

## Blood Coagulation, Fibrinolysis and Cellular Haemostasis

# A single complete ultrasound investigation of the venous network for the diagnostic management of patients with a clinically suspected first episode of deep venous thrombosis of the lower limbs

Antoine Elias<sup>1</sup>, Luc Mallard, Marie Elias, Catherine Alquier, François Guidolin, Bruno Gauthier, Alain Viard, Pierre Mahouin, Anne Vinel, Henri Boccalon

<sup>1</sup>Department of Vascular Medicine, Centre Hospitalier Universitaire Rangueil, Toulouse; Clinic for Cardiology and Vascular Medicine, Clinique d'Occitanie, Muret; Internal Medicine, Centre Hospitalier Général, Foix; and Vascular Medicine, Clinique Sarrus, Teinturier, Toulouse, France

### Summary

In patients clinically suspected of deep-vein thrombosis (DVT) of the lower limbs, it is safe to withhold anticoagulant therapy after a negative ultrasound (US) limited to the popliteal and the femoral veins, provided that this can either be repeated or combined with other diagnostic procedures. To assess the safety of withholding anticoagulants after a single negative complete US, we performed a multicenter, prospective, cohort study including consecutive ambulatory outpatients from institutional and private practice settings, with a clinically suspected first episode of DVT. Patients fulfilling the inclusion criteria were enrolled after careful clinical assessment. A complete US examination of the proximal and the distal veins was performed according to a standardized and detailed protocol. Anticoagulant therapy was administered in patients with proximal or isolated distal DVT and withheld in those with negative

results. The main outcome measure was the occurrence of objectively documented clinical thromboembolic events during a three-month follow-up after a negative US.

Out of 623 patients, 401 (64.4%) had a baseline negative US, were not anticoagulated and could be followed-up for three months. Two patients presented a calf DVT within three months. The incidence of venous thromboembolic events, including distal DVT, was 0.5% [95% confidence interval: 0.1-1.8]. No proximal DVT, or non-fatal or fatal pulmonary embolism occurred (incidence: 0.0% [95% confidence interval: 0.0-0.9]).

In conclusion, it is safe to withhold anticoagulant therapy in patients with clinically suspected DVT after a single, negative, complete US. Integrating this method within diagnostic strategies for DVT could improve management and be more acceptable for patients and physicians.

### Keywords

Ultrasonography, venous thrombosis, calf veins, prospective, cohort

**Thromb Haemost 2003; 89: 221-7**

### Introduction

The objective diagnosis of deep venous thrombosis (DVT) of the lower limbs now relies mainly on the use of ultrasonography (US). In symptomatic patients, the diagnostic performance of venous US as compared to venography, has shown to be highly

specific and sensitive for both proximal (1-4) and distal veins (1, 5-10).

Management studies (11-16) have shown that it is safe to withhold anticoagulant therapy after a negative US test limited to the popliteal and femoral vein segments. However, in order to

Correspondence to:  
Dr Antoine Elias,  
Department of Vascular Medicine,  
Rangueil University Hospital Centre  
1, Avenue Jean Poulhès, 31403 Toulouse cedex 04, France  
Tel.: + 33 5 61 32 30 38, Fax: + 33 5 61 32 26 34  
E-mail: elias.a@chu-toulouse.fr

Received September 22, 2002  
Accepted after revision November 01, 2002

be effective, the US needed to be repeated at least once in 70-80% of patients (11-14, 17) and, in order to be cost effective, to be combined with other diagnostic procedures, namely clinical probability assessment (17-19), D-dimer assay (15, 16, 18) or venography.

No prospective study has been published to date on the clinical outcome of patients after a single negative, complete US test performed only once, at baseline, on the whole venous network.

## Objective

The primary objective of the study was to assess the safety of withholding anticoagulant treatment in patients clinically suspected of having DVT, on the basis of a negative result of a single US examination of the proximal and the distal veins. The secondary objective was to determine the utility of complete US in explaining the cause of signs and symptoms in conjunction with clinical assessment.

## Methods

### Study design

This was a multicenter prospective study performed in an institutional or private practice setting on a cohort of consecutive symptomatic outpatients with clinically suspected DVT. A complete US test was performed. Patients who were positive for either proximal or distal DVT were treated with anticoagulants; those who had a negative US were followed up for three months without anticoagulant treatment. The outcome measure was the occurrence of a thromboembolic event, defined as an objectively documented DVT or pulmonary embolism or a fatal pulmonary embolism, during a three-month follow-up after a negative US.

### Patients

The eligible cohort consisted of ambulatory outpatients referred for clinically suspected DVT exclusively. Non inclusion criteria comprised a previous history of venous thromboembolism, any additional clinical symptom suggestive of a pulmonary embolism not recognized before clinical examination, established diagnosis of DVT, need for anticoagulant therapy or anticoagulation lasting for more than 48 h, immobilization, short life expectancy, as in patients with end-stage cancer, and pregnancy. Patients with a clinical onset of symptoms and signs dating from more than one month previously, patients living far from the investigating center, patients in whom the US test could not be performed and patients refusing to give their consent to participate were also excluded.

### Venous ultrasonography

The complete venous US was performed according to a standardized protocol, by different operators trained at the

same university hospital who had an experience of at least two months of daily practice of venous US and were working either in hospital or in office practice as specialists in vascular medicine. High-definition imaging US equipment was used, with different probes according to the depth of the vessels examined. We applied the same investigation techniques as described previously (20), using only a B-mode US to image the vessels and a doppler US at the common femoral vein to study the venous signal, in order to attest the patency of the iliac vein. The whole venous network was scanned bilaterally: the inferior vena cava and the iliac veins with the patient supine or in the contralateral position, the femoral veins (common, profundus and superficial) and the popliteal vein with the patient in a semi-upright position, and finally the calf veins with the patient in a sitting position with his or her feet on a chair. Study of the calf veins included the posterior tibial and fibular veins, the gastrocnemius (internal and external) veins and the soleal veins, using different incidences: anterior medial, posterior and posterior lateral. The anterior tibial veins were not investigated as they are rarely affected by the thrombotic process in the clinical situation under study. All these venous segments were investigated over their entire length in transverse and longitudinal views. The great and short saphenous veins, at their junctions with the deep venous system, were also studied.

### Diagnostic criteria

The diagnostic criteria used to confirm or exclude DVT relied on the compression test and on the absence or presence of endoluminal material. The US test was considered negative when the veins were fully compressible, with no thrombus visualized, and when the doppler signal at the common femoral vein was phasic during spontaneous respiration (with signal abolition at the end of inspiration). The test was positive when vein non-compressibility was associated with a direct image of an endoluminal thrombus. Finally, the test was considered to be inadequate when vein incompressibility was limited to less than 2 cm with no endoluminal material present.

Data from both US (vein competency, soft tissue abnormalities) and clinical assessment (symptoms and signs, risk factors and context) were combined to identify the underlying cause capable of explaining the clinical manifestations when the baseline US test was negative.

### Follow-up

During the three-month follow-up, patients were asked to come back to the center if any new symptom or sign occurred. They were systematically contacted, either directly or via their general practitioner, by a telephone call on days 15, 30 and 90. The clinical status at the different times was assessed and classified as improved or normal, stabilized, or exacerbated. During follow-up, patients with suspected DVT had their diagnosis confirmed or excluded by US and venography and those with

suspected PE, by lung scanning and if indicated, pulmonary angiography. For patients who died, the cause of death was determined by independent clinical review or by autopsy when available.

### Statistical analysis

We expected that 70% of the patients included would have a negative result. We estimated that 380 patients with a baseline negative result would be the required number for a maximal expected incidence of venous thromboembolic event of 1% and a 95% confidence interval width of 2% (upper limit set at 2%). The exact binomial distribution was used for calculation of the 95% confidence interval.

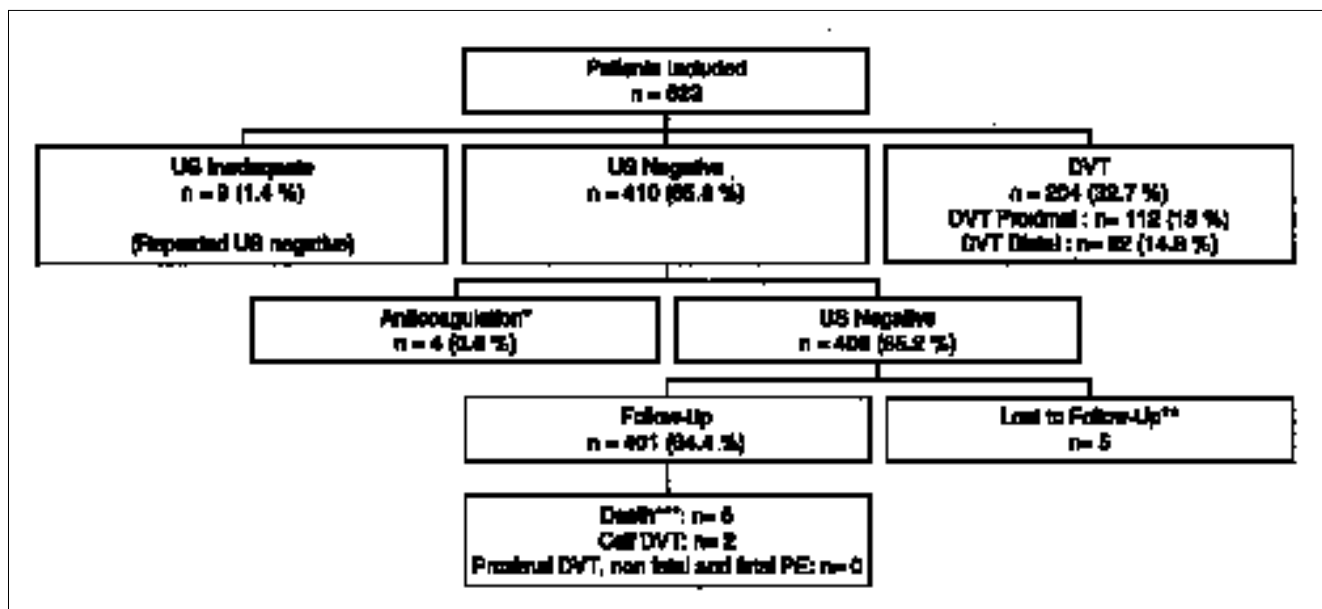
## Results

Out of a study sample of 878 outpatients with clinically suspected DVT and no clinical symptoms or signs suggestive of pulmonary embolism, 623 patients could be included. The reasons for non inclusion in the other 255 patients (29%) were the following: previous history of venous thromboembolism ( $n = 105$ ), additional associated clinical suspicion of pulmonary embolism ( $n = 8$ ), need for long-term anticoagulant therapy or anticoagulation lasting for more than 48 h ( $n = 54$ ), immobilization ( $n = 15$ ), short life expectancy ( $n = 25$ ), pregnancy ( $n = 10$ ), clinical onset dating from more than one month previously ( $n = 8$ ), residence far from the center ( $n = 20$ ), impossibility of performing the US test ( $n = 4$ ), and refusal of consent ( $n = 6$ ).

Ultrasound demonstrated a DVT in 204 patients (32.8%); in 112 patients (18%), DVT was proximal and in 92 patients (14.8%), it was distal (below the popliteal vein). US was inadequate in nine patients (1.4%) and needed to be repeated once within the first week, but remained negative. Finally, baseline US was negative in 410 patients (65.8%). Among these, four were anticoagulated by their attending physician despite the negative result and five moved far from the center and were lost to follow-up (two after day 15 and three after day 30). In total, 401 patients (64.4%) had a negative US and could be followed up for three months (Fig. 1).

The clinical characteristics of the 410 patients with negative US results were the following: mean age 53 years (range 15-102), female/male sex ratio: 2.1 (278/132), mean time from clinical onset of symptoms to inclusion: 11 days. Symptoms and signs were unilateral in 346 patients (84.5%), equally distributed between the right and the left sides. Complaints of pain were expressed by 58% of patients ( $n = 238$ ), swollen leg or edema by 21.5% ( $n = 88$ ) and both of these complaints by 21% ( $n = 84$ ). Despite the negative US results, there was a high clinical suspicion of DVT, based only on subjective assessment, in 9% of the patients ( $n = 38$ ).

Clinical assessment and US investigation in these patients ( $n = 410$ ) allowed a possible explanation for the clinical manifestations to be identified in 248 patients (60.5%). Clinical evaluation showed that the symptoms and signs were related to another underlying condition in 18.5% of the patients ( $n = 76$ ): peripheral arterial disease ( $n = 12$ ), a cutaneous infection ( $n = 13$ ), an iatrogenic cause ( $n = 4$ ), a neurological or rheuma-



**Figure 1:** Results of complete venous ultrasonography (US) in outpatients with clinically suspected first episode of deep vein thrombosis (DVT). Four patients were anticoagulated by their attending physician despite a negative US test (\*). Five patients moved far from the centre and were lost to follow-up (\*\*). Death were not related to venous thromboembolic event (\*\*\*). Two patients had calf DVT on follow-up, none had proximal DVT, non fatal or fatal Pulmonary embolism (PE).

tological condition (n = 29) and a lymphedema (n = 18), respectively, all clinical diagnoses consistent with the negative US test result. In 42% of the patients (n = 172), US showed other pathological conditions that could explain the clinical manifestation: venous reflux (n = 93), muscular lesion (n = 20), haematoma (n = 24) and a Baker's cyst (n = 35), considered to be ruptured in eight cases.

During the three-month follow-up among the patients with negative US results receiving no anticoagulant treatment (n = 406), clinical signs and symptoms improved or normalized in 87% (n = 353), stabilized in 10.6% (n = 43) and worsened in 2.5% (n = 10). In five patients, a cancer was detected. Five patients died. Two deaths were cancer-related and three occurred postoperatively for different reasons: disseminated intravascular coagulopathy after operation for an abdominal aortic aneurysm, leg amputation prompted by severe infectious disease, and acute pancreatitis. No death was related to pulmonary embolism. Two patients who had persistent clinical symptoms presented a distal vein thrombosis. One DVT was detected by US and venography at day 60 and was located in the gastrocnemius veins in a patient with a persistent rheumatological condition leading to immobilization. The other patient presented a posterior tibial vein thrombus on US, located very distally, at day 30. The incidence of venous thromboembolic events, distal DVT included, was 0.5% [95% confidence interval: 0.1-1.8]. No proximal DVT, pulmonary embolism or fatal pulmonary embolism occurred (incidence: 0.0% [95% confidence interval: 0.0-0.9]).

## Discussion

This prospective cohort study evaluated the utility of a single US examination of the proximal and distal veins of the lower extremities to safely exclude first episode of DVT in symptomatic patients.

The study subjects consisted of patients with clinically suspected DVT seen in our current practice, enabling our results to be applied to the average patient presenting with signs and symptoms of DVT. For strategic reasons and differences in diagnostic management, patients were not eligible for inclusion if they had associated clinical manifestations suggestive of pulmonary embolism. Despite these preselection criteria, careful clinical examination revealed such a situation in eight additional patients who were then excluded. Furthermore, for diagnostic reasons, patients with a previous history of DVT were not included. If these two categories of patients had not been selected, the total number of eligible patients would have been 765 and the proportion of "exclusion" would have decreased from 29% to 19%. The 33% prevalence of DVT in our study indicates that this is not such a low-risk group with regard to DVT as suggested by the small proportion of patients with negative US results and a high clinical suspicion of DVT (9%).

This proportion was assessed only in patients with a negative US and was based on the clinical impression, but no *a priori* clinical probability was considered in this study.

In this study, the proximal DVT prevalence is in the lower limit range (18%) of the published series. The prevalence of proximal DVT as detected by limited venous ultrasound (US) in out-patients, varies from 17% (14, 19) to 28% (15). Because in these series, US was not performed in the calf, the prevalence of calf DVT on initial test is unknown. Also, the proportion of calf DVT among all DVT is similar (45%) to that published in US series in out patients (21). These results are slightly different from those obtained with venography for two main reasons. Firstly, US detects more calf DVT than venography and this is explained by their different diagnostic approach for visualizing the vein and detecting the thrombus in the main veins and in the muscular veins. Secondly, the spectrum of the disease is changing. When venography was used as the unique diagnostic method, patients were referred at an advanced stage and DVT were mostly proximal. With US, a non invasive method that replaces now venography, patients are referred earlier and the proportion of calf DVT among all DVT becomes higher.

The outcome measure was an objectively documented symptomatic thromboembolic event. An objective diagnosis was deemed necessary and demonstrated a DVT located in the calf in two patients. In one patient, venography and US were performed and confirmed the diagnosis; in the other patient, only venous US, a method widely accepted for DVT diagnosis or exclusion in the popliteal and the femoral veins. In these two patients, no proximal DVT was detected. On the other hand, as the conditions of the study were the same as in real life clinical practice, the study subjects were not mandated to return for the follow-up evaluation. We considered that a systematic telephone call assessment conducted by a physician, using a standardized questionnaire, at three time points was sufficient to investigate the different possible outcomes and would ensure that the entire study cohort could be evaluated.

The results show that a single, complete negative US test safely excludes the diagnosis of first episode of DVT in out-patients. In this study, a complete US needed to be repeated in only very few patients (1.4%) because of inadequate tests, as compared to 70-80% of patients with the limited compression US method which is repeated in patients with negative test results in order to detect any progression of a missed calf DVT to the proximal veins. In our study, the risk of venous thromboembolism was very low, despite only a single assessment of the veins. These results are consistent with those of prospective studies using strategies including a limited US test either repeated or combined to other diagnostic modalities, and similar to the results shown in three retrospective studies (22-24) using a single complete venous assessment (Table 1). Considering the prevalence of DVT, the excellent predictive value of a negative complete US test could be related to its excellent sensitivity for

**Table 1:** Results of management studies using a single complete venous ultrasound in patients with a clinically suspected first episode of deep vein thrombosis (DVT). VTE = venous thrombo embolism. In our study, the incidence of proximal DVT, non fatal and fatal pulmonary embolism after a single complete US was 0/401 : 0% [95% confidence interval: 0-0.9]. The incidence of calf DVT was 2/401 : 0.5% [95% confidence interval: 0.1-1.8]. Complete US needed to be repeated in only very few patients (1.4%) because of inadequate tests.

MANAGEMENT STUDY	N Patients	DVT Prevalence	Risk VTE (%) [95% CI]	ExtraVisit / Patient
<b>Retrospective Study</b>				
Cornin J et al(22) (Out patients)	977	15 %	0.0 [0.0 - 0.4]	0
Wolf B et al(23) (DVT & PE patients)	537	34 %	1.1 [0.4 - 2.9]	
Schellong B et al(24) (in & out patients)	286	37 %	0.9 [0.1 - 3.3]	0.02
<b>Prospective Study</b>				
Our study (Out patients)	623	33 %	0.0 [0.0 - 0.9]	0.02

detecting not only proximal DVT but also calf thrombosis. It thus confirms the results of previous diagnostic performance studies comparing US to venography. Studies that met the required methodological criteria show a sensitivity of over 95% for detection of proximal DVT and about 90-95% for isolated calf DVT (1, 5-9), provided that the investigation and equipment used were adequate. In our previous study, in 60 patients (92 limbs) with isolated calf DVT on venography, US enabled detection of a thrombus located in either the axial or the muscular veins in 96% of the patients (91% of the limbs), using the same complete US method (1). Despite the high sensitivity of US to detect isolated calf DVT, as compared to venography, we cannot exclude the possibility of false negative results. Given a 33% prevalence of DVT with a 98% sensitivity and a 94-95% specificity for US performance (1), we assume that less than 1% of our patients with a negative complete US had misdiagnosed DVT located in the calf. On follow-up, 0.5% had a clinical manifestation with documented calf DVT and none had a proximal DVT or pulmonary embolism.

The positive results, mainly those within the calf, were not confirmed by venography and a high frequency of false positive results could be expected given the high sensitivity of the test. However, with the same US criteria, a high specificity was found in comparison to venography (1). Criteria for positive test results relied not only on the absence of compressibility but also on its association with a direct image of vein thrombosis. A low positive predictive value in symptomatic patients relying only on vein noncompressibility has been reported, mainly in the common femoral site due to pelvic neoplasm and abscess (25). To avoid false positive results, considerable precautions were taken to ensure that the patient was relaxed, as muscular contraction can cause absence of vein compressibility and lead to a false positive test result. Furthermore, so as not to confound an

extravascular image with an intraluminal thrombus, complete scanning of the vein was performed until the upper or the lower extremity of the thrombus was visualized at the limit with the normal vein portion where it was fully compressible.

How to achieve reliable examination of the distal veins by US is a matter of debate. For better specificity and reliability, color doppler US was not used, but only B-mode US imaging. Using B-mode US, an excellent interobserver agreement has been demonstrated, with the kappa test, in symptomatic and asymptomatic patients (26) provided the US test is performed by experienced operators using a standardized method.

Interestingly, in this study, in about 60% of the patients, complete assessment of the veins helped to identify the origin of signs and symptoms when no venous thrombosis was demonstrated by US (Fig. 2). Either the negative US corroborated the clinical impression (18.5%) or it revealed another cause capable of explaining the clinical manifestations (42%). Similarly to a

Periphrical arterial disease	12 (2.9%)
Cutaneous infection	13 (3.2%)
Iatrogenic cause	04 (1%)
Neurological/Rheumatological cause	29 (7.1%)
Lymphoedema	18 (4.4%)
Venous Insufficiency (Reflex)	93 (22.7%)
Muscular Lesion	20 (4.9%)
Haematoma	24 (5.8%)
Baker's Cyst (8 ruptured)	35 (8.5%)
<b>Total</b>	<b>248 (60.3%)</b>

**Figure 2:** Alternative diagnosis made by clinical assessment and complete venous ultrasound in 410 patients tested negative for DVT (deep vein thrombosis) at baseline.

study (27) evaluating 106 limbs without venous thrombosis, the most frequent ultrasound findings were incompetent leg veins or soft tissue masses (Baker's cyst and calf hematoma).

Many non-invasive strategies are being used for the diagnosis of DVT in outpatients. Integrating a single complete US within these strategies can improve the diagnostic approach. The most interesting strategies are those that used firstly, prior to US, a simple D-dimer assay that is easy to perform, in order to exclude DVT, either combined (28) or not (16) with a pretest probability based on the clinical assessment. The combination of clinical assessment with D-dimer assay depends on both the D-dimer test characteristics (sensitivity and specificity) and the prevalence of DVT (16, 28). With a D-dimer test with about 98% sensitivity and 40% specificity, DVT was excluded (16) on the basis of a negative D-dimer only. With a D-dimer test with about 85% sensitivity and 70% specificity, the diagnostic exclusion of DVT did not rely on a negative D-dimer test alone but needed to be combined with a low clinical probability (28). After the D-dimer test (and clinical assessment), the next step could be to perform either a single complete US or a limited US that could be repeated if negative. Although the "D-dimer then complete US" alternative seems to be cost-effective and preferable, the efficiency of such an approach as compared to the other diagnostic alternatives (D-dimer then limited US repeated or not) needs to be demonstrated in decision analysis models and in management studies. In fact, more detectable DVT could lead to a higher proportion of patients being treated with anticoagulants, and therefore a higher risk of bleeding complications and a higher cost. Conversely, early detection of DVT within the calf might decrease the rate of recurrent venous thromboembolic events (29, 30) and possibly the rates of asymptomatic pulmonary embolism and post-thrombotic syndrome, thereby leading to a lower overall cost. Some of our patients might not have needed anticoagulant treatment, considering solely the criterion

of proximal progression as it is widely recognized that not all isolated calf DVT do extend to the proximal veins, nor do they all give rise to symptomatic pulmonary embolism. However there is no evidence that isolated calf DVT do not progress to subclinical pulmonary embolism and little is known about possible outcomes such as recurrences or post-thrombotic syndromes after a long follow-up period. The sixth ACCP consensus conference on antithrombotic therapy (31) recommend "that patients with a first episode of idiopathic venous thromboembolism should be treated for at least 6 months (grade 1 A)", and "that symptomatic isolated calf vein thrombosis should be treated with anticoagulant for at least 6 to 12 weeks (grade 1 A)". Most outpatients with isolated calf vein thrombosis enter into this category of idiopathic DVT. Besides the important question of whether isolated calf vein thrombosis should be treated systematically or only in those patients who are at risk because these thromboses extend to the proximal veins, it may be of great importance to know the cause of DVT. In some patients who present with isolated calf vein thrombosis, screening for thrombophilia or cancer may be very useful and at least could help to decide on the duration of any long-term anticoagulant treatment.

We believe the results we obtained in outpatients with this method of investigation could be generalized and applied to in-patients although our study did not include a high risk group. In hospitalized patients, a complete US is much more useful, as the D-dimer test is rarely negative and does not contribute to the diagnosis.

In conclusion, it is safe to withhold anticoagulant therapy in patients with clinically suspected DVT after a single, negative, complete US. A complete assessment also aids the diagnosis of other conditions that could explain the clinical manifestations. Finally, a single reliable and safe test may be more acceptable for patients and for physicians than a repeated test and can be integrated in diagnostic management procedures.

## References

- Elias A, Le Corff G, Bouvier JL, Benichou M, Serradimigni A. Value of real time B mode ultrasound imaging in the diagnosis of deep vein thrombosis of the lower limbs. *Int Angiol* 1987; 6 (2): 175-82.
- Lensing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989; 320 (6): 342-5.
- Becker DM, Philbrick JT, Abbitt PL. Real-time ultrasonography for the diagnosis of lower extremity deep venous thrombosis. The wave of the future? *Arch Intern Med* 1989; 149 (8): 1731-4.
- Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. *McMaster Diagnostic Imaging Practice Guidelines Initiative. Ann Intern Med* 1998; 128 (8): 663-77.
- Habscheid W, Landwehr P. [Diagnosis of acute deep leg vein thrombosis with compression ultrasonography]. *Ultraschall Med* 1990; 11 (6): 268-73.
- Yucel EK, Fisher JS, Eglin TK, Geller SC, Waltman AC. Isolated calf venous thrombosis: diagnosis with compression US. *Radiology* 1991; 179 (2): 443-6.
- Wichert C, Gmelin E, Jansen O, Marienhoff N. [Diagnosis of thrombophlebitis of the leg using duplex sonography]. *Aktuelle Radiol* 1993; 3 (1): 37-42.
- Bradley MJ, Spencer PA, Alexander L, Milner GR. Colour flow mapping in the diagnosis of the calf deep vein thrombosis. *Clin Radiol* 1993; 47 (6): 399-402.
- Atri M, Herba MJ, Reinhold C, Leclerc J, Ye S, Illescas FF, et al. Accuracy of sonography in the evaluation of calf deep vein thrombosis in both postoperative surveillance and symptomatic patients. *AJR Am J Roentgenol* 1996; 166 (6): 1361-7.
- Gottlieb RH, Widjaja J, Tian L, Rubens DJ, Voci SL. Calf sonography for detecting deep venous thrombosis in symptomatic patients: experience and review of the literature. *J Clin Ultrasound* 1999; 27 (8): 415-20.
- Sluzewski M, Koopman MM, Schuur KH, van Vroonhoven TJ, Ruijs JH. Influence of negative ultrasound findings on the management of in- and outpatients with suspected deep-vein thrombosis. *Eur J Radiol* 1991; 13 (3): 174-7.
- Heijboer H, Buller HR, Lensing AW, Turpie AG, Colly LP, ten Cate JW. A comparison of

- real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med* 1993; 329 (19): 1365-9.
13. Cogo A, Lensing AW, Koopman MM, Piovello F, Siragusa S, Wells PS, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ* 1998; 316 (7124): 17-20.
  14. Birdwell BG, Raskob GE, Whitsett TL, Durica SS, Comp PC, George JN, et al. The clinical validity of normal compression ultrasonography in outpatients suspected of having deep venous thrombosis. *Ann Intern Med* 1998; 128 (1): 1-7.
  15. Bernardi E, Prandoni P, Lensing AW, Agnelli G, Guazzaloca G, Scannapieco G, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. *BMJ* 1998; 317 (7165): 1037-40.
  16. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; 353 (9148): 190-5.
  17. Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet* 1995; 345 (8961): 1326-30.
  18. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Application of a diagnostic clinical model for the management of hospitalized patients with suspected deep-vein thrombosis. *Thromb Haemost* 1999; 81 (4): 493-7.
  19. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997; 350 (9094): 1795-8.
  20. Elias A. [Role of Doppler echography in the diagnosis of venous thrombosis]. *Arch Mal Coeur Vaiss* 1991; 84 (11 Suppl): 1669-78.
  21. Mattos MA, Melendres G, Sumner DS, Hood DB, Barkmeier LD, Hodgson KJ, et al. Prevalence and distribution of calf vein thrombosis in patients with symptomatic deep venous thrombosis: a color-flow duplex study. *J Vasc Surg* 1996; 24 (5): 738-44.
  22. Cornuz J, Pearson SD, Polak JF. Deep venous thrombosis: complete lower extremity venous US evaluation in patients without known risk factors – outcome study. *Radiology* 1999; 211 (3): 637-41.
  23. Wolf B, Nichols DM, Duncan JL. Safety of a single duplex scan to exclude deep venous thrombosis. *Br J Surg* 2000; 87 (11): 1525-8.
  24. Schellong SM, Schwarz T, Pudollek T, Schmidt B, Schroeder HE. Complete compression ultrasound for the diagnosis of proximal and distal deep venous thrombosis – a retrospective outcome study. *Vasa* 2001; 30 (4): 253-7.
  25. Birdwell BG, Raskob GE, Whitsett TL, Durica SS, Comp PC, George JN, et al. Predictive value of compression ultrasonography for deep vein thrombosis in symptomatic outpatients: clinical implications of the site of vein noncompressibility. *Arch Intern Med* 2000; 160 (3): 309-13.
  26. Barrellier MT, Somon T, Speckel D, Fournier L, Denizet D. [Duplex ultrasonography in the diagnosis of deep vein thrombosis of the legs. Agreement between two operators]. *J Mal Vasc* 1992; 17 (3): 196-201.
  27. Somjen GM, Donlan J, Hurse J, Bartholomew J, Weir E, Johnston AH, et al. Duplex ultrasound examination of the acutely painful and swollen leg. *Dermatol Surg* 1996; 22 (4): 383-7.
  28. Kearon C, Ginsberg JS, Douketis J, Crowther M, Brill-Edwards P, Weitz JI, et al. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. *Ann Intern Med* 2001; 135 (2): 108-11.
  29. Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet* 1985; 2 (8454): 515-8.
  30. Astermark J, Bjorgell O, Linden E, Lethagen S, Nilsson P, Berntorp E. Low recurrence rate after deep calf-vein thrombosis with 6 weeks of oral anticoagulation. *J Intern Med* 1998; 244 (1): 79-82.
  31. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2001; 119 (1 Suppl): 176S-193S.