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### INVITED REVIEW

# Is it worth diagnosing and treating distal deep vein thrombosis? No

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Summary. The standard diagnostic approach to suspected deep vein thrombosis (DVT) is serial lower limb compression ultrasound (CUS) of proximal veins. Although it only assesses the proximal veins, withholding anticoagulant treatment in patients with a negative CUS on day 1 and after 1 week has been proved safe. In particular, studies evaluating CUS limited to the proximal veins showed a good safety profile with a pooled estimate of the 3-month thromboembolic rate of 0.6% (95% CI, 0.4-0.9%) in non-anticoagulated patients. However, performing two lower limbs CUS is cumbersome and expensive. Recently, studies using a unique complete (proximal and distal) CUS showed a similar pooled estimate of the 3-month thromboembolic rate (0.3%; 95% CI, 0.1-0.6%) but distal DVTs accounted for as many as 50% of all diagnosed DVTs in those series. Comparing these studies may suggest that systematically searching for calf DVTs potentially doubles the number of patients given anticoagulant therapy and entails a risk of over-treatment. Admittedly, performing calf CUS is highly useful in diagnosing other conditions such as popliteal cyst, hematoma or muscle rupture. Performing a CUS limited to the popliteal site in the presence of calf pain may be not well accepted by the patient. However, the advantage of calf CUS in diagnosing venous thromboembolism appears to be at the least debatable. Data suggesting that anticoagulation is indicated for distal DVT are limited, and realizing systematic distal CUS entails a risk of over-treatment. There is an urgent need for randomized trials assessing the usefulness of anticoagulant treatment in distal DVT.

**Keywords**: calf thrombosis, compression ultrasonography, distal deep vein thrombosis, proximal deep vein thrombosis.

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#### Introduction

Distal or calf deep vein thrombosis (DVT) involves infrapopliteal veins [i.e. posterior tibial veins, peroneal veins, anterior tibial veins, and muscular calf veins (soleal or gemellar veins)]. The sensitivity and specificity of compression ultrasound (CUS) for proximal DVT are high (97% and 98%, respectively) [1] and the necessity for treating proximal DVT with anticoagulants is widely accepted [2]. On the other hand, the sensitivity and specificity of CUS for distal DVTs are lower [1,3] and a meta-analysis by Kearon *et al.* reported sensitivity of 50% to 75% and specificity of 90% to 95% [1]. The natural history of distal DVT, in particular the rate of extension to proximal veins, is not well known. Therefore, contrary to proximal DVT, the diagnostic and the therapeutic approach of distal DVT remain controversial.

#### Incidence and natural history of distal DVT

In studies including inpatients, 80% of DVTs are proximal and distal DVT accounts for only 20% of all DVTs [3–5]. However, some studies with outpatients report a proportion of distal DVT as high as 60–70%, underlining the potential relevance of the problem in everyday clinical practise [6,7]. The natural history of deep vein thrombosis seems to be in the vast majority of cases the development of a thrombus in the distal veins of the calf that extend proximally, the so-called ascending thrombosis [5]. The embolic potential of proximal vein thrombosis is unanimously recognized. On the other hand, although data are limited, distal clots appear to have a much lower embolic potential [8]. Therefore, the rate of proximal extension of distal DVT is a crucial issue as it largely determines the clinical relevance of distal DVT.

Two reviews of literature data tried to answer this question. In the first one, analyzing studies in which patients were anticoagulated or not, Philbrick *et al.* reported that extension to the proximal veins varied between 0% and 29% [9]. In the second one, rate of extension was 10% (95% CI, 7–12%) in untreated patients and 4% (95% CI, 3–6%) in treated patients [10]. Overall, the rate of extension was highly variable (0% to 44%) and the variations in study design and target population were too large to allow a pooled estimate or a comparison between the proportion of patients in whom distal DVT

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extended to proximal veins in treated and untreated patients. Therefore, it is difficult to establish the definitive rate of extension of distal DVT based on those studies. However, indirect data from studies using serial proximal CUS [11–15], which show a low rate of proximal DVTs (1% to 5.7%) detected by the repeated CUS in patients left untreated, suggest that proximal extension of distal DVTs is quite rare.

#### Proximal serial CUS in outcome studies

The limited performances of distal venous examination reported in most studies may explain why many centres use only proximal CUS (i.e. limited to the popliteal and supra-popliteal veins). As such protocols do not search for distal DVT that could potentially extend to the proximal veins with a significant risk of pulmonary embolism, the standard diagnostic approach consists of performing two CUS limited to the proximal veins on days 1 and 7, the so-called 'serial proximal ultrasonography'. Patients with a proximal DVT on the initial ultrasonographic examination are treated with anticoagulants. When the initial examination is negative, patients are not given anticoagulants, and a second proximal CUS is repeated 1 week later to detect the possible extension of distal DVT. Patients with a second normal CUS are considered as definitely not having a proximal DVT and are not anticoagulated.

Many prospective, well-designed, outcome studies have shown the safety of serial proximal CUS (Table 1). Six studies used only proximal veins CUS [11–16]. Five of these studies used the classical repeated CUS and one used a single proximal CUS associated with D-dimer dosage and pre-test clinical probability [16]. As the second CUS depicts 1% to 5.7% of proximal DVT (see Table 1), it is possible that not carrying out the second CUS results in the slightly higher 3-month thromboembolic risk reported in this study, but the confidence interval for that risk overlaps widely with that of the other similar studies.

The pooled estimate of the 3-month thromboembolic risk of these studies using only proximal veins CUS was 0.6 (95% CI, 0.4–0.9%). There was no significant difference in the estimation of the 3-month thromboembolic risk between these six studies

(P = 0.16). If one considers each study individually, the 3month thromboembolic risk in patients with a negative proximal CUS is low: in management studies, it is lower than 1% in series using serial CUS [11–15] (CUS repeated after 1 week in patients with an initially negative CUS) and 2.6% (95% CI, 0.2–4.9%) in the single study that used a single proximal CUS (Table 3) [16]. This compares favorably with the 3-month thromboembolic risk in patients with clinically suspected DVT who had a negative venogram, which was found to be 1.9% (95% CI, 0.4–5.4%) [17]. Even if serial proximal CUS is very safe, its main limitation is the need for a second ultrasound examination, which is costly and has a very low yield as it reveals a proximal DVT in only around 1% to 5.7% of patients (Table 1).

#### Complete (proximal and distal) CUS in suspected DVT

Four prospective outcome studies using a single complete (i.e. proximal and distal) CUS have been published [18-21]. Patients were treated if CUS showed a proximal or distal DVT and were left untreated if proximal and distal veins were normal. As shown in Table 2. extending the ultrasonographic examination to distal veins is very safe. Indeed, the pooled estimate of the 3month thromboembolic risk is 0.3 (95% CI, 0.1-0.6%) and there is no significant difference in this estimate between these four studies (P = 0.51). However, these studies point to some important problems. First, such an approach may be quite costly and time-consuming as complete CUS is proposed for all patients with suspected DVT. Notably, in outpatients with clinically suspected DVT, a normal enzyme linked immunoadsorbent assay (ELISA) D-dimer test allows the withholding of anticoagulation without further testing in about one-third of outpatients at a much lower expense [16] and with a similar safety. Secondly, the pooled estimate of the 3-month thromboembolic risk of these studies is similar to that computed for studies using only proximal CUS (Table 1). Therefore, detecting calf DVT may be deleterious: it does not reduce the 3-month thromboembolic risk and it entails a significant risk of false positive findings and subsequent unnecessary anticoagu-

 Table 1
 Performances and safety of proximal compression ultrasonography for diagnosing DVT in outcome management studies. Distal DVTs were not searched for in these studies

Source, year	Patients (n)	Incidence of DVT (%)	Proportion of proximal DVTs detected by the second CUS % (95% CI)	3-month thromboembolic risk, % (95% CI)*
Birdwell et al.[15], 1998	405	16	2 (0.8–4.2)	0.6 (0.1–2.1)
Cogo et al.[11], 1998	1702	24	0.9 (0.3–1.2)	0.7 (0.3–1.2)
Bernardi et al.[12], 1998	946	28	5.7 (1.9–12.8)	0.4 (0-0.9)
Wells et al.[13], 1997	593	16	1.8 (0.3–5.2)	0.6 (0.1–1.8)
Perrier et al.[16], 1999	474	24	NA*	2.6 (0.2-4.9)
Kraaijenhagen et al.[14], 2002	1756	22	3 (1.9–5.2)	0.7 (0.3–1.6)
Pooled estimate	5876	23	NA	0.6 (0.4–0.9)

\*During 3-month follow-up in patients left untreated after normal proximal compression ultrasonography.

DVT, deep vein thrombosis; CUS, compression ultrasonography; NA, not applicable.

NA\*: In the study by Perrier et al., only one CUS limited to proximal veins was realized in patients with a positive ELISA D-dimer measurement.

Table 2 Performances and safety of a single proximal and distal compression ultrasonography for diagnosing DVT in outcome management studies

Source, year	Patients (n)	Incidence of DVT %, (n)			3-month thromboembolic risk, % (95% CI) *
		All <i>n</i> (%)	Proximal n (%)	Distal n (%)	Single proximal and distal CUS
Elias et al.[18], 2003	623	204 (33)	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong et al.[19], 2003	1646	275 (17)	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens et al.[20], 2004	445	61 (14)	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam et al.[21], 2005	526	113 (22)	49 (43)	64 (57)	0.2 (0.01–1.3)
Pooled estimate	3240	653 (20)	324 (50)	329 (50)	0.3 (0.1–0.6)

\*During 3-month follow-up in patients left untreated after a normal complete (proximal and distal) compression ultrasonography.

NA, not applicable; DVT, deep vein thrombosis.

lant treatment in patients who could be left untreated. Of note, a pooled analysis of these studies (Table 2) shows that of a total of 3240 included patients, 329/653 (50%) of diagnosed DVTs were distal.

#### Distal CUS in clinical practise: a hypothetical scenario

Table 1 shows the pooled data of studies involving serial proximal CUS. In the worst-case scenario, we could admit that all events (number of patients = 5876; pooled estimate of the 3-month thromboembolic risk of 0.6%, i.e. 35 events) in the 3month follow-up were distal DVTs and could have been avoided by a distal CUS. The hypothetical effect of realizing a complete CUS considering sensitivity and the specificity of distal CUS as reported in the meta-analysis of Kearon et al. [22] (sensibility 50-75%, specificity 90-95%) suggests that this number of 35 thromboembolic events could have been reduced to nine, at the expense of at least 294 false positive distal examinations (5% of 5876 patients). Admitting similar diagnostic performances for proximal and distal CUS (i.e. sensitivity 95% and specificity 97%), these 35 events could have been reduced to two at the expense of 176 unduly anticoagulated patients. This highlights that false positive results at distal CUS may entail unduly administered anticoagulation and is the major drawback of distal CUS.

#### Distal DVT in clinical practise: an unresolved problem

In spite of the reassuring data obtained from the outcome studies using proximal CUS, recent consensus conferences, including those of the American College of Chest Physicians [23] and the Australasian Society of Thrombosis and Haemostasis [24], still recommend treating distal DVT with anticoagulants for 3 months.

The only randomized study about the usefulness of anticoagulation in distal DVT was published by Lagerstedt *et al.* [25]. It included only 51 patients with symptomatic distal DVT diagnosed by phlebography. Recurrence rate at 3 months was 28% in patients not anticoagulated (8/28) compared with 0% in anticoagulated patients. However, extension of DVT was not evaluated by systematic phlebography at 3 months but by physical examination and serial isotopic tests, later abandoned because of insufficient performances. In the non-treated group, eight patients had a proximal extension of their DVT and one experienced PE. However, 50% of these patients had previous thromboembolic events, and were therefore at high risk of recurrence. Therefore, it seems unreasonable to recommend systematically searching for and treating distal DVT on the basis of this single study. Moreover, the results of our pooled analysis of the 3-month thromboembolic risk in studies using CUS limited to proximal veins (Table 1) and in studies using proximal and distal veins (Table 2) are similar and question the benefit of searching for and treating distal veins .

Another potential limitation of searching for distal DVT is the limited reported performance of CUS at the infra-popliteal level. The reported diagnostic performances of CUS for distal DVT are highly variable, with sensitivities ranging from 0% to 92.5% compared with phlebography [26-28]. A meta-analysis by Kearon et al. suggested a sensitivity of 50-75% and an acceptable specificity (90-95%) [22]. Even if better performances may be obtained in some centres [6], with the best ultrasound equipment and in the hands of highly skilled ultrasonographers, they can probably not be translated into everyday clinical practise. Indeed, contrary to proximal compression ultrasonography, examination of the distal veins may be difficult. Simons et al. found that only 55% of patients could benefit from a well-conducted examination [29]. The overall rate of indeterminate distal CUS was 54.6% in a recent meta-analysis, with a wide variation in the reported frequency of indeterminate examinations (9.3-82.7%) [27].

Opting for a 3-month anticoagulant treatment in the presence of a distal DVT raises several problems in clinical practise. First, series using serial ultrasonography indicate that only a small fraction of distal DVTs extend to the proximal veins. Indeed, the rate of proximal DVT detected by the repeated ultrasound varies from 0.9% to 5.7% (Table 1), while at least 20% of DVTs are distal in phlebographic series [5]. Secondly, the randomized DOTAVK study showed a similar safety for an anticoagulant treatment of 6 or 12 weeks for distal DVT, suggesting that a shorter period of anticoagulation (6 weeks) would be safe [30]. Thirdly, muscle vein thromboses (i.e. gemellar and solear thrombosis) are probably less dangerous than thrombosis of the deep distal veins (i.e. peroneal and tibial posterior veins). McDonald et al. [31] showed, in a prospective study where muscular thromboses were not treated but followed by ultrasonography, that only 3% of muscular

thrombosis extended to the popliteal vein. Extension occurred only until the 15th day. This suggests that the vast majority of muscular vein thromboses need no anticoagulation or a shorter period of anticoagulation. Fourthly, in studies using proximal and distal CUS, half of detected thromboses were distal (Table 2) and a risk of over-treatment should not be neglected. This point deserves further comment. It is troublesome that in centres where distal veins are systematically assessed, one of two thromboses is a distal DVT. As shown in Tables 1 and 2, the reported prevalence of DVT is similar in centres using proximal or complete CUS. It is possible that populations screened are different and that physicians working in centres using complete CUS have a lower index of suspicion for DVT. One wonders if adopting a complete examination in centres with experience of CUS limited to proximal veins would really double the incidence of the disease and the proportion of treated patients. Obviously, there is no definitive answer. However, using distal CUS may potentially unnecessarily increase the number of patients given anticoagulant therapy, a treatment associated with a major hemorrhagic risk evaluated at 0.6% to 1.2% and a risk of fatal bleeding of 0.1% to 0.4% for a 3-month period [23].

In conclusion, even if well-conducted management studies have shown the safety of a diagnostic strategy limited to proximal ultrasonography in patients with suspected DVT, many clinicians still search for and treat isolated distal DVT. In fact, distal CUS has probably limited diagnostic performances and its systematic use may result in over-treatment of a substantial proportion of patients, who might have fared well without anticoagulant therapy, as suggested by studies in which distal DVT where not searched for.

Admittedly, complete leg ultrasonography is useful in everyday clinical practise because it can help diagnose other conditions, such as calf hematoma, partial muscle rupture, and popliteal cyst. However, its advantage in diagnosing venous thromboembolism appears to be at least debatable. As distal DVT is a frequently encountered problem, there is an urgent need for randomized trials assessing the usefulness of anticoagulant treatment in symptomatic distal DVT.

#### Disclosure of conflict of interests

The author states that he has no conflict of interest.

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