrasound were treated whereas those with negative ultrasound underwent venography. All patients were followed up for 3 months for thromboembolic complications.

Findings 95 (16.0%) of all 593 patients had deep-vein thrombosis; 3%, 17%, and 75% of the patients with low, moderate, and high pretest probability, respectively, had deep-vein thrombosis. Ten of 329 patients with low pretest probability had the diagnosis confirmed, nine at initial testing and one at follow-up. 32 of 193 patients with moderate pretest probability had deep-vein thrombosis, three diagnosed by the serial (1 week) test, and two during follow-up. 53 of 71 patients with high pretest probability had deep-vein thrombosis (49 by the initial ultrasound and four by venography). Only three (0.6%) of all 501 (95% CI 0.1–1.8) patients diagnosed as not having deep-vein thrombosis had events during the 3-month follow-up. Overall only 33 (5.6%) of 593 patients required venography and serial testing was limited to 166 (28%) of 593 patients.

Interpretation Management of patients with suspected deep-vein thrombosis based on clinical probability and ultrasound of the proximal deep veins is safe and feasible. Our strategy

reduced the need for serial ultrasound testing and reduced the rate of false-negative or false-positive ultrasound studies.

Lancet 1997; **350**: 1795–98

Introduction

Since the late 1980s, high-resolution real-time B-mode ultrasound has been used for the diagnosis of deep-vein thrombosis.¹ Many studies have reported sensitivities and specificities for the various ultrasound imaging modalities to be over 95% for proximal deep-vein thrombosis in symptomatic patients and consequently venous ultrasound imaging is now widely accepted as the non-invasive test of choice for the diagnosis of deep-vein thrombosis. However, ultrasound is relatively insensitive to deep-vein thrombosis isolated to the calf.² Calf deep-vein thrombosis is usually a self-limited condition with a very low risk of pulmonary embolism, but 20% to 30% of calf deep-vein thrombosis may extend to involve the larger more proximal veins, which carry a much higher risk of pulmonary embolism.³ For this reason it is recommended that patients who are initially negative on ultrasound testing have follow-up (serial) tests over the next 7 to 10 days to exclude proximal extension. Two studies involving over 300 patients showed that it was relatively safe to withhold anticoagulants in outpatients with negative serial ultrasound results over 7 days since only 1.3% of these patients developed venous thromboembolic complications over 3-month follow-up periods.^{4,5} However, serial testing is inefficient and inconvenient for patients, and costly for the health-care system since most patients do not have deep-vein thrombosis on the serial test. Ultrasound is also limited by false results. In previous studies the positive and negative predictive values of ultrasound for deep-vein thrombosis were about 94%.^{5,6}

We have previously suggested, on the basis of a large clinical trial, that clinical assessment with a clinical model may overcome the limitations of ultrasound.⁷ The positive and negative predictive values of diagnostic tests are dependent on prevalence and thus should differ depending on the probability category. In our previous study we demonstrated the high positive predictive value of ultrasound in the patients with moderate and high pretest clinical probability and the high negative predictive value in the patients at low probability. Through logistic regression analysis we simplified the original model but we had not prospectively tested the revised model.⁸ It was our impression that we could safely assess patients with significantly fewer diagnostic tests than the serial approach requires. In this report the simplified model was used in combination with ultrasound to guide management of patients with suspected deep-vein thrombosis.

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Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	-2

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

Table 1: Clinical model for predicting pretest probability for deep-vein thrombosis

Methods

This study was a prospective cohort trial of outpatients with symptoms and suspected deep-vein thrombosis referred to the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada, or the Ottawa Civic Hospital, Ottawa, Ontario, Canada. The protocol was approved by the research ethics committees of our institutions. Consecutive patients referred to outpatient clinics or the Radiology Departments with pain or swelling of the lower extremity in whom the diagnosis of deep-vein thrombosis could not be excluded on clinical grounds were eligible for the study.

Patients were enrolled between September, 1994, and September, 1996. The presence of one or more of the following excluded patients from the study: previous episode of objectively documented deep-vein thrombosis or pulmonary embolism; signs or symptoms suggestive of current pulmonary embolism; patients in whom death was imminent; requirement for long-term anticoagulant therapy; age less than 18 years; and geographic location such that follow-up could not be done. Consenting patients were then assessed by one of the study physicians and categorised as being at low, moderate, or high pretest probability for deep-vein thrombosis by the scoring model (table 1). A high score was one of three or more, a moderate score was one or two, and a low score was zero or less. The model was derived from our original study on clinical probability in patients with suspected deep-vein thrombosis.⁷ The original clinical data were analysed retrospectively by univariate and stepwise logistic analysis in which we also included the following variables: age, duration of symptoms, and sex. Recent trauma, family history, erythema, age, sex, duration of symptoms, and hospital admission were not significantly associated with deep-vein thrombosis when assessed by stepwise logistic regression. The coefficients of the nine significant variables were rounded off to a value of one for the positive coefficients and -2 for the single negative variable

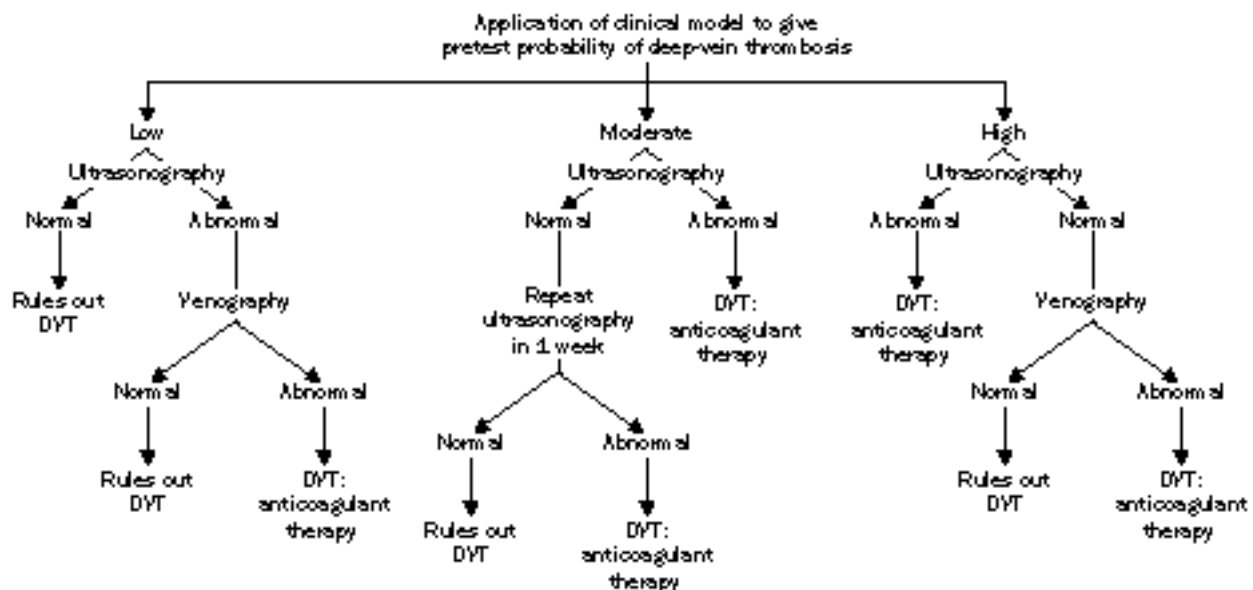
(alternative diagnosis). The sum of the integer values provided a new summary score for each patient (table 1). After the clinical assessment the patient's probability of death in the following 3 months was estimated as less than 5%, 5% to 25%, or more than 25%. Patients then had immediate ultrasound imaging of the symptomatic leg.

Management of the patients was according to the algorithm outlined in the figure. All patients underwent venous ultrasound imaging from the common femoral vein to the point where the popliteal vein divides into multiple calf veins (calf trifurcation). Lack of vein compressibility was the sole diagnostic criterion for a diagnosis of deep-vein thrombosis. Doppler or colour Doppler could be used to identify the deep venous system. Patients at low pretest probability underwent a single ultrasound test. A negative ultrasound excluded the diagnosis of deep-vein thrombosis whereas a positive ultrasound was confirmed by venography. Patients at moderate probability with a positive ultrasound were treated for deep-vein thrombosis whereas patients with an initial negative ultrasound had a single follow-up ultrasound 1 week later. Patients at high pretest probability with a positive ultrasound were treated for deep-vein thrombosis whereas those with negative ultrasound had venography. Venography was done as previously described.⁹ Ultrasonography and venography were done by individuals unaware of the pretest probability. All patients with negative ultrasound or venography studies were not treated with anticoagulants and were followed up for 3 months to monitor any development of symptomatic venous thromboembolic complications. 245 patients were randomly chosen to have their pretest probability determined independently by the study nurse and the study physician to assess the interobserver reliability of the model.

Patients were given a card outlining the signs and symptoms of worsening deep-vein thrombosis and pulmonary embolism and were instructed to contact the physicians if these developed. In addition, all patients were seen or contacted 3 months after the initial evaluation.

We hypothesised that, among patients found by our management plan not to have deep-vein thrombosis the rate of deep-vein thrombosis and pulmonary embolism over 3 months of follow-up would be less than the rate of 1.3% obtained from pooled trials with serial ultrasound in all patients. We anticipated that our management plan would be safer than serial ultrasound due to the identification of high-risk patients with deep-vein thrombosis who have negative ultrasound results. To show with confidence that the risk of venous thromboembolic events over 3 months of follow-up would be low (estimated 0.65% [95% CI 0-1.3]), we needed a sample size of 600 patients.

The primary analysis was to be the 95% CI around the rate of



Diagnostic approach in outpatients with suspected deep-vein thrombosis (DVT)

Characteristics	Venous thromboembolism (n=95)	No venous thromboembolism (n=498)	Total (n=593)
Demographic details			
Mean age (years)	59.9	56.6	57.1
Sex (M/F)	50/45	199/299	249/344
History of cancer			
Mean duration of symptoms	6.6	9.4	8.9
Cases of cancer	37	41	78
Recent surgery	9	29	38
Immobilisation*	23	50	73

*Refers to patients bedridden for more than 3 days in the previous 4 weeks.

Table 2: Baseline characteristics of study patients with and without venous thromboembolism

deep-vein thrombosis or pulmonary embolism developing in follow-up in all patients in whom deep-vein thrombosis was excluded by our management strategy. The initial and follow-up venous-thromboembolic-event rates were also to be recorded and analysed in each of the low, moderate, and high probability groups. The difference in rates of thromboembolic events between the three pretest probability groups and comparisons of other proportions were done with a χ^2 test. The interobserver reliability between the two study nurses (LG and CC) and the two principal investigators (PSW and DRA) was determined using a weighted κ test.

Results

593 of the 918 patients who were eligible were enrolled. 10 patients refused consent. 315 patients were excluded for the following reasons: 194 because of a previous episode of deep-vein thrombosis or pulmonary embolism; 53 had signs or symptoms suggestive of current pulmonary embolism; 42 were geographically located such that follow-up could not be done; 20 had another disease making life expectancy less than 3 months; and six patients required long-term anticoagulant therapy. The mean age of the patients enrolled was 57.1 (SD=17.0) years; 249 were male and 344 female; the mean duration of symptoms before presentation was 8.9 (SD=10.6) days. Other baseline characteristics are outlined in table 2.

92 patients had deep-vein thrombosis on initial or serial testing, three developed deep-vein thrombosis during the 3 months of follow-up, so there was a total of 95 (16%) patients with venous-thromboembolic events. The difference in rates of deep-vein thrombosis between the three pretest probability groups was significant ($p<0.00001$; table 3). 329 (55.5%) patients had a low probability of deep-vein thrombosis and overall 3.0% had venous thromboembolism. 11 patients had an initially positive ultrasound and nine of these were confirmed to be acute proximal deep-vein thrombosis by venography. Therefore, the positive predictive value of ultrasound was 82% (95% CI 48.2–97.7) in the low-probability patients. One patient with a negative ultrasound developed deep-vein thrombosis on day 21 of the 3-month follow-up.

Of the 193 (32.5%) patients with a moderate probability of deep-vein thrombosis, 30 (16%) patients had a positive ultrasound 27 at initial and three at 1-week testing. Two

Patient pretest probability of DVT	Frequency of venous thromboembolism (95% CI)
High	53 (74.6%) of 71 (63%–84%)
Moderate	32 (16.6%) of 193* (12%–23%)
Low	10 (3.0%) of 329† (1.7%–5.9%)

*Includes deep-vein thrombosis on day 41 and 90. †Includes deep-vein thrombosis on day 20. DVT=deep-vein thrombosis.

Table 3: Prevalence of venous thromboembolism initially and on follow-up, according to pretest probability of deep-vein thrombosis derived by the clinical model

had deep-vein thrombosis during the 3 month follow-up (on days 41 and 90), so the overall prevalence was 17%. Only three of 166 patients converted on serial testing.

71 (12%) patients had a high pretest probability for deep-vein thrombosis of whom 53 (75%) were confirmed to have deep-vein thrombosis, 49 by the initial ultrasound and four by a positive venogram. 17 patients with negative ultrasound results underwent venography with four abnormal results, 11 normal and two inconclusive results. The thrombi identified by venography were proximal in three cases (involving the popliteal vein alone in two cases and the calf and popliteal veins in the third) and distal in the fourth. None of the five patients who refused venography were treated and none had follow-up events. Therefore the negative predictive value of ultrasound results in the patients with high pretest probability was at best 82% (18) of 22 (95% CI 59.7–94.8). The negative predictive value of ultrasound in patients with a low pretest probability was 99.7% (317) of 318 (95% CI 98.3–100). Only 0.6% (three) of 481 (95% CI 0.1–1.8) patients with low or moderate pretest probability with a negative initial or serial ultrasound, respectively, developed deep-vein thrombosis or pulmonary embolism in the 3 months of follow-up. Thus, the negative predictive value of ultrasound in the high pretest probability patients was significantly worse than in the moderate and low probability patients ($p<0.00001$). Overall only 33 (5.6%) of 593 required venography (however, six patients refused venography) and serial testing was limited to 166 (28.0%) of 593 patients. Therefore, in patients with an initially normal ultrasound 0.34 extra visits or tests were required per patient. Only three (0.6%) follow-up events (all deep-vein thrombosis) occurred in the 501 patients who were initially considered not to have deep-vein thrombosis. Of the 16 patients who died during the study seven had a deep-vein thrombosis at study entry. 12 of the patients had metastatic cancer at study entry, two had sepsis, one had liver failure, and one had congestive heart failure. Seven patients were thought to have a more than 25% probability of death, five had a 5% to 25% probability, and four had a less than 5% probability. None of the deaths in the nine patients without deep-vein thrombosis were thought to be due to pulmonary embolism. The κ for the comparison of the pretest probability between nurses and physicians was 0.75.

Discussion

In an earlier report we validated a clinical model in patients with suspected deep-vein thrombosis⁷ but we did not use it in a management strategy. The model was simplified after logistic regression analysis⁸ and in this study the new model was used in a management strategy which decreased the number of diagnostic tests required in patients with suspected deep-vein thrombosis. As with the original model physicians were able to accurately stratify patients with suspected deep-vein thrombosis into three distinct pretest probabilities. Most patients required only one ultrasound test to diagnose or exclude deep-vein thrombosis. The frequency of thromboembolic events during the 3 months of follow-up, in patients in whom initial testing ruled out deep-vein thrombosis, was only 0.6%, which is lower than previously reported with serial ultrasonography or serial impedance plethysmography.^{4,5} The low rate of recurrent venous thromboembolism during the follow-up period is not likely to be associated with the lower prevalence of deep-vein thrombosis (16%) in our

study but rather because we determined pretest probability. Determining pretest probability by definition (Bayes theorem) selects the patients most likely to have false-negative results—ie, patients with a high pretest probability of deep-vein thrombosis. When ultrasonography was negative in these patients venography was done. This routine result in less chance of missing deep-vein thrombosis, hence a lower probability of recurrent events.

It has been recommended that patients with symptoms who have positive non-invasive test results should be treated for deep-vein thrombosis while those with negative test results should have the non-invasive test repeated twice in 7 days to detect extending calf-vein thrombi.^{4,5,10} However, the serial-testing strategy is costly because most patients who return for repeat testing do not have deep-vein thrombosis.¹¹ Our findings suggest that this approach may be most appropriate for patients with a high pretest probability of deep-vein thrombosis; the value of serial testing is less in patients with moderate pretest probability of deep-vein thrombosis but it is still a safe strategy. Serial testing is unnecessary in patients with a low pretest probability. A negative non-invasive test in patients with a low pretest probability essentially excludes a diagnosis of deep-vein thrombosis, so these patients can be excluded from serial testing. In the previous studies on the serial testing strategy 1.3–4.1 extra hospital visits or tests per patient have been needed.^{4,5,10,12–14} A recent study in which a single follow-up ultrasound test was done in initially negative patients decreased the rate to 0.8 visits or tests per patient, but only 0.34 extra visits or tests were required in our study.¹² Our study can be compared to these other studies because the exclusion criteria we used were identical to the criteria used in these studies.

Although we hypothesised that patients with a low pretest probability of deep-vein thrombosis should have positive ultrasound results confirmed with venography to avoid unnecessary treatment, the positive predictive value of ultrasound was 82% in this group of patients. It is possible that this good result is due to the small numbers of low-probability patients with positive ultrasound, and perhaps venography should be individualised.

We also hypothesised that in the event of negative ultrasound results in patients with high clinical probability the false-negative rate with ultrasonography would be substantial and that negative ultrasound results should be confirmed with venography. However, the negative predictive value of ultrasound in the high-probability patients was 82%. It is possible that serial testing would be equally safe in these patients but we think the false-negative rate is high enough to warrant venography. If venography is done it is important to be aware that interobserver reliability is less than ideal for distal deep-vein thrombosis and that the test is not infrequently inadequate in centres in which the technique is seldom used.¹⁵ We caution that, although the clinical model is not complex, the examining physician should use a check sheet to ensure it is followed properly.

We believe our model should be generalisable because of the high level of agreement between the study physicians and the research nurses who assisted with the study. The level of interobserver agreement is less than in our previous study,⁷ but nurses were compared with physicians in the current study. The least objective part of the model is the determination of whether there is an alternative diagnosis. Therefore, in cases in which it is unclear as to whether there is an alternative diagnosis, or when the model is used

by an inexperienced observer, the assumption of no alternative diagnosis is likely to ensure the highest level of safety.

In conclusion, the combination of pretest probability with non-invasive diagnostic test results simplifies and improves the diagnostic process in patients with suspected deep-vein thrombosis, and will decrease costs.

Contributors

Philip S Wells and David R Anderson designed the study, co-ordinated the project, assisted with clinical care and recruitment of patients, analysed and interpreted the data, and drafted the manuscript. Janis Bormanis and K Sue Robinson assisted with the clinical care and recruitment of patients, and helped co-ordinate this study. Bernard Lewandowski, Fred Guy, and Michael Mitchell did the radiological tests, and helped co-ordinate the project. Lisa Gray and Cathy Clement helped co-ordinate the project, assisted with clinical care and recruitment of patients, and entered the study data into a computerised database. All authors contributed to writing the manuscript.

Acknowledgments

Funding for this study was provided by the Physician Services Incorporated Foundation and the Heart and Stroke Foundation of Nova Scotia, Canada. Philip Wells and David Anderson are the recipients of Research Scholarships from the Heart and Stroke Foundation of Canada.

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