

Clinical relevance of distal deep vein thrombosis

Marc Righini and Henri Bounameaux

Division of Angiology and Hemostasis, Geneva University Hospital, Geneva, Switzerland

Correspondence to Marc Righini, MD, Division of Angiology and Hemostasis, Geneva University Hospital, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
Tel: +41 22 372 92 94; fax: +41 22 372 92 99; e-mail: Marc.Righini@hcuge.ch

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Purpose of review

To discuss pros and cons of anticoagulant treatment in the presence of symptomatic distal deep vein thrombosis.

Recent findings

Available data are responsible for a lack of consensus regarding treatment of distal deep vein thrombosis.

Summary

One standard diagnostic approach of suspected deep vein thrombosis consists of serial lower limb compression ultrasound of proximal veins. Studies evaluating compression ultrasound limited to the proximal veins performed on two occasions separated by 1 week showed good safety with a pooled estimate of the 3-month thromboembolic events rate of 0.6% (95% confidence interval: 0.4–0.9%) in untreated patients. However, performing two lower limbs compression ultrasound is cumbersome and expensive. Recently, studies using a single complete (proximal and distal) compression ultrasound showed a similar pooled estimate of the 3-month thromboembolic risk (0.3%, 95% confidence interval: 0.1–0.6%) but distal deep vein thrombosis accounted for as many as 50% of all diagnosed deep vein thrombosis in those series. Comparing these studies may suggest that systematically searching for calf deep vein thrombosis potentially doubles the number of patients given anticoagulant treatment without reducing the 3-month thromboembolic risk. Despite these data, many physicians still search for and treat distal deep vein thrombosis in the fear of proximal extension and of pulmonary embolism. However, robust data in favour of anticoagulation for distal deep vein thrombosis are limited. Randomized trials assessing the usefulness of anticoagulation in distal deep vein thrombosis are therefore urgently needed.

Keywords

anticoagulation, calf thrombosis, compression ultrasonography, diagnostic performances, distal deep vein thrombosis, proximal deep vein thrombosis

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Introduction

Distal or calf deep vein thrombosis (DVT) involves infrapopliteal veins, that is 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 absolute necessity for treating proximal DVT with anticoagulants is undisputed [2]. The attitude towards distal DVT is a matter of debate for two main reasons. First, the diagnostic performances of ultrasonography for distal DVT are highly variable according to literature data. For example, the sensitivity and specificity of CUS for distal DVT have been reported to be quite low [1,3] and a meta-analysis by Kearon *et al.* [1] indicated a sensitivity of 50–75% and a specificity of 90–95%. On the contrary, some authors reported a sensitivity as high as 100% in

studies with a limited patient population, however [4,5]. These studies were performed by highly skilled ultrasonographers using the best ultrasound equipment, and it is not sure that these performances may be reproduced in real life. This seems to be confirmed by a more recent meta-analysis [6] that reported a limited sensitivity [75%, 95% confidence interval (CI): 62–82%] of the test even when using duplex and triplex technology. Second, the natural history of distal DVT, in particular the rate of extension to proximal veins, is not well known and wide variations (0–29%) have been reported [7], especially in the nonsurgical setting. Even if quite robust literature evidences suggest that most patients with distal DVT fare well without anticoagulation, many physicians still continue to give anticoagulant therapy in the presence of calf DVT in the fear of a proximal extension or pulmonary embolism. For these reasons, the diagnostic and therapeutic management of distal DVT remains a hot topic.

Prevalence and extension rate of distal deep vein thrombosis

In studies including hospitalized patients, 80% of DVT are proximal and distal DVT accounts for only 20% of all DVT [3,8,9]. 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 practice [5,10]. 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 extends proximally, the so-called ascending thrombosis [9]. The embolic potential of proximal vein thrombosis is unanimously recognized. On the contrary, although data are limited, distal clots appear to have a much lower embolic potential [11]. 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 the literature addressed this question. In the first one, analysing both studies in which patients were anticoagulated – or not, Philbrick and Becker [7] reported that extension to the proximal veins varied between 0 and 29%. In the second one, the rate of extension was 10% (95% CI: 7–12%) in untreated patients and 4% (95% CI: 3–6%) in treated patients [12]. Overall, the rate of extension was highly variable (0–44%), 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 who extended their distal DVT to proximal veins in treated and untreated patients. Therefore, it is difficult to establish the definitive rate of extension of distal DVT on the basis of those studies, even if these data suggest that there is a high percentage of DVT that do not propagate but become ‘abortive’ at some time [13**].

Data suggesting that calf deep vein thrombosis is not a wolf in sheep’s clothing

Indirect data from studies using serial proximal CUS [14–18], which show a low rate of proximal DVT (1–5.7%)

detected by the repeat CUS in patients left untreated, suggest that proximal extension of distal DVT is quite rare.

Proximal serial compression ultrasound in outcome studies

The limited performances of distal venous examination reported in most studies may explain why many centres use only proximal CUS, that is limited to the popliteal, and suprapopliteal 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 in performing two CUS limited to the proximal veins at 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) [14–19]. Six studies used only proximal veins CUS [14–19]. Five of these studies used the classical repeated CUS and one used a single proximal CUS associated with D-dimer dosage and pretest clinical probability [19]. As the second CUS depicts 1–5.7% of proximal DVT (see Table 1), it is possible that not realizing the second CUS results in the slightly higher 3-month thromboembolic risk reported in that study, but CI for that risk widely overlaps with those of the other similar studies [14–18].

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 among these six studies ($P=0.16$). If one considers each study individually, the 3-month thromboembolic risk in patients

Table 1 Performances and safety of proximal compression ultrasonography for diagnosing deep vein thrombosis in outcome management studies

Reference	Patients (n)	Prevalence of DVT (%)	Proportion of proximal DVT detected by the second CUS [% (95% CI)]	Three-month thromboembolic risk [% (95% CI)] ^a
Birdwell <i>et al.</i> [18]	405	16	2 (0.8–4.2)	0.6 (0.1–2.1)
Cogo <i>et al.</i> [14]	1702	24	0.9 (0.3–1.2)	0.7 (0.3–1.2)
Bernardi <i>et al.</i> [15]	946	28	5.7 (1.9–12.8)	0.4 (0–0.9)
Wells <i>et al.</i> [16]	593	16	1.8 (0.3–5.2)	0.6 (0.1–1.8)
Perrier <i>et al.</i> [19]	474	24	NA ^b	2.6 (0.2–4.9)
Kraaijenhagen <i>et al.</i> [17]	1756	22	3 (1.9–5.2)	0.7 (0.3–1.6)
Pooled estimate	5876	23	NA	0.6 (0.4–0.9)

Distal DVT were not searched for in these studies. CI, confidence interval; CUS, compression ultrasonography; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; NA, not applicable.

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

^b 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 Main results of a recent randomized controlled trial comparing proximal with complete ultrasound for the diagnosis of clinically suspected deep vein thrombosis

	Proximal ultrasonography	Complete ultrasonography (proximal and distal)
<i>N</i>	1045	1053
DVT [<i>n</i> (%)]	231 (22.1)	278 (26.4)
Proximal	231	213
Distal	0	65
Three-month thromboembolic risk [% (95% CI)]	0.9 (0.3–1.8)	1.2 (0.5–2.2)

Adapted from [20**]. CI, confidence interval; DVT, deep vein thrombosis.

with a negative proximal CUS is low: in management studies, it is lower than 1% in series using serial CUS [14–18] (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 2) [19,20**]. This compares favourably 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%) [21]. 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 1–5.7% of patients (Table 1).

Complete (proximal and distal) compression ultrasound in suspected deep vein thrombosis

Four prospective outcome studies using a single complete (i.e. proximal and distal) CUS have been published [22–25]. 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 3, these studies show that extending the ultrasonographic examination to distal vein is very safe. Indeed, the pooled estimate of the 3-month thromboembolic risk is of 0.3 (95% CI: 0.1–0.6%), and there is no significant difference in this estimation among 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 to all patients with suspected DVT. Noteworthy, in outpati-

ents with clinically suspected DVT, a normal enzyme-linked immunoadsorbent assay (ELISA) D-dimer test allows to withhold anticoagulation without further testing in about one-third of outpatients at a much lower expense [19] and with a similar safety. Second, 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 anticoagulant treatment in patients who could be left untreated. Of note, a pooled analysis of these studies (Table 3) shows that of a total of 3240 included patients, 329/653 (49%) of diagnosed DVT were distal.

Comparison of serial compression ultrasound and single complete compression ultrasound

A recent randomized study by Bernardi [20**] compared the classical serial CUS with a single complete (proximal and distal) CUS in more than 2000 patients with suspected DVT. The 3-month thromboembolic risk was similar in both arms of the study: 0.9% (95% CI: 0.3–1.8%) in the repeat CUS group and 1.2% (95% CI: 0.5–2.2%) in the single complete CUS group. Of note, in the single complete CUS group, as many as 23% (65/278) of patients were anticoagulated for an isolated distal DVT, without reducing the 3-month thromboembolic risk. Therefore, this randomized study suggests that searching for and treating distal DVT with anticoagulant drugs do not improve the safety of the diagnostic strategies for suspected DVT [20**].

Distal compression ultrasound in clinical practice: 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 3-month follow-up were distal DVT and could have been avoided by a distal CUS. The hypothetical effect of realizing a complete CUS considering

Table 3 Performances and safety of a single proximal and distal compression ultrasonography for diagnosing deep vein thrombosis in outcome management studies

Reference	Patients (<i>n</i>)	Prevalence of DVT [<i>n</i> (%)]			Three-month thromboembolic risk [% (95% CI)] ^a Single proximal and distal CUS
		All	Proximal	Distal	
Elias <i>et al.</i> [22]	623	204 (33)	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong <i>et al.</i> [23]	1646	275 (17)	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens <i>et al.</i> [24]	445	61 (14)	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam <i>et al.</i> [25]	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)

CI, confidence interval; CUS, compression ultrasonography; DVT, deep vein thrombosis.

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

sensitivity and the specificity of distal CUS as reported in the meta-analysis of Kearon *et al.* [26] (sensitivity 50–75%, specificity 90–95%) suggests that the 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.

Other options in the presence of distal deep vein thrombosis

Despite the data presented above, the option of not treating distal DVT is not unanimously accepted. This is due to the intimate relationship between thrombosis and pulmonary embolism that are often considered as the same disease. As a matter of fact, about 90% of DVT are of the ascending type. The potential for embolism depends on the speed and the extent of the clot-growing process, and it is well admitted that the vast majority of pulmonary embolism arises from a formerly distal DVT. This natural history and some clinical observations reporting pulmonary embolism, and even fatal pulmonary embolism, in presence of distal DVT, may explain the fear of not treating distal DVT [27,28]. Obviously, the data presented above clearly suggest that treating all distal DVT would not be an acceptable option as the benefit of anticoagulation would be offset by the haemorrhagic risk. Moreover, as the vast majority of calf DVT never extends, the risk of unduly treating an important number of patients should be considered. An alternative approach, recently proposed by Schellong [13^{••}], would be to search for distal DVT at the first presentation and then to stratify patients for their risk of clot propagation. Treatment and treatment duration would be only offered to patients considered at high risk of propagation. This idea is sound. However, adopting a risk-adapted strategy would need more data regarding progression rates in different populations. Obviously, such data are lacking, even if opting for treatment of distal DVT in cancer patients or in presence of immobilization could seem a reasonable attitude.

Distal deep vein thrombosis in real practice: still an unresolved dilemma

In spite of the reassuring data obtained from the outcome studies using proximal CUS, recent consensus conferences, including that of the American College of Chest Physicians [29] and the Australasian Society of Thrombosis and Haemostasis [30], 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.* [31]. 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 nontreated group, eight patients had a proximal extension of their DVT and one experienced pulmonary embolism. However, 50% of these patients had previous thromboembolic events, and were therefore at high risk of recurrence. Therefore, it seems unreasonable to recommend to systematically search for and to treat 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 3) are similar and questions the interest of searching for and treating distal veins.

Another potential limitation of searching distal DVT is the limited reported performance of CUS at the infrapopliteal level. The reported diagnostic performances of CUS for distal DVT are highly variable, with sensitivities ranging from 0 to 92.5% compared with phlebography [32–34]. A meta-analysis by Kearon *et al.* [26] suggested a sensitivity of 50–75% and an acceptable specificity (90–95%). Even if better performances may be obtained in some centres [5], with the best ultrasound equipment and in the hands of highly skilled ultrasonographers, they can probably not be translated in to every-day clinical practice. Indeed, contrarily to proximal compression ultrasonography, examination of the distal veins may be difficult. Simons *et al.* [35] found that only 55% of patients could benefit from a well conducted examination. 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%) [33].

Opting for a 3-month anticoagulant treatment in the presence of a distal DVT raises several problems in clinical practice. First, series using serial ultrasonography indicate that only a small fraction of distal DVT 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), whereas at least 20% of DVT are distal in phlebographic series [9]. Second, the randomized Duree Optimale du Traitement Anti-Vitamines K (DOTAVK) study showed a similar safety of an anticoagulant treatment of 6 or 12 weeks for distal DVT, suggesting that a shorter period of anticoagulation (6 weeks) would be safe [36]. Third, 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). Macdonald *et al.* [37] showed in a prospective study in which muscular thromboses were not treated but followed by ultrasonography that only 3% of muscular thrombosis extended in 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. Fourth, in studies using proximal and distal CUS, half of detected thromboses were distal (Table 3) and a risk of overtreatment should not be neglected. This point deserves further comment. It is troublesome that in centres in which distal veins are systematically assessed, one of two thromboses is distal. As shown in Tables 1 and 3, 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 can wonder if adopting a complete examination in centres with experience of CUS limited to proximal veins would really double the prevalence 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 haemorrhagic risk evaluated to 0.6–1.2% and a risk of fatal bleeding of 0.1–0.4% for a 3-month period [29].

Conclusion

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

Admittedly, complete leg ultrasonography is useful in everyday clinical practice because it can help diagnose other conditions, such as calf haematoma, partial muscle rupture and popliteal cyst. However, its advantage in diagnosing venous thromboembolism appears to be at least debatable. The proposal of treating only high-risk patients is appealing but is hampered by the limited data dealing with progression rates in various patient populations. However, this option should be further studied.

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, a point on which both detractors and sup-

porters of anticoagulation for distal DVT agree [13^{**},38^{**}].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 493).

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