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

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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

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
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 abolishment at the end of inspiration). The test was positive when vein noncompressibility 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
A single complete ultrasound

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 out patients 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).

Patients Included n = 623

<table>
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<tr>
<th>US Inadequate</th>
<th>US Negative</th>
<th>DVT</th>
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<tr>
<td>n = 9 (1.4%)</td>
<td>n = 410 (65.8%)</td>
<td>n = 204 (32.7%)</td>
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Anticoagulation* n = 6 (0.9%)

Follow-Up n = 401 (64.4%)

Death**; n = 5

Calf DVT; n = 2

Proximal DVT, non fatal and fatal PE; n = 6
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
A single complete ultrasound 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

| 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 (%) | Extra VTE / Patient |
| retrospective study | (Out patients) | (In & out patients) | (In & out patients) | (In & out patients) |
| Conza J et al (22) | 977 | 15 % | 0.1 [0.0 - 0.4] | 0 |
| Wolf B et al (23) | 597 | 34 % | 1.1 [0.4 - 2.9] | - |
| Schallhorn S et al (24) | 266 | 37 % | 0.9 [0.1 - 3.2] | 0.02 |
| Prospective Study | 623 | 23 % | 0.0 [0.0 - 0.9] | 0.02 |

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 hema-

toma).

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 anticoagu-

lants, 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 thrombo-

esis 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


